Author’s response to reviews

Title: Postoperative remote lung injury and its impact on surgical outcome

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Author’s response to reviews:

Point to point response to reviewers’ comments are below

Reviewer #1: A comprehensive summary of findings related, in particular, to the role of inflammatory mediators in the mechanisms of remote lung injury.

General comments:

1. The manuscript would benefit from a synthesis of previous findings into e.g. important remaining questions, directions for future research and clinical use of presented findings, in particular how findings related to mediators should be considered, as this constitutes the bulk of the review.

Response: Thanks for your comments. We have added two sections before conclusions (page 12 line 274 to page 15 line 359). Section 6 shows some detail for how anaesthetics and fluid management affect the outcome of postoperative remote lung injury. Section 7 mainly talks about remaining questions and directions for future research.
2. I also miss an attempt to link findings related to prediction and prevention of remote lung injury to findings related to its pathology and important mediators.

Response: Thanks for your comments. We have amended the manuscript to link them together (page 6, 2nd paragraph, page 7, 1st paragraph, last paragraph, page 8, last paragraph, page 9, 1st paragraph)

Specific comments:

Pg 3, ln 18: revise for language

Response: The language has been revised.

Pg 3, ln 54: Please specify which cohort is referred to here

Response: The cohort is stated in reference 10 which is KCLIP (King County Lung Injury Project) cohort. This study showed that 1113 out of 6235 patients underwent mechanical ventilation were suffered from ALI (page 3 line 59).

Pg 3, ln 56: Definition of ALI/ARDS?

Response: we have amended the sentence to make the definition more clear (page 4 line 60).

Reviewer #2: The authors present with an interesting review about remote PPCs.
The text reads well and not verbose, concepts are adequately explained.
PPC pathophysiology is well presented with nice and clear images.
Major suggestions:

- Also the following study published in 2017 should be considered and commented: Fernandez-Bustamante et al. JAMA Surg 2017 - DOI: 10.1001/jamasurg.2016.4065

Response: Thanks for your kind suggestion. We apologize for missing the key information presented in the study by Fernandez-Bustmante and colleagues. The work analyzed the incidence of PPCs in patients underwent noncardiothoracic surgery of 2 hours or more with ASA physical status III from 7 major US academic centers and the result showed that the development of more than one PPC was associated with increased early postoperative mortality, ICU admission, and prolonged length of stay both in ICU and hospital. We also learned from this research that even mild PPCs should be pay more attention to and the key variables can be divided by modifiable or nonmodifiable (page 11 paragraph 1). Also, we have included a table which showed the modifiable and nonmodifiable factors affected PPCs in the revised manuscript.

- Predictions and prevention for postoperative remote lung injury Section: most readers need a pragmatic take home message. The authors should give more information about clinical risk factors for PPCs and briefly give some suggestion for the daily practice in the operating room: ventilation strategy, fluid management, role of anesthetic drug (even indicating the future area of research).

Response: Thanks for your kind suggestion. First, a table showing the contributing factors for postoperative remote lung injury has been added, which may help clinicians choosing the right therapeutic strategy during surgery. Second, we have added some points regarding future research in section 7 (page 15 paragraph 2).

Minor suggestions:

- Please revise the text for misprints

Response: All the typos and misspellings have been revised.
Reviewer #3: The authors presented a deep narrative review on postoperative remote lung injury. The quality of the manuscript and the review of literature is remarkable. I have some comments for authors. First of all, I would like if a "clinical implication" section could be added. It would be a nice adding to insert a brief resume on "modifiable" and "non-modifiable" risk factors for postoperative remote lung injury to give a clinician some easy advice (in a brief subheading or in a Table).

Response: Thanks very much for your suggestion. We have added a table showing the modifiable and non-modifiable factors for postoperative remote lung injury in the revised manuscript. And we hope this would help physicians in the decision making process.

Other comments:

Introduction

- The terms "ALI" has recently lost his international classification. Please avoid its use and discuss only of mild, moderate and severe ARDS (except when referring to study performed before Berlin consensus)

Response: We all agree with your opinion that the term “Acute Lung Injury” is no longer used after the Berlin consensus. We also tried not to discuss ALI unless the original study state so and apologize for the misunderstanding it may cause.

- The reference used from author to identify the risk of TRALI refers to data prior to 2011; from 2011 transfusion policy is changed, in particular referring to plasma units (and plasma from female donors), which are most responsible of TRALI (now considered a very rare syndrome, ~1 case every 100000 RBCs and 1 every 35000 FFP unit). Probably, TACO and TRIM gain more importance in postoperative reduction in lung function. I would delete the phrase "is the leading cause of transfusion related death in recent years" and I would discuss that transfusion can have detrimental effect in lung function with different pathway, such as TRALI, TACO, and perhaps the absence of leukoreduction and the storage lesions (please cite Risbano AJRCCM 2015 https://doi.org/10.1164/rccm.201501-0145OC and Spadaro Transfusion 2017 10.1111/trf.14249 )

Response: Thanks for your very constructive comments. We have carefully read the references mentioned above. We have deleted the sentence “is the leading cause of transfusion related death
in recent years”. There are already a bunch of reviews discussing the incidence and etiology of TRALI and TACO. As TRALI is not the key point of discussion in this manuscript, so we will discuss this interesting topic in the future.

- I would add a brief report on the effect of fluids administration. It was shown that cytokine release during surgery can be influenced by the kind of fluid (please cite CA Volta, J Inflamm (Lond). 2013) and amount (please cite ARDSnet, NEJM 2006)

Response: Thanks for your advice. It should be noted that fluid management also contributed to inflammatory cytokines release into the circulation system during surgery. One randomized clinical trial conducted by Volta CA et al. showed that patients received balanced solutions experienced lower concentration of active MMP-9 and higher level of TIMP-1 and IL-10 compared to the unbalanced solutions. For those patients with ALI, a conservative strategy of fluid therapy was superior to the liberal strategy which had longer ventilator free time with improved lung function. This result suggests that a conservative management of fluid may be associated with reduced pulmonary inflammation in ARDS patients. We have added this point of view in the manuscript (page 14 paragraph 3).

- Page 11 line 38. When discussing the results of PROVHIL0 trial (ref 67), it has to been kept into account that the individual response to the same protective ventilation strategy can explain the negative results and the same ventilatory set can results in both protective and non-protective ventilation depending on the patient's response (please cite Spadaro, Anesthesiology 2018)

Response: Thanks for your kind suggestion. Patients may response to the same ventilation strategy and the same presumed protective ventilation strategy (Low VT with high PEEP) may produce controversial results. Different from the result from the PROVHIL0 trial, Spadaro et al. showed that low VT together with PEEP at 10cm H2O is protective during one lung ventilation. We have to be careful when interpreting the results from clinical trials and that is why we need more trials and evidence before a conclusion can be made. We have added this point of view in the manuscript (page 12 paragraph 1).

Figures

All the figures and nice and illustrative. However, I see the figures "blurry" in my pdf file. I do not know if it is an author's guilty, please check the quality of the files
Response: We have checked the quality of all figures uploaded and these figures share the same resolution of 600 dpi.