

## Peer Review File

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### Review Comments

#### Reviewer A

The paper is well written and provides a lot of information on EVLP in lung transplantation.

It would help to add a few more scenarios to complete the narrative.

1) DCD Lung with DCD heart-describe nuances and technical modifications

Reply: In general, not many techniques differences between lungs harvest with and without heart harvest between DBD or DCD. However this is more technical aspect of harvest the main topic here in expanding the lung donor pool.

2) Normothermic regional perfusion- how DCD lungs can be procured using this technique.

Reply: This is more technical and out of the main article.

Controlled donation after circulatory death (cDCD) donors are becoming a common source of organs for transplantation globally. However, the graft survival rate of cDCD abdominal organs is inferior to that of organs from brain-dead donors. The rapid retrieval (RR) technique is used by most donor organ procurement teams. The abdominal normothermic regional perfusion (A-NRP) technique has been implemented to minimize warm ischemic damage to the abdominal organs. No difference was observed in lung transplantation outcomes irrespective of the abdominal organ procurement technique used (A-NRP or abdominal RR).

3) Comment on the Toronto technique of storing lungs at 10 degrees Celsius overnight and converting lung transplants to a day time procedure.

Reply: This is still lab trial, Toronto group published their lab work few month ago in the article they were able to practically double the cold ischemia time by keep storing

the lung at 10 degrees, however no clinical trial yet. Below is the link to the article.

<https://www.science.org/doi/10.1126/scitranslmed.abf7601>

4) Uniformity in reporting DCD lung transplant data- how to account for 2 warm ischemia times; what is acceptable

Reply: All transplanted organs have two warm time, the first one is the time from circulatory arrest and to the time to back the organ on Ice, this time in general is around 30-45m in DBD harvest, and 60-90 m in DCD, the second warm time is the implantation time (the time between removing out of ice to lung reperfusion) this varied by surgeons and techniques. These details might not be relevant to the article reader as we focused on expanding the lung transplant pool.

5) Discuss the Lung guard hypothermic transport techniques:

Reply: The Lung guard hypothermic transport techniques (Paragonix or LungGuard) are a method to transport transplanted organ according to the company is better control the temperature around 4 degree centigrade. Not very popular yet in the US due to price and inability to get fully reimbursed, the device never had wide research study to revealed better outcomes or increase in ischemia time or expand the donor pool.

6) How to salvage lungs from donors placed on ECMO- VA vs VV; how to assess those lungs

Reply: ECMO use in lung transplant is for recipient support prior (bridge to transplant) or perioperative period, the donor lung supported by VV or VA ECMO in general are not good lungs, and not included in extended criteria

7) Both XVIVO and OCS are approved by FDA now, but many potential readers want to know the financial issues, such as a costly rig. If the authors can discuss on these issues in this paper, this paper will be much improved.

8) There are many typo mistakes, such as [Loor et al, 2019] (23, 24). Either of the information should be deleted. Please check again.

Reply: This was fixed.

## Reviewer B

I read this review manuscript with great interest.

Whereas there are numerous series of studies and reviews highlighting the technology as well as the role of EVLP not only in clinical lung transplantation but also in broad translational pulmonary medicine that have been published to date, there are some new subtopics or even preliminary but potentially novel findings that remain to be well focused or introduced with expertise to the readership in the countries where the clinical transplant remains to be developed. From this standpoint, an updated EVLP review may be worthwhile at this journal.

Unfortunately, however, the current manuscript attempts to cover such a broad topic including even the history and its common basic knowledge that eventually it fails to duly introduce the up-to-date findings and get ahead of the next stage in this evolving field of EVLP.

First of all, the authors should be advised to follow the guidelines of writing a scientific manuscript in more formal and appropriate manner by avoiding using unnecessary bold, underlined or upsized fonts. And the discussions should be more round, rational and toned down by avoiding using 'must'.

Reply: The article was according to the journal review guidelines, Same for the used verbiage.

In addition, if this is a review instead of an original article with their original or institutional dataset, they should be strictly in line with the prior evidences or the data duly cited and supported by the appropriate and updated references to develop their expertise.

Concerning warm ischemic time for DCD lungs, in one page they state that waiting time might be extended to 2 hours whereas they state in the next page that the initial warm ischemic time should not be more than 60-90 minutes. The readers will find it difficult to understand the differences. Again they need to add the appropriate

references in each point where the controversy or different opinions exist.

Reply: References were added and time was corrected.

Regarding systemic heparin administration, they state that the donor received heparin before extubation. Is it universally accepted? Such antemortem heparin remains controversial in my understanding.

Reply: Heparin use is not universally accepted, as mentioned in line XXX, it is recommended to decrease the intra vascular thrombosis , however, it is a common practice most of centers in USA do after discussing with the OPO and the families who agreed for it. Giving heparin before extubation give sometime for the heparin to act prior the circulation arrest.

With regards to the standard EVLP versus transportable EVLP/OCS, the authors appear to be more enthusiastic about the latter; however, while the data from the reports using OCS remain limited and in particular those over the superiority of OCS to the standard are not sufficient enough to conclude or recommend. In this respect, they should be strongly advised to tone down the current statements and rewrite the associated sections. Indeed quite a few experienced transplant centers still feel comfortable in duly assessing the DCD lungs without additional assessment on EVLP/OCS.

Reply: We do respect the comment however the authors performed transplant using both technologies. We might be more enthusiastic to OCS as by our experience we did shift to more use of OS rather than XVivo. We did modify the section to avoid biases.

In the section of ‘OCS and immune modulation’, which evidences/reports/studies proved that OCS helped ‘totally deplete donor-derived soluble immune mediators via continuous recirculation of the perfusate’? Even if such mediators are at most reduced following on EVLP/OCS, as it is difficult to eliminate all the donor-derived lymphocytes which reside in the grafts out of the circulatory system (extravasation), additional therapy or strategy is relevant for their ideas of immune modulation on machine perfusion for the organ grafts.

Reply: The paragraph was removed to avoid controversy

Reading through it, the goal and the structure of this manuscript remain unclear, if it is a systematic review article or textbook chapter.

If the authors intend to write a systematic review manuscript, they'd be advised to add an appropriate Methods section to duly state their data sources, search strategy, study inclusion and exclusion criteria, data extraction and quality assessment with a PRISMA flow diagram. In addition, they'd add appropriate tables to summarize those study characteristics and key findings so that they can reduce the current redundant descriptions.

[Reply: The section was removed. The article is in publishing process.](#)

In the current version, their references appear to be so limited and disorganized given numerous EVLP and/or DCD-related literatures for longer than a decade that it will be difficult for the readers to accept their biased statements in addition to lack of round discussions.

[Reply: Please refer to the answer 2 question prior.](#)

Lastly, all the current figures and tables are citable from the available EVLP reviews or textbooks of lung transplantation elsewhere. They aren't helpful for the readers.

[Reply: Some figures were delated](#)

### **Reviewer C**

Thank you for giving an opportunity for reading this valuable manuscript regarding the current status of lung transplantation.

Lung transplantation has been performed worldwide and recognized as an effective treatment for patients with various end-stage lung diseases. Although various efforts have been made to promote organ donation, shortage of lung donors is one of the main obstacles in most of the countries. Therefore, use of marginal donors is one of the strategies for organ shortage.

In this manuscript, the authors precisely mentioned the review of the new protocols to verify the "transplantability". There are some typographical errors to be corrected;

however, the contents were easily comprehensible.

As they concluded, EVLP seems to be useful to assess and manage marginal donor lungs. However generally healthy donor lung had better be directly transplanted because EVLP itself can deteriorate the donated lung. Therefore, I would like to know the actual criteria of EVLP use in marginal donor lungs.

Reply: See below

1. The actual criteria in general used for marginal lung, and well described in reference 43 (Sage E, Mussot S, Trebbia G, et al. Lung transplantation from initially rejected donors after ex vivo lung reconditioning: The French experience. *Eur J Cardiothorac Surg* 46:794–799, 2014.)

2. And in the following link

Possoz J, Neyrinck A, Van Raemdonck D. *Ex vivo* lung perfusion prior to transplantation: an overview of current clinical practice worldwide. *J Thorac Dis.* 2019;11(4):1635-1650. doi:10.21037/jtd.2019.04.33

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6531747/>

## Reviewer D

The authors have described a review article on DCD donors with EVLP and OCS in lung transplantation. I have some comments as follows:

Comment 1: Main problem of this paper is that there are a lot of English grammar and spelling mistakes overall, which made this paper difficult to read and understand. The authors should ask an English native language expert to check the paper to ensure correctness of the spelling, grammar and syntax.

Reply: The article was proofread by an English native language expert.

Comment 2: Another main problem is that the authors do not have enough and optimal references overall.

Please put reference, for example;

- The lung remains as unique organ with a low metabolic requirement and 1-2 hrs tolerance of warm ischemia. (line 101-102).
- Figure 2 and 3
- Rapid declining is physiologically better than slow progression (line 216-217).
- Based on the fact that ..... (line 219-226)

Please put correct reference,

- Furthermore, the Toronto Group recently published ..... (line 171-174).

Reply: Appropriate references were added

Comment 3: The authors have the same headings “DCD donation” in line 90 and 127. I think that they do not need and should remove line 111-126. Then they can organize the paragraphs of DCD donation.

Reply: The whole article was reorganized

Comment 4: Did the authors review various techniques of DCD lung procurements in the paragraph of “Techniques of DCD lung procurements” (line 254-)? There are no references. If they just put their own procedure, it is not good for a review article.

Reply: References were added.

Comment 5: The authors put too much detailed data and information on OCS. Readers can get the detailed data from the original paper, so they should summarize and organize the sections on OCS.

I think they can focus on OCS in DCD donors.

Comment 6: The authors do not need to describe the Toronto protocols, because we can get protocols from the Toronto original papers. If they want to put “the Toronto protocols”, they should provide accurate information with references.

Comment 7: The authors should describe the first EVLP case by Sweden group to assess the uncontrolled DCD donor lungs.

Reply: References was added

Comment 8: Did the authors copy the figures 4,5,6 from other sources?

Reply: Figures were rearranged and

## Reviewer E

This narrative review aims to summarize the new donor management modalities that have been positively impacted the lung transplantation. However, the way the authors organized the paper makes it difficult to follow, it is not well structured and is not well written. I have a few minor points to raise about the article, and I think this article should be given a "major revision" proposal.

1. I suggest that article titles should not use abbreviations such as EVLP, OCS, DCD, it is a problem in article formatting.

Reply: Abbreviations were removed

2. The first impression is that the objectives and logical structure of this narrative review are confusing, it is a key question. My advice is that titles should be graded, major and minor titles should be ordered, and arranged to fit the framework of the article. Also, try not to use abbreviations in the content of the title, or the abbreviations should be preceded by the corresponding full terms. Because of the length of this article, the extensive use of abbreviations will interrupt the flow of reading and comprehension.

Reply: Article was rewritten according to the journal review guidelines

3. The EVLP has emerged as a powerful tool for the assessment, rehabilitation, and optimization of donor lungs before transplantation. Its use for standard and extended criteria donors has been widely discussed currently by review previous published works, but the latest advances about the mechanisms of EVLP and potential targets to promote the OCS should be more or less mentioned, I think that it will provide understanding and support from a basic research level for this



future clinical work.

[Reply: The whole section on OCS And EVLP was rewritten](#)

4. The volume of the article should be more concise, and much of the content is repetitive and not relevant to the topic, such as the toronto protocol, which does not need to be displayed in detail.

[Reply: Article was readjusted and the protocol was deleted and](#)

5. The references cited in the article are far from adequate, and do not match the volume of the article, and many key places lack of sources, as a review should pay more attention to the standard citation of references.

[Reply: More references were added](#)

6. The formatting of the figures and tables provided in the article also needs to be carefully revised, especially for Figures 2 and 3, which I think are more appropriate as tables, as using them as figures would bring down the quality of the article.

[Reply: Tables and figures were reconfigured](#)

7. Some of the statements are inaccurate, including the DCD criteria, which change depending on the center. On a review paper I consider they need to actually analyze the different protocols from different centers at least the ones with more known experience.

## **Reviewer F**

I would thank Drs. El Salihi for their well-written article “Boosting Lung Transplant, A Narrative review of the impact of EVLP, OCS, and DCD in Expanding The Donor Pool”. The authors clearly demonstrated their mastering and expertise in the subject, the article offered a lot of information and extensive details about DCD, OCS And EVLP (X-Vivo), there are multiple DCD harvest protocols and criteria, however the protocol described in the article is the most used in the US. Here are some suggestions which might help:

- The article might become more fluent if the authors follow the guidelines and recommended structural for Narrative review article(please attach)

[Reply: The article was reformed according to the review article guidelines.](#)

- There are some typo errors throughout the article, please review and adjust.

Reply: The article was proofread by an English native language expert.

- OCS recently received FDA approval and OCS expanding rapidly to catch EVLP market, most of US transplant centers are split and use only one. It would be great if the authors give their opinion about special conditions, they prefer to use X-Vivo rather than OCS and vice versa.

- Off note, please correct the reference 4. (paper published in 1963 not 1953)

Hardy JD, Erasian S, Dalton ML. Autotransplantation and homotransplantation of the lung: Further studied. J Thorac Cardiovasc Surg. 1963 Nov;46:606-15. PMID: 14087734.

Reply: This was corrected, thank you

Again, I would thank the author for their excellent effort and reporting their expertise in the wide and rapidly growing field in lung transplantation.