

## Peer Review File

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### Reviewer Comments

#### Reviewer A

Comment 1: The authors provided a rudimentary introduction into ECLS. The level of the content is not sufficient for an expert to expand their knowledge, nor is it sufficient to allow a novice to understanding cannulae, terminology, hybrid terms, and the multiplicity of various cannulation strategies (only a few are introduced). Dual stage veno-venous oxy-RVAD V-V ECMO is not addressed or discussed. Terms of V-A+V are not introduced. Differential hypoxemia and ways to mitigate this risk are not discussed. I had anticipated that the authors would spend more time on ECCO2 exchange, that typically only requires 300 mL/min of blood volume flux, allowing it to be achieved with smaller cannulae than those used when oxygenation is required. Focusing on ECCO2 exchange more, and a review of classic literature there, would be a golden opportunity to educate others on this technique.

Reply 1: Thank you for your insightful comment. Regarding the context of the special series on “Extracorporeal Life Support in Thoracic Surgery” for Journal of Thoracic Disease (JTD), the authors decided to keep the introduction limited because specific chapters of this special issue will address the specific points mentioned.

Regarding ECCO2 exchange, the authors agree with the importance in this scenario and decided to expand that section. This paper is intended to be a practical insight about the use of ECLS in general Thoracic Surgery.

Comment 2: The "Methods" for their literature review do not seem to serve any methodical, systematic, concrete role. No criteria beyond a simple search and manual review for pieces of interest to the authors is discussed. As such, the Methods do not contribute meaningfully to this work.

Reply 2: Thank you for your comment. The authors understand and agree about the simplicity of the methods but they provided the needed background to support our work.

The following are additional comments/observations:

Comment 3: Line 53 – Lung resection after pneumonectomy – unclear (redundant?) – perhaps “intrathoracic surgery after pneumonectomy?”

Reply 3: Thank you for your comment. The authors changed the sentence to be specific to the scenario of lung resection in the patient that had a pneumonectomy in the past.

Comment 4: Lines 57-59: Authors describe planned situations; yet trauma may be unplanned. Please reconcile/expand to be less restrictive.

Reply 4: Thank you for your comment. The authors agree and decided to expand.

Comment 5: Line 58 – “cumberstones” – do the authors mean “cornerstones” perhaps?

Reply 5: Thank you for your comment. Changes were made accordingly.

Comment 6: Lines 68-70: Increasing frequency of ECLS in thoracic surgery – add citations/datapoints?

Reply 6: Thank you for your insightful comment. References were added throughout the paper as appropriate.

Comment 7: Line 75: change provide oxygenation to “provide oxygenation and/or ventilation”

Reply 7: Thank you for your insightful comment. Changes were made accordingly.

Comment 8: Line 77: “outflow cannula through a vein and an inflow cannula to pump it back to the patient”

-would instead state “drainage (outflow) cannula and an inflow cannula to return ventilated and/or oxygenated blood back to the patient; although drainage is typically through a vein (e.g. venous drainage cannula), alternative strategies including pulmonary artery or transeptal or direct atrial approaches are all feasible”

Reply 8: Thank you for your insightful comment. Changes were made accordingly.

Comment 9: Lines 78-81 are not needed as they are incomplete and partially replicate the more expansive list at lines 121-125.

Reply 9: Thank you for your insightful comment. Changes were made accordingly.

Comment 10: Line 84: change “rarely” to “infrequently” perhaps?

Reply 10: Thank you for your comment. Rarely was changed to infrequently.

Comment 11: I am unclear why authors chose concatenated terms such as “extracorporeal life support pulmonary resection” rather than breaking them down into “extracorporeal life support” AND “pulmonary resection” or “extracorporeal life support” AND “pulmonary” AND “resection”

Did authors really manually review 5000 abstracts?

More fundamentally, I am unclear what the purpose of the search was.

Reply 11: Thank you for your comment. The authors objective was to provide a search that would retrieve as minimum as possible results concerning cardiac surgery. The authors found this query to be more effective even though a great amount of abstracts were reviewed.

Comment 12: Line 128:

“ECMO is the most popular modality in general thoracic surgery”

-Unclear what the authors are attempting to communicate here. Most popular modality of what?

Reply 12: Thank you for your comment. The sentence was rephrased to become

clearer.

Comment 13: ECMO description beginning at line 127:

-Address the outflow cannula as the “drainage” cannula

Reply 12: Thank you for your comment. Drainage cannula was used throughout the paper.

Comment 14: Lines 131-132: Authors are incorrect – the placement of a return cannula to a vein is not the definition of the second letter “V.” Rather the “venous” of “veno-venous” refers to pre-capillary return, and may be anywhere upstream of the pulmonary capillary bed, including the pulmonary artery itself (which is not a vein).

Reply 14: Thank you for your insightful comment. The sentence was rephrased to avoid incorrections.

Comment 15: Lines 133-134: Incomplete list. Sub-clavian artery and vein, pulmonary artery, others can also be included

Reply 15: Thank you for your insightful comment. The sentence was rephrased to avoid incorrections.

Comment 16: Lines 142-143: “An inflow cannula in a peripheral or central vein will inject oxygenated blood trough the native lungs of the patient. “

-correct spelling of trough to “through”

-it is misleading to describe the mechanical “injection” of blood “through” the lungs, as such active pressurization would result in pulmonary oedema. Reword/rewrite.

Reply 16: Thank you for your insightful comment. The sentence was rephrased.

Comment 17: Lines 144-146: “Additionally, it pulmonary vascular resistance is reduced and this opens the possibility for protective mechanical ventilation strategy if needed”

-Unclear; rewrite for both content and grammar.

Reply 17: Thank you for your comment. The sentence was rephrased.

Comment 18: Lines 156-158: Statement about lower frequency of bifemoral cannulation for V-V ECMO compared to femoral + IJ (Lines 150-155): No objective data is presented to support relative frequency of the various strategies. It may be both context and geographical-specific, and relative frequency statements should be made cautiously and supported by data.

Reply 18: Thank you for your insightful comment. The sentence was rephrased accordingly.

Comment 19: Lines 164-165: “Cardiocirculatory support is assured by decreasing right and left ventricle

preload and increasing left ventricle afterload.”

-Unclear; what are the authors trying to convey? “Assured” ? Decreasing LV preload

and increasing afterload? I disagree, and also modality-specific. Nothing is assured a LV preload may increase or decrease, and if aortic valve does not open, preload will increase massively. No subtlety is provided by the authors, and no subtlety is provided about need to ensure aortic valve opening, or else vent.

Reply 19: Thank you for your insightful comment. The sentence was rephrased accordingly.

Comment 20: Lines 175-176: Central ECMO is not the “only modality that allows for opening and reconstruction of cardiac cavities invaded by the tumor.” If a tumor invaded the right ventricle, a dual-stage oxy-RVAD could potentially be used to permit this under selected circumstances (as long as risk of air-lock from air entrainment is managed).

Reply 20: Thank you for your insightful comment. The authors assume that the reviewer meant CPB and not central ECMO due to the lines mentioned, and the sentence was rephrased accordingly.

Comment 21: Lines 181-187: Expand on differences/distinctions between central ECMO and CPB.

Reply 21: Thank you for your comment. Due to the specific context of the special series, CPB will be addressed in more detail in other chapters, therefore, the authors decided to keep limited and keep the focus on limited lung function.

Comment 22:

Lines 212-214: Risk of acute renal failure – should also discuss risk of hemolysis and pigment nephropathy, and means to monitor and need to avoid excessive rpm. Risk of stroke – particularly when veno-arterial ECMO is required, stroke risk should be specifically discussed, including mechanisms. Risk is non-trivial and modifiable potentially depending both on cannulation strategy, purge/connections, &c.

Reply 22: Thank you for your insightful comment. The authors agree to the value of expanding the description of ECLS complications, but being this chapter a part of the special series “Extracorporeal Life Support in Thoracic Surgery” for Journal of Thoracic Disease (JTD), the authors decided not to expand in that context because there will be a specific chapters dedicated to that subject.

Comment 23: Lines 250-252: Syntax. Unclear what “ECMO, on VA modality” means.

Reply: Thank you for your comment. The sentence was rephrased.

Comment 24: Lines 255-256: What is debated about lung resection surgery in patients with low respiratory reserve? Clarify.

Reply 24: Thank you for your insightful comment. A paragraph was added advising readers to careful select patients with low respiratory reserve for surgery.

Comment 25: Line 266: Authors do not mean “decarboxylation” as written but rather

CO<sub>2</sub> transfer or removal of CO<sub>2</sub> or ventilation. Decarboxylation is a covalent reaction, not removal of a CO<sub>2</sub> gas / alteration of pCO<sub>2</sub>.

Reply 25: Thank you for your comment. Changes were made accordingly.

Comment 26: Lines 297-299: Unclear. “But in some cases, to ensure a secure airway and to avoid hypercapnia or barotrauma may be difficult to avoid.” What is difficult to avoid?

Reply 26: Thank you for your comment. The sentence was rephrased to become clearer.

Comment 27: Lines 315-316: Unclear – “ion its VV form in no hemodynamic instability present.” What does this mean? Please delete “This subject will be further discussed in other papers” as the future cannot be predicted easily.

Reply 27: Thank you for your comment The sentence was rephrased.

Comment 28: Discussion:

Needs to be written for precision, clarity, and purpose.

Authors should not “defend” anything (line 344).

Reply 28: Thank you for your insightful comment. The manuscript was fully revised including discussion.

Comment 29: Figures/Illustrations:

None currently. This is a gap and ought to be addressed.

Reply 29: Thank you for your comment. A summarized table was added.

## **Reviewer B**

Thank you for allowing me to review the manuscript. This is a narrative review of difficult thoracic surgical procedures that require 1 lung ventilation and ECLS modalities that could be used to support them.

Comment 1: This manuscript is not only poorly written from a grammatical and organizational standpoint but also sloppily put together with different text fonts and sizes, paragraphs with only 1 sentence, and different reference formats in the paragraphs. This paper was written in pieces by different authors and just thrown together. It is extremely difficult to follow the flow of this paper. Most importantly, the authors make many unsubstantiated claims without references to back up their falsehoods about ECMO.

Reply 1: The authors thank you for your insightful comment. The manuscript was fully revised regarding language, texting and organization. Regarding falsehoods about ECMO, the authors do not agree that they provide such and, therefore, kindly ask you to point out specifically with scientific background in order for the manuscript to be improved.

## Recommendations

Comment 2: Introduction is not clearly organized.

Reply 2: Thank you for your comment. The manuscript was revised regarding organization and language and changes made accordingly.

Comment 3: Restructure the paper to first talk about difficult surgical procedures that require 1 lung ventilation, then talk about the ECLS modalities that could be used to support those procedures.

Reply 3: Thank you for your comment. The authors understand the comment but decided to keep the main structure unaltered due to the global view of the special series.

Comment 4: Grammar needs to be re-evaluated. Some run-on sentences, sentences that start mid-thought, misplaced commas, using “on” when “of” is the appropriate word, etc.

Many misspellings

Reply 4: Thank you for your comment. The manuscript was revised by proficient English speakers.

Comment 6: VV ECMO needs to be first defined as venovenous (VV) ECMO and no dash in between VV-ECMO.

Reply 6: Thank you for your comment. Changes were made accordingly.

Comment 7: “Inflow” is not a term commonly used in ECMO. I believe it may be used in other forms of mechanical circulatory devices such as ventricular assist devices.

Reply 7: Thank you for your comment. Changes were made accordingly, using “drainage cannula” instead.

Comment 8: Authors' ECMO terminology should reflect these 2 papers:

o Conrad SA, Broman LM, Taccone FS, Lorusso R, Malferteiner MV, Pappalardo F, Di Nardo M, Belliato M, Grazioli L, Barbaro RP, McMullan DM, Pellegrino V, Brodie D, Bembea MM, Fan E, Mendonca M, Diaz R, Bartlett RH. The Extracorporeal Life Support Organization Maastricht Treaty for Nomenclature in Extracorporeal Life Support. A Position Paper of the Extracorporeal Life Support Organization. *Am J Respir Crit Care Med*. 2018 Aug 15;198(4):447-451. doi: 10.1164/rccm.201710-2130CP. PMID: 29614239; PMCID: PMC6118026.

o Broman LM, Taccone FS, Lorusso R, Malferteiner MV, Pappalardo F, Di Nardo M, Belliato M, Bembea MM, Barbaro RP, Diaz R, Grazioli L, Pellegrino V, Mendonca MH, Brodie D, Fan E, Bartlett RH, McMullan MM, Conrad SA. The ELSO Maastricht Treaty for ECLS Nomenclature: abbreviations for cannulation configuration in extracorporeal life support - a position paper of the Extracorporeal Life Support Organization. *Crit Care*. 2019 Feb 8;23(1):36. doi: 10.1186/s13054-019-2334-8. PMID: 30736845; PMCID: PMC6367794.

Reply 8: Thank you for your comment. Changes were made accordingly.

Comment 9: The authors mention the use of lower anticoagulation with VV ECMO, but do not site an appropriate paper.

The authors mention the use of a dual-lumen IJ becoming more popular during this past pandemic but do not cite an appropriate paper.

The authors make unsubstantiated claims that “ VV ECMO using double cannulation of the femoral veins is also an option, although less frequent because it is associated with a higher incidence of recirculation and groin infection.” No paper cited.

No references are cited for the claims made about VA ECMO.

Many more statements do not have appropriate references....I stopped keeping track.

Reply 9: Thank you for your insightful comment. References were added throughout the paper as appropriate.

Comment 10: All abbreviations must be first written out fully before they can be abbreviated.

Reply 10: Thank you for your comment. Changes were made accordingly.

### **Reviewer C**

Comment 1: The title indicate that article will be dedicated ECLS use in difficult/impossible one-lung ventilation (limited lung function).

But authors provide general narrative review of ECLS support in thoracic surgery.

I suggest title:

"Extracorporeal Life Support in Thoracic Surgery – ECLS use in limited lung function"

Reply 1: Thank you for your comment. The title was changed accordingly.

Comment 2: than I will suggest to add:

ECLS support in LTX, and ECMO as support in DGF.

Reply 2: Thank you for your insightful comment. The authors agree to the value of ECLS support for lung transplantation and support during PGD, but being this chapter a part of the special series “Extracorporeal Life Support in Thoracic Surgery” for Journal of Thoracic Disease (JTD), the authors decided not to expand in that context because there will be chapters dedicated to that subjects.

Comment 3: Concept and text narration is proper and good.

Reply 3: Thank you for your comment. The manuscript was fully revised by proficient English speakers.

### **Reviewer D**

I had the opportunity to review your manuscript. This review article describes the application of ECLS in thoracic surgery and provides a good overview on this topic. I also agree with the conclusions of the authors. I would have the following comments:

Comment 1: perioperative use of ECLS occurs for two reasons: to enable technical resectability or in the absence of functional operability. In my opinion, this should be clearly described and, if necessary, also shown in a figure/scheme.

Reply 1: Thank you for your insightful comment. The authors agree to the statement and that it should be present and decided to add a paragraph at the beginning of description of difficult ventilation scenarios and focus on this particular subject.

Comment 2: The different indications for the use of vv-ECMO and va-ECMO/ECB should be presented in a table. This is much clearer for the reader.

Reply 2: Thank you for your insightful comment. A table was created accordingly.

Comment 3. in the literature references you will surely find more recent publications on the topic. Also, publications on complications of ECMO or during ECMO should still be clearly described. Also here a table would be helpful.

Reply 3: Thank you for your insightful comment. The authors have debated and decided to not further explore the complications of ECLS due to the context of this publication. Being one chapter on the special series “Extracorporeal Life Support in Thoracic Surgery”, complications of ECLS is another chapter dedicated exclusively to that subject. Therefore, the authors decided not to expand the manuscript on that subject to avoid duplication of information for readers.

## **Reviewer E**

Comment 1:

Authors applied for a narrative review, and JTD explained in detail the qualifications for a narrative review in the guidelines for authors (<https://jtd.amegroups.com/pages/view/guidelines-for-authors#content-2-2-3>).

The authors did not follow these basic requirements, it cannot be said that the format of the narrative review has been established. For example, 'narrative reviews should also adhere to the narrative review checklist and each submission should include the Checklist as a supplementary material.', 'A statement “We present the following article in accordance with the narrative review reporting checklist” should be included at the end of the “Introduction”', 'The manuscript should also include a Reporting Checklist statement in the footnote (see the “3.5 Footnote” section).', etc.

In addition, there are many typos, and the reference citation method did not follow the guidelines for authors. Also, the inclusion/exclusion criteria for reviews are not presented. It is just a list of journals, and cannot provide additional insight for readers.

This manuscript does not comply with the basic requirements of the narrative review presented in the ‘guidelines for authors’, so I do not think there is a need for further review.

Reply 1: The authors thank you for your comment. This manuscript is a part of a special issue on cardiopulmonary support during general thoracic surgery, and therefore some adaptation were performed as necessary. As the comment does not



provide any other constructive or specific comment, no reply or changes were performed.

### **Reviewer F**

ECLS, as described by the authors, is increasingly used perioperatively. Authors relatively well organized the perioperative use of ECLS, but the following parts seem to need revision.

Major comments:

Comment 1: Please explain why ECMO is preferred over CPB and has a good prognosis.

(eg. reduce bleeding risk ...)

Reply 1: Thank you for the insightful comment. Paragraph on line 207 was rephrased.

Comment 2: ECCO2R is rarely used perioperatively, and there is almost no description in this paper about ECCO2R, so it would be better to remove the ECCO2R part.

Reply 2: Thank you for the insightful comment. Paragraph on line 207 was rephrased.

Comment 3: Is there any study comparing the perioperative risk (ALI, ARDS, bleeding ...) between ECMO and CPB? if yes, please describe it in detail.

Reply 3: Thank you for the insightful comment. Section Complications of ECLS modalities was revised and rephrased as necessary.

Comment 4: English proofreading is required throughout this paper.

Reply 4: Thank you for your comment. The final manuscript was revised by two independent proficient English speakers.

This is my comments for minor revision;

Comment 5: Page 5, Line 92: Traqueostomy --&gt; Tracheostomy

Reply 5: Thank you for your comment. Changes were performed accordingly.

Comment 6: Page 5, Line 93: endotracheal tubes, are --&gt; endotracheal tubes are

Reply 6: Thank you for your comment. Changes were performed accordingly.

Comment 7: Page 6, Line 131 - 132: Please explain the difference of role between VV ECMO and VA ECMO (for pulmonary support only vs. cardiopulmonary support).

Reply 7: Thank you for your comment. Changes were performed accordingly.

Comment 8: Page 7, Line 144-145: Please correct the sentence properly - Additionally, it pulmonary vascular resistance is reduced and~

Reply 8: Thank you for your comment. Changes were performed accordingly.

Comment 9: Page 8, Line 183-184: Please match the citation format of the journal.

Reply 9: Thank you for your comment. Changes were performed accordingly

Comment 10: Page 13, Line 299: kept in my mind --&gt; kept in mind

Reply 10: Thank you for your comment. Changes were performed accordingly

Comment 11: Page 14, Line 314 - 316: Please correct the sentence properly - To allow for postoperative support

Reply 11: Thank you for your comment. Changes were performed accordingly