Peer Review File

Article information: https://dx.doi.org/10.21037/atm-23-1734

Reviewer A

Comment 1. The authors need to comment about the risk of pulmonary edema in the setting of isolated RVAD. As pure RV failure is rare, increasing LV preload can ends up pulmonary edema.

Reply 1. The reviewer makes a good point and we have added this to the manuscript. The following lines have been added:

Changes in text: A theoretical concern while using ProtekDuo as isolated RV MCS is pulmonary edema and pulmonary hemorrhage if flows are greater than what the LV is able to tolerate. However, this is yet to be reported for the ProtekDuo.

Comment 2. Iatrogenic TR, risk of SVC syndrome etc are the complication from Protek Duo

Reply 2: The reviewers' comment is accepted, and we have added this line to the manuscript.

Changes in text: As with any other MCS, ProtekDuo has its own sets of risks including vascular injury, hemolysis, iatrogenic tricuspid regurgitation, pulmonary valve dysfunction, superior vena cava syndrome, cardiac wall perforation, pericardial effusion with tamponade, infection, embolism, and thrombosis as well as cannula migration leading to ineffective unloading of RV.

Comment 3. I agree the IJ cannulation is the benefit of ProtekDuo. However, this is also make the application of ProtekDuo difficult in the unplanned setting. We cannot emergently go on RVAD with ProtekDuo during heart transplant for PGD. Because we have no access to IJ.

Reply 3: The reviewers comment is accepted and the following change has been made to the manuscript.

Changes in text: Moreover, in some instances such as during heart transplant for PGD where there is no access to the internal jugular vein, ProtekDuo may be difficult to deploy.

Comment 4. In ARDS, the benefit of Protek Duo is preferred because we don't have to struggle with recirculation comparing to VV ECMO. As you mentioned, not small number of patient with severe ARDS has RV failure, which worsened the recirculation in the setting of high ECMO flow.

Reply 4 : The reviewer's comment is accepted and the following changes have been made.

Changes in text: Another advantage of ProtekDuo is the absence of recirculation which is seen in the setting of high ECMO flow while managing patients with severe ARDS with RV failure.

Comment 5. I believe the lung transplant should not be done with RV. That was the reason the patient requires VA ECMO with ProtekDuo cannula. How can the one lung

accommodate all the blood flow with acceleration of RVAD. Also, Pittsburgh team published their case series of oxyRVAD bridge to lung transparent with ProtekDuo. I believe this is the largest case series in lung transplant field for protek Duo. Maybe worth citing.

Reply 5 : The reviewer's comment is accepted. In the case report by Budd et al, the lung transplant did not occur with oxyRVAD configuration. We have modified the sentence to make this clear.

We have cited the case series by the Pittsburg team (oxyRVAD bridge to lung transparent with ProtekDuo) in the manuscript.

Changes in text:

After arrival of donor lungs, the configuration was converted to central (dl)V-A ECMO by cannulating the ascending aorta and converting ProtekDuo to double lumen drainage.

Harano et al. reported outcomes of four patients with idiopathic pulmonary fibrosis who were placed on oxyRVAD as a bridge to transplantation, all of whom underwent double lung transplantation.(43) There was one in-hospital mortality due to superimposed pseudomonas pneumonia with influenza virus infection on postoperative day 97, while the other three were alive at 2-year follow up.

Reviewer B

Comment 1. Recommend major critical review of grammar/sentence structure and English language. Many sentences are poorly structured and there is frequent use of odd phrases.

Reply 1: The reviewer's comment is accepted, and we have done a thorough review of sentence structure and grammar.

Comment 2. Recommend incorporating ELSO Maastricht Treaty nomenclature when discussing ECMO (https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2334-8 and https://www.atsjournals.org/doi/epdf/10.1164/rccm.201710-2130CP?role=tab). According to this nomenclature, the abbreviation "RVAD" is reserved for central cannulations. Thus, the abbreviation "Oxy-RVAD" implies a central cannulation with an interposed oxygenator, which is NOT the ProtekDuo. When discussing the ProtekDuo cannula for use in ECMO, the terms/abbreviations "veno-pulmonary," "V-P," or most specifically "(dl)V-P" should be used. Again, please refer and adhere to the ELSO Maastricht Treaty for ECLS Nomenclature. See lines 69, 70 in your manuscript for specific examples of incorrect terms/abbreviations.

Reply 2: The reviewer's comment is accepted, and we have updated the nomenclature in accordance with the ELSO Maastricht Treaty for ECLS Nomenclature

Changes in text: All instances of use

Comment 3. The manuscript seems as though various sections were written by different authors, given the difference in writing style. An effort should be made to unify or harmonize these writing styles.

Reply 3: Thank you for this comment. We have rewritten the manuscript to make the styles uniform.

Specific comments:

Comment 4. I struggle with the second sentence in the Methods section of the abstract (lines 45-46). Is the best way to describe the action of a device such as ProtekDuo really "augment pulmonary flow?" A device can augment flow even when flow is normal. This seems like a good place to describe the ability of ProtekDuo to directly bypass a failing RV to restore output that results in preservation of left-sided filling.

Reply 4: The reviewer's comment is accepted, and we have modified the sentence as follows

Changes in text: In the setting of right ventricular (RV) failure, the ProtekDuo cannula, with its outflow in the main pulmonary artery (PA), can bypass the failing right ventricle, improving pulmonary flow, left atrial (LA) filling pressures, and left ventricular (LV) preload.

Comment 5. The Key Content and Findings section of the abstract needs to be proofread and re-written. For example, "LVAD implantation-associated RV failure" appears twice in the same sentence. Far more attention to detail needs to be dedicated to these types of issues.

Reply 5: This comment has been accepted and the section has been proofread.

Changes in text:

In this narrative review, the key sections expand on the use of the ProtekDuo cannula in the management of critically ill patients, specifically, the use of ProtekDuo for right ventricular myocardial infarction (RVMI) RV failure, left ventricular assist device (LVAD) implantation-associated RV failure, RV failure post-heart transplantation, temporary biventricular mechanical circulatory support (MCS) as bridge to recovery (ECpella 2.0 or PROpella), biventricular support as bridge to recovery or decision, isolated LV failure, post lung transplantation care, and other miscellaneous clinical scenarios.

Comment 6. In the conclusions section of the abstract, what type of configurations are meant (line 56)? The last sentence of this section makes no sense.

Reply 6: The reviewer's comment is accepted, and the conclusions section has been modified as follows

Changes in text: ProtekDuo is an important tool in the armory of RV failure management. The ProtekDuo system is expected to gain more popularity given its clear advantages such as groin-free approach allowing for mobility, easy percutaneous deployment, compatibility with various pumps and oxygenators, and the versatility to be integrated in numerous configurations. In an era of expanding MCS options, further research is needed to better understand the optimal tool for specific patient subsets.

Comment 7. The use of abbreviations is incorrect. For example, right ventricular failure is abbreviated "RVF" on line 94 when it appears much earlier in the text (abstract and line 84) and acute RVF is abbreviated "ARVF," but appears earlier in the text. Please proofread to ensure words are abbreviated correctly and in a conventional way.

Reply 7: The comment is accepted and the uniform abbreviation "RVF" for right ventricular failure has been adopted.

Changes in text: All instances of "RVF"

Comment 8. The first paragraph under Acute RV Failure (lines 94-101) needs major work. On line 94, which type of chronic heart failure is meant? The sentence beginning on line 98 discussing causes of acute RVF needs to be improved. It would actually make more sense at the beginning of the paragraph. Post-transplant of what? The heart I assume. Are you referring to primary graft dysfunction?

Reply 8: This comment is accepted and has been re-worded as follows:

Changes in text:

Acute RVF can stem from various factors such as RV myocardial infarction (MI), myocarditis, pulmonary embolism, arrhythmia, post-surgical myocardial ischemia, RV primary graft dysfunction (PGD) after heart transplant, or LV failure.(7) It is noteworthy that acute RVF occurs in over 20% of cases following isolated left ventricular assist device (LVAD) implantation, significantly contributing to mortality within this cohort.(8) Among patients with chronic heart failure, irrespective of ejection fraction, the incidence of RVF ranges between 48% and 65%, and correlates with diminished exercise capacity and heightened mortality.(9–11)

Comment 9. Line 109: What type of "overload?"

Reply 9: Both pressure and volume overload can lead to these changes. This has been clarified.

Changes in text: Despite these adaptive changes, the RV has a limited capacity for the angiogenic response compared to the LV, leading to greater activation of cell death pathways in the setting of pressure or volume overload.

Comment 10. Line 144: should be "RVAD" instead of RAVD and "Impella RP" instead of RP Impella.

Reply 10: This comment is accepted, and changes have been made. We have changed the description to RV MCS since RVAD refers to central cannulation.

Changes in text: Another option is percutaneous femoral-approach RV MCS such as Impella RP, or V-A ECMO, both of which restricts the patient's mobility.

Comment 11. Please use the abbreviation "V-A" ECMO as per the Maastricht Treaty for ECLS nomenclature.

Reply 11: This comment is accepted, and the change has been made

Changes in text: All instances of VA ECMO have been changed to V-A ECMO

Comment 12. Section 5 ProtekDuo as part of temporary biventricular MCS....: Please adjust the ECMO abbreviations to "V-A ECMO" instead of VA-ECMO. Again, when the ProtekDuo cannula is used as a part of an ECMO system, alone and as intended , the configuration is typically written (dl)V-P ECMO. Please cite a source for PROpella terminology. Suggest citing Maybauer MO, Swol J, Sharif A, Benson C, Brewer JM. The ProtekDuo in percutaneous peripheral venopulmonary-arterial ECMO and PROpella configuration for cardiogenic shock with biventricular failure. Ann Card Anaesth. 2023 Jul-Sep;26(3):339-342.

Reply 12: This commend is accepted. VA-ECMO has been changed to V-A ECMO and V-P ECMO has been used for ProtekDuo in ECMO configuration. We have reserved

the (dl) nomenclature for (dl)V-A ECMO where both lumens of ProtekDuo are used for venous outflow and ascending aorta is cannulated for arterial return since in the typical V-P configuration, only one lumen is used for venous drainage. The above mentioned reference has now been included in the bibliography.

Changes in text:
Of late, percutaneous, temporary, axial flow MCS devices such as Impella have been used as effective LV vents in patients on V-A ECMO, a concept referred to as ECpella. Ruhparwar et al. improved upon this concept with ECpella 2.0/PROpella, a groin-free MCS consisting of a surgically implanted full-flow axial flow pump (Impella 5.0/5.5) as an LVAD in combination with the TandemHeart/ProtekDuo system as an RV MCS.(44,45)

Comment 13. Section 8 ProtekDuo for lung transplantation care: Again, OxyRVAD (line 251) is a term that denotes central cannulation and (dl)V-P ECMO should be used instead. The sentence fragment "That allowed to complete the transplantation" (line 253) should be corrected. When a ProtekDuo cannula is used for drainage, and return occurs to the aorta via central cannulation, the term is venopulmonary to ascending aortic ECMO and the abbreviation is (dl)VP-/AO. Please use correct terminology and abbreviations.
Reply 13: This comment is accepted, and the following changes have been made.
Changes in text: In a case report by Budd et al., a patient undergoing sequential bilateral LT was intraoperatively supported initially with a ProtekDuo V-P configuration. (50) After arrival of donor lungs, the configuration was converted to central (dl)V-A ECMO by cannulating the ascending aorta and converting ProtekDuo to double lumen drainage. Once transplantation was done the circuit was converted back to V-P configuration to decompress the RV.

Comment 12. Section 9 ProtekDuo and VV-ECMO: VV and VP ECMO are distinct modes of ECMO. The ProtekDuo alone is used for VP ECMO mode, not VV ECMO. The first sentence is very confusing. "ECMO/ProtekDuo" and "ProtekDuo-OxyRVAD" are not correct terms. Please use (dl)V-P ECMO where appropriate. Fourth paragraph (lines 282-290), line 285, VV-PA should be changed to "VV-P" and line 287 V-VPA should be changed to "V-VP."
Reply 12: This comment is accepted, and the following changes have been made to the section.
Changes in text:
Paragraph 1 of section:
Heart failure is a common complication seen in 4-21 % of hospitalized COVID-19 patients, 30% of whom have RVF.(34)(35,36) The percentage of patients with RVF may be even higher in those with severe ARDS requiring ECMO support, making them prime candidates for RV MCS support.(37) Patel et al. described a 53-year-old COVID-19 patient on V-V ECMO who developed severe RV failure.(38) The circuit was changed to a ProtekDuo RV MCS cannula (V-P ECMO) for additional RV support,

resulting in a good outcome. In this way, the ProtekDuo can be incorporated into the ECMO circuit, which may be beneficial in situations where an IVC filter precludes IVC cannulation.(39) Another advantage of ProtekDuo is the absence of recirculation which is seen in the setting of high ECMO flow while managing patients with severe ARDS and RVF.

Paragraph 4 of section:

Maybauer and colleagues reported several other ECMO circuit configurations utilizing the ProtekDuo cannula.(42,43) In one configuration, they added a 25 Fr femoral multistage venous drainage cannula to the circuit to enhance venous drainage. The venous return from the femoral drainage was spliced with the venous tubing of the ProtekDuo and directed into the pump, resulting in a VV-P ECMO configuration. In another configuration, the 25 Fr multistage drainage cannula was the sole venous drainage, and both lumens of the ProtekDuo were utilized for arterial flow into the right atrium and pulmonary artery, resulting in a V-(dl)VP ECMO configuration. This configuration resulted in increased blood flow and oxygenation (SpO2 increased from 78% to 100%).(42) The reported flow through the proximal port of the ProtekDuo was 4 L/min, and the flow through the distal port was 3 L/min.

Comment 13. Table 1: Extra Corporeal should be "extracorporeal." ECpella should be "ECPELLA 2.0/PROpella." The advantages and disadvantages for ECMO are not correct. The advantages for ECpella, isolated LV failure, complete biventricular support does not seem correct/do not make sense.

Reply 13: Extra Corporeal has been changed to "extracorporeal". The advantages and disadvantages are vertically listed and are not meant to align with each use case of ProtekDuo.

Changes in text: As above

Comment 14. Line 303: ProtekDUo should be "ProtekDuo."

Reply 14: This has been changed.

Changes in text: ProtekDuo offers clear advantages including groin-free approach allowing for mobility, easy percutaneous deployment, compatibility with various pumps and oxygenators and its versatility to be integrated in numerous configurations.

Comment 15. Conclusion: The sentence on line 309-310 needs to be reworked. The paragraph on lines 311-313 seems random, especially the part about use for mini-AVR.

Reply 15: This comment is accepted, and the sentence has been modified as below:

Changes in text:

It is important to acknowledge that experience in utilization of ProtekDuo in atypical configurations, for instance as a temporary LVAD, remains limited and falls within the realm of experimental usage.

Comment 16. Examples of sentences needing rewording for improved clarity or grammatical structure: lines 71-72 and lines 75-76.

Reply 16: The sentences have been modified as follows.

Changes in text:

The first-in-man use of the ProtekDuo cannula was described in 2016, and clinical outcomes were reported two years later.
The ProtekDuo cannula, in its typical configuration, receives venous drainage from the upper and lower body through its inflow ports in the right atrium

Reviewer C

Comment 1: The topic, the use of the ProtekDuo as mechanical circulatory support, is an important one. Especially in an era where there are many options available, and the different configurations and cannulation strategies and acronyms change so much that no one really knows how to interpret one paper compared to the next.

The authors make several points that I tend to agree with. Most importantly in my opinion, that the ability to add an oxygenator to the circuit in a patient with RV failure can be lifesaving when you are choosing between MCS strategies for the right ventricle. This point is not emphasized enough in the literature. Secondly, that this cannula has a clear advantage when your patient has an IVC filter.

That said, I think that in an effort to be thorough, the manuscript becomes too confusing. It lacks a clear theme and message. It also clearly focuses too much on the device and not on the pathophysiology or even the patient that you wish to treat. As an example; including the use of the Protek as an LVAD probably doesn't belong in a manuscript on "percutaneous ventricular support system" as that application requires a thoracotomy (albeit small) to expose the LV apex and place purse-string sutures to secure the device.

If this were to be redone; I would consider focusing on the options for right ventricular support; maybe even limiting it to percutaneous approaches and highlighting the advantages of each in comparison to the other.
Reply 1: The reviewers' comments are accepted. We have rearranged the manuscript to make the message clearer. For the sake of completeness, we have included the section on ProtekDuo as LVAD but we completely agree with the reviewer that it is technically not "percutaneous".
With regard to the overall theme of the manuscript, we can understand how this can be perceived as a single manuscript attempting to cover this crucial topic and could cause some confusion. The audience/readership for this manuscript is a very focused group with experience and interest in MCS.