Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1199

**Reviewer A**

Comment 1:

First of all, my biggest concern with this manuscript is the small number of cases. Due to the very small number of cases, I felt that it was not possible to draw clear conclusions. As proof of this, the authors state in the discussion that there are many unclear or unknown things. Thus, the current version is not well suited to support the author's hypothesis. I strongly recommend that the authors conduct a similar comparison with a larger number of cases and draw more convincing conclusions.

Answer:

I appreciate your review of our manuscript. I have to agree with the concerns that you have raised. However, we have been prudent not to overstate the conclusion, and we have not stated that our hypothesis is correct. Furthermore, we have described all the outcomes as we had in the research section and added our interpretation in the Discussion section.

Unfortunately, the use of the oxyRVAD was discontinued in 2020 because of the COVID-19 pandemic. That is the prime reason we have only included the outcomes from the year 2019. In 2020, we experienced a totally different clinical practice pattern, which ended up with only three MCS (two ECMOs and one Hemo-lung) bridge to lung transplant cases, including a case of bridge to lung transplant for COVID ARDS. Additionally, I have left the University of Pittsburgh in 2021. Thus, we could only add the cases from 2019 into this manuscript.

Comment2:

Please describe the specific criteria including PA pressure and cardiac index for right heart dysfunction since the current version has descriptive criteria.

Answer:

Thank you for pointing this out. I agree that we should have commented on how we defined the RV dysfunction.

We did not utilize cardiac index for evaluating RV function. The RV dysfunction is solely defined on basis of the finding of the echocardiogram. RV function is measured with multiple measurements, including longitudinal systolic function (Tricuspid Annular Plane Systolic Excursion, TAPSE), global function (pulse doppler right ventricular index of myocardial performance, RIMP) and global systolic function (3D RV ejection fraction) and the cardiologist provides the comprehensive echocardiologic diagnosis of RV function.

Change:
Statement below was added to the Methods section (Line 76-78)
*"Right ventricular function and estimated systolic pulmonary artery pressure were measured on echocardiogram before being placed on mechanical circulatory support."*

The word "right heart" was changed to "*right ventricular*" (Line 75)

Comments 3:
The authors mentioned that the primary outcome of this study is the survival to discharge and successful bridging to lung transplantation. It means the authors are using short-term outcomes. This cohort seems to be for 2019 only, but if the authors add cases for 2020, the results will be more convincing.

Answer:
Please refer to the answer to the comment 1.
Thus, instead of adding cases after 2020, I have added the longer term follow up outcomes.

Change:
I have added another paragraph to the Results section. (Line 170-176)
*"At the 2-year follow-up, three patients in the oxyRVAD group were alive. Whereas, the only patient discharged home in the non-oxyRVAD group died of meningitis 6 months after lung transplantation. First lung biopsy, which was performed 2 weeks after lung transplantation, demonstrated mild to moderate acute cellular rejection in two patients in the oxyRVAD group (50.0 %) and one patient in the non-oxyRVAd group (100 %). Respiratory function test at 2 years follow-up was shown in Table 4. Two patients in the oxyRVAD group were diagnosed with bronchiolitis obliterans syndrome during the follow up periods."*

Comment
OxyRVAD can be a substitute for VA-ECMO, but in this cohort, two patients required arterial cannulation eventually, this result is conflicting with what the authors are trying to state. This is another reason why I recommend increasing the number of cases.

Answer:
Thank you for your comment. I understand your concerns. The aim of this manuscript is not to try and convince that oxyRVAD can be a substitute for VA ECMO. We wanted to report that we have tried to achieve oxyRVAD bridge to lung transplant to prevent the complications that arise from VA ECMO. However, as a matter of fact, two cases required arterial cannulation. We have tried to describe our experience as objectively as possible while writing this manuscript.
To prevent any misunderstanding at the part of the reader, we have added a statement to the

conclusion, as mentioned below. Even with these limited number of experiences, we still believe that publishing this manuscript will be of benefit to the lung transplant community because currently there are only a few case reports regarding this topic.

Change:
I have added statement below to the conclusion. (Line 235-236)
*"Out of these four patients, two patients eventually required arterial cannulation for configuration change."*

**Reviewer B**
Comment 1:
ECMO usually requires anticoagulation for their maintenance. Do oxyRVAD require anticoagulation such as heparinization? If so, how much heparin are usually used?

Answer:
Thank you for reviewing our manuscript and giving us valuable comments.
The oxyRVAD also requires anticoagulation. However, we do not have to be as aggressive as for venoarterial ECMO. Same as venovenous ECMO, oxyRVAD might work fine without any anticoagulation if there are any issues with bleeding. In our program, we preferably use bivalirudin for anticoagulation while the patient is on ECMO. We have used the same Partial thromboplastin time (PTT) target for ECMO and oxyRVAD, aiming to keep the PTT between 61–75 sec.

Change:
The statement below was added to Methods section. (Line 88-90)
*"The patients were placed on anticoagulation with bivalirudin while they were on mechanical circulatory support in the intensive care unit. The target partial thromboplastin time was 61–75 s."*

Comment 2.
The authors reported only the short-term outcomes after lung transplantation in this study. They should also mention the mid-term and long-term outcomes after lung transplantation, especially among recipients with preoperative oxyRVAD support.

Answer:
We agree with this comment. We have added a paragraph to the Results section to demonstrate the mid-long term survival data. (Line 170-176)

Change:

*"At the 2-year follow-up, three patients in the oxyRVAD group were alive. Whereas, the only patient discharged home in the non-oxyRVAD group died of meningitis 6 months after lung transplantation. First lung biopsy, which was performed 2 weeks after lung transplantation, demonstrated mild to moderate acute cellular rejection in two patients in the oxyRVAD group (50.0 %) and one patient in the non-oxyRVAd group (100 %). Respiratory function test at 2 years follow-up was shown in Table 4. Two patients in the oxyRVAD group were diagnosed with bronchiolitis obliterans syndrome during the follow up periods."*

Comment 3.
The information concerning the recipients with preoperative oxyRVAD support didn't include donor information. Do you have any data on donor information such as ischemic time or oxygenation (P/F ratio)?

Answer:
We also agree with this comment. We have added the donor characteristic in Table 3.
Change:
I have added the below sentence and another table to the describe donor characteristic. (line 152)
*"Donor characteristics are shown in Table 3."*

Comment 4.
All the patients with preoperative ECLS support included in this study had idiopathic pulmonary fibrosis. Are there any other diseases requiring preoperative oxyRVAD support in the future?

Answer:
Thank you for commenting about this important perspective. As you know, most of the ECMO bridging cases are IPF cases. However, any patient with secondary pulmonary hypertension will be a candidate. It might be challenging to support super-systemic pulmonary artery pressure (patient with PAH) with this configuration. OxyRVAD is currently utilized to treat severe COVID ARDS (during the Covid pandemic, some centers preferably used Protek Duo to prevent recirculation). Thus, if these patients are indicated for transplant, oxyRVAD will be the bridging ECLS configuration.

Comment 5.
In all five recipients with preoperative ECLS support, cardiopulmonary bypass (CPB) was used intraoperatively during double lung transplantation. Do you use CPB for all recipients requiring intraoperative ECLS support in your institution? Were more postoperative complications seen among these five recipients than other recipients without preoperative ECLS support?

Answer:
We preferably use cardiopulmonary bypass for patients with severe pulmonary hypertension and RV dysfunction. However, this decision comes from the surgeon's preference. Because of the small number of bridge to lung transplant cases, it is hard to demonstrate the difference in postoperative complication. This is a very interesting topic for future research.

**Reviewer C**

Comment 1:
1. Please add echo findings with detailed data for pulmonary hypertension in table 1, in that case, readers can understand why authors choose protect duo for these patients

Answer:
We included the estimated systolic PA pressure on the echocardiogram. This is because the PA pressure measurement with right heart catheterization is a part of lung transplant candidacy evaluation and it does not reflect PA pressure before necessitating ECLS due to exacerbation. Evaluating the most recent measurements before oxyRVAD or ECMO initiation might be beneficial. However, I agree with the reviewer's recommendation to better describe the echo findings. Thus, we have added the RV function on the echocardiogram. We have also added that a footnote regarding the estimated PA pressure.

Change:
Please see revised Table 1.
We have also added a footnote stating: "Pulmonary artery pressure was estimated with tricuspid regurgitation pressure gradient on echocardiogram."

Comment 2:
2. Please make physiologic table for 2 groups before and after ecmo apply such as vital sign, abga, ecmo settings. Vasopressor dosages etc

Answer:
We agree with the reviewer's comment regarding the importance of the physiological findings of the patients. However, it is difficult to capture one point of the vital signs and vasopressor requirements. Especially because the patient who was placed on oxyRVAD required general anesthesia. Additionally, hemodynamics before and after oxyRVAD initiation might have been influenced by the anesthetic. As for the ECMO setting, initial ECMO setting is always based on the estimation (patients' body habitus etc.). Morevoer, we adjust the ECMO settings over the first 6−12 hours. Sometimes we can quickly stabilize the oxygenation and hemodynamics; however, at other times we need to keep changing the ECMO settings and adjusting the vasopressor. For

these reasons, unfortunately, it is hard to provide the physiologic table for the two groups.

Comment 3:
3. Describe details for changing 2 patients from protect duo to modified vav ecmo: how much of flow of ecmo, how long did you use protect duo, how about abga results, etc
Comments for this: In my experience for central cannulation of oxy-rvad, I apply flow ecmo 3 liter/min for 12hrs because of avoiding pulmonary hemorrhage or edema, and then adjust ecmo flow according to oxygenation. Unually 3.5 ~ 4.0 liter/min is enough for oxygenation because oxy-rvad has no recirculation. I apply around 10 cases of oxy-rvad for severe RV dysfunction, but no cases need to change ecmo configuration for long days. But I don't have experience of protect duo, so I am not sure this is device difference or others.

Answer:
Thank you for your comments. Once again, we admit the importance of hemodynamics, especially for the two patients who failed oxyRVAD. We have added detailed information as per your suggestion.

Thank you very much for sharing your experience. From our experience, oxyRVAD for a patient with lung fibrosis/secondary PH and for a patient with RV dysfunction from cardiomyopathy is completely different. We could support RV dysfunction from cardiomyopathy for a longer period time. However, for RV failure from pulmonary fibrosis and secondary PH, we have experienced early failure as described in this manuscript. This may be due to the pathophysiological difference; however, we do not have any objective evidence to prove these assumptions.

Change:
I have extensively revised the Results section to provide detailed information as you have requested. (Line 138-149)
*"Initially pump speed was set at 7500 rpm with Tandem Heart pump, obtaining 4.5 L/min of oxyRVAD flow. Five days after oxyRVAD initiation, the oxygenation could not be maintained by increasing the flow of the oxyRVAD. Thus, an additional arterial cannula was placed in the femoral artery and modified VAV ECMO was initiated. Pump speed was set at 4300 rpm with Centrimag, obtaining a VAV ECMO flow of 3.9 L/min with returning 1.8 L/min of oxygenated blood to the pulmonary artery port of the Protek Duo cannula. Sweep of the oxygenator was 5.0 L/min. A chest radiograph of this patient is shown in Figure 3. There was worsening bilateral infiltration noted on chest X ray. The other patient (Patient #4 in Table 2) was placed on VAV ECMO after the Protek Duo cannula was removed. After the initiation of oxyRVAD, the patient oxygenation could not be improved with increasing flow of oxyRVAD to 5.5 L/min. With increased flow, the patient had pulmonary edema and the ECLS configuration was changed to venoarterial ECMO to VAV ECMO within the first 24 hours."*

**Reviewer D**

Comment 1:

Line 121 - Please provide more information to what kind of patients were included in nonoxyRVAD group

Answer

Thank you for your suggestion. I have added more information. Unfortunately, none of the variables are statistically different between the two groups, likely because of the small sample size. However, the difference might be clinically relevant. Thus, I have added detailed explanation of the non-oxyRVAd group.

Change

I have added the sentences to result section as below. (Line 123-126)

*The non-oxyRVAD group was older than the oxyRVAD group (60.7 ± 7.80 versus [vs.] 52.5 ± 4.04 years old) and their BMI was lower (22.2 ± 3.50 vs. 26.9 ± 3.93). They also required a higher amount of supplement oxygen than the oxyRVAD group (73.3 ± 5.77 vs. 57.5 ± 15.0). However, none of these differences were statistically significant.*

Comment 2:

Line 124 and 127 - Would you be so kind to elaborate what does "ambulate" exactly mean in your facility?

Answer

Thank you for your comments. In our study, ambulated ECMO means active physical therapy with walking inside the ICU or further with the assistance of a physical therapist (perfusionist and nursing stuff.) We have elaborated this point in the manuscript as suggested.

Change

I have described more details about ambulatory ECMO as follows: (128-129)

*"...ambulated for active physical therapy, out from their ICU, and then walked around the ICU, with the assistance of a physical therapist (ambulatory ECMO)*

Comment 3:

Line 136 -"All 4 patients with OxyRVAD underwent lung transplantation" seems a bit misleading because as it was mentioned above: 2 of them required ECMO instead/as well. So in my understanding, maybe this should be clarified.

Answer:
We agree with this comment. We have revised this sentence as mentioned below. Given that we have already explained the details of the configuration change to ECMO in the prior paragraph, we did not repeat those configuration change needs in this sentence. We believe this might be justified in terms of the "intention to treat analysis."

Change:
We have added the words underlined below. (Line 150)
All four patients ~~with~~ *who were initially placed on oxyRVAD* underwent double lung transplantation

We have also added one sentence to the conclusion to prevent any confusion as the reviewer pointed out. (Line 235-236)
In conclusion, we report four cases of oxyRVAD bridge to lung transplantation. "*Out of these four patients, two patients eventually required arterial cannulation for configuration change."*

Comment 4:
Line 140 - Please elaborate, why descirbed patients were transplanted wihile on Cardiopulmonary bypass in the context of its advantages over other methods of cardiopulmonary support

Answer:
In the Results section, we would like to focus on the facts without interpretation. The choice of mechanical circulatory support is based on the surgeon's preference, especially for patients with right heart dysfunction secondary to severe pulmonary hypertension. However, we agree that it would be better to comment about the choice of cardiopulmonary bypass. We have commented about this in the Discussion section.

Change:
I have commented about intraoperative MCS in the Discussion section as follows: (Line 220-224)
Moreover, even though all the patients in this study underwent lung transplantation with cardiopulmonary bypass *at the surgeon's discretion*, it is unknown whether oxyRVAD can be an option for mechanical circulatory support during lung transplantation. *"The benefit of decompressing the heart during implant may outweigh the risk of cardiopulmonary bypass. However, intraoperative venoarterial ECMO would also be an option."*

Comment 5:

Line 146 Abstract states that all of the patients experienced primary graft dysfunction, please elaborate more about this topic

Answer:
As you know, grade 1 primary graft dysfunction indicates a PF ratio > 300 with infiltrates on chest X ray. The clinical importance of grade 1 primary graft dysfunction is minimal. Thus, most of the scientific paper does not include grade 1 PGD into analysis as outcome. Usually "grade 3 PGD" or "grade 2 or higher PGD" are taken into analysis. Thus, clinical implications of grade 1 PGD may not be very important.

Comment 6:
Line 147-154 - Such findings statistically-wise may be connected to the small number of participants.

Answer:
I agree with this comment; we have added this as a limitation of this study.

Change:
We have added the limitation as follows: (Line 232)
The small sample size may have underestimated the influence of significant variables in the analysis.

Comment 7:
Providing information about lung function and need for any cardiopumonary support in the longer-term follow-up would be beneficial for the paper

Answer:
I agree with this comment. The transplant community is seeking an answer to this question. Unfortunately, all the patients in this study required mechanical circulatory support before transplantation, and all were placed on cardiopulmonary bypass during transplantation. Thus, I cannot provide statistical analysis related to this topic. However, we have added most recent post-transplant lung function of this study cohort to the Results section with a new table (Table 4).

Change:
The post-transplant respiratory function was provided in the result section with new Table. (Line 170-176 and newly added Table 4)
*"At the 2-year follow-up, three patients in the oxyRVAD group were alive. Whereas, the only patient discharged home in the non-oxyRVAD group died of meningitis 6 months after lung*

*transplantation. First lung biopsy, which was performed 2 weeks after lung transplantation, demonstrated mild to moderate acute cellular rejection in two patients in the oxyRVAD group (50.0 %) and one patient in the non-oxyRVAd group (100 %). Respiratory function test at 2 years follow-up was shown in Table 4. Two patients in the oxyRVAD group were diagnosed with bronchiolitis obliterans syndrome during the follow up periods."*

**Reviewer E**

Comment 1:
Line 121, Line 150 space bet oxy and RVAD twice, whereas throughout the rest it is previously without space.

Answer:
Thank you for pointing out this spacing. I have removed the space.

Comment 2:
Table 2 data for patient #4 cut off from view in the manuscript upload.

Answer:
We have uploaded Table 2 seperately. This issue might have happened because this table is made in the landscape mode.