Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-485

Reviewer A

Comment 1: Would clarify that you measured respiratory system compliance.
Reply 1: We described in the abstract that we calculated and recorded Crs and RAW.
Changes in the text: We added "Parameters such as the P/F ratio (PaO2/FiO2), oxygenation index (OI), respiratory system compliance (Crs), and airway resistance (RAW) were collected and analyzed at baseline, and at 1, 2, and 3 days post-ECMO initiation." to the abstract section.

Comment 2: It's not clear in the abstract that this was a retrospective study, would add to the methods.
Reply 2: Thanks for reminding us, we made the corresponding changes in the abstract section.
Changes in the text: We added "We conducted a retrospective analysis of clinical data from 17 neonates who received ECMO support in our institution" in the abstract section.

Comment 3: Oxygenation index and PaO_2/FiO_2 are related but distinct concepts. Oxygenation index is mPaw x FiO_2 x100 / PaO_2.
Reply 3: Sorry, we revised the definition of oxygenation index
Changes in the text: Change "PaO_2/FiO_2" to "mPaw x FiO_2 x100 / PaO_2"

Comment 4: What data are available for ECMO improving outcomes in neonates with ARDS?
Reply 4: After ECMO combined with PPV treatment, PaO_2/FiO_2, OI, Crs, RAW may be improved in neonates with ARDS.
Changes in the text: We re-edited the background section.

Comment 5: How many cases were excluded? Why were such a short timeframe chosen? With such a small sample, it seems like extending the timeframe would be warranted.
Reply 5: Two cases were excluded due to missing data, which we explained in the result section. There are not many cases of neonatal ECMO completion in our center, so the sample size was small at the end of the study. We look forward to starting a larger sample size study in the future. We also added relevant explanations in the result and limitation part.
Changes in the text: We revised the result section to describe the number of excluded

cases and the reasons.

Comment 6: How was the sweep gas managed during ECMO? What were the criteria for ECMO initiation?
Reply 6: We added a description of the ECMO indication in materials and methods section and revised the description of the sweep gas adjustment.
Changes in the text: We added “Criteria for ECMO initiation” in materials and methods section and revised the description of sweep gas adjustment in “ECMO Management”.

Comment 7: How is mechanical ventilation managed prior to ECMO cannulation?
Reply 7: We added the content about ventilator support before ECMO in the revision.
Changes in the text: We added “Ventilator Support Prior to ECMO: The ventilator was programmed to pressure assist/control mode. Tidal volume (Vt) was maintained at 6-8 ml/kg. Peak inspiratory pressure (PIP) ranged from 20-25 cmH_2O, while positive end-expiratory pressure (PEEP) was set between 5-10 cmH_2O. The respiratory rate (RR) was adjusted to 30-40 breaths per minute, and the fraction of inspired oxygen (FiO_2) was set to 80-100%. The PEEP settings were tailored primarily based on the patient’s pulmonary status and arterial blood gas analysis results.” to the revision.

Comment 8: Pressure control should be described as pressure assist/control unless the patient is unable to trigger.
Reply 8: Thanks for your reminding, we changed the description of the ventilator mode in the revision.
Changes in the text: Change “pressure control” to “pressure assist/control”.

Comment 9: How was optimal PEEP determined?
Reply 9: The PEEP settings were tailored primarily based on the patient’s pulmonary status and arterial blood gas analysis results. At present, there was no optimal setting for PEEP. We changed the description of PEEP.
Changes in the text: We changed the description of PEEP in the revision.

Comment 10: Airflow rate should be sweep gas. 3-4 LPM is very high for a neonate, what system was used? Rotaflow or the Cardiohelp?
Reply 10: Thanks for your reminding, we revised this statement. The system we use was Rotaflow.
Changes in the text: Change “Airflow rate” to “sweep gas flow” and revised the description of sweep gas adjustment in “ECMO Management”.

Comment 11: This section says PEEP was set 8-10 but earlier you stated 10-15 cmH_2O,

which was it?
Reply 11: The setting for PEEP is different at different times. We made the changes to the description of PEEP.
Changes in the text: We made the changes to the description of PEEP in the “Ventilator Support Prior to ECMO” and “Ventilator Support during ECMO” section.

Comment 12: You obtained consent prior to prone positioning? This seems unusual for a standard clinical intervention.
Reply 12: Prone ventilation was performed with the consent of the patient’s guardian, as explained in the article
Changes in the text: We pointed out in the revision that prone position ventilation was approved by the patient’s guardian.

Comment 13: Examining oxygenation during ECMO is very challenging as PaO_2 is influenced by not only pulmonary mechanics but also ECMO flow, cardiac output, sedation, and secretion management.
Reply 13: Yes, oxygenation results during ECMO would be interfered with by ECMO, but we consider the results to be instructive. We added the indicator of OI in the revision.

Comment 14: How did you measure RAW and compliance?
Reply 14: We collected the data presented on the ventilator and calculated the results by the formulas Crs=VT/(Pplat-PEEP) and RAW= (PIP-Pplat) /Flow.
Changes in the text: We added a description of the calculation formula to the “Data Collection”.

Comment 15: Why were 2 subjects excluded?
Reply 15: Two patients were excluded due to missing data.
Changes in the text: Described in the article as “Two patients were excluded due to incomplete data, resulting in a total of 17 patients included in the study.”

Comment 16: You need to include the ventilator settings and additional data prior to ECMO about the 2 groups. For example, vasopressors, gas exchange beyond P/F.
Reply 16: We provided the patient’s preoperative ventilator setup along with the VIS and OI.
Changes in the text: We added OI and VIS data to table1, and added ventilator settings before ECMO to the Materials and methods section.

Comment 17: The first paragraph is background information that belongs in the introduction in abbreviated form.

Reply 17: This paragraph did mainly describe the research background. We revised the paragraph and added to the introduction section.
Changes in the text: We abbreviated and modified this paragraph and added to the introduction section.

Comment 18: This section lacks rigor about why prone positioning would be beneficial in children with ARDS requiring ECMO.
Reply 18: The purpose of the study was to point out that ECMO combined with PPV would have a better lung improvement effect, so we revised the discussion part to add the detailed mechanism of PPV on lung improvement in children.
Changes in the text: We revised the first paragraph of the discussion part to add the detailed principle of PPV's effect on lung improvement.

Comment 19: Table 2 and 3 contain identical data from different time points. The 2h after treatment and 1 d after treatment numbers are the same. This makes me doubt the veracity of the data shared here.
Reply 19: This was a misunderstanding. Table 3 records the results of ECMO-PPV group after 2 hours of prone position treatment. In the ECMO-PPV group in Table 2, the results recorded were 1d, 2d and 3d after patients received ECMO. But both parts were from the same recording time, so the data was the same.
Changes in the text: We modified the table 2 and changed table3 to figure 1. Such revision seemed more concise.

Reviewer B

Comment 1: Overview: The division of the study into prone and supine positioning groups raises questions about the study's design. While it is understandable that the patients had severe hypoxic respiratory failure warranting ECMO, differences in ARDS etiology and severity between the groups may exist. Therefore, comparing data for prone and supine positioning within the same patients might provide a more robust comparison, such as using Table 3 data for all patients.
Reply 1: We agreed with your opinion. The study was a retrospective study to compare lung function in supine versus prone patients treated with ECMO. Patients were not divided into two groups in advance. Also, due to the retrospective study, not all patients underwent prone ventilation. We have also considered comparing supine and prone position ventilation in the same group of patients, but the small number of cases may lead to a large deviation in the results. Although the design was not rigorous enough, we still thought that the results had some clinical significance. We added this part of the

explanation in the limitation part.

Comment 2: Conclusions: The statement in both the abstract and the main text that "Implementing PPV in neonates undergoing ECMO can enhance respiratory compliance and reduce airway resistance, thereby improving hypoxemia" raises concerns. It may be inadequate to conclude that hypoxemia is relatively improved compared to SPV without more data and statistical evidence.
Reply 2: Based on the available data, it may not be sufficient to demonstrate that PPV under ECMO can improve hypoxemia, so we have revised our conclusions.
Changes in the text: We revised our conclusion to “Implementing PPV in neonates undergoing ECMO may improve respiratory compliance and decrease airway resistance, potentially aiding in the recovery of lung function.”

Comment 3: Title: The paper’s title lacks explicit reference to venoarterial extracorporeal membrane oxygenation (VA-ECMO). It may need modification to better reflect the main research focus.
Reply 3: We revised the title.
Changes in the text: We revised the title as “Effect of prone positioning on pulmonary ventilation function in neonates during venous-arterial extracorporeal membrane oxygenation”.

Comment 4: Abstract: Including the total number of patients (N) in the abstract is crucial to understanding the overall scope of the study.
Reply 4: Thanks for your reminding, we described the number of patients in the abstract
Changes in the text: Described in the abstract as “We conducted a retrospective analysis of clinical data from 17 neonates who received ECMO support in our institution, divided into two groups based on ventilation strategy: ECMO with PPV (ECMO-PPV, n=8) and ECMO with supine positioning ventilation (ECMO-SPV, n=9).”

Comment 5: Methods: The substantial difference between the PEEP range specified for “Ventilator Support during ECMO” (10-15 cmH_2O) and “ECMO management” (8-10 cmH_2O) raises questions about the reliability of the study's results. Addressing this difference and discussing its potential impact is essential.
Reply 5: We revised the description of ventilator support before and during ECMO. The setting for PEEP is different at different times.
Changes in the text: We made the corresponding change in the revision.

Comment 6: Results: It is necessary to provide a detailed explanation for the exclusion of two patients. These exclusions can significantly affect the interpretation of results

and should be elaborated on.
Reply 6: Your reminder is meaningful, and we have explained it in the result part.
Changes in the text: Change the description to “Two patients were excluded due to incomplete data, resulting in a total of 17 patients included in the study.”.

Comment 7: Discussion: Some content in lines 180-195 of the Discussion section does not directly relate to the current study and is more suitable for the introduction. The Discussion section should primarily focus on scientifically interpreting the results and providing evidence-based insights
Reply 7: We agreed with this opinion and amended this part of the content and added to the introduction part.
Changes in the text: We amended this part of the content and added to the introduction part.

Comment 8: The Discussion section should elaborate on the scientific interpretation of results. It is essential to check a well-written previous study (PMID #32941739) conducted on adults that employed a similar approach and provide insights on how this study's findings align or differ. This will enrich the discussion with scientific evidence and build upon the existing literature.
Reply 8: Marco Giani’s research results were significant, and we described the related content and cited their results in the revision.
Changes in the text: We described the related content and cited Marco Giani’s results in the revision.

Reviewer C

Comment 1: there is no rationale to use P/F ratio in patients ventilated. The OI is the best measure as it takes into account the setting of the mechanical ventilator
Reply 1: We added the OI in the revision and the table 2.
Changes in the text: We modified the table 2 and included the OI results.

Comment 2: I think that it is not wise compare these two cohorts: PPV vs SPV. PPV is a good strategy to reduce the risk of VILI but the patient must be a recruiter. So, it would be useful to evaluate these results considering the recruitability of the lung. Patient not recruiting will not show an improvement of Crs and a decrease in the RAW.
Reply 2: This study was a retrospective study, so patients could not be recruited in advance. We hope to conduct a multicenter prospective study on ECMO in the future, so as to meet the recruitment requirements of the study and enhance the credibility of

the conclusions. We agreed with the reviewer's opinion, which was also the limitation of this article. Given the cause of our disease, the lungs of these patients are recruitable. We added relevant content in the limitation part.

Comment 3: It is not clear why for some patient PPV was chosen during ECMO.
Reply 3: Due to the evolution of clinical expertise and technology, patients with VA-ECMO were initially treated with supine positioning ventilation (SPV) from June 2021 to March 2022. Subsequently, from March 2022 to June 2023, these patients were transitioned to PPV. In some patients, lung recovery under ECMO was still slow. In order to minimize ECMO during time and promote lung repair, PPV was used to improve lung function. so, we revised the discussion section to add the detailed mechanism of PPV on lung improvement.
Changes in the text: We made the corresponding revision in the materials and methods section.

Reviewer D

Comment 1: Please state the type of Maquet / Getinge centrifugal pump, coating of ECMO tubing, type and brand of cannulae used.
Reply 1: We completed the relevant information on ECMO instruments.
Changes in the text: Change the content of "ECMO treatment details" to: The ECMO system consisted of a centrifugal pump (MAQUET, RF-32, Germany), a membrane oxygenator (MEDOS, 800LT, Germany), an air-oxygen blender, a heparin-coated circuit, and a heater unit.

Comment 2: The number of included patients (17) and excluded (2) patients in the text does not match the results (17-2=15 patients in study?), and why were included patients being excluded?
Reply 2: This could be a misunderstanding. What this article wants to express was that after excluding 2 patients, a total of 17 patients were included in the study. We changed the description in the result section.
Changes in the text: Change the description to "Two patients were excluded due to incomplete data, resulting in a total of 17 patients included in the study".

Comment 3: Gestational age and weight are (almost) significant, which appears unlikely from the numbers in the table, please verify this
Reply 3: This was a calculation error. After recalculating the data, there was no significant difference in gestational age and weight between the two groups.

Changes in the text: We made changes to Table 1.

Comment 4: The SPV group appears to trend to being older and the PPV group trends to longer ventilation duration, both of which are not mentioned in the discussion
Reply 4: While not reaching statistical significance, the ECMO-PPV group exhibited a prolonged duration of mechanical ventilation compared to the ECMO-SPV group. This observation may be attributed to the limited sample size in this study, and the potential data bias from individual patients could influence the results. Future endeavors will involve expanding the sample size to mitigate the impact of data bias.
Changes in the text: We made the corresponding revision in the discussion part.

Comment 5: What type of complications did arise in both groups?
Reply 5: We described the complications in both groups.
Changes in the text: We added a specific description of the complications of ECMO-PPV group and ECMO-SPV group in the result section.

Comment 6: These tables contain many duplicate data (and in case of CRS-PPV-2d these do not correspond). I would suggest to merge these tables, and/or to use a bar graph to make your results clearer.
Reply 6: Thanks for your suggestion, we checked the data in Table 3 and modified it into Figure 1.
Changes in the text: Table 3 has been modified to Figure 1.

Comment 7: The paper describes the feasibility of prone positioning on ECMO, however the number of treated patients in both groups appear not sufficient to convincingly exclude differences between the treatment groups. In addition, it would enhance the article if more data was collected regarding the efficiency of the prone positioning treatment. Although statistical significance would be difficult to reach, if the authors could show a general trend towards shorter treatment (e.g., ECMO and/or ventilation) using prone positioning, the results would be more compelling.
Reply 7: Indeed, the number of patients treated in both groups did not appear to be convincing enough to rule out differences between the treatment groups. As mentioned earlier, the number of patients who could be included in the study was limited, and we also added this section to limitation part. The current data was also not enough to verify the conclusion, and we added the results of OI in Table 2 to show the treatment efficiency.
Changes in the text: We modified Table 2 to include the OI results, and we rewrote the discussion part and the conclusion.