Bulletin of the National Research Centre

LETTER TO THE EDITOR

Open Access

Optimizing PEEP levels during injury development is essential to achieve clinically relevant ARDS in animal models

Keibun Liu[1,2,3*], Jacky Y. Suen[1,2,4,5], Karin Wildi[6,7], Gianluigi Li Bassi[1,2] and John F. Fraser[1,2,8,9,10]

Keywords Acute respiratory distress syndrome, Extracorporeal membrane oxygenation, Positive end-expiratory pressure, Preclinical study, Translation

To the Editor

Preclinical animal models of acute respiratory distress syndrome (ARDS) are a critical component of knowledge generation in the quest to advance the clinical management of human ARDS. However, there is a paucity of positive preclinical findings translated into clinical practice that subsequently impacts patient outcomes (i.e., mortality) (Pham and Rubenfeld 2017). One possible contributor to this issue is a lack of positive end expiratory pressure (PEEP) optimization during the injury development before reaching the ARDS criteria triggering observation phase, which may impact the translatability of animal findings to human clinical practice. By addressing this and other similar issues, the preclinical knowledge may be more efficiently and effectively translated into clinical practice.

Although PEEP optimisation is essential to improve oxygenation and achieve an appropriate level of lung injury, our systematic review of PEEP in ARDS showed that this ventilatory strategy has not been appropriately applied in preclinical settings (Millar et al. 2019). PEEP optimization must be prioritized, especially in circumstances where adjunctive therapies, such as extracorporeal membrane oxygenation (ECMO), are required. However, past animal models of ARDS and ECMO consistently applied insufficient levels of PEEP during injury development (Millar et al. 2019), with ECMO initiated immediately after achieving the target PaO_2/FiO_2 ratio, as a surrogate endpoint of severity, rather than achieving clinically relevant ventilator settings (Battaglini et al. 2024). Since insufficient PEEP levels could often introduce severe hypoxaemia in a short period, this approach might result in subjects with mild lung injury (i.e., not ARDS) being included, leading to erroneous conclusions and difficulty applying preclinical findings to clinical human scenarios. Thus, we call for PEEP optimization, adjusting PEEP levels according to the injury progression (e.g., increase in PEEP as PaO_2/FIO_2 ratio decreases), to be incorporated in all preclinical ARDS model development to achieve consistent and clinically relevant lung injury.

In an ovine model of ARDS instigated by the administration of oleic acid and lipopolysaccharide, we

*Correspondence:
Keibun Liu
keiliu0406@gmail.com
[1] Critical Care Research Group, The Prince Charles Hospital, 627 Rode Rd, Chermside, Brisbane, QLD 4032, Australia
[2] Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia
[3] Non-Profit Organization ICU Collaboration Network (ICON), Tokyo, Japan
[4] Faculty of Medicine, School of Biomedical Sciences, University of Queensland, Brisbane, Australia
[5] School of Pharmacy and Medical Sciences, Griffith University, Southport, Australia
[6] Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland
[7] Intensive Care (K.W.), University Hospital Basel, University of Basel, Basel, Switzerland
[8] Adult Intensive Care Services, The Prince Charles Hospital, Brisbane, Australia
[9] Queensland University of Technology, Brisbane, Australia
[10] St. Andrews War Memorial Hospital, Brisbane, Australia

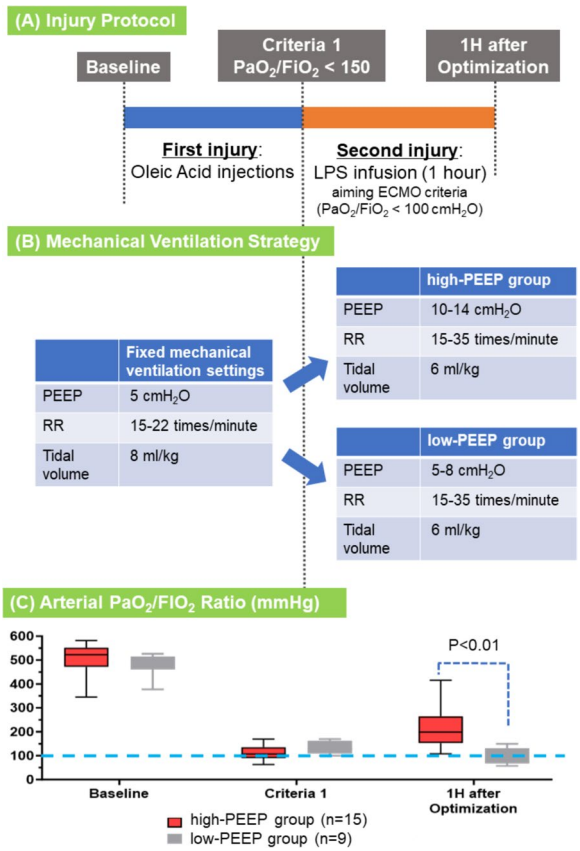

Fig. 1 **A** Injury Protocol, **B** Mechanical Ventilation Strategy, **C** PaO_2/FiO_2 ratio based on the results of arterial blood gas. ECMO extracorporeal membrane oxygenation, FiO_2 fraction of inspiratory oxygen, LPS lipopolysaccharides, PaO_2 partial pressure of arterial oxygen, PEEP positive end-expiratory pressure, RR respiratory rate A 0.03 ml/kg of oleic acid injection was repeated every 30 min until the PaO_2/FiO_2 ratio met Criteria 1 (PaO_2/FiO_2 ratio < 150 cmH_2O). After the initiation of the PEEP adjustment, 0.5 µg/kg of LPS in 50 ml of saline was continuously infused for one hour. Arterial blood gas was measured every 15 min and when necessary, since the first oleic acid injection over the injuries

investigated the effects of PEEP optimisation during the injury phase and before achieving the target criteria (Fig. 1A) using data from two randomised controlled preclinical studies [Wildi et al. 2023, Unpublished study]. These studies used the same injury protocol and hemodynamic management, but a different PEEP strategy (Table 1). Upon achieving $PaO_2/FiO_2 < 150$ cmH_2O and using similar tidal volumes (6 ml/kg) and respiratory rate, two different levels of PEEP were applied during the second injury with lipopolysaccharide: (1) high-PEEP group ($n = 15$, PEEP 10–14cmH_2O) [Unpublished study], and (2) low-PEEP group ($n = 9$, PEEP 5–8cmH_2O) (Wildi et al. 2023) (Fig. 1B).

Despite similar oleic acid doses, we found a notable discrepancy in PaO_2/FiO_2 ratios between the groups within just one hour from PEEP adjustment (Fig. 1C). In the high-PEEP group, the PaO_2/FiO_2 ratio improved to 218 ± 21 mmHg, exceeding the typical clinical indication threshold for ECMO (i.e. PaO_2/FiO_2: 80–120). Consequently, ECMO would likely be not clinically indicated in such a scenario. Conversely, in the low-PEEP group, the PaO_2/FiO_2 ratio declined to 102 ± 11 mmHg, supporting the clinical initiation of ECMO.

Our findings suggest that optimizing PEEP during injury development could substantially alter injury levels in preclinical ARDS models, and more accurately align ARDS characteristics with those seen in clinical practice. Preclinical models must reproduce clinical settings and adhere to clinical guidelines as closely as possible during the development of ARDS (Grasselli et al. 2023) in order to ascertain relevant, clinically applicable results in this area. Additional research is imperative to explore how to effectively refine the application of PEEP in preclinical ARDS models, aiming to provide guidance for its application and establish reliable models capable of replicating the complexity of ARDS, thereby facilitating translatable discoveries. Finally, future preclinical studies should incorporate clinically relevant adjunctive therapies, such as neuromuscular blockade and prone positioning, to better replicate the complexity of ARDS in real-world scenarios.

Table 1 Differences in protocol between the two groups

Protocol	High-PEEP group ($n=15$)	Low-PEEP group ($n=9$)
Data source	An randomized controlled preclinical study	A 2×2 intervention randomized controlled preclinical study (Wildi et al. 2023)
Period	2021–2023	2018–2020
Settings	Medical Engineering Facility (MERF) based at the Prince Charles Hospital (Queensland University of Technology (QUT), Brisbane, Australia)	
Project ID under QUT Ethics	4067 (Project No. 21-260)	1955 (Project No. 18-606)
Subject	Sheep	Sheep
Weight (kg)	52.2 ± 1.6	50.0 ± 0.6
Injury Protocol		
Injections of Oleic Acid (OA)	An injection of 0.03 ml of OA was repeated until the PaO2/FiO2 ratio reached below 150 (Criteria 1)	
Infusion of Lipopolysaccharide (LPS)	A 0.5 μg/kg of LPS in 50 ml of saline for one hour	
Mechanical ventilation strategy		
Mode	Volume controlled	
Tidal volume	8 ml/kg during OA injections and 6 ml/kg during LPS	
Respiratory Rate	Adjusted according to the result of arterial blood gas aiming at $PaCO_2$ between 35 and 45 mmHg	
PEEP during OA	5 cmH_2O	
PEEP during LPS	10–14 cmH_2O	5–8 cmH_2O
Hemodynamic Protocol	With targets of mean arterial pressure above 65 mmHg and heart rate below 120 times/minute, 250 ml of fluid bolus and catecholamine (i.e., Noradrenaline, vasopressin, metaraminol, and adrenaline) were used	

Numbers are described as mean with standard deviation

FiO_2 fraction of inspiratory oxygen, LPS OA Oleic Acid, PaO_2 partial pressure of arterial oxygen, PEEP positive end-expiratory pressure

*Only the data with completion of oxygenation result 1 h after initiation of LPS infusion of the OA-LPS group in the main study (Pham and Rubenfeld 2017)

Abbreviations

ARDS	Acute respiratory distress syndrome
ECMO	Extracorporeal membrane oxygenation
PaO_2/FiO_2	Partial pressure of oxygen in blood/ fraction of oxygen in the inhaled air
PEEP	Positive end-expiratory pressure

Acknowledgements
We would like to thank the members of Critical Care Research Groups and the staff at Medical Engineering Facility (MERF) based at the Prince Charles Hospital (Queensland University of Technology (QUT), Brisbane, Australia), who helped and supported the submitted projects.

Author contributions
KL drafted the letter. JS, KW, GB, and JF contributed substantially to revising and approving the final version of the letter.

Funding
This study was funded by MERA (Senko Medical Instrument Mfg, Tokyo, Japan), Japan Society for the Promotion of Science (Tokyo, Japan), the Wesley Medical Research Foundation (QLD, Australia), and the Prince Charles Hospital Foundation (QLD, Australia).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The animal studies were assessed and approved by the QUT Office of Research Ethics and Integrity (No. 18-606), the University Animal Ethics Committee of the Queensland University of Technology (QUT) (202100026), and the University of Queensland (2022/AE000077), following the ARRIVE guidelines. All experiments were performed in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and the Animal Care and Protection Act 2001 (QLD).

Consent for publication
Not applicable.

Competing interests
The authors declare that they do not have any competing interests related to the submitted work.

Received: 12 July 2024 Accepted: 24 September 2024
Published online: 14 October 2024

References

Battaglini D, Roca O, Ferrer R (2024) Positive end-expiratory pressure optimization in ARDS: physiological evidence, bedside methods and clinical applications. Intensive Care Med. https://doi.org/10.1007/s00134-024-07397-5
Grasselli G, Calfee CS, Camporota L et al (2023) ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 49:727–759
Millar JE, Bartnikowski N, von Bahr V et al (2019) Extracorporeal membrane oxygenation (ECMO) and the acute respiratory distress syndrome (ARDS): a systematic review of pre-clinical models. Intensive Care Med Exp 7:18
Pham T, Rubenfeld GD (2017) Fifty years of research in ARDS. The epidemiology of acute respiratory distress syndrome. A 50th birthday review. Am J Respir Crit Care Med 195:860–870
Wildi K, Livingstone S, Ainola C et al (2023) Application of anti-inflammatory treatment in two different ovine acute respiratory distress syndrome injury models: a preclinical randomized intervention study. Sci Rep 13:17986