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DOI
10.1007/s00134-025-07825-0

Publication date
2025

Document Version
Final published version

Published in
Intensive Care Medicine

Intensive Care Med
https://doi.org/10.1007/s00134-025-07825-0

CORRESPONDENCE

Analyzing PaO_2/FiO_2?: mind the interaction with PEEP!

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We read with great interest the recent study by Catozzi et al. [1]. They present an important and thought-provoking perspective on the limitations of classifying Acute Respiratory Distress Syndrome (ARDS) severity based solely on PaO_2/FiO_2. Their findings highlight how severity based on oxygenation impairment does not align with determinants of ventilator-induced lung injury (VILI), such as mechanical power ratio (MPR) and driving pressure (DP), thereby questioning the usefulness of tailoring respiratory support based on PaO_2/FiO_2 thresholds. We strongly support their stance on re-evaluating the pivotal role of oxygenation impairment in ARDS management, particularly the centrality of PaO_2/FiO_2.

As we reflect on these findings, we wish to highlight a key limitation: the study's analysis included PaO_2/FiO_2 that was obtained at various ventilation settings, which was used to stratify ARDS severity-groups. However, it is well-known that the positive end-expiratory pressure (PEEP) level could directly influence the oxygenation response and thus PaO_2. While the authors extensively discuss that VILI determinants arise from the interplay between several factors, we argue that classification by PaO_2/FiO_2 without considering its interaction with PEEP is incomplete. In the study by Catozzi et al. [1], baseline PEEP levels during PaO_2/FiO_2 measurements ranged widely from 5 to 20 cmH_2O (as displayed in Figure S29). This variability raises concerns about the findings' reliability as the authors combined all PaO_2/FiO_2 measurements in the analysis regardless of the corresponding PEEP level.

PEEP could affect lung recruitment and oxygenation. Thus, PaO_2/FiO_2 reflects not only the patient's underlying lung pathology but also depends on the applied ventilatory strategy. Palanidurai et al. [2] have proposed 'normalizing' PaO_2/FiO_2 by dividing it by PEEP. A more straightforward approach might be to stratify patients by the PEEP level at which PaO_2 was measured, ensuring comparisons are made within comparable conditions.

We highlight the importance of such stratification with our preliminary findings, recently shared as a preprint on medRxiv [3]. In our study on the heterogeneity of treatment effects of high PEEP strategies, we revisited earlier work by Briel et al. [4], who reported greater survival benefits from high PEEP in patients with baseline $PaO_2/FiO_2 \leq 200$ mmHg. By grouping patients based on baseline PEEP, we found that this relationship was evident *only* when PaO_2/FiO_2 was measured during low PEEP settings, disappearing at higher PEEP levels. Without stratification, these findings—critical for PEEP management—would have been misleading.

Applying this reasoning to the study under discussion, we posit that stratifying patients based on baseline PEEP could uncover stronger associations between oxygenation impairment and respiratory mechanics, including MPR and DP. Beyond this specific study, we advocate for a broader call to action in intensive care medicine research to stratify PaO_2/FiO_2 by PEEP level. Furthermore, it may be time to reconsider how we currently define ARDS and its severity classifications, which presently place central importance on PaO_2/FiO_2 regardless of the PEEP level at which it is measured [5].

Finally, we wish to take a moment to acknowledge the unfortunate recent passing away of Professor Gattinoni, whose transformative and inspiring work profoundly shaped our understanding of ARDS and mechanical

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This comment refers to the article available online at https://doi.org/10.1007/s00134-024-07712-0.

ventilation. This study stands as a testament to his enduring legacy. We extend our heartfelt condolences to his colleagues and loved ones.

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Declarations

Conflicts of interest
A. H. Jonkman declares research funding paid to her institution, for studying new esophageal pressure sensor.

Publisher's Note

Accepted: 29 January 2025
Published online: 17 February 2025

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