


LETTER TO THE EDITOR

Open Access



Comment on “Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study”

Elisa Damiani, Andrea Carsetti, Erika Casarotta, Roberta Domizi, Claudia Scorcella, Erica Adrario and Abele Donati* 

Dear Editor,

We have read with great interest the article by Diehl et al. on the evaluation of respiratory mechanics and gas exchanges in patients with acute respiratory distress syndrome (ARDS) due to COVID-19 that was recently published in the *Annals of Intensive Care* [1]. In 22 patients with moderate-to-severe ARDS, the authors observed high physiological dead space (V_D/V_T) and ventilatory ratio (VR). Several hypotheses are made to explain the pathogenesis of increased V_D/V_T , namely pulmonary embolism, alveolar overdistension, increased instrumental dead space, and diffuse microcirculatory dysfunction [1]. Even if alveolar overdistension due to high PEEP-protective ventilation, with regional compression of alveolar vessels, is likely to exert a major impact on lung mechanics in ARDS, the hypothesis of a contributing role of microvascular derangement is particularly captivating.

Lung injury in ARDS (and COVID-19 pneumonia) seems mainly driven by a dysregulation of the renin-angiotensin system, leading to increased vascular permeability, inflammation, pneumocyte apoptosis, and fibrosis [2]. Pulmonary microvascular injury, with leaky

blood vessels, interstitial oedema, microthrombosis, and heterogeneous perfusion, may be the first responsible for ventilation/perfusion mismatch and increased dead space in ARDS. In 42 patients with early moderate or severe ARDS, Ospina-Tascon et al. showed an inverse correlation between V_D/V_T and sublingual microcirculatory blood flow distribution [3]. In their study, Diehl et al. reported an elevation of markers of endothelial damage and thrombosis (i.e., circulating endothelial cells and D-dimers); however, they did not show any statistical correlation with variables of respiratory mechanics and/or gas exchange [1].

In a recent report, we described the sublingual microcirculation of mechanically ventilated patients with severe SARS-COV-2 pneumonia and showed an inverse correlation between perfused vessel density (PVD) and D-dimers [4]. This relationship was confirmed in SARS-COV-2 patients on veno-venous extracorporeal membrane oxygenation [5]. Unfortunately, we could not evaluate the relationship with physiological dead space, because V_D/V_T data were not available for our cohort. We calculated the VR for 6 patients who were not receiving extracorporeal membrane oxygenation (median VR = 1.9 [1.4–2.5]); however, we could not find any significant correlation with D-dimers (Spearman's $\rho = -0.1$, $p = 0.950$) or microcirculatory variables (Spearman's ρ for PVD = 0.232, $p = 0.650$). The extremely low sample size significantly limits these analyses.

This comment refers to the article available at <https://doi.org/10.1186/s13613-020-00716-1>.

*Correspondence: a.donati@univpm.it
Anesthesia and Intensive Care Unit, Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, via Tronto 10/a, 60126 Ancona, Italy



© The Author(s) 2020. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Taken together, all these data would suggest a connection between microvascular dysfunction, coagulopathy, and increased physiological dead space in the genesis of respiratory failure in COVID-19 pneumonia. Nonetheless, the cause–effect relationship remains to be proven. An altered sublingual microcirculation could just be an epiphenomenon of a hemodynamic compromise in patients with worse respiratory mechanics: in our cohort, sublingual microvascular perfusion tended to decrease with increasing driving pressures [4]. Further investigations are imperative to gain a more comprehensive understanding of the pathophysiology of COVID-19 and select the best treatment strategy. Appropriately designed clinical and laboratory-controlled studies are needed to prove any causal relationship between microvascular derangements and increased dead space ventilation.

Finally, a consideration must be made regarding the article by Diehl et al. [1]: the authors used side-stream capnography, which may be inaccurate for calculations of V_D/V_T as compared to main-stream capnography. The transport delay of the gas in the sampling tube with axial mixing of the gas residing in the tube, together with the variable sampling flow rate resulting from the alternating positive airway pressure during mechanical ventilation, leads to underestimation and distortion of the capnogram, with consequent inaccurate V_D/V_T calculations.

Abbreviations

ARDS: Acute respiratory distress syndrome; COVID-19: Severe coronavirus disease 2019; V_D/V_T : Physiological dead space; VR: Ventilatory ratio; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus 2; PVD: Perfused vessel density.

Acknowledgements

Not applicable.

Authors' contributions

All authors equally contributed to the study's conceptualization, methodology, and analysis. ED, AC, EC wrote the manuscript. RD, CS, EA, and AD revised the manuscript critically. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 29 July 2020 Accepted: 15 October 2020

Published online: 23 October 2020

References

1. Diehl JL, Peron N, Chocron R, Debuc B, Guerot E, Hauw-Berlemont C, et al. Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study. *Ann Intensive Care*. 2020;10:95.
2. Sarzani R, Giulietti F, Di Pentima C, Giordano P, Spannella F. Angiotensin system and its opposing arm in SARS-COV-2 related lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2020. <https://doi.org/10.1152/ajplung.00189.2020>.
3. Ospina-Tascón GA, Bautista DF, Madriñán HJ, Valencia JD, Bermúdez WF, Quiñones E, et al. Microcirculatory dysfunction and dead-space ventilation in early ARDS: a hypothesis-generating observational study. *Ann Intensive Care*. 2020;10(1):35.
4. Damiani E, Carsetti A, Casarotta E, Scorcella C, Domizi R, Adrario E, et al. Microvascular alterations in patients with SARS-COV-2 severe pneumonia. *Ann Intensive Care*. 2020;10:60.
5. Carsetti A, Damiani E, Casarotta E, Scorcella C, Domizi R, Montomoli J, et al. Sublingual microcirculation in patients with SARS-CoV-2 undergoing veno-venous extracorporeal membrane oxygenation. *Microvasc Res*. 2020;132:104064.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)