Pulmonary air leak in COVID-19: time to learn from our mistakes

Mohamed Boussarsar1,2 and Alessandro Protti3,4*

Since the late 90s, pulmonary air leak, including pneumothorax and pneumomediastinum, has been considered an uncommon complication of invasive mechanical ventilation, occurring in < 10% of patients with acute respiratory distress syndrome (ARDS) [1]. However, soon after the novel coronavirus disease 2019 (COVID-19) appeared, many of us began to see it more frequently than before [2]. Several questions arose. Did this finding depend on the very high prevalence of ARDS during the pandemic? Did it reflect a specific trait of COVID-19? Was it our responsibility?

Knox et al. [3] aimed to address the first two questions in this issue of Intensive Care Medicine. They reviewed the chest imaging reports of 2211 patients with ARDS due to COVID-19 and 5522 with ARDS of different origin and found that the incidence of pneumothorax or pneumomediastinum in the two groups was similar, 24% and 22.5%. However, following adjustment for confounders, it was higher in the former than in the latter group (odds ratio 1.31, 95%-confidence interval 1.13–1.52).

The overall incidence of a pulmonary air leak (22.9%) was very high. This result is partly explained by the decision to include subjects with trauma, any pneumothorax or pneumomediastinum regardless of its volume or need for drainage, cases due to invasive procedures, and by considering the entire hospital stay. Even so, we are still surprised to read that approximately one-fourth of the patients had an air leak.

Unfortunately, the authors did not address the third question. While answering, it is crucial not to blame ourselves but to cure the next patients with COVID-19 better.

In the following sections, we will briefly describe the pathogenesis of alveolar rupture, focus on mechanisms that may explain the findings of Knox et al. [3], and conclude with the most important lessons we have recently learned on this topic.

Alveolar rupture usually results from a large alveolar deformation generated by a high transpulmonary pressure that is the pressure gradient across the alveolar wall. The maximal transpulmonary pressure reached during ventilation can be reasonably measured as the difference between the end-inspiratory plateau airway pressure (inside the alveoli) and the corresponding esophageal pressure (a surrogate of the pleural pressure outside of the alveoli). The safe upper limit of transpulmonary pressure for healthy human alveoli is probably 20–25 cmH₂O [4].

Ventilator-induced lung injury (VILI)

In the study by Knox et al. [3], 400 patients developed a pneumothorax or pneumomediastinum after receiving invasive mechanical ventilation with a plateau pressure up to 34 (30–40) cmH₂O and positive end-expiratory pressure (PEEP) up to 16 (14–20) cmH₂O. The driving (plateau minus PEEP) airway pressure probably exceeded 15 cmH₂O in many of them. Similar ventilatory settings increase the risk of alveolar rupture during ARDS.
unrelated to COVID-19 [5, 6] and possibly even during COVID-19.

Large tidal volumes, high respiratory rates, and high inspiratory flows could have contributed to an air leak by increasing the total amount of energy delivered to the alveoli over time (the so-called mechanical power [7]). However, these variables were not reported in the study.

**Patient-self-inflicted lung injury (P-SILI)**

One hundred thirty one patients developed a pneumothorax or pneumomediastinum without receiving invasive mechanical ventilation. Eighty-one were treated with non-invasive ventilation, and the others with low or high-flow oxygen for a few days (on average, the air leak was diagnosed 7 days [3–13] after hospital admission). In these patients, the alveolar rupture was probably caused by repeated vigorous inspiratory efforts with large decreases in pleural pressure and increases in transpulmonary pressure [4]. Just as invasive assisted ventilation, non-invasive ventilation could have been particularly risky. In fact, with these two modes, the alveolar and pleural pressure change in opposite directions, driven by the ventilator’s and the patient’s activity, and the transpulmonary pressure can easily become too high. Poor patient-ventilator interaction up to the extreme where patients “fight” against the ventilator, favored by an elevated respiratory drive [8], severe cough due to non-vented circuits, and poor management of hyperactive delirium [9], may have all contributed to rising this risk.

**Lung inhomogeneities**

Early COVID-19 frequently presents with large areas of poorly aerated lung tissue or ground glass opacities, where inhomogeneities can act as “stress risers”: aerated alveoli adjacent to collapsed ones are exposed to excessive tension even when the overall lung inflation is not that large due to local pressure multiplication [10].

**Decreased tissue resistance to inflation**

During COVID-19, pneumocyte necrosis and emphysematous changes are common, especially in sub-pleural regions. With time, lung lesions can progress toward fibrosis and parenchymal destruction. Pulmonary embolism with multiple infarcts may be an additional insult [11]. The resulting tissue frailty can predispose to alveolar rupture independently from exposure to very high transpulmonary pressure [12].

**Iatrogenic procedures**

Finally, pulmonary air leak may have resulted from invasive procedures such as central line insertion, especially if performed by inexperienced personnel or with limited access to ultrasound guidance, as possible during a pandemic.

In Table 1, we summarize the most important lessons we learned during the pandemic, which are indirectly supported by the findings of Knox et al. [3]. Translating
them to the bedside will hopefully make pulmonary air leaks uncommon even in patients with COVID-19.

Author details
1 Faculty of Medicine of Sousse, University of Sousse, 4000 Sousse, Tunisia. 2 Medical Intensive Care Unit, Research Laboratory “Heart Failure”, Farhat Hached University Hospital, LR12SP09, 4000 Sousse, Tunisia. 3 Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. 4 Department of Anesthesia and Intensive Care Units, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.

Author contributions
The two authors equally and substantially contributed to the conception and design of this manuscript, drafted and revised it critically for intellectual content, and finally approved this version to be published.

Declarations

Conflicts of interest
All the authors certify that they have no affiliations with/or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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

Received: 24 July 2022   Accepted: 10 August 2022   Published: 20 August 2022

References
1. Ricard JD (2004) Barotrauma during mechanical ventilation: why aren’t we seeing any more? Intensive Care Med 30:533–535. https://doi.org/10.1007/s00134-004-2186-8
2. Protti A, Greco M, Filippini M et al (2021) Barotrauma in mechanically ventilated patients with coronavirus disease 2019: a survey of 38 hospitals in Lombardy, Italy. Minerva Anestesiologica 87:193–198. https://doi.org/10.23736/S0375-9393.20.15002-8
3. Knox DB, Brunhoeber A, Peltan ID et al (2022) Comparison of radiographic pneumothorax and pneumomediastinum in COVID-19 vs. non-COVID-19 acute respiratory distress syndrome. Intensive Care Med. https://doi.org/10.1007/s00134-022-08681-9
4. Coppola S, Chiumello D, Busana M et al (2021) Role of total lung stress on the progression of early COVID-19 pneumonia. Intensive Care Med 47:1130–1139. https://doi.org/10.1007/s00134-021-06519-7
5. Boussarsar M, Thierry G, Jaber S et al (2002) Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. Intensive Care Med 28:406–413. https://doi.org/10.1007/s00134-001-1178-1
6. Amato MB, Meade MO, Slutsky AS et al (2015) Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 372:747–755. https://doi.org/10.1056/NEJMoa1410639
7. Gattinoni L, Tonetti T, Cressoni M et al (2016) Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 42:1567–1575. https://doi.org/10.1007/s00134-016-4505-2
8. Esnault P, Cardinale M, Hraiech S et al (2020) High respiratory drive and excessive respiratory efforts predict relapse of respiratory failure in critically ill patients with COVID-19. Am J Respir Crit Care Med 202:1173–1178. https://doi.org/10.1164/rcrm.202005-1582LE
9. Pun BT, Badenes R, Heras La Calle G et al (2021) Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med 9:239–250. https://doi.org/10.1016/S2213-2600(20)30552-X
10. Cressoni M, Cadringher P, Chiurazzi C et al (2014) Lung inhomogeneity in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 189:149–158. https://doi.org/10.1164/rcrm.201308-156OC
11. Lax SF, Skok K, Zechner P et al (2020) Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 173:350–361. https://doi.org/10.7326/M20-2566
12. Lemmers DHL, Abu Hilal M, Brná C et al (2020) Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? ERJ Open Res 6:00385–02020. https://doi.org/10.1183/23120541.00385-2020
13. Protti A, Santini A, Pennati F et al (2022) Lung response to a higher positive end-expiratory pressure in mechanically ventilated patients with COVID-19. Chest. 161:979–988. https://doi.org/10.1016/j.chest.2021.10.012
14. Protti A, Santini A, Pennati F et al (2022) Lung response to prone positioning in mechanically-ventilated patients with COVID-19. Crit Care 26:127. https://doi.org/10.1186/s13054-022-03996-0
15. Colombo J, Spinelli E, Grasselli G et al (2020) Detection of strong inspiratory efforts from the analysis of central venous pressure swings: a preliminary clinical study. Minerva Anestesiologica 86:1296–1304. https://doi.org/10.23736/S0375-9393.20.14323-2