Diagnostic, prognostic and therapeutic strategies in critically ill COVID–19 patients

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CHAPTER 11

General Discussion and Future Perspectives

This thesis is a collection of clinical investigations in critically ill intensive care unit (ICU) patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID–19). This chapter places the findings in a broader context, and discusses the potential implications for future investigations.

Diagnosing and severity classification in ARDS

In 2012, a panel of experts defined the Berlin definition for acute respiratory distress syndrome (ARDS) (1). According to this definition, a patient with acute hypoxemic respiratory failure ARDS can be diagnosed if the following criteria are fulfilled: (i.) presence of new or worsening respiratory symptoms within one week after an insult; (ii.) having a $PaO_2/FiO_2 < 300$ mm Hg; and (iii.) presence of bilateral opacities on chest radiography (CXR) or chest computer tomography (CT) that cannot be explained by cardiac failure. The PaO_2/FiO_2 is to be calculated at a minimum of 5 cm H_2O positive end–expiratory pressure (PEEP). For risk of death classification, the Berlin definition uses PaO_2/FiO_2 cutoffs: (i.) when the PaO_2/FiO_2 is between 200 mm Hg and 300 mm Hg, ARDS is classified as 'mild'; (ii.) when between 100 mm Hg and 200 mm Hg, ARDS is classified as 'moderate'; and (iii.) when $<$ 100 mm Hg, ARDS is classified as 'severe'. Patients in these three classes have increasing risks for death.

High–flow nasal oxygen (HFNO) is a highly effective and increasingly used strategy to overcome severe hypoxemia. The strongest increase in use of HFNO was noticed in recent years, at least in part in response to the overwhelming numbers of patients with acute hypoxemic respiratory failure due to COVID–19 (2). This major change in oxygen support forces the ICU community to reconsider the current definition for ARDS. Indeed, as explicitly stated in the Berlin definition, for a patient to have ARDS the ventilatory support must use at least 5 cm H_2O PEEP. With HFNO, no or only minimal –and if present unmeasurable– PEEP is provided.

Recently, it was suggested to adjust the Berlin definition for ARDS, by replacing the required lower limit of 5 cm H2O PEEP during mechanical ventilation with a lower limit of 30 L/min air flow if a patient receives HFNO (3). It is uncertain, though, whether letting go of the requirement of a minimal level of PEEP will result in comparable patient cohorts as when using the 'full' Berlin definition, i.e., pertaining a minimal level of PEEP. It could even be that patients that receive HFNO are entirely different from patients that receive mechanical ventilation for acute hypoxemic respiratory failure. It is also uncertain whether use of PaO_2/FiO_2 cutoffs, as now done in the Berlin definition, will lead to groups of patients with meaningful differences in mortality.

We were the first to test the hypothesis that using the suggested adjusted definition in acute hypoxemic patients under HFNO results in comparable patient groups as when using the original definition for ARDS in acute hypoxemic patients under mechanical ventilation, with regard to baseline characteristics and outcomes. In our analysis of a national multicenter observational study named 'PRactice of Adjunctive Therapies in COVID–19' (PRoAcT–COVID) (4), we tested the prognostic capacity value of the original PaO_2/FiO_2 cutoffs and in addition, we tested whether tertiles of PaO_2/FiO_2 at baseline would increase the prognostic capacity. Our findings suggest that an adjustment in the definition for ARDS in which a minimum level of PEEP is replaced by a minimum air flow in patients under HFNO results in comparable groups and mortality of patients with COVID–19 pneumonia. However, severity classification using PaO_2/FiO_2 is not possible in patients under HFNO, probably because of the skewed PaO_2/FiO_2 distribution in these patients. Of note, in these patients the median PaO_2/FiO_2 was much lower than in patients ventilated with PEEP. It is uncertain whether this is caused by a true need for higher FiO_2, or because FiO_2 is set more liberal with HFNO. Our sample size was small, and larger cohorts are certainly needed for confirmation. Indeed, the diagnostic capacity of the Berlin definition, and the prognostic capacity of the original PaO_2/FiO_2 cutoffs were tested in much larger cohorts.

It remains uncertain if we can use the suggested adjusted definition in patients with acute hypoxemic respiratory failure due to other causes than COVID–19. This question is important, as HFNO is increasingly used not only in patients with acute hypoxemic respiratory failure due to COVID–19 but also in patients with other causes for acute hypoxemia. Whether the adjusted definition leads to comparable patient groups in these patients remains to be established. Of note, acute hypoxemic critically ill COVID–19 patients frequently have a 'single–organ' disease, i.e., they have pneumonia, and maybe also microthrombi and pulmonary embolism—this is very different from patients with acute hypoxemic respiratory failure due to other causes.

Also important in the context of patient classification is that previous studies have shown that disease severity, and with that severity classification, can change over the first days of ventilation (5), and this 'evolution' is associated with a change in risk for death. Indeed, patient that 'move' from having severe ARDS to having moderate or even mild ARDS in successive days have a lower risk for death than patients that continue to have severe ARDS. Whether this is also true when using the adjusted definition for ARDS, in patients under HFNO, is unknown but can be expected. Herein, future studies are also urgently needed.

We and others have shown that the SpO_2/FiO_2 cutoffs perform as good as PaO_2/FiO_2 cutoffs in the prognostication of patients with ARDS, including in patients with ARDS due to COVID–19 (6, 7). Benefits of using SpO_2/FiO_2 cutoffs instead of using the PaO_2/FiO_2 cutoffs are that the SpO_2/FiO_2 is easier to obtain as it does not require an arterial puncture or indwelling arterial catheter for arterial blood draws. If a further adjustment of the Berlin definition, one in which the SpO_2/FiO_2 replaces the PaO_2/FiO_2, has comparable diagnostic and prognostic capacities mandates further investigations.

Imaging in COVID–19

Quantitative scores for pulmonary infiltrates of lung images like the CXR and the chest CT are increasingly used in critically ill mechanically ventilated patients. The 'Radiographic Assessment for Lung Edema' (RALE) score was recently introduced in an attempt to improve the quantification of pulmonary abnormalities on the CXR and diagnosing ARDS (8, 9). The 'CT severity score' is another recently introduced score to improve the quantification of pulmonary abnormalities on the chest CT scan, in ARDS due to COVID–19 (10). However, these scores were not yet used for prognostication in patients with ARDS due to COVID–19.

We performed two studies, one named 'Prognostic Capacity of the Radiographic Assessment for Lung Edema Score in Patients with COVID–19 Acute Respiratory Distress Syndrome '(RALE–COVID) and one named 'Prognostic Capacity of the RALE–score versus the CT Severity Score in Invasively Ventilated COVID-19 patients' (RALE–CORADS), that both focused on the prognostic value of quantitative scores of lung images.

We showed that patients with ARDS due to COVID–19 had very high RALE scores— much higher than in cohorts of patients with ARDS due to another cause (8, 11). We found that the RALE score at start of ventilation had no prognostic capacity. However, an increase in the RALE score over successive days was associated with worse outcome. In the second study, we showed that the CT severity score had an association with outcome in patients with ARDS due to COVID–19. Of interest, there was no correlation between the RALE score and the CT severity scores in this study.

In the RALE score approach, the chest is 'divided' in quadrants, which makes it relatively easy to calculate the RALE score. The RALE score, however, is a simplification of the extent of consolidations—and could be an inadequate tool for prognostication in cases of extensive consolidations, like we have seen in our cohort of patients with COVID–19 ARDS. The RALE score could gain in prognostic value if the lungs are divided in more than the 4 fields, but this needs to be tested in future studies. In addition, while the RALE score seems a relatively easy to obtain and reproducible score, obtaining this score is rather time–consuming and requires extensive training. It could be, though, that automated algorithms can perform better than individual scorers. Such algorithms may not necessarily divide the lungs in four quadrants, but 'built' a score on many more, if not uncountable fields or just the entire lung. Hopefully, this approach will save time, improve quantification, and with that maybe even increase the prognostic capacity.

One reason to conduct the RALE–CORADS study was to determine whether a CXR–based approach would be as efficient in prognostication as one based on chest CT scans. Advantages of a score that uses CXRs are that a CXR is easier, cheaper, and also safer to obtain, as it would reduce the number of dangerous transports outside of the ICU to a CT scanner. A CXR–based approach would also reduce the amount of radiation to which patients are exposed. Surprisingly, we found no correlation between the CXR–based score and the one based on chest CT. Next, the 'overall' diagnostic performance of the CXR will always be lower than that of a chest CT scan—for example, a CT–scan has a higher diagnostic yield with respect to pulmonary embolism, pneumothorax, and also often present secondary pulmonary infections. Furthermore, the amount of aerated lung tissue can be better determined compared to the CXR. Thus, the CXR will probably not replace the chest CT–scan in COVID–19 patients.

Ventilation in COVID–19

In ARDS patients, a ventilation strategy with higher PEEP may prevent atelectasis but at the same time may induce overdistension. While prevention of atelectasis may translate in an improved oxygenation, overdistension may increase the risk of ventilator–induced lung injury, and with that worsen outcome. In patients with ARDS due to other causes than COVID–19, there have been no studies that showed benefit of higher PEEP with respect to mortality—in fact, one study showed harm from a strategy that used higher PEEP (12).

We showed that higher PEEP resulted in a better aeration. In one study in which we compared aeration at two different PEEP levels—the use of higher PEEP improved lung aeration and oxygenation. This is in line with studies in patients with ARDS due to other causes than COVID–19. In an analysis of another study, named the 'Practice of Ventilation in COVID–19 Patients' (PRoVENT–COVID) (13), we found no benefit of using a higher PEEP strategy in an unmatched analysis, and even harm in a matched analysis. The use of a higher PEEP strategy was associated with more acute kidney injury and more frequent use of renal replacement therapy. With an increase in PEEP, the elevated intrathoracic pressures may decrease cardiac output, and with that systemic circulation may worsen. This may be one of the reasons for why we found a higher incidence of kidney injury and increased use of renal replacement therapy in our study (14).

Despite our finding of harm with a higher PEEP strategy in a cohort of patients with ARDS due to COVID–19, and findings of harm in cohorts of patients with ARDS due other causes, higher PEEP remains to be used. This is probably caused by the fact that higher PEEP levels do improve oxygenation almost immediately, which is often seen as beneficial by the healthcare workers at the bedside – at times called 'immediacy bias'. We need to educate much better that such improvements do not translate in better patient outcomes, if not worse. We should not strive for physiology, i.e., trying to reach normal oxygenation levels, but rather accept the pathophysiology, i.e., accept lower oxygenation levels.

It has been suggested that COVID–19 ARDS patients present with distinct respiratory sub phenotypes than patients with ARDS due to another cause. A recent study in COVID–19 patients, showed a homogenous and single respiratory sub phenotype at the initiation of invasive ventilation—however, in this study it was seen that the cohort diverged to a more heterogeneous population at later timepoints. In the study of PEEP in this thesis we focused on PEEP settings in the first four days of ventilation. Future studies are needed to understand the role of higher PEEP in the different sub phenotypes.

Prone positioning

Prone positioning has been shown to improve outcomes in patients with moderate to severe ARDS. Before the COVID–19 pandemic, prone positioning remained relatively underused (15, 16). This could be due to the prevailing opinion that prone position should only be used as rescue therapy for severe hypoxemia. Several reports on practice of ventilation in COVID–19 patients showed an increased use of prone positioning. Mechanically ventilated COVID–19 patients often have severe hypoxemia that is refractory to higher PEEP and higher oxygen fractions—this may, at least in part explain the increased use. While current guidelines suggest to use prone positioning only if the PaO_2/FiO_2 drops to $<$ 150 mmHg at a PEEP level of $\geq$ 5 cm H2O with a FiO2 $\geq$ 0.6 (17), we found that early prone positioning was used also in patients that did not meet these criteria. Whether this results in better outcomes in these patients, however, is uncertain – prone positioning is often used in combination with more use of sedation, and even of neuromuscular blocking agents (NMBA). Both may have negative effects on outcome. Besides, prone positioning can be a risky procedure, especially in unexperienced hands. Therefore, further research is needed to determine the impact of more extensive use of prone positioning.

By now, prone positioning is also used to avoid endotracheal intubation. This so–called awake prone positioning became popular in the COVID–19 pandemic, and the beneficial effects with regard to oxygenation even triggered several randomized clinical trials that found benefit of this intervention. In one analysis of a large observational study in COVID - 19 patients in the Netherlands, named ‘Practice of Adjunctive Therapies in COVID–19’ (PRoAcT–COVID), we showed that approximately one in every six patients underwent awake proning. We found no benefit from the intervention, but this may very well be explained by the sample size, and also the rather unstructured use of the intervention. Nevertheless, awake prone positioning is an attractive approach to increase the oxygenation, as this intervention is rather simple, and in itself has an oxygen–sparing effect that could be beneficial in settings that suffer from oxygen scarcity.

Future studies of awake prone positioning are definitely needed, not only in patients with COVID–19, but also in patients with ARDS due to another cause. Our group, therefore, recently started the ‘Awake prone positioning in non-intubated spontaneous breathing ICU patients with acute hypoxemic respiratory failure (PRONELIFE)’ study (18).

REFERENCES

1. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-33.
2. Mellado-Artigas R, Ferreyro BL, Angriman F, Hernández-Sanz M, Arruti E, Torres A, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care. 2021;25(1):58.
3. Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? Lancet Respir Med. 2021;9(8):933-6.
4. Valk CMA, Swart P, Boers LS, Botta M, Bos LDJ, de Abreu MG, et al. Practice of adjunctive treatments in critically ill COVID-19 patients-rational for the multicenter observational PRoAcT-COVID study in The Netherlands. Ann Transl Med. 2021;9(9):813.
5. Schuijt MTU, Martin-Loeches I, Schultz MJ, Paulus F, Neto AS. Mortality associated with early changes in ARDS severity in COVID-19 patients - Insights from the PRoVENT-COVID study. J Crit Care. 2021;65:237-45.
6. Roozeman JP, Mazzinari G, Serpa Neto A, Hollmann MW, Paulus F, Schultz MJ, et al. Prognostication using SpO(2)/FiO(2) in invasively ventilated ICU patients with ARDS due to COVID-19 - Insights from the PRoVENT-COVID study. J Crit Care. 2021;68:31-7.
7. Pisani L, Roozeman J-P, Simonis FD, Giangregorio A, van der Hoeven SM, Schouten LR, et al. Risk stratification using SpO2/FiO2 and PEEP at initial ARDS diagnosis and after 24 h in patients with moderate or severe ARDS. Annals of Intensive Care. 2017;7(1):108.
8. Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax. 2018;73(9):840-6.
9. Zimatore C, Pisani L, Lippolis V, Warren MA, Calfee CS, Ware LB, et al. Accuracy of the Radiographic Assessment of Lung Edema Score for the Diagnosis of ARDS. Frontiers in Physiology. 2021;12(731).
10. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiol Cardiothorac Imaging. 2020;2(2):e200047.
11. Jabaudon M, Audard J, Pereira B, Jaber S, Lefrant JY, Blondonnet R, et al. Early Changes Over Time in the Radiographic Assessment of Lung Edema Score Are Associated With Survival in ARDS. Chest. 2020;158(6):2394-403.
12. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2017;318(14):1335-45.
13. Boers NS, Botta M, Tsonas AM, Algera AG, Pillay J, Dongelmans DA, et al. PRactice of VENTilation in Patients with Novel Coronavirus Disease (PRoVENT-COVID): rationale and protocol for a national multicenter observational study in The Netherlands. Ann Transl Med. 2020;8(19):1251.
14. Joannidis M, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, et al. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive Care Med. 2020;46(4):654-72.

15. Duggal A, Rezoagli E, Pham T, McNicholas BA, Fan E, Bellani G, et al. Patterns of Use of Adjunctive Therapies in Patients With Early Moderate to Severe ARDS: Insights From the LUNG SAFE Study. Chest. 2020;157(6):1497-505.
16. Guerin C, Beuret P, Constantin JM, Bellani G, Garcia-Olivares P, Roca O, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med. 2018;44(1):22-37.
17. Gattinoni L, Carlesso E, Taccone P, Polli F, Guerin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol. 2010;76(6):448-54.
18. Morales-Quinteros L, Schultz MJ, Serpa-Neto A, Antonelli M, Grieco DL, Roca O, et al. Awake prone positioning in nonintubated spontaneous breathing ICU patients with acute hypoxemic respiratory failure (PRONELIFE)-protocol for a randomized clinical trial. Trials. 2022;23(1):30.