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

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CHAPTER 1

General Introduction and Outline of the Thesis

INTRODUCTION

Acute respiratory distress syndrome and COVID–19

The acute respiratory distress syndrome (ARDS) is a diffuse inflammatory lung injury that presents clinically with acute hypoxemic respiratory failure and can be caused by a variety of etiologies (1). The mortality of ARDS is high (2). A timely diagnosis and prompt adjustments in treatment may reduce mortality (2, 3). ARDS can be diagnosed using the Berlin definition (4). Patients with ARDS benefit from lung–protective ventilation and prone positioning.

Coronavirus disease 2019 (COVID–19) is an infectious disease caused by the highly contagious 'Severe Acute Respiratory Syndrome Corona Virus 2 (SARS–CoV–2)'. Most of the patients that get infected remain asymptomatic or experience only mild symptoms. However, some of the SARS–CoV–2 infected patients need hospitalization, usually for supplementary oxygen. One in every five hospitalized COVID–19 needs to be admitted to an Intensive Care Unit (ICU), most often for intensification of oxygen support, including invasive ventilation (5). These patients usually meet the Berlin definition for ARDS.

Diagnosis of and severity classification in ARDS

The criteria in the Berlin definition for ARDS include: (i.) presence of new or worsening respiratory symptoms within one week after an insult; (ii.), a $PaO_2/FiO_2 < 300$ mm Hg at a minimum of 5 cm H_2O positive end–expiratory pressure (PEEP); and (iii.) presence of bilateral opacities on a chest radiograph (CXR) or chest computer tomography (CT) that (iv.) cannot be explained by cardiac failure (4). For risk for death classification, the Berlin definition uses PaO_2/FiO_2 cutoffs; when the PaO_2/FiO_2 is $<$ 100 mm Hg ARDS is classified as 'severe', when the PaO_2/FiO_2 is between 100 and 200 mm Hg ARDS is classified as 'moderate', and when the PaO_2/FiO_2 is between 200 and 300 mm Hg ARDS is classified as 'mild'.

The requirement that a patient should receive ventilatory support with at least 5 cm H_2O PEEP starts to become a limitation. High–flow nasal oxygen therapy (HFNO) is increasingly used to overcome severe hypoxemia, in particular in patients with acute hypoxemic respiratory failure due to COVID–19, and its use may prevent the need for ventilatory support with PEEP. As such, by the current definition, these patients do not have ARDS, which of course can be doubted: if these patients would have

received noninvasive or invasive ventilation, and thus have received at least 5 cm H_2O PEEP, the definition would have allowed the diagnosis of ARDS (6). A more extensive definition would make the diagnosis of ARDS independent of ventilatory support with PEEP, as such improving early recognizing of ARDS.

Another challenge with the Berlin definition is that severity classification does not consider extent of consolidation and density of infiltrates at the CXR, while these could help in prognostication. The 'Radiographic Assessment of Lung Edema' (RALE) score is a numeric scoring system, recently introduced in an attempt to better quantify pulmonary abnormalities in case of edema and lung injury (7). The RALE score not only has diagnostic accuracy (8-10), but also prognostic capacity in patients with ARDS (7). It is uncertain whether the RALE score helps in diagnosing of and prognostication in patients with ARDS due to COVID–19.

Mechanical ventilation for ARDS

In patients with ARDS, a ventilation strategy with higher PEEP may prevent atelectasis, improve oxygenation, and reduce ventilator–induced lung injury (11). Three well–powered high–quality randomized clinical trials, though, failed to show mortality benefit from a higher PEEP strategy (12-14), and one recent study even showed an increased mortality with this approach (15). There is growing evidence that a higher PEEP strategy may only benefit patients with 'recruitable' ARDS, and that a lower PEEP strategy should be used in patients with 'non–recruitable' ARDS (16).

Patients with ARDS due to COVID–19 typically suffer from severe and often refractory hypoxemia, and have a low respiratory system compliance (17-19). There is substantial debate whether COVID–19 ARDS differs from ARDS from other causes (20), and also whether COVID–19 patients have 'recruitable' or 'non–recruitable' lung lesions (21, 22). COVID–19 patients frequently also have microthrombi and pulmonary embolism as one other reason for hypoxemia (23). Thus, a strategy aiming at recruitment of these lesions may not necessarily correct hypoxemia. A higher PEEP strategy may even cause further injury by causing over distension of the open lung tissue (24).

Prone positioning for ARDS

Prone positioning has been shown to improve outcome in patients with moderate to severe ARDS (25-27). The mechanisms by which prone positioning improves outcome are not fully understood, and several mechanisms could act in concordance. Prone

positioning can improve oxygenation, as it may reduce intrapulmonary shunt (28). This, however, does not fully explain the survival benefit, as benefit from prone positioning is also seen in patients who do not show an improvement in oxygenation when placed in a prone position (29). Prone positioning may also result in recruitment of collapsed lung tissue. Last but not least, prone positioning could help evacuate sputum from the airways.

Invasively ventilated patients with ARDS due to COVID–19 often have an indication for prone positioning because of the severity and the consolidation may behave as focal lesions (30, 31), which is another reason to apply prone positioning early after start of invasive ventilation (32). Several reports in COVID–19 patients have shown an increased and frequent use of prone positioning, but the best timing, frequency and duration remain uncertain (30, 32-35). Non–intubated patients with acute hypoxemic respiratory failure due to COVID–19 may also benefit from 'awake prone positioning'. Indeed, so–called awake proning has a great potential to improve oxygenation, as such reducing the need for noninvasive or invasive ventilation (36, 37).

AIMS OF THIS THESIS

Studies in this thesis focused on classification and prognostication, and strategies to improve oxygenation in patients with acute hypoxemic respiratory failure due to COVID–19.

The overarching aims of this thesis are to:

1. determine how ARDS can be diagnosed in patients with acute hypoxemic respiratory failure due to COVID–19 that do not receive ventilatory support with a minimum of 5 cm H_2O PEEP;
2. study the prognostic performance of the RALE score and the CT severity score in patients with ARDS due to COVID–19;
3. investigate the association of PEEP with outcome in patients with ARDS due to COVID–19;
4. investigate the association of prone positioning with outcome in patients with ARDS due to COVID–19; and
5. investigate the association of awake prone positioning with outcome in non–intubated COVID–19 patients.

HYPOTHESES IN THIS THESIS

The overarching hypothesis of this thesis are:

1. ARDS can be diagnosed in patients with ARDS due to COVID–19 that do not receive ventilatory support with a 5 cm H_2O PEEP;
2. the RALE score and the CT severity score have a prognostic capacity in patients with ARDS due to COVID–19;
3. early PEEP settings are associated with outcome in patients with ARDS due to COVID–19;
4. use of prone positioning is associated with outcome in patients with ARDS due to COVID–19; and
5. use of awake prone positioning is associated with outcome in non–intubated COVID–19 patients.

OUTLINE OF THE THESIS

This thesis reports the findings of 2 single center and 5 multicenter retrospective studies.

In **Chapter 2** we report the results of an observational study including 109 COVID–19 patients with acute hypoxemic respiratory failure; of them, 33 patients received ventilatory support in the form of HFNO, and 76 ventilatory support in the form of invasive ventilation. For the diagnosis of ARDS, we used the original Berlin definition in patients ventilated with PEEP, and the adjusted definition in patients under HFNO. In the HFNO group, the minimum level of 5 cmH_2O PEEP was ignored and replaced by a minimum level of 30L/min air flow. For mortality risk assessments, we created tertiles of PaO_2/FiO_2 in patients under HFNO, and we used the PaO_2/FiO_2 cutoffs as proposed in the Berlin definition in patients under invasive ventilation to create different severity groups of patients. The primary outcome of this study was 28–day mortality. Secondary outcomes included epidemiological characteristics, and ICU– and hospital–mortality. We hypothesized that both severity categorizations would result in comparable groups with regard to baseline characteristics and outcomes.

Chapter 3 contains the results of an international multicenter observational study. In this study, we RALE–scored 350 CXRs in 139 invasive ventilated COVID–19 ARDS patients. We scored only CXRs that were obtained within the first 48 hours after start of invasive ventilation. First, we determined the prognostic capacity of the RALE score

of the first available CXRs that was obtained under invasive ventilation for COVID–19 ARDS. In a second analysis, we determined the prognostic capacity of changes in the RALE score over the first 14 days after initiation of invasive ventilation. The primary endpoint of both analyses was mortality at day 90. One secondary endpoint was the number of days free from the ventilator and alive at day 28 (VFD–28). We hypothesized that the RALE score has prognostic capacity in patients with COVID–19 ARDS.

In **Chapter 4** we report the results of a national multicenter observational study. In this study, we compared CXR with lung CT scans in 82 invasive ventilated patients with COVID–19-related ARDS. The aim of this study was to investigate if the RALE score and the CT severity score have comparable prognostic value and correlate well in critically COVID–19 ARDS patients. The primary outcome was ICU mortality; secondary outcomes were duration of ventilation in survivors, length of stay in ICU, and hospital–, 28–, and 90–day mortality. We hypothesized that the RALE score and the CT severity score have comparable prognostic value, and that they correlate well in critically COVID–19 ARDS patients.

In **Chapter 5** we present the findings of a single center observational retrospective study in critically ill invasive ventilated COVID–19 ARDS patients. This retrospective analysis used the data of 82 patients with COVID–19-related ARDS who underwent chest CT at a low level of PEEP and at PEEP of 20 cm H_2O after a recruitment maneuver. The aim of this study was to investigate the potential to reaerate lung tissue in COVID–19 ARDS patients. The primary outcome was the percentage of reaerated nonaerated lung tissue at high PEEP after a recruitment maneuver. Secondary endpoints included the end–expiratory lung volume, the total lung volume, the weight of nonaerated lung tissue, and the change in hyper inflated lung tissue. We hypothesized that patients with COVID–19 ARDS have lung consolidations that can be reaerated.

Chapter 6 shows the results of an analysis of a multicenter, observational cohort study undertaken in 22 ICUs in the Netherlands, named the Practice of Ventilation in patients with COVID–19 (PRoVENT–COVID) study (38). This analysis included 933 invasive ventilated COVID–19 ARDS patients who were categorized retrospectively as having received invasive ventilation according to a higher or lower PEEP strategy. The aim of this study was to investigate whether a higher PEEP strategy is superior to a

lower PEEP strategy regarding the number of VFDs. The primary outcome was VFD–28. Secondary outcomes included acute kidney injury (AKI), use of renal replacement therapy (RRT) and mortality rates in the ICU, the hospital, at 28 and at 90 days. We hypothesized that a higher PEEP strategy would be superior to a lower PEEP strategy.

Chapter 7 contains the results of another analysis of the above–mentioned PRoVENT–COVID study. We used the data of 734 ICU patients who received prone positioning within the first four calendar days of invasive ventilation. The aim of this study was to investigate the incidence and practice of prone positioning in the first wave of the national outbreak in the Netherlands. The primary outcome was 28–day mortality. Secondary outcomes were 90–day mortality, and ICU– and hospital length of stay (LOS). We hypothesized prone positioning to be used often, and that its use has an association with outcome in invasively ventilated COVID-19 patients.

In **Chapter 8** we describe the rationale for a multicenter, observational cohort study undertaken in 16 ICUs in the Netherlands, named the Practice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019 (PRoAcT–COVID study). We planned to collect data of at least 1000 ICU patients with COVID–19 ARDS in the second wave of the national outbreak in the Netherlands, to investigate practice of adjunctive and supportive treatments, and their associations with outcome, in critically ill COVID–19 patients.

In **Chapter 9** we report one of the analyses of the PRoAcT–COVID study. Here we investigated the incidence, timing, frequency and duration of awake proning, and the association of awake proning with need for invasive ventilation and mortality. The primary endpoint of this analysis was a combination of the incidence, timing, frequency and duration of awake proning. Secondary endpoints included a composite endpoint of treatment failure, defined as intubation for invasive ventilation or death before day 28, length of stay (LOS) in ICU and hospital, and the mortality rates in the ICU and hospital at day 28, and 90. We hypothesized that there is substantial variation in use and practice of awake proning, and that its use has an association with outcome.

Chapter 10 summarizes the findings of the studies bundled in this thesis, and

Chapter 11 places the findings in a broader context.

Chapter 12 contains a summary in Dutch.

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