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COVID-19 disease: Acute respiratory distress syndrome and prone position

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Abstract
Patients who develop severe COVID-19 disease can develop respiratory failure and subsequently Acute Respiratory Distress Syndrome (ARDS). However, it has to be noted that these patients may not follow the typical ARDS disease trajectory. The causes of this paradox are complex and not yet fully understood, with the result that varying pathophysiological hypotheses have been proposed. This article describes ARDS in COVID-19 patients and the use of the conscious and unconscious prone position as an intervention to improve oxygenation.

Keywords ARDS; COVID-19; Critical care; Pandemic; Prone position; SARS-CoV-2

COVID-19 causes acute respiratory failure, with an estimated 10% of patients developing acute respiratory distress syndrome (ARDS) This is associated with a high mortality rate of approximately 30–40% despite advanced treatment. In consequence, the rapid increase in critical care need, resulted in many hospitals, regions and countries coming close to, or being overwhelmed, by the unprecedented number of patients. As knowledge and understanding of this new Coronavirus advances, effective treatment measures have been increasingly identified. One of these, prone positioning, was not commonly used in critical care units prior to the COVID-19 pandemic, but has revolutionised the treatment of both ventilated and non-ventilated patients. However, its re-introduction has confirmed that it should not be seen as a stand-alone measure. To be effective it needs to be a core component of a series of structured interventions. This article explores the use of the prone position in ARDS arising from COVID-19.

Respiratory failure
The COVID-19 disease progression may range from mild to severe. High numbers of hospitalised patients develop respiratory symptoms, with reported incidence of over 80% of patients needing oxygen therapy. Patients with increasingly severe COVID-19 symptoms may go on to develop acute respiratory failure and subsequently Acute Respiratory Distress Syndrome (ARDS). It has to be noted that these patients may not follow the typical ARDS disease trajectory. Within the literature, this has been described by the term ‘happy hypoxemia’ or ‘silent hypoxia’, when an individual has profound hypoxia caused by COVID-19, but does not have the proportional signs of respiratory distress. In consequence, there has been a suggestion that the term CARDs (COVID-19 with ARDS) should be used instead of the traditional ARDS definition. The causes of this paradox is complex and not yet fully understood, with the result that varying pathophysiological hypotheses have been proposed.

The phenotype theory hypothesis is that in severe COVID-19 disease, there is a systemic impact on the vascular endothelium, causing lung injury. Marini andGattinoni propose that in COVID-19, Type L and Type H phenotypes cause different variants of respiratory failure. Type L patients have a scattered ground glass appearance on chest X-ray, with good lung compliance and tend not to be Positive End Expiratory Pressure (PEEP) responsive. Contrastingly, individuals with Type H respiratory failure have extensive infiltrates with both atelectasis and oedema on chest X-ray, adding further complexity to the disease management. These patients have a lower lung

Key points

- COVID-19 can lead to respiratory failure and Acute Respiratory Distress Syndrome.
- The cause of ARDS in COVID-19 is complex and not completely understood.
- The high incidence of ARDS in COVID-19 patients has resulted in the use of the prone position being undertaken early because for both conscious and unconscious patients’ it can improve oxygenation.

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compliance and are PEEP responsive. However, Marini and Gattinoni\textsuperscript{13} describe the type L and H phenotypes as a continuum, with some stages and characteristics overlapping. They argue that during the early phases of respiratory failure, a complex process of pulmonary vascular dysregulation occurs, which instead of causing alveolar oedema, leading to hypoxemia, and a high minute volume ventilation, but they exhibit no signs of respiratory failure. As the pulmonary vascular dysregulation continues and extends, vasopedia causes the lungs to become increasingly unable to regulate perfusion and maintain adequate ventilation. This exacerbates hypoxemia, causes decreased space ventilation and hypercapnia, leading to ARDS.

Jain and Doyle\textsuperscript{12} dispute the above phenotype hypothesis and argue that the Type L phenotype relates to stage 2 or 3 of COVID-19 pneumonia. They propose a different pathophysiological process for the cause of severe hypoxia. They suggest that the SARS-CoV-2 enters the type II alveolar epithelial cells binding to the spike protein of the ACE-2 receptor. This in turn leads to downregulation of the alveolar epithelium, allowing for ACE-1 to have an unregulated effect on the pulmonary capillary endothelial cells. The level of protective ACE2-Ang-1-7-mas-R production is reduced, resulting in a harmful increase in the level of ACE 1_AngII-ATI-R. Vasoconstriction in the pulmonary epithelium is caused by endothelin-1. This causes a complex cascade effect, which results in endothelial nitric oxide being inhibited. The associated severe pulmonary vasocostriction is unevenly distributed within the lungs, as when the shunt fraction increases with the increasing hypoxia, the alveolar-capillary barrier is disrupted. The flooding of proteins, fibrin, cells and fluid into the alveolar space causes bilateral patchy group glass opacities noted on CT scan or Chest X-Ray. The development of pulmonary symptoms and rapid disease progression associated with COVID-19 may be linked to the ‘endothelial-epithelial’ interaction. Following alveolar-capillary membrane disruption, SARS-CoV-2 is able to enter the pulmonary capillary membrane via the pulmonary capillaries. The pulmonary endothelial cells become infected via the ACE-2 protein on the luminal surfaces, to assume a ‘proinflammatory/procoagulant’ phenotype. This accelerates apoptosis of alveolar epithelial and endothelial cells and causes a cytokine storm.\textsuperscript{13}

The decision on when to intubate patients remains largely subjective and based on practitioner experience and the patient’s condition.\textsuperscript{14} Mohlenkamp et al.\textsuperscript{15} found that 5–15% of patients with COVID-19 require critical care and ventilatory support, with 17% patients developing ARDS.\textsuperscript{1} ARDS was first described in critically ill patients in 1967 by Ashbaugh et al.\textsuperscript{16} However, it was not until 1994 that the first clinical definition was agreed by the International American European Consensus Conference (AECC).\textsuperscript{17} The Berlin Definition aimed to classify the severity of ARDS and to publish treatments and ventilatory strategies depending on the degree of hypoxemia.\textsuperscript{18} ARDS is defined using the Berlin Criteria and is based on timing, imaging, evidence of oedema and oxygenation. ARDS is described as respiratory failure with an acute onset which affects both lungs and occurs within one week of either a clinical insult or deterioration in respiratory symptoms. Chest imaging reveals bilateral opacities not fully explained by effusions, lung collapse, and nodules. Respiratory failure not explained by cardiac failure and fluid overload and oxygenation can be categorised as:

- **Mild PaO2/FiO2 ≤39.9 kPa (≤300 mmHg) with PEEP or CPAP ≥5 cmH2O**
- **Moderate PaO2/FiO2 ≤26.6 kPa (≤200 mmHg) with PEEP ≥5 cmH2O**
- **Severe PaO2/FiO2 ≤13.3 kPa (≤100 mmHg) with PEEP ≥5 cmH2O**

Limitations with the current ARDS definition includes that severity can be assessed on a single blood gas without prior standardisation of ventilator settings including PEEP which may affect oxygenation. In consequence, it is recommended that ventilator settings are optimised using tidal volumes of 6 ml/kg of predicted body weight and a high PEEP level.\textsuperscript{22} Furthermore, the time from optimising ventilator settings and assessing PaO2/FiO2 is deemed more clinically relevant in ARDS classification when measured 24 h after ARDS onset.\textsuperscript{22}

ARDS is an acute inflammatory lung condition not a disease, with multi-factorial causes and no proven drug treatments. Therefore, ARDS is always caused by an underlying pulmonary or extra-pulmonary condition. Pulmonary ARDS occurs when there is a direct insult to the lung damaging the alveolar epithelium, while extra-pulmonary ARDS is caused by an indirect lung injury due to inflammatory mediators damaging the vascular endothelium.\textsuperscript{23,24} Pulmonary ARDS can be caused by bacterial, viral or fungal pneumonia, aspiration of gastric contents, inhalation contusion, pulmonary contusion, and pulmonary vasculitis or near drowning. Extra-pulmonary ARDS can be triggered by non-pulmonary sepsis, non-cardiogenic shock, pancreatitis, major trauma, multiple transfusion or transfusion-related acute lung injury, severe burns or drug overdose.\textsuperscript{25,26}

The majority of patients with COVID-19 who develop ARDS meet the Berlin Criteria.\textsuperscript{27} In patients who develop ARDS, management includes using lung protection strategies: low volume, low pressure ventilation. Initial ventilation strategies may include pressure controlled modes, with tidal volumes aimed at 6 ml/kg using predicted body weight and plateau airway pressure <30cmH2O. Initial ventilator settings may include a higher respiratory rate (20/min), with positive end expiratory pressure (PEEP). Early evidence suggests pressures may need to be lower than previously recommended.\textsuperscript{4} There needs to be pre-oxygenation of patients prior to any intervention e.g. suctioning to prevent prolonged periods of desaturation, and moderate hypoxemia with SpO2 targets of >90% and PaO2 of >8 kPa with permissible hypercapnia.

The use of nitric oxide or nebulised prostacyclin if using a wet circuit has been noted to improve vasodilatation and thus improve oxygenation and reducing airway pressures.\textsuperscript{4} PEEP may be used to recruit collapsed alveoli; however, high PEEP should be avoided. Recruitment manoeuvres are used to improve oxygenation by providing brief inspiratory flow cycles to maximum plateau pressure and inflating collapsed alveoli. Recruitment
manoeuvres tend to be used as a rescue therapy in severe refractory hypoxia or following accidental disconnection from the ventilator. The procedure remains controversial in routine care, as it provides a temporary increase in oxygenation which is not sustained, and therefore must only be performed by an experienced practitioner.

For patients who do not respond and become increasingly difficult to ventilate and oxygenate, the prone position may be considered. With Extra Corporeal Oxygenation Membrane (ECMO) services being limited in many settings during a pandemic, the prone position may be used as an alternative in an attempt to improve oxygenation and optimise lung compliance. Conservatory use of intravenous fluids and careful fluid balance monitoring, with the use of diuretics to remove excess fluid, should be considered provided it is not detrimental to other organs.

Considerations for resource limited environments

It is accepted that identifying and applying the internationally agreed ARDS definition in a resource limited setting may be difficult, due to limited availability of resources. In these situations, it may be appropriate to use the Kigali modified ARDS definition and criteria (Table 1). The main difference relates to assessment of deteriorating respiratory deterioration, using the SpO2/FiO2 calculation.

Prone position

The prone position involves repositioning the patient from the supine position onto their abdomen. It redistributes perfusion and improves ventilation/perfusion (VQ) matching, through maximising dorsal ventilation. This results in recruitment of the posterior lung segments reverse atelectasis and improved secretion clearance. The prone position was first described in the literature in 1974, as a way to improve oxygenation. Since that date, research has consistently shown that oxygenation can be improved in ventilated patients with ARDS by turning them into the prone position. However, more recent studies have shown that prone position improves mortality in moderate to severe ARDS if undertaken early. The position needs to be maintained for 16–18 h or more while using protective lung strategies. This is a change from traditional practice, in which the prone position was solely used for ventilated patients, however, more recently, experience has shown a beneficial response to prone position by COVID-19 patients not yet requiring invasive ventilation. Early recommendations are that proning patient on admission to ICU during the early phase of their disease may be beneficial and avoid more aggressive ventilation strategies. It can be used irrespective of the PF ratio. Both conscious and unconscious prone position methods are described here.

Conscious prone position

For conscious patients with suspected or confirmed COVID-19 requiring oxygen of >28% or basic respiratory support to achieve SaO2 92–96% (88–92% if high risk of hypercapnia respiratory failure), they may gain benefit from the conscious prone position. If tolerated, this position can improve oxygenation, reducing the need for non-invasive ventilation (NIV). It has been found that it can delay and/or avert the need for intubation and mechanical ventilation. The current pandemic has also revealed that this is a simple and safe intervention that is suitable for use on general wards.

If there is an improvement in SaO2 92–96% (88–92% if risk of hypercapnic respiratory failure) and no obvious distress, the prone position should continue, with a view of changing the patients position every 1–2 h or longer if possible. When not in the prone position, the patient should be nursed in a 30–60° upright position. Vital signs including oxygen saturations and early warning scores should be monitored after every position change and oxygen titrated accordingly. If tolerated, continued timed position changes can be used. A proposed regimen includes 30 min to 2 h in the following positions: lying fully prone with the bed flat; lying on their right side with the bed flat; sitting upright 30–60°; lying on left side with the bed flat; prone position again and then repeated. The position should be discontinued if there is no improvement, if the patient is unable to tolerate the position, if the respiratory rate is ≥ 35 or there is evidence of tiring and/or the use of accessory muscles. If appropriate, the patient should be reviewed by critical care and assessment made regarding transfer into critical care.

Absolute contraindications include respiratory distress (RR ≥ 35, PaCO2 ≥ 6.5, and/or accessory muscle use), the

### Similarities and differences between Kigali modified ARDS Definition and Berlin Definition of ARDS.

| Kigali modified ARDS definition | Berlin Definition of ARDS |
|--------------------------------|--------------------------|
| Acute onset affecting both lungs occurring within one week of: | Acute onset affecting both lungs occurring within one week of: |
| - Clinical insult #Deterioration in respiratory symptoms | - Clinical insult |
| | - Deterioration in respiratory symptoms |
| Chest X-ray or ultrasound showing: | Chest imaging showing: |
| - Bilateral opacities not fully explained by effusions, | - Bilateral opacities not fully explained by effusions, |
| - Lobär lung collapse | - Lung collapse |
| - Nodules. | - Nodules. |
| Respiratory failure not fully explained by cardiac failure or fluid overload | Respiratory failure not explained by cardiac failure and fluid overload |
| SpO2/FiO2 < 315 | Mild PaO2/FiO2 ≤ 39.9 kPa (≤ 300 mmHg) with PEEP or CPAP ≥ 5cmH2O |
| No Positive End Expiratory Pressure (PEEP) requirement | Moderate PaO2/FiO2 ≤ 26.6 kPa (≤ 200 mmHg) with PEEP ≥ 5cmH2O |
| | Severe PaO2/FiO2 ≤ 13.3 kPa (≤ 100 mmHg) with PEEP ≥ 5cm20 |

Table 1
immediate need for intubation, haemodynamic instability (systolic blood pressure < 90 mmHg) or arrhythmia, agitation or altered mental status, unstable spine/thoracic injury/recent abdominal surgery. Relative contraindications include facial injuries, neurological issues, morbid obesity, pregnancy (2nd/3rd trimesters) and pressure sores/ulcers.28

To turn a conscious patient into the prone position, it is important to explain the importance of the procedure to the patient, to provide reassurance, to improve oxygenation and reduce their chance of requiring invasive ventilation. Patients should be encouraged to remain in the prone position for as long as possible, ideally up to 18 h per 24 h. Patients must be assisted into and out of the prone position, and patients should not do this without assistance in case their oxygen levels drop during the turn. There are two ways the patient can position themselves in the prone position either from a sitting or lying position.

**Prone position (unconscious)**

During the pandemic, the increasing numbers of patients requiring prone positioning has led to the establishment of ‘proning teams’. Led by an Anaesthetist (or suitably trained advanced airway provider) the team is pre-trained and when necessary are able to turn a patient into the prone or supine position. Local and national guidelines and checklists are being developed to guide and support these teams.4

Careful monitoring of patients is essential as there is some evidence that the prone position has been associated with a higher incidence of adverse effects than identified in patients placed in the supine position.37 Potential complications include airway obstruction from a kinked or displaced ETT. Once in the prone position, frequent oral suctioning and mouth care is required as secretions may reduce the integrity of ETT securing devices. In addition, proning can lead to facial swelling causing retinal nerve compression, ETT ties becoming too tight and pressure ulcers. Electrodes for cardiac monitoring need to be applied posteriorly on the patient’s back and in the event of cardiac arrest, the anterior/posterior placement of defibrillator pads/paddles should be used.37 Enteral feeding can continue in the prone position; however, the procedure is high risk for vomiting and/or increased gastric residual vomiting. Absolute contraindications for prone position include spinal instability, unstable fractures, burns, open wounds, pregnancy, and recent tracheal surgery and raised intracranial pressure. Relative contraindications include haemodynamic instability (including the use of vasopressors), cardiac pacemakers and abdominal surgery.37

Neuromuscular blocking agents may be required to maintain gaseous exchange. This reduces extrapulmonary resistance and ventilatory desynchrony which in turn results in improved oxygenation. Paralysis of the diaphragm allows for metabolic rest, reduced oxygen consumption and invasive control of breathing mechanic.36 Neuromuscular blockage may be required in patients with ARDS as this allows for less PEEP to maintain oxygenation, and reduces mortality.

Once turned into the prone position, patients may remain in this position for 12–16 h per day. In addition, patients may need to be placed into this position several times. Patients in the prone position should be nursed on a pressure relieving mattress to reduce pressure damage and, periodically, it will be necessary to change the position of the head and arms every 2–4 h. To maintain the prone position, ventilated patients must be adequately sedated with the use of neuromuscular blockade.37

It is important to note that critically ill patients are at high risk of developing malnutrition and sarcopenia. Therefore, it is accepted practice that early enteral feeding should be established unless contraindicated. The enteral route is preferred over the parental route (e.g. Total Parental Nutrition (TPN)). However, there is an increased risk of gastric aspiration during repositioning, therefore interruptions in the enteral feeding regimens have to occur when positioning a patient from supine to prone and vice-versa. Enteral feeding should be resumed once the patient has been re-positioned, NG tube position confirmed and vital signs recorded.

Research into the impact of prone position on tolerance and gastrointestinal complications is still ongoing. De la Fuente et al.’s small scale study of enteral feeding tolerance in ventilated proned patients concluded that enteral feeding did not increase the risk of gastrointestinal problems. In contrast, Malhotra et al.37 found patients in the prone position developed a higher incidence of vomiting and/or increased gastric residual volumes. As a result of their findings, Malhotra et al.37 recommend patients’ heads should be elevated at least 25° while receiving enteral feeding and that prokinetic drugs such as erythromycin may be appropriate.

**Conclusion**

Nurses need understanding of the complex pathophysiological processes that arise from COVID-19 infection. However, as this article has indicated, the pathophysiology associated with the development COVID-19 related ARDS is still being investigated. Nevertheless, the high incidence of ARDS in COVID-19 patients has resulted in recognition that use of the prone position undertaken early, for both conscious and unconscious patients, can improve oxygenation. It has been identified as an intervention that for some patients may reduce or avoid the need for invasive ventilation. Nevertheless, it has to be accepted that it poses potential risks and complications. Protocols, guidelines and training are essential to minimize the risk of adverse events during or after prone positioning. The COVID-19 pandemic is relatively new therefore further research is needed before definitive guidelines and recommendations can be made.

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