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Prone positioning in COVID-19 acute respiratory failure: just do it?

Bairbre McNicholas[1,2], David Cosgrave[1,2], Camilla Giacomini[1], Aoife Brennan[1,2] and John G. Laffey[1,2,3,*]

[1]Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Galway, Ireland, [2]Anaesthesia and Intensive Care Medicine, School of Medicine, National Unversity of Ireland, Galway, Ireland and [3]Regenerative Medicine Institute at the CURAM Centre for Medical Devices, National University of Ireland, Galway, Ireland

*Corresponding author. E-mail: john.laffey@nuigalway.ie

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The coronavirus disease 2019 (COVID-19) outbreak is a pandemic respiratory infection that can worsen rapidly into severe hypoxaemic respiratory failure and acute respiratory distress syndrome (ARDS) in some patients. To date, there are no specific pharmacological therapies for COVID-19-induced respiratory failure, although several are undergoing clinical trials. Of particular concern is the high mortality rate in patients with severe respiratory failure requiring invasive mechanical ventilation, ranging from 40% to 80% in different reports. Accordingly, significant efforts are being made to support patient respiratory function and avoid the need for invasive mechanical ventilation.

Prone positioning constitutes an important part of the management of confirmed moderate-to-severe ARDS receiving invasive mechanical ventilation. In these patients, prone positioning promotes lung homogeneity and improves gas exchange and respiratory mechanics, permitting the reduction of ventilation intensity and reducing lung injury. Prone positioning saves lives in confirmed moderate-to-severe ARDS, and is recommended in evidence-based guidelines for the management of these patients.[1]

With the advent of the COVID-19 pandemic, interest has grown regarding the potential for awake prone positioning of patients to improve gas exchange and reduce the need for more invasive respiratory support. Anecdotal and case series reports of improved oxygenation after self-prone positioning have received significant favourable media attention.[2,3] Consequently, awake prone positioning use is increasingly reported outside the ICU setting even in patients receiving noninvasive ventilation.[4] However, use of proning in awake self-ventilating patients to improve oxygenation has not been formally studied outside of case series. Furthermore, simply improving oxygenation may not alter more clinically meaningful outcomes, such as the need for invasive mechanical ventilation. In addition, a recent case series of awake proning found oxygenation improved in only 25% of patients and that it was non-sustained in half after resupination.[5] Despite this, awake proning has been included in guidelines for the management of COVID-19 pneumonia treatment protocols by institutions, such as the UK Intensive Care Society, the Brigham and Women's Hospital (Boston, MA, USA), and others.[6,7]

Some clinicians have adopted the approach that awake proning is a simple low-risk intervention and should simply be implemented without further study. This approach mirrors the 'compassionate' use of antiviral and immunosuppressive therapies also being advocated for COVID-19 severe respiratory failure. However, extrapolations from the known benefits in moderate-to-severe ARDS[1] to awake COVID-19 patients are undermined by the lack of efficacy of prone positioning in mild-to-moderate ARDS.[8] Given this, it is important to carefully consider whether this 'just do it' approach is justified.

Physiological effects of awake proning

The original description of prone positioning in 1977 described improvement in arterial oxygenation after prone positioning of both awake and mechanically ventilated patients.[9] The physiological mechanisms by which prone positioning improves oxygenation in moderate-to-severe ARDS patients receiving invasive mechanical ventilation are well understood, and include decreasing ventilation/perfusion heterogeneity; decreasing pleural pressure; and increasing regional ventilation in dependent lung regions near the diaphragm, reduced airway closure in dorsal lung regions attributable to a more uniform gravitational pleural pressure gradient, better secretions removal, increases in functional residual capacity, changes in regional diaphragm motion, and redistribution of blood flow.[10–12]

The physiological effects of awake prone positioning in patients with acute respiratory failure are not well understood. However, studies in awake healthy volunteers[10,13–15] and in volunteers under hypergravity conditions (to increase capillary hydrostatic pressure)[16,17] suggest that prone positioning can exert favourable physiological effects. Overall, lung volume increases in the prone position, being 17% greater in the prone position compared with the supine in one study.[14] Gravitational gradients in perfusion and ventilation of lung parenchyma are reduced in the prone *vs* supine position.[14,15] Some studies have found an increase in global perfusion in the prone position[15] and a more homogeneous distribution of perfusion,[18] but other reports have found no changes in perfusion in the prone position.[14,19] In a volunteer study using functional lung imaging with proton MRI to assess regional ventilation, prone positioning was associated with a reduction in regional transpulmonary pressure gradients and reduced regional ventilation/perfusion heterogeneity, largely because of more homogeneous ventilation attributable to an increased functional residual capacity and a reduced gravitational gradient of ventilation.[14]

Gravity and compression from mediastinal and abdominal organs contribute to changes in perfusion and ventilation of lung tissue going from supine to prone in healthy volunteers.[19,20] Methodological advances in MRI studies have allowed insights into postural changes in pulmonary blood flow and the effect of the heart on lung perfusion in response to proning.[13,14,21] In the prone position, the heart 'falls' anteriorly and away from the lung and the left lower pulmonary vein.[13,21] A higher functional residual capacity contributes to a more favourable venous return to the heart,[14] which might explain the improvement in haemodynamic parameters noted in patients in the prone position.

However, extrapolating findings from proned healthy volunteers to hypoxaemic patients who are undergoing awake proning should be done with caution. Differences in lung physiology in health may not mirror that in illness. Other factors, including the effect of respiratory muscles, factor into the effect of prone positioning in awake *vs* mechanically ventilated patients.[22] In spontaneously breathing subjects, the diaphragm displaces the dorsal (dependent) portion of the lung, resulting in a favourable position for dependent alveolar units along their pressure/volume curves with greater ventilation in the dependent lung matched by an increase in chest wall stiffness.[23–25]

Equipoise for trials of awake proning

There is some evidence from other patient populations supporting awake proning. Before the COVID-19 epidemic, clinical descriptions of awake proning were limited to case reports or neonatal studies.[26,27] In a randomised controlled study of neonates with bronchiolitis undergoing nasal continuous positive airway pressure treatment, prone positioning decreased inspiratory effort estimated by the oesophageal pressure swing and the metabolic cost of breathing estimated by the oesophagus pressure time product.[28] Prone positioning has been used as a rescue manoeuvre to prevent intubation or in

subjects with ceilings of care of noninvasive ventilation.[3,26,27,29] More recently, in a study of COVID-19 patients presenting to an emergency department in New York City, consecutive patients with hypoxaemia were placed in the prone position with 13/50 going on to require tracheal intubation.[2] Unfortunately, the study did not report on the total number of patients screened or on the number of patients not offered prone positioning.[2]

Given emerging data suggesting that awake proning improves oxygenation and the apparent low risk of awake proning, some clinicians question whether there is equipoise for a clinical trial. Some suggest that there is a lack of equipoise, and therefore, clinical studies should not be done, and even that it would be unethical to 'withhold' such a strategy, if it could be of help.

We caution against this line of argument. The data supporting awake proning are quite limited and confined to isolated uncontrolled case series that report interim outcomes. We suggest that not using an unproven therapy can never be unethical. In fact, implementing awake proning protocols is not without cost or risk. Awake proning requires close input from nursing staff, physiotherapy, and occupational therapy to ensure it is successful, especially during the initial proning sessions. Patients need greater reassurance, support, and feedback to tolerate the position. The effort of awake proning can even destabilise sicker patients, causing desaturation and increased work of breathing. Management of the conscious but rapidly deteriorating patient in the prone position can be extremely difficult at the ward level.

One underlying assumption in arguments to implement awake proning programmes is that a therapy that provides short-term benefit will improve patient outcome. However, there are examples of therapies, such as inhaled nitric oxide, that improve oxygenation in patients with ARDS, but do not improve patient outcomes.[30] In fact, by delaying invasive mechanical ventilation, awake proning could even worsen outcomes by allowing patients to cause self-inflicted lung injury, as has been shown with noninvasive ventilation.[31,32] The fact that respiratory effort and mechanics are less accurately measured and uncontrolled during noninvasive ventilation may increase the risk in awake prone positioning. Unfortunately, there are multiple examples of interventions that appeared physiologically sound and relatively low in risk that subsequently turned out to be harmful in the critically ill. Rapidly normalising blood pressure in trauma victims reduces survival,[33] whilst maintaining a higher haemoglobin in the critically ill causes harm.[34] An apparently sound physiological rationale is therefore an insufficient basis in itself to implement a therapy into clinical practice.

Clinical research in a pandemic: challenges and solutions

Clinical research, whilst always challenging, is particularly difficult during a pandemic. Increased clinical workloads attributable to high numbers of patients, expanded ICU capacity, staff fatigue and burnout, fears regarding infection transmission to staff members, and challenges in maintaining standards of clinical care are just some of the issues that make research seem less relevant during a pandemic. The concern is expressed that waiting for the results of an RCT in this context will delay the implementation of effective therapies.

These practical difficulties do not negate the need to find out whether awake proning of patients with COVID-19 acute respiratory failure is beneficial, ineffective, or harmful. Given these challenges, a pragmatic approach to developing the evidence base is needed. Establishing an international registry to record data and outcomes of awake proning patients while designing and performing RCTs in the centres who have the capacity/expertise to do them could be an effective and pragmatic 'twin-track' approach. Designing complementary RCTs of awake proning in different countries will enable the data generated to be combined, further expediting the research process. Several research groups across Europe and North America are doing just this, designing their studies to enable a meta-study to be conducted. In Ireland, the study is called the Awake Prone Positioning to Reduce Invasive Ventilation in COVID-19 Induced Acute Respiratory Failure trial (NCT04347941). Each study will examine the potential for awake proning to reduce the need for invasive mechanical ventilation, whilst the studies in combination will have sufficient power to examine the effect of awake proning on mortality. This international collaborative approach is expected to recruit a large number of patients rapidly, but without the increased administrative burden associated with starting a new international multicentre trial.

Conclusions

There is low-quality evidence that awake prone positioning in COVID-19 hypoxaemic respiratory failure might improve oxygenation based on case reports and case series. However, evidence for effect on longer-term outcomes and hard endpoints, such as rates of intubation and mortality, is lacking. History has shown that changing practice based on surrogate endpoints and case series data does not necessarily improve patient outcomes. The need to identify and test therapeutic strategies for COVID-19-induced severe respiratory failure can be met by rapid implementation of clinical trials and the expedited publication of their findings rather than a rush to implement unproven therapies. We suggest that a 'meta-trial' of ongoing international randomised clinical trials of awake proning can quickly determine whether this intervention can improve outcomes for COVID-19 patients.

Authors' contributions

Writing first draft of the paper and revisions: BM, JGL.
Revision of paper for important intellectual content: DC, CG, AB.

Declarations of Interest

The authors declare that they have no conflicts of interest.

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