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RESEARCH ARTICLE

Awake Prone Positioning for Acute Hypoxaemic Respiratory Failure in COVID-19

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ABSTRACT

Prone positioning has been demonstrated to significantly reduce mortality in invasively ventilated patients with moderate to severe acute respiratory distress syndrome through several physiological mechanisms, including optimization of ventilation and perfusion and a reduction in ventilator-associated lung injury. The marked increase of hospitalisation rates of patients with acute hypoxaemic respiratory failure during the COVID-19 pandemic, and associated strain on healthcare resources, led to interest in the use of prone positioning in conscious self-ventilating, or "awake", patients, as an adjunct to the provision of oxygen therapy and respiratory support. The adoption of this technique was with the intent of reducing the likelihood of progressive respiratory failure and thus the need for invasive mechanical ventilation. In this review we summarize the background, physiological mechanisms and current evidence for the use of awake prone positioning in both COVID-19 related hypoxaemic respiratory failure and that attributed to other aetiologies. Whilst several studies note an improvement in respiratory parameters including oxygenation, the effect on clinically important outcomes such as rates of intubation and mortality remain unclear. The evidence base beyond COVID-19 related respiratory failure remains constrained and there is a paucity of evidence to help identify those most likely to benefit from this therapy. There remains no agreed consensus on how to implement awake prone positioning and significant variation exists in practice. Several clinical questions should be the focus for future research studies of this treatment modality including how to identify early responders and non-responders to therapy.

INTRODUCTION

Prone positioning has been demonstrated to significantly improve oxygenation and reduce mortality in invasively ventilated patients with moderate to severe acute respiratory distress syndrome (ARDS), and is strongly advocated by international guidelines. Several meta-analyses support its efficacy, particularly when the duration prone exceeds 12 hours per day and is accompanied by lung protective ventilation strategies [1–4]. The COVID-19 pandemic beginning in early 2020, led to a marked increase in hospitalisation rates of patients with acute hypoxaemic respiratory failure. This caused substantial strain on healthcare resources, and demand for critical care services was especially high. Treatments that might reduce the likelihood of worsening respiratory failure and thus the need for invasive mechanical ventilation were, therefore, of particular interest. In addition, the inherent risk of mechanical ventilation, such as ventilator associated pneumonia and the need for adjunctive sedative and neuromuscular blocking agents with their own complications, prompts the need to consider whether techniques can mean this can be avoided or its duration reduced.

The use of "awake" prone positioning (APP) in conscious, self-ventilating patients, in conjunction with oxygen therapy and non-invasive modes of respiratory support, requires few resources and thus garnered significant interest as a modality that could be implemented in environments where such are limited [5]. Its use was recommended by the Intensive Care Society in the United Kingdom for use in COVID-19 as early as April 2020, despite a lack of high-quality evidence of efficacy [6]. There has since been significant interest in this treatment and a large body of evidence has been gathered into its use during the COVID-19 pandemic.

PHYSIOLOGICAL MECHANISMS

There are several mechanisms by which prone positioning improves gas exchange and therefore oxygenation (figure 1). The heart and abdominal contents compress the lung when supine, with the diaphragm being displaced cranially. When prone, it shifts caudally and the heart lies adjacent to the sternum, improving ventilation and therefore oxygenation. On adopting a supine position there is significant ventilation-perfusion mismatch as perfusion of alveolar units is greatest in the dorsal lung where ventilation is impeded by factors including the weight of the lung itself. Transitioning to a prone position improves ventilation to the dorsal lung and leads it to become more homogenous throughout the lung [7]. As pulmonary perfusion is relatively constant and unchanged by positioning the matching of ventilation and perfusion is thus more effective and intra-pulmonary shunting is reduced [8]. Given the significant alveolar volume in the dorsal lung prone positioning also promotes recruitment of alveolar units, increasing end-expiratory lung volume, preventing atelectasis and increasing the overall surface area for gas exchange [9].

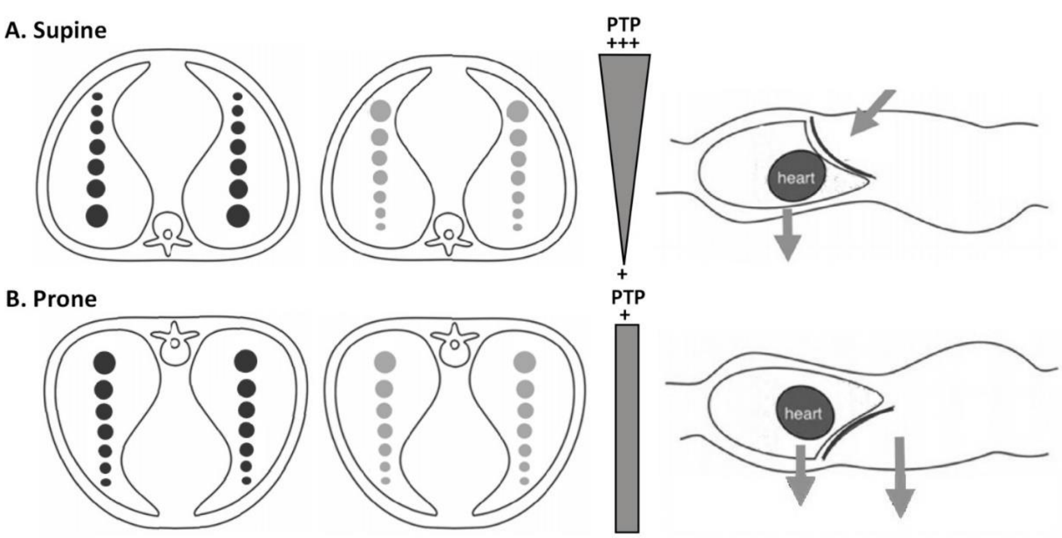

Figure 1: Shown in the figure are axial (left) and sagittal views (right) of the thoracic cage representing the physiological changes achieved by supine (A) and prone (B) positioning. Perfusion of the lung represented by the black circles (●) is greatest in the dorsal regions of the lung regardless of position. Ventilation represented by grey circles (●) is position dependent and improved in the dorsal regions by prone positioning. Distention of the lung is determined by the transpulmonary pressure gradient (PTP) and is more homogeneously distributed in the prone than supine position, avoiding over distension of ventral alveoli and atelectasis and collapse of dorsal alveoli. The sagittal views show how the prone position avoids the movement of intrathoracic and intraabdominal organs impeding ventilation.

One key factor in the development and perpetuation of ARDS is the effect of swings in the transpulmonary pressure, this being the difference between airway and pleural pressure. This phenomenon is exaggerated in ARDS, in part because there is increased lung weight due to oedema and inflammation. Whilst the concept of ventilator-associated lung injury is well recognized in the mechanically ventilated patient, in those spontaneously breathing it is likely similar pathophysiological mechanisms apply, and can be termed patient-associated lung injury. Thus, an awake patient with a high respiratory drive and forceful inspiratory effort will have exaggerated swings in transpulmonary pressure, leading to both shear and strain forces which themselves perpetuate the underlying lung injury. Any therapy which reduces these forces will assist in preventing progression of the ARDS, and whilst this is achieved in mechanically ventilated patients by applying lung protective ventilation strategies and prone positioning, similar effects can be hypothesised in those spontaneously breathing by reducing their respiratory drive and work of breathing [10].

When supine, the pleural pressure is greater in the dorsal aspect of the lung, compared to the ventral aspect. This leads to the transpulmonary pressure being higher ventrally, causing regional hyperinflation of the alveoli. When prone, the transpulmonary pressure gradient is reduced, and this in part reduces the lung injury and improves outcomes. The use of prone positioning alongside supportive treatment strategies such as continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) additionally provides an alternative to increasing either the positive end-expiratory pressure or pressure support, which may be both poorly tolerated in conscious patients and lead to barotrauma.

HISTORY

The first description in the published literature of the value of the prone position in a ventilated patient was made in 1974, stimulating interest in this as a treatment modality [11]. The first published study of conscious prone positioning from 1977 reported on 6 patients, showing improved oxygenation parameters when moving from a supine to prone position [12]. However, there remained little published literature prior to the COVID-19 pandemic, with only a handful of small, non-randomised observational studies of patients with varying aetiologies leading to hypoxaemic respiratory failure [13–15]. The largest of these was a retrospective observational review of 15 patients with hypoxaemic respiratory failure over a period of 5 years and yet only included 43 distinct episodes prone, although did show a beneficial effect on oxygenation [15]. APP was for the large part tolerated in self ventilating patients, with only a small number of patients unable to complete their prescribed periods during the study due to discomfort.

Prior to the pandemic there had been a paucity of studies investigating the use of APP in conjunction with other modes of respiratory support. One research paper looked at 20 patients with moderate to severe ARDS using APP alongside hi-flow nasal cannula (HFNC) or NIV [16]. An improvement in oxygenation was demonstrated in this prospective observational cohort study, however, this small study was insufficient to conclude that APP could reduce the rates of mechanical ventilation, although the periods prone were short in duration. As a note of caution, 78% of those with severe ARDS eventually required invasive mechanical ventilation, and a small number of patients went on to receive extra-corporeal membrane oxygenation, raising the possibility that in a cohort of severe ARDS patients APP may delay necessary intubation and may not be beneficial.

IMPACT OF THE COVID-19 PANDEMIC

As the international community wrestled with the challenges of dealing with COVID-19 associated ARDS there was a sharp rise in the publication of observational studies as clinicians and researchers sought to share learning. Several observational studies showed an improvement in parameters of oxygenation with APP [17–20]. Despite consistency in the signal on parameters of oxygenation, meta-analyses have shown varying signals in whether APP translates to reduced rates of endotracheal intubation and mortality. Some meta-analyses have shown no effect on intubation [21–23] or mortality rates [23,24], whilst others have demonstrated a lower rate of progression to intubation and ventilation [24] or improved survival [21,22]. Thus, changes in oxygenation may not always translate to tangible clinical benefits and caution should be expressed in reaching premature conclusions in the absence of robust clinical evidence.

The pandemic did call for novel ways or working and in a bid to expedite the delivery of results and boost effect size, one large collaboration joined to form a meta-trial, consisting of a prospective meta-analysis of six randomised control trials from sites in Europe and North America [25]. This studied APP alongside HFNC versus usual care of HFNC alone, for patients with hypoxaemic respiratory failure due to COVID-19. It remains the largest trial of APP enrolling over a thousand patients. The primary outcome was selected as treatment failure at 28 days using a composite outcome of intubation and death, which was substantially reduced in the group randomised to APP. The secondary outcomes demonstrated a reduced need for intubation with APP and no clinical signal of harm was found, however, the meta-trial was unable to demonstrate any effect on overall mortality.

Many studies have reported the use of APP alongside other advanced modes of respiratory support and one meta-analysis of 10 randomised controlled trials showed the use of APP alongside NIV or NHFC reduced the need for intubation, an effect not seen in those receiving conventional oxygen therapy alone [26]. This systematic review also demonstrated a significant difference dependent on the place of care, with a beneficial effect on intubation rates only seen within a critical care environment and not when care was provided outside of this area. Whilst the cause of this finding remains unclear it raises an important signal about the monitoring and staffing outside of critical care and the ability to respond to deteriorating patients, although the underlying severity of illness is likely to be a significant confounding factor.

With the need to expedite learning during an active pandemic much of the published research has been observational in nature, raising questions about the inherent bias [27]. Even randomised controlled trials on this subject have often used methods such as cluster randomization which are noted to have significant drawbacks [28]. Thus although the wealth of clinical data arising on APP during the pandemic was much needed, reaching firm conclusions can be challenging with the quality of studies published.

Since the publication of meta-analyses looking at data from patient cohorts in 2020-21 further randomised controlled trials have been published, and this field is one in which the relevance remains high given further surges of COVID-19 and its likely applicability to other causes of hypoxaemic respiratory failure [29,30]. The effect of APP on clinically significant outcomes such as rates of endotracheal intubation and mortality remains unclear, however, given the dynamic nature of this field it is likely that newly published data would contribute significantly to future meta-analyses.

FACTORS ASSOCIATED WITH SUCCESS

One of the key factors influencing success in the use of prone positioning in mechanically ventilated patients is the need for prolonged periods to be spent prone. The landmark PROSEVA study randomised patients to at least 16 hours prone a day and showed a significant mortality benefit when applied early in severe ARDS which had failed to be demonstrated in prior trials implementing shorter periods [31]. In a similar vein, its use in conscious patients has been shown to be more successful when conducted for periods of at least 8 hours [25,32,33]. However, whether a defined dose-response relationship exists has yet to be clarified [22]. Further data has suggested that early adoption of APP in the disease process is also associated with improved outcomes, in particular when introduced within 24 hours of hospital admission [34].

It has been hypothesised that due to more favorable staffing ratios in critical care environments patients are able to prone for longer periods due to the active encouragement to do so. However, a meta-analysis has clearly demonstrated that even within critical care the period of APP can vary widely from 1-2 hours to 8-10 hours in a 24 hour period [26]. Thus this cannot be taken for granted and there remains a need for active education of both staff and patients of its potential benefits to increase the duration spent prone.

Considering the mechanisms by which APP is thought to reduce patient-induced lung injury, factors which suggest the perpetuation of large swings in transpulmonary pressure have been dampened are also associated with its success. The PRO-CARF trial demonstrated that a reduction in respiratory rate and an increased ROX index from baseline after the first session of APP ($\geq$1.25), indicating an improved composite marker of oxygenation and work of breathing, was significantly associated with intubation-free survival [33]. Further study is required of how changes in physiological state relate to both changes in oxygenation and long-term clinical outcomes, and whether such signals may help identify ‘responders’ to therapy at an early stage.

FUTURE RESEARCH QUESTIONS

The learning that occurred in refining the role of prone positioning in mechanically ventilated patients suggests that understanding the specifics of the intervention is key to maximizing benefit [2]. Whilst protocols for APP have been described the optimum conditions, period prone, timing of initiation, frequency, and which patients are most likely to benefit need to be further evaluated [35,36].

The threshold of hypoxaemic respiratory failure in COVID-19 at which prone positioning is beneficial in conscious patients has not been clearly defined, although it is currently advocated even in those requiring fairly low concentrations of inspired oxygen [6]. In conscious patients it is unlikely the majority will be able to tolerate periods seen to benefit the mechanically ventilated, where 12-16 hours/day has been shown to be beneficial. Some patient cohorts are also likely underrepresented in the current body of evidence such as those with obesity, pregnant women and those unable to adopt a prone position independently, such as those with significant frailty.

At present there is disparity between the improvements in oxygenation seen in APP and lack of clarity over whether this leads to improved clinical outcomes, such as reduced rate of progression to invasive mechanical ventilation and mortality. Some of this signal may be lost by the heterogeneity of published studies, with some opting for APP as an early adjunctive strategy and some choosing it as a late rescue therapy. Different centres will also have variable thresholds for intubation depending on their clinical experience and resources. To answer some of the questions about clinical outcomes will require large, multicenter, randomised controlled trials appropriately powered to look at these endpoints. The PRONELIFE trial being rolled out in 35 intensive care units worldwide is powered for a primary endpoint of a composite of tracheal intubation and mortality within 14 days of enrolment and may contribute to the body of research in this area [37]. Whilst the majority of the clinical data of APP now exists in the context of COVID-19 further studies are needed to look at this mode of therapy in other causes of hypoxaemic respiratory failure. The PRONELIFE trial should hopefully also provide data in these additional patients cohorts [37].

Given that some patients struggle to maintain a prone position for significant periods of time, there have been limited descriptions of an alternative semi- prone or lateral position [36]. Subgroup analysis from a single-center observational study found mortality was lower in those who were able to fully prone compared with those who failed or were only able to semi-prone [38]. Thus, although the benefits may be limited there remains interest in whether a posture approximating this may lead to clinical benefits.

It remains possible that in some subgroups conscious proning leads to adverse effects by delaying necessary intubation and mechanical ventilation and worsening patient-associated lung injury [16]. It is crucial to delineate which groups come with a higher risk and how they may be safely managed, or whether a therapeutic window exists after which either the duration or severity of hypoxaemia means APP no longer has an overall beneficial effect and should not be commenced. Physiological factors indicating an early response to prone positioning may help delineate who might be deemed a 'responder' over a 'non-responder' [33]. This should be a focus in future research as identifying those who lack adequate response and require escalation of therapy without delay is essential. There may be a role for bedside testing such as lung ultrasound to clarify this issue [33]. Whilst APP may require few resources it does require adequately trained staff to respond to signals of concern and the infrastructure to act upon this. The PROVID-19 protocol aims to look at the implementation of APP on general medical wards and will provide information on safety outside of a critical care setting [39].

Limited published data exists on the adverse effects, and some of this may be due to inherent bias in the published observational studies. Most suggest any adverse effects are infrequent and relatively minor, including discomfort and anxiety, and the serious adverse effects seen with unconscious, paralyzed patients are largely avoided. There are, however, currently no published studies looking at the rates of nosocomial pneumonia in this group and this warrants further study. Tolerance, however, is frequently noted as limiting adherence and studies to investigate how to improve this are welcomed. Innovative technologies such as the use of a mobile telephone app to give instructions on APP are in process and may have a future role [40].

CONCLUSION

There is evidence that APP improves oxygenation for patients with acute hypoxaemic respiratory failure secondary to COVID-19 but as yet this has not be shown to reliably correlate with reduced rates of mechanical ventilation or mortality. Aside from COVID-19 little data exists for this modality in other disease aetiologies. APP is a low-cost intervention that can therefore be employed outside of critical care units and used in conjunction with other modes of respiratory support where it may have an adjunctive effect. Much research is needed to clarify the groups most likely to be benefit and the details of how this intervention can be most effectively delivered.

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All authors provided approval of the final manuscript.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.

PATIENT CONSENT FOR PUBLICATION
Not required

REFERENCES

1. Park SY, Kim HJ, Yoo KH, et al. The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomised controlled trials. J Thorac Dis. 2015;7(3):356-367. doi:10.3978/j.issn.2072-1439.2014.12.49
2. Munshi L, del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2017;14(Supplement_4):S280-S288. doi:10.1513/AnnalsATS.201704-343OT
3. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019;9(1):69. doi:10.1186/s13613-019-0540-9
4. Fan E, del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST
5. Dueñas-Castell C, Borre-Naranjo D, Rodelo D, et al. Changes in Oxygenation and Clinical Outcomes with Awake Prone Positioning in Patients with Suspected COVID-19 In Low-Resource Settings: A Retrospective Cohort Study. J Intensive Care Med. 2021;36(11):1347-1353. doi:10.1177/08850666211049333
6. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. ICS Guidance for Prone Positioning of the Conscious COVID Patient 2020. Intensive Care Society. April 12, 2020. Accessed July 29, 2022. https://emcrit.org/wp-content/uploads/2020/04/2020-04-12-Guidance-for-conscious-proning.pdf.
7. Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med. 1994;150(1):184-193. doi:10.1164/ajrccm.150.1.8025748
8. Mure M, Domino KB, Lindahl SG, Hlastala MP, Altemeier WA, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. J Appl Physiol (1985). 2000;88(3):1076-1083. doi:10.1152/jappl.2000.88.3.1076
9. Gattinoni L, Taccone P, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. Am J Respir Crit Care Med. 2013;188(11):1286-1293. doi:10.1164/rccm.201308-1532CI
10. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med. 2017;195(4):438-442. doi:10.1164/rccm.201605-1081CP
11. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis. 1974;110(6 Pt 2):143-144. doi:10.1164/arrd.1974.110.6P2.143
12. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis. 1977;115(4):559-566. doi:10.1164/arrd.1977.115.4.559
13. Valter C, Christensen AM, Tollund C, Schønemann NK. Response to the prone position in spontaneously breathing patients with hypoxaemic respiratory failure. Acta Anaesthesiol Scand. 2003;47(4):416-418. doi:10.1034/j.1399-6576.2003.00088.x
14. Feltracco P, Serra E, Barbieri S, et al. Non-invasive ventilation in prone position for refractory hypoxaemia after bilateral lung

transplantation. Clin Transplant. 23(5):748-750. doi:10.1111/j.1399-0012.2009.01050.x

15. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxaemic acute respiratory failure: A retrospective study. J Crit Care. 2015;30(6):1390-1394. doi:10.1016/j.jcrc.2015.07.008
16. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020;24(1):28. doi:10.1186/s13054-020-2738-5
17. Weatherald J, Solverson K, Zuege DJ, Loroff N, Fiest KM, Parhar KKS. Awake prone positioning for COVID-19 hypoxaemic respiratory failure: A rapid review. J Crit Care. 2021;61:63-70. doi:10.1016/j.jcrc.2020.08.018
18. Ferrando C, Mellado-Artigas R, Gea A, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care. 2020;24(1):597. doi:10.1186/s13054-020-03314-6
19. Coppo A, Bellani G, Winterton D, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. The Lancet Respiratory Medicine. 2020;8(8):765-774. doi:10.1016/S2213-2600(20)30268-X
20. Ponnapa Reddy M, Subramaniam A, Afroz A, et al. Prone Positioning of Nonintubated Patients With Coronavirus Disease 2019-A Systematic Review and Meta-Analysis. Critical Care Medicine. 2021;49(10):e1001-e1014. doi:10.1097/CCM.0000000000005086
21. Chua EX, Zahir SMISM, Ng KT, et al. Effect of prone versus supine position in COVID-19 patients: A systematic review and meta-analysis. J Clin Anesth. 2021;74:110406. doi:10.1016/j.jclinane.2021.110406
22. Fazzini B, Page A, Pearse R, Puthucheary Z. Prone positioning for non-intubated spontaneously breathing patients with acute hypoxaemic respiratory failure: a systematic review and meta-analysis. Br J Anaesth. 2022;128(2):352-362. doi:10.1016/j.bja.2021.09.031
23. Pavlov I, He H, McNicholas B, et al. Awake Prone Positioning in Non-Intubated Patients With Acute Hypoxaemic Respiratory Failure Due to COVID-19. Respir Care. Published online July 7, 2021. doi:10.4187/respcare.09191
24. Schmid B, Griesel M, Fischer AL, et al. Awake Prone Positioning, High-Flow Nasal Oxygen and Non-Invasive Ventilation as Non-Invasive Respiratory Strategies in COVID-19 Acute Respiratory Failure: A Systematic Review and Meta-Analysis. J Clin Med. 2022;11(2). doi:10.3390/jcm11020391
25. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. The Lancet Respiratory Medicine. 2021;9(12):1387-1395. doi:10.1016/S2213-2600(21)00356-8
26. Li J, Luo J, Pavlov I, et al. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. Lancet Respir Med. 2022;10(6):573-583. doi:10.1016/S2213-2600(22)00043-1
27. Padrão EMH, Rahhal H, Valente FS, Besen BAMP. Methodological issues in meta-analyses of observational studies: the need for attention to the details. Br J Anaesth. 2022;128(5):e303-e305. doi:10.1016/j.bja.2022.01.033
28. Li Q, Zhou Q, Yang K, Luo Z, Chen Y. Rethinking the efficacy of awake prone positioning in COVID-19-related acute hypoxaemic respiratory failure. Lancet Respir Med. 2022;10(6):e53. doi:10.1016/S2213-2600(22)00164-3
29. Fralick M, Colacci M, Munshi L, et al. Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ. 2022;376:e068585. doi:10.1136/bmj-2021-068585
30. Alhazzani W, Parhar KKS, Weatherald J, et al. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomised Clinical Trial. JAMA. 2022;327(21):2104-2113. doi:10.1001/jama.2022.7993

31. Guérin C, Reignier J, Richard JC, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2013;368(23):2159-2168. doi:10.1056/NEJMoa1214103

32. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxaemic respiratory failure: The utility of the ROX index. Journal of Critical Care. 2016;35:200-205. doi:10.1016/j.jcrc.2016.05.022

33. Ibarra-Estrada M, Li J, Pavlov I, et al. Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxaemic respiratory failure: analysis of a randomised controlled trial. Critical Care. 2022;26(1):84. doi:10.1186/s13054-022-03950-0

34. Kaur R, Vines DL, Mirza S, et al. Early versus late awake prone positioning in non-intubated patients with COVID-19. Critical Care. 2021;25(1):340. doi:10.1186/s13054-021-03761-9

35. Joseph B, Mackinson LG, Sokol-Hessner L, Law AC, DeSanto-Madeya S. CE: A Prone Positioning Protocol for Awake, Nonintubated Patients with COVID-19. Am J Nurs. 2021;121(10):36-44. doi:10.1097/01.NAJ.0000794108.07908.54

36. Brazier DE, Perneta N, Lithander FE, Henderson EJ. Prone Positioning of Older Adults with COVID-19: A Brief Review and Proposed Protocol. The Journal of Frailty & Aging. Published online 2021:1-6. doi:10.14283/jfa.2021.30

37. Morales-Quinteros L, Schultz MJ, Serpa-Neto A, et al. Awake prone positioning in nonintubated spontaneous breathing ICU patients with acute hypoxaemic respiratory failure (PRONELIFE)—protocol for a randomised clinical trial. Trials. 2022;23(1):30. doi:10.1186/s13063-021-05991-2

38. Hallifax RJ, Porter BM, Elder PJ, et al. Successful awake proning is associated with improved clinical outcomes in patients with COVID-19: single-centre high-dependency unit experience. BMJ Open Respiratory Research. 2020;7(1):e000678. doi:10.1136/bmjresp-2020-000678

39. Nay MA, Planquette B, Perrin C, et al. Does awake prone positioning prevent the use of mechanical respiratory support or death in COVID-19 patients on standard oxygen therapy hospitalised in general wards? A multicentre randomised controlled trial: the PROVID-19 protocol. BMJ Open. 2022;12(7):e060320. doi:10.1136/bmjopen-2021-060320

40. Garcia MA, Rampon GL, Doros G, et al. Rationale and Design of the Awake Prone Position for Early Hypoxaemia in COVID-19 Study Protocol: A Clinical Trial. Ann Am Thorac Soc. 2021;18(9):1560-1566. doi:10.1513/AnnalsATS.202009-1124SD