Awake prone positioning in acute hypoxaemic respiratory failure: an international expert guidance

Pavlov, I., Li, J., Kharat, A., Luo, J., Ibarra-Estrada, M., Perez, Y., McNicolas, B., Poole, D., Roca, O., Vines, D., Tavernier, E., Allen, T., Shyamsundar, M., Ehrmann, S., Simpson, S. Q., Guérin, C., & Laffey, J. G. (2023). Awake prone positioning in acute hypoxaemic respiratory failure: an international expert guidance. *Journal of Critical Care*, *78*, Article 154401. https://doi.org/10.1016/j.jcrc.2023.154401

Published in:
Journal of Critical Care

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Download date:26. Jun. 2024

J Crit Care 78 (2023) 154401

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Awake prone positioning in acute hypoxaemic respiratory failure: An international expert guidance

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ARTICLE INFO

Keywords:
COVID-19
Awake prone positioning
Prone position
Acute hypoxaemic respiratory failure
Guideline
High flow nasal cannula
Oxygen therapy
Non-invasive ventilation

ABSTRACT

Background: Awake prone positioning (APP) of non-intubated patients with acute hypoxaemic respiratory failure (AHRF) has been inconsistently adopted into routine care of patients with COVID-19, likely due to apparent conflicting evidence from recent trials. This short guideline aims to provide evidence-based recommendations for the use of APP in various clinical scenarios.

Methods: An international multidisciplinary panel, assembled for their expertise and representativeness, and supported by a methodologist, performed a systematic literature search, summarized the available evidence derived from randomized clinical trials, and developed recommendations using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

Results: The panel strongly recommends that APP rather than standard supine care be used in patients with COVID-19 receiving advanced respiratory support (high-flow nasal cannula, continuous positive airway pressure or non-invasive ventilation). Due to lack of evidence from randomized controlled trials, the panel provides no

Abbreviations: APP, awake prone positioning; AHRF, acute hypoxaemic respiratory failure; RCT, randomized controlled trial; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; COT, conventional oxygen therapy; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; PICO, Population, Intervention, Comparator, and Outcome; RR, risk ratio; CI, confidence interval; PP, prone positioning; ARDS, acute respiratory distress syndrome.

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https://doi.org/10.1016/j.jcrc.2023.154401

Available online 28 August 2023
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recommendation on the use of APP in patients with COVID-19 supported with conventional oxygen therapy, nor in patients with AHRF due to causes other than COVID-19.
Conclusion: APP should be routinely implemented in patients with COVID-19 receiving advanced respiratory support.

1. Introduction

Awake prone positioning (APP), prone positioning of non-intubated patients with acute hypoxaemic respiratory failure (AHRF), has been rapidly adopted in the clinical management of patients with COVID-19 (Coronavirus Disease 2019) [1]. Although its benefit was initially demonstrated in large randomized controlled meta-trial [2] and reaffirmed in a recently published meta-analysis of randomized controlled trials (RCTs) [3], subsequent negative trials [4,5] have generated uncertainty about the benefits and the feasibility of routine application of APP to patients with COVID-19 [6].

Conflicting evidence generated from variable implementations of APP in dissimilar populations is not easy to translate to simple and actionable advice at the bedside, and there is a risk of losing the signal in the noise, thus depriving patients of a potentially useful treatment modality [7,8]. Therefore, an international panel of experts was convened in order to provide contemporary guidance on the routine application of APP in adult patients hospitalized with AHRF. The resultant guideline was endorsed by the United Kingdom Intensive Care Society on December 13th, 2022.

2. Methods

2.1. Panel composition

This short guidance was developed by an international multidisciplinary panel of experts which included respiratory therapists, a nurse, a patient representative, a biostatistician with special interest in meta-analysis, a guideline methodologist, and physicians with expertise in critical care or intensive care medicine, pulmonology, and emergency medicine. To ensure broad representation, panel members were selected from academic and community institutions, and included bedside clinicians, experienced clinical trialists and physicians with executive and leadership roles. All panel meetings were held online and co-chaired by IP and JLi.

2.2. Conflicts of interest and funding

All panelists disclosed their potential conflicts during the inaugural panel meeting. The panelists did not receive any funding or honoraria for their participation and there was no industry input in the development of this guidance. A significant proportion of panelists had previously been involved in clinical trials of APP.

2.3. Definitions

AHRF was defined as hypoxaemia, demonstrated by arterial blood gas or by pulse oximetry, that required oxygen supplementation according to the individual trial's criteria. This pragmatic definition reflects the inclusion criteria of many trials [2,4,5,9], as well as common clinical practice. Oxygen supplementation with a heated and humidified high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) were defined as advanced respiratory support. Conventional oxygen therapy (COT) refers to the provision of supplemental oxygen through an interface that does not generate positive airway pressure and cannot finely and precisely modulate the fraction of inspired oxygen, such as nasal cannulas, venturi masks, simple facemasks, and non-rebreather masks.

2.4. Formulation of the questions

The panel met initially in June 2022 and, after extensive discussion, identified two key questions formulated in the Population, Intervention, Comparator, and Outcome (PICO) format, as presented in Table 1. The questions and the outcomes of interest were decided based on relevance to patients and clinicians, the availability of evidence, and the need to produce brief and timely guidance for the upcoming pandemic waves of COVID-19.

2.5. Evidentiary base

To ensure the highest standard of evidence, and informed by previous systematic reviews [3,10] which demonstrated the significant limitations of non-randomized studies of APP, the panel agreed to consider only evidence derived from RCTs with low risk of bias.

2.6. Literature search, evidence synthesis, and assessment of bias

Two independent groups of panelists searched MEDLINE, Embase and PubMed for RCTs of APP compared to standard supine positioning from 1966 to September 15, 2022. The detailed search strategy, rationale, and PRISMA flowchart are provided in the online supplement. Any disagreement regarding the selection of studies was resolved by consensus.

The risk of bias in each trial was assessed with the Cochrane risk-of-bias tool for randomized trials (RoB2) [11]. The outcomes of interest were the cumulative intubation risk, and the reported all-cause mortality. For both outcomes, the measure of effect was the risk ratio (RR) with a corresponding 95% confidence interval (CI). The random-effects model was used for meta-analysis, and trial sequential analysis [12] was

Table 1
Population, intervention, comparison, and outcome (PICO) questions and recommendations.

1. Should APP be used in non-intubated patients with AHRF receiving advanced respiratory support?	We recommend that APP be used in patients with Covid-19 receiving advanced respiratory support (strong recommendation*; moderate certainty of evidence) There is insufficient evidence to recommend for or against APP in patients receiving advanced respiratory support for AHRF due to causes other than Covid-19 (no recommendation by strong consensus, no evidence).
2. Should APP be used in non-intubated patients with AHRF supported with COT?	There is insufficient evidence to recommend for or against APP in patients with Covid-19 supported with COT (no recommendation by strong consensus, low certainty of evidence). There is insufficient evidence to recommend for or against APP in patients receiving COT for AHRF due to causes other than Covid-19 (no recommendation by strong consensus, no evidence).

* A strong recommendation implies that most patients would prefer, and should be offered, the suggested intervention. Adherence to this intervention could be used as a quality criterion or performance indicator [49].
Abbreviations: APP: awake prone positioning; AHRF: acute hypoxaemic respiratory failure; COT: conventional oxygen therapy; Covid-19: coronavirus disease 2019.

performed to quantify the uncertainty and imprecision of the results. The planned statistical analysis is described in full detail in the online supplement.

Subsequently, subcommittees of panelists were assigned to the task of extracting and evaluating the quality of the evidence according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [13] for each PICO question, as described in detail in the online supplement. The GRADE assessment was then independently reviewed by the designated methodologist (DP).

2.7. Formulation of recommendations

To reach consensus recommendations, we followed the RAND/UCLA Appropriateness Method [14]. In short, the results of the GRADE assessment were first presented and discussed with the whole panel. The panel used the Evidence to Decision framework to generate recommendations for each PICO question, documenting the factors underpinning its decisions. The recommendations were then individually presented to the panelists through an online anonymous voting form. Each panelist was required to express their level of agreement with the statements on a 9-point Likert scale (from 1 for full disapproval to 9 for full approval), and was encouraged to comment and challenge the suggested recommendations, as well as to suggest others. The aggregate results were reported as medians, with corresponding interquartile range and disagreement index. The disagreement index is a validated measure of the dispersion of the vote, with values ≤ 1 indicating agreement among panelists [14]. The panel then met online, reviewed the results, discussed the collected commentaries, and agreed upon an amended set of recommendations, which were submitted to the second round of individual anonymous voting with the same methodology.

Recommendations are reported as strong or conditional, based on the quality of evidence, the balance of desirable and undesirable effects, the value of the outcomes, acceptability, feasibility, the resources required for the implementation of APP, and the quality of the panel consensus. Recommendations could be ranked as strong only if the lower quartile of the agreement was at least 7. All recommendations required consensus, defined as disagreement index ≤ 1. Otherwise, the lack of consensus would be reported and discussed, but no recommendation would be made.

3. Results

The results of the literature search, the risk of bias assessment, the summary GRADE tables, and the evidence to decision frameworks, as well as the summary forest plots, including the sensitivity analyses performed to assess the robustness of data are available in the online supplement. For the two PICO questions, the panel formulated one recommendation and identified three clinical scenarios for which no recommendation could be made due to lack of data. All four statements reached a high consensus (median 9 for all, minimal lower quartile 8, maximal disagreement index 0.13).

PICO question 1: Should awake prone positioning be used in non-intubated patients with AHRF receiving advanced respiratory support?

1. We recommend that APP be used in patients with COVID-19 receiving advanced respiratory support (strong recommendation; moderate certainty of evidence).
2. There is insufficient evidence to recommend for or against APP in patients receiving advanced respiratory support for AHRF due to causes other than COVID-19 (no recommendation by strong consensus, no evidence).

4. Background

Improved oxygenation with prone positioning (PP) in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) was first described almost half a century ago [15]. The first clinical trial of PP was published a quarter century later [16], and an additional decade passed before the conclusive demonstration of a mortality benefit in the landmark PROSEVA trial [17]. Implementation in clinical practice has been slow; less than a third of patients with severe ARDS were treated with PP in recent pre-pandemic studies [18,19].

The COVID-19 pandemic provided a strong impetus to the worldwide adoption of PP. In recently published cohort studies, 60% to 70% of patients with severe ARDS were treated with PP [20,21]. The pandemic has also ignited interest in applying PP to spontaneously breathing, non-intubated patients, an approach previously described in observational reports [22-24].

A detailed description of the physiology of PP is beyond the scope of this guidance and has been extensively reviewed elsewhere [25-27]. In short, lung inflation is more homogenous in PP (especially in the so-called "wet sponge" lung in ARDS), while perfusion is minimally impacted. This results in improved ventilation/perfusion matching and may reduce shear forces on the lung parenchyma.

4.1. Summary of the evidence

Four trials, three published [2,4,28] and one still unpublished (NCT04853979) compared APP to standard care in patients with COVID-19 undergoing advanced respiratory support (Figs. E3 and E5 in the online supplement). APP reduced the risk of intubation (RR 0.82, 95% CI 0.71 to 0.93; moderate certainty). The median duration of APP varied from 4.8 to 9.0 h daily, with wide interquartile ranges in all trials. Higher durations of APP correlated with better outcomes in the single trial [2] that attempted to quantify the dose-response relationship of APP. Of note, the majority of included patients were supported with HFNC at enrollment, with only 49 of the 1521 (3.2%) patients supported with CPAP or NIV.

APP did not alter mortality (RR 1.23, 95% CI 0.54 to 2.80, moderate certainty). Trial sequential analysis suggests that the optimal information size was not reached for mortality (Fig. E6 in the online supplement). Mortality in the subgroup of patients who progressed to mechanical ventilation was reported only in one trial and was not altered by APP: 79 of 185 (43%) compared to 98 of 223 (44%) with standard care [2].

We did not identify any RCTs that compared APP to standard care in patients with AHRF due to causes other than COVID-19.

4.2. Justification

The panel makes a strong recommendation in favor of APP in patients with COVID-19 receiving advanced respiratory support. This decision is based on the moderate certainty (the highest possible level of certainty for an unblinded intervention) of reduced risk of intubation, an important patient-oriented outcome, and an overall strongly positive balance of effects. Avoidance of intubation is beneficial only to the extent that it does not lead to worse outcomes downstream. Reassuringly, there was no signal of harm in any of the included trials. The composite outcome of intubation or death was reported in the two larger trials [2,4], with a reduced relative risk similar to that of intubation. Moreover, there was no evidence of increased mortality in patients who progressed to mechanical ventilation [2], which is consistent with a recent meta-analysis in which the timing of intubation was not associated with mortality [29]. Nonetheless, the panel's recommendation is based on the understanding that APP is to be provided under appropriate clinical monitoring, with immediate access to mechanical ventilation if the need arises. The overall safety profile of APP seemed reassuring, with rare and relatively minor side effects (such as catheter dislodgement, back pain, or skin breakdown) reported in the included trials. The panel did not identify any feasibility barriers to APP.

APP did not seem to alter mortality, but the evidence is limited by high imprecision and moderate inconsistency among trials. Mortality

was reported as a secondary outcome in all included trials and the length of follow-up was short, which further limits the quality of the available evidence. The existing evidence cannot exclude a potential, small effect on mortality, as the optimal information size has not been reached. The panel considered that a lack of mortality benefit should not detract from the reduced risk of intubation, as delineated above.

We used the level of respiratory support (advanced respiratory support versus COT) as a proxy for disease severity. This conforms to the WHO Clinical Progression Scale [30] and common clinical practice but does not directly, nor necessarily, reflect the degree of physiological derangement [31]. The overwhelming majority (96.8%) of patients included in this analysis were supported with HFNC at enrolment, and we cannot exclude that the observed benefit is at least partially mediated by a synergistic interaction between APP and HFNC. HFNC is well-tolerated [32], reduces work of breathing [33], homogeneously increases the end-expiratory lung volume in prone position [34], reduces dead space [35], and reduces $PaCO_2$ [36]. The reduction of dead space may be especially significant, as prone positioning may increase the physiological dead space fraction, at least in some patients [27]. These considerations remain theoretical, however, and the panel's consensus is that APP is beneficial in all COVID-19 induced AHRF patients whose disease severity warrants the provision of advanced respiratory support, regardless of the specific modality.

The optimal duration of APP is unknown, although evidence from secondary analyses suggests that durations of at least 8 h daily are associated with improved outcomes [2,37]. Challenges in ensuring continual patient cooperation with APP have been identified in all trials, and further research on strategies to improve patients' comfort and compliance is needed.

We did not identify any trials that compared APP to standard care in patients with AHRF due to causes other than COVID-19. The pathophysiology of severe COVID-19 is likely similar to other causes of AHRF [38-41], and it may be tempting to extrapolate the benefit of APP observed in patients with severe COVID-19 to other types of AHRF. However, the panel considers that separate trials in AHRF of other causes are warranted, and that no recommendation can be formulated for this population. The decision to implement APP in those patients should be based on each individual patient's values and preferences, and motivated patients should be encouraged to enroll in clinical trials whenever possible. Among panelists, 47% would recommend APP outside of a clinical trial, although the rest of the panel disagreed (Table E6 in the online supplement).

PICO question 2: Should awake prone positioning be used in non-intubated patients with AHRF supported with COT?

3. There is insufficient evidence to recommend for or against APP in patients with COVID-19 supported with COT (no recommendation by strong consensus, low certainty of evidence).
4. There is insufficient evidence to recommend for or against APP in patients receiving COT for AHRF due to causes other than COVID-19 (no recommendation by strong consensus, no evidence).

4.3. Summary of the evidence

Seven trials, six published [4,9,42-45] and one still unpublished (NCT04853979) compared APP to standard care in patients with COVID-19 supported with COT (Figs. E7 and E9 in the online supplement). APP had no effect on the risk of intubation (RR 1.07, 95% CI 0.66 to 1.73; moderate certainty) and no effect on the risk of mortality (RR 1.14, 95% CI 0.47 to 2.75; low certainty). For both outcomes, trial sequential analysis showed that the optimal information size had not been reached (Figs. E8 and E10 in the online supplement).

Compliance with APP was not consistently reported among trials but was generally low, with a median of 6 h accrued during the first three days in one trial [9], and only 35.7% of patients reporting proning >6 h at least once in another trial [45].

We did not identify any RCTs that compared APP to standard care in patients with AHRF due to causes other than COVID-19.

4.4. Justification

The panel does not make any recommendation for or against APP in patients with COVID-19 supported with COT. This decision is based on the uncertainty regarding the balance of effects, as the absence of evidence of benefit is limited by the high imprecision of the relative risk estimate, and the optimal information size has not been reached according to trial sequential analysis. In fact, one trial [45] reported an exploratory per-protocol analysis suggesting a 90% posterior probability for superiority of APP in reducing the rate of respiratory deterioration and ICU transfer, although this finding may have been confounded by post-randomization factors that predict both adherence and outcomes. The panel notes that although no benefit was demonstrated with APP, no harm was seen, either.

It is possible that APP is beneficial only in patients with more severe alterations of lung physiology, and with a higher ventilation/perfusion mismatch. In other words, patients supported with COT may simply be not sick enough to benefit from APP. On the other hand, we cannot discount the possibility that the lack of benefit is explained by the low adherence to APP in this patient population.

As previously mentioned, the modality of oxygen support is an imperfect surrogate of disease severity. In particular, advanced respiratory support may not be available in some resource-poor settings. In those settings, support with COT is not associated with lower disease severity, and should not preclude provision of APP, if warranted by the disease severity.

5. Discussion

The panel developed one actionable recommendation to help patients, clinicians, and other stakeholders in their decision process, namely that APP should be routinely implemented in patients with COVID-19 receiving advanced respiratory support. The panel has further identified three commonly encountered clinical scenarios for which no recommendation could be formulated at present due to a lack of data, and for which decisions must be made based on patients' values and preferences, as outlined above. Further research is needed to provide evidence-based guidance for those scenarios.

Our findings are broadly consistent with those of other expert panels [46-48], although there are some important differences. In assessing the risk of study bias, we considered APP to be a behavioral intervention that cannot be blinded; thus we considered the risk of bias for intubation to be moderate, in contrast to Weatherald et al. who evaluated this same risk as low in their meta-analysis [48]. In our analysis, we prospectively decided to group patients supported with COT separately to those receiving advanced respiratory support. In contrast, Weatherald et al., in their meta-analysis, lumped these patients into a single group in their primary analysis. Reassuringly, Weatherald's findings in their subsequent subgroup analyses did not demonstrate any statistically significant effect of APP in patients receiving COT, which is consistent with our recommendations in this guideline.

The rapid APP practice guideline developed by Myatra et al [46] and the just published ARDS management guideline by the ESICM [47], also considered all non-intubated patients as a single group, and both advised the use of APP in this population, albeit with a low level of confidence in the ESICM guideline. By separating the patients into a COT group and an advanced respiratory support group, and evaluating the evidence on this basis, we are able to make a strong recommendation for APP in COVID-19 patients receiving advanced respiratory support. Furthermore, we identify a lack of available evidence to support any recommendation regarding the use of APP in patients with COVID-19 receiving COT. We contend that the distinction between advanced respiratory support and COT is highly relevant, and is of practical clinical importance at the

bedside. Our findings will allow clinicians to focus their APP efforts and resources on those patients most likely to benefit.

There are a number of limitations to be considered. Firstly, while we made every effort to ensure panel diversity, and achieved it in several respects (gender mix; medical specialties mix, bedside versus academic clinicians; allied health disciplines; methodological experts, patient participation, etc.), participation from lower- and middle-income countries was limited. Secondly, a significant proportion of panelists had previously been involved in clinical trials of APP, which could present a potential conflict of interest. To address this concern, the guideline methodology was developed by an independent panel member (DP), was strictly adhered to, and all GRADE recommendations were ultimately reviewed by the independent methodologist.

6. Conclusion

The panel strongly recommends that APP should be routinely implemented in patients with COVID-19 receiving advanced respiratory support. There is insufficient evidence to support any recommendation regarding the use of APP in patients with COVID-19 supported with conventional oxygen therapy, or in patients with AHRF due to causes other than COVID-19.

Contributions

IP and JLi conceived of the project, served as co-chairs, organized the panel meetings and managed the whole project. AK, YP, BM, MIE, JLu, IP and JLi searched the literature, extracted and summarized the data. JLu and ET performed data analysis. DP reviewed the GRADE tables, the evidence to decision frameworks, and provided methodological guidance throughout the project. All authors participated in online panel meetings, had full access to the data, and contributed significantly to guidance development. IP drafted the manuscript, which was reviewed for important intellectual content and approved before submission by all authors. IP and JLi were conjointly responsible for the decision to submit the manuscript.

Funding

None.

Declaration of Competing Interest

IP discloses an unrestricted research grant and speaker fees from Fisher & Paykel Healthcare Ltd. and an unrestricted research grant from OpenAI Inc. JLi discloses research funding from Fisher & Paykel Healthcare, Aerogen, Rice Foundation, and the American Association for Respiratory Care, and speaker fees from the American Association for Respiratory Care, Aerogen, Heyer, and Fisher & Paykel Healthcare. SE discloses consultancy fees from Aerogen, research support from Aerogen and Fisher & Paykel Healthcare, and travel reimbursements from Aerogen and Fisher & Paykel Healthcare. DV discloses research funding from Teleflex Medical and Rice Foundation. OR discloses a research grant from Hamilton Medical and Fisher & Paykel, and speaker fees from Hamilton Medical, Ambu, Fisher & Paykel and Aerogen, and non-financial research support from Timpel. YP discloses research support and travel reimbursement from Fisher & Paykel Healthcare. JGL discloses consulting fees from Baxter Healthcare and Cellenkos. MS discloses speaker fees from Fisher & Paykel Healthcare Ltd. and consultancy fees from Aerogen. All other authors have no conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154401.

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