Editorial Commentary

When hope meets reality: the challenges of awake proning in unmonitored settings

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The prone position has been used in the management of severe acute respiratory failure (ARF) since the 1970s (1). In one of the first reports, Mellins *et al.* observed that patients with advanced cystic fibrosis spontaneously adopted the prone position to improve ventilation (2). From these early experiences, the beneficial effects of the prone position began to be documented.

In the supine position, the dorsal areas of the lung are compressed by the weight of the mediastinal structures, the pleural pressure gradient, and the rest of the lung itself. In contrast, in the prone position, these areas are relieved of this pressure, with an increase in functional residual capacity, resulting in improved ventilation/perfusion ratio, cardiac output, and diaphragm function (3).

Prone positioning in intubated and mechanically ventilated patients has been shown to improve pulmonary gas exchange and lung mechanics in patients with severe hypoxemic respiratory failure. In fact, it is part of most intensive care unit protocols. There are current guidelines (4) that support this intervention in intubated patients with acute respiratory distress syndrome (ARDS), specifying that patients must be in the prone position for at least 16 hours per day to be effective.

During the coronavirus disease (COVID) pandemic, different strategies have been tried in the management of patients with COVID and moderate hypoxaemia to prevent worsening of the disease. Perhaps the most studied has been the early administration of therapy with high flow nasal cannula (HFNC). Crimi *et al.* found no significant difference in disease progression in a cohort of patients with an arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio between 200 and 300 after randomisation to high flow or conventional oxygen therapy (5). In contrast, differences in intubation rates have been demonstrated in patients with PaO_2/FiO_2 below 200 (6,7).

Awake proning position (APP) has been also used as a strategy, suggesting that it could improve the prognosis of non-intubated patients with moderate or severe respiratory failure. The aim of APP would be to prevent the progression of ARF, thereby reducing the need for orotracheal intubation and ultimately improving survival. Some early studies demonstrated a lower rate of intubation in patients under APP (8). However, the results of the studies are conflicting and merit careful consideration (9). Although considered a non-invasive treatment, tolerance to APP is highly variable, with most patients not tolerating it for long periods of time. For example, in the meta-trial published by Ehrmann *et al.*, which included 6 RCTs, the number of hours of pronation per day ranged from 1.6 to 8 hours (10). Some other studies achieved a mean duration of 12 hours in the first day of admission to intensive care unit (ICU) (11). Although no ideal number of hours of compliance has been defined for awake patients, in the aforementioned meta-trial, the rate of APP failure and progression of lung disease was significantly lower in patients with longer hours of compliance. *Table 1* shows the most relevant studies on APP.

Table 1 Summary of the most relevant studies (including >15 patients in each arm) on APP in COVID-19

Reference	Study type/setting	N (prone/control)	Groups comparators	% of patients under NIRS	Time on prone position planned/reported	Main outcome
Gad (12)	Single center RCT/ICU	15/15	Face mask oxygen + APP *vs.* NIV	50% (control group)	1–2 h shifts between 3 h rest/not reported	No difference in mortality or intubation
Johnson *et al.* (13)	Single center RCT/ward	15/15	APP/usual care (nasal cannula)	0%	1–2 h every 4 h/not reported	No differences in oxygenation
Taylor *et al.* (14)	Single center/RCT/ward	27/13	APP/usual care	1%	12–16 h/10–120 min per day	No improvements in oxygenation. Low adherence and low tolerance to APP
Rosén *et al.* (15)	Multicenter RCT ICU	36/39	Required NIV/HFNC	100%	>16 h a day/14% patients were able to perform >16 h a day	Safe, but no differences in intubation
Jayakumar *et al.* (16)	Multicenter RCT/ICU	30/30	Usual care *vs.* APP	Baseline 10% on NIRS	>6 h per day/43% tolerate >6 h per day	No differences in outcomes
Gopalakrishnan *et al.* (17)	Single center/ward	257/245	Usual care *vs.* APP	0% baseline	6–8 h/23 % did not tolerate >2 h/day	No differences in outcomes
Ehrmann *et al.* (10)	Multicenter RCT ICU (60%), intermediate care unit (35%)	554/567	Usual care *vs.* APP	HFNC (not available)	As long as possible/5 h per day	Positive effects of APP in intubation and mortality
Hashemian *et al.* (18)	Single center RCT/ICU	30/45	NIV *vs.* NIV + APP	100% on NIV	Not available	Improve in oxygenation in the most severe group, favouring the APP + NIV group. Lower need for intubation (22% *vs.* 40%, P=0.082) and mortality (20% *vs.* 33%, P=0.152) in NIV + APP
Alhazzani *et al.* (19)	Multicenter RCT/ICU	205/195	Usual care *vs.* APP	–	8–10 h a day/5 h a day	No reduction in intubation
Rampon *et al.* (20)	Single center RCT/ward	159/134	Usual care *vs.* APP	1% on HFNC	4 times/day for 1–2 h + 12 h night/only 2% achieved >12 h	Smartphone-guided self-prone positioning. No improvement in APP adherence
Fralick *et al.* (21)	Multicenter RCT/ward	126/122	Usual care *vs.* APP	2–4% on HFNC	2 h 4 times a day/6 h a day	No differences in death or mechanical ventilation

APP, awake prone position; COVID-19, coronavirus disease 2019; RCT, randomized control trial; ICU, intensive care unit; NIV, non-invasive ventilation; HFNC, high flow nasal cannula; NIRS, noninvasive ventilator support.

But the question did not stop at critical care. In a randomised controlled trial, Nay *et al.* recruited 265 patients on inpatient wards in 15 hospitals. Patients were randomised to awake proning plus usual care in the intervention arm and usual care in the control arm. The target time interval for patients to be in the prone position was 270 min/day. The results of the study showed no significant differences in the primary composite endpoint [non-invasive ventilation (NIV) or intubation or death] but did show differences in intubation and death (secondary endpoints). Interestingly and counter-intuitively, patients with milder ARF, defined by oxygen saturation (SpO_2) >95% on admission, showed a greater benefit than patients with more severe ARF (SpO_2 <95%) (22). Due to the important limitations, the results of the study are highly controversial and deserve further analysis. Four important questions arise from the results of the study: what would be the minimum monitoring requirements to implement APP? Could APP prevent deterioration in patients with mild ARF? Is it a worthwhile intervention? Does APP work the same in patients on conventional oxygen as it does in patients on NIV?

Regarding the first question, the study was conducted in a completely different setting (conventional ward) than where most studies have shown benefits of prone positioning (monitored/intermediate care units or intensive care units). Therefore, there is no way of knowing whether the patients had any kind of continuous monitoring. Even more, as shown in the supplemental data, there can be huge differences in ward management, with different thresholds to start NIV or to move to ICU, similar to the absence of pre-established intubation criteria in ICU studies. Finally, the use of monitoring could have identified those patients with oximetry improvement or deterioration after APP. On the other hand, it is understandable that in the early stages of the pandemic, monitoring facilities in wards were scarce. In a very similar study, Gopalakrishnan *et al.* found no significant difference in mortality or need for intubation in a cohort of 502 patients with mild ARF randomised to APP versus usual care (17) in an unmonitored environment. These results suggest the need for monitoring, that should include cardiorespiratory parameters [electrocardiogram (ECG) and oximeter]. As shown in *Table 1*, trials conducted in non-monitored wards showed no differences between groups and, on the other hand, reported significant problems with adherence and tolerability.

Concerning second question, the prone position had shown benefits mainly in non-intubated patients when used in conjunction with high nasal flow or continuous positive airway pressure (CPAP), and Nay and coworkers reported better results in the subgroup with mild hypoxaemia. They argue that APP would have had a protective effect in these patients by reducing stress and strain. However, the definition of moderate hypoxaemia using a not-so-accurate SpO_2 threshold of 95% under nasal prongs with a 5 L/min oxygen flow may pose a potential source of relevant variability of disease severity. Inspired oxygen fraction under nasal prongs may vary widely according to different respiratory rates and tidal volume. In addition, it may not account for other physiological variables as respiratory effort. Some authors have suggested the need to look also to arterial blood carbon dioxide tension ($PaCO_2$) as a relevant disease severity marker and highlighted the limitations of SpO_2/FiO_2 ratio (23).

Thirdly, it should be noted that a high level of willingness and effort on the part of the patient is required to acquire sufficient time in the prone position. Furthermore, there may be individual differences in tolerance, which could confound the results. In the same way that one patient in the control group decided to prone himself despite being advised not to, patients assigned to the self-proning arm may not have been adherent enough, as stated in the limitations. It is also an intervention that can be very staff-intensive in lower-resource settings such as conventional wards. The lack of continuous monitoring may have reduced the ability to identify those who could be considered responders and those who worsened with APP. In a very small study, Solverson showed that half of the patients in the prone position experienced pain and discomfort (24). Even more, in a very recent study (25), a review on the trends of prone position use in ICU showed a steady decrease of its use between 2020 and 2022 in COVID-19 related ARDS patients. Significantly, that decrease took place in intubated, ICU patients, where a better nurse-to-patient ratio is assumed. If in a high resource area, such as an ICU, is a decrease in its use despite being considered an evidence-based intervention, the explanation could be related to the high significant resources needed to prone an ICU patient, and to lower patient tolerance. To improve tolerance some authors combined prone and lateral decubitus (with non-invasive respiratory support), without significant results, but expanding the definition of therapeutic intervention (26). All these limitations and biases were addressed by the authors.

Finally, only about 5% of the patients in the study received NIV. A full understanding of the different physiological mechanisms that may influence the effects of prone positioning in spontaneously breathing patients,

intubated patients or patients receiving NIV (HFNC or NIV) is essential. In a recent letter, Shao and Shao (27) discussed the physiological differences in the effects of the prone position in patients receiving non-invasive respiratory support compared to those receiving conventional oxygen support. It appears that the recruitment effect associated with NIV and HFNC, which increases end-expiratory lung volume, may have a synergistic effect with APP, resulting in improved compliance, reduced strain and stress forces and more homogeneous lung inflation. Whether the presence of "advanced non-invasive respiratory support" can facilitate prolonged periods of prone positioning remains to be demonstrated.

We believe that the concept of APP responder is key to defining future strategies, especially because it is of questionable benefit to maintain the prone position in non-responders after the first therapy sessions. If we analyse the premises under which the benefit in intubated patients was established, one of them may have important implications for the application in the awake, non-intubated patient, such as the distribution or pattern of pulmonary involvement. None of the studies published to date provide information on the topographical distribution of lung involvement. However, there are tools that, because of their simplicity, such as bedside (point-of-care) ultrasound, could help to select those patients most likely to respond. In intubated patients, Prat *et al.* demonstrated that the presence of a normal lung ultrasound (LUS) score in the anterior fields was predictive of a favourable response to prone positioning in patients with ARDS (28). However, this was not confirmed in a later study, although it was possible to monitor changes in ventilation with APP using ultrasound (29). Another potentially useful tool for indicating and monitoring the response to APP may be electrical impedance plethysmography, although its complexity and high cost clearly limit its widespread use (30,31). Future trends may make this technique more affordable and accessible, even in intermediate care units or wards, in a similar way to chest radiography (32).

In conclusion, the efficacy of prone positioning in non-intubated patients remains controversial. For the future, it seems to be of paramount importance to define the implementation scenarios, considering the control and monitoring needs of APP patients. Based on current data, it seems advisable to restrict APP to monitored environments with trained personnel. In addition, the strategy of demonstrating benefit in the short or medium term would require the inclusion of patients with the highest *a priori* probability of response. A better characterisation of the patterns of respiratory failure and the severity of ARDS is needed to avoid that false hopes are met with harsh reality.

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