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WHAT'S NEW IN INTENSIVE CARE

Awake prone positioning

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Proning reduces mortality in invasively mechanically ventilated (IMV) patients with moderate–severe acute respiratory distress syndrome (ARDS) [1]. Prior to the coronavirus disease 2019 (COVID-19) pandemic, studies of awake prone positioning (APP) of non-intubated patients were limited to case series, which demonstrated tolerance and oxygenation improvement [2]. Following the onset of COVID-19, many case reports, case series and prospective cohort studies suggested benefits for APP. Consequently, APP was rapidly incorporated into clinical practice guidelines and widely used.

The initial rationale for APP in COVID-19 was derived from insights in healthy volunteers or surgical patients, and invasively ventilated ARDS patients [1, 3]. Potential mechanisms of action of APP include increased regional ventilation in dependent lung regions, better secretion removal, increased functional residual capacity, better regional diaphragm movement and blood flow distribution and relief from compression from mediastinal and abdominal organs [4]. Proning reduced inspiratory effort in spontaneously breathing mechanically ventilated ARDS patients [5]. In COVID-19, APP may redistribute blood flow from dilated interalveolar capillaries surrounding under-ventilated alveoli to under-perfused normal lung regions [6]. While concerns existed that APP might delay the initiation of IMV, increasing the risk of self-inflicted lung injury [7, 8], APP might also reduce this risk by decreasing inspiratory effort [5].

Recent data from randomised controlled trials (RCTs) are prompting a reassessment of the role of APP in COVID-19 patients. The largest study to date enrolled 1126 patients with COVID-19 receiving high-flow oxygen to receive APP versus standard care, using a meta-trial design which pooled data from 6 independent randomised controlled trials with harmonised eligibility, randomisation procedures and outcomes [9, 10]. APP reduced the composite outcome of treatment failure defined by either intubation or death within 28 days, with the results primarily driven by a reduction in intubation. The meta-trial was underpowered to determine differences in mortality [9]. The mean SpO_2 to FiO_2 ratio (SFR) was < 150 and most patients were in an intermediate or intensive care setting. Patients receiving APP spent an average of 5.0 h (interquartile range, IQR 1.6–8.8) per day in prone position, with longer treatment associated with less likelihood of treatment failure. The number needed to treat to avoid death or IMV was 14 and there was no signal for harm in terms of increased mortality or duration to extubation and discharge for APP patients subsequently requiring IMV [9]. In a subsequent multicentre RCT of 400 patients with COVID-19 in Canada and Saudi Arabia, in a similar population (70% receiving high flow oxygen) to the meta-trial, Alhazzani et al. reported that intubations rates of 34% in the APP group versus 41% in the standard care group, rates almost identical to that in the meta-trial [11]. While this smaller study was underpowered for this outcome, the intubations rates in both groups were nearly identical to those reported in the meta-trial [9].

In contrast, other studies have not demonstrated similar benefits for APP. Qian and colleagues' compared APP to usual care in a COVID-19 cohort predominantly receiving low flow oxygen therapy [12]. Median time spent in prone was 4.2 h, only marginally less than in the meta-trial study [9]. APP increased modified World Health Organization (WHO) scale severity score on day 5, though not at day 28, while the need for invasive MV, length of stay and 28 day mortality did not differ between the two groups. The study was underpowered for differences in invasive MV requirement, while 40% of patients

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that died were never intubated, raising concerns about the inter-group distribution of do-not-intubate status in this quasi-randomised study [12]. In the COVID-prone pragmatic RCT, APP was ineffective in a non-critically ill inpatient population [13]. Adherence to APP was low (7/72 h in prone position), raising the possibility that the intervention was not applied for sufficient periods to be effective [13].

These studies highlight the importance of ensuring APP is applied in the patient population most likely to benefit, in an appropriately resourced environment, and for longer time periods. A recent meta-analysis has provided further insights. Li et al. reported reduced intubation rates among patients requiring advanced respiratory support and/or an intensive care unit (ICU)-type setting [14]. In contrast, APP had no benefit in patients requiring conventional oxygen therapy and/or not in an ICU-type setting [14]. Another study found that patients who failed APP had a greater diaphragmatic fractional thickening compared to those who avoided intubation [7]. The ineffectiveness of APP in less sick, ward-managed patients supports the findings of the studies discussed earlier [11, 12], and suggest there is no role for APP in this population.

Tolerance of longer APP sessions is important, heterogeneity exists between trials and patients populations, with patients who can tolerate > 8 h of APP having the lowest intubation risk. Potential for confounding exists, as patient tolerance of APP depends on dyspnoea severity, musculoskeletal discomfort levels, and patient body habitus. APP is labour-intensive and the adequacy of nursing/medical support available to support patients to remain prone is important. Ibarra-Estrada et al. reported that patients with silent hypoxaemia in the Mexico RCT tolerated much longer APP sessions than dyspnoeic patients, and were most likely to benefit from APP [15]. Analgesia and anxiolytics such as opiates and dexmedetomidone may improve APP tolerance, though sedation and/or delirium is a risk [7]. ICU capacity influences adherence to APP, particularly where constraints on staff and equipment exist [3]. Post hoc studies from the meta-trial have yielded further insights. Ibarra-Estrada et al. demonstrated that APP improved lung aeration over time, strengthening the pathophysiological rationale for APP [15]. Gershengorn et al. demonstrated no increased risk of APP failure over time, suggesting that even prolonged use of APP is safe [16].

An important issue is the fact that no study to date has shown that APP reduces patient mortality. The meta-trial, which is the largest study to date, showed a 3% absolute reduction in mortality (from 24 to 21%) with APP, suggesting that studies to date are all underpowered for this outcome. Other reasons for this may include the low mortality rate in some studies, heterogeneity of the patient populations (COVID-19 severity, respiratory support type, location of care), and heterogeneity in the duration of APP sessions across studies. Of interest here is the demonstration by Ibarra-Estrada

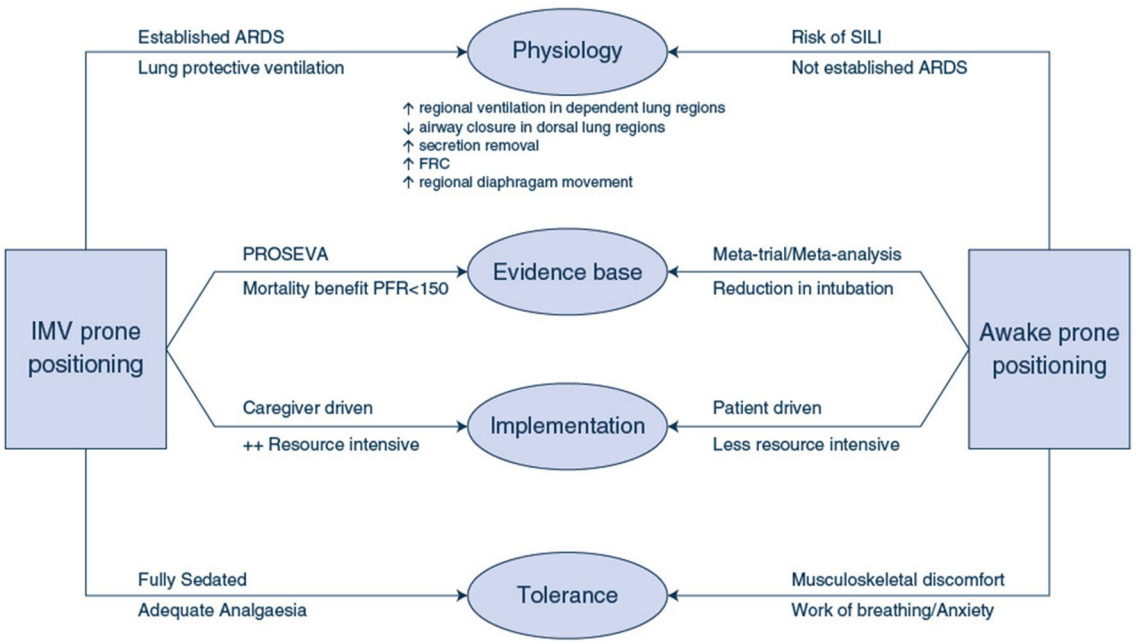

Fig. 1 Similarities and differences between Prone positioning invasively mechanically ventilated patient and patients undergoing awake prone positioning

of an increase in survival without intubation in patients tolerating APP sessions over 8 h per day compared patients who tolerated less than 8 h of APP per day [15]. Further studies are needed examining factors related to tolerance of APP and the potential for confounding factors such as a disease severity and/or degree of dyspnoea to partially explain these findings (Fig. 1).

In conclusion, the evidence base for APP has improved, with substantial evidence that more hypoxaemic patients requiring advanced respiratory support, who are managed in higher care environments, and who can prone for time periods of several hours, benefit most from APP use. In contrast, APP appears ineffective in less sick, ward managed patients. However, unanswered questions remain, which will be addressed in a planned individual patient meta-analysis of the studies to date and this will influence the design and execution of subsequent studies in APP, particularly in non-COVID-19-related acute hypoxemic respiratory failure for which the data is limited.

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