Rationale and significance of patient selection in awake prone positioning for COVID-19 pneumonia

To the Editors:

We read with interest the research letter by NG *et al.* [1], which described their experience in prone positioning (PP) for awake patients with coronavirus disease 2019 (COVID-19) pneumonia, and concluded that this manoeuvre could delay or reduce the need for intensive care. We agree that the authors demonstrated safety and feasibility of PP in COVID-19 pneumonia patients. However, we humbly suggest a few crucial points be addressed before drawing conclusions on the efficacy of PP.

First, the median time from illness onset to starting oxygen therapy (OT) and awake PP was 9 and 11 days, respectively. In a study reported by YOUNG *et al.* [2], six out of 18 COVID-19 patients received OT as their oximetry saturations (S_{pO_2}) were <92%, and median time from symptom onset to OT initiation was 4 days. Two among these six patients eventually needed intensive care for worsening respiratory failure. However, they had contrasting clinical trajectories, particularly in relation to tempo and extent of deterioration. The first patient desaturated at day 3, with rapid declining oxygenation that necessitated mechanical ventilation by day 8, while the second only developed hypoxia later at day 10 of illness. Although the latter was admitted to intensive care 3 days later, the patient needed at most venturi mask 50% and was successfully weaned by day 20 of illness. By referencing local data, it is plausible that most patients in the series reported by NG *et al.* [1] were at low risk of developing severe COVID-19 pneumonia prior to awake PP.

Second, there was considerable patient heterogeneity with regard to severity of hypoxaemia. Unreported information, *e.g.* chest radiology and protocol to guide PP management, limit data interpretation. COVID-19 pneumonia is increasingly recognised to manifest phenotypic diversity, rather than a strict dichotomy, *i.e.* phenotype L and H [3, 4]. Moreover, PP's physiological effects would only benefit phenotype H, *i.e.* typical acute respiratory distress syndrome (ARDS), as characterised by predominantly dorsal consolidation and poor respiratory compliance [4]. Studies on PP in non-intubated ARDS patients pre-dating COVID-19 reported oxygenation improvement but there was no demonstrable improvement in clinical outcomes [5]. There was, however, an increased risk of death attributed to delayed intubation in severe ARDS regardless of choice/combination of adjunct therapies, *e.g.* noninvasive ventilation/high flow nasal therapy (HFNT) [5, 6].

Third, all but one patient had S_{pO_2} >90% on room air at OT initiation. S_{pO_2} ⩾90% is an American Thoracis Society/Infectious Diseases Society of America 2007 criterion for clinical stability in hospitalised patients with community-acquired pneumonia [7]. Current guidelines do not recommend OT in acute myocardial infarction and stroke patients with S_{pO_2} 90–92%, as evidence on its potential harm continues to emerge [8]. Similarly, we recommend judicious use of OT, as hyperoxia could exacerbate cytokine release syndrome – the main immunopathological driver implicated in severe coronavirus infections [9]. It is regretful that the study of NG *et al.* [1] did not define indications for OT, which could explain the remarkably discrepant intubation rates (10% *versus* 60%) of COVID-19 pneumonia patients treated at the same centre.

Finally, we would like to share our experience on using awake PP and HFNT (PP+HFNT) in three patients since late April 2020 (table 1). They were managed with the strategy below:

TABLE 1 Patient characteristics and parameters trends on PP+HFNT

Patient		Patient 1						Patient 2			Patient 3			
Age and sex		55 years, male						61 years, female			61 years, male			
Day of illness at OT initiation (S_{pO_2} <92% on room air)		7						5			3			
At PP+HFNT initiation	Days of O$_2$ received (cumulative)	7						12			2			
	PF ratio	84.8						160			60.6			
Time interval	Day of illness	13	14	15	16	17	18	16	17	18	8	9	10	11
	Day of PP	1	2	3	4	5	6	1	2	3	1	2	3	4
Oxygen requirement	O$_2$ devices	HFNT	HFNT	HFNT	HFNT	HFNT	iNO$_2$	HFNT	HFNT	VM	HFNT	HFNT	HFNT	HFNT
	F_{IO_2} %	100	40	70	40	40		40	40	40	50	50	60	100
	Flow L·min^{-1}	60	55	60	50	50	4	55	55	12	50	60	70	70
Respiratory parameters	S_{pO_2} %	100	98	92	93	95	98	93	89	94	94	95	94	90
	PF ratio	114	170	77		158		169		165	133	111	91	49
	ROX index	4.2	8.8	8.2	10.1	10.3	11.3	12.9	6.5	7.8	8.5	5.2	5.5	2.9

PP: prone positioning; HFNT: high flow nasal therapy; OT: oxygen therapy; S_{pO_2}: peripheral oxygen saturation; iNO$_2$: intranasal oxygen; VM: Venturi mask; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; PF ratio: P_{aO_2}/F_{IO_2} ratio; ROX index: ratio of S_{pO_2}/F_{IO_2} to respiratory rate; Day of illness at OT initiation (S_{pO_2} <92% on room air): total days of symptoms onset before receiving supplemental oxygen (date of receiving supplemental oxygen – date of symptoms onset + one day); Day of illness at PP+HFNT initiation: total days of illness before PP+HFNT (date of PP+HFNT initiated – date of illness onset + one day); Days of O$_2$ received at PP+HFNT initiation (cumulative): duration of patient on supplemental oxygen before PP+HFNT (date of PP+HFNT initiated – date of receiving supplemental oxygen + one day).

1) Inclusion criteria
- S_{pO_2} <92% on intranasal oxygen ⩾6 L·min^{-1} or venturi mask 50%; or PF ratio <200
- Considerable bilateral opacities on chest radiograph, *i.e.* compatible with degree of hypoxaemia
- Respiratory rate <30 breaths·min^{-1}
- Not using accessory muscles of respiration, *i.e.* sternocleidomastoids
- No contraindications to PP, *e.g.* cervical spine instability, pregnancy

2) Manoeuvre
- Four 2-h sessions of PP daily

3) Termination criteria
- ROX index persistently <4.88 despite optimising HFNT and/or worsening clinical status requiring intubation
- Patient's inability to tolerate PP

All three patients required OT to keep S_{pO_2} >92% by one week of illness. Patients were at day 13, 16 and 8 of illness when PP+HFNT was started. The first two required 5 and 2 days of PP+HFNT while the last was intubated for worsening hypoxaemia after 4 days. Our observations echo those of YOUNG *et al.* [2]. Just as the importance of personalised mechanical ventilation strategies cannot be overemphasised in COVID-19 ARDS, we maintain that selecting the appropriate patient subgroup for awake PP on OT is equally crucial. While we await more data, we opine that awake PP may work in hypoxic COVID-19 whereby the trajectory in oxygenation deterioration is less precipitous, meaning cytokine release syndrome is more indolent (thus causes ARDS over a longer time span), or already abating (the worst is over). Development of a prognostic model derived from clinical, laboratory and physiological data may predict risk of severe hypoxaemia requiring mechanical ventilation and guide personalised treatment in COVID-19 pneumonia.

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From the authors:

We thank C.F. Huang and co-workers for the points raised regarding our published paper entitled "Awake prone positioning for non-intubated oxygen dependent COVID-19 pneumonia patients" [1].

Our study aimed to provide preliminary data that prone positioning can potentially reduce the need for intensive care in patients with coronavirus disease 2019 (COVID-19) pneumonia. With global teams facing resource depletion in the face of a COVID-19 pandemic, the advent of a low-risk and low-cost manoeuvre could potentially offload our healthcare burden. We left the decision to initiate oxygen therapy and prone positioning in the general ward to the attending clinician. When faced with a hypoxic patient, it would have been ideal, albeit not practical, to wait for phenotypic L or H observations [2] before deciding on therapy. We agree with C.F. Huang and co-workers that patients with one phenotype may benefit more from awake prone positioning, but our small series was not statistically powered to stratify the differences. In addition, the authors compared our data to the study by Young *et al.* [3], in which patients were recruited from January to February 2020, *i.e.* a different time frame from our study.

While bearing in mind that the ROX index is not validated in patients with COVID-19 pneumonia, we recognise the efforts of C.F. Huang and co-workers to explore the effects of prone positioning in various settings, including the use of it in patients who are on high flow nasal cannula therapy.

Awake prone positioning is gaining traction by intensive care societies [4] as an early intervention for patients with COVID-19 pneumonia. We present our experience where awake prone positioning proved to be a logistically easy-to-execute intervention with the potential to reduce intensive care unit workload. We believe that further studies are needed to confirm our results and to evaluate its clinical relevance, which may be addressed with ongoing randomised clinical trials (NCT04347941, NCT04350723).

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