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Prone positioning in COVID-19 ARDS: more pros than cons

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Patients with severe COVID-19 may develop acute respiratory failure requiring mechanical ventilation.(1) Prone positioning is a rescue therapy for ARDS patients with hypoxemia refractory to protective mechanical ventilation with high FIO_2.(2)

In non-COVID-19 ARDS, prone positioning has been shown to improve oxygenation and is associated with improved outcomes. The improvement in oxygenation and the reduction in the risk of ventilation-induced lung injury have been explained by a more homogeneous distribution of transpulmonary pressures, which opens the dorsal atelectatic areas, thus reducing regional lung stress.(3)

In COVID-19 ARDS, different phenotypes have been proposed.(1) In phenotype 1, lung weight and lung compliance may be relatively normal, alveolar recruitment is minimal, and hypoxemia is mainly due to increased lung regions with low ventilation/perfusion ratios.(4) On the other hand, in phenotype 2, lung weight is increased, lung compliance is markedly reduced, alveolar recruitment is variable, and hypoxemia is mainly due to increased true shunting. Both phenotypes are characterized by increased wasted ventilation (high dead space ventilation and lung regions with high ventilation/perfusion ratios).(5) Therefore, the effects of prone positioning in COVID-19 ARDS may differ from those seen in non-COVID-19 ARDS. To date, few randomized controlled trials have reported benefits of prone positioning in COVID-19 ARDS.

In a study published in this issue of *Jornal Brasileiro de Pneumologia,* Cunha et al.(6) aimed to identify factors that lead to a positive oxygenation response and predictors of mortality after prone positioning in mechanically ventilated patients with COVID-19. A multicenter cohort study was performed across seven hospitals in Brazil, including patients with a suspected or confirmed diagnosis of COVID-19 who were on invasive mechanical ventilation, had a $PaO_2/FIO_2 < 150$ mmHg, and were prone positioned. An improvement in the PaO_2/FIO_2 ratio of at least 20 mmHg after the first prone positioning session was defined as a positive response. Of the 574 patients studied, 412 (72%) responded positively to the first prone positioning session. Multiple logistic regression showed that "responders" had lower Simplified Acute Physiology Score III and SOFA scores, lower D-dimer levels, and lower baseline PaO_2/FIO_2 ratios. Age, time to the first prone positioning session, number of sessions, pulmonary impairment, and immunosuppression were associated with increased mortality. Overall, although prone positioning led to an improvement in oxygenation, this improvement was not associated with better survival.

The definition of "responders" in COVID-19 patients is heterogeneous across studies,(7-9) including the use of different thresholds for response in oxygenation (e.g., a PaO_2/FIO_2 increase ≥ 20 mmHg; a PaO_2/FIO_2 increase ≥ the median percent change in PaO_2/FIO_2; a PaO_2/FIO_2 ≥ 150 mmHg after returning to the supine position) and the use of ventilatory ratio.

The impact of improvement in oxygenation during prone positioning on ultimate outcomes is controversial. A beneficial effect of early prone positioning on survival has been reported in patients with a $PaO_2/FIO_2 \leq 150$ mmHg or a $PaO_2/FIO_2 \leq 100$ mmHg.(7) Other authors(8,9) found higher mortality in nonresponders (Table 1). In the study by Cunha et al.,(6) prone positioning increased oxygenation and respiratory rate, but it was not associated with improvement in respiratory system mechanics (compliance, driving pressure, or plateau pressure).

In responders, prone positioning promotes alveolar recruitment with higher regional perfusion of dorsal areas. In nonresponders, prone positioning does not redistribute lung densities, and perfusion is mainly redistributed toward dependent lung regions. In COVID-19 phenotype 2, oxygenation may improve due to the redistribution of pulmonary blood flow from dorsal to ventral lung regions but not due to effective alveolar recruitment.(10)

Data suggest that early use of prone positioning, as well as the number of prone positioning sessions, may be associated with better outcomes.(11,12) In the study by Cunha et al.,(6) the time to prone positioning was not fixed nor was it defined *a priori*, which may account for the nonresponders whose first prone positioning session occurred late in the course of COVID-19, even though the number of sessions did not differ between nonresponders and responders. This can be explained by the fact that clinicians play a crucial role in decision making, individualizing the timing and number of sessions. In most previous studies, the decision to prone patients was at the discretion of the attending physician rather than being standardized across centers (Table 1).

Data on timing of intubation have not been reported. Yet, optimal timing of intubation has become a cornerstone in COVID-19 management and is known to be associated with outcomes. Patients with COVID-19 phenotype 1 can initially benefit from noninvasive respiratory support, since they respond better to the higher oxygen fraction and moderate PEEP levels delivered by noninvasive CPAP.(13)

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Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.*

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Dell'Anna et al.[14]	9	Case series, single center	NR	NR	NR	Prone positioning increased PaO_2/FiO_2 compared with supine positioning	Prone positioning decreased pulmonary shunt fraction compared with supine positioning	NR
Concha et al.[15]	17	Case series, single center	Day 1	46 ± 18 h	3 ± 1	NR	No clear differences were found between supine and prone positioning	17.65%
Lucchini et al.[16]	96	Retrospective single center	8 (4-45) h	18 (16-32) h (standard < 24 h; extended > 24 h)	1 cycle in 31%, 2 cycles in 22%, 3 in 17%, > 3 in 30%	Significant changes in PaO_2/FiO_2 were detected before and after proning	NR	18%
Rossi et al.[10]	25	Case series, single center	NR	NR	NR	PaO_2/FiO_2 did not change significantly between supine and prone positioning	Ventilatory ratio, V_E, V_T, Ppeak, Pplat, ΔP, C_{rs} changed between supine and prone positioning	32%
Binda et al.[17]	34	Prospective, single center	NR	72 (60-83) h	NR	NR	NR	NR
Stilma et al.[18]	438	Observational prospective, multicenter	0 (0-1)	16 (11-23) h in patients with an indication for prone positioning 14 (10-19) h in patients without an indication for prone positioning	NR	$PaO_2/FiO_2 \leq 150$ mmHg was found in 90 (38.8) of the patients in the no-indication+no-prone group and in 104 (47.9) of those in the no-indication+prone group, as well as in 56 (87.5) of those in the indication+no-prone group and in 189 (85.5) of those in the indication+prone group	Significant changes in Ppeak were found between patients in the no-indication+no-prone group vs. those in the no-indication+prone group Differences in ΔP, C_{rs}, and RR were found between those in the indication+no-prone group vs. those in the indication+prone group	28.6% in the no-indication+prone group vs. 31.3% in the no-indication+no-prone group 41.3% in the indication+no-prone group vs. 34.1% in the indication+prone group

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Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Oujidi et al.[19]	23 patients on ECMO	Retrospective, single center	NR	16 h	NR	PaO_2/FiO_2 improved significantly after prone positioning during ECMO	V_T, Pplat, and FiO_2 were significantly higher before than after prone positioning	NR
Longino et al.[20]	27 of 49	Retrospective, multicenter	NR	NR	NR	PaO_2/FiO_2 in the prone group was lower than that in the non-prone group.	C_{rs} in the prone group was lower over days 1-10 but higher over days 1-35	NR
Park et al.[21]	23 COVID-19 ARDS patients vs. 45 non-COVID-19 ARDS patients	Retrospective, single center	9 (4-12) days in the COVID-19 group	18 (17-19) h in the COVID-19 group vs. 18 (16-19) h in the non-COVID-19 group	4 (3-9) in the COVID-19 group vs. 2 (1-4) in the non-COVID-19 group	PaO_2/FiO_2 was 107 (92-132) mmHg in the COVID-19 group vs. 96 (74-120) mmHg in the non-COVID-19 group	ΔP, RR, and V_E were higher in the non-COVID-19 group; static C_{rs} was higher in the COVID-19 group	21.7% in the COVID-19 group vs. 73.8% in the non-COVID-19 group
Rezoagli et al.[22]	23, standard prone (16 h) vs. 15, prolonged prone (40 h)	Retrospective, single center	NR	Overall, 76 ± 45 h, standard vs. 118 ± 79 h, prolonged Each cycle, 17 ± 3 h, standard vs. 39 ± 6 h, prolonged	4 (2-5), standard vs. 2 (2-4), prolonged	Oxygenation improved during prone positioning and after resupination compared with baseline	No significant differences were found in mechanics	22%, standard vs. 33% prolonged
Cour et al.[23]	18 (9 low recruiters vs. 9 high recruiters)	Case series, single center	NR	NR	1 (0-2)	In high responders, PaO_2/FiO_2 improved between supine and re-supine positioning after prone positioning; this did not happen in low responders	An increase in C_{rs} and a reduction in ventilatory ratio with improved oxygenation were found in responders during prone positioning	NR
Scaramuzzo et al.[9]	191 (96 responders vs. 95 nonresponders)	Observational prospective, multicenter	NR	16.0 (16.0-16.7) h in responders vs. 16 (16-17) h in nonresponders	NR	PaO_2/FiO_2 improved after prone positioning: 100% (67-155 mmHg) in responders vs. 19% (3-31 mmHg) in nonresponders	Nonresponders had lower C_{rs} supine and higher Pplat	33.3% in responders vs. 53.7% in nonresponders

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Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Liu et al.[24]	29 (13, early prone vs. 16, control prone)	Observational retrospective, single center	Within 24 h in the early group vs. after day 3 in the control group	NR	NR	PaO_2/FIO_2 improved more in the early group, but improvement was seen in both groups after prone positioning	RR improved in the early group	0% in both groups
Langer et al.[8]	648 proned patients vs. 409 non-proned patients	Observational retrospective, multicenter	NR	18.6 (16-22) h in a subgroup of 78 patients	NR	PaO_2/FIO_2 improved after prone positioning and decreased after resupination in the subgroup of 78 patients (61 responders vs. 17 nonresponders)	Pplat was higher in the prone group. In the subgroup of 78 patients, C_{rs} and ventilatory ratio did not change with prone positioning, RR increased between supine and prone positioning ΔP and Pplat were higher in nonresponders; C_{rs} was higher in responders	In-hospital mortality: 45% in the prone group vs. 33% in the non-prone group ICU mortality: 41% in the prone group vs. 28% in the non-prone group Mortality was higher among nonresponders (65%) than among responders (38%)
Vollenberg et al.[25]	13	Observational retrospective, multicenter	NR	NR	1-6	In responders, PaO_2/FIO_2 improved by 38.4%	No significant reduction was found in C_{rs} in the prone position	53.85%
Mathews et al.[7]	702 proned patients vs. 1,636 non-proned patients	Observational prospective, multicenter	Within the first 2 days of ICU admission	NR	NR	PaO_2/FIO_2 improved significantly with prone positioning	NR	46.6% in the prone group vs. 47.3% in the non-prone group

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Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Sang et al.[26]	20	Observational retrospective, single center	NR	NR	NR	PaO_2 improved with prone positioning	Static C_{rs} improved with prone positioning	NR
Clarke et al.[27]	20	Observational prospective, single center	1.00 (1.00-1.75) days	16.2 (15.6-17.4) h	NR	PaO_2/FIO_2 improved significantly before and after prone positioning	No differences were found in C_{rs} before vs. after prone positioning	15%
Douglas et al.[28]	61 (42 survivors vs. 19 nonsurvivors)	Observational retrospective, single center	0.28 (0.11-0.80) days	4.44 (1.97-6.24) days in survivors vs. 3.99 (3.00-9.48) days in nonsurvivors	1 session in 31 survivors (50.8) and in 15 nonsurvivors (24.6); 2 sessions in 7 survivors (11.5) and in 4 nonsurvivors (6.6); 3 sessions in 3 survivors (4.9) and in 1 nonsurvivor (1.6)	PaO_2/FIO_2 was higher in survivors vs. nonsurvivors PaO_2/FIO_2 significantly worsened between prone positioning and resupination	NR	68.85%
Shelhamer et al.[29]	62 proned patients vs. 199 non-proned patients	NR	NR	NR	NR	PaO_2/FIO_2 improved after prone positioning	NR	77.4% in the prone group vs. 83.9% in the non-prone group
Gleissman et al.[30]	44	Observational retrospective, single center	NR	14 (12-17) h	NR	PaO_2/FIO_2 improved after prone positioning	No significant changes were reported	NR

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Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Weiss et al.[31]	42 (26 responders vs. 16 nonresponders)	Observational retrospective, single center	NR	16 (16-17) h	3 (2-6)	PaO_2/FiO_2 improved after prone positioning and remained improved after resupination	No differences were found between responders and nonresponders Ventilatory ratio changed between supine and prone positioning	26%
Abou-Arab et al.[32]	25	Observational single center	NR	NR	NR	PaO_2/FiO_2 improved after prone positioning	C_{rs}, Pplat, and ventilatory ratio remained unchanged before and after prone positioning	16%
Berrill[33]	34	Observational retrospective, single center	23.0 ± 62.7 h	63.5 ± 38.2 h; each patient, 16.5 ± 2.7 h	4.0 ± 2.4	PaO_2/FiO_2 improved after prone positioning	No changes from baseline were reported	NR
Zang et al.[34]	23 proned patients vs. 37 non-proned patients	Observational prospective, single center	NR	NR	NR	SpO_2 and the ROX index increased between supine and prone positioning	Not evaluated	43.5% in the prone group vs. 75.7% in the non-proned group
Garcia et al.[35]	14 patients on ECMO (11 patients on ECMO alone)	Observational retrospective, single center	NR	NR	NR	PaO_2/FiO_2 improved after prone positioning	V_T, Pplat, C_{rs}, and ΔP remained unchanged between supine and prone positioning Changes were found in RR	78.6% in the prone+ECMO group vs. 27.3% in the ECMO-only group
Carsetti et al.[36]	6	Case series, single center	NR	16 h, standard; 36 h, prolonged	NR	PaO_2/FiO_2 improved after prone positioning and after resupination	C_{rs} did not change	NR

NR: not reported; Ppeak: peak pressure; Pplat: plateau pressure; ΔP: driving pressure; C_{rs}: respiratory system compliance; ECMO: extracorporeal membrane oxygenation; and ROX index: SpO_2/FiO_2 ratio divided by RR. *Values expressed as n, n (%), mean ± SD, or median (IQR).

On the other hand, worsening of oxygenation during noninvasive respiratory support or the presence of COVID-19 phenotype 2 requires prompt and early intubation and invasive mechanical ventilation.

Cunha et al.[6] listed some limitations of their study, including its retrospective design (not all data could be found in the electronic medical records, and they were unable to control for the prescription and timing of prone positioning), the absence of an *a priori* power analysis or preplanned protocol, the small sample size, the lack of control groups, and the lack of description of other rescue therapies (e.g., inhaled nitric oxide, recruitment maneuvers, and extracorporeal membrane oxygenation), which may affect patient outcomes.

Overall mortality in the study by Cunha et al.[6] was 69.3%, which suggests that those patients with severe COVID-19 are at high risk of death. This mortality rate is high compared with those reported in other studies involving COVID-19 patients who underwent prone positioning (Table 1). Prone positioning is just one part of a therapeutic concept including a sophisticated ventilation strategy, strict fluid balance control, and dedicated hemodynamic management, all of which may affect outcomes.[3]

In conclusion, the study by Cunha et al.[6] improves our knowledge about the use of prone positioning in COVID-19 patients with severe hypoxemic respiratory failure, suggesting that this maneuver should be used early regardless of oxygenation response. However, their findings cannot be generalized without confirmation in larger randomized controlled trials.

AUTHOR CONTRIBUTIONS

DB: review and approval of the final manuscript. PP and PRMR: senior authorship and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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