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.1,2 Prone positioning is a rescue therapy for ARDS patients with hypoxemia refractory to protective mechanical ventilation with high FiO2.2

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.4,5 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 PaO2/FiO2 < 150 mmHg, and were prone positioned. An improvement in the PaO2/FiO2 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, 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 PaO2/FiO2 increase ≥ 20 mmHg; a PaO2/FiO2 increase ≥ the median percent change in PaO2/FiO2; a PaO2/FiO2 ≥ 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 PaO2/FiO2 ≤ 150 mmHg or a PaO2/FiO2 ≤ 100 mmHg.7 Other authors8,9 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 prone 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$$_{p}$, Ppeak, Pplat, ΔP, C$$_{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 and 14 (10-19) h in patients without an indication for prone positioning | NR                                   | PaO$_2$/FiO$_2$ ≤ 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+prone group vs. those in the no-indication+no-prone group and 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 and 41.3% in the indication+no-prone group vs. 34.1% in the indication+prone group |
### Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

| Study | Number of prone patients | Study design | Initiation of prone positioning | Duration of prone positioning | Number of prone positioning sessions | Oxygenation | Pulmonary mechanics | Mortality |
|-------|--------------------------|--------------|---------------------------------|-------------------------------|--------------------------------------|-------------|---------------------|-----------|
| Ojjidi et al. (19) | 23 patients on ECMO | Retrospective, single center | NR | 16 h | NR | PaO2/FiO2 improved significantly after prone positioning during ECMO | Vr, Pplat, and FiO2 were significantly higher before than after prone positioning | NR |
| Longino et al. (20) | 27 of 49 | Retrospective, multicenter | NR | NR | NR | PaO2/FiO2 in the prone group was lower than that in the non-prone group. | Cc, 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 | NR | NR | NR | PaO2/FiO2 improved during prone positioning and after resupilation compared with baseline | No significant differences were found in mechanics | 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 (3-9), standard vs. 2 (2-4), prolonged | Oxygenation improved during prone positioning and after resupilation 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, PaO2/FiO2 improved between supine and re-supine positioning after prone positioning; this did not happen in low responders | An increase in Cc 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 | PaO2/FiO2 improved after prone positioning; 100% (67-155 mmHg) in responders vs. 19% (3-31 mmHg) in nonresponders | Nonresponders had lower Cc, supine and higher Pplat in responders vs. 33.3% in responders vs. 53.7% in nonresponders | |
| 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                                  | PaO₂/FIO₂ 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 | 18.6 (16-22) h in a subgroup of 78 patients | NR                            | NR                                  | PaO₂/FIO₂ 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, C₁, and ventilatory ratio did not change with prone positioning, RR increased between supine and prone positioning. ΔP and Pplat were higher in nonresponders; C₁ 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, PaO₂/FIO₂ improved by 38.4% | No significant reduction was found in C₁ 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 | PaO₂/FIO₂ improved significantly with prone positioning | | 46.6% in the prone group vs. 47.3% in the non-prone group |
| Study | Number of prone 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 | PaO₂ improved with prone positioning | Static Cₐ, 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 | PaO₂/FIO₂ improved significantly before and after prone positioning | No differences were found in Cₐ, 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) | PaO₂/FIO₂ was higher in survivors vs. nonsurvivors | PaO₂/FIO₂ significantly worsened between prone positioning and resupination | 68.85% |
| Shelhamer et al. (29) | 62 prone patients vs. 199 non-proned patients | NR | NR | NR | NR | PaO₂/FIO₂ 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 | PaO₂/FIO₂ improved after prone positioning | No significant changes were reported | NR |
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 |
|------------------------------|---------------------------|--------------|---------------------------------|-------------------------------|--------------------------------------|-------------|---------------------|-----------|
| Weiss et al. (31)            | 42 (26 responders vs. 16 nonresponders) | Observational retrospective, single center | NR | 16 (16-17) h | 3 (2-6) | PaO₂/FiO₂ improved after prone positioning and remained improved after resupination | No differences were found between responders and nonresponders | 26% |
| Abou-Arab et al. (32)        | 25                        | Observational single center | NR | NR | NR | PaO₂/FiO₂ improved after prone positioning | Crs, 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 | PaO₂/FiO₂ 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 | SpO₂ 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 | PaO₂/FiO₂ improved after prone positioning | V̇, Pplat, Crs, and ΔP remained unchanged between supine and prone positioning | 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 | PaO₂/FiO₂ improved after prone positioning and after resupination | Ccr did not change | NR |

NR: not reported; Ppeak: peak pressure; Pplat: plateau pressure; ΔP: driving pressure; Crs: respiratory system compliance; ECMO: extracorporeal membrane oxygenation; and ROX index: SpO₂/FiO₂ 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. listed some limitations of their study, including its retrospective nature (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. 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.

In conclusion, the study by Cunha et al. 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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