**Prone position in COVID-19 and non-COVID-19 acute respiratory distress syndrome: an international multicentre observational comparative study.**

**Authors**

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SUPPLEMENTAL DIGITAL CONTENT

Ethics (IRBO)

Approval for data collection was obtained at each participating institution (Comité d'éthique du CHU de Lyon Number of approval 20-42 – France; Approval n. 10796 – London, and (Comitato Etico Milano Area I; 17263/2020- 2020/ST/095), consent was waived, and data were anonymised before collating into the central database.

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**Table E1: Baseline characteristics at the time of intubation, in each etiology cohort.**

|  |  |
| --- | --- |
|  | **Baseline (Intubation)** |
| **Characteristic** | **Overall**,N = 376 | **ARDS**,N = 156 | **C-ARDS**,N = 220 | **p** |
| Gender, Male | 276 (73%) | 99 (63%) | 177 (80%) | <0.001 |
| Age, yr | 62 [54, 71] | 63 [52, 71] | 62 [56, 70] | 0.5 |
| Predicted Body Weight, kg | 66 [57, 72] | 65 [54, 72] | 69 [60, 73] | 0.006 |
| BMI, kg/m2 | 28 [24, 33] | 28 [23, 34] | 28 [25, 32] | 0.2 |
| Admission SOFA | 7 [5, 10] | 9 [7, 12] | 6 [4, 8] | <0.001 |
| **Aetiology** |  |  |  |  |
| COVID-19 | 220 (58.5%) | - | 220 (100%) | - |
| Pneumonia | 100 (26.6%) | 100 (64.1%) | 0 | - |
| Aspiration | 11 (2.9%) | 11 (7.1%) | 0 | - |
| Non-pulmonary sepsis | 45 (12%) | 45 (28.8%) | 0 | - |
| **Respiratory Variables** |  |  |  |  |
| Respiratory Rate, /min | 22 [18, 25] | 24 [20, 28] | 20 [18, 24.5] | <0.001 |
| Peak Airway Pressure, cmH2O | 31 [27, 38] | 35 [29, 41] | 30 [26, 35] | <0.001 |
| Plateau Airway Pressure, cmH2O | 23 [21, 27] | 22.0 [18, 27] | 23 [21, 27] | 0.07 |
| PEEP, cmH2O | 10 [8, 12] | 10 [7, 12] | 12 [10, 14] | <0.001 |
| Mechanical Power, J/min | 22 [17, 26] | 20 [15, 27] | 23 [19, 25] | 0.04 |
| Tidal Volume, ml | 422 [373, 480] | 400 [352, 450] | 440 [388, 498] | <0.001 |
| Tidal Volume per PBW, ml/kg | 6.4 [6.0, 7.3] | 6.3 [5.9, 7.0] | 6.5 [6.0, 7.5] | 0.1 |
| Driving Pressure, cmH2O | 13.0 [10.0, 16.0] | 13.0 [10.0, 16.0] | 12.0 [9.0, 14.0] | 0.04 |
| Compliance, ml/cmH2O | 33 [26, 45] | 32 [24, 39] | 36 [28, 47] | 0.002 |
| FiO2, % | 75 [60, 90] | 80 [60, 100] | 70 [58, 90] | 0.1 |
| PaO2, kPa | 10.3 [9.1, 12.3] | 10.2 [8.8, 11.9] | 10.5 [9.3, 12.4] | 0.08 |
| PaCO2, kPa | 6.0 [5.2, 6.8] | 6.1 [5.3, 7.1] | 5.7 [5.1, 6.8] | 0.01 |
| PaO2/FiO2 ratio, kPa | 15 [12, 20] | 14 [11, 18] | 16 [12, 20] | 0.02 |
| Minute Volume, L/min | 9.3 [7.9, 10.5] | 9.5 [8.0, 11.2] | 9.1 [7.9, 10.2] | 0.07 |
| Corrected Minute Volume, L/min | 10.3 [8.3, 12.7] | 11.0 [8.7, 13.5] | 9.7 [8.1, 12.0] | <0.001 |
| Ventilatory Ratio | 1.68 [1.37, 2.09] | 1.91 [1.56, 2.35] | 1.54 [1.25, 2.00] | <0.001 |
| Mechanical Power per PBW, J/min/kg | 0.33 [0.25, 0.42] | 0.34 [0.23, 0.43] | 0.33 [0.29, 0.42] | 0.5 |
| **Disease Severity, n** | 372 | 152 | 220 | 0.003 |
| Severe | 141 (37.9%) | 68 (44.7%) | 73 (33.2%) |  |
| Moderate | 203 (54.6%) | 70 (46.1%) | 133 (60.5%) |  |
| Mild | 28 (7.5%) | 14 (9.2%) | 14 (6.3%) |  |

The conversion factor between kPa and mmHg is (1 kPa = 7.500617 mmHg)

Table E2: Baseline organ failure prevalence by etiology cohort and absolute PaO2/FiO2 response to proning

|  |
| --- |
| **Organ failure prevalence** |
|  | **Overall**, N = 376 | **ARDS**, N = 156 | **C-ARDS**, N = 220 | **p-value** |
| Vasopressors | 299 (80%) | 144 (92%) | 155 (70%) | <0.001 |
| Renal Replacement Therapy | 40 (12%) | 25 (16%) | 15 (8.1%) | 0.023 |
| Neuromuscular Blockade | 308 (82%) | 147 (94%) | 161 (73%) | <0.001 |
| Inhaled Nitric Oxide | 15 (4.0%) | 6 (3.8%) | 9 (4.1%) | >0.9 |
| **Organ failure prevalence stratified by aetiology and absolute PaO2/FiO2 response to proning** |
| **C-ARDS** |   |   |   |   |
|  | **Overall**, N = 210 | **NON-RESPONDER**, N = 50 | **RESPONDER**, N = 160 | **p-value** |
| Vasopressors | 147 (70%) | 40 (80%) | 107 (67%) | 0.077 |
| Renal Replacement Therapy | 15 (8.5%) | 5 (11%) | 10 (7.6%) | 0.5 |
| Neuromuscular Blockade | 151 (72%) | 36 (72%) | 115 (72%) | >0.9 |
| Inhaled Nitric Oxide | 9 (4.3%) | 4 (8.0%) | 5 (3.1%) | 0.2 |
| **ARDS** |   |   |   |   |
|  | **Overall**, N = 141 | **NON-RESPONDER**, N = 31 | **RESPONDER**, N = 110 | **p-value** |
| Vasopressors | 130 (92%) | 27 (87%) | 103 (94%) | 0.3 |
| Renal Replacement Therapy | 24 (17%) | 8 (26%) | 16 (15%) | 0.14 |
| Neuromuscular Blockade | 134 (95%) | 31 (100%) | 103 (94%) | 0.3 |
| Inhaled Nitric Oxide | 6 (4.3%) | 1 (3.2%) | 5 (4.5%) | >0.9 |

Table E3: Baseline characteristics by etiology cohort and absolute PaO2/FiO2 response to proning

|  |  |  |
| --- | --- | --- |
|  | **ARDS,** N = 141 | **C-ARDS**, N = 213 |
|  | NON-RESPONDER N = 31 (22%) | RESPONDERN = 110 (78%) | p | NON-RESPONDER N = 50 (24%) | RESPONDER N = 160 (76%) | p |
| Male | 19 (61%) | 70 (64%) | 0.8 | 41 (82%) | 128 (80%) | 0.8 |
| Age, yr | 65 [56, 69] | 60 [49, 71] | 0.7 | 64 [57, 70] | 62 [54, 70] | 0.5 |
| Predicted Body Weight, kg | 66 [56, 70] | 65 [54, 73] | 0.5 | 64 [57, 70] | 62 [54, 70] | >0.9 |
| BMI | 27 [24, 34] | 29 [24, 34] | 0.8 | 27.8 [25.3, 31.0] | 28.6 [25.2, 32.7] | 0.3 |
| Admission SOFA | 9.0 [5.0, 12.5] | 10.0 [8.0, 12.0] | 0.3 | 6.00 [4.00, 8.00] | 6.00 [4.00, 8.00] | 0.7 |
| Hospital to ICU Admission, days | 0.0 [0.0, 1.5] | 0.0 [0.0, 1.8] | 0.6 | 0.71 [0.00, 3.00] | 1.00 [0.46, 3.00] | 0.2 |
| Intubation to Initial Proning, days | 1.1 [0.7, 3.0] | 1.0 [0.5, 2.0] | 0.3 | 3.1 [0.7, 5.6] | 1.9 [0.7, 5.0] | 0.3 |
| Proning Duration, hours | 16.0 [13.5, 20.0] | 16.0 [14.1, 18.0] | 0.6 | 16.8 [16.0, 18.1] | 16.0 [15.2, 18.0] | 0.2 |
| Heart Rate, /min | 94 [78, 108] | 105 [84, 118] | 0.090 | 96 [81, 116] | 89 [71, 101] | 0.017 |
| Mean BP, mmHg | 75 [68, 78] | 76 [68, 83] | 0.5 | 77 [70, 87] | 76 [70, 85] | 0.7 |
| Respiratory Rate, /min | 28.0 [23.0, 31.5] | 26.0 [24.0, 30.0] | 0.2 | 24 [19, 30] | 22 [18, 26] | 0.039 |
| Peak Airway Pressure, cmH2O | 36 [32, 46] | 38 [32, 43] | 0.7 | 34 [30, 39] | 31 [27, 36] | 0.034 |
| Plateau Airway Pressure, cmH2O | 23.5 [20.0, 30.2] | 25.0 [23.0, 29.5] | 0.3 | 24.0 [23.0, 28.0] | 26.0 [22.0, 29.0] | 0.8 |
| PEEP, cmH2O | 10.0 [8.0, 11.0] | 10.0 [8.0, 12.0] | 0.11 | 12.0 [10.0, 13.8] | 12.0 [10.0, 14.0] | 0.4 |
| Mechanical Power, J/min | 25 [18, 29] | 26 [19, 31] | 0.4 | 27 [22, 32] | 24 [19, 29] | 0.084 |
| Tidal Volume, mls | 400 [345, 440] | 400 [350, 443] | 0.7 | 440 [394, 500] | 443 [382, 518] | 0.9 |
| Tidal Volume per PBW, mls/kg | 6.1 [5.9, 6.5] | 6.1 [5.8, 6.7] | 0.9 | 6.5 [6.0, 7.6] | 6.5 [6.0, 7.6] | >0.9 |
| Driving Pressure, cmH2O | 12.5 [10.0, 21.0] | 14.0 [11.0, 18.8] | >0.9 | 12.0 [10.0, 15.0] | 11.0 [8.0, 15.0] | 0.4 |
| Compliance, mls/cmH2O | 31 [17, 39] | 30 [22, 36] | 0.9 | 36 [25, 46] | 41 [28, 55] | 0.3 |
| FiO2, % | 60 [52, 82] | 70 [60, 100] | 0.13 | 70 [60, 85] | 75 [60, 95] | 0.2 |
| PaO2, kPa | 11.60 [9.73, 12.80] | 9.43 [8.40, 10.51] | <0.001 | 9.94 [8.76, 11.26] | 9.04 [8.27, 10.27] | 0.008 |
| PaCO2, kPa | 6.20 [5.63, 6.93] | 6.13 [5.34, 7.07] | 0.7 | 6.54 [5.56, 7.46] | 6.36 [5.47, 7.35] | 0.7 |
| PaO2/FiO2, kPa | 17 [13, 28] | 14 [10, 17] | <0.001 | 14.5 [10.5, 20.2] | 12.8 [10.7, 15.0] | 0.015 |
| Minute Volume, l/min | 10.56 [8.77, 12.10] | 10.50 [8.54, 11.70] | >0.9 | 10.50 [8.60, 12.70] | 9.78 [8.01, 11.22] | 0.057 |
| Corrected Minute Volume, l/min | 11.7 [10.1, 13.5] | 12.0 [9.5, 14.8] | >0.9 | 13.2 [9.6, 16.6] | 11.2 [8.9, 14.2] | 0.051 |
| Ventilatory Ratio | 2.03 [1.69, 2.51] | 2.05 [1.58, 2.55] | 0.6 | 2.00 [1.43, 2.67] | 1.90 [1.44, 2.29] | 0.068 |

The conversion factor between kPa and mmHg is (1 kPa = 7.500617 mmHg)

#  Relative change in parameters on prone positioning, by COVID-19 status and absolute PaO2/FiO2 response to proning

Table E4: Relative change in parameters on prone positioning, stratified by aetiology cohort and absolute PaO2/FiO2 response to proning

|  |  |  |
| --- | --- | --- |
|  | **ARDS,** N = 141 | **C-ARDS**, N = 213 |
|  | NON-RESPONDER N = 31 | RESPONDER N = 110 | p | NON-RESPONDER N = 50 | RESPONDER N = 160 | p |
| Heart Rate, /min | -3 [-14, 6] | -3 [-14, 8] | 0.9 | -2 [-12, 8] | -3 [-12, 7] | 0.7 |
| Mean BP, mmHg | -1 [-6, 6] | 2 [-9, 10] | 0.8 | 2 [-8, 9] | 2 [-7, 11] | 0.8 |
| Respiratory Rate, /min | 0.0 [-1.0, 0.0] | 0.0 [-2.0, 2.0] | 0.5 | 0.0 [0.0, 2.0] | 0.0 [-1.0, 2.0] | >0.9 |
| Peak Airway Pressure, cmH2O | -1.0 [-6.5, 1.5] | -1.0 [-5.0, 2.0] | 0.9 | 0.0 [-3.0, 2.0] | 0.0 [-3.0, 3.0] | >0.9 |
| Plateau Airway Pressure, cmH2O | -1.0 [-2.0, 2.0] | -2.0 [-5.0, 0.0] | 0.026 | -0.5 [-2.0, 3.5] | 0.0 [-2.0, 1.0] | 0.6 |
|  PEEP, cmH2O | 0.00 [0.00, 0.55] | 0.00 [-2.00, 2.00] | 0.5 | 0.0 [-1.0, 0.0] | 0.0 [-1.2, 0.0] | >0.9 |
|  Mechanical Power, J/min | -1.1 [-2.6, 2.3] | -1.7 [-4.6, 1.5] | 0.4 | 0 [-6, 4] | 0 [-4, 3] | >0.9 |
|  Tidal Volume, mls | 0 [-18, 7] | 0 [-20, 8] | >0.9 | 0 [-39, 20] | 0 [-24, 22] | 0.4 |
|  Tidal Volume per PBW, mls/kg | 0.00 [-0.30, 0.13] | 0.00 [-0.32, 0.13] | >0.9 | 0.00 [-0.53, 0.31] | 0.00 [-0.40, 0.34] | 0.4 |
|  Driving Pressure, cmH2O | -1.0 [-3.0, 0.0] | -2.0 [-4.2, 0.0] | 0.2 | 0.0 [-2.0, 2.0] | 0.0 [-2.0, 1.0] | 0.2 |
|  Compliance, mls/cmH2O | 2 [-2, 8] | 4 [0, 9] | 0.4 | -1 [-10, 5] | 3 [-3, 10] | 0.024 |
|  FiO2, % | 0 [-12, 0] | -30 [-40, -18] | <0.001 | 0 [-10, 5] | -25 [-40, -20] | <0.001 |
|  PaO2, kPa | -2.0 [-3.8, -0.6] | 1.6 [0.1, 4.8] | <0.001 | -0.4 [-2.6, 1.0] | 1.6 [0.0, 3.2] | <0.001 |
|  PaCO2, kPa | -0.31 [-1.02, 0.23] | -0.39 [-1.27, 0.30] | 0.6 | 0.37 [-0.64, 1.44] | -0.23 [-0.80, 0.52] | 0.026 |
|  PaO2/FiO2, kPa | -3 [-8, 0] | 12 [7, 21] | <0.001 | 0 [-3, 2] | 10 [6, 18] | <0.001 |
|  Minute Volume, l/min | 0.00 [-0.75, 0.20] | 0.00 [-1.01, 0.78] | 0.4 | 0.03 [-0.59, 1.17] | 0.00 [-0.76, 1.15] | >0.9 |
|  Corrected Minute Volume, l/min | -1.47 [-2.40, 0.57] | -0.68 [-2.49, 0.71] | 0.7 | 0.4 [-1.1, 2.4] | 0.2 [-1.8, 1.6] | 0.2 |
| Ventilatory Ratio | -0.24 [-0.37, 0.09] | -0.13 [-0.38, 0.11] | 0.8 | 0.05 [-0.18, 0.45] | 0.03 [-0.26, 0.24] | 0.3 |
| **Outcome** |  |  |  |  |  |  |
| Hospital to ICU Admission, days | 0 [0, 1.5] | 0 [0, 2] | 0.6 | 0.7 [0, 3] | 1 [0.5, 3] | 0.2 |
| ICU Length of Stay, days | 15 [8, 24] | 17 [10, 26] | 0.5 | 22 [12, 41] | 22 [14, 39] | >0.9 |
| Hospital Admit to Proning, days | 3 [2, 10] | 3 [1, 6] | 0.12 | 6 [3.8, 10.5] | 5.0 [2.8, 7.7] | 0.06 |
| Intubation to Proning, days | 1.1 [0.7, 3.0] | 1.0 [0.6, 2.0] | 0.3 | 3.1 [0.7, 5.6] | 1.9 [0.7, 5.0] | 0.3 |
| Duration of Initial Proning Session, hours | 16.0 [13.5, 20.0] | 16.0 [14.1, 18.0] | 0.6 | 16.8 [16.0, 18.1] | 16.0 [15.2, 18.0] | 0.2 |
| Number of Proning Sessions | 2 [1, 3] | 1.5 [1, 3] | 0.5 | 4 [2, 5] | 4 [2, 6] | 0.4 |
| Total Proning Duration, hours | 32 [16, 48] | 22 [16, 44] | 0.6 | 50 [23, 74] | 64 [32, 96] | 0.2 |
| Period of Proning, days | 2.0 [0.7, 5.9] | 1 [0.7, 4.3] | 0.4 | 6 [2, 14] | 4 [1, 9] | 0.1 |
| Predicted Hospital Mortality, % | 58 [33, 81] | 58 [29, 83] | 0.8 | 18 [12, 31] | 20 [12, 31] | 0.9 |
| ICU Mortality | 17 (55%) | 53 (48%) | 0.5 | 27 (54%) | 63 (39%) | 0.07 |
| : change between supine and prone computed for each variable as (supine-prone)/supine median [IQR], p-values: Mann-Whitney U Test |

# Change in PaO2/FiO2 ratio from baseline to prone positioning



Figure E1 - Change in PaO2/FiO2 ratio from baseline to prone positioning

# Prediction of change in PaO2/FiO2 ratio on pronePositioning – OLS Linear Model

## Delay from Intubation to Proning

Although the delay to proning was negatively associated with the change in PaO2/FiO2 ratio on proning, we found this effect was different, but near constant before and after the first 24 hours. Figure 1 below, indicates the negative association when considered over the entire range of delay to proning, with the black trend line. The differing response in the early (<24 hour) period vs the later (>24 hour) can be clearly seen, furthermore over the scale of each period it can be seen that the response is constant within the calculated confidence intervals for each period.



Figure E2 - Change in PaO2/FiO2 ratio upon proning vs Time from Intubation to Proning

Supine PaO2/FiO2 was negatively associated with a 0.7kPa (95% CI: -0.9, -0.5) reduction in predicted PaO2/FiO2 increase per supine kPa. Proning after 24 hours reduced the predicted PaO2/FiO2 increase by -3.0 kPa (95% CI: -5.4, -0.6), and C-ARDS reduced predicted PaO2/FiO2 increase by -2.8 kPa (95% CI: -5.3, -0.4) (E-Figure 3).

Therefore, we included delay to proning as a dichotomous indicator variable indicating proning within 24 hours of intubation.

## OLS Model

We fitted a linear model (estimated using OLS) to predict the change in PaO2/FiO2 ratio on proning with PaO2/FiO2 ratio prior to proning, whether proning occurred more than or equal to twenty four hours after intubation, and COVID-19 status.

If:

$$∆PaO\_{2}:FiO\_{2}= \frac{PaO\_{2}}{FiO\_{2}}\_{prone}- \frac{PaO\_{2}}{FiO\_{2}}\_{supine}$$

$$ T\_{prone} = 0 if proned within 24 hours of intubation, 1 otherwise$$

COVID19$ = 0 if ARDS, 1 if C-ARDS$

Then our regression model was defined as:

$$∆PaO\_{2}:FiO\_{2}= β\_{0}+ β\_{1}.\frac{PaO\_{2}}{FiO\_{2}}\_{supine}+ β\_{2}.COVID19+β\_{3}. T\_{prone} + ε$$

The model explained a significant and moderate proportion of the variance in change in PaO2/FiO2 ratio (R2 = 0.15, F(3, 344) = 20.06, p < .001, adjusted R2 = 0.14). The model’s intercept, corresponding to supine PaO2/FiO2 ratio = 0, proned within 24 hours of intubation and aetiology of ARDS (ie non COVID-19), is at 23.92 kPa (95% CI [20.17, 27.68], t(344) = 12.54, p < .001). Within this model:

* The effect of supine PaO2/FiO2 ratio is significantly negative (β1 = -0.70, 95% CI [-0.90, -0.50], t(344) = -6.84, p < .001; Std. beta = -0.35, 95% CI [-0.45, -0.25])
* The effect of COVID [C-ARDS] is significantly negative (β2 = -2.84, 95% CI [-5.31, -0.37], t(344) = -2.26, p < .05; Std. beta = -0.23, 95% CI [-0.44, -0.03])
* The effect of proning more than or equal to 24 hours after intubation is significantly negative (β3 = -3.01, 95% CI [-5.44, -0.58], t(344) = -2.44, p < .05; Std. beta = -0.25, 95% CI [-0.45, -0.05])

Standardized parameters were obtained by fitting the model on a standardized version of the dataset.

The multivariable linear regression model described, can be illustrated by examination of the plots in Figure 2, where the model regression lines are plotted for the aetiology indicator variable (A) and delay to proning from intubation indicator variable (B).



Figure E3 - Multiple linear regression model indicating C-ARDS and delay to intubation indicator variables. The conversion factor between kPa and mmHg is (1 kPa = 7.500617 mmHg)

## Regression Diagnostics

We include some OLS linear regression diagnostic plots below in figure 3. From this outliers were noted, which on removal from the model, did not qualitatively effect the findings either of effect size or significance of coefficients and so are retained in the model presented here. Some minor deviation from normal distributed residuals, and non-constant variance in the spread-variance plot were also noted, but accepted for this regression.



Figure E4: OLS model diagnostics