Landmark studies in critical care medicine

# Prone Position in ARDS

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# Conflict of interest

No conflict of interest to declare

# History of Prone ventilation

## Comments of a Devil's Advocate[1]

**A. CHARLES BRYAN**

Prone position would reduce pleural pressure gradients and restore aeration to dorsal lung segment.

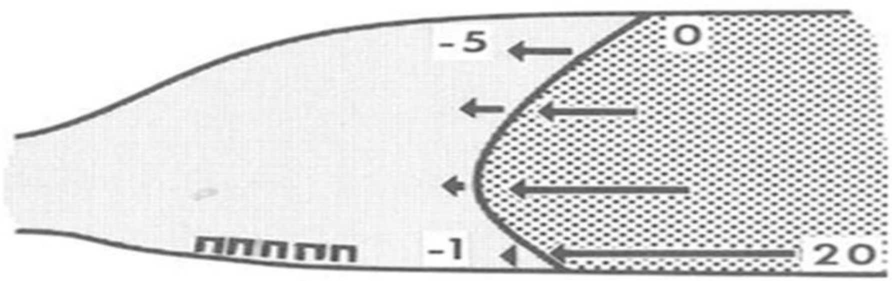



**Fig. 1. In this supine model, the abdominal contents are represented as a liquid hydrostatic column exerting 20 cm $H_2O$ pressure in the lowermost portion. This gradient is transmitted across the diaphragmatic barrier to the dependent region of the intrathoracic cavity. The mechanical consequences include a lesser gradient of pressure (−1 cm $H_2O$) in dependent portions of the lung, leading in turn to reduced inflation during inspiration.**

*AJRCCM 1974: 110 : 143-144*
*Respiratory care: 2015: 60(11): 1660-168*
*CHEST 2017: 151(1) : 215-224*

# History of Prone ventilation

## Use of extreme position changes in acute respiratory failure

MARGARET A. PIEHL, RN, ROBERT S. BROWN, MD

Circle O electric BED

*Protocol*

Arterial samples were obtained by radial artery puncture or from indwelling arterial catheters just before, and 30–120 min after, the position changes. The patients were then turned 180 degrees from supine to prone on the CircOlectric Bed. All determinations were performed on an IL blood gas analyzer. $FIO_2$ and ventilator setting were held constant during the periods of observations.

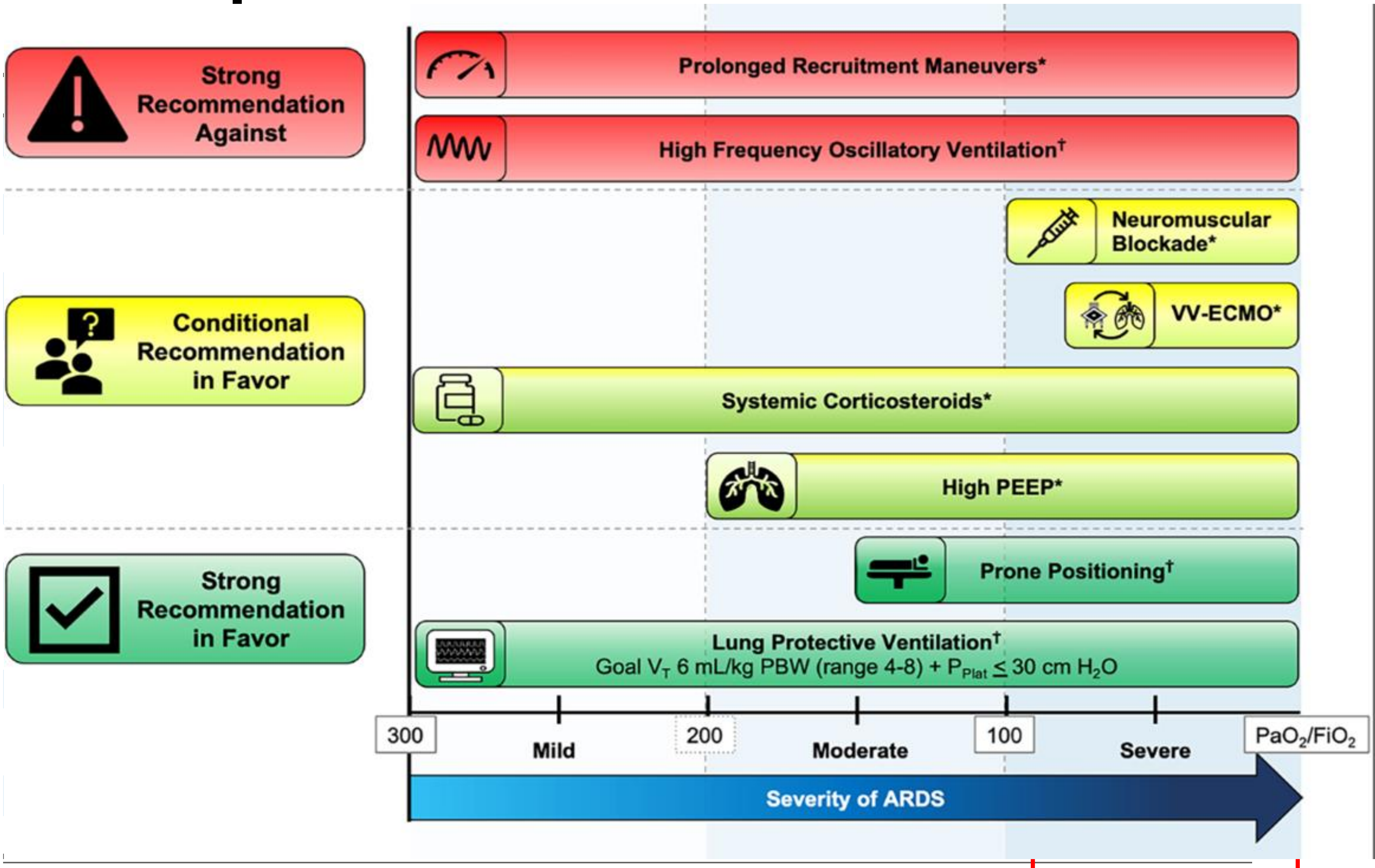
RESULTS

Five patients who had ARDS and who required mechanical ventilation with PEEP were studied; all had documented reductions in $PaO_2$ below 50 torr before or in the early period of therapy. The average control $PaO_2$ of these patients before turning was 82 ± 3 torr. The mean $PaO_2$ increased 47 ± 16 torr after the patient was turned from supine to prone; all other aspects of therapy were held constant.

Torr 1/760 atm

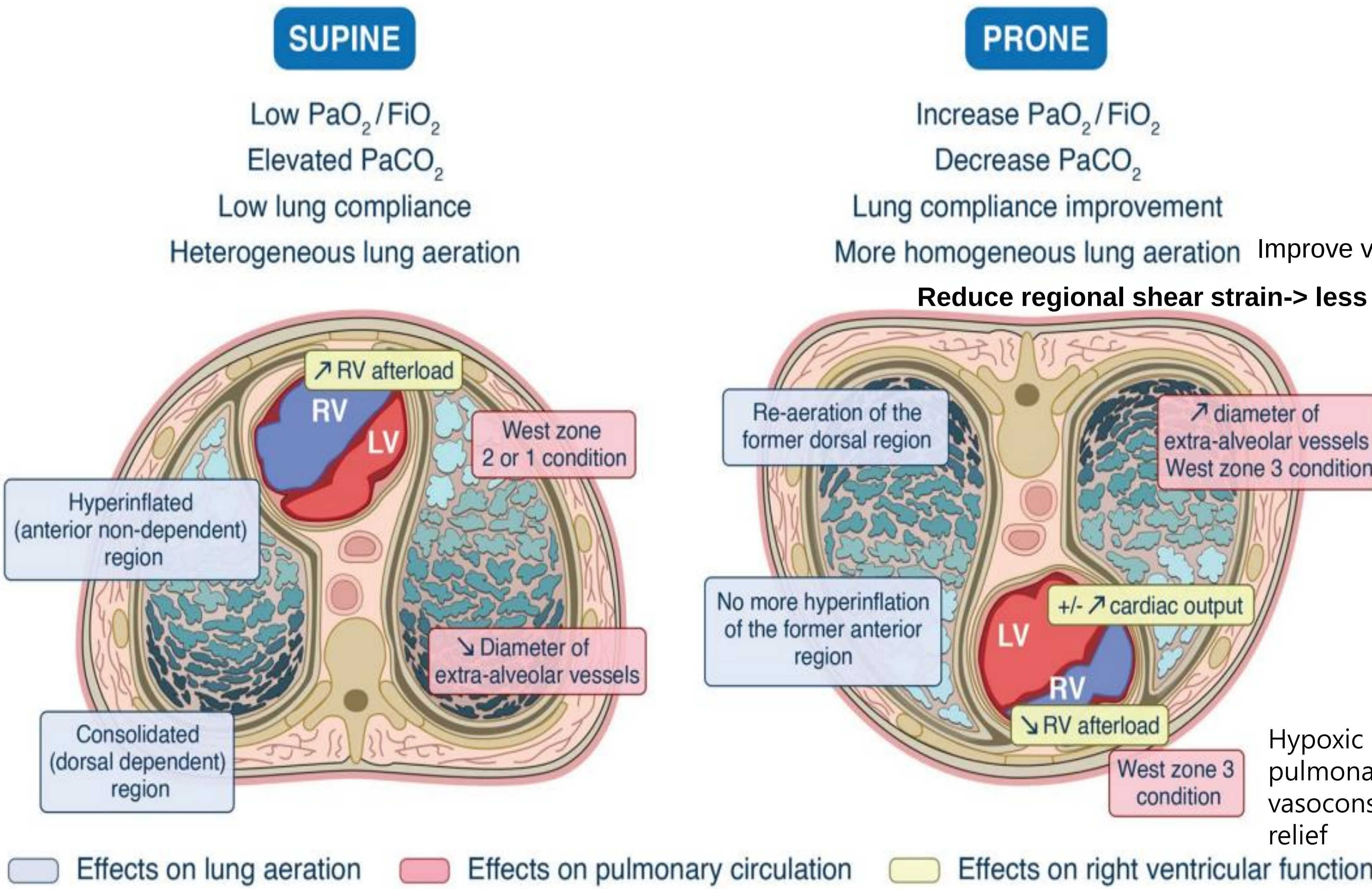
*Critical Care Medicine 1976: 4: 13-14*

# Clinical Trials and Aligning Therapeutic Options with New Guideline




Am J Respir Crit Care Med 2024 Jan 1;209(1):24-36.

# The effects of prone position




Improve v/q mismatch

**Reduce regional shear strain-> less VILI**

Hypoxic pulmonary vasoconstriction relief

*Intensive Care Med (2016) 42:862–870*
*Intensive Care Med (2023) 49:692–694*

- **Physiology, outcome, extended duration**
- **Awakening Prone Position**
- **Prone Position on ECMO**

# Effects of Prone Position on Lung Recruitment and Ventilation-Perfusion Matching in Patients With COVID-19 Acute Respiratory Distress Syndrome: A Combined CT Scan/Electrical Impedance Tomography Study*

Twenty-one intubated patients with moderate or severe COVID 19 -ARDS.
From October 2020 to March 2021 in an Italian
CT scan : prone-> supine position.
Back to the ICU, gas exchange, respiratory mechanics,
ventilation and perfusion EIT-based analysis

Exclusion criteria were: age less than 18 years old, pregnancy, **intubation more than 7 days**, confirmed diagnosis of hospital-acquired bacterial pneumonia, contraindications to the prone position or to EIT monitoring

| Variable | All Patients, $n = 21$ |
|---|---|
| Patients characteristics | |
| Age, yr | 67 (61–72) |
| Comorbidities, $n$ (%) | |
| Hypertension | 12 (57) |
| Diabetes mellitus | 5 (24) |
| Male, $n$ (%) | 17 (81) |
| Body mass index, kg/m$^2$ | 28.6 (26.3–32.0) |
| Sequential Organ Failure Assessment score | 6 (3–7) |
| C-reactive protein, mg/L | 179 (81–211) |
| d-dimers, µg/L | 1,360 (815–5,333) |
| Severe acute respiratory distress syndrome, $n$ (%) | 11 (52) |
| Days from onset of symptoms, d | 12 (8–17) |
| Days from intubation, d | 2 (1–4) |
| Days from first pronation, d | 1 (1–2) |
| Hours spent in prone position before enrollment, hr | 36 (16–72) |
| Ventilator settings | |
| Positive end-expiratory pressure, cm $H_2O$ | 10 (± 1) |
| $Fio_2$, % | 83 (± 16) |
| Tidal volume, mL/kg predicted body weight | 7.5 (± 0.8) |
| Respiratory rate, breaths/min | 19 (± 2) |
| Gas exchange and mechanics in supine at enrollment | |
| $Pao_2/Fio_2$, mm Hg | 105 (84–121) |
| Ventilatory ratio | 1.74 (1.50–2.25) |
| Respiratory system compliance, mL/cm $H_2O$ | 39 (32–52) |

*CCM 2022(50) 723-732*

# Regional Quantitative CT Scan and EIT Analysis Between the Supine and Prone Positions

| Variable | Supine, $n = 21$ | Prone, $n = 21$ | $p$ |
|---|---|---|---|
| CT scan global analysis | | | |
| Total lung weight, g | 1,466 (± 378) | 1,394 (± 381) | 0.007 |
| Hyperinflated lung weight, g | 14 (± 12) | 12 (± 9) | 0.008 |
| Normally aerated lung weight, g | 356 (± 132) | 400 (± 164) | 0.004 |
| Poorly aerated lung weight, g | 525 (± 192) | 505 (± 173) | 0.335 |
| Nonaerated lung weight, g | 571 (± 294) | 477 (± 249) | 0.001 |
| CT scan recruitment analysis | | | |
| Recruitment, % | Baseline | 6.0 (± 6.7) | < 0.001 |
| Ventral derecruitment, % of lung weight | Baseline | −6.9 (± 5.2) | < 0.001 |
| Dorsal recruitment, % of lung weight | Baseline | 12.5 (± 8.0) | < 0.001 |

Prone position
Less Hyperinflation  / More lung aeration /More overall recruitment

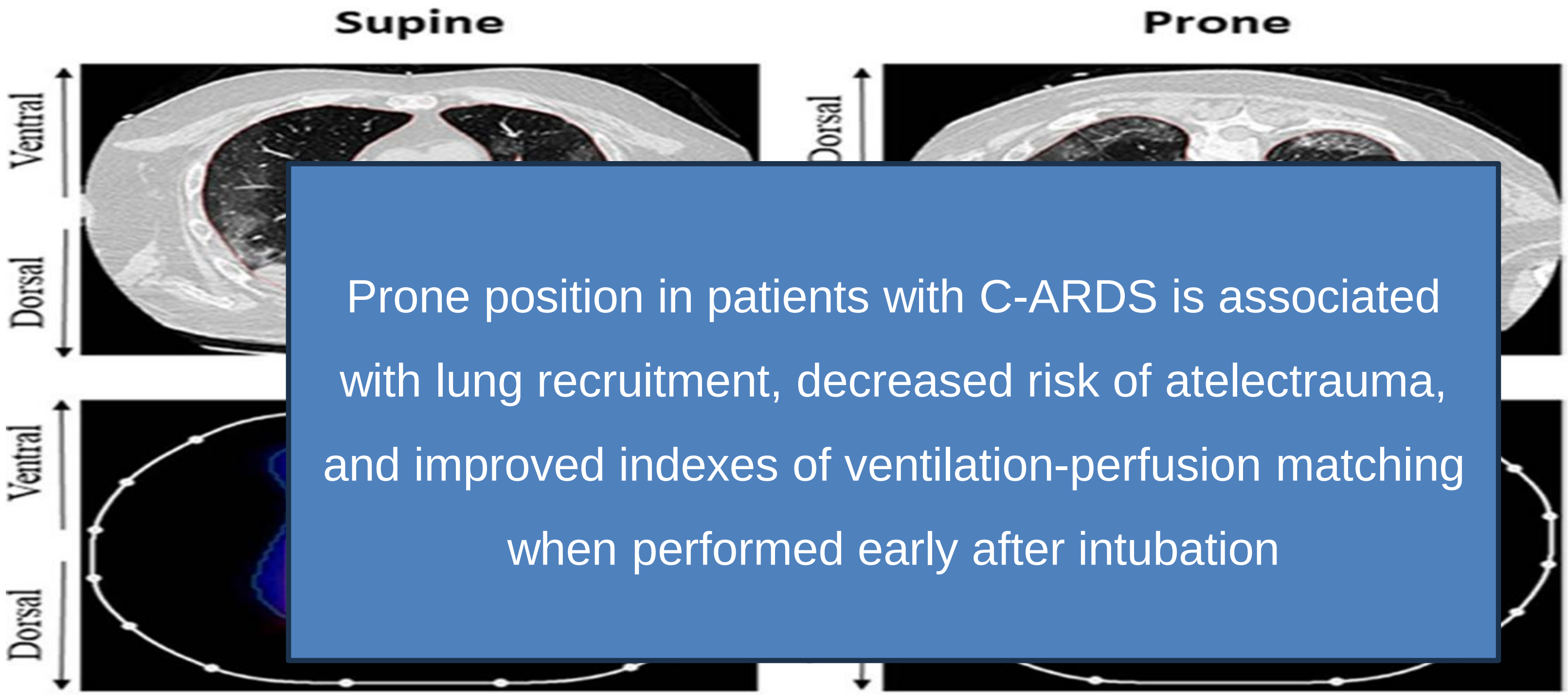
*CCM 2022(50) 723-732*

# Respiratory Mechanics and Gas Exchange Between the Supine and Prone Positions

| Variable | Supine, $n = 21$ | Early Prone, $n = 21$ | $p$ |
|---|---|---|---|
| Respiratory mechanics | | | |
| Plateau pressure, cm $H_2O$ | 23 (± 3) | 23 (± 4) | 0.294 |
| Driving pressure, cm $H_2O$ | 12 (± 3) | 12 (± 4) | 0.456 |
| Respiratory system compliance, mL/cm $H_2O$ | 45 (± 15) | 45 (± 18) | 0.957 |
| Oxygenation | | | |
| $Pao_2$, mm Hg | 85 (± 21) | 142 (± 90) | < 0.001 |
| $Pao_2/Fio_2$, mm Hg | 108 (± 41) | 176 (± 100) | 0.002 |
| Arterial dioxygen saturation, % | 95 (± 4) | 97 (± 3) | 0.003 |
| Alveolo-arterial difference in dioxygen partial pressure, mm Hg | 441 (± 124) | 379 (± 134) | 0.003 |
| Measured venous admixture, % Shunt | 49 (39–55) | 35 (27–46) | 0.007 |
| Central venous dioxygen saturation, % | 81 (± 6) | 81 (± 10) | 0.973 |
| $CO_2$ clearance | | | |
| $Paco_2$, mm Hg | 53 (± 7) | 53 (± 8) | 0.542 |
| pH | 7.38 (± 0.07) | 7.37 (± 0.06) | 0.134 |
| Corrected minute ventilation, L/min | 11.9 (± 2.3) | 12.2 (± 2.6) | 0.369 |
| Ventilatory ratio | 2.03 (± 0.41) | 2.06 (± 0.44) | 0.477 |

*CCM 2022(50) 723-732*

# The effect of prone position on recruitment and V/Q matching by EIT




Prone position in patients with C-ARDS is associated with lung recruitment, decreased risk of atelectrauma, and improved indexes of ventilation-perfusion matching when performed early after intubation

the large fraction of only-ventilated units (dead space) in the ventral lung regions during supine position, largely decreased by prone position (right)

ventilation (blue) and perfusion (red)

*CCM 2022(50) 723-732*

ORIGINAL

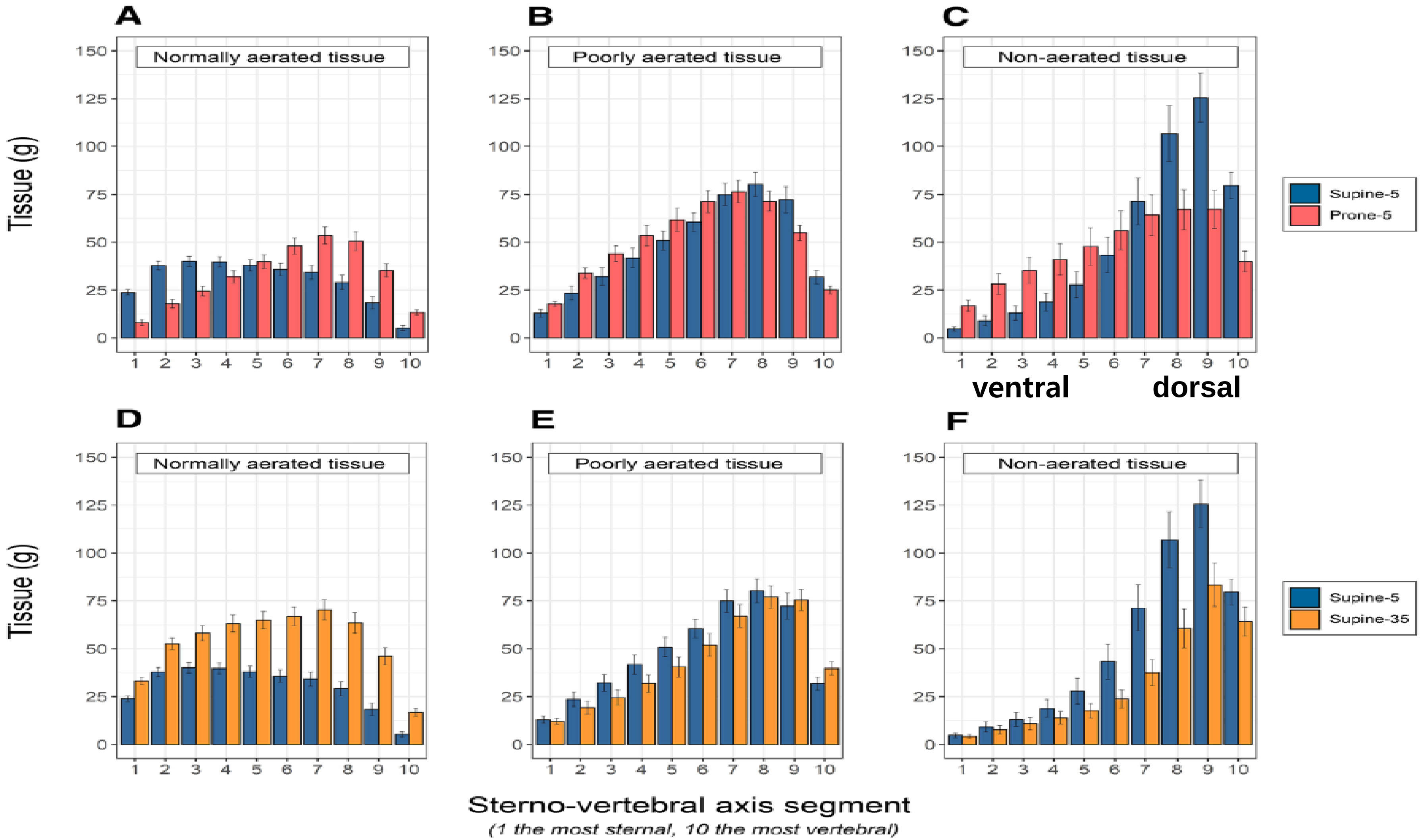
# Mechanisms of oxygenation responses to proning and recruitment in COVID-19 pneumonia

Sandra Rossi[1], Maria Michela Palumbo[2], Nicola Sverzellati[3], Mattia Busana[2], Laura Malchiodi[1], Paolo Bresciani[3], Patrizia Ceccarelli[1], Emanuele Sani[1], Federica Romitti[2], Matteo Bonifazi[2], Simone Gattarello[2,8], Irene Steinberg[2], Paola Palerm… Stefano Lazzari… Francesca Collino… Massimo Cressoni… Peter Herrmann[2], Leif Saager[2], Konrad Mei… attinoni[2*]

| Variables | Population (*n* = 25) |
|---|---|
| Female (*n*—%) | 5 (20) |
| Age (years) | 62.6 ± 8.4 |
| Height (cm) | 171 ± 9.7 |
| Body mass index—BMI (kg/m$^2$) | 28.9 ± 4.3 |
| Simplified acute physiology score II | 36.7 ± 10.3 |
| Days from symptoms onset to study day | 18.2 ± 8 |
| Days from hospital admission to study day | 11 ± 6 |
| Days of non-invasive support prior to mechanical ventilation | 5.5 ± 3.9 |
| Days of mechanical ventilation to study day | 4.9 ± 4.7 |
| Berlin ARDS category at the study day—*n* (%) | |
| - Mild | 2 (8) |
| - Moderate | 16 (64) |
| - Severe | 7 (28) |
| Hospital length of stay | 60.7 ± 32 |
| Intensive care unit length of stay | 27.8 ± 18.15 |
| Mortality (*n*—%) | 8 (32) |

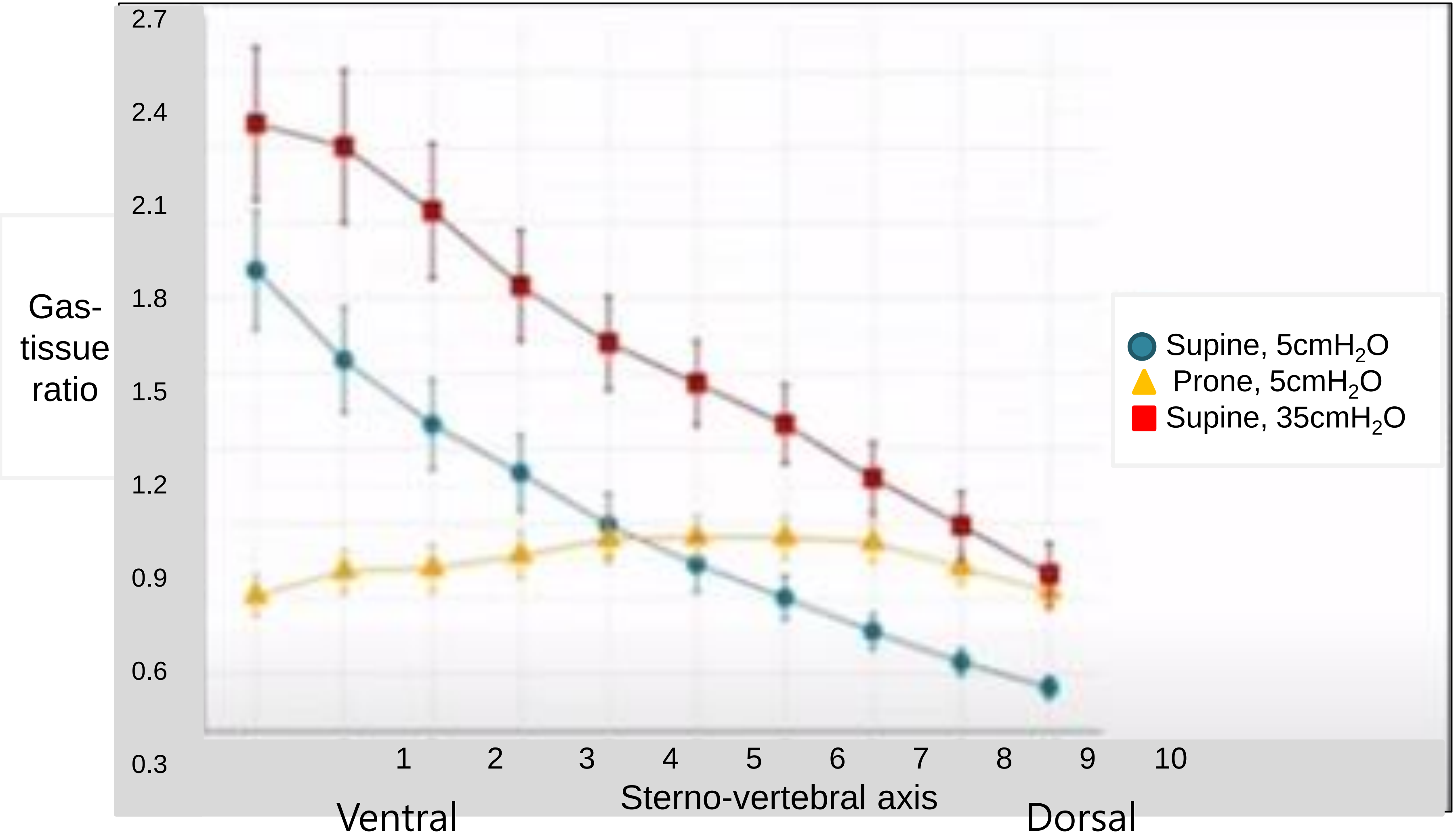
- Twenty-
- March 2
- CT, gas … nent –
- supine … ry airway pressure) recruitir … essure 35 cmH$_2$O). from 1 t
- the non … idated tissue (recruit… airway pressure).
- Positive … : increas

# The tissue distribution



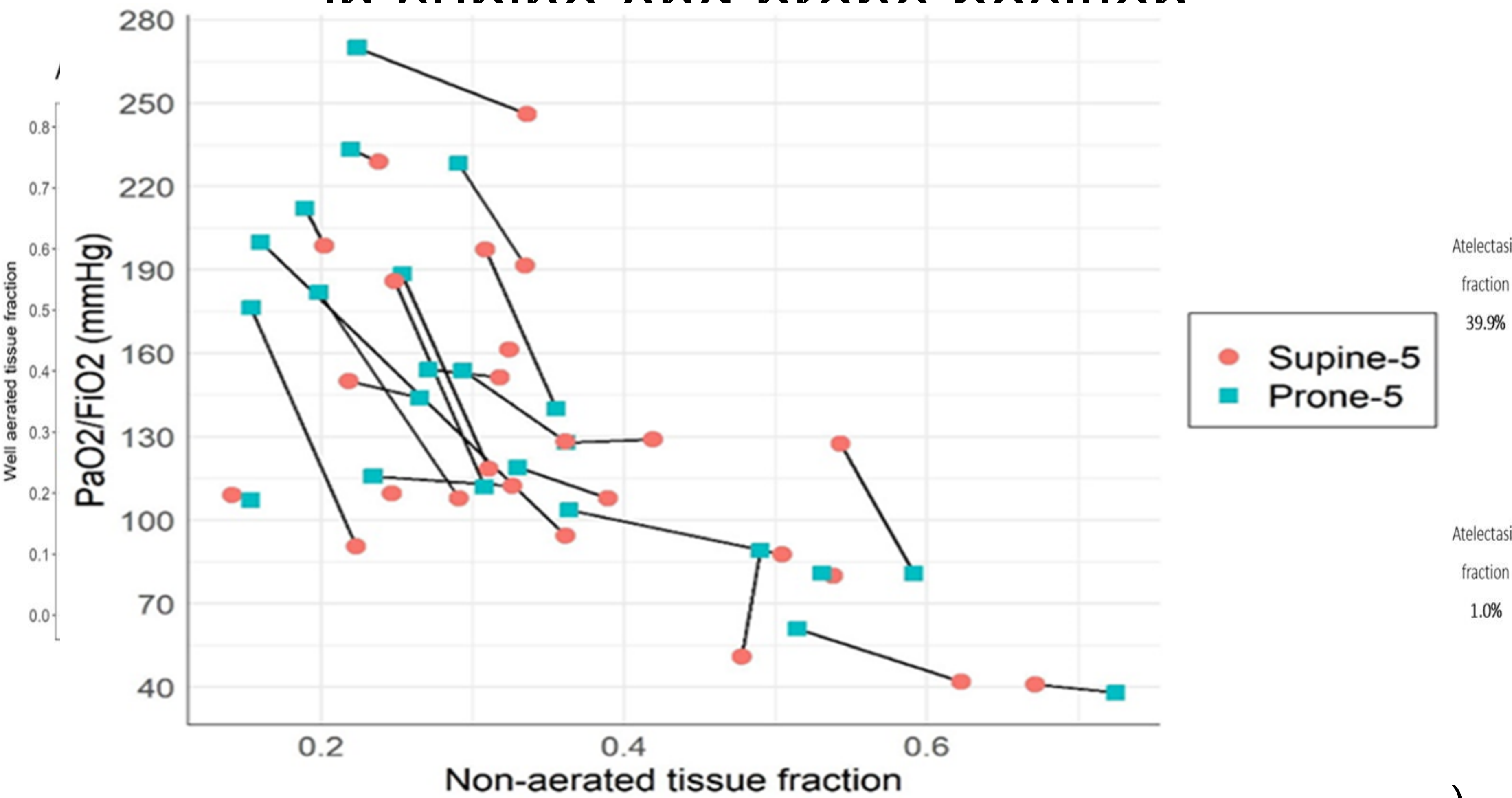

*Intensive Care Med (2022) 48:56–66*

# Distribution of ventilation in prone and supine position: homogeneity of ventilation




*Intensive Care Med (2022) 48:56–66*

# Distribution of well-aerated tissue in supine and prone position

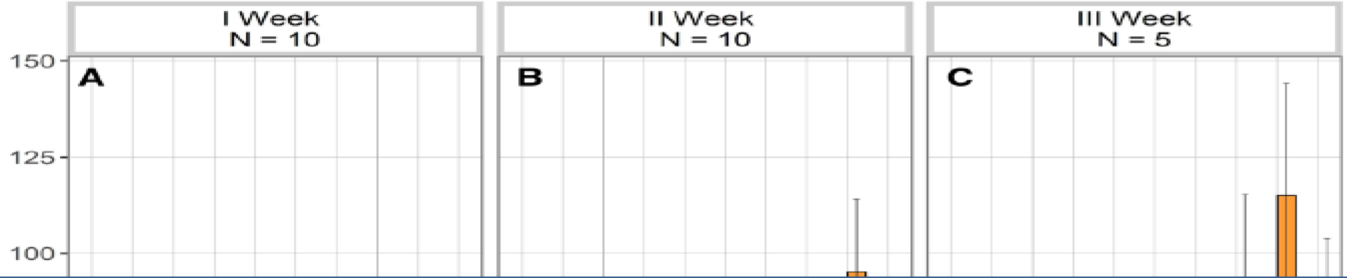



Atelectasis vs consolidation

well-aerated tissue in dorsal regions

The well-aerated tissue (green shade) greatly increases, and more poorly-aerated tissue develops (orange shade) non-aerated tissue (red shade)

# Distributions of atelectasis and consolidation




The amount of consolidated tissue was higher in patients assessed during the third week and determined the oxygenation responses following pronation and recruitment maneuvers

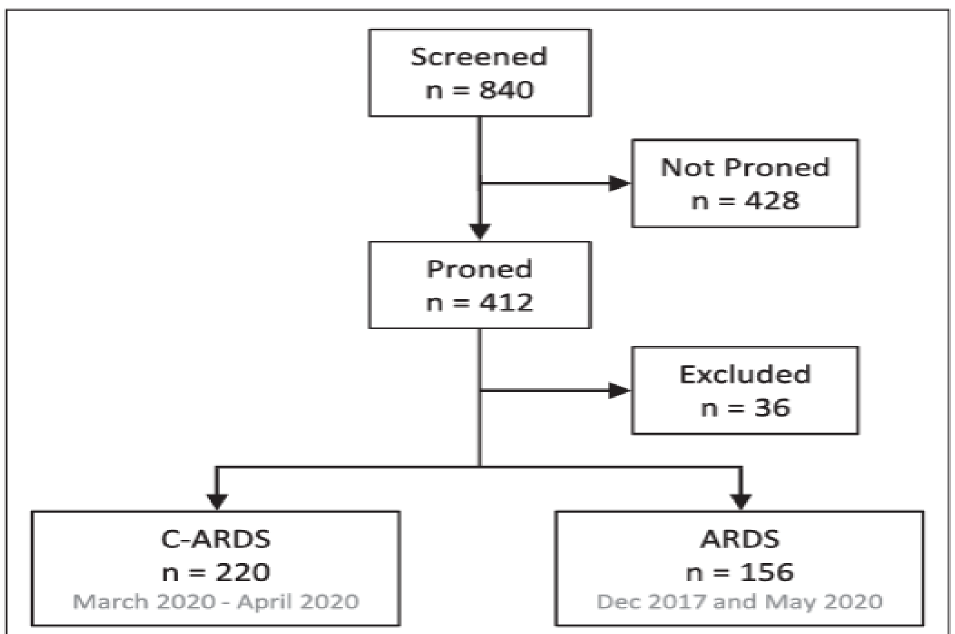
Limitation

1. Small sample size
2. Lack of formal randomization of prone
3. Total recruitment 35cm $H_2O$ – over estimation of consolidation

| | | | | |
|---|---|---|---|---|
| Patients—decrease $PaO_2/FiO_2$ during recruitment (%) | 20 | 50 | 100 | 0.014 |
| Total non-invasive ventilatory support before intubation (days) | 2.6 ± 1.6 | 7.3 ± 2.4 | 9 ± 5.4[bc] | 0.001 |
| Invasive ventilatory support before study (days) | 3 ± 1.7 | 4.4 ± 3 | 10.6 ± 7 | 0.07 |
| Simplified Acute Physiology Score II (SAPS II) | 33 ± 9 | 34 ± 6 | 48 ± 14[cd] | 0.1 |
| Mortality (%) | 10 | 30 | 80 | 0.02 |

## Prone Position in COVID-19 and -COVID-19 Acute Respiratory Distress Syndrome: An International Multicenter Observational Comparative Study*

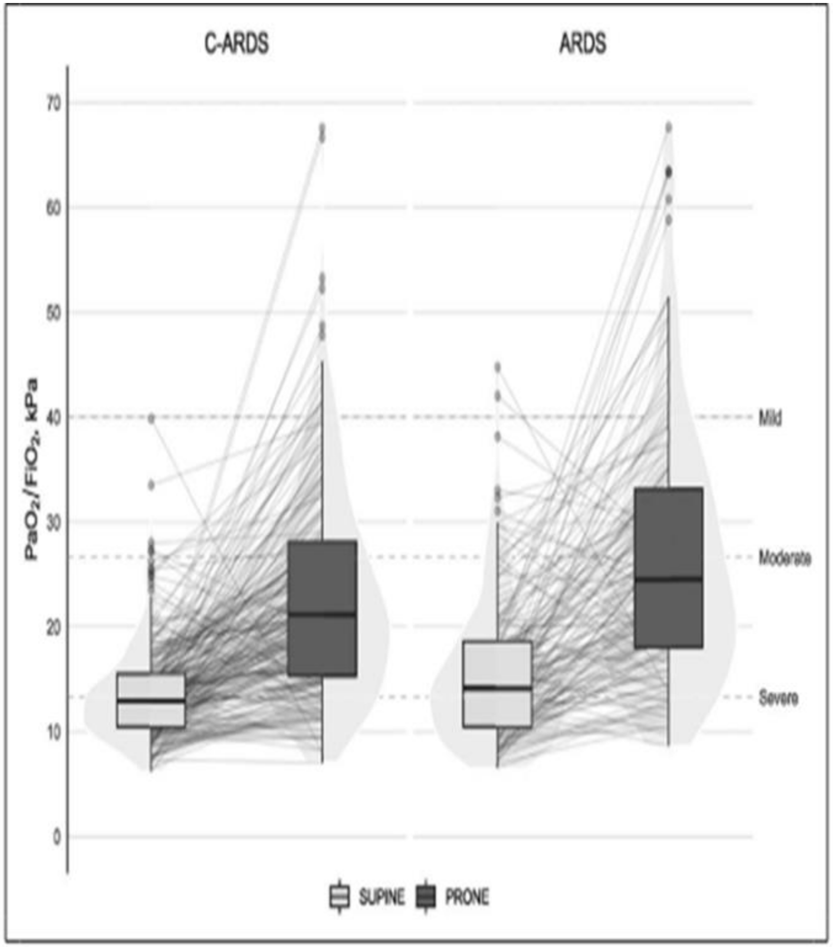
- Retrospective, observational, multicenter, international cohort study.
- Seven ICUs in Italy, United Kingdom, and France.




Prone position
P/F <150 mmHg
$FiO_2$ > 60%, optimized PEEP

*CCM 2022 50(4): 633–643.*

## Prone position, achieved a significant oxygenation response in 80% of CARDS, similar to ARDS,
## -> Independently associated with improved survival

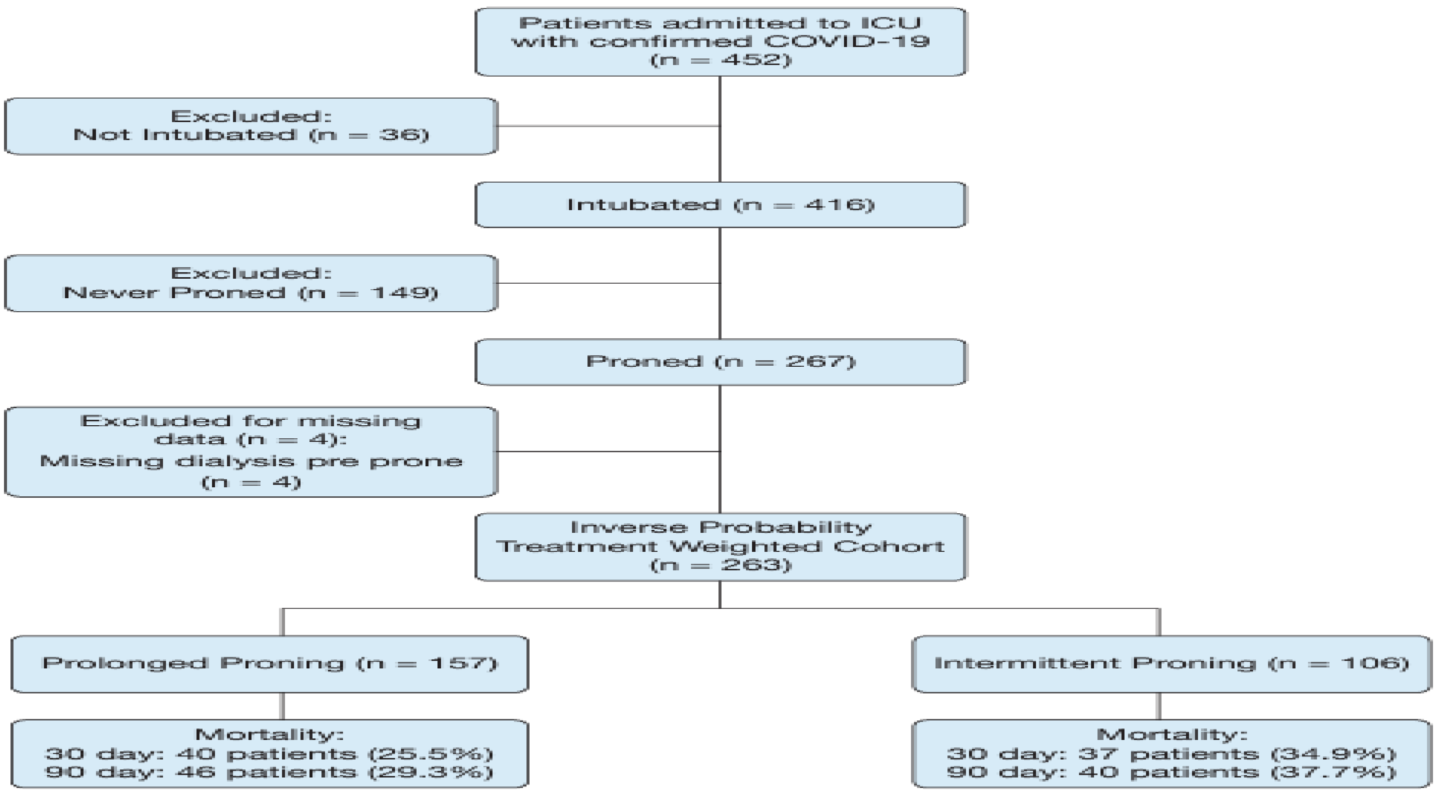



PP< 24 hours from intubation greater improvement in oxygenation (p=0.002)

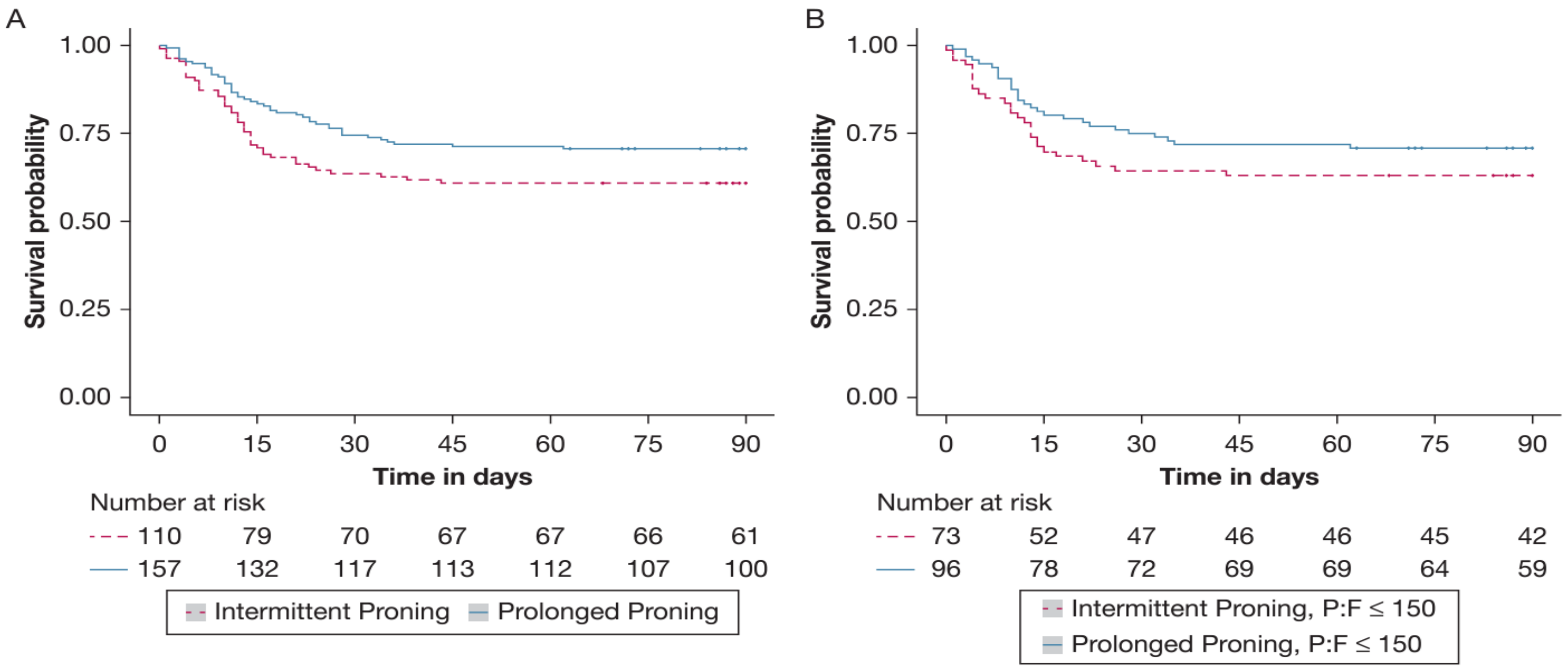
*CCM 2022 50(4): 633–643.*

# Prolonged Prone Position Ventilation Is Associated With Reduced Mortality in Intubated COVID-19 Patients

- Prolonged (24 or more h) vs intermittent (16 h with daily supination)
- Multicenter, retrospective cohort study, March 11 and May 31, 2020
- Outcome: 30-day all-cause mortality, 90-day all-cause mortality and prone-related complications.




*CHEST 2023; 163(3):533-542*




Prolonged PPV : reduced 30-day mortality (aHR, 0.475; 95% CI, 0.336-0.670, P < 0.001) and 90-day mortality (aHR, 0.638; 95% CI, 0.461-0.883; P =0.006) compared with intermittent PPV.

**P/F ≤ 150 at the time of pronation,**
Prolonged PPV reduced 30-day (aHR, 0.357; 95% CI, 0.213-0.597; P < 0.001)
90-day mortality (aHR, 0.562; 95% CI, 0.357-0.884; P =0 .008)

*CHEST 2023; 163(3):533-542*

# Complication in Prone Position

| Complication | Overall (n = 267) | Prolonged Prone (n = 157) | Intermittent Prone (n = 110) | P[a] |
|---|---|---|---|---|
| Any complication of proning | 129 (48.3) | 73 (46.5) | 56 (50.9) | .558 |
| Early cessation of proning | 30 (23.3) | 13 (17.8) | 17 (30.4) | .144 |
| Arrhythmias | 6 (2.2) | 5 (3.2) | 1 (0.9) | .415 |
| Hypotension | 10 (3.7) | 2 (1.3) | 8 (7.3) | .027 |
| Loss of vascular access | 5 (1.9) | 1 (0.6) | 4 (3.6) | .187 |
| Chest tube displacement | 1 (0.4) | 0 (0.0) | 1 (0.9) | .858 |
| OG/NG tube displacement | 2 (0.7) | 0 (0.0) | 2 (1.8) | .330 |
| Accidental extubation | 2 (0.7) | 2 (1.3) | 0 (0.0) | .640 |
| Endotracheal tube displacement | 9 (3.4) | 6 (3.8) | 3 (2.7) | .886 |
| Worsening ventilator mechanics | 8 (3.0) | 5 (3.2) | 3 (2.7) | 1 |
| Facial edema | 31 (11.6) | 24 (15.3) | 7 (6.4) | .041 |
| Pressure injuries | 78 (29.2) | 48 (30.6) | 30 (27.3) | .655 |
| Conjunctival hemorrhage | 1 (0.4) | 1 (0.6) | 0 (0.0) | 1 |
| Vomiting | 6 (2.2) | 1 (0.6) | 5 (4.5) | .089 |
| Oropharyngeal injury | 7 (2.6) | 4 (2.5) | 3 (2.7) | 1 |
| Rhabdomyolysis | 2 (0.7) | 2 (1.3) | 0 (0.0) | .640 |

Prolonged PPV has a favorable safety profile and reduces resource utilization because of the need for fewer pronation and supination episodes

# Conclusion and Limitations

Prolonged PPV is a safe, effective strategy for mortality reduction in intubated COVID-19 patients.

Limitation

Multicenter –same hospital system (General Brigham hospitals in the Boston)

Retrospective nature- potential treatment selection bias

The patient population represents the first wave of the COVID-19 pandemic in Boston, when there were no proven COVID-19 specific treatments.

RESEARCH Open Access

# Extended prone positioning duration for COVID-19-related ARDS: benefits and detriments

- N= 81
- PP 39hr
- Stage II > pressure sore 26%
- Stage III-IV pressure sore 2.5%
- 48hr –brachial plexus injury

| Variables | Patients without pressure injury ($n = 60$) *n/N* (%) or med (Q1–Q3) | Patients with at least one pressure injury ($n = 21$) *n/N* (%) or med (Q1–Q3) | OR (95% CI) | *p* |
|---|---|---|---|---|
| Sex, male | 40/60 (67) | 18/21 (86) | 3.00 (0.88–13.88) | 0.081 |
| Age, years | 60 (51–68) | 58 (52–63) | 1.00 (0.96–1.05) | 0.91 |
| BMI, kg/m$^2$ | 30 (27–37) | 33 (29–36) | 0.99 (0.94–1.01) | 0.54 |
| Type 2 diabetes | 13/60 (22) | 7/21 (33) | 1.43 (0.50–3.88) | 0.49 |
| History of cardiovascular disease* | 7/60 (12) | 1/21 (5) | 0.38 (0.02–2.32) | 0.33 |
| History of respiratory disease** | 6/60 (10) | 2/21 (10) | 0.95 (0.13–4.53) | 0.95 |
| SAPS II score | 36 (30–48) | 39 (33–42) | 0.99 (0.95–1.02) | 0.43 |
| $PaO_2/FiO_2$ ratio before first pronation session, mmHg | 82 (68–114) | 88 (75–99) | 1.00 (0.98–1.01) | 0.65 |
| ECMO | 12/60 (20) | 5/21 (24) | 1.25 (0.35–3.96) | 0.71 |
| Nitric oxide | 25/60 (42) | 9/21 (43) | 1.05 (0.38–2.86) | 0.92 |
| At least one proning session with catecholamines | 28/60 (47) | 9/21 (43) | 0.86 (0.31–2.33) | 0.76 |
| Duration of mechanical ventilation, days | 14 (9–25) | 29 (22–34) | 1.01 (1.00–1.02) | 0.12 |
| ICU length of stay, days | 17 (11–26) | 29 (19–34) | 1.05 (1.01–1.10) | **0.021** |
| Median duration of each proning sessions, h | 40 (35–43) | 36 (32–40) | 0.96 (0.89–1.03) | 0.26 |
| Cumulated duration of all proning sessions, days*** | 3 (2–5) | 6 (4–8) | 1.33 (1.11–1.63) | **0.0015** |

*Critical Care (2022) 26:208*

# Extended prone positioning > 24 hours for intubated ARDS

**Two possible implementations:**

1) Proned until clinical improvement
2) Fixed increased duration e.g : 48 hours

## Benefits +

- **Reduced mortality ?**
- **Avoid derecruitment** associated with turning over maneuvers
- **Reduce** ventral pulmonary units **overdistension**
- **Organizational benefits**

**Decrease work load**

## Risks -

- Potential increased incidence of **pressure injuries** and **plexopathy**
- Potential increased risk of **central catheter-related bloodstream infection**
- Potentially hampered **enteral feeding**

*Critical Care (2023) 27:264*

# Awakening Prone position

# Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial

Canada, France, Ireland, Mexico, USA, Spain

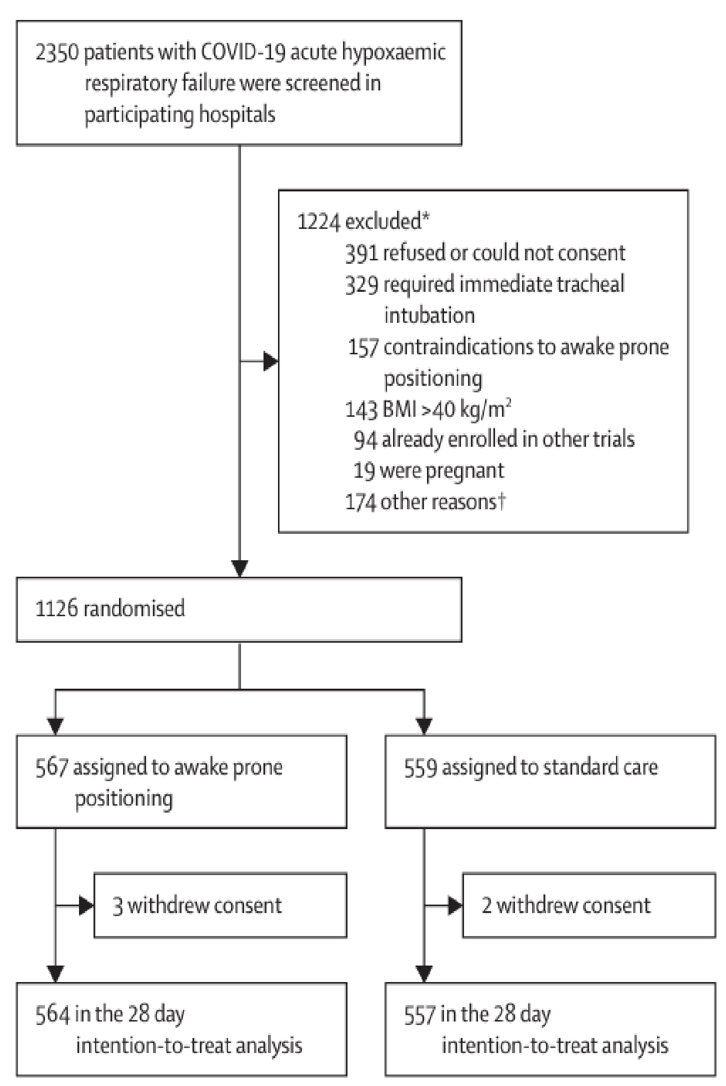
- Inclusion criteria
- All adults (>18 years old) with acute hypoxemic respiratory failure) COVID-19 pneumonia
- High flow nasal cannula
- Acute hypoxemic respiratory failure was defined as a requirement of respiratory

- Exclusion criteria
- Immediate tracheal intubation
- Progressive circulatory failure
  : fluid loading 1000ml,
  0.1 ug/kg/min of NE
- Impaired alertness, confusion
- BMI ≥ 40 $kg/m^2$

The primary outcome treatment failure within 28 days -intubation or death.
Main secondary outcomes  intubation; mortality; use of noninvasive ventilation; length of hospital stay

*Lancet Respir Med 2021; 9: 1387–95*

# Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial




| | Awake prone positioning group (n=564) | Standard care group (n=557) |
|---|---|---|
| Age, years | 61·5 (13·3) | 60·7 (14·0) |
| Female sex | 184 (33%) | 191 (34%) |
| Male sex | 380 (67%) | 366 (66%) |
| Body-mass index, kg/m² | 29·7 (4·6) | 29·7 (4·6) |
| Clinical parameters at enrolment | | |
| Respiratory rate, breaths/min | 24·7 (5·1) | 24·9 (5·6) |
| Mean arterial pressure, mmHg | 88·2 (12·1) | 87·4 (11·4) |
| $SpO_2:FiO_2$ | 147·9 (43·9) | 148·6 (43·1) |
| Location at enrolment | | |
| Intensive care unit | 336 (60%) | 339 (61%) |
| Intermediate care unit | 197 (35%) | 189 (34%) |
| Emergency department | 5 (1%) | 5 (1%) |
| General ward | 26 (5%) | 24 (4%) |
| Coexisting illness | | |
| Chronic heart disease* | 120 (21%) | 127 (23%) |
| Chronic lung disease† | 63 (11%) | 64 (12%) |
| Chronic kidney disease‡ | 45 (8%) | 35 (6%) |
| Severe liver disease§ | 8 (1%) | 6 (1%) |
| Diabetes (type 1 and 2) | 176 (31%) | 173 (3%) |
| Obesity¶ | 221 (39%) | 231 (42%) |
| Active malignancy | 45 (8%) | 31 (6%) |

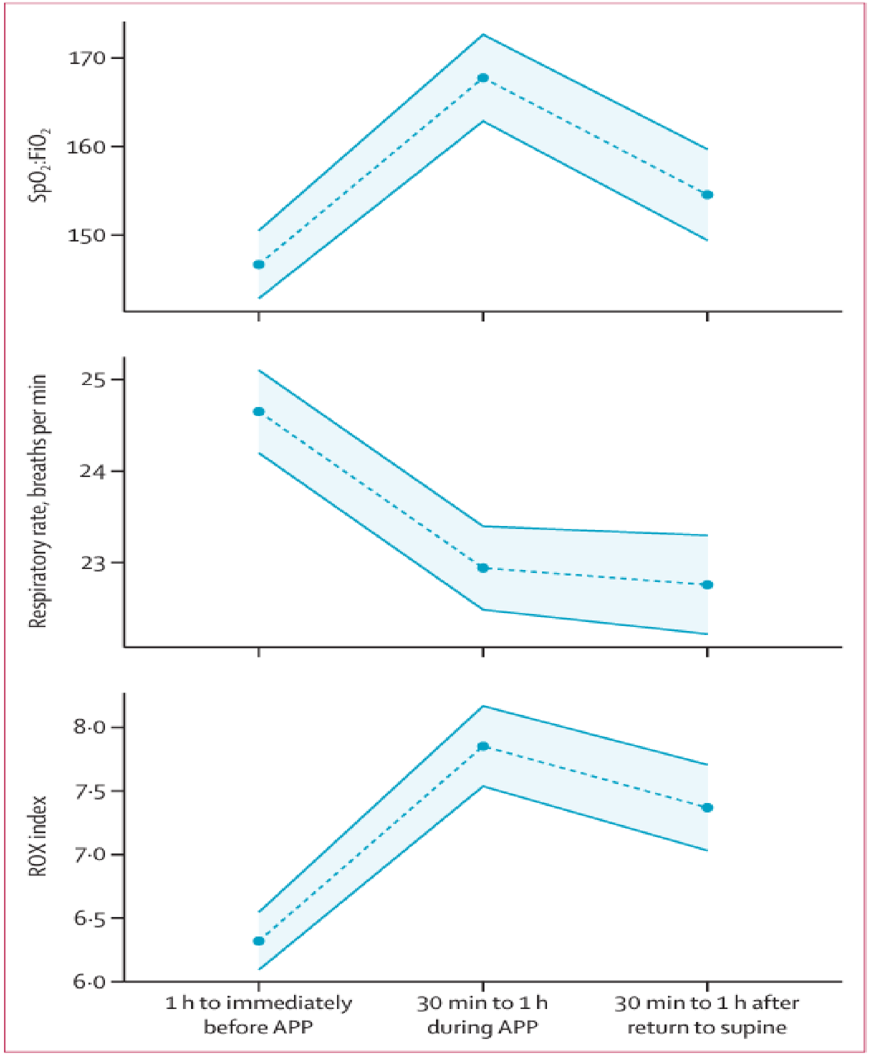
*Lancet Respir Med 2021; 9: 1387–95*

# Physiological effects of awake prone positioning

**Mean $SpO_2/FiO_2$=148**

Proning :

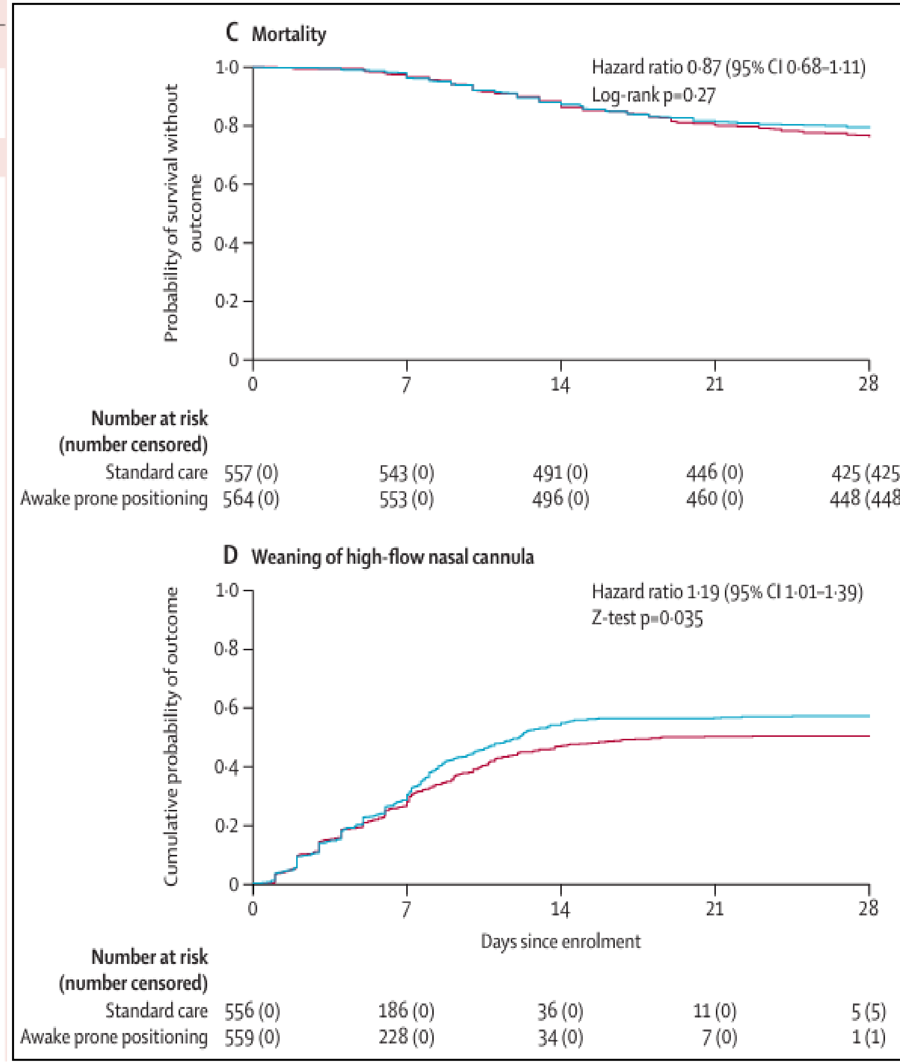
5 hours/day(1.6h-8.8h)




*Lancet Respir Med 2021; 9: 1387–95*

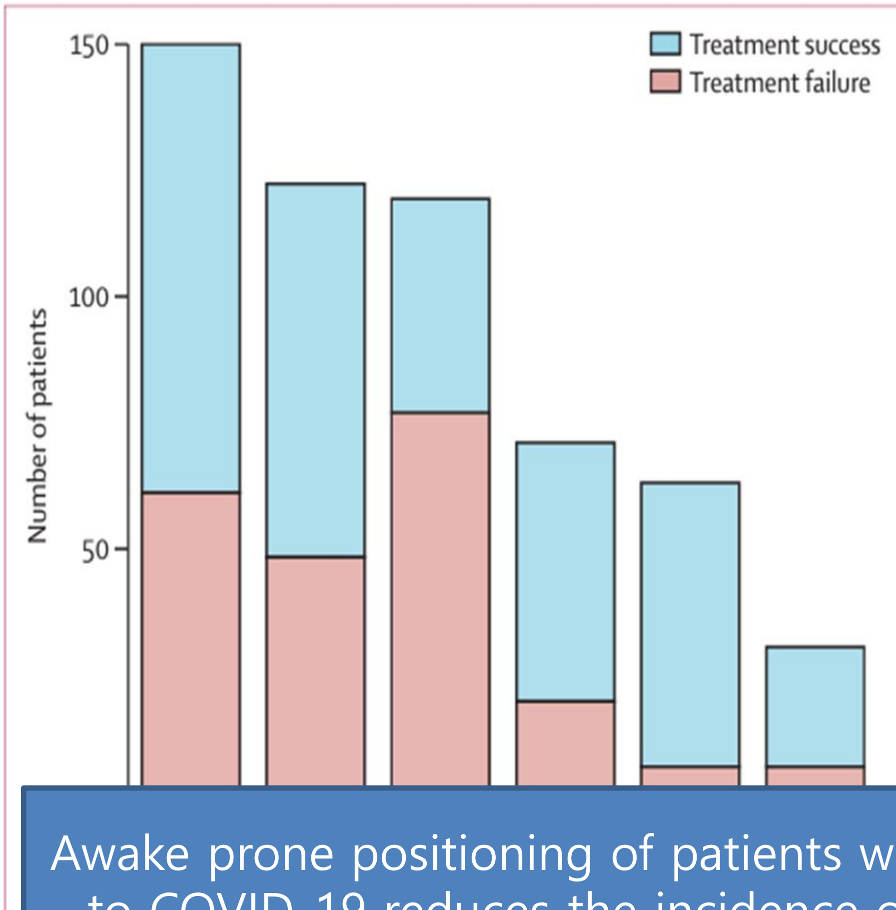
# Kaplan-Meier probabilities estimates over 28 days

| | Awake prone positioning group (n=564) | Standard care group (n=557) | RR (95% CI), HR (95% CI), or mean difference (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Treatment failure at day 28 (intubation or death) | 223/564 (40%) | 257/557 (46%) | RR 0·86 (0·75 to 0·98) |
| **Secondary outcomes** | | | |
| Intubation rate at day 28 | 185/564 (33%) | 223/557 (40%) | .. |
| Mortality at day 28 | | | |
| All patients | 117/564 (21%) | 132/557 (24%) | RR 0·87 (0·71 to 1·07) |
| Invasively mechanically ventilated patients | 79/185 (43%) | 98/223 (44%) | .. |
| Time to event analysis, median days* | | | |
| Treatment failure (intubation or death) | 2·0 (1·0 to 4·3) | 2·0 (1·0 to 3·8) | HR 0·78 (0·65 to 0·93) |
| Intubation | 2·3 (1·3 to 5·0) | 2·0 (1·0 to 3·8) | HR 0·75 (0·62 to 0·91) |
| Death | 12·0 (9·0 to 17·0) | 14·0 (9·8 to 19·0) | HR 0·87 (0·68 to 1·11) |
| Non-invasive ventilation, intubation or death | 3·0 (1·0 to 7·4) | 2·3 (1·0 to 5·0) | HR 0·79 (0·67 to 0·94) |
| Weaning of high-flow nasal cannula | 6·9 (3·3 to 9·2) | 6·0 (3·0 to 9·8) | HR 1·19 (1·01 to 1·39) |
| Mean duration, days | | | |
| Hospital length of stay | 16·4 (10·5) | 16·5 (9·7) | Mean difference −0·2 (−1·3 to 1·0) |
| Mechanical ventilation among intubated patients who survived until day 28 | 12·4 (9·0) | 12·4 (8·4) | Mean difference 0·2 (−1·9 to 2·3) |
| Safety outcomes | | | |
| Skin breakdown | 8 (1%) | 10 (2%) | .. |
| Vomiting | 15 (3%) | 18 (3%) | .. |
| Central or arterial line dislodgement | 26 (5%) | 17 (3%) | .. |
| Cardiac arrest at any time† | 3 (1%) | 1 (0%) | .. |




*Lancet Respir Med 2021; 9: 1387–95*

# Daily mean duration of prone positioning and outcomes in patients allocated to awake prone positioning

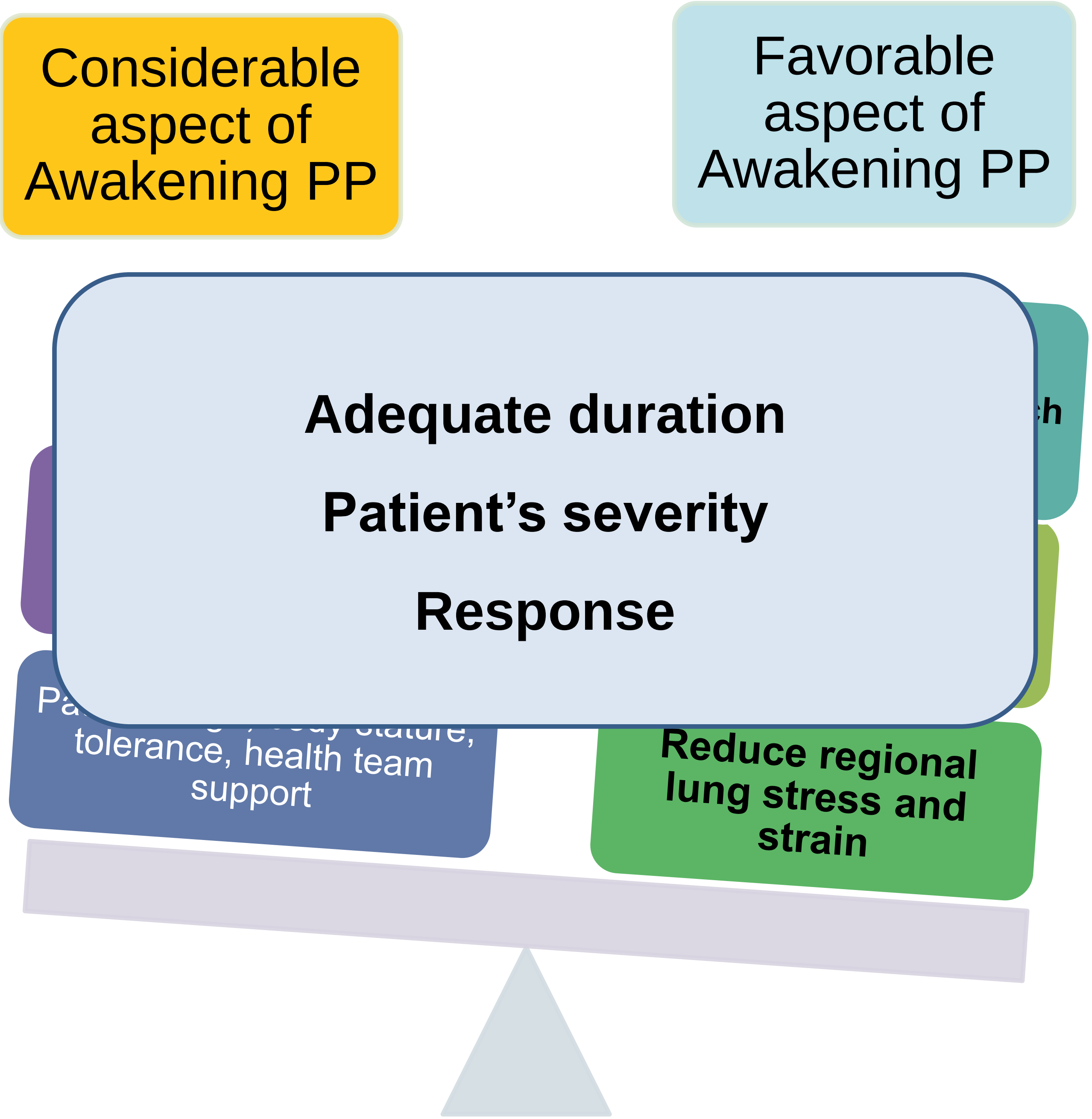



**PP< 8hr treatment failure 194/413 (48%)**

**PP ≥ 8hr treatment failure 25/151(17%)**

14 patients needed to be treated with awake PP to avoid intubation

Awake prone positioning of patients with hypoxaemic respiratory failure due to COVID-19 reduces the incidence of treatment failure and the need for intubation without any signal of harm.

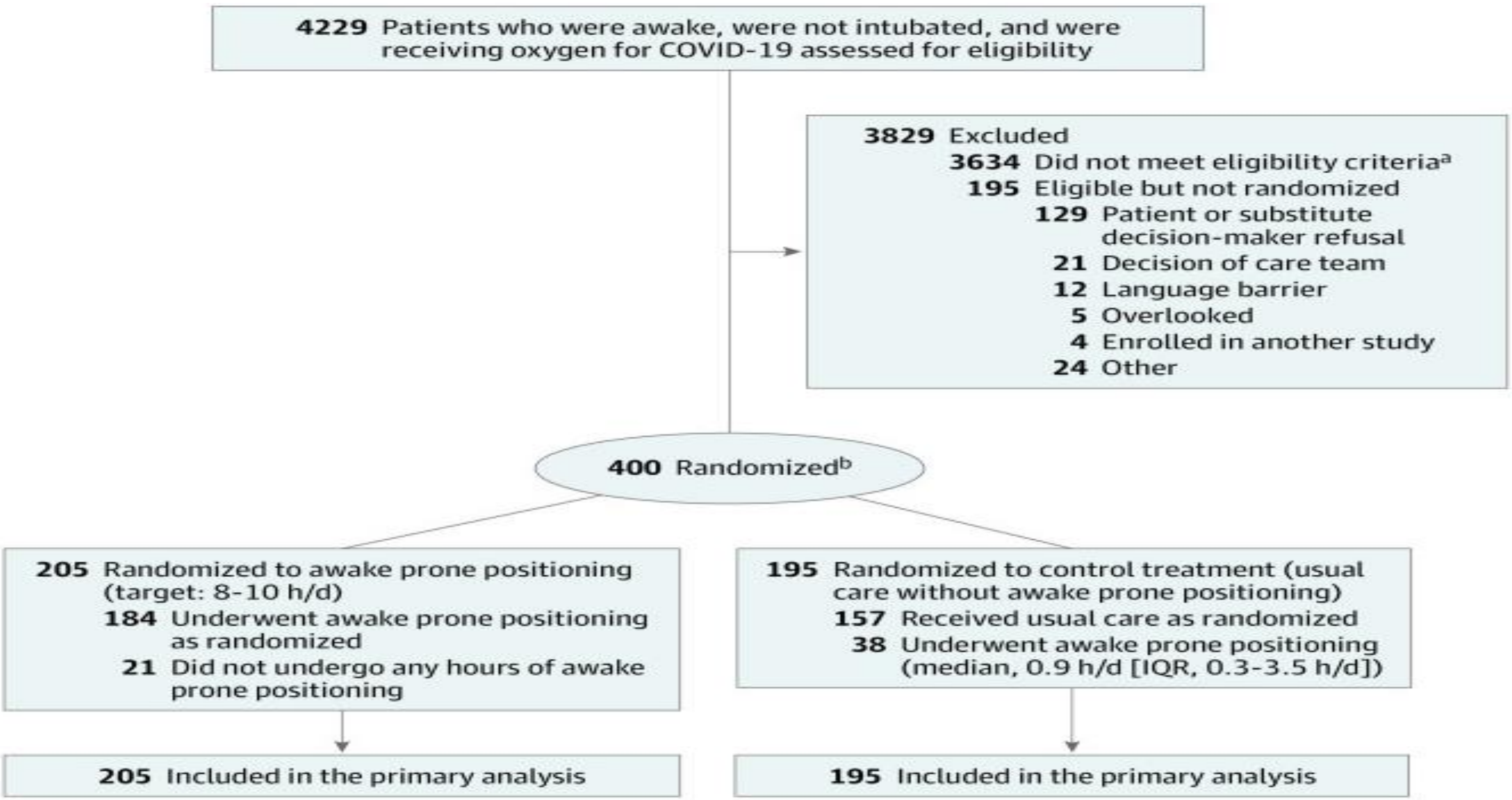


Considerable aspect of Awakening PP
Favorable aspect of Awakening PP
Adequate duration
Patient's severity
Response
tolerance, health team support
Reduce regional lung stress and strain

# Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure

## A Randomized Clinical Trial

- a pragmatic, unblinded randomized clinical trial at 21 hospitals in Canada, Kuwait, Saudi Arabia, and the US.




*JAMA.2022;327(21):2104-2113.*

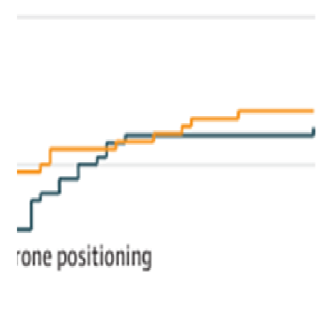
# Outcomes

400 pts: 60% S/F < 150
Proning : 4.5 hours/day (1.6h-8.8h)
Primary outcome: intubation within 30days

A Endotracheal intubation outcome at 30 d

B Mortality outcome at 60 d

| | Prone positioning (n = 205) | Control (n = 195) |
|---|---|---|
| Serious adverse events, No. of patients[a] | 0 | 0 |
| Adverse events, No. (%) of patients | 21 (10) | 0 |
| Total reported adverse events, No. | 26 | 0 |
| Type of adverse event, No. (%) | | |
| Coughing | 1 (4) | 0 |




No.

In patients with acute hypoxemic respiratory failure from COVID-19, prone positioning, compared with usual care without prone positioning, did not significantly reduce endotracheal intubation at 30 days.
However, the effect size for the primary study outcome was imprecise and does not exclude a clinically important benefit

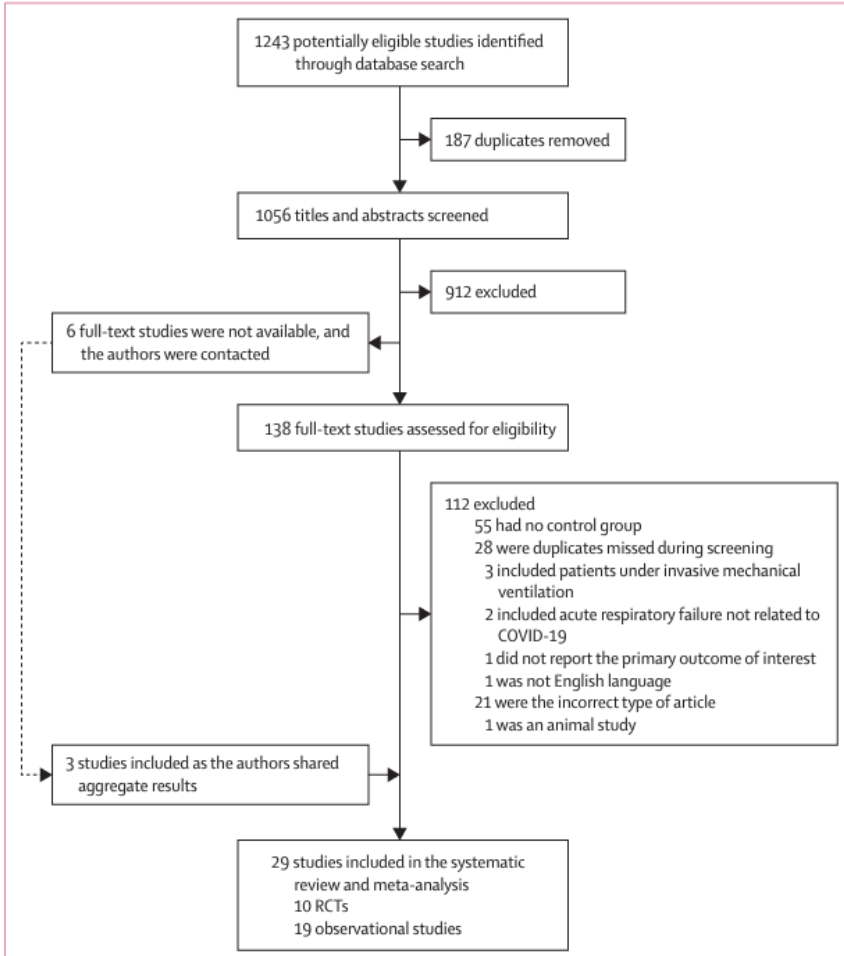
Not decrease treatment failure & intubation rate

*JAMA.2022;327(21):2104-2113.*

# Limitation

- The study sample size is small
- Patient preference and health care team request 19% of patients in the control group undergoing some prone positioning
- The median duration of daily prone positioning <1 hour
- Non blind, lack of structured criteria for endotracheal intubation.

# Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis




English from Jan 1, 2020, to Nov 8, 2021.
Excluded trials that included patients intubated before or at enrolment, younger than 18 years, or trials that did not include the supine position in the control group.

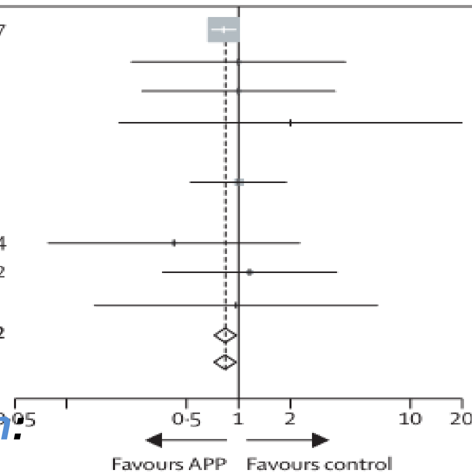
*Lancet Respir Med* 2022; 10: 573–83

# Outcomes

**A**

| | Awake prone positioning n/N | Control n/N | Risk ratio (95% CI) | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|
| Ehrmann et al[11] | 185/564 | 223/557 | 0·82 (0·70–0·96) | 87·5% | 89·0% |
| Gad et al[17] | 3/15 | 3/15 | 1·00 (0·24–4·18) | 1·2% | 1·1% |
| Jayakumar et al[16] | 4/30 | 4/30 | 1·00 (0·28–3·63) | 1·6% | 1·3% |
| Johnson et al[13] | 2/15 | 1/15 | 2·00 (0·20–19·78) | 0·4% | 0·4% |
| Kharat et al[15] | 0/10 | 0/17 | | 0·0% | 0·0% |
| Rosen et al[14] | 12/36 | 13/39 | 1·00 (0·53–1·90) | 4·9% | 5·3% |
| Taylor et al[12] | 0/27 | 0/13 | | 0·0% | 0·0% |
| Garcia et al[19] | 2/159 | 4/134 | 0·42 (0·08–2·26) | 1·7% | 0·8% |
| Fralick et al[18] | 6/126 | 5/122 | 1·16 (0·36–3·71) | 2·0% | 1·6% |
| Harris et al (NCT04853979) | 2/31 | 2/30 | 0·97 (0·15–6·44) | 0·8% | 0·6% |
| **Fixed-effects model** | **216/1013** | **255/972** | **0·84 (0·72–0·97)** | **100·0%** | ·· |
| **Random-effects model** | | | **0·84 (0·72–0·97)** | ·· | **100·0%** |

Heterogeneity: $I^2$=0%, $\chi^2_7$=2·03 (p=0·96)

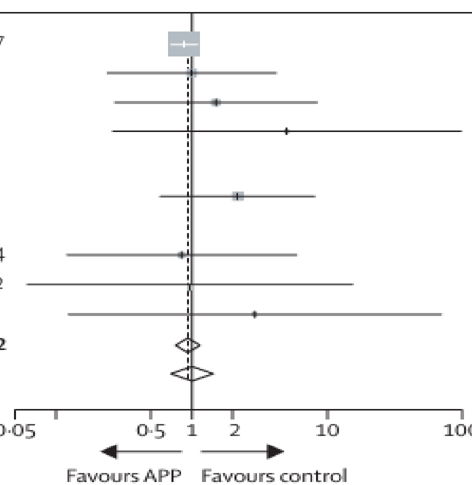



***Reduced the need for intubation*:**
**RR 0·84 [95% CI 0·72–0·97]**

**B**

| | Awake prone positioning n/N | Control n/N | Risk ratio (95% CI) | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|
| Ehrmann et al[11] | 117/564 | 132/557 | 0·88 (0·70–1·09) | 91·7% | 74·8% |
| Gad et al[17] | 3/15 | 3/15 | 1·00 (0·24–4·18) | 2·1% | 6·0% |
| Jayakumar et al[16] | 3/30 | 2/30 | 1·50 (0·27–8·34) | 1·4% | 4·3% |
| Johnson et al[13] | 2/15 | 0/15 | 5·00 (0·26–95·88) | 0·3% | 1·5% |
| Kharat et al[15] | 0/10 | 0/17 | | 0·0% | 0·0% |
| Rosen et al[14] | 6/36 | 3/39 | 2·17 (0·58–8·03) | 2·0% | 7·1% |
| Taylor et al[12] | 0/27 | 0/13 | | 0·0% | 0·0% |
| Garcia et al[19] | 2/159 | 2/134 | 0·84 (0·12–5·90) | 1·5% | 3·3% |
| Fralick et al[18] | 1/126 | 1/122 | 0·97 (0·06–15·31) | 0·7% | 1·7% |
| Harris et al (NCT04853979) | 1/31 | 0/30 | 2·90 (0·12–68·58) | 0·4% | 1·3% |
| **Fixed-effects model** | **135/1013** | **143/972** | **0·93 (0·76–1·15)** | **100·0%** | ·· |
| **Random-effects model** | | | **1·00 (0·70–1·44)** | ·· | **100·0%** |

Heterogeneity: $I^2$=0%, $\chi^2$=[illegible]

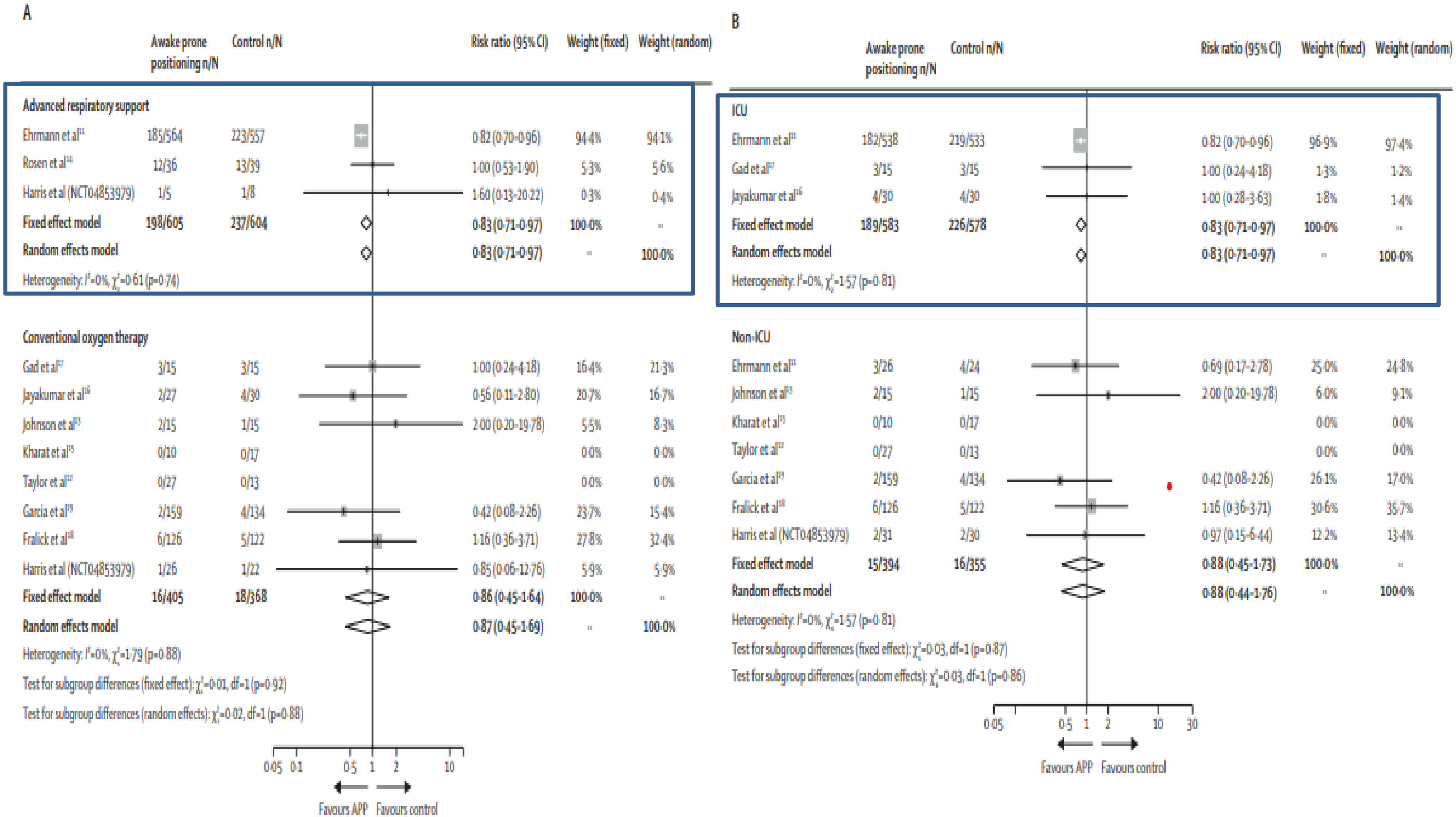



**Did not significantly reduce mortality**
**RR 1·00 [95% CI 0·70–1·44]**

*Lancet Respir Med* 2022; 10: 573–83

# Outcomes

## Subgroup analysis of intubation




*Lancet Respir Med 2022; 10: 573–83*

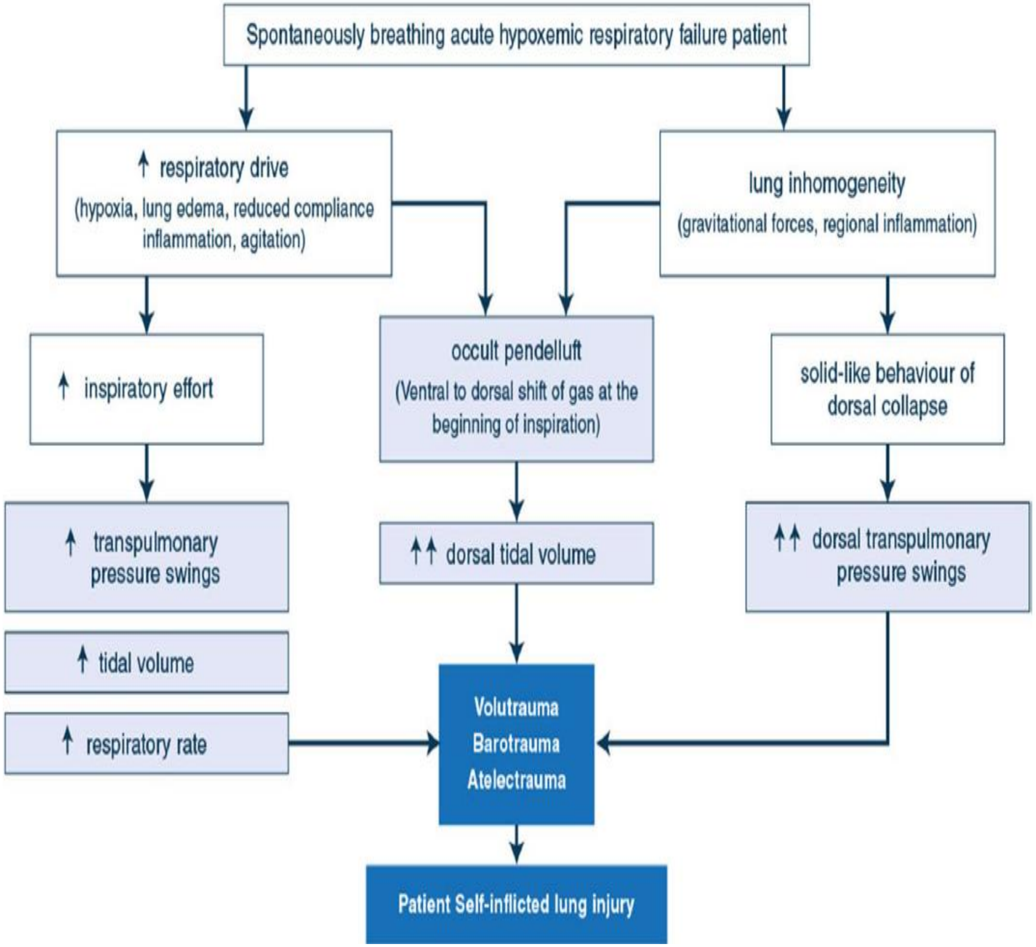
# Discussion

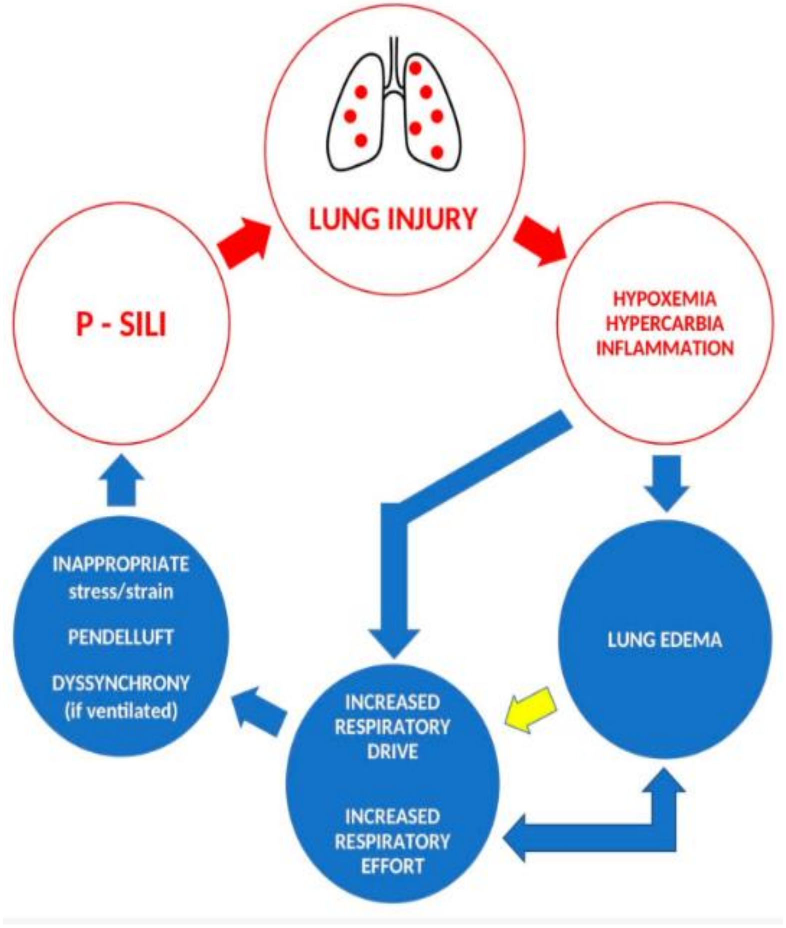
- **Physiologic  benefit- HFNC or NIPPV**
  : an increase in end-expiratory lung volume
  a more homogeneous distribution in lung aeration,
  improved gas exchange, decreased inspiratory effort

- **Encouragement or assistance** to help them prone
  clinician-driven awake prone positioning

**Optimal sample size was not reached**

# Why was there no difference in mortality rates? Patient self-inflicted lung injury




*Intensive Care Med (2021) 47:851–866*

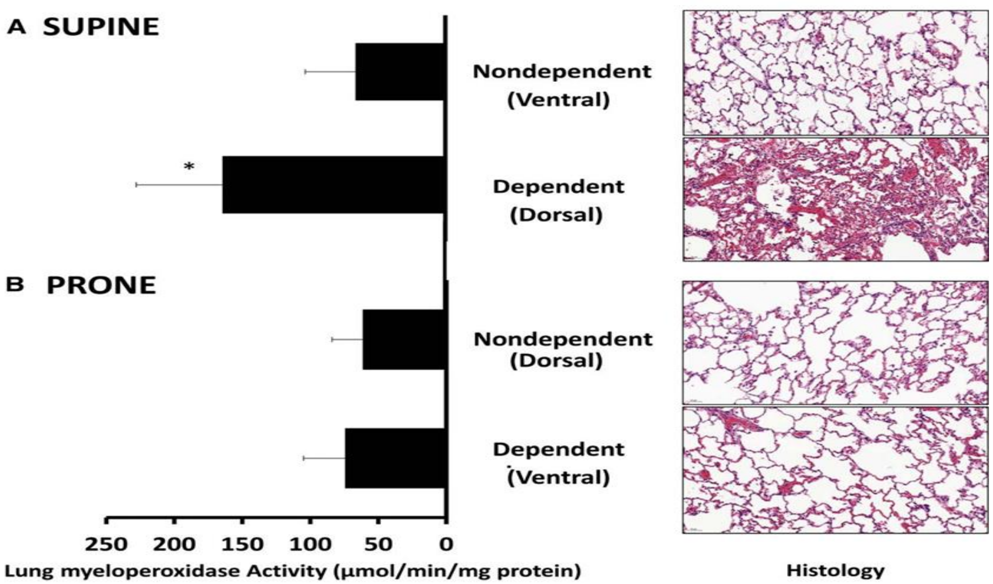
# Can awakening prone position reduce the risk of P-SILI?

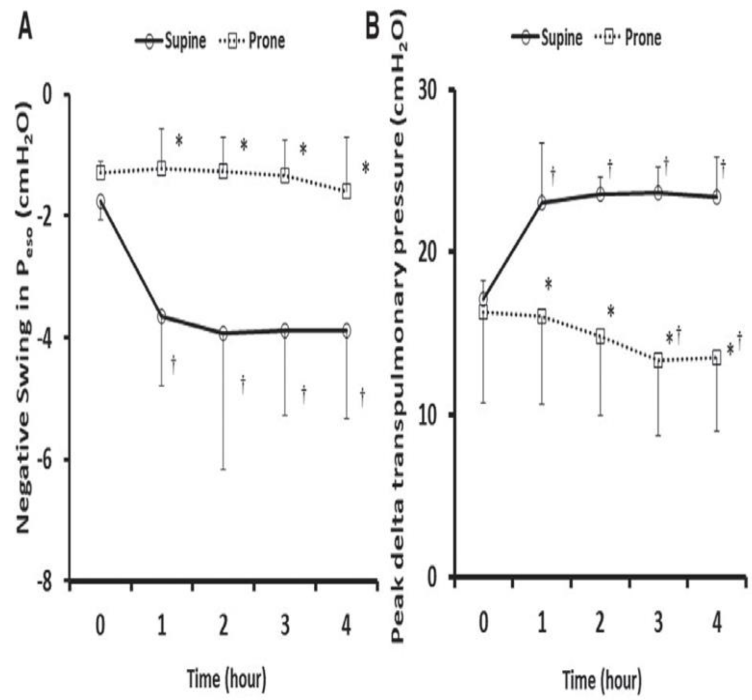
ANESTHESIOLOGY

**Prone Position Minimizes the Exacerbation of Effort-dependent Lung Injury: Exploring the Mechanism in Pigs and Evaluating Injury in Rabbits**

Takeshi Yoshida, M.D., Ph.D., Doreen Engelberts, Han Chen, M.D., Xuehan Li, M.D., Bhushan H. Katira, M.D., Ph.D., Gail Otulakowski, Ph.D., Yuji Fujino, M.D., Ph.D.

*ANESTHESIOLOGY 2022; 136:779–91*




Annals of Intensive Care 2021 : 11: 179

# Impact of exposure time in awake prone positioning on clinical outcomes of patients with COVID-19-related acute respiratory failure treated with high-flow nasal oxygen: a multicenter cohort study

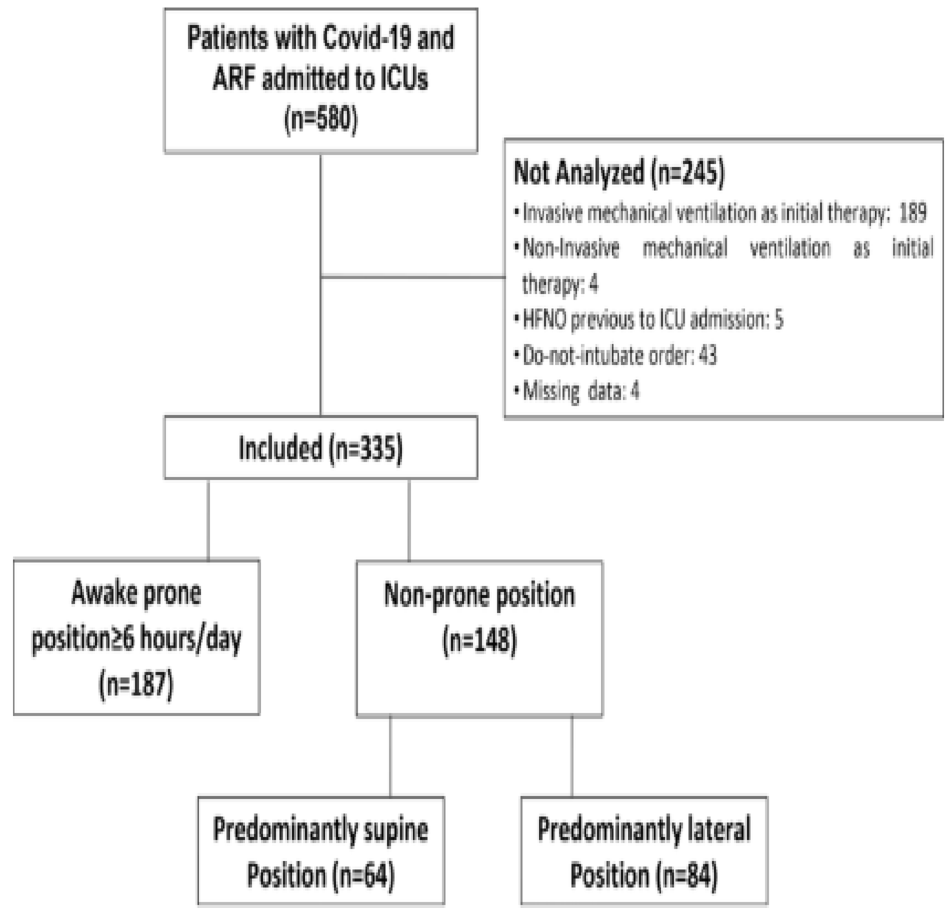
Prospective multicenter cohort study at 6 ICUs of 6 centers in Argentina

**Inclusion criteria**

$SpO_2 < 92\%$ oxygen > 4 L/min

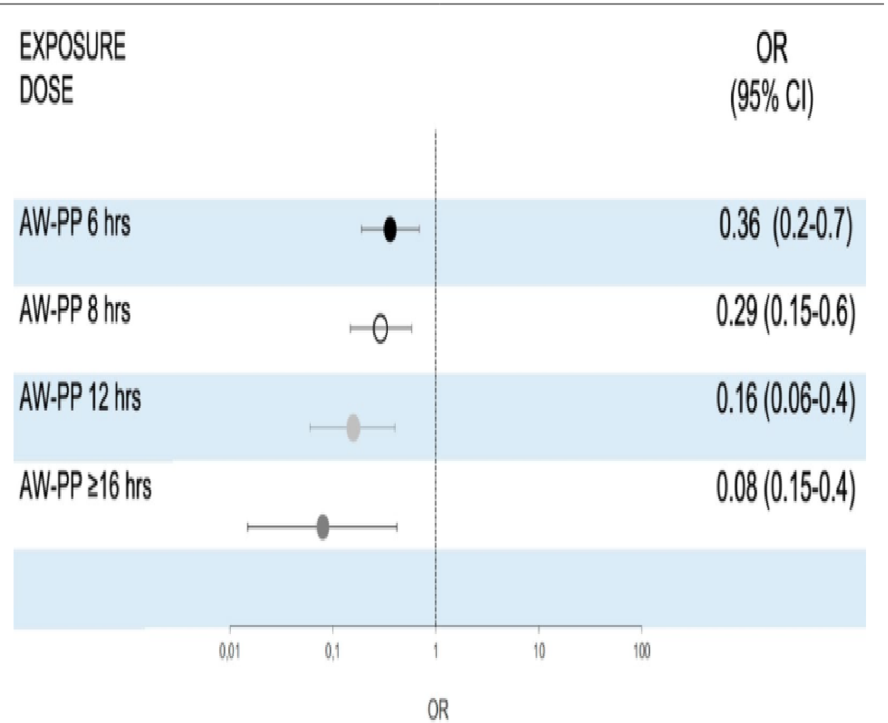
increased work of breathing with use of accessory respiratory muscles, and a respiratory rate > 30/min

$PaO_2/FiO_2$ ratio < 200 mmHg.

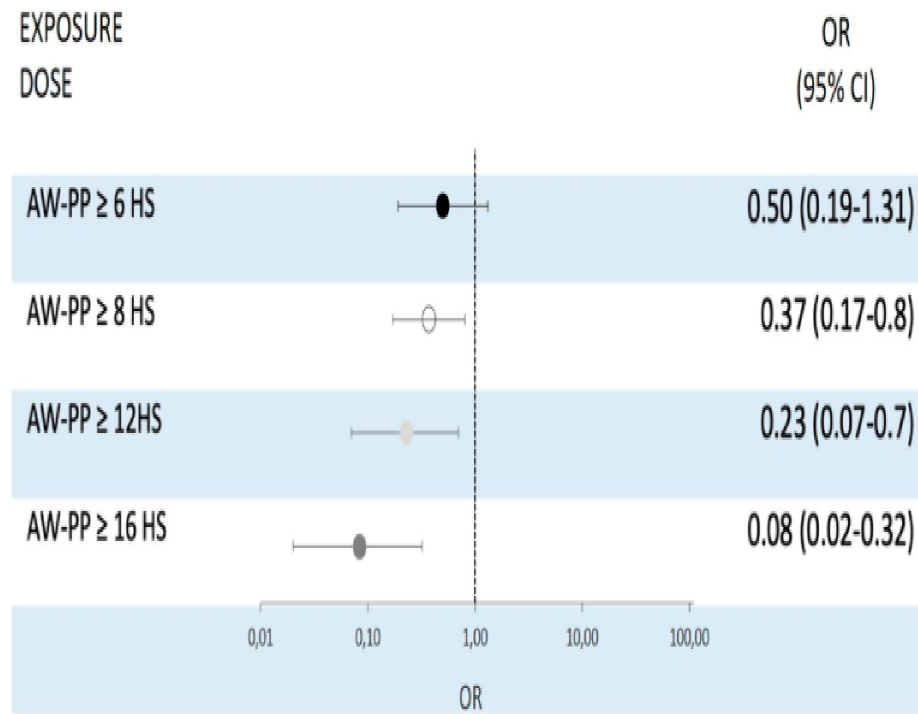



*Critical Care (2022) 26:16*

# Outcomes between awake PP and SP




Intubation




Mortality

AW-PP for≥6 h/day reduced the risk of endotracheal intubation
≥8 h/d reduced the risk of hospital mortality.

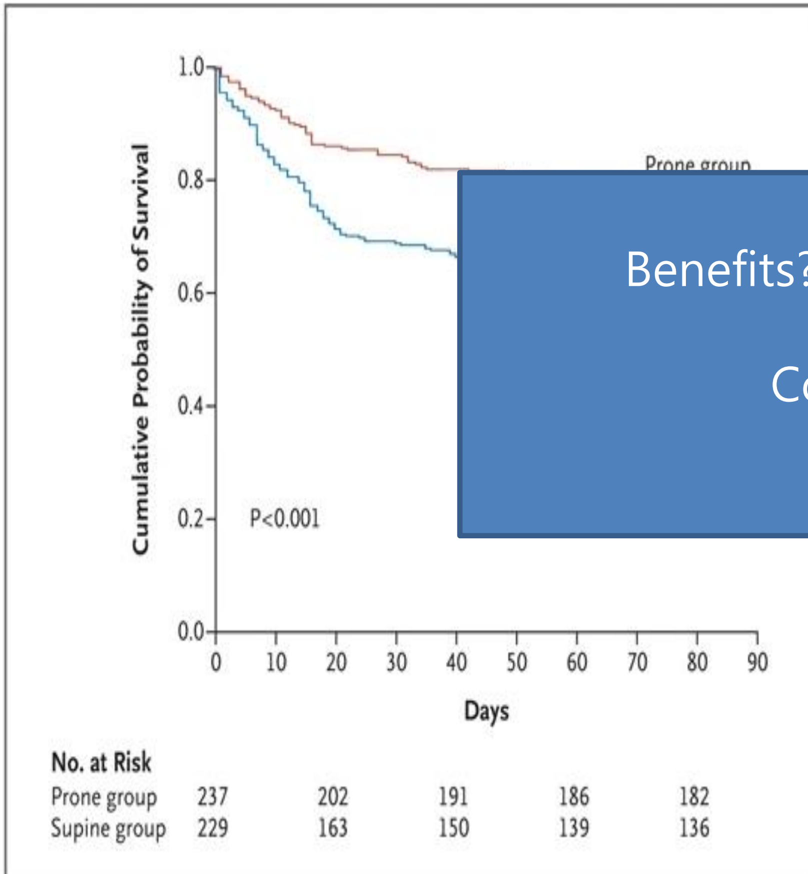
*Critical Care (2022) 26:16*

# Future directions

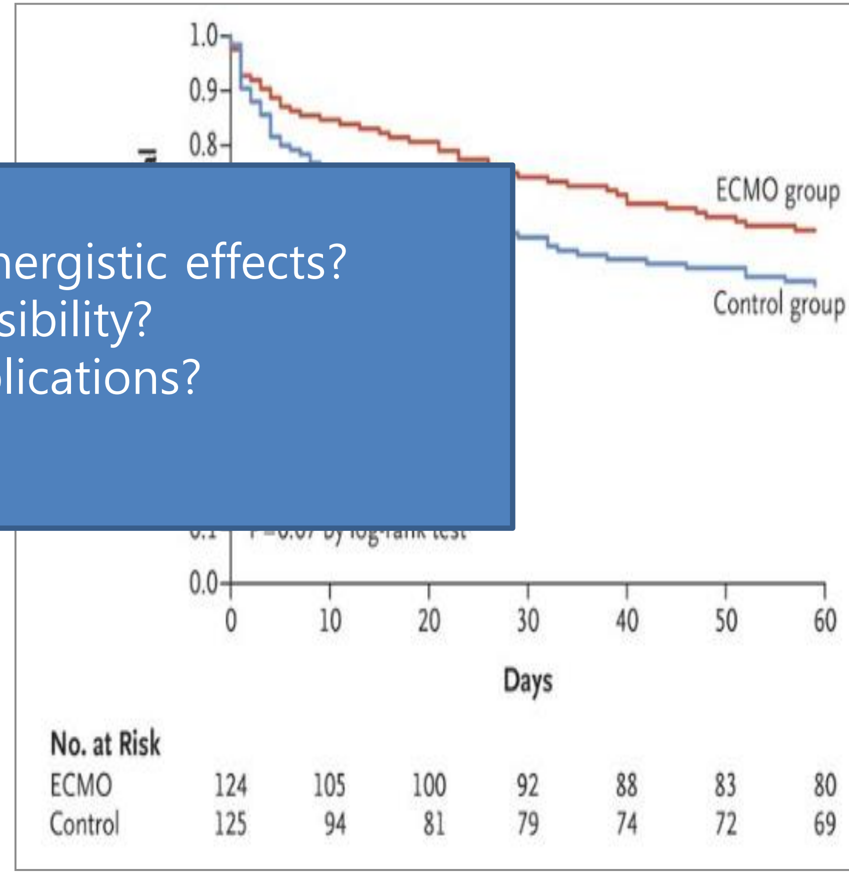

- Refining the criteria to identify patients who will benefit most from APP
- Actual prone duration, Start / end point
- Modulation of P-SILI
- Generalized all ARDS patients
- APP technique's feasibility, tolerability
- Improving the tolerance and comfort of patients deserves investigation with multidisciplinary input from patients, nurses and respiratory therapists

# Proning on ECMO

Prone Positioning in Severe Acute Respiratory Distress Syndrome




Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome




Benefits? Synergistic effects?
Feasibility?
Complications?

More homogeneous distibution ->
Improvement V/Q mismatch
Reduce VILI

Granting protective or ultraprotective ventilation, allowing lung "rest", reducing the risk of VILI.

*N Engl J Med 2013; 368:2159-2168*

*N Engl J Med 2018; 378:1965-1975*

# Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

## A Multicenter Cohort Study and Propensity-matched Analysis

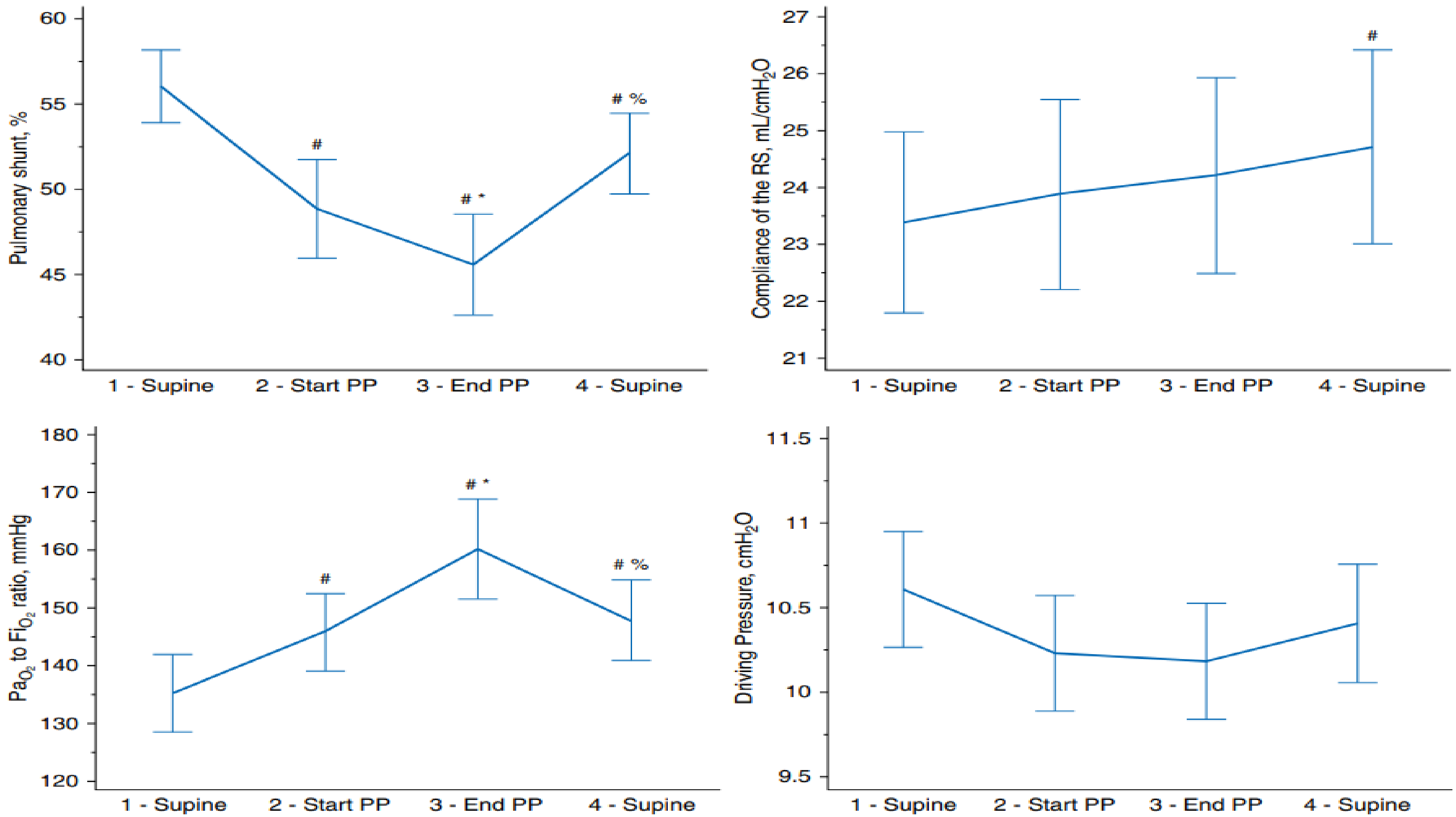
Multicenter retrospective study, six Italian ECMO referral centers
January 2014 and December 2018.   ARDS -Berlin definition

Characteristics of study population stratified by treatment

| | Prone Group (*n* = *107*) | Control Group (*n* = *133*) |
|---|---|---|
| Sex, M | 73 (68.2) | 83 (62.4) |
| Age, yr | 48 ± 13 | 49 ± 13 |
| BMI, kg/m$^2$ | 28.5 ± 6.5 | 28.4 ± 8.1 |
| Cause of ARDS | | |
| Pneumonia | 99 (92.5) | 121 (91.0) |
| Other | 8 (7.5) | 12 (9.0) |
| $Pa_{O_2}:FI_{O_2}$ before ECMO, mm Hg | 73 ± 29 | 76 ± 34 |
| SOFA score | 9 ± 3 | 10 ± 4 |
| Prone positioning before ECMO | 34 (31.8) | 38 (35.2) |
| Nitric oxide before ECMO | 8 (7.5) | 20 (9.8) |
| AKI requiring RRT before ECMO | 17 (15.9) | 9 (6.8) |
| Duration of MV before ECMO, d | 2 (1–6) | 2 (1–6) |
| Comorbidities | | |
| Hypertension | 22 (20.6) | 46 (34.6) |
| Diabetes mellitus | 17 (15.9) | 17 (12.8) |
| Immunodeficiency | 15 (14.0) | 30 (22.6) |
| Active malignancy | 2 (1.9) | 9 (6.8) |
| Autoimmune disorders | 10 (9.4) | 16 (12.0) |
| Immunosuppression | 7 (6.5) | 10 (7.5) |
| Other chronic diseases | 21 (19.6) | 27 (20.3) |
| Asthma-COPD | 7 (6.4) | 17 (12.78) |
| Peripheral vasculopathy | 6 (5.6) | 4 (3.0) |
| Chronic heart failure | 6 (5.6) | 7 (5.3) |
| Chronic renal disease | 4 (3.7) | 2 (1.5) |
| Chronic liver disease | 5 (4.7) | 6 (4.5) |
| Patients referred from other centers | 94 (88) | 101 (77) |
| Patient retrieved on ECMO | 86 (80) | 72 (59) |

*Ann Am Thorac Soc Vol 18, No 3, pp 495–501, Mar 2021*

# Oxygenation and respiratory mechanics at the different time points




*Ann Am Thorac Soc Vol 18, No 3, pp 495–501, Mar 2021*

**Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome**
**A Multicenter Cohort Study and Propensity-matched Analysis**

# Outcomes

**The median duration was 15 (12–18) hours**

| | Prone Group (*n* = 107) | Control group (*n* = 133) | *P* Value |
|---|---|---|---|
| Duration of ECMO support, d | | | |
| All patients | 16 (11–30) | 10 (6–18) | <0.0001 |
| Alive on ECMO | 14 (10–24) | 10 (6–16) | 0.0011 |
| Length of ICU stay, d | | | |
| All patie | | | |
| Alive at | | | |
| Mortality a | | | |

| Complication | Results (*N* = 21) |
|---|---|
| Desaturation | 8 (2.5) |
| Bleeding | 4 (1.2) |
| Decrease of extracorporeal blood flow | 4 (1.2) |
| Hemodynamic instability | 2 (0.6) |

When PP should be initiated
How long it should be performed.
Standardizing mechanical ventilation and ECMO weaning procedures

PP during ECMO improved oxygenation and was associated with a reduction of hospital mortality

*Ann Am Thorac Soc Vol 18, No 3, pp 495–501, Mar 2021*

# Prone-Positioning for Severe Acute Respiratory Distress Syndrome Requiring Extracorporeal Membrane Oxygenation

26-bed ICU severe ARDS patients
VV-ECMO support (2012–2020)
Indication of PP on ECMO

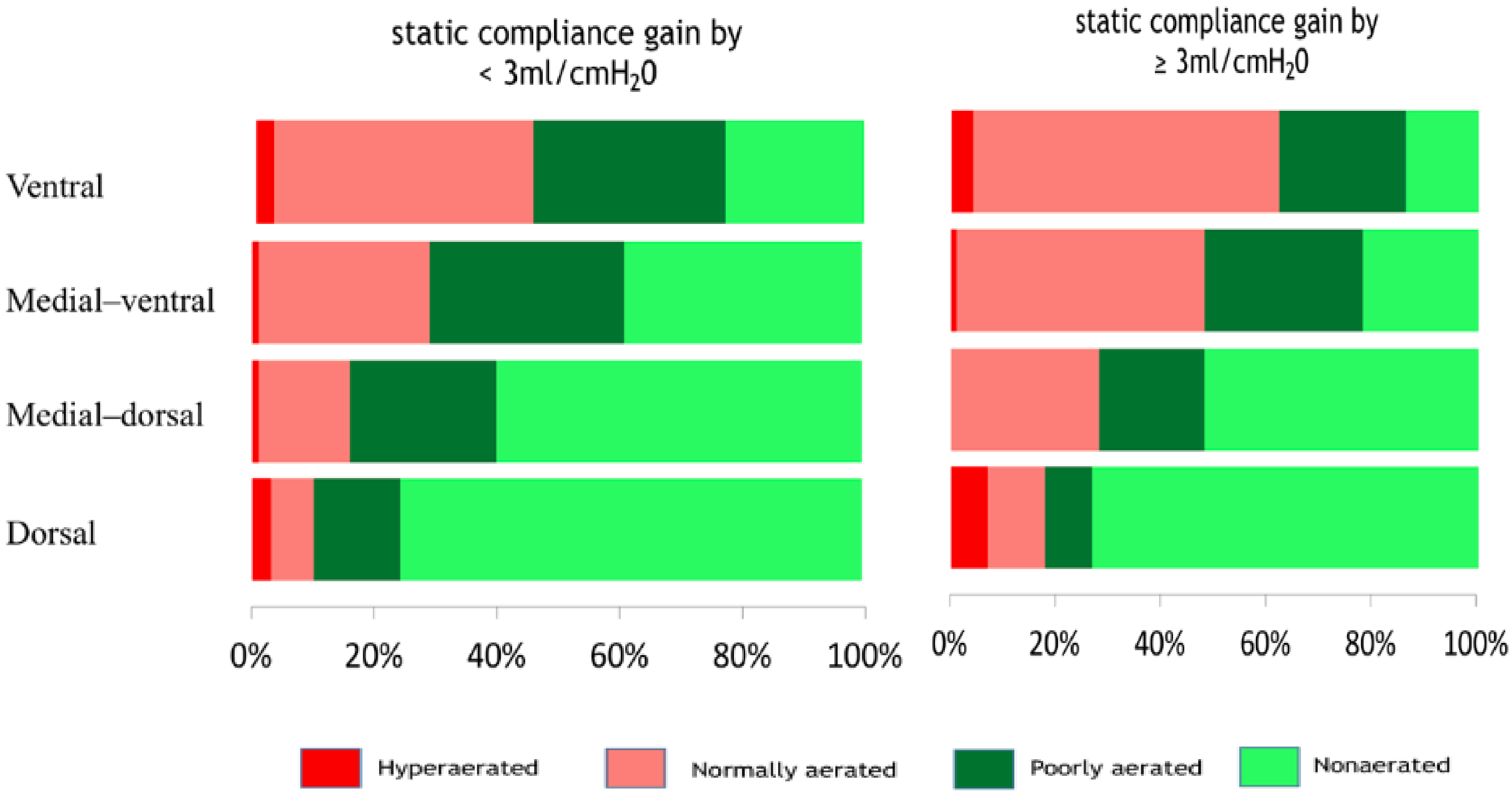
severe hypoxemia, extensive lung consolidation, or difficult ECMO weaning.
The PP sessions lasted for 16 hours

During which patients were maintained deeply sedated with neuromuscular blockade.

| | Nonmatched Cohort | | | Propensity-Score Matched | | |
|---|---|---|---|---|---|---|
| Parameter | PP-ECMO (*n* = 64) | No-PP-ECMO (*n* = 234) | *p* | PP-ECMO (*n* = 59) | No-PP-ECMO (*n* = 59) | *p* |
| Complications | | | | | | |
| Accidental decannulation | 0 (0) | 5 (2) | 0.52 | 0 (0) | 2 (3) | 0.48 |
| Cannula bleeding | 16 (25) | 52 (22) | 0.76 | 15 (25) | 16 (27) | 1 |
| Cannula-site infection | 17 (27) | 89 (38) | 0.12 | 16 (27) | 25 (42) | 0.12 |
| Ventricular arrhythmia | 2 (3) | 17 (7) | 0.36 | 2 (3) | 6 (10) | 0.27 |
| Gas embolism | 2 (3) | 1 (0.4) | 0.23 | 2 (3) | 1 (2) | 0.23 |
| Cardiac arrest | 3 (5) | 27 (12) | 0.19 | 3 (5) | 9 (15) | 0.13 |
| Outcomes | | | | | | |
| Tracheostomy | 19 (30) | 101 (43) | 0.07 | 18 (31) | 28 (47) | 0.09 |
| ECMO duration, d | 16 (9–29) | 11 (4–30) | 0.01 | 15 (8–31) | 15 (7–30) | 0.66 |
| ICU length of stay, d | 38 (27–60) | 25 (11–43) | < 0.01 | 37 (25–60) | 27 (17–49) | 0.04 |
| 90-d probability of being weaned-off ECMO and alive (95% CI) | 0.75 (0.62–0.84) | 0.49 (0.43–0.55) | < 0.01 | 0.75 (0.61–0.84) | 0.54 (0.41–0.66) | 0.03 |
| 90-d probability of being weaned-off mechanical ventilation and alive (95% CI) | 0.64 (0.51–0.75) | 0.46 (0.4–0.53) | 0.05 | 0.62 (0.46–0.74) | 0.52 (0.39–0.65) | 0.35 |
| 90-d mortality | 13 (20) | 113 (48) | < 0.01 | 12 (20) | 25 (42) | < 0.01 |

*Critical Care Medicine 2022 : 50(2): 264-274*

# Outcomes




’90-day probability of being weaned-off ECMO (0.75 vs 0.54, $p = 0.03$)

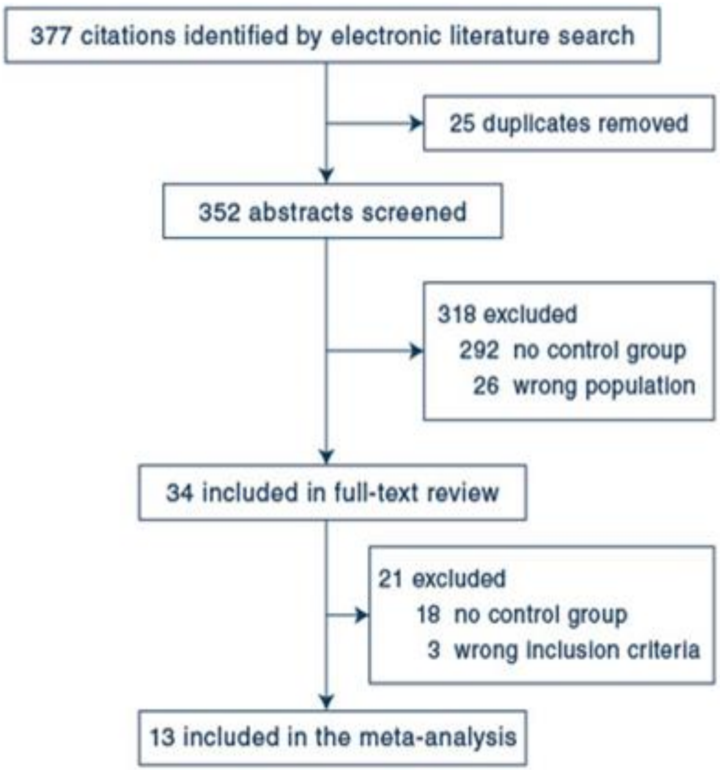
90-day mortality (20% vs 42%, $p < 0.01$)

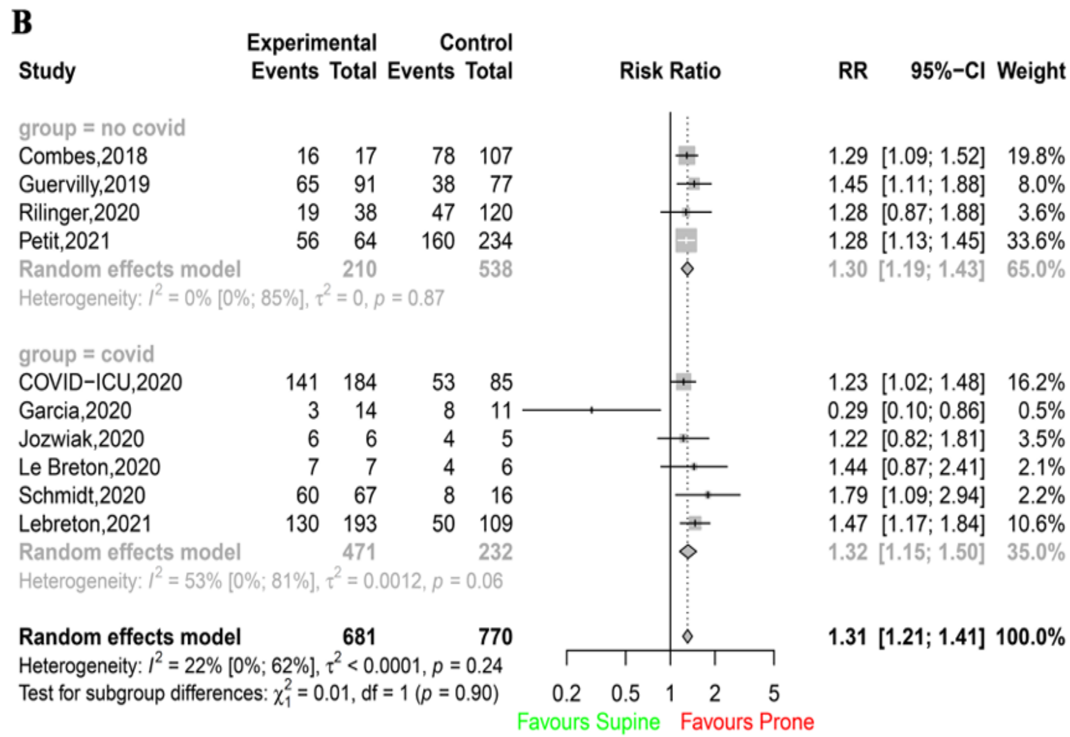
*Critical Care Medicine 2022 : 50(2): 264-274*

# Conclusions

- PP during VV-ECMO for severe ARDS was safe when done in an **experienced center**.
- PP during VV-ECMO higher weaned-off ECMO at 90 days and lower 90-day mortality.
- **Patients with greater normally aerated lung tissue in the ventral and medial-ventral regions** improve their static compliance after that procedure during ECMO.

# Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis




Survival at day 28

*Intensive Care Med (2022) 48:270–280*

# Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS

## The PRONECMO Randomized Clinical Trial

- VV-ECMO for less than 48 hours at 14 intensive care units (ICUs) in France between March 3, 2021, and December 7, 2021.

- The primary outcome

  time to successful ECMO weaning within 60 days

Secondary outcomes : ECMO and mechanical ventilation–free days, ICU and hospital length of stay, skin pressure injury, serious adverse events, and all-cause mortality at 90-day follow-up

JAMA. 2023;330(24):2343-2353

## Inclusion criteria

1. Severe acute respiratory distress syndrome refractory to conventional therapy placed on VV-ECMO support in the preceding 48h.  2. Obtain informed consent from a close relative or surrogate. 3. Social security registration

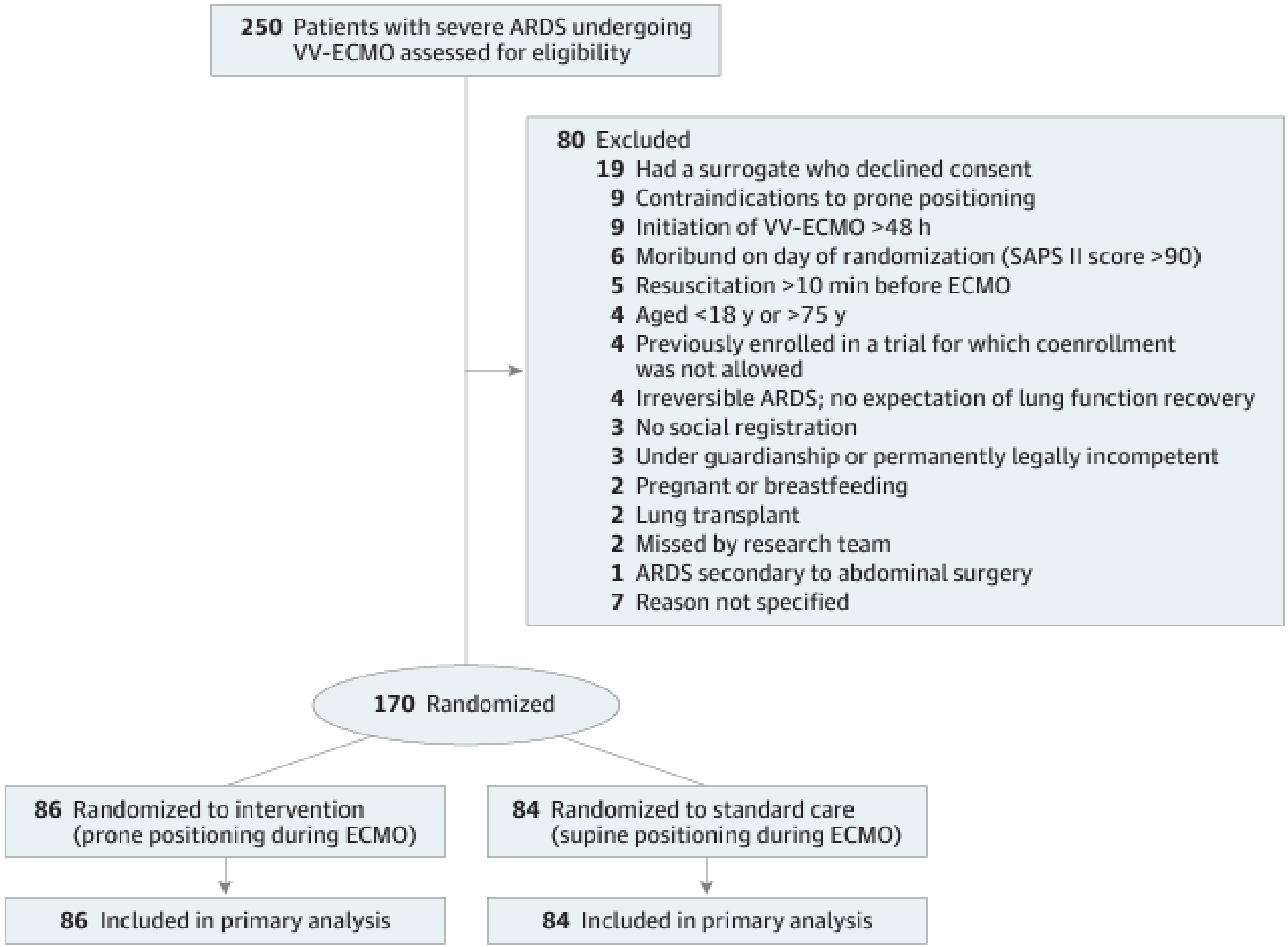
## Exclusion criteria

1. Age <18 and >75 years 2. Pregnancy and breast-feeding woman 3. **Initiation of VV-ECMO >48 h** 4. Cardiopulmonary resuscitation >10 minutes before ECMO 5. Irreversible neurological pathology 6. End-stage chronic lung disease  7. ARDS secondary to an abdominal surgery  **8. Contraindications for prone positioning** (Intracranial pressure >30 mm Hg or cerebral perfusion pressure <60 mmHg; Massive hemoptysis; Tracheal surgery or sternotomy during the previous 15 days; Serious facial trauma or facial surgery during the previous 15 days; Deep venous thrombosis treated for less than 2 days; Cardiac pacemaker inserted in the last 2 days;  Unstable spine, femur, or pelvic fractures; Mean arterial pressure lower than 65 mm Hg;  Single anterior chest tube with air leaks) 9. Irreversible ARDS with no hope for lung function recovery   10. Patient moribund on the day of randomization, SAPS II >90 11. Liver cirrhosis (Child B or C) 12. Chronic renal failure requiring hemodialysis 13. Lung transplantation  14. Burns on more than 20 % of the body surface 15. Individuals under guardianship, or permanently legally incompetent adults

JAMA. 2023;330(24):2343-2353

| |
|---|
| **Criteria for possible prone positioning in the supine ECMO group** |
| **Refractory hypoxemia on ECMO $SaO_2$ ≤80% for more than 6 hours, despite a mandatory ECMO flow >5L/min, FiO2 and $FmO_2$ set at 100%,** hypothermia at 35°C, adequate placement of the cannula to minimize recirculation, hemoglobin above 9g/dl to increase O2 transport, use of beta-blockers if heart rate <120/min to decrease the cardiac output, and only if the patient had no irreversible multiple organ failure and if the physician in charge of the patient believed that this could change the outcome |
| **Criteria for stopping prone treatment** |
| **Patients achieving $PaO_2$>60mmHg, $SaO_2$>90%, $PCO_2$<50mmHg or pH>7.36 with a $FiO_2$ on the ventilator <60%, Vt 6ml/kg and a plateau pressure <28cm$H_2$0, a RR<28/min, a driving pressure ≤ 14cm$H_2O$ and no sign of acute cor pulmonale at 0 sweep gas flow for at least 24 hours** Complications occurring during a prone session and leading to its immediate interruption, such as non-scheduled extubation, accidental decannulation, mainstem bronchus intubation, endotracheal tube obstruction, hemoptysis, $SpO_2$<85% or $PaO_2$<55mmHg for more than one hour under FIO2 100% |

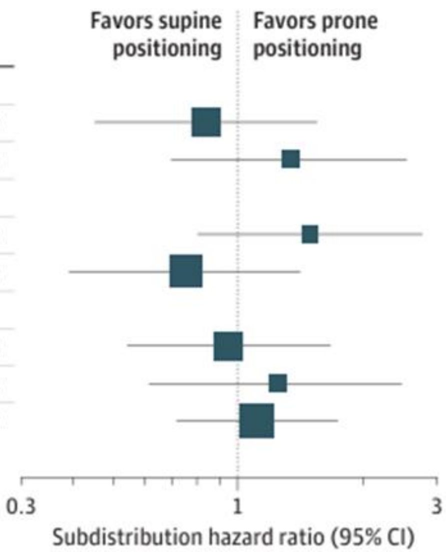
*JAMA.* 2023;330(24):2343-2353




*JAMA.* 2023;330(24):2343-2353

# Primary and Secondary End point


| Subgroup | No./total No. Prone ECMO group (n=86) | Supine ECMO group (n=84) | Subdistribution hazard ratio (95% CI) | P value for interaction[a] |
|---|---|---|---|---|
| Respiratory system compliance at randomization, mL/cm $H_2O$[b] | | | | |
| ≤20 | 18/40 | 22/42 | 0.84 (0.45-1.56) | |
| >20 | 20/46 | 15/42 | 1.34 (0.69-2.57) | .16 |
| Body mass index[c] | | | | |
| ≤33 | 22/44 | 16/41 | 1.50 (0.80-2.81) | |
| >33 | 16/40 | 21/43 | 0.75 (0.39-1.42) | .15 |
| High ECMO volume center[c,d] | | | | |
| Yes | 22/49 | 24/50 | 0.95 (0.54-1.68) | |
| No | 16/37 | 13/34 | 1.25 (0.61-2.50) | .79 |
| All patients | 38/86 | 37/84 | 1.11 (0.71-1.75) | |




| No. of events[a] | 0 | 19 | 34 | 48 | 59 | 64 | 71 |
|---|---|---|---|---|---|---|---|

*JAMA.* 2023;330(24):2343-2353

# Adverse event

| Outcomes/events | Prone ECMO (n = 86) | Supine ECMO (n = 84) | Mean, median, or risk difference, (95% CI) | Relative difference (95% CI) | *P* value |
|---|---|---|---|---|---|
| **Adverse events by day 60** | | | | | |
| Serious adverse events, No. (%) | | | | | |
| ≥1 Cardiac arrest | 3 (3.5) | 11 (13.1) | −9.6 (−19 to −0.2) | 0.27 (0.08-0.92) | .05 |
| Bleeding event requiring packed red blood cell transfusion | 24 (27.9) | 32 (38.1) | −3.0 (−17.3 to 11.4) | 0.89 (0.54-1.48) | .79 |
| Hemorrhagic stroke | 2 (2.3) | 1 (1.2) | 1.1 (−3.9 to 6.2) | 1.95 (0.18-21.14) | >.99 |
| Unintentional ECMO decannulation | 0 | 0 | | | |
| Nonscheduled extubation, No. (%) | 0 | 0 | | | |
| Severe hemoptysis, No. (%) | 0 | 0 | | | |
| Maximum Revised Pressure Injury Staging System score, median (IQR)[e] | 8 (4-11) | 6 (2-10) | 2 (−1 to 6) | | .14 |

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## Despite promising findings in observational studies, prone positioning of patients undergoing ECMO failed to reduce ECMO duration or mortality in this randomized trial. Why?

Prone position before ECMO

COVID 19 ARDS

Delta variants was predominant in France

Limitations

Small sample size

69 of 170 patients were enrolled from a single very experienced center, which could limit the generalizability

the trial was unblinded due to the nature of the intervention, and this design may introduce bias.

# Is the PP+ECMO feasible?

**How to define which patient will benefit from prone position on ECMO**

-ARDS (COVID 19 vs Non COVID 19)

-When (start/ stop), Duration of PP

**Potential complications**

Transient desaturation, lower ECMO flow, hemodynamic instability, accidental extubation, decannulation, increased sedation

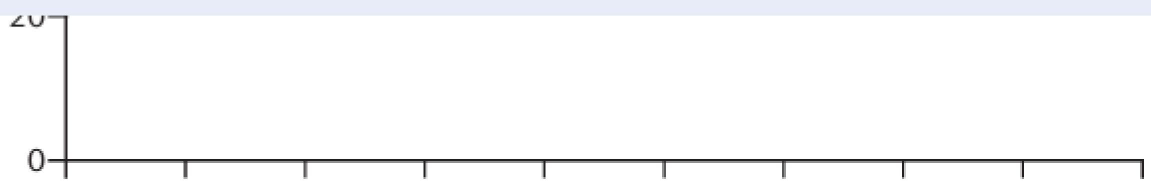
# Is the PP+ECMO feasible?

## Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study

**Recommendation 9.1**

We **recommend** that patients with severe ARDS not due to COVID-19 as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO center which meets defined organizational standards, adhering to a management strategy similar to that used in the EOLIA trial.
*Strong recommendation, moderate level of evidence in favor*

This recommendation applies also to patients with severe ARDS due to COVID-19.
*Strong recommendation; low level of evidence in favor for indirectness.*




*Lancet Respir Med 2021; 9: 851–62*

# Summary

CONFERENCE REPORTS AND EXPERT PANEL

**ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies**

Check for updates

- We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as $PaO_2$/ $FiO_2$ < 150 mmHg and PEEP ≥ 5 $cmH_2O$, despite optimization of ventilation settings) to reduce mortality.- Low tidal, 16 consecutive hours or more

- We **suggest** awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation.

# Unanswered issues

Optimal indication- Awakening PP, ECMO PP

Optimal duration and implementation

Ventilator setting

Adequate PEEP –EIT

The understanding of pathophysiologic feature ARDS patients-RV Failue.

**Individualized Prone Position**

# Mechanical Ventilation : ***A necessary evil in ARDS***

"If correctly performed,
mechanical ventilation *"buys time"*
to allow other therapies to take effect;

if performed incorrectly, it may kill the patient."

*Dr. Luciano Gattinoni*

*CMAJ 2008;178:1174-1176*

## ***Role of prone position***