An exploration of oxygenation indices in proned patients

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Introduction

The Acute Respiratory Distress Syndrome (ARDS) was initially identified as a clinical entity in the 1960s[1]. ARDS consists of diffuse alveolar damage due to the activation of alveolar macrophages to release pro-inflammatory cytokines[2] that attract neutrophils to the lungs where they damage the alveolar and capillary epithelium by release of toxic mediators. This leads to the alveoli being filled with bloody, proteinaceous fluid. Consequently, the surfactant can no longer support the alveoli[3]. The end result is that these damaged alveoli lead to impaired gas exchange, which is the pathophysiolgic hallmark of ARDS.

Patients with certain clinical conditions are at higher risk for developing ARDS. These can broadly be grouped into direct lung injury risk factors like pneumonia, aspiration, pulmonary contusion, inhalational injury, near drowning etc. (heretofore referred to as 'ARDSp') and indirect lung injury risk factors such as sepsis, non-thoracic injuries/hemorrhagic shock, pancreatitis, burns, drugs/toxins, blood transfusions, cardiopulmonary bypass and reperfusion injury after lung transplant or embolectomy (which will now be referred to as 'ARDSexp')[4]. Severe lung injury secondary to Covid-19 has certain unique features, and has been termed 'C-ARDS'[5].

To date, there are no specific drugs or therapies available to directly treat/prevent ARDS. Mechanical ventilation that aims to protect injured lungs and minimize Ventilator Induced Lung Injury (VILI), and management of refractory hypoxaemia, are the keystones in supportive management of ARDS[6]. Part of the above can include placing a patient in the prone (i.e. 'face down') position. This was first described as a therapy for ARDS in the 1970s[7]. The mechanism by which prone positioning improves oxygenation is multifactorial. It reduces the ventral to dorsal transpulmonary pressure difference, ventilation-perfusion mismatch and lung compression[8,9]. Other potential physiological effects of prone positioning include a decrease in proinflammatory cytokines and improvement in right ventricle dysfunction by preserving pulmonary circulation[10].

The first prospective randomized control trial (known as the 'PROSEVA' trial) that showed a mortality benefit from prolonged prone positioning was conducted in France and published in 2013[11]. Prone positioning for at least 12 to 16 hours per day, while administering low tidal volumes (4-6ml/kg of ideal body weight), is now strongly recommended in ventilated patients with severe ARDS[12].

Many questions regarding the utility and efficacy of the prone position remain. An important issue lies in identifying patients who, although they fit the criteria to undergo prone positioning, are unlikely to receive a mortality benefit and in whom other therapies may be effective[13].

Population

Initial selection

This section shows details of the population involved in this study. The data was gathered by interrogating the Electronic Health Record system used in the Intensive Care Unit (ICU) of University Hospital Galway (UHG). The system was queried to return all patients on record whp fulfilled the following criteria:

- over 18 years of age
- invasively ventilated
- placed in the prone position whilst invasively ventilated

Study population

A total of 133 records were isolated from the servers. These records date from between 14/07/2013 and 20/03/2022. They consisted of patients who had been placed in the prone position secondary to a pulmonary insult (ARDSp), and extrapulmonary insult (ARDSexp), and Covid-19 (C-ARDS). Patients in the dataset were proned between 1 and 13 times. Full details of these demographics can be seen overleaf in Table 01.

Characteristic	**Overall**, N = 133[1]	**Covid_19**, N = 51[1]	**ARDSp**, N = 73[1]	**ARDSexp**, N = 5[1]	**Unknown**, N = 4[1]
Gender					
f	45 (34%)	15 (29%)	28 (38%)	1 (20%)	1 (25%)
m	88 (66%)	36 (71%)	45 (62%)	4 (80%)	3 (75%)
Age (years)	58 (15)	60 (13)	57 (16)	52 (13)	64 (14)
Height (cm)	169 (13)	171 (10)	167 (16)	178 (12)	173 (9)
Not recorded	27	9	17	1	0
Weight (kg)	86 (21)	93 (21)	81 (21)	85 (12)	94 (14)
Admitting location					
cath lab	1 (0.8%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
ccu	3 (2.3%)	0 (0%)	3 (4.1%)	0 (0%)	0 (0%)
ed	27 (20%)	8 (16%)	17 (23%)	1 (20%)	1 (25%)
guh_ward	58 (44%)	25 (49%)	31 (42%)	2 (40%)	0 (0%)
theatre (elective)	3 (2.3%)	0 (0%)	3 (4.1%)	0 (0%)	0 (0%)
theatre (emergency)	4 (3.0%)	0 (0%)	3 (4.1%)	1 (20%)	0 (0%)
transfer	37 (28%)	18 (35%)	15 (21%)	1 (20%)	3 (75%)
LOS (days)	19 (18)	18 (13)	21 (22)	14 (7)	8 (3)
Apache II	19 (8)	14 (5)	21 (7)	27 (10)	31 (11)
Proning sessions	3 (2)	3 (2)	2 (2)	1 (0)	2 (1)
Outcome					
dc	72 (54%)	29 (57%)	39 (53%)	3 (60%)	1 (25%)
rip	61 (46%)	22 (43%)	34 (47%)	2 (40%)	3 (75%)
BMI	31 (8)	32 (7)	30 (8)	28 (3)	31 (3)
Not recorded	27	9	17	1	0

[1] n (%); Mean (SD)

Figure 1: Summary of patient demographics

Data gathered around prone-positioning

For each patient, values relating to ventilation and oxygenation were isolated around every session of prone positioning that took place whilst the patient was invasively ventilated. The following values were recorded:

Ventilation

- Fraction of inspired oxygen (FiO_2)
- Minute Volume (MV), measured in L/min
- Positive End-Expiratory Pressure (PEEP), measured in cmH_2O
- Peak Inspiratory Pressure (PIP), measured in cmH_2O
- Mean Airway Pressure (P_{aw}), measured in cmH_2O

Oxygenation

- peripheral oxygen saturation (SpO_2), recorded using bedside pulse oximetry
- saturation of oxygen (SaO_2), recorded from arterial blood gas
- partial pressure of oxygen (PaO_2), recorded from arterial blood gas

Other

- partial pressure of carbon dioxide ($PaCO_2$), recorded from arterial blood gas
- haemoglobin concentration (g/dL), recorded from arterial blood gas

These values were recorded at three key time-points. One ABG and corresponding venstilatory values were recorded from immediately before being turned to the prone position. The same set of values was recorded at the end of the session of prone positioning, prior to returning to the supine position. Finally, recordings were taken from within four hours of returning to the supine position.

Oxygenation indices

The following indices of oxygenation will be examined. Some have been recorded directly from monitoring equipment to which the patient was attached in ICU, and some have been calculated. The indexes are outlined below.

The following recorded *directly*:

- SpO_2
- SaO_2
- PaO_2

The following were *calculated* from recorded values:

- P/F ratio
- Ventilatory ratio
- Oxygenation index
- Oxygenation factor
- A-a O_2 gradient
- Arterial O_2 content (CaO_2)

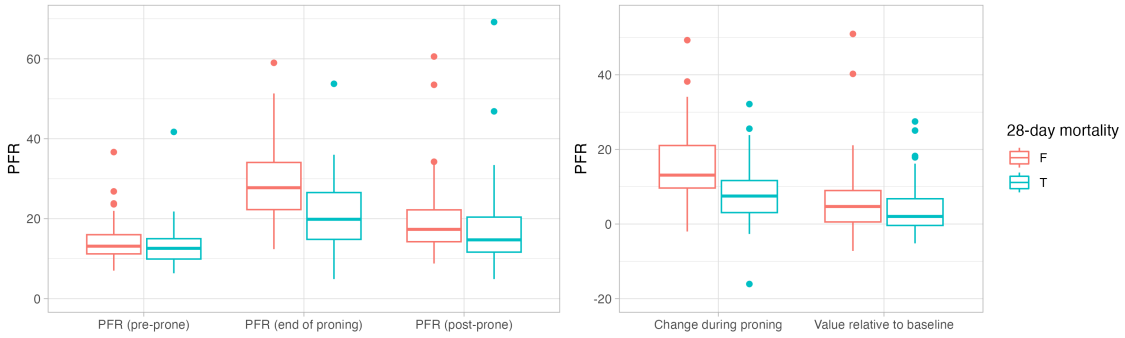
The above have been documented and the data relating to the initial session of prone position were analysed. The following pages contain a series of boxplots allowing a rapid visual assessment of the presence or absence of trends.

P/F ratio

PaO_2/FiO_2 ratio (PFR) is the ratio of arterial oxygen partial pressure to fractional inspired oxygen. The equation used to calculate it is given below.

$$P/F\ ratio = \frac{PaO_2}{FiO_2}$$

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) PFR by position (b) PFR changes

Figure 2: PF ratio around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 57 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	13.0 (12, 14)	14.0 (13, 15)	0.27
At end of proning (prone)	21 (19, 23)	29 (27, 31)	<0.001
After proning (supine)	17 (15, 20)	20 (17, 22)	0.22
Change during proning session	8 (5.9, 10)	15 (13, 17)	<0.001
Change relative to before proning	4 (2.6, 6.2)	6 (3.2, 7.8)	0.48

[1] Mean
[2] CI = Confidence Interval
[3] One-way ANOVA

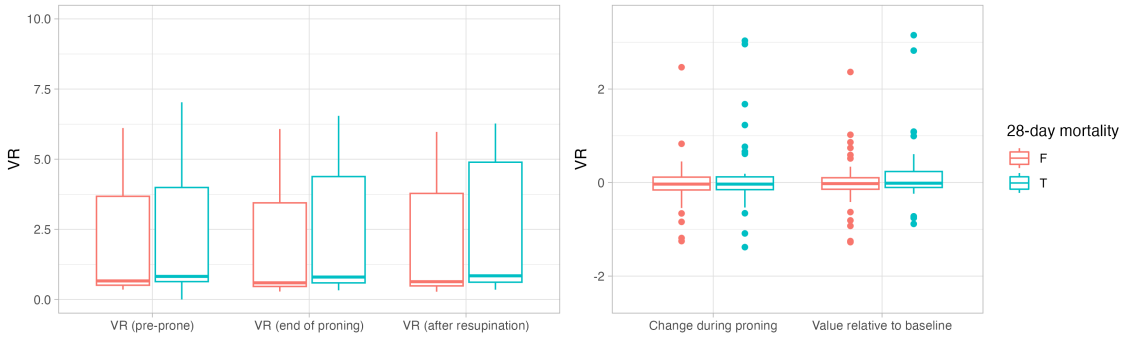
Figure 3: Response of PFR to initial session of prone positioning

Ventilatory ratio

The ventilatory ratio (VR) is a simple bedside index that can be calculated using routinely measured respiratory variables and is a measure of impaired ventilation.

$$Ventilatory\,ratio = \frac{MV \times Pa_{CO_2}}{PBW \times 100 \times 5}$$

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) VR by position

(b) VR changes

Figure 4: Ventilatory ratio around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 57 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	2.13 (1.5, 2.8)	2.26 (1.6, 3.0)	0.80
At end of proning (prone)	2.40 (1.8, 3.1)	1.94 (1.4, 2.4)	0.24
After proning (supine)	2.52 (1.8, 3.2)	1.91 (1.4, 2.4)	0.13
Change during proning session	0.14 (-0.11, 0.39)	-0.21 (-0.59, 0.17)	0.15
Change relative to before proning	0.19 (-0.05, 0.42)	-0.19 (-0.61, 0.23)	0.14

[1] Mean

[2] CI = Confidence Interval

[3] One-way ANOVA

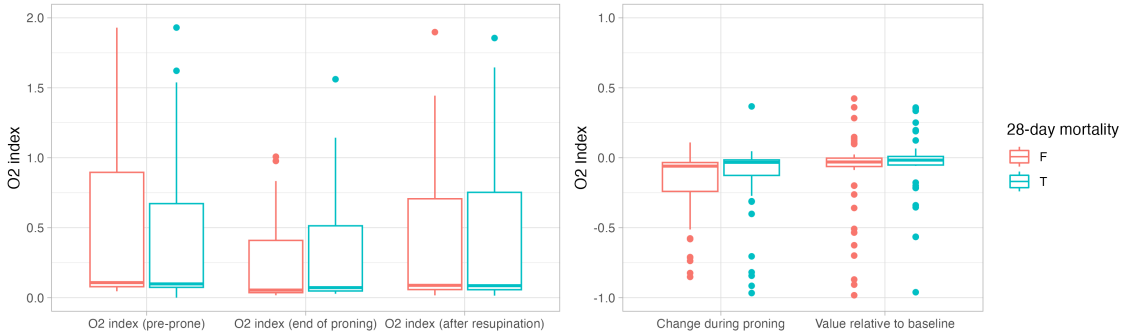
Figure 5: Response of VR to initial session of prone positioning

Oxygenation index

This oxygenation index can be an important prognostic indicator, especially in paediatric patients. It can assist in determining the need for ECMO.

$$Oxygenation\ index = \frac{FiO_2 \times P_{AW}}{PaO_2}$$

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) O2 index by position

(b) O2 index changes

Figure 6: Oxygenation index around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 57 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	0.45 (0.28, 0.62)	0.53 (0.38, 0.67)	0.52
At end of proning (prone)	0.33 (0.22, 0.45)	0.24 (0.18, 0.31)	0.15
After proning (supine)	0.49 (0.31, 0.67)	0.40 (0.29, 0.50)	0.36
Change during proning session	-0.16 (-0.25, -0.07)	-0.28 (-0.38, -0.18)	0.092
Change relative to before proning	-0.04 (-0.11, 0.02)	-0.14 (-0.23, -0.05)	0.090

[1] Mean

[2] CI = Confidence Interval

[3] One-way ANOVA

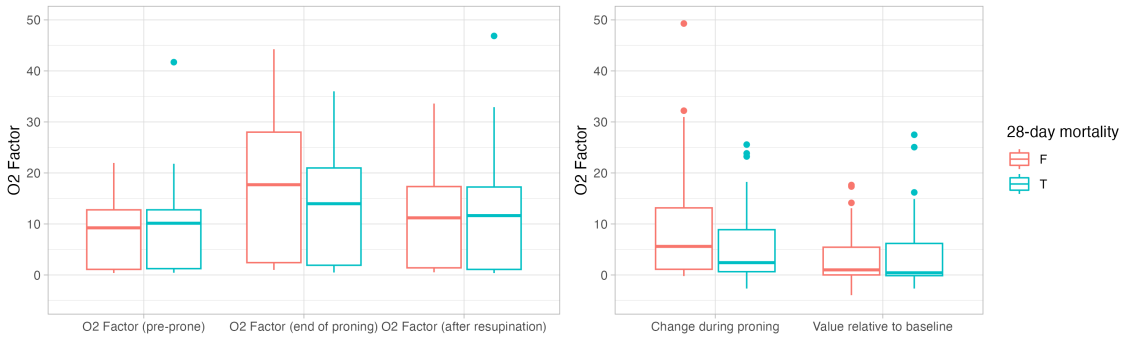
Figure 7: Response of Oxygenation Index to initial session of prone positioning

Oxygenation factor

This index is similar to the above, and is essentially the PF ratio normalised for the mean airway pressure at the time of measure.

$$Oxygenation\ factor = \frac{PF\ ratio}{P_{AW}}$$

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) OF by position

(b) OF changes

Figure 8: Oxygenation factor around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 56 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	9.0 (6.8, 11)	7.8 (6.3, 9.3)	0.35
At end of proning (prone)	13 (10, 16)	17 (14, 20)	0.13
After proning (supine)	12 (8.6, 16)	11 (8.7, 14)	0.72
Change during proning session	5 (2.8, 7.0)	9 (6.7, 11)	0.015
Change relative to before proning	3.8 (1.9, 5.6)	3.7 (1.9, 5.6)	0.98

[1] Mean

[2] CI = Confidence Interval

[3] One-way ANOVA

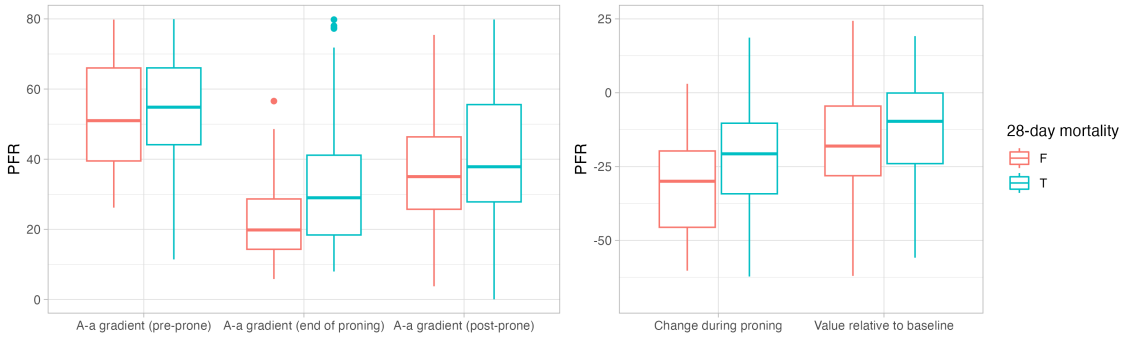
Figure 9: Response of Oxygenation factor to initial session of prone positioning

A-a O_2 gradient

This calculation allows one to broadly determine the source of hypoxaemia in a patient. It also acts as an imperfect surrogate to measure the magnitude of shunt

$$A-a\ gradient = [FiO_2 \times (P_{atm} - P_{H_2O}) - \frac{Pa_{CO_2}}{0.8}] - Pa_{O_2}$$

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) Aa gradient by position

(b) Aa gradient changes

Figure 10: A-a gradient around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 57 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	55 (50, 59)	53 (49, 56)	0.46
At end of proning (prone)	34 (28, 39)	22 (20, 25)	<0.001
After proning (supine)	42 (37, 48)	36 (33, 40)	0.057
Change during proning session	-22 (-26, -17)	-30 (-34, -27)	0.004
Change relative to before proning	-13 (-17, -7.9)	-17 (-21, -12)	0.21

[1] Mean

[2] CI = Confidence Interval

[3] One-way ANOVA

Figure 11: Response of A-a O2 gradient to initial session of prone positioning

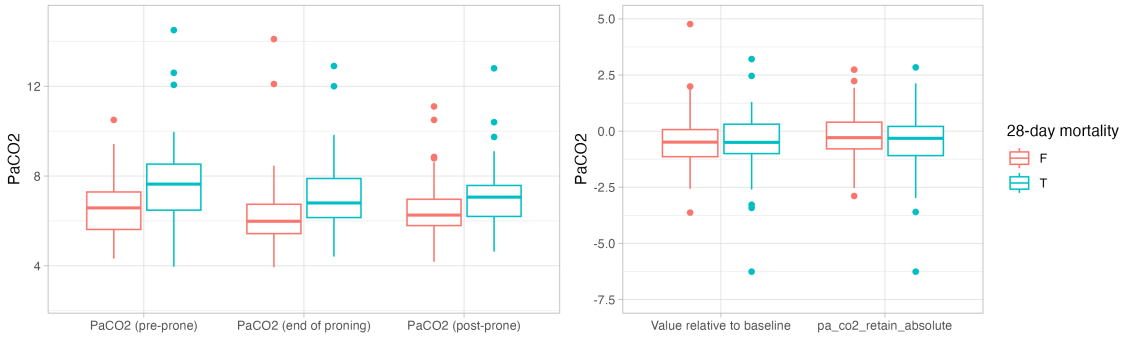
Other

There has been a suggestion that the response of PaCO2 to the prone position can be related to mortality.

PaCO2

This value is measured directly from the ABG, and there is no formula for its calculation.

Below are boxplots that allow for a basic visual assessment of the distribution of the data. It shows the data separated by 28 day mortality from the patients initial session of prone positioning.



(a) O2 index by position (b) O2 index changes

Figure 12: PaCO2 around initial session of prone positioning

The table below shows the mean and 95% confidence intervals for the patients in the study.

	28 Day Mortality		
Patient position	**T**, N = 57 (**95% CI**)[1,2]	**F**, N = 74 (**95% CI**)[1,2]	**p-value**[3]
Before proning (supine)	7.69 (7.2, 8.2)	6.68 (6.4, 7.0)	<0.001
At end of proning (prone)	7.15 (6.8, 7.5)	6.25 (5.9, 6.6)	<0.001
After proning (supine)	7.11 (6.7, 7.5)	6.48 (6.2, 6.8)	0.007
Change during proning session	-0.54 (-0.93, -0.16)	-0.43 (-0.71, -0.15)	0.64
Change relative to before proning	-0.58 (-0.95, -0.20)	-0.20 (-0.46, 0.07)	0.094

[1] Mean

[2] CI = Confidence Interval

[3] One-way ANOVA

Figure 13: Response of PaCO2 to initial session of prone positioning

Impressions

There appears to be a strong difference in how measures of oxygenation change in response to the patient being placed in the prone position between patients who survive and who die within 28 days of the proning procedure. This appears especially strong for PF ratio, and for A-a O2 gradient. It is weakest for Ventilatory Ratio.

Conversely, there seems to be signal that is much weaker regarding PaCO2. Whilst there are strong differences between groups who did and did not die at 28 days post proning, there appeared to be a much less significant difference when it came to measuring how much PaCO2 changed over the course of a session of prone positioning, or when the degree to which this change is maintained was calculated.

The two largest groups of pathology within the study population are Covid-19 and ARDSp. It might be interesting to see if the observed significant differences are different between these groups.

In conclusion, changes in indices of oxygenation around the initial session of prone positioning appeared to be strongly associated with 28 day mortality, while changes in PaCO2 did not.

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