Title: **A**wake **P**rone **P**ositioning to **R**educe invasive **VE**ntilation in **C**OVID-19 induced **A**cute **R**espiratory failur**E** (APPROVE-CARE)

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1. Study summary

The coronavirus disease 2019 (COVID-19) outbreak is a pandemic associated with a pneumonia which can worsen rapidly into respiratory failure known as acute respiratory distress syndrome (ARDS). There is a high rate of mortality in patients with severe respiratory failure requiring mechanical ventilation. Adjunctive therapies constitute an important part of the management of early moderate to severe ARDS. In patients with confirmed moderate-severe ARDs receiving invasive mechanical ventilation, prone position promotes lung homogeneity, improves gas exchange and respiratory mechanics permitting reduction of ventilation intensity, and reducing lung injury. Prone positioning has been demonstrated to save lives and is recommended in evidence-based guidelines for the management of moderate-severe ARDS.

The use of proning outside of mechanically ventilated patients to improve gas exchange and reduce the end for invasive ventilation has not been extensively studied outside of case series. There is no physiological reason why it should not benefit to the same extent in self ventilating patients requiring supplemental oxygen. Maintaining self ventilation is associated with increased aeration of dependent lung regions, less need for sedation, improved cardiac filling, and better matching of pulmonary ventilation and perfusion and thus oxygenation.

In this protocol, we outline details for a registry study and a randomized clinical trial to determine whether placing patients who have hypoxemia related to COVID19 into a prone position can improve oxygenation and reduce the requirement for mechanical ventilation. If effective, this simple intervention could be widely and rapidly implemented, potentially reducing the need for ICU admission and invasive ventilation, and potentially even saving lives.

2. Study team

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3. Study sponsor

Pending acceptance from Clinical research facility, National University of Ireland, Galway

4. Background and rationale

a. COVID19 and Hypoxemia

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) first appeared in Wuhan China in December 2019. It has since spread and was declared a worldwide pandemic by the World Health Organisation in March 2020.(1) Its main route of infection are respiratory droplets and contact transmission. Many infections will be asymptomatic or mild, but a subset require hospitalization and admission to critical care is associated with a high morbidity and mortality from the disease. Acute respiratory distress syndrome requiring mechanical ventilation is associated with a 40-60% mortality. To date, there are no specific pharmacological therapies currently although many are being trialled.(2)

b. Prone position physiology

Prone position is a non-pharmacological treatment used in patients with severe ARDS which has proven mortality benefits in this population. (3)

Physiological studies have shown differences in ventilation pressures in distinct regions of the chest depending on whether one is in the prone or supine position. While breathing in a supine position, the ventral chest wall is lifted by a driving pressure driven by the difference between pleural pressure and atmospheric pressure ($P_{pleural}$ - $P_{atmospheric}$): the diaphragm moves caudally (Ppl - Pabdomen), and the dorsal chest wall moves minimally as lying in contact with a rigid surface. In the supine position, there is a reduction in alveolar size from sternum to vertebra in the supine position at the end of the expiration. This phenomenon has also been clearly identified with CT scans (6-9), and leads to a greater expansion of the nondependent regions and lesser expansion of the dependent parenchyma (6-8).

Contrarily while prone, the dorsal chest wall lifts, the diaphragm shifts similarly to supine position, and the ventral chest wall, now in contact with the firm surface of the bed, is impeded from expanding (8). In the prone position the gravitational forces compress the ventral region, but this effect is damped by regional expansion due to shape matching between lung parenchyma and vertebrae. As the lung mass is anatomically greater in dorsal regions (nondependent when prone) than in ventral region (dependent when prone), the increased aeration and recruitment of the dorsal region tends to exceed the decreased aeration and derecruitment of the ventral regions. That generates a more homogenous ventilation (6) across the entire lung, resulting in a reduction in transpulmonary pressure (Ptp), which is defined as the difference between the airway pressure (Paw) and pleural pressure (Ppl) (Ptp = Paw – Ppl).

Furthermore, when an individual is supine the heart compresses the medial posterior lung parenchyma (10) and the diaphragm compresses the posterior-caudal lung parenchyma, with the abdominal contents displacing the diaphragm cranially (8,10). Compression by either the heart and/or the diaphragm may exaggerate dependent lung collapse in the supine position (9). During prone ventilation, the heart becomes dependent, lying on the sternum, potentially decreasing medial-posterior lung compression (10). In addition, the diaphragm is displaced caudally, decreasing compression of the posterior-caudal lung parenchyma.

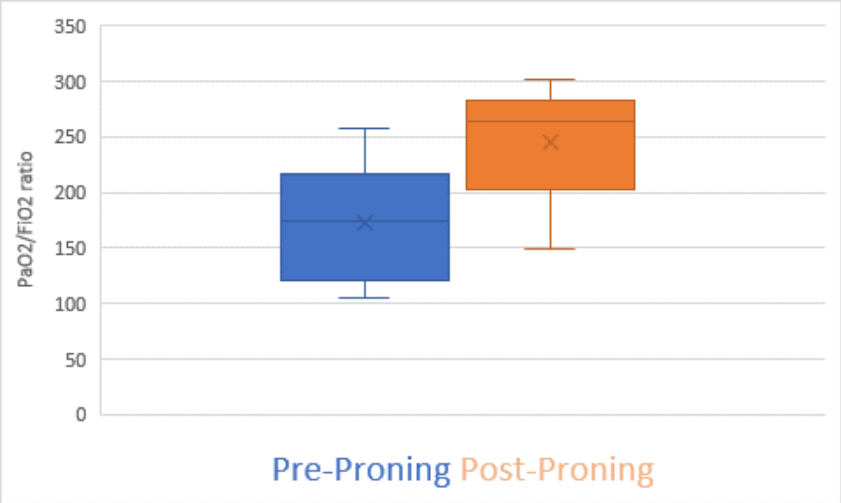
A further advantage observed in prone position is both an improvement of ventilation/perfusion match and an increase in cardiac output: the latter is thought to be due to the effect of increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction, resulting in increases in right ventricular preload and decreased right ventricular afterload and a decrease in pulmonary vascular resistance (11,12).This is how prone position can lead to consistent improvement in oxygenation and gas exchange. An important recent study by Guerin et al. showed that prone positioning applied for at least 16 hours per day in patients with ARDS and PaO2/FiO2 < 150 mmHg significantly reduced 28-day mortality (16% vs 32%).(15) From currently available evidence, prone positioning may be of value even if there is no improvement in gas exchange [10-14].

Experience with proning self-ventilating patients

Prone position results in improved ventilation and blood flow ratios. In mechanically ventilated and often paralysed patients, proning requires a high nursing input and patients are at risk for pressure sores related to the position. These issues are less pertinent in patients who are self-ventilating. Proning self-ventilating patients is not commonly carried out as patients with reduced oxygenation generally require assisted ventilation. However, avoidance of mechanical ventilation by improving oxygenation may be importance in COVID19 as outcomes for patients who require mechanical ventilation are poor and resources become limited. We report experience with proning in self ventilating patients at both ward level and in the ICU for patients with confirmed COVID19 and in a patient without COVID19 with ARDS (table 1). Increase in P/F ratio before and after proning is demonstrated in figure 1.

				PRE-Proning						POST-Proning						
covid	SESSION	Gender	Age	rr (average	hr	pH	paO2	PaCO2	PF	rr (average	hr	pH	paO2	PaCO2	PF	Notes
1_ICU	1	F	31	28	102	7.53	8.37	3.91	105	15	76	7.51	11.9	4.23	149	Tolerated well
1_ICU	2			20	82	7.47	11.4	4.78	171	18	81	7.41	17.6	5.35	264	
2_ICU	1	M	79	34	91	7.43	12	4.79	257	35	100	7.42	12.9	5.06	276	Did not tolerate well- uncomfortable but otherwise no Adverse events
					HR	spO2	fiO2				HR	spO2	fiO2			
3_Shannon	1	F	79		72	94	0.4		204		68	95	0.3		301	Tolerated well
4_Shannon	2	M	81			92	0.15		654			95	0.15		678	Mod well tolerated
				Non covid												
1_ICU	1	M	62	21	83	7.51	8.35	4.99	125	24	72	7.48	17.5	5.51	263	Tolerated reasonably well
	2			25	81	7.46	9.51	5.6	178	28	94	7.49	13.2	5.32	220	

Table 1 Patients with (n=4) and without (n=1) COVID19 who underwent proning whilst self-ventilating are demonstrated. Patients underwent 1-2 sessions with physiological data and tolerability demonstrated. RR respiratory rate, HR heart rate, PF paO2 to FiO2 ratio



Rationale for treating patients with COVID19 pneumonia with proning

Patients with COVID19 that require invasive mechanical ventilation have a high mortality. We hypothesis that early proning for self-ventilating patients with suspected or confirmed COVID19 who have hypoxemia (spO2 <94%) despite high flow nasal cannula or face mask oxygen via venturi (fiO2 40%) will result in improved oxygenation, reduced work of breathing and a reduced the need for invasive mechanical ventilation.

Bioimpedance study on the effect of Proning

Bioimpedance, specifically across the lungs, has been studied in Chronic Heart Failure (CHF) and Acute Respiratory Distress Syndrome (ARDS). This measurement can provide a number of useful indicators of respiration rate, respiration volume, and fluid in the lungs. Bioimpedence may be useful to predict who will benefit from proning and give an indicator of changes in fluid dynamics within the lung non-invasively. In a subset of patients, we will apply a bioimpedance device to assess for changes in depth of respiration, changes in lung edema following supine to proning in self ventilating patients. (16)

Study Aims and objective

c. Research hypothesis

In patients that are hypoxic secondary to COVID19, the use of prone positioning will result in a reduction in requirement for invasive mechanical ventilation. Key secondary hypothesis include that prone positioning will result reduced requirement for assisted ventilation, in improved oxygenation as measured by either S/F or P/F ratio, reduced work of breathing and these can be detected in a subset of patients using a bioimpedance monitor.

d. Study aim

The study aims to assess the effect of prone positioning in patients who have hypoxemia related to COVID19 on:

1. need for mechanical ventilation
2. Improvement in oxygenation as measured by S/F or P/F ratio
3. Patient work of breathing as measured by the respiratory distress observation scale (table 2)
4. tolerability of the position as measured by the total number of hours in prone position

e. Study objective

Primary objective

To assess the effect of prone positioning on requirement for mechanical ventilation in patients with suspected or confirmed COVID 19 infection.

Secondary objective

To assess the effect of prone positioning on:

i. Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
ii. SpO2: FiO2 ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
iii. Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)
iv. Work of breathing assessment
v. Feasability of detecting changes in lung edema and respiratory pattern in patients in prone position using bioimpedance

5. Study design

a. Study design

Registry study of patients undergoing proning study followed by Multi centre open label randomized controlled study in which patients are randomized to prone positioning or standard care. Study within a study assessment of bioimpedance to assess changes in lung edema with

b. Study timeline

Study will begin 4th April 2020 and until 28 days following the last enrolled patient

c. End of study

Study will continue until 28 days after the last enrolled patient or for 6 months until October 2020, depending on levels of enrolment.

6. Study outcome measure

a. Primary outcome measure

i. Requirement for invasive mechanical ventilation

b. Secondary outcome measure

i. Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
ii. SpO2 : FiO2 ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
iii. Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)
iv. Work of breathing assessment
v. Feasability of detecting changes in lung edema and respiratory pattern in patients in prone position using bioimpedance

7. Patient Eligibility

a. Study setting

A ward in which patients with COVID19 are receiving supplemental oxygen, high flow nasal cannula, high dependency unit, and intensive care unit

Study population

Patients who have *suspected or confirmed* COVID19 who have infiltrates on CXR and who have an oxygen requirement of >4L to keep oxygen saturations about 94% by either venturi mask or high flow nasal cannula

b. Eligibility criteria

Inclusion criteria

Suspected or confirmed COVID19 infection

Bilateral Infiltrates on CXR

SpO2 <94% on FiO2 40% by either venturi facemask or high flow nasal cannula

RR>40

Able to provide written informed consent

Exclusion criteria

Age <18

Uncooperative or likely to be unable to lie on abdomen for 16 hours

Vomiting or bowel obstruction

Palliative care

Multiorgan failure

Standard contraindications to prone positioning include the presence of an open abdominal wound, unstable pelvic fracture, spinal lesions and instability, pregnancy > 20/40 gestation and brain injury without monitoring of intracranial pressure.

c. Co-enrolment guidelines

Patients will be eligible for inclusion in other studies

8. Patient screening, consent and recruitment

a. Patient screening

All patients admitted to a COVID19 ward, COVID ICU or HDU will be screened for inclusion in the study.

b. Informed consent procedure

As patients will be self-ventilating, written informed consent or witnessed consent to reduce fomite transmission will be obtained for each patient enrolled in the study. A patient information leaflet will be given to all patients screened as eligible. After a period of time to read and consider the information leaflet time will be given for questions, and then if the patient consents to be involved, written consent will be obtained. Due to the risk of fomite transmission of SARS-CoV-2 a photo will be taken of the signature pages of the consent, and stored in a password protected encrypted database, stored under the title "STUDYNUMBER_CONSENT". The original consent form will be disposed of in yellow waste from the patient room, which should be destroyed.

9. Assignment of intervention

Patients assigned to the intervention will be asked to remain in prone position for at least 1 hour and if possible as close to 16 hours per day with 45 minute breaks permitted for meal times. Call bell will be given to the patient and an oxygen probe will be attached to the patient to monitor spO2 during the procedure. IN a subset of patients, a bioimpedance device will be applied to assess pattern of respiratory rate and for lung edema. Proning procedure will continue until oxygen requirements are below FiO2 0.4 via venturi mask or high flow to maintain SpO2>94% or intubation or discharge or death.

a. Allocation

Patients will be allocated to either arm of the study based on data from registry study.

b. Blinding

It is not feasible to blind staff or patients as to the procedure. Study data will be blinded for the purposes of analyses, assigned as group 1 or group2 rather than prone / not proned.

10. Schedule of assessment

a. Study visit and procedure

See CRF attached

11. Data collection and management

a. Data collection

Data will be collected using paper case report form initially followed by an electronic case report form. Details of CRF attached. No patient identifiers will leave hospital unit and all data sent to CRF at NUI Galway will be pseudoanonymised.

b. Data management

See CRF attached

c. Data quality

Data quality will be audited by the CRF at NUI Galway as responsibility of the study sponsor.

12. Statistical Considerations

a. Sample size

A registry study of patients undergoing proning will be started immediately in centres to give further information on the feasibility of the study. From ICNARC data on patients admitted to ICU with COVID19, 60% required advanced respiratory support. From this, we propose a 60% intubation rate in this cohort as defined above and that proning will decrease it to 40%. From this, 97 patients per group for a beta of 0.2 and alpha 0.05, requiring the need to recruit 200 patients.

b. Analysis population

Data will be analysed on an intention to treat basis with all data for patients who consented to be involved included in baseline data analysis. Outcome data will be analysed for all patients who were positioned in the prone position for any length of time. A further per protocol analysis will be carried out on all patients who tolerated at least 1 hour of the daytime proning time and at least 2 hours of the night time proning period in any 24 hour period.

c. Missing data

Missing data will be completed using last observation carried forward and the percentage of datasets with full or missing data will be reported.

13. Data monitoring

a. Data access and Monitoring arrangement

The eCRF will be secured and compliant with 21 CFR part 11. eCRF has an audit trail in place, participating centers only have accounts available for delegated people and specific login accounts are created to only edit for their own site. External monitors can only view data and enter queries, they cannot change data. No directly identifiable data will be stored in the eCRF, e.g. only year of birth and no date of birth will be captured Audit trail in place (eCRF) compliant with 21 CFR part 11. Also compliant with the EU Directive on data protection 95/46/EC. eCRF only accessible via site-specific (password-regulated) delegated log-in. (21 CFR part 11 compliance). Also compliant with the EU Directive on data protection 95/46/EC. A

Standard contractual clauses for the transfer of personal data from the Community to third countries (controller to controller transfers) has been signed

14. Regulation, Ethics and governance

a. Regulatory and ethics approval

A submission for approval from the Galway University Hospitals Research ethics committee has been filed.

b. Protocol compliance

A Request for sponsorship from the CRFG at NUI Galway has been sought which will provide the necessary manpower for trial oversight, quality, statistical analysis.

c. Good clinical practice

All individuals who will participate in conducting this study and have signed a delegation log will require an up to date certificate of good clinical practice.

d. Indemnity

Patients will be covered under the HSE Clinical Indemnity Scheme

e. Patient confidentiality

A Data privacy impact assessment has been filed for the study. Patient confidentiality will be maintained by keeping data collected in the study coded. The key will be at the local study site where patient is included. No Personal detailr or identifying data will be transferred from the site to the sponsor where the data will be analysed. The coded data will be securely entered via the electronic case report form which will be managed by Nui Galway. The naed data controlled will be the principal investigator, associate investigators, biostatisticians affiliated with NUI Galway. The site lead will have received training in regard to the requirements under GDPR that relate to health research. A data protection impace assessment will be completed and submitted to the SAOLTA data protection officer.

f. Data access

The data will be collected using a paper or digital case report form and the data will be collected in a coded form. The key for the data will be at the local study site in which the patient is included. Data will only be stored on protected and accredited servers. No personal details or identifying data will be transferred from the site to the coordinating centre at NUI Galway where the data will be analysed. The data will be retained for 15 years or as long as local legislation requires. Confidentiality will be maintained by sponsor only having access to coded data and the key only available at the local site. Clinical notes will need to be reviewed by the clinical research team on site. No identifiable data will be collected in the process. Information regarding current clinical presentation and clinical trajectory over the course of hospitalization will be collected Information regarding the patient will be taken out of the record and added to the crf

g. Record retention

Participants are requested to give consent to store their data for 15 years (without this permission, patient cannot participate). Next, participants are asked whether there coded data can be used for future

research in the field of lung infections (data will also be stored 15 years for this purpose, with extra consent as described).

h. Competing interest

The principal investigators have no conflict of interest related to this study.

15. Dissemination

Results of both registry and randomised controlled trial will be published in an international journal following peer review. To incentivise participation in the study, centers that recruit a patient will be permitted to have one author on final publication. For each additional 10 patients recruited, a further author from that centre will be added to the authors list.

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