Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure (PHARLAP): a protocol for a phase 2 trial in patients with acute respiratory distress syndrome

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Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lung that affects up to 10% of critically ill patients admitted to the intensive care unit (ICU) for mechanical ventilation.[1,2] It has been associated with a high in-hospital mortality of between 35% and 46% and with poor long term outcomes, including disability and reduced health-related quality of life.[1,3]

While mechanical ventilation is a lifesaving intervention that maintains gas exchange, it can augment, or even initiate, lung injury in the critically ill. Mechanical ventilation using protective lung strategies such as low tidal volumes and plateau pressures (6 mL/kg predicted bodyweight [PBW] tidal volume and ≤ 30 cmH_2O plateau pressure) have been associated with higher survival rates compared with strategies that use larger tidal volumes and plateau pressures.[4,5] Other research has shown that lung regions remain collapsed throughout tidal ventilation and may contribute to ongoing lung injury, and that recruiting these lung regions to accommodate tidal volume ventilation may further reduce lung injury and its selequae.[6,7]

A Cochrane systematic review[5] and an American Thoracic Society guideline[2] recently recommended the use of recruitment manoeuvres as part of an open lung ventilation strategy to improve outcomes during mechanical ventilation in patients with moderate to severe ARDS. However, the studies included in the systematic review used several different types of recruitment manoeuvres, with varying airway pressure targets, duration and modes of ventilation. One of the included studies, a pilot randomised trial, showed a reduction in cytokines and an improvement in lung compliance with a ventilation strategy that included a staircase recruitment manoeuvre (SRM) to 55 cmH_2O,

ABSTRACT

Background: Mechanical ventilation is a life-saving intervention that maintains gas exchange in patients with acute respiratory distress syndrome (ARDS); however, it is associated with high mortality and it may augment, or even initiate, lung injury. An open lung ventilation strategy that combines alveolar recruitment manoeuvres with individually titrated positive end-expiratory pressure (PEEP) and targeting lower tidal volumes, or driving pressures by a permissive approach to hypercapnia, may reduce the lung injury associated with mechanical ventilation. This protocol reports the rationale, study design and analysis plan of the Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure (PHARLAP) trial.

Methods and design: PHARLAP is a phase 2, international, multicentre, prospective, randomised, controlled, parallel-group clinical trial, which aims to determine if staircase alveolar recruitment and individually titrated PEEP, when combined with permissive hypercapnia and low airway pressures, increases ventilator-free days to Day 28 when compared with conventional mechanical ventilation (Acute Respiratory Distress Syndrome Clinical Network [ARDSNet] strategy) in patients with moderate to severe ARDS. This study will enrol 340 patients. The intervention group will receive daily staircase alveolar recruitment manoeuvres with incremental PEEP to a maximum of 40 cmH_2O and peak pressures to a maximum of 55 cmH_2O. PEEP will be titrated individually against peripheral oxygen saturation, targeting lower tidal volumes by a permissive approach to hypercapnia. In the control group, patients will receive mechanical ventilation following the ARDSNet-ARMA trial protocol, including PEEP titrated with a PEEP/fraction of inspired oxygen (Fio_2) chart. Both groups will receive airway pressures ≤ 30 cmH_2O and tidal volumes of ≤ 6 mL/kg predicted bodyweight or less. The primary outcome is ventilator-free days to Day 28. Secondary outcomes include oxygenation and lung compliance, intensive care unit (ICU) and hospital length of stay, use of rescue therapies for refractory hypoxaemia, rate of barotrauma, mortality (ICU, hospital and at 28, 90 and 180 days), quality of life and a health economic analysis at 6 months.

Discussion: The PHARLAP trial will determine whether the intervention strategy is effective in increasing ventilator-free days in patients with ARDS. If the PHARLAP strategy is proven to improve ventilator-free days, it will provide a strong impetus to conduct an international phase 3 trial to determine the effects of this strategy on mortality.

Trial registration: ClinicalTrials.gov identifier NCT01667146.

Crit Care Resusc 2018; 20 (2): 139-149

and positive end-expiratory pressure (PEEP) titrated according to peripheral oxygen saturation compared with the Acute Respiratory Distress Syndrome Clinical Network (ARDSNet) controlled mechanical ventilation strategy.[8] In addition, recent work suggests that strategies that aim to reduce the driving pressure (plateau pressure minus PEEP), such as lung recruitment, high PEEP and lower tidal volumes, may be associated with improved outcomes.[9] Nevertheless, the recent Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) showed that many clinicians do not recognise ARDS, and when they do, they are still using relatively low levels of PEEP, and recruitment manoeuvres and tidal volumes in excess of 6 mL/kg in patients with ARDS.[1]

The effect of an open lung ventilation strategy that includes an "ideal" combination of limited tidal volume by allowing permissive hypercapnia, in combination with recruitment strategies followed by high PEEP in patients with ARDS, needs to be determined. Therefore, the aim of this phase 2 randomised controlled trial was to determine the effect of a strategy combining Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure (PHARLAP) compared with conventional ventilation strategy using low tidal volumes, plateau pressures and moderate levels of PEEP (as described in the ARDSNet ARMA trial[4]) in increasing ventilator-free days at Day 28 after randomisation.

Methods

Study design

The PHARLAP study is a 340-patient, international, multicentre, prospective, randomised, controlled, parallel-group clinical trial designed to determine if permissive hypercapnia, alveolar recruitment with individual PEEP titration and low airway pressure (PHARLAP intervention), when compared with conventional ventilation strategy (control), increases ventilator-free days to Day 28. The trial is a two-sided superiority trial that will randomly allocate patients with moderate to severe ARDS to the PHARLAP ventilation strategy (the intervention group) or conventional ventilation strategy (the control group) in a 1:1 ratio. The PHARLAP trial has been designed with reference to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.[10] The PHARLAP study has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the Irish Critical Care Clinical Trials Group (ICC CTG) and is coordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC RC) and the Irish Critical Care Clinical Trials Network (ICC CTN).

Study setting

This study will be conducted in ICUs located in Australia, New Zealand, Ireland, Saudi Arabia and the United Kingdom. A range of hospital types, including large tertiary ICUs and smaller rural and metropolitan ICUs will participate.

Eligibility criteria

Patients will be included if they meet all of the following inclusion criteria:

- the patient is currently intubated and receiving mechanical ventilation;
- the patient is within 72 hours of mechanical ventilation for a diagnosis of moderate to severe ARDS based on the Berlin definition,[11] including within one week of a known clinical insult or new or worsening respiratory symptoms, bilateral opacities on chest x-ray which are not fully explained by effusions, lobar or lung collapse or nodules; and
- the patient has a respiratory failure not fully explained by cardiac failure or fluid overload, and has an arterial partial pressure of oxygen/fraction of inspired oxygen (Pao_2/Fio_2) ratio < 200 mmHg, with PEEP ≥ 5 cmH_2O.

Patients will be excluded if any one of the following is present:

- the consent was not obtained or refused by the patient's legal surrogate;
- there have passed 72 hours or more since the diagnosis of ARDS;
- the patient has had 10 days or more of continuous mechanical ventilation;
- the patient is less than 16 years of age;
- barotrauma is present (ie, pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak);
- there is significant chest trauma, such as multiple rib fractures;
- the patient has active bronchospasm or a history of significant chronic obstructive pulmonary disease or asthma;
- there is a clinical suspicion of significant restrictive lung disease (ie, history of pulmonary fibrosis or suggestive pulmonary function tests);
- there is moderate or severe traumatic brain injury, the presence of an intracranial pressure monitor, or any medical condition associated with a clinical suspicion of raised intracranial pressure;
- there is an unstable cardiovascular status defined as sustained heart rate < 40 beats/min or more than 140 beats/min, ventricular tachycardia, or systolic blood pressure < 80 mmHg;

- the patient is pregnant;
- the patient is receiving extracorporeal membrane oxygenation;
- the patient is receiving high frequency oscillatory ventilation;
- death is deemed imminent and inevitable; or
- the treating physician believes it is not in the best interest of the patient to be enrolled in the trial.

Allocation generation will be completed by computer-generated random numbers. Randomisation to either the PHARLAP group or the control group will be by permuted blocks and stratified for site and for the cause of ARDS (direct or indirect), when direct ARDS (eg, pneumonia, aspiration) has been hypothesised to cause more severe lung epithelial injury than indirect ARDS (eg, non-pulmonary sepsis).[12,13] Site personnel will enrol patients using a web-based system hosted by the ANZIC RC.

Interventions

PHARLAP (intervention group) strategy

After randomisation, patients will be commenced in a controlled rate ventilation, either assist-control or synchronised intermittent mandatory ventilation (SIMV), using a pressure control mode (Table 1). The PEEP level will remain at the pre-randomisation level. Static lung compliance will be measured at baseline and at Day 3.

The initial procedure of the PHARLAP mechanical ventilation strategy will be to perform the combined open lung procedure (Figure 1), which consists of an SRM, followed by individual PEEP titration, and followed by a brief recruitment manoeuvre (BRM). This initial combined open lung procedure will be performed within 4 hours of randomisation and when haemodynamic resuscitation is complete and circulatory parameters are stable, followed by tidal volume titration below 6 mL/kg. If there is no improvement in the static lung compliance from baseline to Day 3, no further SRM or BRM will be conducted from Day 3.

There are several contraindications to both SRM and BRM, including a mean systemic blood pressure ≤ 60 mmHg despite attempts to augment blood pressure with vasopressors and/or fluids; an active air leak through an intercostal catheter; any radiographic evidence of pneumatoceles, subpleural cysts, or pericardial or mediastinal emphysema; subcutaneous emphysema not related to trauma, surgical or ICU procedures; a supraventricular tachycardia associated with a mean systemic blood pressure ≤ 70 mmHg or any ventricular tachycardia.

If there are no contraindications, the combined open lung procedure will be performed from the day of randomisation until Day 5 as follows:

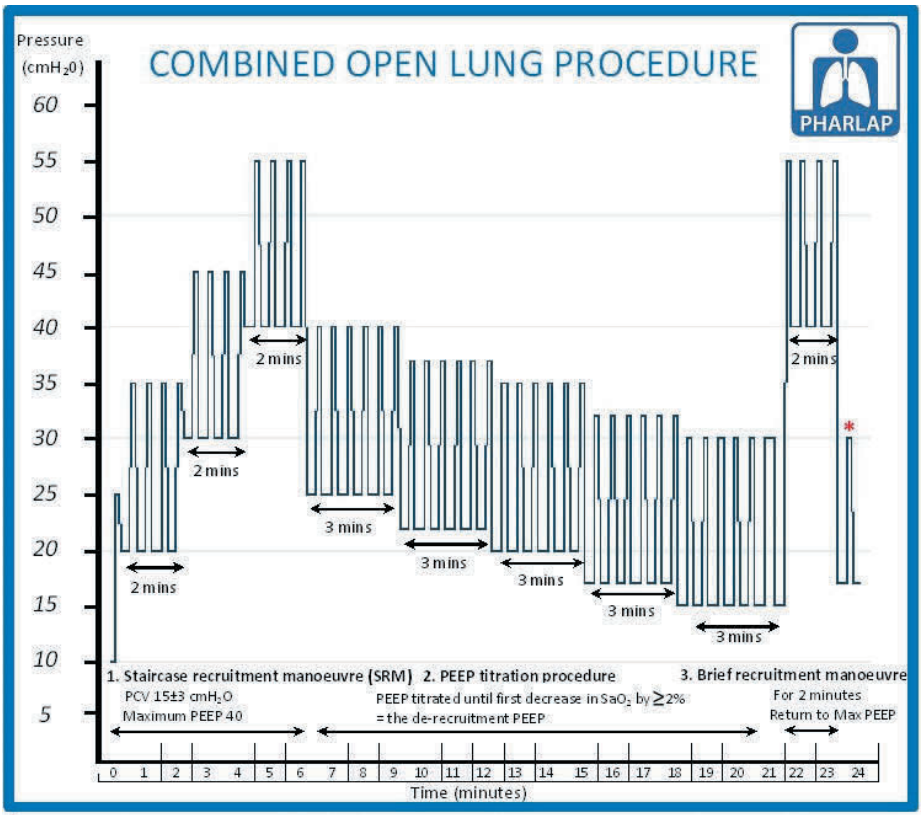
- **Staircase recruitment manoeuvre** (Figure 1). The mechanical ventilator settings used will be pressure control with an inspiratory pressure of 15 ± 3 cmH_2O depending on tidal volume achieved (pre-SRM tidal volume target, 4–6 mL/kg PBW). The PEEP level will be left at the level it had been immediately before this procedure. The Fio_2 is adjusted until the arterial oxygen saturation (Sao_2) is stable between 90% and 92% for at least 15 minutes. Then, the PEEP is increased from the pre-randomisation baseline to 20 cmH_2O. In a stepwise fashion, this should be increased after 2 minutes to 30 cmH_2O (for 2 minutes) and then 40 cmH_2O (for 2 minutes), unless there is occurrence of:

Table 1. Summary of mechanical ventilation procedures in the PHARLAP (intervention) group *v* the conventional ventilation (control) group

Ventilation strategies	Intervention group	Control group
Staircase recruitment manoeuvres	Yes	No
Brief recruitment manoeuvres	Yes	No
Target plateau pressure	≤ 30 cmH_2O	≤ 30 cmH_2O
Target tidal volume	6 mL/kg PBW	6 mL/kg PBW
Respiratory rate	≤ 30	≤ 35 breaths/min
Target pH	7.30–7.45	7.30–7.45
Target Pao_2	60–80 mmHg	60–80 mmHg
Target Sao_2	90–95%	90–95%
PEEP titration	Minimum 15 cmH_2O until the patient meets weaning criteria	Titrated by the PEEP/Fio_2 chart until the patient meets weaning criteria

Fio_2 = fraction of inspired oxygen. Pao_2 = arterial partial pressure of oxygen. PBW = predicted bodyweight. PHARLAP = Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure trial. PEEP = positive end-expiratory pressure. Sao_2 = arterial oxygen saturation.

Figure 1. The combined open lung procedure including (1) the staircase recruitment manoeuvre, (2) the positive end-expiratory pressure titration, and (3) the brief recruitment manoeuvre



PCV = pressure control ventilation. PHARLAP = Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure trial. PEEP = positive end-expiratory pressure. Sao_2 = arterial oxygen saturation. * PHARLAP ventilation at 2.5 cmH_2O PEEP higher than derecruitment PEEP (minimum PEEP 15 cmH_2O until weaning and plateau pressure < 30 cmH_2O); for example, if patient has ≥ 2% drop in Sao_2 at 17.5 cmH_2O PEEP, then PHARLAP ventilation after brief recruitment manoeuvre at 20 cmH_2O PEEP.

> haemodynamic instability (defined as heart rate < 40 or > 140 beats/min, ventricular tachycardia, or systolic blood pressure < 80 mmHg);

> marked oxygen desaturation (Sao_2 < 85%); or

> new air leak through an intercostal catheter.

The tidal volume is not to be altered at each PEEP level, unless the tidal volume is > 6 mL/kg PBW. If haemodynamic instability, marked oxygen desaturation or a new air leak occur during SRM, the manoeuvre will be abandoned (with no further increases in PEEP above the level where this occurred). If the patient is considered to be inadequately haemodynamically resuscitated for their underlying condition, then it is preferable if vasopressor or fluid resuscitation occurs over the next 30–60 minutes, and then the combined open lung procedure be resumed. If the patient is considered to be adequately haemodynamically resuscitated, then fluid loading purely for SRM will not be undertaken. Vasopressor dose may be increased during SRM if needed to manage haemodynamic instability. The PEEP level one step below the PEEP level at which SRM was abandoned should be determined as the maximum tolerated PEEP for this specific SRM and the PEEP titration manoeuvre should now occur (ie, if marked desaturation occurs at 40 cmH_2O, the maximum tolerated PEEP should then be determined as 30 cmH_2O). The maximum tolerated PEEP for SRM will be determined daily and may be a different value on subsequent days.

If there is no occurrence of haemodynamic instability, marked oxygen desaturation or new air leak, the PEEP should be increased to the highest level of 40 cmH_2O. This should be determined as the maximum tolerated PEEP for this SRM.

- **PEEP titration manoeuvre.** After the final SRM step has been completed (or abandoned, as above), the PEEP will immediately be reduced to 25 cmH_2O. If, however, the SRM was abandoned at 20 cmH_2O, the PEEP titration will begin at 17.5 cmH_2O. The PEEP will be left at this first setting for 3 minutes, then decreased in steps of 2.5 cmH_2O for 3 minutes at each PEEP level to a minimum of 15 cmH_2O until the derecruitment PEEP is reached. The derecruitment PEEP is defined as the PEEP level at which the Sao_2 first decreases by 2% or more. Once the derecruitment PEEP level has been reached, there will be no further reductions in PEEP, and the BRM should now occur. The PEEP will not be reduced below 15 cmH_2O if desaturation does not occur.
- **Brief recruitment manoeuvre.** After this derecruitment, a 2-minute BRM should be performed (with the inspiratory pressure set at 15 ± 3 cmH_2O) using the PEEP level that was the maximum tolerated PEEP for the recently performed SRM. After this BRM, the PEEP should be returned to the level that is 2.5 cmH_2O above the derecruitment PEEP. If there was no desaturation to determine the derecruitment PEEP, the PEEP should be set at 15 cmH_2O and no BRM is required. This final PEEP

level should be considered the daily optimal PEEP (for the subsequent period, usually 24 hours) until a subsequent combined open lung procedure is performed.

- **Ongoing mechanical ventilation in the PHARLAP group.** Once the combined open lung procedure has been completed, the pressure control level will be reduced to achieve a total pressure (ie, inspiratory pressure + PEEP) of 30 cmH_2O or less (targeting 25–28 cmH_2O) and a tidal volume of 4–6 mL/kg PBW. The tidal volume will be titrated down from 6 mL/kg towards 4 mL/kg if possible. The set breath rate may also be reduced aiming for a pH in the range of 7.15–7.30. The actual pH in an individual patient will depend on other factors, including level of sedation and metabolic status, and should be a clinical decision at the time. Immediately after the combined open lung procedure, the Fio_2 will be decreased until the Sao_2 is in the target range of 90–95%. One hour after the combined open lung procedure, the Sao_2 should be noted and recorded as the subsequent daily precise Sao_2 target for that day.

  After this one-hour time point, a decrease in the Sao_2 of 2% or more below the daily precise Sao_2 target should prompt strong consideration of re-recruitment using a BRM. The goals of mechanical ventilation will remain as follows: a tidal volume of 4–6 mL/kg PBW, a respiratory rate of 35 breaths/min or less, a total pressure (ie, inspiratory pressure + PEEP) of 30 cmH_2O or less (with an ideal range of 25–28 cmH_2O), and the Sao_2 between 90–95%. Within this range, re-recruitment using a BRM is encouraged for reductions in Sao_2 of 2% or more below the daily precise Sao_2 target.

Conventional ventilation (control group) strategy

After randomisation, patients will be ventilated in a volume control mode using either assist-control or synchronised intermittent mandatory ventilation mode with a controlled respiratory rate. The tidal volume will be set at 6 mL/kg PBW. The initial respiratory rate should be determined by aiming to deliver similar minute ventilation to the pre-randomisation settings. The maximum rate is 35 breaths/min and the plateau pressure aim is 30 cmH_2O or less. If the plateau pressure exceeds 30 cmH_2O, the tidal volume should be reduced, but to no less than 4 mL/kg PBW.

The Fio_2 and PEEP should be set using Table 2.[4] The initial setting should be the combination of Fio_2 and PEEP that is closest to the pre-randomisation settings. The Sao_2 aim is 90–95% using the lowest possible Fio_2/PEEP combination to achieve this goal. If control group patients have a Pao_2 < 60 mmHg or a Sao_2 < 90% while receiving a Fio_2 and PEEP combination in any of the five columns at the right end of the Fio_2 and PEEP combination table (Table 2) (ie, $Fio_2 \geq 0.8$ and PEEP ≥ 14), hypoxaemic rescue therapies should then be considered (supplementary Appendix; online at cicm.org.au/Resources/Publications/Journal).

The arterial pH goal for control group patients is 7.30–7.45. However, there is no actual arterial partial pressure of carbon dioxide ($Paco_2$) target and it is more important to maintain a tidal volume ≤ 6 mL/kg and a plateau pressure < 30 cmH_2O. Throughout the study, the goals of mechanical ventilation for patients in the control group should always remain as follows: tidal volume ≤ 6 mL/kg PBW, ≤ plateau pressure 30 cmH_2O, respiratory rate ≤ 35 breaths/min, pH 7.30–7.45, and Sao_2 90–95%. Acidaemia is permitted unless it is considered clinically relevant, in which case consider the following: if the pH is 7.15–7.30, the set mechanical ventilator rate should be increased up to a maximum of 35 breaths/min, or until pH > 7.30, or $Paco_2$ < 25 mmHg. If the pH is < 7.15, increase the set mechanical ventilator rate up to a maximum of 35 breaths/min. If the pH remains < 7.15, tidal volume can be increased in 1 mL/kg steps until pH > 7.15. Bicarbonate may be administered if felt clinically indicated. Neuromuscular blockers may be administered if clinically indicated. Other mechanical ventilation strategies may be considered, but only after a dose of a neuromuscular blocking drug (in addition to suggestions for pH < 7.15). If the acidosis is predominantly metabolic, continuous renal replacement therapy may be required at this point. If pH > 7.45, and this is considered clinically relevant, we suggest decreasing the set mechanical ventilator rate (if possible) or decreasing plateau pressure by decreasing tidal volumes (not ≤ 4mL/kg PBW).

For information about co-enrolment into other studies and the use of rescue therapies in both intervention and control groups, please refer to the online supplementary Appendix.

Weaning protocol in both the intervention and control groups

Pressure support ventilation mode should be used to transition the patient from controlled to spontaneous mechanical ventilation. Pressure and volume targets remain unchanged in a spontaneous mode.

Table 2. ARDSNet table of Fio_2 and PEEP values used to titrate PEEP in the control group

	Titration values													
Fio_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

ARDSNet = Acute Respiratory Distress Syndrome Clinical Network strategy. FiO_2 = fraction of inspired oxygen. PEEP = positive end-expiratory pressure.

Patients in both groups will be deemed to have met readiness for weaning criteria when for the first time the patient has a $Sao_2 \geq 90\%$ while receiving $Fio_2 \leq 0.4$ for ≥ 6 continuous hours, and they are considered otherwise clinically stable. If the patient does not meet readiness for weaning criteria, mechanical ventilation aims should remain as recommended above for the patient's group assignment.

Once a patient meets readiness for weaning criteria the first time, no further recruitment manoeuvres (combined open lung procedure or BRM) should be performed in the PHARLAP group. If possible, the patient should have the PEEP reduced by 2.5 cmH_2O (rounded up by 0.5 if the ventilator does not use 0.5 cmH_2O settings) at a time. Subsequent reductions in PEEP should be no sooner than 4 hours after the previous reduction. All other mechanical ventilation aims should remain as recommended above for the patient's group assignment.

Patients in both groups will be deemed to have met readiness for spontaneous breathing trial (SBT) criteria when the patient meets all of:

- $Sao_2 \geq 90\%$ while receiving $Fio_2 \leq 0.4$ and PEEP ≤ 10 cmH_2O for ≥ 6 continuous hours;
- has intact airway reflexes and low amounts of sputum;
- has a reasonable level of consciousness while receiving low doses of or no sedative infusions; and
- is considered otherwise clinically stable and mechanical ventilator liberation is not deemed inappropriate (eg, imminent procedure requiring ongoing mechanical ventilation).

If the patient does not meet readiness for an SBT, mechanical ventilation aims should remain as recommended above for the patient's group assignment, including ongoing progressive weaning of PEEP as possible in the PHARLAP group.

Once a patient is ready for an SBT, a period of unassisted breathing should commence on the same day. An SBT is allowing the patient to breathe spontaneously on any one of a T-tube circuit, a tracheostomy mask, hood or shield; or a mechanical ventilator circuit using continuous positive airway pressure 5 cmH_2O with minimal support (ie, pressure support ventilation ≤ 10 cmH_2O).

Patients in both groups will be deemed to have met readiness for mechanical ventilator liberation criteria if after at least 30 minutes of an SBT, the patient meets all of:

- breath rate < 35 breaths/min;
- $Sao_2 > 90\%$ while receiving $Fio_2 \leq 0.5$;
- systolic blood pressure > 90 and < 180 mmHg;
- heart rate either < 140 beats/min or not increased by > 20% since the beginning of the unassisted breathing period; and
- is considered otherwise clinically stable and mechanical ventilator liberation is not considered inappropriate.

If the patient does not meet readiness for mechanical ventilator liberation criteria, mechanical ventilation aims should remain as recommended above for their group assignment until the next day, when readiness for weaning should be reassessed. If the SBT led to desaturation, this may require an increase in Fio_2 or PEEP. In the PHARLAP group, no further recruitment manoeuvres should be performed unless severe desaturation occurs (requiring $Fio_2 \geq 0.8$). In this situation, a brief recruitment manoeuvre should be considered.

Once a patient meets readiness for mechanical ventilator liberation criteria, they should, on the same day, be either extubated or placed on a tracheostomy mask, hood or shield for an indefinite period. Intermittent periods of mechanical ventilation and tracheostomy mask, hood or shield breathing should only occur once it has been deemed clinically necessary by the patient meeting the criteria for consideration for further invasive mechanical ventilation.

For the management of reconnection to invasive mechanical ventilation after liberation, fluid management, use of steroids and other interventions, please refer to the online supplementary Appendix.

Blinding

It is not possible to blind clinicians to treatment allocation. Likewise, it is likely that next of kin will be aware of treatment allocation. Bias is minimised by the use of a protocolised weaning and discontinuation of ventilation protocols. Furthermore, assessments at 6 months will be performed by trained assessors who will be blinded to treatment allocation. Data analysis will be performed by an independent, blinded statistician.

Study outcome measures

The primary outcome is the number of ventilator-free days at Day 28 after randomisation, and will be defined as the total number of days from Day 1 to Day 28 on which a patient is alive and receives no assistance from mechanical ventilation, if any period of ventilator liberation lasts at least 48 consecutive hours. To be considered truly liberated from mechanical ventilation, the patient will need to have at least 48 consecutive hours liberated from mechanical ventilation. Non-invasive ventilation will not be considered assistance if it is provided by face or nasal mask, but will be considered assistance if it is provided by tracheostomy. Any patient who dies before weaning from mechanical ventilation will be allocated the value of 0 ventilator-free days. Any patient who dies after weaning from mechanical ventilation (ie, they have at least 48 consecutive hours off mechanical ventilation) but before Day 28 will not have the days after their death until Day 28 considered as ventilator-free days.

Secondary outcome measures include:

- physiological outcomes, such as the Pao_2/Fio_2 ratio, and the static lung compliance;
- clinical outcomes, such as the use of adjunctive therapies or rescue therapies for severe hypoxaemia (specifically, inhaled nitric oxide, inhaled prostacyclin, prone positioning, high frequency oscillatory ventilation and extracorporeal membrane oxygenation), and ICU and hospital length of stay;
- patient-centred outcomes, including quality of life assessment measured using the five-level EuroQol five dimensions questionnaire (EQ-5D-5L), and the Short Form 36 (SF-36) survey at 6 months; mortality at ICU and hospital discharge, 28 days, 90 days and 6 months; cause of death; and
- safety outcomes, including the rate of barotrauma, severe hypotension and serious adverse effects.

Specified incremental cost-effectiveness ratios will be reported using an analytic timeframe of 6 months, including the cost per additional quality-adjusted-life-year (QALY) and cost per additional ventilator-free day compared with conventional ventilation. The EQ-5D-5L, performed at 6 months after randomisation, will enable utilities to be determined and subsequent calculation of QALYs. Hospital costs will be determined using clinical costing systems at each participating site.

Power calculations and sample size

With 282 subjects, this study will have an 80% power to detect a difference equal to 33% of a standard deviation (equal to 3 ventilador-free days) with a two-sided *P* value of 0.05.[8] To account for likely occurrence that ventilador-free days will not follow a normal distribution, the sample size has been inflated by 15% to 324 in accordance with Lehmann.[14] Allowing for up to a 5% rate for withdrawal or loss to long term follow-up, 340 patients will be enrolled.

Data management

All study-related data will be collected by trained staff at each study site using a paper source document (case report form) developed by the coordinating centre. Data will then be entered into an internet-based database hosted by Monash University. Data queries will be automatically generated as they are entered into this database.

Enrolled patients will be followed up to death or 6 months after enrolment. Data will be collected in all patients, including those for whom the study is discontinued before the end of the study period (Table 3). Patients who are alive at 6 months after enrolment will be interviewed by a trained follow-up assessor from the coordinating centre. This follow-up assessor will use a standardized structured telephone questionnaire to measure the quality of life assessments EQ-5D-5L[15] and SF-36 version 2.[16,17]

Statistical analysis plan

Independent senior statisticians at Monash University will perform the data analysis. All data will initially be assessed for normality and log-transformed as required. Baseline and outcome variables will be compared using χ^2 tests for categorical variables, Student *t* test for normally distributed continuous variables, and Wilcoxon rank-sum tests otherwise, with results presented as frequency (%), mean (standard deviation) and median (interquartile range) respectively. To account for survival bias, duration variables and lengths of stay will be analysed using Cox proportional hazards regression with all patients censored at the last known point of contact. Results will be presented as Kaplan–Meier curves with a log-rank test for survival equality. For increased transparency, between-group results will also be reported non-parametrically with additional stratification by survival status.

Where possible, to ensure that observed results were not due to heterogeneity between sites or baseline imbalance, an additional hierarchical multivariable sensitivity analysis will be conducted adjusting for site and imbalanced variables.

Where outcome data are collected on multiple occasions, (eg, Pao_2/Fio_2 ratio) repeat measure mixed modelling will be employed fitting main effects for treatment and time and an interaction between treatment and time to determine if groups behave different over time.

All analyses will be conducted on an intention-to-treat basis using SAS version 4 (SAS Institute Inc, Cary, NC), and a two sided *P* value of 0.05 will be used to indicate statistical significance.

Interim analysis

One midpoint interim analysis (after primary outcome data are available for 170 patients) will be performed to assess accumulated safety data. This will be reported to the Data Safety Monitoring Committee, but will not be made available to the Management Committee or to study sites.

For planned substudies, please refer to the online supplementary Appendix.

Subgroup analyses

We plan to compare study outcomes in the following pre-specified subgroups among patients:

- who have severe ARDS (Pao_2/Fio_2 < 100) versus patients who have moderate ARDS (Pao_2/Fio_2 100–200 mmHg) at enrolment;
- who have diffuse ARDS versus patients who have focal ARDS at enrolment (determined by independent radiologists);[18] and
- who are responders to the open lung strategy versus patients who are non-responders (defined as meeting lack of improvement in static lung compliance definition).

Table 3. Schedule of events for the PHARLAP study

Assessments/ procedures	Pre-random-isation/ baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 till liberation of mechanical ventilation	ICU discharge	Hospital discharge	Follow-up 28 days	Follow-up 90 days	Follow-up 6 months
Inclusion and exclusion criteria	X											
Consent	X											
Randomisation	X											
Demographic data	X											
Height and weight measurement	X											
CXR	X											
Download CXR image	X											
APACHE II score	X											
APACHE III diagnosis	X											
SOFA score	X	X	X	X	X	X	X					
Ventilation observations	X	X	X	X	X	X	X					
Static respiratory compliance		X		X								
Combined open lung procedure		X*	X*	X*	X*	X*						
Sputum sample (non-bronchoscopy BAL)		X		X								
Blood sample		X		X								
Adverse events		X	X	X	X	X	X	X				
Serious adverse events		X	X	X	X	X	X	X	X			
Survival status								X	X	X	X	X
SF-36 $V_{ersion\ 2}$												X
EQ-5D-5L												X

APACHE = Acute Physiology and Chronic Health Evaluation. BAL = bronchoalveolar lavage. CXR = chest x-ray. EQ-5D = EuroQol five dimensions questionnaire. ICU = intensive care unit. PHARLAP = Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure trial. SF-36 = 36-item short form health survey. SOFA = Sequential Organ Failure Assessment. * Only for patients randomised to PHARLAP treatment group (combined open lung procedure).

Monitoring

The study will be monitored by a representative of the coordinating centres. Before study commencement, a start-up teleconference or visit will be conducted at each site. Monitoring of the data collection and protocol adherence will occur after study completion for the first intervention and control patient at each site. The database will be developed to routinely report queries and protocol violations. Additional on-site monitoring will also be performed if the routine reviews indicate any significant issues at individual sites.

Data safety and monitoring

An independent Data Safety Monitoring Committee, comprising experts in clinical trials, biostatistics and intensive care, was established before patient enrolment

(see online supplementary Appendix). The committee will be responsible for monitoring mortality, serious adverse events and reviewing the interim safety analysis. Serious adverse events — defined as an event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is an important medical event that may require intervention to prevent one of the previously listed outcomes — will be reported regardless of suspected causality. However, consistent with the advice of Cook and colleagues,[19] adverse events already defined and reported as study outcomes (mortality) will not be labelled and reported a second time as serious adverse events.

Ethics

Ethics approval for all aspects of the trial will be obtained before the commencement of recruitment at each study site. In all regions except New Zealand, consent will be obtained from the legal surrogate, who will be able to withdraw their consent for the patient to participate in the study at any time. Participants who recover sufficiently to provide their own informed consent will be asked to consent to continue in the study or offered the chance to withdraw. In New Zealand, the family will be asked permission to include participants in the study, but the participant will consent for themselves when they are conscious and able to communicate.

Discussion

There is substantial experimental evidence, biological rationale, and supportive pooled clinical evidence to suggest the efficacy of an open lung strategy such as PHARLAP ventilation strategy in ARDS.[2,5] However, mostly because of concern that SRMs and high PEEP may cause barotrauma and haemodynamic instability in critically ill patients, previous trials may have been suboptimally designed to determine the true safety or efficacy of such an open lung strategy.

The PHARLAP strategy applies more intensive recruitment manoeuvres, with more individual patient-tailored PEEP and tidal volume titration, and in our pilot studies, it appeared at least as safe as current ventilation strategies. In addition, the PHARLAP strategy can be delivered by almost any clinician using any conventional mechanical ventilator, and, if proven effective and safe, it would be highly applicable for widespread use (including lower-income countries). The PHARLAP protocol was developed before the publication of the ART study (Alveolar Recruitment for ARDS Trial) — an international prospective phase 3 trial of maximal lung recruitment in moderate to severe ARDS.[20] The ART study showed that the maximal lung recruitment strategy, compared with a low PEEP strategy, increased 28-day all-cause mortality, with a signal for increased barotrauma within the first 7 days.

Given the significance and cost of ARDS, the possible benefits of this strategy, and the growing number of recommendations for the use of lung recruitment manoeuvres with elevated levels of PEEP,[21-23] it is important that we assess the safety and efficacy of the PHARLAP strategy. The trial will determine whether the PHARLAP ventilation strategy is effective in increasing ventilator-free days in patients with ARDS. If the PHARLAP strategy is proven to improve ventilator-free days, it will provide a strong impetus to conduct an international phase 3 randomised controlled trial to determine the effects of this strategy on mortality.

Acknowledgements: We thank our independent statistician, Michael Bailey; our Data Safety and Monitoring Committee, including Maureen Meade (Chair), Niall Ferguson, Roy Brower and Lehana Thabane; and the Intensive Care National Audit and Research Centre, United Kingdom, including Paul Mouncey and Kathy Rowan, for their assistance.

Competing interests

None declared.

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Trial status

This trial is still recruiting patients.

Authors contribution

CH and AN drafted the manuscript. CH, AN, DT, AD, JF, AB and DJC conceived the study and participated in its design. All authors read and approved the final manuscript.

Funding

The PHARLAP trial is funded by the National Health and Medical Research Council of Australia, the Health Research Council of New Zealand, Alfred Health and the Health Research Board of Ireland. The study was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Irish Critical Care Clinical Trials Group.

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