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Careful ventilation in acute respiratory distress syndrome: the protocol of the CAVIARDS international multicentre randomised basket trial

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ABSTRACT

Introduction Acute respiratory distress syndrome (ARDS) is a major public health problem, accounting for 23% of intubated patients and associated with high mortality rates. Although lifesaving, invasive mechanical ventilation can worsen lung injury when ventilator settings are poorly adjusted to lung physiology. We hypothesise that individualising ventilator settings via (1) the bedside assessment of lung recruitability using a one-breath derecruitment manoeuvre and measurement of airway opening pressure to set positive end-expiratory pressure (PEEP), (2) controlling the distending pressure and (3) controlling respiratory drive improves ARDS outcomes.

Methods and analysis The CAreful Ventilation In ARDS trial is an investigator-led multicentre (33 centres in eight countries), open-label, randomised controlled basket trial comparing two ventilation strategies in two subpopulations of moderate-to-severe ARDS: induced or not by COVID-19. A total of 740 patients will be randomised (370 in each substudy) in a 1:1 ratio to individualised ventilator settings or to using traditional PEEP to inspired fraction of oxygen tables for PEEP setting. Indications for proning and weaning strategies are similar in both arms. The primary outcome is all-cause mortality at day 60. Secondary outcomes include duration of mechanical ventilation, duration of intensive care unit (ICU) and hospital stay, organ dysfunction, barotrauma and mortality in ICU, at day 28 and in hospital.

Ethics and dissemination Ethics approval has been obtained for all participating centres: Unity Health Toronto Research Ethics Board (for three centres: St Michael's Hospital, Toronto General Hospital and Toronto Western Hospital); Comité de Ética de Investigación con Medicamentos del Hospital Universitari Vall d'Hebron; Comité de protection des personnes Ile de France III; Comité d'Ética de la Investigatción con Medicamentos de la Fundació de Gestió Sanitària del Hospital de la Santa Creu i Sant Pau; Comitato Etico—Fondazione Policlinico Gemelli; Comitato Etico di Area Vasta Emilia Centro; NYU Langone Health Institutional Review Board; Comité Ético Científico de Ciencias de la Salud; Il Comitato Etico Area 1 dell'Azienda Ospedaliero-Universitaria 'Ospedali Riuniti'

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The large-scale multicentre international nature of the trial which will confer high external validity.
⇒ Individualising ventilator settings to limit ventilation-induced lung injury based on respiratory physiology and assessment of recruitability (respiratory system rather than lung mechanics to facilitate the generalisability and implementation of the interventions).

di Foggia; HIGA 'Eva Perón' Comité de Bioética; Comité de Revisión Institucional del Hospital Británico Comité de Ética en Investigación; Complejo Médico Churruca-Visca Comité de Ética Biomédica; Comité de Ética SATI Comité de Ética en Investigación; Comité de Ética en Investigación del CEMIC; Comité de Ética SATI Comité de Ética en Investigación; Medical Research Ethics Committees United. Findings will be disseminated in peer review journals and conference presentations.

Trial registration number NCT03963622.

INTRODUCTION

Background

Acute respiratory distress syndrome (ARDS) is a major public health problem. It accounts for 10% of patients admitted to intensive care units (ICUs), and for 23% of all ventilated patients.[1] Short-term mortality remains as high as 40%, and better use of mechanical ventilation has the greatest potential to improve outcome.[1]

Caused by pneumonia, sepsis or systemic inflammation such as trauma or pancreatitis, ARDS lungs are inflamed and edematous,[2] markedly reducing lung volume and compliance, and making ventilation difficult and potentially harmful. Although mechanical ventilation is the mainstay of supportive therapy, it can generate secondary injury and inflammation, called ventilator-induced lung injury (VILI), and result in adverse haemodynamic consequences.[3] COVID-19-induced ARDS (c-ARDS) is an extreme example of a severe form of ARDS where respiratory physiology is complex, varies widely, and where recommendations have been uncertain.[4] Initial reports showed a very high mortality of patients with c-ARDS.[5 6] Whether the ventilator management of c-ARDS should differ from all other ARDS has been debated.[7]

There is no treatment for the alveolar-capillary leak characterising ARDS and the main supportive therapy is mechanical ventilation. A number of randomised clinical trials over the past few decades have led to evidence-based guidelines for patients with ARDS that mitigate the risk of VILI by limiting tidal volume (V_T) and airway pressure[8] to reduce excessive stress and strain, as well as using neuromuscular blockers[9] and prone position.[10 11] However, accumulating studies have shown that the contemporary ventilator strategies are often not sufficiently protective.[12–14] Despite current 'best practice', alveolar overdistension[12] and inappropriate positive end-expiratory pressure (PEEP) is common.[15] An adequate PEEP can be potentially beneficial by reducing atelectrauma (ie, repeated opening and closing of alveoli) and promoting recruitment (ie, increasing the size of the aerated lung and, therefore, decreasing stress and strain). Excessive PEEP can harm the patients and induce excessive mortality when the alveoli are not recruitable, by promoting overdistension and adverse haemodynamic consequences. We have recently described a technique to measure alveolar recruitability at the bedside (response to PEEP), which could improve ventilatory strategy[16] allowing adjustment of PEEP by maximising recruitment potential and minimising overdistension, which may result in less VILI and a better haemodynamic profile.[17 18]

Finally, once spontaneous breathing has resumed and is assisted by the ventilator, it has been suggested that an additional phenomenon could occur, called patient self-induced lung injury (PSILI).[19] Respiratory drive in many patients is stimulated by lung and systemic inflammation[20 21] as well as activation of unmyelinated afferent fibres and slow and rapid adaptive receptors resulting in nociceptor stimuli and a blunted inhibitory response to lung inflation.[22] A strong inspiratory effort can generate high distending (transpulmonary) pressure, causing lung (and systemic) inflammation and organ dysfunction.[23–25] Studies suggest that respiratory drive is high in many patients with ARDS,[26 27] particularly in the context of c-ARDS.[26 28 29] High respiratory drive has been associated with prolonged duration of mechanical ventilation and increased mortality.[25 27]

Rationale

To reduce the risks associated with mechanical ventilation, we hypothesised that lung injury might be reduced and survival improved through: (1) individualising PEEP settings; (2) limiting maximal inspiratory distending pressure and (3) limiting the magnitude of spontaneous breathing efforts.

PEEP

PEEP is currently set without knowledge of the potential to recruit (reopen) the atelectatic lung. It is often based on oxygenation, which is not a good indicator of recruitment.[30 31] None of the previous randomised clinical trials comparing two levels of PEEP attempted to determine the potential for lung recruitment.[11] Thus, patients who may benefit (rather than be harmed) by higher PEEP could not be identified.[15] Non-recruitable lungs are exposed to harmful overdistension with high PEEP, whereas recruitable alveoli are exposed to repetitive lung opening and closure (cyclic stretch and atelectrauma) in the absence of sufficient PEEP. Recommendations propose high PEEP but individual recommendations vary.[32–34] The only trial comparing two PEEP strategies with potentially positive results was the EXPRESS trial.[35] It showed a positive effect of high PEEP on duration of ventilation in patients with moderate-to-severe ARDS: this was the only trial using some measurements of mechanics to titrate PEEP instead of oxygenation. Excessive PEEP may be set incorrectly for c-ARDS if recruitability is not assessed.[4] We will apply a modification of the EXPRESS strategy after assessment of recruitability.

We propose that PEEP should be set according to two criteria:

The recruitment-to-inflation ratio (R/I ratio) for predicting alveolar recruitability

We described a simple bedside technique to assess the potential for lung recruitment for the individual patient. This one-breath decremental PEEP manoeuvre (figure 1)[36 37] distinguishes 'recruitable' from 'non-recruitable' lungs. The manoeuvre takes less than 5 min and is explained online with videos (https://rtmaven.com). It should avoid harm of high

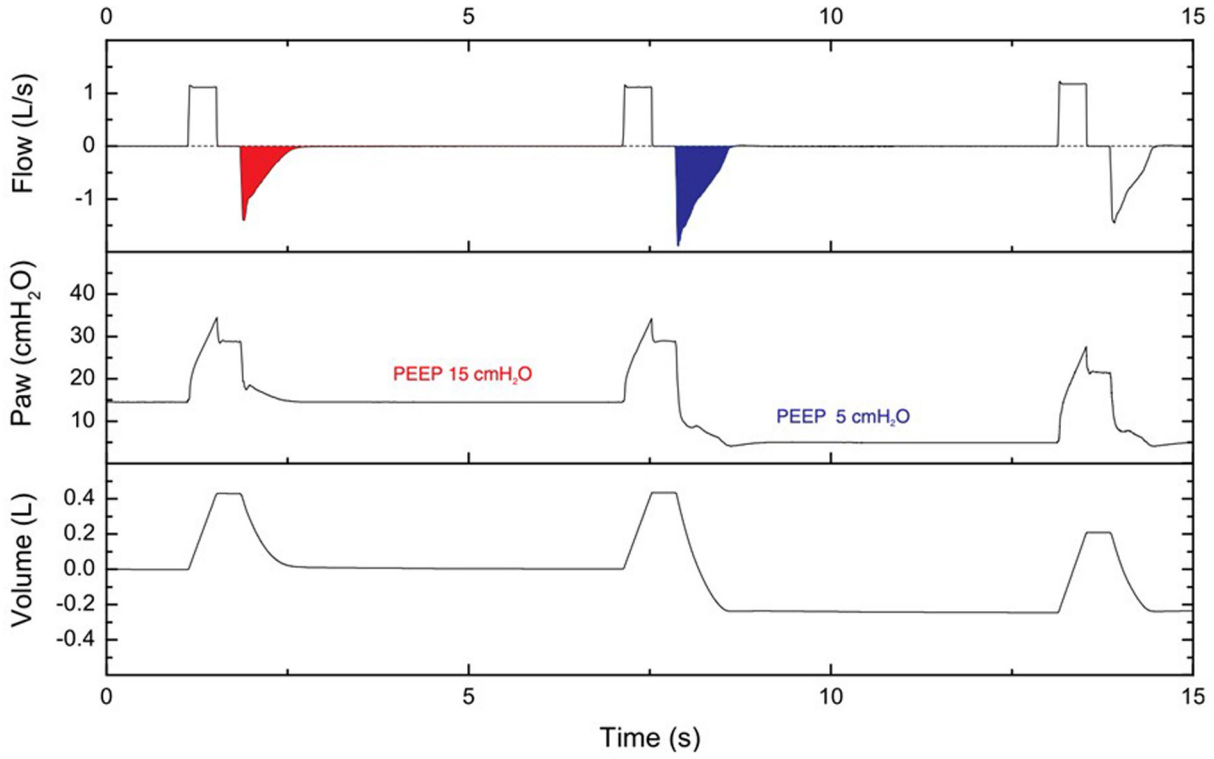

Figure 1 The one-breath decremental PEEP manoeuvre. PEEP is set at 15 cm H_2O during 15 min, then respiratory rate is decreased to 8 breaths/min for a few breaths to limit auto-PEEP. Then PEEP is decreased to 5 cm H_2O over one breath, and the large tidal volume expired is collected. Respiratory mechanics at PEEP 5 cm H_2O are collected, and a low-flow inflation airway pressure-time curve is performed (see figure 2) before the initial ventilator settings are resumed. Reproduced from Chen *et al*.[37] Paw, airway pressure; PEEP, positive end-expiratory pressure.

PEEP when the alveoli are not recruitable and allow high PEEP only when alveoli are recruitable, which is considered when the R/I ratio is >0.5.[16]

Airway closure

We have also described that 30%–40% of ARDS patients have complete airway closure above 5 cm H_2O.[38] When present, this should determine the minimal level of PEEP to keep airways open. The possibility of small airway injury is consistent with experimental[39 40] and human[41] data. Airway closure can be detected on the pressure-time curve during a simple low-flow inflation (https://rtmaven.com).[42] When present, it yields the minimal PEEP level to avoid repeated airway opening and closure (figure 2). This also 'corrects' assessment of plateau and driving pressures because it better reflects pressure in alveoli than airway pressure (vs in closed airways).[43] It is a necessary step to be performed before measuring alveolar recruitability.

Maximal inspiratory distending pressure

The safe maximal inspiratory distension can be assessed by the plateau pressure to individually titrate V_T. Guidelines suggest limits for V_T, airway pressure and PEEP.[11]

Respiratory drive and spontaneous breathing effort

During spontaneous breathing, increased respiratory drive and large respiratory efforts have been suggested to cause PSILI[19] and diaphragm dysfunction.[44 45] We have recently shown that a simple monitoring tool available on the ventilator, the occlusion pressure at 100 ms (P0.1), which reflects respiratory drive, can guide the level of assistance and sedation, and may thereby limit the risk of excessive transpulmonary pressure, thus lowering risks of PSILI.[23 46]

The bedside assessment of respiratory mechanics provides the information needed to control the above three risk factors. We have shown that implementation of respiratory mechanics (alveoli recruitability, R/I ratio, total PEEP, plateau pressure, driving pressure, respiratory system compliance and P0.1) in the clinical setting is feasible.[37] We hypothesise that individualising ventilator settings according to respiratory mechanics with a focus on minimising injurious ventilation will be more effective than current strategies. In the current proposal, we propose to test this new ventilatory strategy.

METHODS AND ANALYSIS

Primary research question

In adults with ARDS (due to COVID-19 or not), does adjustment of ventilation parameters based on recruitability and respiratory effort to reduce lung strain and inflammation reduce 60-day all-cause mortality as compared with a standard ventilation protocol?

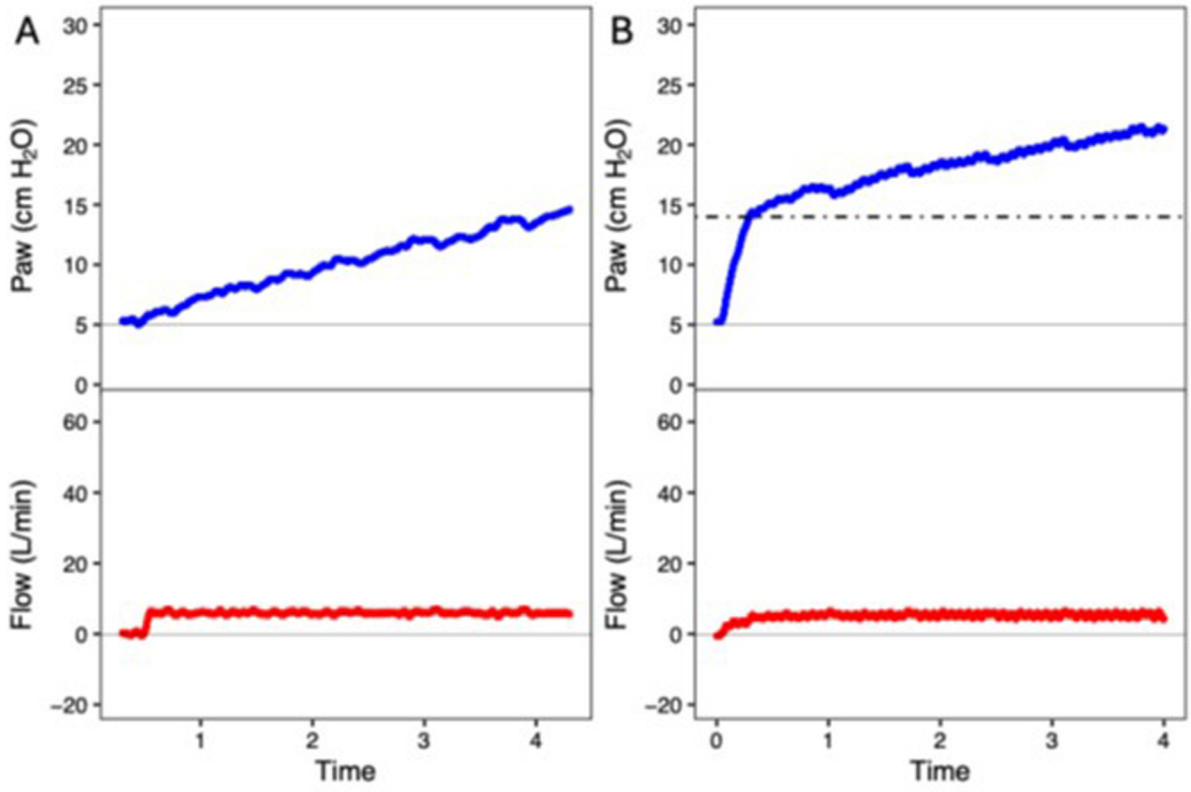

Figure 2 Low-flow inflation airway pressure-time curves for the diagnosis of airway closure. Panel (A) no airway closure. Panel (B) presence of airway closure. The level of airway pressure corresponding to the inflexion point (dot-dashed line) is the airway opening pressure. Paw, airway pressure.

Secondary research questions

What is the effect of an individualised respiratory mechanics-based ventilation versus conventional ventilation on:

1. Duration of mechanical ventilation.
2. Duration of ICU and hospital stay.
3. Organ dysfunction.
4. Barotrauma.
5. Mortality in-ICU, at day 28, in-hospital.

Trial design

The CAreful Ventilation In ARDS (CAVIARDS) trial was initially designed as an open-label, phase III, multicentre randomised controlled trial comparing two ventilation strategies in c-ARDS. By 8 November 2023, due to the major decrease in the incidence of COVID-19, the design of the CAVIARDS trial was modified to a basket design. A basket trial design examines a single intervention in multiple disease populations.[47] It consists of an identical two-arm mechanical ventilation protocol implemented in two different study populations (CAVIARDS-19 for c-ARDS; and CAVIARDS-all for patients with non-COVID ARDS). As per a typical basket trial design, the operational structure of both CAVIARDS-19 and CAVIARDS-all substudies is shared (recruitment, procedures, data collection, analysis, management, etc), and all procedures are identical between the two substudies in this basket trial. The only differences between the two studies will be the randomisation stratified by suspicion of COVID-19.

Settings and trial status

The trial is being conducted in 33 ICUs in eight countries, all of which have established expertise in ventilation and respiratory mechanics in ARDS: Argentina (Hospital Churruca, Buenos Aires; Sanatorio Anchorena Recoleta, Buenos Aires; Sanatorio Mater Dei, Buenos Aires; CEMIC—Sede Pombo, Buenos Aires; Hospital Británico de Buenos Aires, Buenos Aires; Sanatorio Anchorena San Martín, San Martín), Canada (St. Michael Hospital, Toronto, ON; Toronto General Hospital, Toronto, ON; Toronto Western Hospital, Toronto, ON), Chile (Pontificia Universidad Católica de Chile—Departamento de Medicina Intensiva, Santiago de Chile), France (CHU de Poitiers, Poitiers; CH Victor Dupouy, Argenteuil; CHU Bordeaux—Hôpital Haut Lévêque, Bordeaux; Hôpital de la Cavale Blanche—CHRU Brest, Brest; CH de Cholet, Cholet; Hôpital Intercommunal de Créteil, Créteil; CHU Grenoble-Alpes, Grenoble; Hôpital Roger Salengro—CHU Lille, Lille; Hôpital de l'Archet 1—CHU de Nice, Nice; Hôpital Européen Georges-Pompidou, Paris; CH Bretagne Atlantique, Vannes-Auray; HIA Robert Picqué, Villenave d'Ornon; CH de Beauvais, Beauvais; GHR Mulhouse Sud-Alsace, Mulhouse; CHU d'Angers, Angers; CHU Amiens-Picardie, Amiens), Italy (Policlinico

Universitario Agostino Gemelli IRCCS, Roma; Arcispedale Sant'Anna, Ferrara; University of Foggia, Foggia), Spain (Vall d'Hebron University Hospital, Barcelona; Hospital de la Santa Creu i Sant Pau, Barcelona), the Netherlands (OLVG—Oost, Amsterdam) and USA (NYU School of Medicine, New York). The complete list of collaborators is displayed in the online supplemental appendix. At the time of manuscript submission, the trial has been actively recruiting patients (start date was 23 November 2020, anticipated end date July 2026).

Eligibility criteria

Patients are eligible for inclusion if they meet the following criteria: age ≥18 years old; moderate or severe ARDS within 48 hours of meeting Berlin ARDS criteria (eg, within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral opacities not fully explained by effusions, lung collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload; PaO_2/FiO_2 ≤200 mm Hg with PEEP ≥5 cm H_2O).[48] Patients who were eligible at the time of screening and whose PaO_2/FiO_2 became >200 mm Hg under prone positioning when starting the protocol remained eligible.

Patient are excluded from the trial if they have one or more of the following criteria: received continuous mechanical ventilation >7 days; known or clinically suspected elevated intracranial pressure (>18 mm Hg) necessitating strict control of $PaCO_2$; known pregnancy; broncho-pleural fistula; severe liver disease (Child-Pugh Score ≥10); body mass index >40 kg/m^2; anticipating withdrawal of life support and/or shift to palliation as the goal of care; already receiving extracorporeal membrane oxygenation at time of randomisation.

Randomisation

We use central, web-based randomisation to conceal allocation. The allocation sequence is computer generated, stratified by site, severity (PaO_2/FiO_2> or ≤150 mmHg), and suspected COVID-19 status; there are also randomly varied block sizes.

Patients with suspected COVID-19 are defined according to the WHO criteria in conditions of the pandemic and at the discretion of the local investigator using the following criteria: a patient with severe acute respiratory illness including fever and at least one sign/symptom of respiratory disease, for example, cough, shortness of breath; AND requiring hospitalisation; AND in the absence of an alternative diagnosis that fully explains the clinical presentation. They are enrolled in the CAVIARDS-19 substudy, while patients without suspicion of COVID-19 are enrolled in the CAVIARDS-all substudy.

Due to the nature of the intervention, clinicians are not blinded. However, the statistical team remains blinded throughout data analysis.

Study interventions

Experimental group

General approach

For the first 2 days, tidal volume and PEEP are individualised daily according to alveolar recruitability using the one-breath decremental PEEP manoeuvre (figure 1),[16 37] and to airway closure using low-flow pressure-time curve (figure 2).[42] PEEP is set at high levels only if alveoli are recruitable to maximise recruitment. If alveoli are non-recruitable, PEEP is set at a low level to minimise overdistension. From day 3, spontaneous breathing is allowed with respiratory drive limited to a safe range (figure 3).

Initial settings

The ventilator is set in volume-control mode. Initial V_T is set at 6 mL/kg of predicted body weight (PBW), and FiO_2 is adjusted for SpO_2 between 90% and 95% or PaO_2 between 60 and 80 mm Hg.

Ventilator settings in the first 2 days

Recruitable alveoli

If alveoli are recruitable, as assessed by a R/I ratio ≥0.5,[16] PEEP is set at 15 cm H_2O to maximise alveolar recruitment, then:

- If plateau pressure is lower than 28 cm H_2O, PEEP is increased to reach a plateau pressure of 28 cm H_2O.
- If plateau pressure is >28 cm H_2O or driving pressure >15 cm H_2O, then V_T is reduced first to a minimal V_T of 4 mL/kg of PBW (or the lowest V_T at which $PaCO_2$ ≤50 mm Hg with pH >7.25 and respiratory rate 35/min). If reducing V_T induces high $PaCO_2$ >50 mm Hg, PEEP is decreased and V_T is increased up to 7 mL/kg PBW.

If airway closure is present, PEEP is set at least at the level of the airway opening pressure.[38]

For obese patients with body mass index between 35 and 40 kg/m^2, the plateau pressure limit will be 31 cm H_2O.

Non-recruitable alveoli

If alveoli are non-recruitable, defined by a R/I ratio <0.5,[16] PEEP is set between 8 and 12 cm H_2O. If airway closure is present, PEEP is set at least at the level of the airway opening pressure.[38]

If plateau pressure is >28 cm H_2O with a PEEP of 8 cm H_2O, then V_T is reduced.

Ventilator settings from day 3

From day 3, spontaneous breathing efforts are allowed, and P0.1 is measured daily. Changing to pressure support ventilation (or a proportional mode) is left at the discretion of the attending physician but recommended when FiO_2 <60%. Then, pressure support levels and sedatives are titrated to keep V_T between 6 and 8 mL/kg PBW and P0.1 between 1 and 3.9 cm H_2O (the average of three measurements with 15 s between them). If the respiratory drive is excessive (P0.1 >3.9 cm H_2O), interventions are proposed to reduce P0.1, such as increased FiO_2 to reach SpO_2 of 98% to 99%, incremental titration of PEEP by

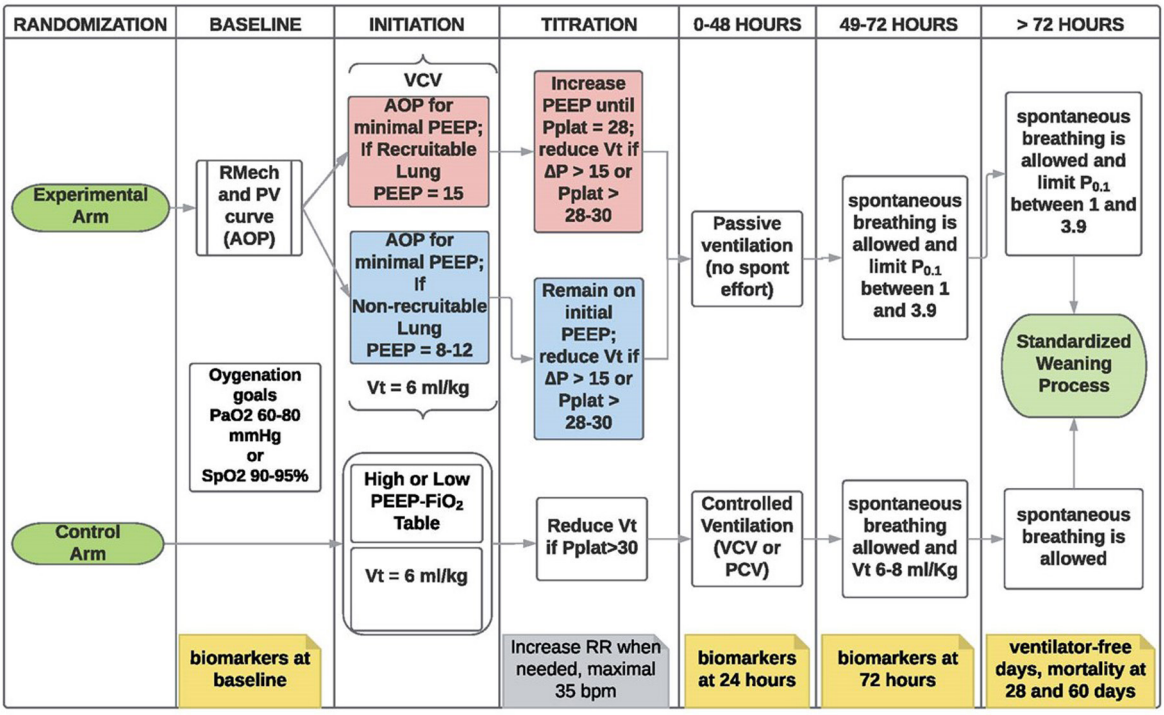

Figure 3 Study interventions. AOP, airway opening pressure; ΔP, driving pressure; FiO_2, fraction of inspired oxygen; P0.1, occlusion pressure during the first 100 ms; PaO_2, partial pressure of arterial oxygen; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; PV curve, pressure-volume curve; RMech, respiratory mechanics; VCV, volume-controlled ventilation; Vt, tidal volume.

2 cm H_2O steps, reduction of dead space, or increased sedatives. If pressure support level ≤10 cm H_2O and FiO_2 ≤40%, there is no restriction placed on the V_T.

From day 3, weaning of PEEP is tested daily, by a decrease in PEEP to 8 cm H_2O. Criteria for successful weaning of PEEP include V_T remaining in the safety range (6–8 mL/kg PBW), PaO_2/FiO_2 ≥150 mm Hg, and P0.1 remaining in the safety range (1–3.9 cm H_2O).

Oxygenation

Oxygenation is not used to titrate PEEP in the experimental group. In case of dissociation between oxygenation and recruitment, we recommend trying to determine the reasons for the discrepancy[49] (eg, hypovolaemia that decreases venous return, patent foramen ovale that causes intra-cardiac shunt,[31] or right ventricular failure that causes low central venous oxygen saturation).

Control group

General approach

PEEP and FiO_2 are adjusted based on oxygenation and a PEEP-FiO_2 table, as used in several randomised controlled trials (RCTs).[8 50–53] There are two approaches: a low PEEP-FiO_2 table and a high PEEP-FiO_2 table (figure 4), that did not show any difference in outcome.[8] The choice of the PEEP/FiO_2 table is left at the discretion of the attending physician for each patient but one PEEP-FiO_2 table is used for the whole ICU stay. Adjustments of PEEP and FiO_2 are made once per day, and more often if SpO_2 or PaO_2 is out of the range. When both are available and discordant, PaO_2 takes preference (figure 3).

Initial settings

The ventilator is set in volume-control mode. Initial V_T is set at 6 mL/kg PBW.

Ventilator settings in the first 2 days

For a given FiO_2, a corresponding PEEP is set. PEEP and FiO_2 are adjusted for SpO_2 between 90% and 95% or PaO_2 between 60 and 80 mm Hg. Patients are managed as far to the left on the PEEP-FiO_2 charts as possible, employing the lowest PEEP-FiO_2 combination. If oxygenation is lower than the target, PEEP and FiO_2 settings corresponding to the next step to the right are set. If oxygenation is higher than the target, PEEP and FiO_2 settings corresponding to the next step to the left are set. With each change in PEEP, V_T and plateau pressure are checked and adjusted. V_T may be reduced to keep plateau pressure <30 cm H_2O. If SpO_2 is <88% and the next step to the right calls for an increase in PEEP, recruitment manoeuvres are not encouraged nor required.

Ventilator settings from day 3

From day 3, spontaneous breathing efforts are allowed. Changing to pressure support ventilation (or a proportional mode) is left at the discretion of the attending physician but recommended when FiO_2<60%. Then, pressure support levels and sedatives are titrated to keep V_T between 6 and 8 mL/kg PBW. PEEP and FiO_2 remain

A

Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FiO_2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.0
PEEP	5	8	10	10	12	14	16	18	18	20	20	20	20	22	22	22	24

B

Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14
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	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Figure 4 PEEP-FiO_2 tables. (A) High PEEP-FiO_2 table. (B) Low PEEP-FiO_2 table. For a given FiO_2, a corresponding PEEP is set. If oxygenation is lower than the target, PEEP and FiO_2 settings corresponding to the next step to the right are set. If oxygenation is higher than the target, PEEP and FiO_2 settings corresponding to the next step to the left are set. FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

adjusted according to the PEEP-FiO_2 table chosen for the patient.

From day 3, PEEP weaning is tested daily, by a decrease in PEEP to 8 cm H_2O. Criteria for successful weaning of PEEP include V_T remaining in the safety range (6–8 mL/kg PBW) and PaO_2/FiO_2 ≥150 mm Hg.

Procedures common to both groups

Patients with PaO_2/FiO_2 <150 mm Hg are sedated and paralysed in the first 48 hours (also recommended, but at physician's discretion, for PaO_2/FiO_2 between 150 and 200 mm Hg). This approach confers a survival benefit according to a large RCT.[9]

Prone positioning is as per standard guidelines for 16 hours,[11] mandatory with PaO_2/FiO_2 <100 mm Hg and recommended if PaO_2/FiO_2 ratio is between 100 and 150 mm Hg.

Criteria for readiness to wean from the ventilator will be assessed daily following the guidelines[54] and according to each centre's procedure. If there is no procedure for assessing readiness to wean, a spontaneous breathing trial will be performed according to the following criteria: (1) FiO_2 ≤40% and PEEP ≤8 cm H_2O; (2) the patient has spontaneous breathing efforts to trigger the ventilator in pressure support ventilation and (3) systolic blood pressure is ≥80 mm Hg without vasopressor requirements.

Implementation strategies

The study was designed and implementation started during the COVID-19 pandemic; therefore, several strategies were designed to ensure feasibility and protocol compliance as described in online supplemental file 1.

Data collection and measurements

Baseline characteristics including age, sex, height, weight, date of hospital and of ICU admission, date and hour of intubation, comorbidities, mean reason for intubation, risk factors for ARDS, COVID-19 status, severity scores (Simplified Acute Physiology Score II (SAPS II) at ICU admission[55] and Sequential Organ Failure Assessment (SOFA) Score at randomisation[56]), arterial blood gas analysis and ventilator settings prior to randomisation will be collected.

From day 1 to day 14 between 08:00 and 12:00, medications (such as sedatives, opioids, neuromuscular blocking agents), vital signs, ventilator settings, respiratory mechanics, arterial blood gas analysis, SOFA score and adverse events of interest (such as persistent hypotension with mean arterial pressure <55 mm Hg, refractory hypoxemia with SpO_2<88% despite increased FiO_2, new onset of barotrauma such as pneumothorax, pneumomediastinum or subcutaneous emphysema, and cardiac arrest) will be collected. Additionally, for day 1 and day 2 in both randomisation groups, respiratory mechanics and arterial blood gas analysis will be collected using a PEEP of 15 cm H_2O to ensure comparability of the two groups using the same PEEP levels, then ventilator settings will be resumed according to the allocation group.

At days 21, 28, 35, 42, 49, 56 and 60, vital signs and ventilator settings according to the allocation group will be collected.

We will also collect whether a spontaneous breathing trial was performed, the patient was extubated, a tracheostomy was performed, the patient was successfully separated from the ventilator (defined as extubation without reintubation within 7 days or disconnection from mechanical ventilation without reconnection for 7 days in patients tracheostomised), the existence of an infectious cause of ARDS, and the use of corticosteroids, prone positioning, tocilizumab or dexamethasone, during the ICU stay.

We will check the vital status at ICU discharge, at day 28, at hospital discharge and at day 60.

Serious adverse events will be documented during the follow-up until Day 60.

Major violations of the protocol for ventilator settings detected on the electronic Case Report Form (eCRF) will be recorded and may be (1) generally in accordance with the protocol but explained by an intercurrent condition or event or by an extreme severity, or (2) related to a lack of measurements or monitoring, or (3) violating the principles of the protocol. Direct contacts with the centres will be favoured.

On additional informed consent and in centres with biomarker collection possibilities, biological samples will be collected at randomisation, day 1 and day 3 for exploratory analyses related to circulating biomarkers, transcriptomics and epigenetics.

Study outcomes

The primary outcome is all-cause mortality within 60 days of randomisation.

Secondary outcomes are:

1. Duration of invasive ventilation.
2. Duration of ICU stay.
3. Duration of hospital stay.
4. Organ dysfunction measured by the SOFA score.
5. Barotrauma (*i.e.* new onset pneumothorax, pneumomediastinum and subcutaneous emphysema if not directly related to an intervention such as central line insertion).
6. All-cause mortality in ICU.
7. All-cause mortality within 28 days of randomisation.
8. All-cause mortality in hospital.
9. Changes in circulating biomarkers of systemic inflammation (interleukin 6, 8 and tumour necrosis factor receptor 1)[57] and of epithelial injury (soluble receptor of advanced glycation end products, and surfactant protein D)[58–60] between randomisation and 72 hours.

Additional outcomes are:

1. Hierarchical outcome using the following hierarchy: (1) death (all cause), (2) duration of invasive mechanical ventilation, (3) duration of ICU stay, (4) duration of hospital stay and (5) discharge home.
2. Process outcome pertaining to the success with which the physiologic targets were received (in patients with resumption of spontaneous breathing, the proportion of patients remaining within the protocol target within the first 48 hours of resumption of spontaneous breathing, between 48 hours and 7 days of resumption of spontaneous breathing, between 7 and 14 days of resumption of spontaneous breathing).

Statistical analysis

Sample size calculation

We estimated the sample size on the assumption that our intervention could reduce mortality at day 60 by 15%. According to early observational studies from China and Germany, mortality of c-ARDS was about 60%.[61 62] According to the largest observational study on ARDS, mortality at day 60 for moderate-to-severe ARDS is 41%.[1] The randomisation of 346 patients in each substudy (173 in each group) would provide a power of 80% (beta risk of 0.20) to detect an absolute reduction in risk of mortality at day 60 by 15% (from 60% in the control group to 45% in the interventional group of the CAVIARDS-19 substudy, and from 41% in the control group to 26% in the interventional group of the CAVIARDS-all substudy) at a two-sided alpha level of 0.05. To account for potential losses to follow-up and uncertainty regarding incidence and mortality of ARDS in the post-COVID era, we will randomise 370 patients in the CAVIARDS-19 substudy and 370 in the CAVIARDS-all substudy (740 patients in total in the overall study).

Conditional power analysis will be conducted after recruitment of 70% of the patients to each substudy by an independent statistician. If the conditional power at that time is ≥70% but <80%, the Data and Safety Monitoring Board (see below) can recommend increasing the sample size to achieve 80% power. Different analyses have shown how stopping early for futility might lead to inflation of type II (false negative) error,[63] failing to identify the benefit of an effective intervention. Given the low risk and cost of this trial, we opted to minimise this risk of bias by not including a stopping rule for futility.

Type of analysis

All analyses will follow the prespecified statistical analysis plan (which can be found in the online supplemental appendix). Analyses will follow the intention-to-treat principle including all randomised patients, irrespective of compliance to their randomised group. To reflect the basket trial design, the initial primary analysis will be performed separately for each of the designed subpopulations, suspected c-ARDS and non-suspected c-ARDS. The per protocol analyses will include only subjects who meet the following qualifications: for the experimental group, patients in whom PEEP was set according to the R/I ratio at day 1 and day 2, for the control group: patients in whom PEEP followed the PEEP-FiO_2 table (high or low as stated by the investigator in the eCRF) at days 1 and 2.

Primary outcome

As primary analysis, all-cause mortality at day 60 will be compared by a χ^2 test. The unadjusted treatment effect will be expressed as an absolute risk difference with 95% CI, as well as the OR and 95% CI.

As secondary analysis, logistic regression will be used to adjust for the following baseline variables: age, PaO_2/FiO_2 ratio, SAPS II score, shock and SOFA score. The adjusted OR and 95% CI will be used to express the treatment effect.

As an additional secondary analysis, time to death will be summarised using Kaplan-Meier curves and compared with a log-rank test. The treatment effect and 95% CI will be expressed using survival time ratio or HR.

Additionally, the primary analysis will be repeated by substudy using evidential (likelihood) methods.

Similarly, the primary analysis will be repeated by substudy using Bayesian methods, using priors centred around no change in mortality. Sensitivity analyses will

be performed using more strongly or weakly informative priors.

Cluster analyses will be performed to identify potential patient subgroups based on their baseline, pre-randomisation, factors, and then determine whether there is heterogeneity of treatment effect on primary and secondary outcomes across the clusters/subgroups.

Sub-group analyses will explore whether the treatment effect is affected by the PaO_2/FiO_2 ratio.

Severity of ARDS will also be considered in a subgroup analysis of the combined subpopulations.

Additional subgroup analyses of the combined data will explore suspected ARDS cause (COVID-19 or not) and actual ARDS cause (COVID-19 or not).

Secondary outcomes

Times to liberation from the ventilator, to ICU discharge and to hospital discharge will be summarised by cumulative incidence curves accounting for the competing risk of death. Cause-specific proportional hazard models will be fit to estimate the treatment effect as an HR with 95% CI. In case the treatment has a strong effect on mortality, the cause-specific models could be biased. In that case, multi-state (or other intensity-based) models will be employed. These outcomes will also be looked at in their day 60 ventilator-free or days-free variants and compared by a t-test or Wilcoxon test. CIs on the mean difference will be obtained by bootstrapping due to the expected lack of normality.

The remaining secondary outcomes are binary and can be analysed with standard χ^2 tests and summarised with risk differences and ORs along with 95% CIs.

The evidential and Bayesian methods described for the primary outcome will be repeated for four of the secondary outcomes, specifically: duration of ventilation, duration of ICU stay, duration of hospital stay and organ dysfunction.

Additionally, subgroup analyses will be performed for the secondary outcomes using the clusters identified previously.

Additional outcomes

The hierarchical outcome will be compared between groups using the Win ratio methodology.

The process outcome will be summarised descriptively.

Combined analysis

Additionally, the two subpopulations of the basket trial will be combined and secondary analyses will adjust for suspected or actual ARDS cause.

Data monitoring

The Data and Safety Monitoring Board committee includes an independent statistician and two international independent investigators. Safety will be reviewed on all patients combined, irrespective of the subpopulation, while efficacy will be subpopulation specific. They meet after 15% and 30% of the total patients have been enrolled (or immediately, if urgent) to review severe adverse events and outcomes. Recommendations for trial termination would be based on safety concerns alone, rather than efficacy on the primary outcome.

ETHICS AND DISSEMINATION

Ethics

The CAVIARDS trials received the ethics approval for each of the participating centres. The specific ethics committees that have approved our study are:

- Unity Health Toronto Research Ethics Board (CTO) for St Michael's Hospital, on 9 April 2019.
- Comité de Ética de Investigación con Medicamentos del Hospital Universitari Vall d'Hebron for Vall D'Hebron University Hospital on 14 April 2020.
- Comité de protection des personnes Ile de France III for participating centres in France, on 6 May 2020 (number 2020-A01179-30).
- CEIm (Comité de Ética de la Investigatción con Medicamentos) de la Fundació de Gestió Sanitària del Hospital de la Santa Creu i Sant Pau for L'Hospital de la Santa Creu i Sant Pau, on 22 July 2020.
- Comitato Etico—Fondazione Policlinico Gemelli for Policlinico Universitario Agostino Gemelli IRCCS on 18 September 2020.
- Comitato Etico di Area Vasta Emilia Centro for Arcispedale Sant'Anna, on 18 September 2020.
- NYU Langone Health Institutional Review Board on 21 September 2020.
- Unity Health Toronto Research Ethics Board (CTO) for Toronto General Hospital, on 2 October 2020.
- Comité Ético Científico de Ciencias de la Salud for the centre Hospital Clínico Red UC-Christus on 6 October 2020.
- Unity Health Toronto Research Ethics Board (CTO) for Toronto Western Hospital, on 15 January 2021.
- Il Comitato Etico Area 1 dell'Azienda Ospedaliero-Universitaria 'Ospedali Riuniti' di Foggia for University of Foggia, on 27 July 2021.
- HIGA 'Eva Perón' Comité de Bioética for Sanatorio Anchorena San Martin, on 24 February 2022.
- Comité de Revisión Institucional del Hospital Británico Comité de Ética en Investigación for Hospital Británico, on 2 May 2022.
- Complejo Médico Churruca-Visca Comité de Ética Biomédica for Hospital Churruca, on 9 June 2022.
- Comité de Ética SATI Comité de Ética en Investigación for Sanatorio Anchorena Recoleta, on 10 December 2022.
- Comité de Ética en Investigación del CEMIC for CEMIC, on 23 October 2023.
- Comité de Ética SATI Comité de Ética en Investigación for Sanatorio Mater Dei, on 24 August 2024.
- Medical Research Ethics Committees United (MEC-U) for OLVG, on 20 November 2024.

Informed consent

At the time of meeting study criteria, the patient is incapable of providing consent (eg, patient is sedated

with or without paralysis, and mechanically ventilated). Therefore, written informed consent for participation in the trial is obtained from the patient's substitute decision maker (SDM) by the local investigator. As the study procedures are critical to the first 48 hours or earlier after meeting criteria for enrolment, enrolling patients as soon as they meet criteria is of utmost importance. Because there could be no substitute decision maker present at the bedside, for example, due to the no-visitor policy during the pandemic, we therefore aim to obtain telephone consent from the SDM prior to study procedures, but if the SDM cannot be located to provide consent, or when there is no SDM known at the time of meeting criteria, we will enrol patients under a deferred consent procedure. As soon as possible, consent from the SDM will be obtained, and after patient recovery, written informed consent will be obtained from the patient included in the trial (see online supplemental appendix). Telephone and deferred consent procedures will follow local protocols as approved by the respective ethics boards.

For exploratory analyses of biomarkers, additional written informed consent is obtained from the patient's substitute decision maker and from the patient as soon as possible after recovery.

Dissemination

Study results will be submitted for publication in peer-reviewed journals and presented at national and international critical care and respiratory meetings. We will follow the International Committee of Medical Journal Editors criteria and will include investigators who contributed meaningfully to trial design, implementation and analysis.

Data sharing

The final anonymised trial database will be available on reasonable written request to the principal investigators, 1 year after publication of the main manuscript.

Patient and public involvement

Patients and public were not involved in the study design.

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Contributors The protocol was developed by the trial steering committee. LB, NF, ASS, LDS, LC, RC, IT, TP, AJ and PJ were involved in the conception, design, writing and editing of the study protocol. All authors approved the final protocol and manuscript. RC acted as the guarantor.

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