

COMMENTARY

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Ultra-protective ventilation and hypoxemia

Luciano Gattinoni

See related research by Fanelli et al., <http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1211-y>

Abstract

Partial extracorporeal CO₂ removal allows a decreasing tidal volume without respiratory acidosis in patients with acute respiratory distress syndrome. This, however, may be associated with worsening hypoxemia, due to several mechanisms, such as gravitational and reabsorption atelectasis, due to a decrease in mean airway pressure and a critically low ventilation-perfusion ratio, respectively. In addition, an imbalance between alveolar and artificial lung partial pressures of nitrogen may accelerate the process. Finally, the decrease in the respiratory quotient, leading to unrecognized alveolar hypoxia and monotonous low plateau pressures preventing critical opening, may contribute to hypoxemia.

The capability to remove some of the metabolically produced CO₂ with artificial lungs using a low extracorporeal blood flow (<1 l/min) and a high extracorporeal gas flow provides a key to significantly reduce mechanical ventilation (the ultra-protective strategy) [1]. This, and the easily established vascular access, make the method attractive for acute respiratory distress syndrome (ARDS) patients, in whom even the standard 6 ml/kg tidal volume (TV) may still produce unacceptable stress and strain [2]. In a recent multicenter study, Fanelli et al. [1] tested the feasibility of the ultra-protective strategy in combination with extracorporeal carbon dioxide removal (ECCO₂R) in 15 patients with moderate ARDS. The authors concluded that one could use ultra-protective ventilation with a TV of 4 ml/kg without resulting relevant respiratory acidosis. The price of attaining this goal, however, appears quite high. Six of

the 15 patients (40 %) with initially moderate ARDS experienced life-threatening hypoxemia and required either extracorporeal membrane oxygenation (ECMO) or the prone position. The authors concluded that the impact of the ultra-protective strategy, ECCO₂R, on hypoxemia is not clear. We believe, however, that the observed hypoxemia is due to well-defined mechanisms acting simultaneously, which may be summarized as follows:

- 1) *Gravitational atelectasis*: Whenever ventilation decreases (reduction of TV and/or respiratory rate) the mean airway pressure decreases, and the lungs tend to collapse. The greater the decrease in ventilation and the greater the lung weight, the greater will be the collapse. This phenomenon, albeit to a lesser extent, occurs in normal lungs on induction of anesthesia [3]. This has been observed experimentally during ECCO₂R and mechanical ventilation [4]. Positive end-expiratory pressure (PEEP) must be increased by an amount sufficient to maintain the same mean airway pressure in order to preserve the open lung volume [5] otherwise some amount of gravitational collapse is unavoidable. In the study of Fanelli et al., the PEEP increase was so low as to be non-significant.
- 2) *Absorption atelectasis*: At least two conditions favor the appearance of absorption atelectasis. Firstly, when ventilation is very low the amount of oxygen provided to some pulmonary units may be lower than the amount removed by the blood perfusing those units. This produces a collapse of the pulmonary unit when its ventilation (VA)/perfusion (Q) ratio reaches a critical level [6]. Secondly, if the artificial lung is ventilated with a fraction of inspired oxygen (FiO₂) greater than that used for the natural lung, the partial pressure of nitrogen in the blood perfusing the natural lung is lower than that in the alveoli [7]. Under these conditions the critical VA/Q is reached more rapidly, since not only oxygen but

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also nitrogen leaves the alveoli. In the study by Fanelli et al., the artificial lungs were ventilated with an FiO_2 of 1.0 in some of the centers, while the natural lungs were ventilated with an FiO_2 of 0.5.

- 3) **Opening pressures:** Sufficient pressure must be applied to reopen the atelectatic areas. Studies show that at least one normal TV every 2 min was mandatory in order to correct or prevent atelectasis, otherwise a consistent reduction in lung volume was observed [4]. This low frequency has an effect similar to sighing [8]. In ARDS patients with a plateau pressure of 25 cmH₂O, as employed in the study by Fanelli et al., we may estimate that 30 to 40 % of the recruitable lung always remains closed [9, 10]. This implies that oxygenation cannot take place even during inspiration [11], and that newly formed atelectasis cannot be reopened.
- 4) **Alveolar PaO_2 and respiratory quotient:** During ECCO₂R, the respiratory quotient (R) decreases when the CO₂ eliminated by the natural lungs decreases. To maintain the same alveolar partial pressure of oxygen (PaO_2), the FiO_2 must be increased. This has been proved experimentally [12] and can be easily derived from the alveolar gas equation [13]. The lower the FiO_2 , the greater the impact of R on alveolar PaO_2 . For example, with $\text{FiO}_2 = 0.3$, partial pressure of CO₂ = 50 mmHg, and R = 1.0, PaO_2 is approximately 164 mmHg. With FiO_2 kept constant at 0.3, alveolar PaO_2 decreases to 113 mmHg when R is reduced to 0.5 and to as low as 48 mmHg when R is decreased to 0.3. The risk of unrecognized alveolar hypoxia as the cause of hypoxemia must be kept in mind during ECCO₂R, particularly if a FiO_2 below 0.4 is being used.

All discussed causes of hypoxemia may be prevented or corrected with the proper use of PEEP, FiO_2 and recruitment maneuvers, e.g., intermittent sighs.

Abbreviations

ARDS: acute respiratory distress syndrome; ECCO₂R: extracorporeal carbon dioxide removal; FiO_2 : fraction of inspired oxygen; PaO_2 : alveolar partial pressure of oxygen; PEEP: positive end-expiratory pressure; Q: perfusion; R: respiratory quotient; TV: tidal volume; VA: ventilation.

Competing interests

The author declares that he has no competing interests.

Published online: 12 May 2016

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RESEARCH

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Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome

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Abstract

Background: Mechanical ventilation with a tidal volume (V_T) of 6 mL/kg/predicted body weight (PBW), to maintain plateau pressure (P_{plat}) lower than 30 cmH₂O, does not completely avoid the risk of ventilator induced lung injury (VILI). The aim of this study was to evaluate safety and feasibility of a ventilation strategy consisting of very low V_T combined with extracorporeal carbon dioxide removal (ECCO₂R).

Methods: In fifteen patients with moderate ARDS, V_T was reduced from baseline to 4 mL/kg PBW while PEEP was increased to target a plateau pressure – (P_{plat}) between 23 and 25 cmH₂O. Low-flow ECCO₂R was initiated when respiratory acidosis developed (pH < 7.25, PaCO₂ > 60 mmHg). Ventilation parameters (V_T , respiratory rate, PEEP), respiratory compliance (C_{RS}), driving pressure ($\Delta P = V_T/C_{RS}$), arterial blood gases, and ECCO₂R system operational characteristics were collected during the period of ultra-protective ventilation. Patients were weaned from ECCO₂R when PaO₂/FiO₂ was higher than 200 and could tolerate conventional ventilation settings. Complications, mortality at day 28, need for prone positioning and extracorporeal membrane oxygenation, and data on weaning from both MV and ECCO₂R were also collected.

Results: During the 2 h run in phase, V_T reduction from baseline (6.2 mL/kg PBW) to approximately 4 mL/kg PBW caused respiratory acidosis (pH < 7.25) in all fifteen patients. At steady state, ECCO₂R with an average blood flow of 435 mL/min and sweep gas flow of 10 L/min was effective at correcting pH and PaCO₂ to within 10 % of baseline values. PEEP values tended to increase at V_T of 4 mL/kg from 12.2 to 14.5 cmH₂O, but this change was not statistically significant. Driving pressure was significantly reduced during the first two days compared to baseline (from 13.9 to 11.6 cmH₂O; $p < 0.05$) and there were no significant differences in the values of respiratory system compliance. Rescue therapies for life threatening hypoxemia such as prone position and ECMO were necessary in four and two patients, respectively. Only two study-related adverse events were observed (intravascular hemolysis and femoral catheter kinking).

Conclusions: The low-flow ECCO₂R system safely facilitates a low volume, low pressure ultra-protective mechanical ventilation strategy in patients with moderate ARDS.

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Keywords: Acute respiratory distress syndrome, Protective mechanical ventilation, Extracorporeal carbon dioxide removal, Extracorporeal membrane oxygenation, Positive end-expiratory pressure, Driving pressure, Ventilator-induced lung injury

Background

Over-distention of the normally aerated lung and/or opening and closing of collapsed alveoli may worsen pulmonary damage in patients with acute respiratory distress syndrome (ARDS). Current guidelines for ARDS recommend a protective ventilation strategy based on limitation of tidal volume (V_T) to 6 mL/kg predicted body weight and plateau pressure (P_{plat}) to 30 cmH₂O, an approach that has been shown in a randomized clinical trial to reduce mortality by 9 % [1]. However, recent studies have shown that ARDS patients who are ventilated according to the ARDS Network (ARDSnet) protective ventilatory strategy may still be exposed to forces that can induce lung injury [2–5], thus challenging current recommendations on how to minimize the risk of ventilator-induced lung injury (VILI) [3]. Moreover, Hager and coworkers [6] showed that mortality decreases as P_{plat} is reduced. However, as this relationship appears to be linear [6], several authors have postulated that an ultra-protective ventilation strategy based on further reduction in V_T from 6–4 mL/kg and P_{plat} from 30–25 cmH₂O may improve outcomes [3]. Such tidal volumes reduce alveolar ventilation resulting in respiratory acidosis, which can be mitigated through the application of extracorporeal carbon dioxide removal (ECCO₂R) [7–9].

The feasibility and safety of ultra-protective ventilation strategies facilitated by ECCO₂R has been tested in several studies using a pump-less arteriovenous device operating at a blood flow rate of 1.0–1.5 L/min [10–12]. Information on feasibility and safety of ultra-protective ventilation strategies facilitated by low-flow venous-venous ECCO₂R are limited to a single-center study [8].

The aim of the current study was to assess in a multi-center trial the feasibility and safety of an ultra-protective ventilation strategy facilitated by low-flow veno-venous ECCO₂R in patients with moderate ARDS. We used an ECCO₂R system (Hemolung Respiratory Assist System, ALung Technologies), which is specifically designed to provide clinically significant CO₂ removal at low blood flow rates (350–550 mL/min).

Methods

Patients were enrolled in four European intensive care units of academic hospitals. Local ethics committees approved the study protocol. Informed consent was obtained from the patients. In the case of incompetent patients, consent was obtained in accordance with local ethics committee procedures [13].

Patients

The study included fifteen adult patients with moderate ARDS according to the Berlin definition (PaO_2/FiO_2 (P/F) 100–200 mmHg, with positive end-expiratory pressure (PEEP) >5 cmH₂O) [14], who were mechanically ventilated with an expected duration of ventilation longer than 24 h. Exclusion criteria were age <18 years, pregnancy, decompensated heart insufficiency or acute coronary syndrome, severe chronic obstructive pulmonary disease (COPD), respiratory acidosis with arterial PCO₂ ($PaCO_2$) >80 mmHg, acute brain injury, severe liver insufficiency (Child-Pugh score >7) or fulminant hepatic failure, heparin-induced thrombocytopenia, contraindication for systemic anticoagulation, patient moribund, decision to limit therapeutic interventions, catheter access to femoral vein or jugular vein impossible, pneumothorax, or platelet count <50 × 10³/mL.

ECCO₂R System

Low-flow ECCO₂R was provided with the Hemolung Respiratory Assist System (RAS) (ALung Technologies, Inc, Pittsburgh, PA, USA) [15]. Briefly, venous blood is circulated through a 15.5-Fr dual lumen venous catheter (jugular or femoral) by a magnetically driven centrifugal pump at a flow rate of 350–550 mL/min. The pump is integrated within a cylindrical bundle of hollow fiber membranes, creating a flow pattern, which improves CO₂ transfer efficiency relative to passive oxygenators. Sweep gas (air or 100 % O₂) is drawn through the hollow fibers under negative pressure by a vacuum pump, creating a gradient for CO₂ diffusion. Maintaining the sweep gas under negative pressure mitigates the risk of air embolism across the membrane, and also allows for automatic removal of plasmatic water condensation from the fiber lumens in order to preserve gas exchange efficiency. Level of blood flow, pump speed (RPM) and extracorporeal CO₂ removal rate (vCO_2) are displayed on a controller.

Study protocol

Patients were sedated, paralyzed and ventilated in accordance with the EXPRESS trial protocol [16]: V_T of 6 mL/kg (ideal body weight); PEEP set to achieve P_{plat} of 28–30 cmH₂O; respiratory rate (RR) set to 20–35 to maintain approximately the same minute ventilation as before study initiation. Percutaneous venous femoral or jugular cannulation was performed through insertion of a single dual-lumen catheter (15.5 Fr) after administration of a heparin bolus (80 IU/kg). The device was

activated at a blood flow rate of 350–550 mL/min and a sweep gas of 0 L/min such that no CO₂ removal was initially performed.

Following a 2-h run-in time, V_T was gradually reduced from 6 to a minimum value of 4 mL/kg by 0.5 mL/kg every 30 minutes and PEEP was increased to target a P_{plat} between 23 and 25 cmH₂O. If arterial pH was <7.25 with PaCO₂ >60 mmHg, despite an increase in RR up to 35/min, sweep gas through the ECCO₂R device was switched on with 100 % oxygen at 10 L/min to obtain an arterial pH ≥7.25 with a PaCO₂ ≤60 mmHg and RR ≤35/min. If PaCO₂ was >75 mmHg and/or pH <7.20, despite a respiratory rate of 35/min and optimized ECCO₂R, sodium bicarbonate could be infused. If undesirable hypercapnia/acidosis persisted, V_T was increased at the discretion of the treating physician. Refractory hypoxemia and/or hypercapnia could be managed at the discretion of the attending physician using venovenous extracorporeal membrane oxygenation (ECMO), prone positioning, or nitric oxide (NO) inhalation. If PaCO₂ was constantly <35 mmHg and/or pH was >7.50 under the aforementioned ECCO₂R settings, the respiratory rate was decreased to 18–22/min and sweep gas flow was decreased to 2–5 L/min.

The ECCO₂R-facilitated ultra-protective ventilation strategy was continued for at least 24 h. The potential for weaning from ultra-protective ventilation and ECCO₂R was assessed daily if PaO₂/FiO₂ (P/F) was >200 by setting mechanical ventilation according to conventional ARDSnet settings (V_T = 6 mL/kg, PEEP 5–10 cmH₂O, RR 20–30/min, inspired O₂ fraction (FiO₂) = 40 %) and switching off sweep gas through the ECCO₂R device. Under these conditions, if the patient remained stable for at least 12 h with P_{plat} <25 cmH₂O and PaCO₂ <50 mmHg (allowing for RR up to 30–35/min), ECCO₂R was discontinued and the venous catheter removed.

ECCO₂R parameters (blood flow, sweep gas flow, and CO₂ removal rate), ventilator settings (V_T , PEEP, RR, P_{plat} , mean airway pressure, minute ventilation, inspiratory-to-expiratory ratio, inspired fraction of oxygen), hemodynamics (mean arterial pressure, heart rate, dose of vasopressor) and arterial blood gas values (pH, PaO₂, PaCO₂, HCO₃⁻, lactate), heparin dose and activated partial thromboplastin time ratio (aPTTr) were collected at baseline, after run-in time, 30 minutes after every V_T reduction and at least twice a day (08:00 am ± 2 h and 08:00 pm ± 2 h) in the subsequent days on ECCO₂R. Blood chemistry data were collected daily. Respiratory system compliance [17] and driving pressure [18] were calculated according to the standard formula.

Serious adverse events (SAE) were prospectively defined as: (a) any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating or requires prolonged hospitalization; or (b) any event that may jeopardize the patient and requires medical or

surgical intervention to prevent one of the outcomes listed above; and (c) which the attending physician perceives might be directly related to enrollment in the clinical trial. Adverse events were considered to be study-related if the event followed a reasonable sequence from a study procedure and could readily have been produced by the study procedure. Adverse events were considered non study-related if they were related primarily to the underlying disease or to ARDS and its sequelae. Other adverse events not fulfilling the above definition were recorded in the patients' case report forms (CRFs). Following discontinuation of ECCO₂R, subjects were monitored for adverse events until hospital discharge or day 8 after enrollment, whichever occurred first.

Data are expressed as mean ± SD. Statistical analysis was performed by one-way analysis of variance for repeated measures, followed by Bonferroni post-hoc test for comparison between different time points (Stata Corp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Fifteen patients with moderate ARDS were included in the period April to November 2014. Baseline characteristics of patients enrolled in the study are shown in Table 1.

Ventilation settings during the V_T reduction phase are shown in Table 2. At baseline, all patients had PaO₂/

Table 1 Baseline characteristics of patients

| Variables | Patients (n = 15) |
|--|-------------------|
| Age (years) | 55 ± 19 |
| Gender (male/female), number | 11/4 |
| Body mass index (kg/m ²) | 24 ± 8 |
| Lung injury score (Murray) | 3 ± 0.9 |
| Risk factors for acute respiratory distress syndrome, number of patients | |
| Pulmonary | |
| Pneumonia | 12 |
| Non-pulmonary | |
| Sepsis | 3 |
| Comorbidities, number of patients | |
| Diabetes mellitus | 3 |
| Chronic obstructive pulmonary disease | 1 |
| Arterial hypertension | 5 |
| Coronary artery disease | 1 |
| Chronic renal impairment | 2 |
| Atrial fibrillation | 2 |
| Alcohol use disorder | 4 |
| Obesity | 2 |
| Simplified acute physiology score II | 51 ± 14 |
| Sequential organ failure assessment | 10 ± 4 |

Table 2 Time course of ventilation variables during the run-in phase

| Variables | Baseline | V _T 5 mL/kg | V _T 4.5 mL/kg | V _T 4 mL/kg |
|--|------------|------------------------|--------------------------|------------------------|
| V _T (mL/kg) | 6.2 ± 0.7 | 5.02 ± 0.1* | 4.48 ± 0.1* | 3.96 ± 0.1* |
| Respiratory rate (beats/minute) | 28 ± 7 | 29 ± 4 | 30 ± 4* | 30 ± 5* |
| Positive end-expiratory pressure (cmH ₂ O) | 12 ± 3 | 13.8 ± 3 | 13.6 ± 4 | 13.0 ± 4.0 |
| Plateau pressure (cmH ₂ O) | 27.7 ± 1.6 | 25.2 ± 1.6* | 23.6 ± 1.3* | 22.7 ± 1.8* |
| Patients who reached the pH threshold for ECCO ₂ R, n | | 0 | 2 | 15 |

*P < 0.05 vs baseline. V_T tidal volume, ECCO₂R extracorporeal carbon dioxide removal

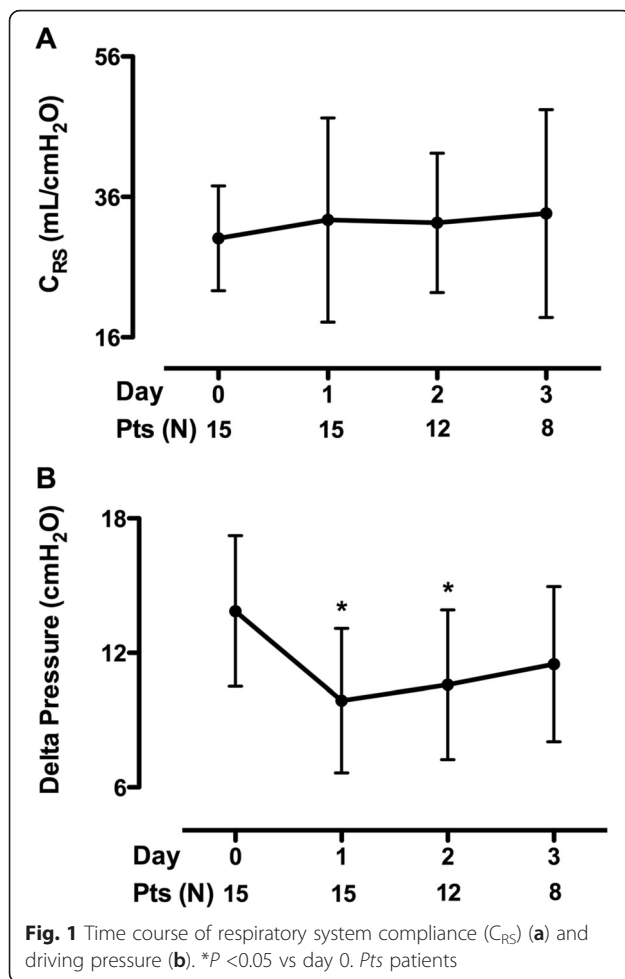
FiO₂ ≤ 200, they were ventilated with a conventional protective ventilation strategy according to the EXPRESS trial protocol, and were paralyzed for a median time of 1 day. The initial stepwise reduction in V_T, without ECCO₂R, resulted in significant respiratory acidosis (pH < 7.25) in all 15 patients at a mean V_T of 3.96 ± 0.1 mL/kg. After initiation of ECCO₂R, a V_T of 4.29 ± 0.5 mL/kg was achieved and respiratory acidosis was significantly corrected, with pH and PaCO₂ returning to within 10 % of baseline values obtained at V_T = 6 mL/kg. The median number of days on ECCO₂R was 3 (2–4). The reduction in V_T was associated with a significant reduction in P_{plat} from 27.7 ± 1.6 to 23.9 ± 1 cmH₂O (p < 0.05) at day 1 and this difference remained significant throughout the

study period (Table 3). PEEP tended to increase from 12 ± 3 to 14 ± 2 cmH₂O at day 1, however, this difference was not statistically significant over time (Table 3). Driving pressure (P_{plat} – PEEP) was significantly reduced during the first 2 days compared to baseline (p < 0.05); there were no significant differences in the values of respiratory system compliance (Fig. 1). At day 1, the ECCO₂R device provided CO₂ removal of 81 ± 9 mL/min at a blood flow rate of 435 ± 60 mL/min and sweep gas flow rate of 10 ± 0.3 L/min. The efficiency of the ECCO₂R system was stable throughout the study period (Table 3). Infusion of bicarbonate and renal replacement therapies for acute kidney injury were never used in this cohort of patients.

Table 3 Time course of ventilation variables, blood gases, ECCO₂R operational characteristics and hemodynamics at V_T 4 mL/kg plus ECCO₂R

| Variables | Baseline | V _T 4 mL/kg plus ECCO ₂ R | | | | |
|--|------------|---|-------------|-------------|------------|-------------|
| | | Day 1 | Day 2 | | Day 3 | |
| Time (h) | 8.00 | 8.00 | 8.00 | 20.00 | 8.00 | 20.00 |
| Patients (number) | 15 | 15 | 10 | 10 | 8 | 6 |
| V _T (mL/kg) | 6.2 ± 0.7 | 4.29 ± 0.5* | 4.58 ± 0.7* | 4.59 ± 0.8* | 4.8 ± 0.7* | 4.8 ± 0.7* |
| Respiratory rate (beats/minute) | 28 ± 7 | 31.6 ± 4.6* | 29.6 ± 6.8 | 29.6 ± 6.8 | 28 ± 7 | 27.4 ± 8.6 |
| Positive end-expiratory pressure (cmH ₂ O) | 12 ± 3 | 14 ± 2 | 13 ± 3 | 12 ± 4 | 13 ± 5 | 13 ± 3 |
| Arterial partial pressure of oxygen/inspired oxygen fraction | 159 ± 34 | 175 ± 45 | 185 ± 91 | 190 ± 57 | 176 ± 59 | 176 ± 80 |
| Plateau pressure (cmH ₂ O) | 27.7 ± 1.6 | 23.9 ± 1* | 24 ± 4* | 24 ± 3* | 24 ± 3* | 23 ± 3* |
| Blood flow (mL/min) | | 435 ± 60 | 424 ± 63 | 423 ± 35 | 424 ± 29 | 436 ± 39 |
| Rotations per minute (RPM) | | 1407 ± 26 | 1408 ± 30 | 1409 ± 32 | 1411 ± 36 | 1414 ± 41 |
| Sweep gas (L/min) | | 8.6 ± 3.5 | 9.2 ± 2.9 | 9 ± 3 | 9.9 ± 0.3 | 8.7 ± 3.2 |
| CO ₂ removal (mL/min) | | 81 ± 9 | 70 ± 29 | 70 ± 31 | 81 ± 22 | 71 ± 11 |
| Ph | 7.36 ± 0.1 | 7.33 ± 0.1 | 7.39 ± 0.1 | 7.36 ± 0.1 | 7.33 ± 0.1 | 7.4 ± 0.1 |
| PaO ₂ (mmHg) | 95 ± 29 | 90 ± 22 | 91 ± 26 | 84 ± 10 | 81 ± 15 | 99 ± 29 |
| PaCO ₂ (mmHg) | 51 ± 15 | 53 ± 15 | 51 ± 18 | 52 ± 17 | 55 ± 20 | 49 ± 11 |
| HCO ₃ (mmol/L) | 28 ± 5 | 27.6 ± 6.1 | 28.7 ± 6.2 | 28 ± 6.9 | 28.1 ± 7.4 | 28.3 ± 6.03 |
| Lactate (mmol/L) | 2 ± 1 | 2.9 ± 4.8 | 1.9 ± 1.7 | 1.8 ± 1.8 | 1.9 ± 2.0 | 1.3 ± 0.4 |
| Heart rate (beats/minute) | 76 ± 9 | 90 ± 17 | 86 ± 15 | 95 ± 21 | 94 ± 19 | 94 ± 17 |
| Mean arterial pressure (mmHg) | 98 ± 20 | 74 ± 14 | 80 ± 10 | 76 ± 12 | 76 ± 19 | 85 ± 14 |
| Norepinephrine dose (mcg/kg/min) | 0.51 ± 0.6 | 0.45 ± 0.4 | 0.34 ± 0.3 | 0.29 ± 0.27 | 0.57 ± 0.4 | 0.5 ± 0.6 |

*P < 0.05 vs baseline. V_T tidal volume, ECCO₂R extracorporeal carbon dioxide removal



At day one, the heparin dosage was 341 ± 138 IU/kg/day with an aPTT ratio of 1.77 ± 0.7 , and remained stable over time. The average baseline value of hemoglobin (Hb) was 10.4 ± 2 gr/dL, and the median Hb threshold for transfusion was 6.9 gr/dL (6.9–7.0). On day 1, four patients received 2.25 ± 0.5 red blood cell (RBC) units and 1.25 ± 2.5 pools of platelets. On day 2, only two patients received 1.5 ± 0.7 units of RBCs. On day 3, only one patient received two units of RBCs.

Two study-related adverse events were observed. In one patient, intravascular hemolysis (plasma-free hemoglobin 401.4 mg/dL) was observed resulting in a discontinuation of ECCO₂R after 2 days. Kinking of the ECCO₂R catheter caused a reduction in circuit blood flow in another patient. Individual data for patients who needed rescue therapies for worsening hypoxemia are given in Table 4. The overall mortality at day 28 was 47 %. Among the eight survivors, six were successfully weaned from both ECCO₂R and mechanical ventilation; while two patients were still dependent on ventilator support at 28 days.

Table 4 Oxygenation and outcomes of patients who required rescue therapies

| Patients | Time of PaO ₂ /FiO ₂ worsening (day) | PaO ₂ /FiO ₂ before rescue therapy | | Outcome (at 28 days) |
|----------|--|--|------|----------------------|
| | | Prone position | ECMO | |
| # 1 | 5 | 108 | | Dead |
| # 5 | 6 | | 78 | Alive |
| # 8 | 2 | | 75 | Dead |
| # 11 | 2 | 115 | | Alive |
| # 12 | 1 | 158 | | Dead |
| # 13 | 1 | 162 | | Alive |

PaO₂/FiO₂ arterial partial pressure of oxygen/inspired oxygen fraction, ECMO extracorporeal membrane oxygenation

Discussion

The main finding of the current study is that the low-flow ECCO₂R system effectively prevents respiratory acidosis consequent to the reduction of tidal volume to 4 mL/kg in patients with moderate ARDS. Severe hypoxemia occurred in about one third of the patients and was managed by prone positioning in conjunction with ECCO₂R; conversion to VV-ECMO was required in two patients. Side effects related to ECCO₂R (intravascular hemolysis and pump malfunction by femoral catheter kinking) were observed in two patients.

The landmark study by the ARDSnet demonstrated a 9 % mortality reduction in patients with ARDS by limiting plateau pressure to <30 cmH₂O [1]. However, recent studies have shown that patients with ARDS may still be at risk of VILI despite values of $P_{plat} \leq 30$ cmH₂O [2, 4, 5]. Terragni [2] and Bellani [4] showed that in some patients, tidal hyperinflation may still occur despite limiting V_T to 6 mL/kg and P_{plat} to 30 cmH₂O, and that this is associated with biological signs of VILI, such as higher levels of inflammatory mediators and increased metabolic activity of the lungs. Grasso and coworkers showed that hyperinflation might be attenuated by reducing the levels of PEEP based on the shape of the airway pressure time curve and that this is associated with lower levels of pulmonary inflammatory cytokine release [5]. Moreover, Hager and coworkers found that ARDS patients may benefit from V_T reduction even if they already have $P_{plat} < 30$ cmH₂O [6].

ECCO₂R has been proposed to partially clear CO₂ and consequently reduce the need of minute ventilation as delivered by conventional mechanical ventilation [9]. The first evidence that ECCO₂R might be a safe adjunctive therapy to conventional mechanical ventilation for ARDS patients dates back to the early 1980s [19, 20]. At that time, a modified veno-venous ECMO circuit with a blood flow not >1 L/min allowed for dramatic reductions of minute ventilation and ventilator-applied pressure [19]. More recently, Terragni and colleagues

demonstrated that a modified renal replacement therapy circuit with an oxygenator in series with the hemofilter could facilitate an ultra-protective ventilation strategy, which may mitigate VILI [8]. Our results extend these findings by performing a prospective multicenter study in 15 ARDS patients across four European ICUs.

Monitoring of respiratory mechanics may help clinicians in assessing the risk of VILI [17]. In the presence of normal chest wall elastance, values of P_{plat} around 30 cmH₂O may increase the risk of alveolar hyperinflation, which is the main determinant of VILI [2]; analysis of a large dataset including ARDS patients previously enrolled in clinical trials, shows that driving pressure (i.e., the ratio of tidal volume to respiratory system compliance) is an independent risk factor for hospital mortality, because regardless of the changes in V_T and PEEP, only changes in driving pressure affected the outcome [18]. Our data show that an ultra-protective ventilation strategy facilitated by low-flow veno-venous ECCO₂R resulted in values of respiratory mechanics associated with enhanced protection from VILI as: (1) values of P_{plat} around 25 cmH₂O, as achieved in this study, have been associated with lower serum levels of the pro-inflammatory cytokine interleukin-6 and a smaller percentage of lung hyperinflation, as demonstrated by computed tomography [2, 7, 8]; and (2) our ultra-protective ventilation strategy resulted in a significant reduction in driving pressure. These findings allow us to speculate that in our patients, global interaction between moderate-to-high levels of PEEP and very low tidal volume, facilitated by ECCO₂R, might be beneficial to minimize the risk of VILI.

In recent years, advances in technology have generated renewed interest in all extracorporeal support techniques. While high flow veno-venous ECMO has been increasingly used to treat life-threatening hypoxemia [21, 22], ECCO₂R systems are used to provide partial-to-full CO₂ removal with minimal effects on oxygenation [9]. Appropriate strategies to manage worsening hypoxemia during ECCO₂R treatment is a compelling issue. In fact, depending on the severity of lung injury, patients with ARDS may experience worsening of arterial oxygenation that might be life threatening [23]. Moreover, the use of very low tidal volumes may expose patients to the risk of de-recruitment in the event that insufficient PEEP is applied. Consequently, prone positioning while the patient is still on ECCO₂R, or shift to high-flow veno-venous ECMO, might be necessary. In this regard, prone positioning has been demonstrated to be effective not only in improving oxygenation but also in decreasing early and late mortality [24]. In the current study, indication for rescue therapies for profound hypoxemia was not established by protocol. Within the first week of enrollment 27 % of patients in our cohort required

prone positioning when their PaO₂/FiO₂ dropped to a median value of 137. Notably, patients underwent prone position without any interruption of ECCO₂R and had improvement in arterial oxygenation. Only two patients required escalation from ECCO₂R to ECMO because of life-threatening hypoxemia. Mortality at 28 days was 47 %, which was expected in a cohort of patients with moderate and severe ARDS.

Previous-generation ECCO₂R systems have carried a high rate of mechanical complications such as pump malfunction, membrane clotting, and catheter displacement [8]. In the current study, target blood flow rates were not reached in one case only due to a kinked catheter; otherwise, the treatment was consistent over time. Compared with arterio-venous systems in which limb ischemia, compartment syndrome, and intracranial hemorrhage have been described [7], only one case of intravascular hemolysis requiring transfusion was reported in our series.

Some limitations of this study should be addressed. First, inferences from this study are limited by its small sample size. Second, although we speculate that the strategy tested in this multicenter study was lung-protective, we did not measure pro-inflammatory mediators associated with VILI and we did not evaluate lung volume/densities distribution with computed tomography of the chest. The precise impact of worsening oxygenation during ECCO₂R treatment is also not clear. Consequently, this approach will be systematically tested in an upcoming randomized clinical trial, such as that under the auspices of European Society of Intensive Care Medicine, which will test the feasibility, safety and efficacy of several ECCO₂R systems to facilitate ultra-protective ventilation - V_T of 4 mL/kg predicted body weight (PBW) and P_{plat} <25 cmH₂O - in patients with moderate and severe ARDS (SUPERNOVA: a strategy of ultraprotective lung ventilation with extracorporeal CO₂ removal for new-onset moderate to severe ARDS) [25].

Conclusions

In conclusion, low-flow ECCO₂R is feasible, safe and efficient. It facilitates an ultra-protective mechanical ventilation strategy for reducing tidal volume to 4 mL/kg to maintain P_{plat} <25 cmH₂O. This approach allows the delivery of mechanical ventilation with relatively low driving airway pressures while preserving sufficient gas exchange and preventing hypercapnia and respiratory acidosis due to reduced ventilation. The current study provides a clinical and physiological rationale for testing whether ultra-protective mechanical ventilation improves clinical outcomes of patients with moderate and severe ARDS in randomized control trials.

Key messages

- Low-flow extracorporeal CO₂ removal safely and effectively facilitates an ultra-protective ventilation strategy in patients with moderate ARDS
- The current study provides a clinical and physiological rationale to study whether ultra-protective mechanical ventilation improves clinical outcomes of patients with moderate and severe ARDS in randomized control trials

Competing interests

V. Fanelli: speaker honoraria for educational programs from ALung Technologies. J. Mancebo: steering committee member for ALung Technologies Registry. O. Moerer: none. M. Quintel: none. S. Morley: employee of ALung Technologies receiving salary and stock compensation. I. Moran: none. F. Parrilla: none. A. Costamagna: none. M. Ranieri: Medical advisory board for ALung Technologies. A. Combes: Medical advisory board and speaker honoraria from ALung Technologies.

Authors' contributions

Study conception and design: AC and VMR. Acquisition of data: VF, VMR, JM, OM, MQ, IM, FP, AC MG, and AC. Analysis and interpretation of data: VF, VMR, JM, OM, and AC. Drafting the manuscript: VF. Critical revision of the manuscript for important intellectual content: VF, VMR, JM, OM, AC, and SM. Supervision: VMR and AC. All authors read and approved the final manuscript.

Acknowledgements

Financial support for the study was provided by ALung Technologies, Inc.

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Received: 28 September 2015 Accepted: 31 January 2016

Published online: 10 February 2016

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