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Feasibility and safety of low-flow extracorporeal CO₂ removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS

Matthieu Schmidt^{1,2}, Samir Jaber³, Elie Zogheib⁴, Thomas Godet^{5,6}, Gilles Capellier^{7,8} and Alain Combes^{1,2*}

Abstract

Background: Extracorporeal carbon-dioxide removal (ECCO₂R) might allow ultraprotective mechanical ventilation with lower tidal volume (VT) (< 6 ml/kg predicted body weight), plateau pressure (P_{plat}) (< 30 cmH₂O), and driving pressure to limit ventilator-induced lung injury. This study was undertaken to assess the feasibility and safety of ECCO₂R managed with a renal replacement therapy (RRT) platform to enable very low tidal volume ventilation of patients with mild-to-moderate acute respiratory distress syndrome (ARDS).

Methods: Twenty patients with mild (*n* = 8) or moderate (*n* = 12) ARDS were included. VT was gradually lowered from 6 to 5, 4.5, and 4 ml/kg, and PEEP adjusted to reach $23 \leq P_{\text{plat}} \leq 25$ cmH₂O. Standalone ECCO₂R (no hemofilter associated with the RRT platform) was initiated when arterial PaCO₂ increased by > 20% from its initial value. Ventilation parameters (VT, respiratory rate, PEEP), respiratory system compliance, P_{plat} and driving pressure, arterial blood gases, and ECCO₂R-system operational characteristics were collected during at least 24 h of very low tidal volume ventilation. Complications, day-28 mortality, need for adjuvant therapies, and data on weaning off ECCO₂R and mechanical ventilation were also recorded.

Results: While VT was reduced from 6 to 4 ml/kg and P_{plat} kept < 25 cmH₂O, PEEP was significantly increased from 13.4 ± 3.6 cmH₂O at baseline to 15.0 ± 3.4 cmH₂O, and the driving pressure was significantly reduced from 13.0 ± 4.8 to 7.9 ± 3.2 cmH₂O (both *p* < 0.05). The PaO₂/FiO₂ ratio and respiratory-system compliance were not modified after VT reduction. Mild respiratory acidosis occurred, with mean PaCO₂ increasing from 43 ± 8 to 53 ± 9 mmHg and mean pH decreasing from 7.39 ± 0.1 to 7.32 ± 0.10 from baseline to 4 ml/kg VT, while the respiratory rate was not altered. Mean extracorporeal blood flow, sweep-gas flow, and CO₂ removal were 421 ± 40 ml/min, 10 ± 0.3 L/min, and 51 ± 26 ml/min, respectively. Mean treatment duration was 31 ± 22 h. Day-28 mortality was 15%.

Conclusions: A low-flow ECCO₂R device managed with an RRT platform easily and safely enabled very low tidal volume ventilation with moderate increase in PaCO₂ in patients with mild-to-moderate ARDS.

Trial registration: ClinicalTrials.gov, NCT02606240. Registered on 17 November 2015.

Keywords: Extracorporeal carbon-dioxide removal, Acute respiratory distress syndrome, Protective ventilation

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Background

Over the past few decades, highly significant progress has been made in understanding the pathophysiology of the acute respiratory distress syndrome (ARDS). Recognition of ventilation-induced lung injuries (VILIs) has led to radical modifications of the ventilatory management of these patients [1, 2]. The landmark trial by the ARDSNet group demonstrated that ventilating ARDS patients with a low tidal volume (VT) of 6 ml/kg (vs 12 ml/kg) significantly decreased mortality [3]. However, recent results showed that lung hyperinflation still occurs in approximately 30% of ARDS patients, despite ventilation with the ARDSNet strategy [4]. That analysis suggested a beneficial effect of VT reduction, even for patients already with plateau pressure (P_{plat}) < 30 cmH₂O [5]. Decreasing VT and P_{plat} will also lower the driving pressure, which was recently identified as a major risk factor for mortality in ARDS patients [6].

VT reduction to < 6 ml/kg to achieve very low P_{plat} induces severe hypercapnia, which raises intracranial pressure, causes pulmonary hypertension, decreases myocardial contractility, reduces renal blood flow, and releases endogenous catecholamines [7, 8]. This strategy is therefore not possible for most ARDS patients on conventional mechanical ventilation (MV) [9]. Extracorporeal carbon-dioxide removal (ECCO₂R) may be used to achieve VT < 6 ml/kg, thereby lowering P_{plat} and driving pressure in this setting [10–13]. However, the ability to decrease MV intensity with these ECCO₂R devices, especially those based on a renal replacement therapy (RRT) platform, are limited to animal [14] or single-center [11, 15–17] studies.

The aim of this prospective, multicenter study was to evaluate the safety and feasibility of a low-flow ECCO₂R device managed by an RRT platform (PrismaLung[®]; Gambro-Baxter, Meyzieu, France) to enable very low tidal volume ventilation in patients with mild-to-moderate ARDS.

Methods

Study design and procedure

This pilot study was conducted during a 14-month period (March 2016–June 2017) in five medical and surgical intensive care units (ICUs) experienced in the care of ARDS patients and use of extracorporeal gas-exchange devices. It was approved by appropriate legal and ethics authorities (Comité de Protection des Personnes Ile-de-France 6, Paris, France; no. 15.1026). The clinical trial protocol was registered with www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02606240).

Patients

As predefined, 20 consecutive patients were included. Inclusion criteria were: mild-to-moderate ARDS according to the Berlin definition [18], 100 mmHg < partial alveolar oxygen pressure/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) <

300 mmHg with positive end-expiratory pressure (PEEP) > 5 cmH₂O on MV expected to last > 24 h; and bilateral opacities on chest imaging. Exclusion criteria were: age < 18 years, pregnancy, patients with decompensated heart failure or acute coronary syndrome, severe chronic-obstructive pulmonary disease, respiratory acidosis with partial pressure of blood carbon dioxide (PCO_2) > 80 mmHg, acute brain injury, severe liver insufficiency (Child–Pugh scores > 7) or fulminant hepatic failure, heparin-induced thrombocytopenia, systemic anticoagulation contraindicated, decision to limit therapeutic interventions, catheter access to femoral vein or jugular vein impossible, pneumothorax, and platelet count < 50 G/L.

ECCO₂R system

ECCO₂R was provided by a low-flow, standalone (without concomitant RRT), CO₂-removal device (PrismaLung[®]; Gambro-Baxter) integrated into the Prismaflex[®] platform (Gambro-Baxter). The polymethylpentene, hollow fiber, gas-exchanger membrane (surface area 0.32 m²) was connected to the extracorporeal circuit, with standard tubes and a Luer-Lock system. A 13-Fr hemodialysis venous catheter (Gamcath[™]; Gambro-Baxter) was aseptically and percutaneously inserted under ultrasonography guidance into the right jugular (15 cm) or the femoral (25 cm) vein after an unfractionated heparin bolus (80 IU/kg). Systemic heparinization was started after catheter insertion aiming for an activated partial thromboplastin time ratio (aPTTr) 1.5–2.0× that of the control. Blood was drawn from the superior vena cava and reinjected into the right atrium through the distal lumen. The Prismaflex[®] device monitored continuous venous, arterial line, and filter pressures.

Study protocol

Patients were sedated, paralyzed, and ventilated in accordance with the EXPRESS trial protocol [19]: VT at 6 ml/kg of predicted body weight (PBW); PEEP set to achieve P_{plat} of 28–30 cmH₂O; and respiratory rate (RR) set at 20–35 breaths/min to maintain approximately the same minute ventilation as before study initiation. After priming, the Prismaflex[®] device was connected to the patient and extracorporeal blood flow was progressively increased to 400–450 ml/min. Sweep-gas flow through the membrane remained at 0 L/min during this phase such that, initially, no CO₂ was removed.

Following a 2-h run-in time, VT was gradually reduced from 6 to 5, 4.5, and 4 ml/kg PBW every 30 min and PEEP adjusted to reach $23 \leq P_{\text{plat}} \leq 25$ cmH₂O. At each VT level: if arterial PaCO₂ rose by > 20% from the baseline PaCO₂ obtained at 6 ml/kg, the sweep-gas flow through the ECCO₂R device was switched on with 100% oxygen at 10 L/min; if PaCO₂ was maintained within $\pm 20\%$ of baseline PaCO₂, VT was gradually decreased to a minimum of 4 ml/kg; and if PaCO₂ remained < 20% at 4 ml/kg PaCO₂

under the aforementioned ECCO₂R settings, the RR could be decreased to 15–18 breaths/min. On the other hand, the RR could also be increased up to 35 breaths/min to maintain PaCO₂ within the targeted range. If undesirable hypercapnia/acidosis persisted (i.e., >20% 6 ml/kg PaCO₂), VT was reincreased to the previous step level. Refractory hypoxemia and/or hypercapnia could be managed, at the attending physician's discretion, with nitric oxide, prone positioning, and/or venovenous extracorporeal membrane oxygenation (ECMO).

The ECCO₂R-facilitated very low tidal volume ventilation strategy was continued for at least 24 h. The potential for weaning off very low tidal volume ventilation and ECCO₂R was assessed daily if PaO₂/FiO₂ > 200 by setting MV according to conventional ARDSnet settings (VT = 6 ml/kg, PEEP = 5–10 cmH₂O, RR = 20–30 breaths/min, FiO₂ = 40%) and switching off the sweep-gas flow through the ECCO₂R device. If, under these conditions, 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 breaths/min), the ECCO₂R device and venous catheter were removed. The manufacturer determined the Prisma-lung[®] membrane's maximum duration to be 72 h.

Data collection

Ventilator settings (VT, PEEP, RR, P_{plat}, minute ventilation, FiO₂), hemodynamic parameters (mean arterial pressure, heart rate, vasopressor dose) and arterial blood-gas values (pH, PaO₂, PaCO₂, HCO₃⁻, lactate), heparin dose, and aPTT_r were collected at baseline, after the run-in-time, 30 min after every VT reduction, and at least twice a day during the subsequent days on ECCO₂R. Blood-chemistry determinations were obtained daily. Respiratory-system compliance and driving pressure were calculated according to the standard formulas [6, 20]. CO₂ clearance by ECCO₂R (ml/min) during the first 24 h was calculated as follows [17]:

$$(\text{CtCO}_{2\text{PRE}} - \text{CtCO}_{2\text{POST}}) \times 22.4 \times \text{ECCO}_{2\text{R}} \text{ blood flow} / 1000,$$

where CtCO_{2PRE} and CtCO_{2POST} were the pre and post oxygenator blood CO₂ content, and CtCO₂ (mmol/l) = (0.0307 × PCO₂) + HCO₃⁻_{actual}.

Serious adverse events (SAEs) were prospectively defined as: any event that is fatal or immediately life-threatening, permanently disabling, severely incapacitating, or requires prolonged hospitalization; OR any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of these outcomes; AND any event that the attending physician perceives might be directly related to enrollment in the clinical trial. An AE was defined as: study related when it could be attributed to a study procedure and could readily have been produced by the study procedure; or nonstudy related when it was related primarily to the underlying

disease or to ARDS and its sequelae. Other AEs not fulfilling this definition were recorded in the patients' case-report forms. After ECCO₂R discontinuation, subjects were monitored for AEs until hospital discharge or day 8 post enrollment, whichever occurred first.

Statistical analyses

Statistical analysis was performed by one-way analysis of variance (ANOVA) for repeated measures, followed by a Bonferroni post-hoc test for comparison between different times. Results are expressed as mean ± SD and *p* < 0.05 defined statistical significance. Analyses were computed with StatView v5.0 (SAS Institute Inc., Cary, NC, USA) and SPSS v22 (SPSS Inc., Chicago, IL, USA) software.

Results

Twenty patients with mild (*n* = 8) or moderate ARDS (*n* = 12) were included; 18 underwent jugular cannulation. Patients' baseline characteristics are reported in Table 1. Neuromuscular blockade, nitric oxide, and prone positioning were applied before inclusion to 16, 9, and 8 patients, respectively. Ventilator settings during the VT reduction phase are presented in Table 2 and Fig. 1. At baseline, all patients received protective ventilation with VT set at 6.10 ± 0.30 ml/kg PBW and PEEP at 13.4 ± 3.6 cmH₂O. VT was gradually lowered to 4 ml/kg for all but one patient (who remained at the 4.5 ml/kg step because PaCO₂ increased >20% from baseline at the 4.5 ml/kg step despite ECCO₂R; see Table 2). While P_{plat} was decreased < 25 cmH₂O with VT reduction to 4 ml/kg, PEEP was significantly increased from 13.4 ± 3.6 cmH₂O at baseline to 15.0 ± 3.4 cmH₂O, according to the very low tidal volume ventilation strategy. As a result, the driving pressure was reduced from 13.0 ± 4.8 to 7.9 ± 3.2 cmH₂O (*p* < 0.05). Mean PaCO₂ increased from 43 ± 8 to 53 ± 9 mmHg and mean pH decreased from 7.39 ± 0.1 to 7.32 ± 0.10 from baseline to 4 ml/kg VT, while RR was not modified. The mean CO₂-removal rate was 51 ± 26 ml/min with 421 ± 40 ml/min blood flow and sweep-gas flow set at 10 ± 0.3 L/min. Importantly, VT and driving pressure reductions with ECCO₂R were not accompanied by significant changes of PaO₂/FiO₂, respiratory-system compliance, and hemodynamic status (Table 2). In the 24 h following ECCO₂R initiation, nitric oxide was applied to four patients, of whom two also received prone positioning. No patients required ECMO for worsening hypoxemia while receiving very low tidal volume ventilation.

Operational characteristics of the ECCO₂R device recorded in the hour following therapy initiation, including access, return, and filter pressures, are presented in Table 3. Overall mean duration of ECCO₂R was 31 ± 21 h. It was continued up to 41 ± 24 h until weaning because of improved respiratory condition for 10 patients

Table 1 Baseline characteristics of the 20 patients

Characteristic	Value
Sex (male/female)	11/9
Age (years)	60 ± 12
Body mass index (kg/m ²)	30 ± 7
Medical/surgical	14/6
SAPS II	56 ± 21
SOFA score at ECCO ₂ R insertion	9.3 ± 4.3
Pulmonary ARDS risk factor	
Community-acquired pneumonia	5 (25)
Nosocomial pneumonia	6 (30)
Inhalation pneumonia	5 (25)
Nonpulmonary ARDS risk factor	
Pancreatitis	2 (10)
Other	2 (10)
Pre-ECCO ₂ R adjuvant therapy	
Neuromuscular blockade	16 (80)
Prone positioning	8 (40)
Nitric oxide	9 (45)
Recruitment maneuvers	0 (0)
ECMO	0 (0)
Time from intubation to ECCO ₂ R initiation (days)	4 (2–7)
Outcome	
Mechanical ventilation duration (days)	13 (9–38)
ICU length of stay (days)	18 (14–41)
Day-28 mortality	3 (15)

Data presented as n (%), mean ± standard deviation, or median (25–75% interquartile range)

ARDS acute respiratory distress syndrome, ECCO₂R extracorporeal carbon-dioxide removal, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, SAPS Simplified Acute Physiology Score, SOFA Sequential Organ-Failure Assessment

and was stopped early because of ECCO₂R-membrane clotting for 10 patients after 20 ± 10 h. The mean daily heparin dose was 19,900 ± 7710 IU/24 h and the mean aPTT_r was 1.8 ± 0.6. No cannulation-related complication occurred. One patient suffered a nonfatal cardiac arrest while on ECCO₂R but this was unrelated to the device. Other AEs included two mild hemoptyses that resolved rapidly without embolization and were not related to heparin overdose. The overall day-28 mortality was 15%.

Discussion

The results of this multicenter pilot study showed that a low-flow ECCO₂R device managed by the RRT platform easily and safely enabled very low tidal volume ventilation with highly significant decreases of P_{plat} and driving pressure in patients with mild-to-moderate ARDS.

Total energy determinants (i.e., mechanical power) are transmitted to the lung by the ventilator-generated volume, pressure, flow, and RR [21]. Decreasing MV intensity and, thereby limiting VILI, requires a diminution of the total mechanical power transferred to the lung [21]. More than 15 years ago, it was demonstrated that volume-limited ventilation with 6 ml/kg PBW significantly lowered ARDS-associated mortality [3]. However, recent data suggested that some ARDS patients are exposed to hyperinflation and overdistension, despite protective ventilation with 6 ml/kg VT and P_{plat} limited to < 30 cmH₂O. Pertinently, Hager et al. [5] demonstrated that lower P_{plat} was associated with less mortality and that no safe low P_{plat} threshold could be identified in patients with acute lung injury/ARDS. Furthermore, based on a prospective series of 485 consecutive patients with acute lung injury on MV, Needham et al. [22] showed that, compared with a mean VT < 6.5 ml/kg PBW, the adjusted hazard ratios for 2-year mortality for a mean VT of 6.5–8.5 ml/kg PBW was 1.59 (95% CI 1.19–2.14; *p* = 0.001). Amato et al. [6] recently reported that, in addition to VT, P_{plat}, and PEEP, normalizing VT to respiratory-system compliance (C_{rs}) and using a ratio as an index indicating the “functional” size of the lung might provide a better predictor of ARDS patients’ outcomes than VT alone. That ratio, termed the driving pressure ($\Delta P = VT / C_{rs}$), can be routinely calculated as the P_{plat} – PEEP for patients who are not making inspiratory efforts. Their analyses indicated that VT reductions or PEEP increases driven by random treatment-group assignment were beneficial only when associated with ΔP decreases and that no other ventilation variable had such a mediating effect on mortality [6]. More recently, lower ΔP was also associated with lower ARDS-patient mortality in the large LUNG-SAFE cohort [23].

Furthermore, reducing VT to 4 ml/kg PBW in patients already receiving protective ventilation was associated with less inflammatory and morphological signs of VILI in ARDS patients [11]. This particular study used ECCO₂R to mitigate the respiratory acidosis, and its potent deleterious effects [7, 8, 24], which developed in all patients receiving VT < 6 ml/kg IBW [10, 11]. Results based on previous case series using various ECCO₂R devices showed the feasibility of this strategy in ARDS patients, although AEs (e.g., cannulation-related accidents, limb ischemia, hemorrhage, hemolysis, infections, pump malfunction, membrane clotting, and catheter displacement) were reported [10, 11, 25–28].

Our results demonstrated that this strategy might be safely, efficiently, and easily applied to ARDS patients in most ICUs worldwide, because it did not require specific or large venous accesses and the RRT platform we used is widely available with minimal modification of existing devices and a simple software update. ECCO₂R with this RRT platform has indeed obtained promising results in animals [14]. By decreasing VT to 4 ml/kg PBW and

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

Parameter	Baseline (n = 20)	VT 5 ml/kg (n = 20)	VT 4.5 ml/kg (n = 20)	VT 4 ml/kg (n = 19) ^a
Ventilation variable				
VT (ml/kg PBW) ^b	6.10 ± 0.30	5.04 ± 0.22 ^c	4.49 ± 0.12 ^c	3.98 ± 0.18 ^c
RR (breaths/min)	26 ± 4	26 ± 4	26 ± 4	25 ± 6
PEEP (cmH ₂ O) ^b	13.4 ± 3.6	13.4 ± 3.3	14.4 ± 3.3 ^v	15.0 ± 3.4
P _{plat} (cmH ₂ O) ^b	26.3 ± 3.5	24.1 ± 3.0 ^c	23.3 ± 2.8 ^c	22.8 ± 2.6 ^c
Driving pressure (cmH ₂ O) ^b	13.0 ± 4.8	10.7 ± 3.8 ^v	8.9 ± 3.3 ^v	7.9 ± 3.2 ^c
Compliance (ml/cmH ₂ O)	33.8 ± 14.2	33.6 ± 12.7	36.0 ± 13.3	36.9 ± 13.4
PaO ₂ /FiO ₂	188 ± 75	192 ± 80	191 ± 71	184 ± 67
Blood gases				
pH ^b	7.39 ± 0.1	7.36 ± 0.10	7.34 ± 0.10 ^c	7.32 ± 0.10 ^c
PaO ₂ (mmHg)	96 ± 36	93 ± 30	96 ± 24	89 ± 19
PaCO ₂ (mmHg) ^b	43 ± 8	46 ± 7	49 ± 9 ^c	53 ± 9 ^c
HCO ₃ (mmol/L)	26 ± 4	26 ± 4	27 ± 5	27 ± 4
Lactate (mmol/L)	1.4 ± 0.6	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.4
Patients on ECCO ₂ R, n ^d	–	7	14	19
Patients with PaCO ₂ > 50 mmHg	2	9	9	11
ECCO ₂ R				
Blood flow (ml/min)	–	424 ± 39	425 ± 38	421 ± 40
Sweep-gas flow (L/min)	–	10 ± 0.3	10 ± 0.3	10 ± 0.3
CO ₂ removal (ml/min)	–	–	–	51 ± 26
Hemodynamic				
Mean arterial pressure (mmHg)	76 ± 11	79 ± 20	76 ± 12	77 ± 19
Heart rate (beats/min)	86 ± 15	85 ± 13	85 ± 14	83 ± 15
Patients on norepinephrine	9	9	9	10
Norepinephrine dose (μg/kg/min)	0.61 ± 1.10	0.55 ± 1.00	0.55 ± 0.99	0.50 ± 0.97

Values presented as mean ± standard deviation or n (%)

ECCO₂R extracorporeal carbon-dioxide removal, FiO₂ fraction of inspired oxygen, HCO₃ bicarbonate, PaCO₂ partial alveolar carbon dioxide pressure, PaO₂ partial alveolar oxygen pressure, PBW predicted body weight, PEEP end-expiratory positive pressure, P_{plat} plateau pressure, RR respiratory rate, VT tidal volume

^aOne patient's PaCO₂ increased > 20% at the VT 4.5 ml/kg step and did not undergo further VT reduction

^bp < 0.05, analysis of variance

^cp < 0.05 vs baseline

^dECCO₂R initiated according to the study protocol when patients had a 20% increase in PaCO₂ from baseline following VT decrease

adjusting PEEP to a lower P_{plat} target of 23–25 cmH₂O, we were able to drastically decrease the driving pressure to < 8 cmH₂O, which might mean less VILI and ultimately fewer deaths [6]. Importantly, we did not observe worsening oxygenation that might have indicated lung derecruitment following the mean airway-pressure decrease [28, 29], although some patients with the most severe forms of ARDS continued to receive nitric oxide or prone positioning following ECCO₂R initiation. The PEEP increase resulting from the ventilator strategy used might have counterbalanced that potential hazard [11, 13, 28, 30]. The absence of worsening oxygenation also argues against alveoli nitrogen washout and potential absorption atelectasis, which is less likely to occur in low-flow ECCO₂R than during high-flow VV-ECMO.

Several limitations of our work should be addressed. First, because our population was small, this study should only be considered “a proof-of-concept” demonstrating the feasibility and safety of the strategy tested. We cannot rule out that there is still a substantial risk of adverse events that could have been missed in this small study. Second, our population included only patients with mild or moderate ARDS. Because severe ARDS patients might experience greater PaCO₂ increases and more severe hypoxemia after VT reduction, the PrismaLung® performance remains unknown in this context. Third, to achieve VT reduction down to 4 ml/kg in a larger population of patients without the risks of inducing major PaCO₂ increases not compensated by the low-flow ECCO₂R device, we also applied the modified EXPRESS strategy to patients with mild ARDS. Because of higher PEEP settings in this population of

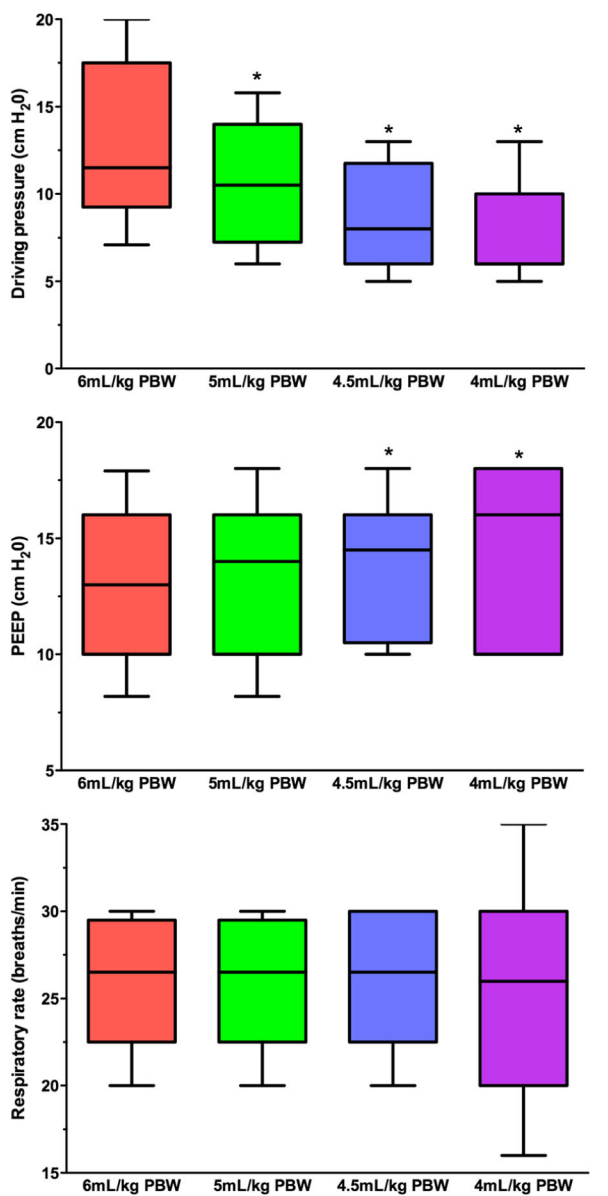


Fig. 1 Evolution of driving pressure, PEEP, and respiratory rate when tidal volume reduced on ECCO₂R. Horizontal lines, median; lower and upper box limits, 25th–75th percentiles; T-bars, 10th–90th percentiles. **p* < 0.05 vs 6 ml/kg tidal volume step. PBW predicted body weight, PEEP positive end-expiratory pressure

patients with higher compliance, it should be acknowledged that this approach may induce overdistension despite lowering the driving pressure. In addition, potential benefits of a very low tidal volume ventilation strategy have only been suggested in moderate-to-severe ARDS patients until now [10, 11]. Fourth, we did not evaluate lung morphological and inflammatory markers or the long-term clinical efficacy of the device. Fifth, due to its smaller membrane oxygenator surface, the CO₂-removal rate of the PrismaLung® was lower than those reported in other studies using similar blood flows [17, 28], explaining the gradual increase in

Table 3 Operational characteristics of extracorporeal carbon-dioxide removal for the 20 patients with acute respiratory distress syndrome

Characteristic	Value
Blood flow (ml/min) ^a	421 ± 42
Time of utilization (h)	30.6 ± 21.0
Access pressure (mmHg) ^a	-145 ± 14
Filter pressure (mmHg) ^a	301 ± 19
Return pressure (mmHg) ^a	154 ± 21
Heparin bolus at insertion (IU)	3100 ± 1330
Heparin (IU/kg/24 h)	230 ± 78
Activated partial thromboplastin time ratio	1.8 ± 0.6
Serious adverse event ^b	
Nonfatal cardiac arrest	1 (5)
Study-related adverse event	
Mild hemoptysis resolved with stopping anticoagulation ^c	2 (10)
Membrane clotting	10 (50)
Time it occurred (h)	20.0 ± 9.7

Values presented as mean ± standard deviation or *n* (%)

^aRecorded in the hour following initiation of extracorporeal carbon-dioxide removal

^bNot device related

^cResolved without embolization and not related to heparin overdose

PaCO₂ observed during the VT reduction phase. This mild respiratory acidosis might have been corrected by increasing the RR, at the expense of an increase in mechanical power. Indeed, the physicians treating these patients decided to tolerate this mild acidosis, as recent data also suggest an increased RR might be associated with a poorer ARDS prognosis [31]. Lastly, despite our heparin-infusion protocol that also included a bolus at catheter insertion, 50% of the treated patients experienced membrane clotting before the end of the experimental protocol, as reported previously for other case series given low-flow ECCO₂R [11, 15]. This technical downside deserves further investigations as it could limit the efficacy and impact the cost-benefit ratio of the device. The development of regional circuit anticoagulation strategies, with blood flows up to 500 ml/min, might enhance ECCO₂R membrane duration, as was the case for RRT hemofilters [32].

Conclusions

In summary, our pilot study findings demonstrated that a low-flow ECCO₂R device managed by an RRT platform enabled very low tidal volume ventilation with moderate increase in PaCO₂ in patients with mild-to-moderate ARDS. This less-invasive ECCO₂R technique was easily and safely implemented. However, before this technique can be widely disseminated, more data are needed to demonstrate the clinical benefit of VT, P_{plab}, and driving pressure reductions rendered possible by ECCO₂R [33]. The ongoing international randomized clinical trials SUPER

NOVA (ClinicalTrials.gov identifier: NCT02282657) and REST (Clinical-Trials.gov identifier: NCT02654327) focused on moderate ARDS will help clarify this potential.

Abbreviations

AE: Adverse event; ANOVA: One-way analysis of variance; aPTT: Activated partial thromboplastin time ratio; ARDS: Acute respiratory distress syndrome; C_{rs} : Respiratory-system compliance; ECCO₂R: Extracorporeal carbon-dioxide removal; ECMO: Extracorporeal membrane oxygenation; FiO_2 : Fraction of inspired oxygen; MV: Mechanical ventilation; PaO_2 : Partial alveolar oxygen pressure; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; P_{plat} : Plateau pressure; RR: Respiratory rate; RRT: Renal replacement therapy; SAE: Severe adverse event; VILI: Ventilator-induced lung injury; VT: Tidal volume

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Gambro-Baxter provided devices and CO₂-removal kits, and financial support to conduct this study.

Availability of data and materials

Please contact author for data requests.

Authors' contributions

MS and AC contributed to the conception of the study, data collection, data analysis and interpretation, and drafted the manuscript. SJ, EZ, TG, and GC contributed to data collection and interpretation, and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Comité de Protection des Personnes Ile-de-France 6, Paris, France (no. 15.1026). The clinical trial protocol was registered with www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02606240, 17 November 2015). Informed consent was obtained from all patients or their surrogates.

Competing interests

MS has received lecture fees from Maquet. SJ has received lecture fees from Drager, Fisher-Paykel, and Xenios. EZ has received consultant fees from Gambro. TG has received lecture fees and travel reimbursements for meetings from Gambro-Baxter and General Electric. GC has received lecture fees from Alung and Baxter. AC has received lecture fees from Baxter and Maquet. AC is the primary investigator of the EOLIA trial (ClinicalTrials.gov identifier: NCT01470703), partly supported by Maquet.

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References

1. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med.* 1998;157(1):294–323.
2. Frank JA, Parsons PE, Matthay MA. Pathogenetic significance of biological markers of ventilator-associated lung injury in experimental and clinical studies. *Chest.* 2006;130(6):1906–14.
3. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301–8.
4. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Herrmann P, Mascia L, Quintel M, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2007;175(2):160–6.
5. Hager DN, Krishnan JA, Hayden DL, Brower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med.* 2005;172(10):1241–5.
6. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med.* 2015;372(8):747–55.
7. Curley G, Contreras MM, Nichol AD, Higgins BD, Laffey JG. Hypercapnia and acidosis in sepsis: a double-edged sword? *Anesthesiology.* 2010;112(2):462–72.
8. Vadasz I, Hubmayr RD, Nin N, Sporn PH, Sznajder JI. Hypercapnia: a nonpermissive environment for the lung. *Am J Respir Cell Mol Biol.* 2012;46(4):417–21.
9. Feihl F, Eckert P, Brimiouille S, Jacobs O, Schaller MD, Melot C, Naeije R. Permissive hypercapnia impairs pulmonary gas exchange in the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2000;162(1):209–15.
10. Bein T, Weber-Carstens S, Goldmann A, Muller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO₂ removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med.* 2013;39(5):847–56.
11. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology.* 2009;111(4):826–35.
12. Combes A, Pesenti A, Ranieri VM. Fifty years of research in ARDS. Is extracorporeal circulation the future of acute respiratory distress syndrome management? *Am J Respir Crit Care Med.* 2017;195(9):1161–70.
13. Schmidt M, Hodgson C, Combes A. Extracorporeal gas exchange for acute respiratory failure in adult patients: a systematic review. *Crit Care.* 2015;19:99.
14. Godet T, Combes A, Zogheib E, Jabaudon M, Futier E, Slutsky AS, Constantin JM. Novel CO₂ removal device driven by a renal-replacement system without hemofilter. A first step experimental validation. *Anaesth Crit Care Pain Med.* 2015;34(3):135–40.
15. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, Dell'Amore A, Urbino R, Mascia L, Evangelista A, et al. Extracorporeal CO₂ removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med.* 2015;43(1):120–7.
16. Peperstraete H, Eloit S, Depuydt P, De Somer F, Roosens C, Hoste E. Low flow extracorporeal CO₂ removal in ARDS patients: a prospective short-term crossover pilot study. *BMC Anesthesiol.* 2017;17(1):155.
17. Allardet-Servent J, Castanier M, Signouret T, Soundaravelou R, Lepidi A, Seghboyan JM. Safety and efficacy of combined extracorporeal CO₂ removal and renal replacement therapy in patients with acute respiratory distress syndrome and acute kidney injury: The Pulmonary and Renal Support in Acute Respiratory Distress Syndrome Study. *Crit Care Med.* 2015; 43(12):2570–81.
18. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med.* 2012;38(10):1573–82.
19. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszowska A, et al. Positive end-expiratory pressure setting

in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299(6):646–55.

20. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196(7):822–33.
21. Gattinoni L, Tonetti T, Cressoni M, Cadringer P, Herrmann P, Moerer O, Protti A, Gotti M, Chiruzzi C, Carlesso E, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*. 2016;42(10):1567–75.
22. Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Dennison Himmelfarb CR, Desai SV, Shanholtz C, Brower RG, Pronovost PJ. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ*. 2012;344:e2124.
23. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788–800.
24. Nin N, Muriel A, Penuelas O, Brochard L, Lorente JA, Ferguson ND, Raymonds K, Rios F, Violi DA, Thille AW, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med*. 2017;43(2):200–8.
25. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, Butz B, Birnbaum D, Taeger K, Schlitt HJ. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med*. 2006;34(5):1372–7.
26. Braune S, Sieweke A, Brettner F, Staudinger T, Joannidis M, Verbrugge S, Frings D, Nierhaus A, Wegscheider K, Kluge S. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med*. 2016;42(9):1437–44.
27. Burki NK, Mani RK, Herth FJF, Schmidt W, Teschler H, Bonin F, Becker H, Randerath WJ, Stieglitz S, Hagemeyer L, et al. A novel extracorporeal CO₂ removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest*. 2013;143(3):678–86.
28. Fanelli V, Ranieri MV, Mancebo J, Moerer O, Quintel M, Morley S, Moran I, Parrilla F, Costamagna A, Gaudiosi M, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care*. 2016;20:36.
29. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Extracorporeal carbon dioxide removal (ECCO₂R) in patients with acute respiratory failure. *Intensive Care Med*. 2017;43(4):519–30.
30. Serpa Neto A, Schmidt M, Azevedo LC, Bein T, Brochard L, Beutel G, Combes A, Costa EL, Hodgson C, Lindskov C, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: Mechanical ventilation during ECMO. *Intensive Care Med*. 2016;42(11):1672–84.
31. Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, Brochard L, Clarkson K, Esteban A, Gattinoni L, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med*. 2016;42(12):1865–76.
32. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. *Crit Care*. 2016;20(1):144.
33. Combes A, Pesenti A, Brodie D. Do we need randomized clinical trials in extracorporeal respiratory support? Yes. *Intensive Care Med*. 2017;43:1862–65.