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Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

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Abstract

Purpose: We assessed feasibility and safety of extracorporeal carbon dioxide removal ($ECCO_2R$) to facilitate ultra-protective ventilation (V_T 4 mL/kg and $P_{PLAT} \leq 25$ cmH_2O) in patients with moderate acute respiratory distress syndrome (ARDS).

Methods: Prospective multicenter international phase 2 study. Primary endpoint was the proportion of patients achieving ultra-protective ventilation with $PaCO_2$ not increasing more than 20% from baseline, and arterial pH > 7.30. Severe adverse events (SAE) and $ECCO_2R$-related adverse events ($ECCO_2R$-AE) were reported to an independent data and safety monitoring board. We used lower CO_2 extraction and higher CO_2 extraction devices (membrane lung cross-sectional area 0.59 vs. 1.30 m^2; flow 300–500 mL/min vs. 800–1000 mL/min, respectively).

Results: Ninety-five patients were enrolled. The proportion of patients who achieved ultra-protective settings by 8 h and 24 h was 78% (74 out of 95 patients; 95% confidence interval 68–89%) and 82% (78 out of 95 patients; 95% confidence interval 76–88%), respectively. $ECCO_2R$ was maintained for 5 [3–8] days. Six SAEs were reported; two of them were attributed to $ECCO_2R$ (brain hemorrhage and pneumothorax). $ECCO_2R$-AEs were reported in 39% of the patients. A total of 69 patients (73%) were alive at day 28. Fifty-nine patients (62%) were alive at hospital discharge.

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Conclusions: Use of $ECCO_2R$ to facilitate ultra-protective ventilation was feasible. A randomized clinical trial is required to assess the overall benefits and harms.

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Keywords: Acute respiratory distress syndrome, Mechanical ventilation, Extracorporeal carbon dioxide removal, Ventilator-induced lung injury

Introduction

Mechanical ventilation may cause a form of injury (ventilator-induced lung injury, VILI) that is clinically indistinguishable from the acute respiratory distress syndrome (ARDS) [1, 2]. The ARDSNet investigators demonstrated that limiting tidal volume (V_T) to 6 mL/kg of predicted body weight (PBW) and end-inspiratory plateau pressure (P_{PLAT}) to ≤ 30 cmH_2O improves survival [3], but in some patients these settings may not be fully protective [4, 5]. Reduction of V_T to 3–4 mL/kg and $P_{PLAT} \leq 25$ cmH_2O has been proposed to further minimize the risk of VILI [6], but this entails a significant risk of severe respiratory acidosis [7].

Extracorporeal carbon dioxide removal ($ECCO_2R$) can minimize this acidosis by clearing carbon dioxide (CO_2). In this way, less CO_2 has to be eliminated from the lungs enabling strategies that are more lung protective than the ARDSNet strategy. Such strategies might improve outcomes by (a) using V_T as low as 3–4 mL/kg and further decreasing P_{PLAT} below 30 cmH_2O (often termed ultra-protective strategy [6, 8–11], (b) decreasing respiratory rates [12], and/or (c) minimizing driving pressures [13] or mechanical power [14].

Several $ECCO_2R$ devices have recently been made available utilizing blood flow rates ranging from about 450 mL/min to 1000 mL/min, but there is a lack of data demonstrating how effective these devices would be in eliminating CO_2 and hence supporting any of these lung protective strategies [15]. We therefore performed a multicenter, international study in patients with moderate ARDS to determine the feasibility and safety of $ECCO_2R$ to inform the design of a future randomized clinical trial. The primary endpoint was the number of patients who successfully achieved a V_T of 4 mL/kg PBW with $PaCO_2$ not increasing more than 20% from baseline with a value of arterial pH > 7.30. Secondary endpoints included (a) assessment of physiological variables during ultra-protective strategy and (b) frequency of adverse events.

Methods

The study was approved by institutional review boards at each of the 23 study sites. Informed consent was obtained from patients or legally authorized surrogates. Patients with moderate ARDS (PaO_2/FiO_2 100–200 mmHg, with PEEP ≥ 5 cmH_2O) [16], > 18 years old, and expected to receive invasive mechanical ventilation for > 24 h were included. Exclusion criteria were decompensated heart insufficiency or acute coronary syndrome; severe chronic obstructive pulmonary disease; major respiratory acidosis with $PaCO_2 > 60$ mmHg; acute brain injury; severe liver insufficiency (Child–Pugh scores > 7) or fulminant hepatic failure; heparin-induced thrombocytopenia; contraindication for systemic anticoagulation; platelet < 50 G/L; patient moribund, decision to limit therapeutic interventions; catheter access to femoral vein or jugular vein impossible; pneumothorax; refused consent; inclusion in other trials (ClinicalTrials.Gov Identifier NCT02282657). Study protocol is available online.

Take-home message

Use of $ECCO_2R$ to facilitate ultra-protective ventilation is feasible. A randomized clinical trial is required to assess the overall benefit and harm

We used the Hemolung Respiratory Assist System (ALung Technologies, Pittsburgh, USA), the iLA activve (Novalung, Heilbronn, Germany) and the Cardiohelp® HLS 5.0 (Getinge Cardiopulmonary Care, Rastatt, Germany) devices. The first device employs a membrane lung with a cross-sectional area of 0.59 m^2 and is run at an extracorporeal blood flow between 300 and 500 mL/min (lower extraction). The other two devices employ membrane lungs of 1.30 m^2 and blood flows to 800–1000 mL/min[1] (higher extraction). Each center was assigned one device for the purposes of the trial on the basis of that center's previous experience with the specific devices.

After enrollment, sedation and neuromuscular blockade were administered for a minimum of 24 h. V_T was set at 6 mL/kg PBW and positive end-expiratory pressure (PEEP) was adjusted to obtain a P_{PLAT} between 28 and 30 cmH_2O [17]. Percutaneous vascular access was provided using a double lumen catheter inserted in the internal jugular vein or in the femoral vein. Sweep gas flow was set to zero (baseline). Continuous infusion of

[1] Blood flow with the iLA activve (Novalung) and Cardiohelp® HLS 5.0 (Getinge) can range between 0.5 and 4.5 L/min, but was limited by study protocol to 800–1000 mL/min.

unfractionated heparin was used to maintain values of activated partial thromboplastin time (aPTT) in the range 35–80 s.[2]

V_T was reduced to 4 mL/kg PBW in three steps (from 6.0 to 5.0, from 5.0 to 4.5, and from 4.5 to 4 mL/kg PBW). At each step, PEEP was titrated to a target P_{PLAT} of 23–25 cmH_2O [6, 8–11]. Sweep gas and blood flow were set to maintain a partial pressure of arterial CO_2 ($PaCO_2$) between 80% and 120% of the baseline value. If $PaCO_2$ exceeded 75 mmHg and/or pH was < 7.30 despite optimal $ECCO_2R$ settings and a respiratory rate of 35 breaths/min, V_T was increased to the last previously tolerated value.

$ECCO_2R$ and ultra-protective ventilation were continued, and data collected (baseline, 8 h, and 24 h). After completing the study protocol, the attending physician determined the ventilatory strategy and use of $ECCO_2R$, and $ECCO_2R$ settings as well as physiological variables were recorded until $ECCO_2R$ discontinuation. Patients were monitored for adverse events until hospital discharge or day 28 after enrollment, whichever came first.

The primary outcome was the number of patients who successfully achieved a V_T of 4 mL/kg PBW with $PaCO_2$ not increasing more than 20% from baseline with a value of arterial pH > 7.30.[3] Duration of $ECCO_2R$ was recorded.

Secondary endpoints included (a) assessment of physiological variables and $ECCO_2R$ settings and (b) frequency of adverse events.

Severe adverse events (SAE) in the trial were defined as (1) any fatal or immediately life-threatening event, permanently disabling, severely incapacitating, or requiring prolonged hospitalization, or any event jeopardizing the patient and requiring medical or surgical intervention and that the attending physician perceived might be directly related to $ECCO_2R$; (2) any clinically important untoward medical occurrence that was different from what is expected in the clinical course of ARDS. Investigators reported severe adverse events to the clinical coordinator. An independent data and safety monitoring board (DSMB) received a detailed written report and evaluated whether the SAE was attributable to $ECCO_2R$. SAE 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. SAE were not study related if they were thought to be primarily related to the underlying disease or to ARDS and its sequelae.

Other adverse events not fulfilling the above definition were recorded as $ECCO_2R$-related adverse events ($ECCO_2R$-AE) and classified as previously described [6, 8–11] as mechanical or clinical. Definitions of $ECCO_2R$-AE are provided in the online supplement.

Length of invasive mechanical ventilation, survival at day 28, and survival at hospital discharge were also recorded.

Power and data analysis

On the basis of previous data [6, 8–11] we predicted that (a) $PaCO_2$ with 6 mL/kg would be 40–60 mmHg; (b) the reduction of V_T to 4 mmHg would increase $PaCO_2$ to 65–85 mmHg. To demonstrate the ability of $ECCO_2R$ to re-establish $PaCO_2$ values close to the ones observed with a V_T of 6 mL/kg (± 20%) we estimated that a sample size of 90 patients would detect a proportion of patients who successfully achieved this condition with a two-sided 95% confidence interval of 70–90% when incidence is 80% and 54–75% when incidence is 65%. In both estimates, the width of confidence interval is 0.211. For calculation of two-sided confidence intervals for the single proportion, we used the Clopper–Pearson method. To take into consideration a possible 3% of dropout due to $ECCO_2R$ malfunction the sample size was increased to 100 patients.

To ensure quality control, (a) data were collected and checked for consistency before the analysis was finalized; (b) queries to confirm or correct outlier values were directly sent to local investigators; (c) analyses were performed by a researcher (TP) who did not participate in data collection and was not a member of the study steering committee.

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range [IQR]) and categorical variables as count and proportion. Comparisons of proportions were made using Chi-square or Fisher exact tests, as appropriate. Data at different times during $ECCO_2R$ were compared by analysis of variance (ANOVA) for repeated measures. If significant ($P \leq 0.05$), values obtained after 8 h and 24 h of $ECCO_2R$ were compared with those obtained at baseline by using paired Student t test adjusting P value using Bonferroni correction for multiple comparisons.

[2] The study protocol (see online supplement) originally said: "aPTT ratio is maintained at 1.5–2.0 × baseline". However, the case report form did not ask for aPTT ratio but for absolute aPTT values (see online supplement). This inconsistency was communicated to investigators at the beginning of the study and readers at the moment of publication. For the sake of transparency, we left unchanged study protocol and statement on ClinicalTrials.Gov.

[3] On ClinicalTrials.Gov (NCT02282657) and in the study protocol (see online supplement) the primary endpoint is formalized as: "achievement of V_T reduction to 4 mL/kg while maintaining pH and $PaCO_2$ to ± 20% of baseline values obtained at V_T of 6 mL/kg". This formulation contains an obvious error that is the phrase "maintaining pH to ± 20% of baseline values". Such variability of pH in fact does not make sense, allowing pH values ranging between 5.92 and 8.88. To avoid confusion and bias we (a) clarified the issue on the protocol with investigators at the beginning of the study; (b) left unchanged the statement on ClinicalTrials.Gov informing the readers about the mistake at the moment of publication.

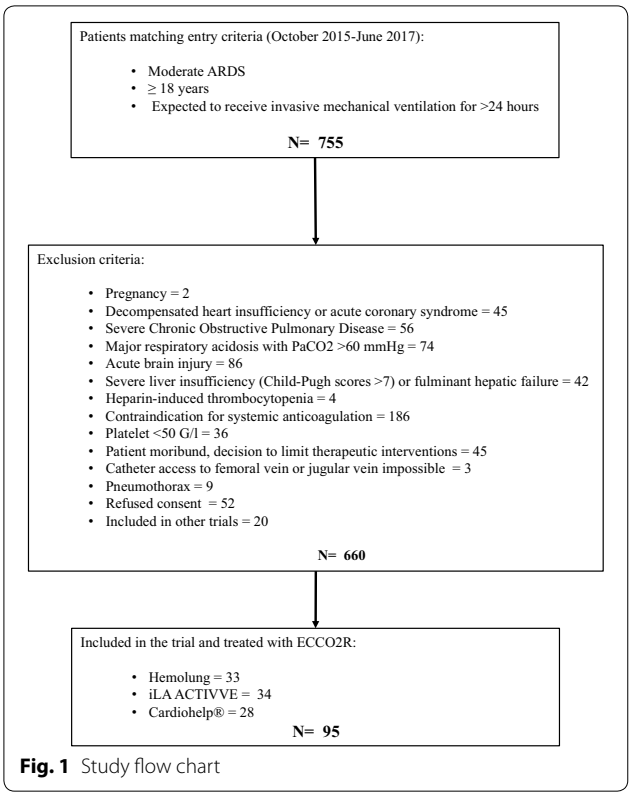

Fig. 1 Study flow chart

No assumptions were made for missing data. Statistical analyses were performed using R (version 3.5.1). All p values were two-sided and values < 0.05 were deemed significant. The statistical analysis plan is available online.

Results

Of the 483 patients matching entry criteria, 95 patients were enrolled between October 2015 and June 2017 at 23 centers in Europe and Canada. Thirty-three patients were treated with the Hemolung device at five sites. Ten sites used the iLA activve device and treated 34 patients; eight sites used the Cardiohelp® HLS 5.0 device and treated 28 patients (Fig. 1). The centers enrolled a median of 3 [1–5] patients. Baseline characteristics and concomitant treatments at inclusion are shown in Table 1. No patient was lost to follow-up.

The proportion of patients who achieved ultra-protective settings by 8 h and 24 h was 78% (confidence interval 68–89%) (74 out of 95) and 82% (confidence interval 76–88%) (78 out of 95), respectively. $ECCO_2R$ was maintained for 5 [3–8] days.

Cannulation was performed through the internal jugular vein in 57% and through the femoral vein in 43% of patients. Catheter size was 15.5 Fr in patients on the Hemolung device and 18 [18–20] Fr in patients on the iLA activve and Cardiohelp® HLS 5.0 devices ($p < 0.001$).

Table 1 Characteristics of patients at study inclusion

Age (years)	60.2 ± 14.0
Female (*n*, %)	31 (32.6%)
BMI (kg/m^2)	29.2 ± 8.79
SAPS II	45.9 ± 15.5
SOFA score	7.42 ± 3.22
Cause of ARDS (*n*, %)	
Pneumonia	78 (82.1%)
Non-pulmonary sepsis	3 (3.2%)
Pancreatitis	2 (2.1%)
Pulmonary contusion	2 (2.1%)
Other	10 (10.5%)
Ventilatory settings	
V_T (mL/kg)	6.0 ± 0.2
RR (breaths/min)	27.3 ± 4.8
V_E (L/min)	10.2 ± 2.3
PEEP (cmH_2O)	15.5 [10.0;16.0]
P_{PLAT} (breaths/min)	26.6 ± 3.0
ΔP (cmH_2O)	13.2 ± 4.3
$PaCO_2$ (mmHg)	47.8 ± 9.4
pH	7.34 ± 0.08
FiO_2	0.57 [0.50;0.70]
PaO_2 (mmHg)	101.2 ± 34.5
PaO_2/FiO_2	173 ± 61
Adjunctive treatments before inclusion (*n*, %)	
Muscle paralysis	80 (84.2%)
Prone position	23 (24.2%)
Pulmonary vasodilator	8 (8.42%)
Recruitment maneuvers	26 (27.4%)

Data are mean (standard deviation) or median [interquartile range]

BMI body mass index, *SAPS* simplified acute physiological score, *SOFA* sequential organ failure assessment, V_T tidal volume, *RR* respiratory rate, V_E minute ventilation, P_{PLAT} end-inspiratory plateau pressure, *PEEP* positive end-expiratory pressure, ΔP delta pressure ($\Delta P = P_{PLAT}$ minus PEEP), $PaCO_2$ partial pressure of arterial CO_2, PaO_2 arterial oxygen fraction, FiO_2 inspiratory oxygen fraction, PaO_2/FiO_2 ratio of arterial-to-inspiratory oxygen fraction

Operational characteristics of $ECCO_2R$ are shown in Table 2.

The time course of the respiratory variables in the first 24 h is reported in Fig. 2. V_T, respiratory rate, minute ventilation, P_{PLAT}, and ΔP were significantly lower at 8 h and 24 h compared to baseline ($p = 0.001$). Compared to baseline, $PaCO_2$ and PaO_2/FiO_2 ratio remained stable, while pH significantly increased at 8 h ($p < 0.05$) and 24 h ($p < 0.001$). Trend of respiratory variables until $ECCO_2R$ discontinuation was consistent with the one observed in the first 24 h (Table 1_online supplement).

Six SAE were reported (massive right frontal parenchymal hematoma, severe hematemesis and melena, superior vena cava thrombosis; sudden death, severe hypoxemia, pneumothorax at cannula insertion in the

Table 2 Operational characteristics of extracorporeal CO_2 removal

	Blood flow (mL/min)		Sweep gas flow (L/min)		Heparin (IU/kg/day)		Activated partial thromboplastin time	
	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)
8 h	440 [410;465]	970 [800;1000]*	10.0 [10.0;10.0]	6.00 [3.00;10.0]*	21,000 [18,000;27,950]	20,000 [14,000;26,400]	48.4 ± 18.5	55.0 ± 21.3
24 h	440 [430;480]	960 [800;1000]*	10.0 [10.0;10.0]	8.00 [5.00;10.0]*	20,000 [12,750;26,000]	20,160 [16,000;29,000]	49.1 ± 14.9	57.6 ± 21.6

Data are mean (standard deviation) or median [interquartile range]

*$p < 0.05$ lower vs. higher CO_2 extraction

Table 3 Numbers of patients experiencing $ECCO_2R$-related adverse events occurring between enrollment and day 28

$ECCO_2R$-related adverse events	Patients experiencing $ECCO_2R$-related adverse events, *n* (%)
Mechanical	
Membrane lung clotting	13 (14)
Leading to circuit change	6 (6)
Leading to $ECCO_2R$ discontinuation	7 (7)
Pump malfunction	3 (3)
Catheter displacement	2 (2)
Clinical	
Hemolysis	11 (12)
Bleeding	13 (14)
Related to cannula insertion	3 (3)
At cannula site	7 (7)
Significant	6 (6)
Infectious complications	2 (2)
Thrombocytopenia	12 (13)
Hypofibrinogenemia	2 (2)

$ECCO_2R$ extracorporeal carbon dioxide removal. *Hemolysis*: serum free hemoglobin ≥ 100 mg/L or hematocrit reduction not related to hemorrhage or other causes of blood loss, jaundice, hemoglobinuria, impaired renal function; *significant bleeding*: any bleeding event requiring administration of 1 unit of packed red cells; *thrombocytopenia*: platelet count below 50,000 per microliter; *hypofibrinogenemia*: fibrinogen < 1.5 g/L

internal jugular vein). Two SAEs (massive right frontal parenchymal hematoma and pneumothorax at cannula insertion in the internal jugular vein) were considered attributable to $ECCO_2R$. $ECCO_2R$-AE were reported in 37 patients (39%). Adverse events occurred in the first 24 h of $ECCO_2R$ in 26 patients (Table 3).

Duration of invasive mechanical ventilation was 17 [11–29] days. A total of 69 patients (73%) were alive at day 28. Fifty-nine patients (62%) were alive at hospital discharge. Ventilator-free days were 11 [0–17] days.

Discussion

This study shows that $ECCO_2R$ can be used to minimize respiratory acidosis while applying an ultra-protective ventilatory strategy in patients with moderate ARDS. However, the relatively high numbers of observed adverse events confirm the need for randomized clinical trial(s) to assess if benefits outweigh the risks.

A number of lung protective strategies such as decreasing P_{PLAT}, driving pressure, power, respiratory rate, or tidal volume have been suggested to decrease VILI. These approaches are often associated with hypercapnia and respiratory acidosis [18]. Although hypercapnia may be well tolerated [19], there are a number of important side effects [20, 21], and recent data suggest an association between values of $PaCO_2 > 50$ mmHg and increased mortality [22]. In the present study we tested the efficacy of $ECCO_2R$ to decrease tidal volume below 6 mL/kg because it is the variable most commonly associated with lung protective strategies, has a clear physiologic linkage to CO_2 removal, and has been studied in previous studies [6, 8, 9, 11].

Recent data have demonstrated that there is no safe upper limit for P_{PLAT} or ΔP [13, 23]. For example, the mortality rate in ARDS patients with ΔP values ≤ 14 cmH_2O is still as high as 20% [13, 23]. Patient outcomes may therefore be improved by aggressively lowering ventilatory variables such as V_T, P_{PLAT}, or ΔP as facilitated by $ECCO_2R$ devices that remove CO_2. In addition, $ECCO_2R$ might further decrease VILI by allowing lower respiratory rates, which have been shown to be lung protective [12], perhaps by decreasing mechanical power delivered to the lungs [14].

A few studies have examined the feasibility of ultra-protective ventilation facilitated by $ECCO_2R$. Two studies were single-center studies and included small numbers of patients [6, 10]. Other multicenter observational [8, 9] or randomized [11] studies treated patients with a single device. A survey of 239 French intensive care units found that 15% of the units used $ECCO_2R$ at least once (total

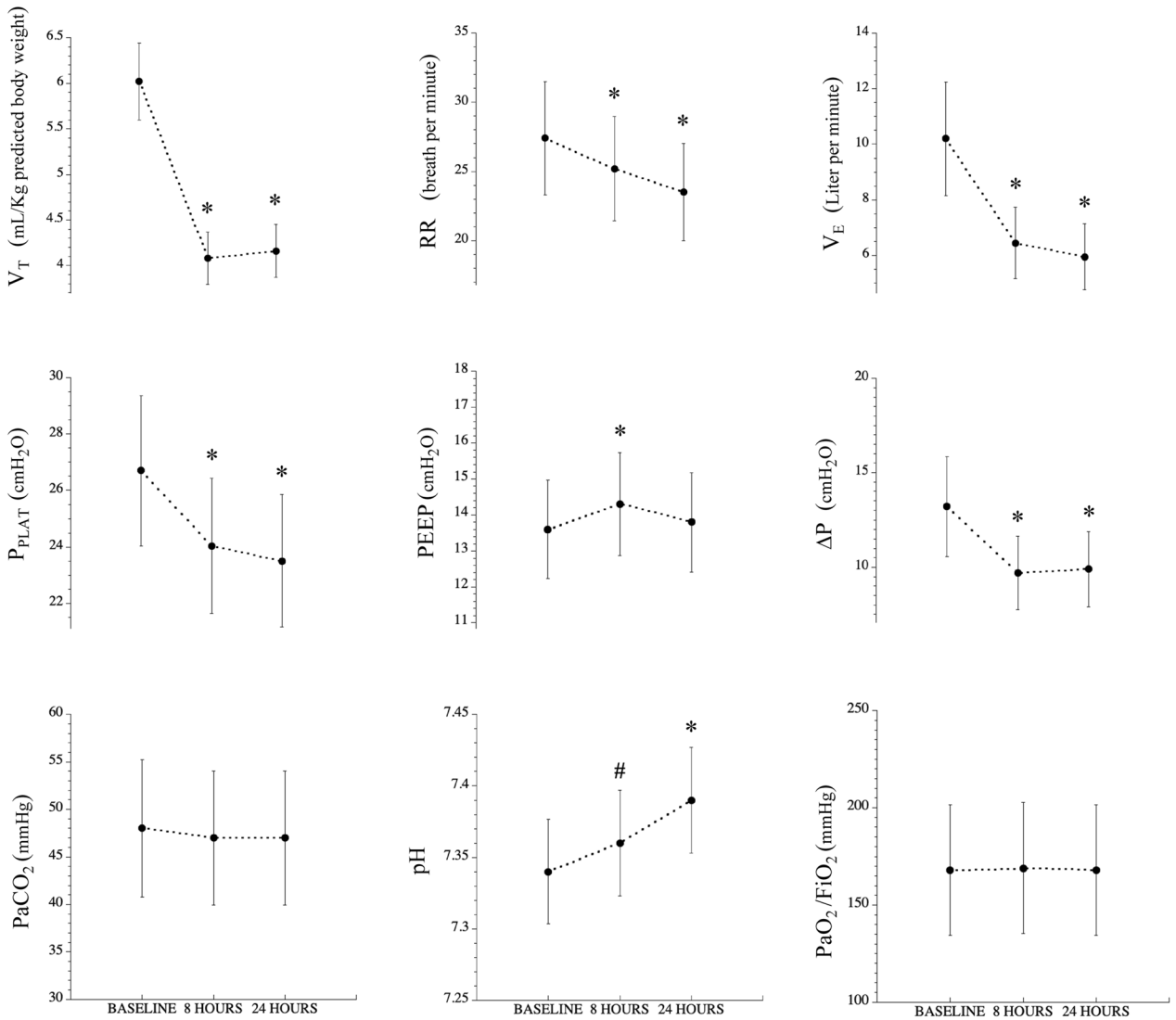

Fig. 2 Time course of respiratory variables. V_T tidal volume, RR respiratory rate, V_E minute ventilation, P_{PLAT} end-inspiratory plateau pressure, PEEP positive end-expiratory pressure, ΔP delta pressure ($\Delta P = P_{PLAT}$ minus PEEP), $PaCO_2$ partial pressure of arterial CO_2, PaO_2/FiO_2 ratio of arterial-to-inspiratory oxygen fraction. $^{\#}P < 0.05$ vs baseline. $^{*}P < 0.001$ vs baseline

of 303 patients) from January 2010 to January 2015, and that the most frequent indication was ultra-protective ventilation for ARDS (54%) [15].

A major strength of this study is the relatively large number of patients, from multiple centers in Europe and Canada. At the same time, the following major limitations of the study should be acknowledged: First, analysis of $ECCO_2R$ safety may be somewhat underpowered in that we only studied 95 patients. Second, although originally planned as secondary endpoints (see ClinicalTrials.Gov Identifier NCT02282657) we were not able to quantify clearance and total amount of CO_2 removed by $ECCO_2R$. Recent experimental data show that these measurements are essential to assess effectiveness of CO_2 removal capacity during $ECCO_2R$ [24]. Third, although sample size was inflated to take into consideration a possible 3% of dropout due to $ECCO_2R$ malfunction, we studied 95 out of the 100 patients planned as a result of lack of equipment during the final phase of the study period.

Assessment of safety in the context of a large international cohort of patients is of paramount importance for the clinical implementation of $ECCO_2R$ and to move to a phase III randomized clinical trial. Previous data on safety of $ECCO_2R$ to support ultra-protective ventilation are limited to three small case series all using lower

extraction devices. In a single-center study, Terragni and coworkers reported only adverse mechanical events that occurred in 8 out of the 10 patients [6]. Fanelli and coworkers in a four-center study that included 15 patients reported bleeding in 7 patients, hemolysis in 1 patient, and catheter kinking in 1 patient [8]. Schmidt and coworkers in a five-center study that included 20 patients reported bleeding in 2 patients and membrane-lung clotting in 10 patients [9]. A randomized clinical trial that included 79 patients from eight sites and that used a pumpless arterial-venous $ECCO_2R$ device showed that the number of units of red blood cells transfused was significantly higher in the $ECCO_2R$ group compared with control (3.7 ± 2.4 vs. $1.5 \pm 1.3\%$, $p < 0.05$) but the incidence of $ECCO_2R$-related adverse events was low (3 patients; 7.5%) [11].

$ECCO_2R$-AE were a priori defined and collected systematically. $ECCO_2R$-AE were observed in 39% of patients; 70% of these patients experienced adverse events in the first 24 h of $ECCO_2R$. Bleeding and hemolysis were the most common $ECCO_2R$-AEs. An independent DSMB adjudicated SAEs as attributable or not to $ECCO_2R$. Six SAEs were reported. The DSMB considered only two as attributable to $ECCO_2R$: a massive right frontal parenchymal hematoma, and a pneumothorax secondary to cannula insertion in the internal jugular vein. With respect to bleeding episodes, events requiring administration of at least 1 unit of packed red cells were reported in 6% of patients.

These data strongly support the need for a well-designed randomized clinical trial to confirm that the clinical benefits of an ultra-protective strategy supported by $ECCO_2R$ would compensate for the serious side effects associated with $ECCO_2R$. The REST trial (pRotective vEntilation with veno-venouS lung assisT in respiratory failure; NCT02654327) is currently ongoing and is randomly assigning adult patients with acute hypoxemic respiratory failure ($PaO_2/FiO_2 < 150$ mmHg) to either conventional lung protective ventilation or $ECCO_2R$ using a lower extraction device (Hemolung Respiratory Assist System; ALung Technologies, Pittsburgh, USA). Given the relatively high risk of adverse events, future trials might aim to enhance the ratio of benefit to risk by selecting patients likely to have the greatest clinically relevant physiological response, as suggested previously [25]. However, data of the present study outline the difficulties a prospective randomized clinical trial on $ECCO_2R$ may incur. First, only 12.6% of the patients admitted in the study period for moderate ARDS could be enrolled and treated with $ECCO_2R$. Second, contraindications for systemic anticoagulation and bleeding disorders (heparin-induced thrombocytopenia; platelet < 50 G/L) were observed in 30% of patients, thus limiting a wider use of $ECCO_2R$ in the clinical settings. Third, although we included study centers with substantial experience in $ECCO_2R$, only 3 [1–5] patients per site were enrolled during the 21-month study period. These data emphasize the importance of providing a learning curve for the use of $ECCO_2R$ to those centers that, although without specific experience, will have to be included in the study to allow the recruitment of a sufficiently large number of patients.

In conclusion, this study demonstrates that ultra-protective ventilation facilitated by $ECCO_2R$ is feasible, mitigating respiratory acidosis in patients with moderate ARDS. A randomized clinical trial is required to assess overall benefits and harms.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05567-4) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

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Ethical approval

The study was approved by institutional review boards at each of the 23 study sites.

Informed consent

Informed consent was obtained from patients or legally authorized surrogates.

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