Daily use of extracorporeal CO$_2$ removal in a critical care unit: indications and results

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Abstract

Background: While outcome improvement with extracorporeal CO$_2$ removal (ECCO$_2$R) is not demonstrated, a strong pathophysiological rational supports its use in the setting of acute respiratory distress syndrome (ARDS) and COPD exacerbation. We aimed to describe our single-center experience of ECCO$_2$R indications and outcome.

Methods: Patients treated with ECCO$_2$R in our medical ICU, from March 2014 to November 2017, were retrospectively enrolled. Primary end point was evolution of ventilator settings during the two first days following ECCO$_2$R start.

Results: Thirty-three patients received ECCO$_2$R. Seventeen were managed with Hemolung®, 10 with Prismalung®, 4 with ILA®, and 2 with Cardiohelp®. Indications for ECCO$_2$R were mild or moderate ARDS (n = 16), COPD exacerbation (n = 11), or uncontrolled hypercapnia due to other causes (n = 6). Four patients were not intubated at the time of ECCO$_2$R start. Median duration of ECCO$_2$R treatment was 7 days [5–10]. In ARDS patients, between baseline and day 2, median tidal volume and driving pressure decreased from 5.3 [4.4–5.9] mL/kg and 10 [8–15] to 3.8 [3.3–4.1] mL/kg and 9 [8–11], respectively. Prone positioning was performed in 10 of the 16 patients, without serious adverse event. In COPD patients, between baseline and day 2, median ventilation minute and PaCO$_2$ decreased significantly from respectively 7.6 [6.6–8.7] L/min and 9.4 [8.4–10.1] kPa to 5.8 [4.9–6.2] L/min and 6 [5.3–6.8] kPa. Four out of 11 COPD patients were extubated while on ECCO$_2$R. Device thrombosis occurred in 5 patients (15%). Hemolysis was documented in 16 patients (48%). One patient died of intracranial hemorrhage, while on ECCO$_2$R. Twenty-four patients were discharged from ICU alive. Twenty-eight day mortality was 31% in ARDS, 9% in COPD patients, and 50% in other causes of refractory hypercapnic respiratory failure.

Conclusion: ECCO$_2$R was useful to apply ultra-protective ventilation among ARDS patients and improved PaCO$_2$, pH, and minute ventilation in COPD patients.

Keywords: Extracorporeal CO$_2$ removal, Acute respiratory distress syndrome, Chronic obstructive pulmonary disease exacerbation

Background

There is not yet enough data to make strong recommendation about extracorporeal CO$_2$ removal (ECCO$_2$R) devices, as the benefits-risks ratio is not established. Because of its low flow, this technology is unable to provide adequate extracorporeal oxygenation. However, 350 to 500 mL/min is sufficient to remove half of CO$_2$ production, making ECCO$_2$R an interesting tool in several situations.

First, in the setting of acute respiratory distress syndrome (ARDS), it is well established that low tidal volume and limited plateau pressure are associated with better survival [1]. Recent guidelines recommend to aim for tidal volume of 4–8 mL/kg of predicted body weight (PBW) and plateau pressure less than 30 cmH$_2$O [2]. However, ventilator-induced lung injury (VILI) due to hyperinflation has been documented even with low tidal volume [3]. Because some data suggest that decreasing plateau pressure, even if it is < 30 cmH$_2$O, might be associated with reduced mortality [4], using tidal volume lower than 6 mL/kg has been proposed [5]. Three studies have showed the feasibility and safety of ultra-protective ventilation, with 4 mL/kg
tidal volume and plateau pressure < 25 cmH\textsubscript{2}O \cite{6-8}. However, at this time, no prospective trial has demonstrated an impact on outcome.

Second, in the setting of chronic obstructive pulmonary disease (COPD) exacerbation, noninvasive ventilation is the first option \cite{9}. Indeed, the need for invasive mechanical ventilation is associated with higher mortality \cite{10}. By providing extracorporeal CO\textsubscript{2} clearance, ECCO\textsubscript{2}R might decrease respiratory rate and limit auto-PEEP, resulting in reduced respiratory work. Three case-control studies have suggested that ECCO\textsubscript{2}R decrease the intubation rate of severe COPD exacerbation \cite{11-13}. It might also allow an earlier extubation and rehabilitation.

Finally, ECCO\textsubscript{2}R might also be useful in the setting of refractory respiratory acidosis with pH < 7.20 despite usual care. For example, successful treatment of near-fatal asthma using ECCO\textsubscript{2}R has been reported \cite{14}.

In this monocentric retrospective cohort study, we aimed to describe indications, ventilatory settings, gas exchanges, and outcome of patients receiving ECCO\textsubscript{2}R in our ICU.

Methods

Patients

We performed a retrospective chart review of all patients admitted to our tertiary regional intensive care unit (ICU) and started on ECCO\textsubscript{2}R from March 2014 to November 2017. Cases were identified through a prospectively maintained electronic database.

Ethical issues

ECCO\textsubscript{2}R therapy was started while all patients were on high-intensity treatment. Families were informed of the rescue treatment and the benefits-risks ratio. As a rule, all COPD patients required either to be intubated or to fail noninvasive ventilation (NIV) or refuse intubation to be started on ECCO\textsubscript{2}R. Four ARDS patients were involved in ongoing studies related to ECCO\textsubscript{2}R.

ECCO\textsubscript{2}R system

Four veno-venous ECCO\textsubscript{2}R systems were used, including ILA\textsuperscript{*} (Novalung, Germany), Hemolung\textsuperscript{*} (ALung Technologies, Inc., Pittsburgh, PA, USA), Prislamulung\textsuperscript{*} (Baxter Healthcare/Gambro Lund, Sweden), and CardioHelp\textsuperscript{*} (Maquet, Germany). CardioHelp\textsuperscript{*} was the only system using two venous canulas. Others were associated to dual-lumen catheters, usually inserted by jugular access. There was no protocol guiding the choice of ECCO\textsubscript{2}R device, which was let to the clinician in charge. When renal replacement therapy was required, Prislamulung\textsuperscript{*} was preferentially used. ECCO\textsubscript{2}R weaning strategy was let to clinician’s discretion.

Data recording

Demographic data collected included age, gender, primary admission diagnosis, cause of respiratory failure, and any known comorbidities. Physiologic data collected included vasopressor therapy and renal replacement therapy. Ventilatory data included ventilator mode, respiratory rate, tidal volume, plateau pressure when available, minute ventilation, and results of daily arterial blood gases (Additional file 1). ECCO\textsubscript{2}R-related data included indication of extracorporeal support, type of device, blood flow, sweep gas flow, and anticoagulation level evaluated by anti-Xa activity. Ventilation settings were gathered just before starting ECCO\textsubscript{2}R, at 4 hourly intervals for the first 24 h, and at day 2. Arterial blood gases were recorded once a day for 48 h.

ECCO\textsubscript{2}R-related or potentially linked complications included bleeding, catheter or pump thrombosis, hemolysis, thrombocytopenia, obvious local infection, and bacteremia. Bleeding at catheter insertion site was considered if associated with at least one red blood cell transfusion. Because plasma-free hemoglobin assessment was not available in our center, hemolysis was defined as anemia associated to haptoglobin less than 0.1 g/L. Thrombocytopenia was defined as a platelet count inferior to 150 G/L or a decrease of more than 50% since ECCO\textsubscript{2}R start.

Statistical analysis

Qualitative variables were expressed as number percentage. Quantitative variables were expressed as median and interquartile range. Comparisons between two qualitative variables were performed using the Fischer exact test. Comparisons between two quantitative variables were performed using the Wilcoxon test. For the study of the evolution of quantitative variables over time among patients, the Wilcoxon rank sum test was performed. All analyses were performed using SAS 9.4.

Results

Description of the overall population

Over 4 years, 33 patients received ECCO\textsubscript{2}R therapy, including 16 mild or moderate ARDS patients, and 11 COPD patients with severe exacerbation. The remaining six patients had refractory hypercapnic acidosis secondary to severe acute asthma \((n = 2)\), nosocomial pneumonia, bronchiolitis obliterans, exacerbation of pulmonary fibrosis, and bilateral bronchial compression by geriminal tumor. Among ARDS patients who received ECCO\textsubscript{2}R, three were enrolled in SUPERNOVA study (NCT02282657), and one in PRISMA-LUNG study \cite{15}. All COPD patients except one were intubated. Among COPD patients, 7 (63%) benefited from long-term oxygen therapy and 4 (36%) from noninvasive home ventilation. Baseline characteristics of the study population are shown in Table 1.
For the 29 invasively ventilated patients, ECCO2R therapy was started after a median time of 1 [1–5] day of invasive mechanical ventilation. In the overall population, median duration of ECCO2R therapy was 7 [5–10] days, with no obvious difference between ARDS and COPD patients. Twenty-one patients were weaned from ECCO2R while on ECCO2R therapy. Patient no. 1 was a 61-year-old man with refractory hypercapnic COPD exacerbation with NIV failure. He received 2 days of ECCO2R by Hemolung® device until venting. Median duration of ECCO2R therapy was 7 [5–10] days, with no increase of PaCO2. Although there was no difference for plateau pressure, driving pressure significantly decreased to 7 [6–10] cmH2O. The decrease of respiratory rate was not significant. However, minute ventilation significantly decreased to 4.6 [3.9–5.8] L/min. Neuromuscular blockers were used in 94, 81, and 56% of patients at baseline, day 1, and day 2. Among the 16 ARDS patients, 10 were proned while on ECCO2R support. Among those 10 patients, two supported by ILA®, one by Hemolung®, and one by PrismaLung® had three sessions of prone positioning or more.

Considering ultra-protective ventilation when tidal volume was ≤ 4 mL/kg of PBW and plateau pressure ≤ 25 cmH2O, ECCO2R did not allow a complete target attainment. Indeed, at baseline, 3/16 patients (19%) were ventilated with tidal volume ≤ 4 mL/kg of PBW. Plateau pressures at baseline were known for only 12/16 patients (75%) and was ≤ 25 cmH2O in 6/12 (50%). At baseline, only 1/12 patient (8%) has both tidal volume ≤ 4 mL/kg of PBW and plateau pressures ≤ 25 cmH2O (Additional file 1). Twenty-four hours after ECCO2R beginning, 8/16 patients (50%) were ventilated with tidal volume ≤ 4 mL/kg of PBW, 5/12 (42%) with plateau pressures ≤ 25 cmH2O, and 2/12 (17%) with both tidal volume ≤ 4 mL/kg of PBW and plateau pressures ≤ 25 cmH2O.

Table 1 Baseline characteristics

| Variables                          | Patients (n = 33) |
|------------------------------------|------------------|
| Age (years)                        | 63 [59–68]       |
| Gender (male/female)               | 20/13            |
| Body mass index (kg/m²)            | 26 [23–30]       |
| IGS2 score                         | 49 [36–65]       |
| SOFA score                         |                  |
| At ICU admission                   | 7 [5–10]         |
| At the time of ECCO2R start        | 10 [7–12]        |
| Indication                         |                  |
| Mild or moderate ARDS              | 16 (48)          |
| COPD exacerbation                  | 11 (33)          |
| Other                              | 6 (19)           |
| Associated organ dysfunction        |                  |
| Maximum noradrenaline dose (μg/kg/min) | 0.16 [0.00–0.25] |
| Need for renal replacement therapy | 7 (21)           |
| Comorbidities                      |                  |
| Chronic obstructive pulmonary disease | 16 (48)       |
| Arterial hypertension              | 22 (66)          |
| Coronary artery disease            | 7 (21)           |
| Cardiac insufficiency              | 6 (18)           |
| Chronic renal impairment           | 2 (6)            |
| Stroke                             | 2 (6)            |
| Obesity                            | 9 (27)           |
| Ongoing treatments                 |                  |
| Antiplatelet therapy               | 10 (30)          |
| Anticoagulation                    | 4 (12)           |
| Home oxygen therapy                | 11 (33)          |
| Home noninvasive ventilation       | 4 (12)           |

Numbers are n (%) and median [interquartile range]

Outcome

For the 29 invasively ventilated patients, ECCO2R therapy was started after a median time of 1 [1–5] day of invasive mechanical ventilation. In the overall population, median duration of ECCO2R therapy was 7 [5–10] days, with no obvious difference between ARDS and COPD patients. Twenty-one patients were weaned from ECCO2R while still intubated. Median duration of invasive mechanical ventilation after ECCO2R weaning was 2 [0–6] days. Four COPD patients were extubated while on ECCO2R therapy. Only 2 ARDS patients have benefited from a tracheostomy for respiratory support weaning. Mortality at day 28 was 27% in the whole cohort and seemed to be higher in ARDS patients than in COPD patients (31 vs 9%). Three of the 6 patients with refractory respiratory acidosis died. Median length of stay in ICU was 16 [10–22] days (Table 2).

Description of ECCO2R therapy in ARDS patients

Results of ECCO2R therapy in ARDS patients are shown in Table 3. Median baseline tidal volume, plateau pressure, driving pressure, and respiratory rate were 5.3 [4.4–5.9] mL/kg, 26 [24–27] cmH2O, 10 [8–15] cmH2O, and 26 [22–28] respectively. Twenty-four hours after ECCO2R start, tidal volume significantly decreased to 3.9 [3.5–4.2] mL/kg, without increase of PaCO2. Although there was no difference for plateau pressure, driving pressure significantly decreased to 7 [6–10] cmH2O. The decrease of respiratory rate was not significant. However, minute ventilation significantly decreased to 4.6 [3.9–5.8] L/min. Neuromuscular blockers were respectively used in 94, 81, and 56% of patients at baseline, day 1, and day 2. Among the 16 ARDS patients, 10 were proned while on ECCO2R support. Among those 10 patients, two supported by ILA®, one by Hemolung®, and one by PrismaLung® had three sessions of prone positioning or more.

Description of ECCO2R therapy in COPD patients

Results of ECCO2R therapy in COPD patients are shown in Table 4. Median baseline tidal volume, respiratory rate, minute ventilation, and PaCO2 were 5.5 [5.5–5.9] mL/kg; 22 [20–23]; 7.6 [6.6–8.7] L/min; and 9.4 [8.4–10.1] kPa respectively. Forty-eight hours after ECCO2R start, minute ventilation significantly decreased to 5.8 [4.9–6.2] L/min, while PaCO2 significantly decreased to 6 [5.3–6.8] kPa. Sedation was used in 72, 54, and 45% of patients at baseline, day 1, and day 2 respectively.

Description of ECCO2R therapy in non-intubated patients

Only four patients were not intubated at the beginning of ECCO2R therapy. Patient no. 1 was a 61-year-old man who had a history of kidney transplantation. He had refractory hypercapnic COPD exacerbation with NIV failure. He received 2 days of ECCO2R by Hemolung® device until successful weaning without need for intubation. Patient no. 2 was a 90-year-old woman with refractory hypercapnic pneumonia without hypoxemia. She was weaned from PrismaLung® device after 5 days, but she died 48 h later in...
a context of withdrawal of active treatments. Patient no. 3 was a 59-year-old man with a history of lung transplantation and chronic graft rejection. He was assisted by Hemo-
lung*. As he was not eligible for re-transplantation, he died at day 19 while still on Ecco2R, in a context of withdrawal of active treatments. Patient no. 4 was a 29-year-old man with microscopic polyangeitis with end-stage renal failure associated to lung fibrosis. He benefited from Prismalung* at day 0. He was intubated at day 6 and died at day 17 of septic shock.

**Ecco2R devices**
Among the 33 enrolled patients, 17 were treated with Hemolung*, 10 with Prismalung*, 4 with ILA, and 2 with Cardiohelp*. Hemolung* was used in 9 of 11 COPD patients, whereas Prismalung* was used in 6 of 16 ARDS patients. ILA and Cardiohelp were used only in ARDS patients. Evolution of anti-Xa activity and platelet levels are reported in Table 5.

**Complications**
No decannulation was reported during the studied period. Thrombocytopenia was the most frequently reported adverse event (72%). Since day 2 of Ecco2R treatment, at least half of treated patients have less than 150 G/L of platelets and at least 25% have less than 90 G/L of platelets. However, only four patients (12%) received platelet transfusion. Half of the treated patients received at least one red blood cell transfusion during Ecco2R therapy. One patient treated with Hemolung* died of intracranial hemorrhage, while on Ecco2R. At the diagnosis, he had 189 G/L of platelets, and 0.44 UI/mL of antiXa. Hemolysis was reported in 16 patients (48%) but did not lead to Ecco2R withdrawal. Device thrombosis occurred in 5 patients (15%). Among them, one ARDS patient treated with CardioHelp* has necessitated urgent circuit change for complete pump thrombosis. Interruption of CO2 removal for Ecco2R change or withdrawal was well tolerated in all cases.

**Discussion**
In this retrospective chart review, we aimed to describe our experience of Ecco2R devices and to help clinician volunteers to use those devices beyond the scope of experimental studies. We have found that Ecco2R system allowed ultra-protective ventilation in ARDS patients by decreasing tidal volume. We also found that Ecco2R was effective to reduce minute ventilation and improve blood pH in ventilated COPD patient. Furthermore, it

### Table 2: Outcomes of the 33 patients receiving Ecco2R

| Outcome                        | Total (n = 33) | ARDS (n = 16) | COPD (n = 11) | Others (n = 6) |
|--------------------------------|---------------|--------------|--------------|---------------|
| 28-day mortality               | 9 (27)        | 5 (31)       | 1 (6)        | 3 (50)        |
| Length of stay in ICU, days    | 16 [10–22]    | 18 [11–26]   | 14 [11–19]   | 11 [8–18]     |
| Duration of invasive ventilation before Ecco2R, days | 1 [1–5]       | 3 [1–5]      | 1 [1–3]      | 0 [0–0]       |
| Duration of Ecco2R therapy     | 7 [5–10]      | 6 [5–9]      | 7 [5–11]     | 6 [5–15]      |
| Prone positioning, number of patients | 15 (45)       | 10 (62)      | 3 (27)       | 2 (33)        |
| Duration of invasive ventilation after Ecco2R weaning | 2 [0–6]       | 4 [2–10]     | 2 [0–4]      | 1 [0–2]       |
| Extubated while on Ecco2R, number of patients | 4 (12)        | 0 (0)        | 4 (36)       | 0 (0)         |

Numbers are n (%) and median (interquartile range)

### Table 3: Evolution of ventilatory settings and gas exchanges in 16 ARDS patients

| Ventilatory parameters | Baseline | 4 h | 8 h | 12 h | 24 h | 48 h |
|------------------------|----------|-----|-----|------|------|------|
| Ventilatory mode (VC/PSV), number | 16/0     | 16/0| 16/0| 16/0 | 15/1 | 14/2 |
| TV (mL kg⁻¹)           | 5.3 [4.4–5.9] | 3.8 [3.5–4.1] | 3.7 [3.5–4.1] | 3.7 [3.6–4.1] | 3.9 [3.5–4.2] | 3.8 [3.3–4.1] |
| RR (min⁻¹)             | 26 [22–28] | 23 [20–25] | 22 [19–25] | 22 [20–25] | 21 [18–23] | 23 [17–26] |
| Minute ventilation (L min⁻¹) | 8.5 [6.0–9.5] | 5.2 [4.0–6.1] | 4.5 [3.9–6.3] | 4.3 [3.9–6.3] | 4.6 [3.9–5.8] | 5.3 [4.0–6.9] |
| PEEP (cmH₂O)           | 13 [10–15] | 14 [10–15] | 14 [10–18] | 14 [10–18] | 14 [12–18] | 14 [11–17] |
| Plateau pressure (cmH₂O) | 26 [24–27] | – | 26 [22–29] | 25 [22–27] | – | – |
| Driving pressure (cmH₂O) | 10 [8–15] | – | 7 [6–10] | 9 [8–10] | 5.6 [4.8–7.6] | 5.4 [4.8–8.2] |
| PaCO₂ (kPa)            | 6.7 [6.1–7.5] | 5.7 [5.1–7.0] | 5.6 [4.8–7.6] | 5.4 [4.8–8.2] | – | – |
| pH                     | 7.31 [7.25–7.41] | 7.39 [7.30–7.42] | 7.40 [7.33–7.45] | 7.41 [7.35–7.43] | – | – |
| PaO₂/FiO₂              | 145 [116–161] | 207 [127–226] | 182 [149–211] | 201 [168–263] | – | – |

Neuromuscular blockers use, number = 15 (94%)

*p < 0.05 vs baseline; V volume control, PSV pressure support ventilation; numbers are n (%) and median (interquartile range)
allowed extubation in some patients while on extracorporal support.

In the setting of ARDS patients, our results are in line with those of the three main studies assessing veno-venous low-flow ECCO2R. Indeed, in a recent pilot study in 15 mild to moderate ARDS patients, the use of Prismlung® allowed ultra-protective ventilation with tidal volume of 4 mL/kg [8]. Some similar results have been observed with Polystan SAFE® (Maquet, Rastatt, Germany), a membrane lung connected to a veno-venous hemofiltration system [6]. Interestingly, in our ARDS cohort, 6 of the 16 patients have benefited from Prismlung® device, connected to a renal replacement machine. In a recently published proof-of-concept study, Prismlung® allowed ultra-protective ventilation in 20 mild-to-moderate ARDS patients. However, mean duration treatment was only 31 h (±22), limiting conclusion about longer use and safety [15]. Although significant, the reduction of driving pressure secondary to tidal volume decrease was quite small in our study. This could be due to a relatively low tidal volume at baseline. Indeed, in our practice, we usually target low plateau pressure, with tidal volume lower than 6 mL/kg as reported by other authors [16]. After ECCO2R start, we have noted a trend to decrease of respiratory rate. This is another potential aspect of the ultra-protective strategy, as some authors have suggested that respiratory rate could be a determinant of VILI [17]. Because median baseline PaO2/FiO2 ratio was 145 [116–161] mmHg, patients were a priori susceptible to have an indication for prone positioning. It is noteworthy that 10 patients have benefited from this therapy without any adverse event. Because prone positioning has been found to decrease mortality in ADRS with PaO2/FiO2 ratio less than 150 mmHg, it is mandatory that novel therapy do not limit its use [18]. While neuromuscular blockers use in moderate to severe ARDS is recommended for 48 h [19], we have noted a trend towards early interruption. This might be explained by the early improvement of oxygenation and the control of hypercapnia. In this situation, our clinicians favored decrease sedations and awareness.

In the three largest studies enrolling COPD patients, the primary end point was the avoidance of intubation [11–13]. In our cohort, only one COPD patient has benefited from such pre-intubation strategy. However, whether ECCO2R should be started before or after intubation is still a matter of debate. Indeed, because NIV failure is hard to predict, and ECCO2R is associated with additional septic and hemorrhagic risks, appropriate selection of patients which might benefit from ECCO2R is difficult. Considering this, our policy is to start ECCO2R early after intubation. Moreover, such strategy may facilitate insertion of the ECCO2R catheter, allowing safe conditions, as no complication was reported during catheter insertion in our patients. In our cohort, 50% of the patients were started on day 1 and 75% before day 3 of mechanical ventilation. While the global effect of ECCO2R was the lowering of minute ventilation and PaCO2 in our cohort, it was more marked during the 24 first hours. This might be potentially explained by the decrease of sedative use, resulting in more patients with spontaneous ventilation, with uncontrolled tidal volume and respiratory rate.

Considering safety, our data point out that ECCO2R use cannot be dissociated from the potential risks of anticoagulation in critically ill patients. Indeed, as it occurred during ECCO2R therapy, the fatal case of intracranial hemorrhage has to be underlined. Even if no heparin overdosing has been reported, there is an obvious link between anticoagulation and this complication. Even if the hemorrhagic risk was not obvious, as there was no other indication for anticoagulation, responsibility of ECCO2R therapy is here plausible. Otherwise, although frequent, thrombocytopenia was moderate, and hemolysis did not result in need for ECCO2R withdrawal. Finally, because interruption of CO2 removal was well tolerated, ECCO2R circuit thrombosis

| Table 4: Evolution of ventilatory settings and gas exchanges in 11 COPD patients |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Ventilatory parameters     | Baseline            | 4 h                 | 8 h                 | 12 h                | 24 h                | 48 h                |
| Ventilatory mode (VC/PSV/NIV), number | 8/2/1              | 7/3/1               | 7/3/1               | 7/3/1               | 5/5/1               | 5/5/1               |
| TV (mL kg⁻¹)               | 5.5 [5.5–5.9]       | 5 [4.4–6.1]         | 4.6 [4.4–4.8]*     | 4.5 [4.2–5]*        | 5.6 [4.4–5.8]       | 5.2 [4.1–5.8]       |
| RR (min⁻¹)                | 22 [20–23]          | 18 [17–22]          | 18 [15–24]          | 18 [15–21]          | 20 [17–20]          | 20 [16–24]          |
| Minute ventilation (L min⁻¹) | 7.6 [6.6–8.7]      | 5.9 [5–7.2]         | 4.7 [3.8–5.2]*     | 4.9 [3.8–5.9]*      | 6.2 [4.1–6.8]       | 5.8 [4.9–6.2]*      |
| PEEP (cmH2O)              | 6 [4–8]             | 6 [5–8]             | 6 [5–8]             | 6 [5–8]             | 8 [5–10]            | 8 [7–10]            |
| PaCO2 (kPa)               | 9.4 [8.4–10.1]      | 6.6 [5.7–7.1]*      | 6 [5.1–7.1]*        | 6 [5.3–6.8]*        |                     |                     |
| pH                        | 7.32 [7.26–7.34]    | 7.43 [7.41–7.45]*   | 7.45 [7.41–7.47]*   | 7.44 [7.42–7.46]*   |                     |                     |
| PaO2/FiO2                 | 174 [158-207]      | 192 [177–254]       | 225 [186–262]       | 210 [181–254]       |                     |                     |
| Sedative use, number      | 8 (72%)             | –                   | 6 (54%)             | 5 (45%)             |                     |                     |
| Neuromuscular blockers use, number | 6 (54%)           | –                   | –                   | 4 (16%)             | 3 (27%)             |

*p < 0.05 vs baseline; VC volume control PSV pressure support ventilation, NIV noninvasive ventilation; ¹ when VC is used; numbers are n (%) and median (interquartile range)
| Devices      | Duration of therapy (days) | Platelets count (G/L) | Anti-Xa activity (UI/mL) | Hemolysis | RBC transfusion during ECCO2R |
|--------------|---------------------------|-----------------------|--------------------------|-----------|-------------------------------|
|              |                           | J0        | J1        | J2        | J3        | J4        | J5        |               |               |
| All patients | 7 [5–10]                  | 202 [137–286] | 167 [95–243] | 143 [88–199] | 130 [79–192] | 128 [89–156] | 124 [86–153] | 0.22 [0.14–047] | 0.26 [0.16–0.40] | 0.33 [0.24–0.44] | 0.33 [0.25–0.41] | 0.30 [0.20–0.39] | 0.35 [0.21–0.47] | 16 (48) | 16 (48) |
| Hemolung®    | 7 [5–10]                  | 210 [163–264] | 184 [108–243] | 136 [88–208] | 128 [79–174] | 128 [89–153] | 130 [88–151] | 0.24 [0.15–0.50] | 0.26 [0.20–0.36] | 0.41 [0.30–0.53] | 0.31 [0.25–0.42] | 0.30 [0.20–0.38] | 0.35 [0.30–0.49] | 13 (76) | 9 (53)  |
| Prismalung®  | 5 [3–6]                   | 153 [104–272] | 126 [65–241] | 124 [72–195] | 105 [57–183] | 82 [57–98]   | 77 [55–87]   | 0.13 [0.10–0.43] | 0.17 [0.10–0.24] | 0.25 [0.10–0.41] | 0.37 [0.14–0.40] | 0.23 [0.12–0.35] | 0.20 [0.11–0.36] | 1 (10)  | 4 (40)  |
| ILA® (n = 4) | 10 [5–19]*                | 226 [150–288] | 181 [115–225] | 172 [142–206] | 168 [167–208] | 161 [134–184] | 173 [146–199] | 0.19 [0.16–0.28] | 0.36 [0.29–0.39] | 0.26 [0.25–0.29] | 0.37 [0.32–0.42] | 0.31 [0.24–0.34] | 0.26 [0.22–0.31] | 1 (25)  | 3 (75)  |
| Maquet®      | 6.5 (6–7)*                | 258 [205–311] | 179 [163–196] | 151 [141–162] | 142 [130–153] | 142 [130–153] | 153 [153–153] | 0.27 [0.25–0.30] | 0.49 [0.44–0.53] | 0.47 [0.46–0.47] | 0.45 [0.42–0.47] | 0.98 [0.55–0.61] | 0.47 [0.46–0.47] | 1 (50)  | 0 (0)   |

Numbers are n (%) and median (interquartile range), except for * which corresponds to min and max. RBC red blood cells.
only resulted in loss of 250 mL of blood, corresponding to the circuit volume of purge. Because, no trial demonstrating its clinical benefit has been published, ECCO2R systems are not widely used. Indeed, in a recent survey, among 239 French ICUs, only 15% declared having used at least once ECCO2R between 2010 and 2015 [20]. However, ECCO2R technology has improved, and because of a strong rational, several randomized trials enrolling ARDS and COPD patients are ongoing [21]. The mortality rate in our ARDS and COPD patients is in the lower range [16, 22], and early use of ECCO2R might contribute to our results. If well-designed studies bring proof of the ECCO2R benefit, a very large number of patients would be concerned, asking the question of where to perform ECCO2R. Indeed, in the setting of ECMO, a large retrospective cohort analysis has suggested a negative link between ECMO cases volume and hospital mortality [23]. As well as the concept of “ECMO center,” the need for “ECCO2R center” has to be assessed.

Our study has several limitations. First, because of the retrospective design, some data are lacking. Whereas tidal volume, respiratory rate, and positive end expiratory pressure are monitored hourly by the nurses in our unit, plateau pressure is usually monitored by the clinicians and not systematically reported in the medical record. It explains why complete data on plateau pressure and driving pressure were available for only 8 on 16 ARDS patients. Second, heterogeneity and small sample size limit internal validity. However, ECCO2R is not widely used, and previous studies in the setting of ECCO2R have included no more than 40 ARDS patients [7] and 25 COPD patients [12, 13]. Third, we reported a single-center experience limits the generalization of our conclusions. For example, our paramedical team is widely used to prone positioning and extracorporeal circulations. Even if prone positioning in patients receiving ECCO2R has only concerned a few patients, team practice might have decreased the risk of severe adverse events such as accidental decanulation. Our patients represent 256 ECCO2R days. Fourth, except in the setting of SUPERNOVA or PRISMALUNG studies, we did not have preset criteria for ECCO2R implantation, which was left to the clinician’s judgment. Fifth, we reported only initial ECCO2R settings. However, because of maximal CO2 is targeted, sweep gas was usually kept at his maximal value. ECCO2R rotation per minute (RPM) was set to reach a blood flow of at least 300, 450, 700 and 1000 mL/min, with Prismalung®, Hemolung®, ILA®, and CardioHelp® respectively. ECCO2R RPM were decreased only when significant hemolysis was documented. Finally, plasma-free hemoglobin assessment was not available in our center, resulting in a more difficult diagnosis of hemolysis.

**Conclusion**

In ARDS patients, ECCO2R use was associated with a significant decrease of tidal volume and driving pressure during the first 48 h of therapy. Prone positioning was performed in 10 (62%) patients without adverse event. In COPD patients, ECCO2R use was associated with a significant decrease of minute ventilation, normalization of pH, and decrease of PaCO2. Although ECCO2R therapy was globally well tolerated, a case of fatal intracranial hemorrhage points out that this procedure cannot be dissociated from the potential risks of anticoagulation in critically ill patients.

**Additional file**

Additional file 1: Figure S1. Scatter plots representing evolution of tidal volume (a), respiratory rate (b), plateau pressure (c) and driving pressure (d) of the 16 ARDS patients. (DOCX 80 kb)

**Availability of data and materials**
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**
HW helped analyze the data, write the manuscript, and perform the literature search. FA, FB, NB, CCh, CP, CCJ, ED, JCN, GL, GP, and GC helped analyze the data and write the manuscript. All authors read and approved the final manuscript.

**Consent for publication**
According to French law, written inform consent is not required for a retrospective case series. All patients (or proxy) admitted in our ICU are informed that medical data may be used for research. If they wish, they may refuse that (approved by an Ethic Committee on March 2013). In this clinical case, no opposition was expressed for using data for research.

**Competing interests**
Pr Capellier has received lecture fees from Baxter and Alung. Prismalung® devices were provided by Baxter. The other authors declare that they have no competing interests.

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