A 2-year multicenter, observational, prospective, cohort study on extracorporeal CO₂ removal in a large metropolis area

J. L. Augy, N. Aissaoui, C. Richard, E. Maury, M. Fartoukh, A. Mekontso-Dessap, R. Paulet, N. Anguel, C. Blayau, Y. Cohen, J. D. Chiche, S. Gaudry, S. Voicu, A. Demoule, A. Combes, B. Megarbane, E. Charpentier, S. Haghighat, M. Panczer and J. L. Diehl

Abstract

Background: Extracorporeal carbon dioxide removal (ECCO₂R) is a promising technique for the management of acute respiratory failure, but with a limited level of evidence to support its use outside clinical trials and/or data collection initiatives. We report a collaborative initiative in a large metropolis.

Methods: To assess on a structural basis the rate of utilization as well as efficacy and safety parameters of 2 ECCO₂R devices in 10 intensive care units (ICU) during a 2-year period.

Results: Seventy patients were recruited in 10 voluntary and specifically trained centers. The median utilization rate was 0.19 patient/month/center (min 0.04; max 1.20). ECCO₂R was started under invasive mechanical ventilation (IMV) in 59 patients and non-invasive ventilation in 11 patients. The Hemolung Respiratory Assist System (Alung) was used in 53 patients and the iLA Active iLA kit (Xenios Novalung) in 17 patients. Main indications were ultraprotective ventilation for ARDS patients (n = 24), shortening the duration of IMV in COPD patients (n = 21), preventing intubation in COPD patients (n = 9), and controlling hypercapnia and dynamic hyperinflation in mechanically ventilated patients with severe acute asthma (n = 6). A reduction in median VT was observed in ARDS patients from 5.9 to 4.1 ml/kg (p <0.001). A reduction in PaCO₂ values was observed in AE-COPD patients from 67.5 to 51 mmHg (p <0.001). Median duration of ECCO₂R was 5 days (IQR 3–8). Reasons for ECCO₂R discontinuation were improvement (n = 33), ECCO₂R-related complications (n = 18), limitation of life-sustaining therapies or measures decision (n = 10), and death (n = 9). Main adverse events were hemolysis (n = 21), bleeding (n = 17), and lung membrane clotting (n = 11), with different profiles between the devices. Thirty-five deaths occurred during the ICU stay, 3 of which being ECCO₂R-related.

Conclusions: Based on a registry, we report a low rate of ECCO₂R device utilization, mainly in severe COPD and ARDS patients. Physiological efficacy was confirmed in these two populations. We confirmed safety concerns such as hemolysis, bleeding, and thrombosis, with different profiles between the devices. Such results could help to design future studies aiming to enhance safety, to demonstrate a still-lacking strong clinical benefit of ECCO₂R, and to guide the choice between different devices.

Trial registration: ClinicalTrials.gov: Identifier: NCT02965079 retrospectively registered https://clinicaltrials.gov/ct2/show/NCT02965079

Keywords: Extracorporeal CO₂ removal, Acute respiratory distress syndrome, COPD exacerbation, Safety
Introduction
Extracorporeal CO₂ removal (ECCO₂R) is potentially a major therapeutic breakthrough in critical care [1, 2]. The two main conditions that could benefit from this technique are acute respiratory distress syndrome (ARDS) and very severe acute exacerbations of chronic obstructive pulmonary disease (AE-COPD). The main objective of ECCO₂R in ARDS is to implement an ultraprotective invasive mechanical ventilation (IMV) strategy, mainly by decreasing the tidal volume (from the usually recommended value of 6 ml/kg (predicted body weight) to a value of 3–4 ml/kg) [3–8], and including as complementary options a rise in positive end-expiratory pressure (PEEP) as well as a diminution in respiratory rate [9]. The goals in AE-COPD are to prevent tracheal intubation and to shorten IMV duration [10–14]. Corresponding physiological respiratory benefits have been demonstrated, at the price however of hemolytic, hemorrhagic, and thrombotic complications [1, 2, 15]. Awaiting the results of current or planned RCTs, it has been suggested to use ECCO₂R within clinical trials and/or to contribute to data registries [1, 2, 15, 16]. Accordingly, within the great Paris area, the use of the ECCO₂R as part of the current care was rigorously organized. As a result of a referral, a report (supported by a clinician’s interviews and by a systematic analysis of the literature) was released in June 2014 by an institutional Agency for Health Technology Assessment attached to the Assistance Publique–Hôpitaux de Paris (AP-HP) [17]. The main recommendations were to establish a working group led by clinicians able to give a scientific opinion on the appropriateness of the ECCO₂R activity, to authorize the use of ECCO₂R in selected voluntary centers, to organize a systematic recording of the activity on an individual basis, and to reassess periodically the ECCO₂R activity (on the basis of the available literature and of results of records). The project was supported by the Office of Technology Transfer and Partnerships Industrialists of the AP-HP and by the Institutional Pharmacy Agency (AGEPS). Test markets were concluded by the AGEPS with industrial firms, with a strict follow-up of the orders. We here report our initial experience based on the first 70 patients included in the corresponding registry.

Methods
Ethical and regulatory aspects
The study was approved by the Ethical Committee of the French Intensive Care Society and by the “Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé,” a governmental committee on the use of information in the health domain. The study was registered on ClinicalTrials.gov: Identifier: NCT02965079. A written information form was given and orally explained to patients or proxies, who had the possibility to decline the utilization of data.

Patient population and general organization
Patients were prospectively recruited during a 2-year period in 10 voluntary centers in Paris and its suburb. Initial training on how to operate devices was provided by the firms to nurses and medical teams in each center before any utilization. New training sessions were regularly organized, as requested by medical teams. Clinicians were asked to fill a dedicated form for each ECCO₂R patient and to strictly follow user’s guides developed by the firms.

ECCO₂R management
Two devices, Hemolung Respiratory Assist System (Alung Technologies, Pittsburgh, USA) and iLA Activve iLA kit (Xenios Novalung, Heilbronn, Germany), were used during the period. The vascular access was achieved by mean of a specific double-lumen 15.5-Fr veno-venous catheter (either right jugular or femoral site) for the Hemolung device and by mean of double-lumen 18 Fr (right jugular site) or 24 Fr (femoral site) for the iLA Activve system, using Novaport TWIN (18, 22, or 24 Fr) catheters (Xenios Novalung, Heilbronn, Germany). Extracorporeal blood flow rates are generally comprised between 350 and 550 ml/min for the Hemolung system and between 500 ml/min and 1500 ml/min for the iLA Activve system. The sweep gas flow was adjusted for controlling hypercapnia, for achieving protective or ultraprotective ventilation, and for unloading the respiratory muscles depending on the indications for ECCO₂R and on the clinical courses of the patients. All patients were treated by continuous intravenous infusion of unfractionated heparin and monitored by serial measurements of anti-Xa activity, with a therapeutic range between 0.3 and 0.6 IU/ml.

Data collection
The individual dedicated form included the following information: baseline characteristics, indication for ECCO₂R, type of ECCO₂R device, type and site of veno-venous ECCO₂R catheter, type of ventilatory support, concomitant treatments, adverse events (AE) and serious adverse events (SAE), reason for ECCO₂R discontinuation, and respiratory and general follow-up until ICU discharge or death.

Endpoints
The primary outcome was the number of patients treated by ECCO₂R per month and per center during the 2-year study period. Based mainly on the annual number of ARDS and AE-COPD admissions, a recruitment of 200 patients (100 patients per year) was roughly
anticipated. Secondary endpoints were related to 
ECCO2R physiological efficacy (based mainly on respiratory 
assessment after 24 h of use) and safety, length of 
mechanical ventilation, and ICU and hospital survival. 
Main safety endpoints were defined as follows: bleeding 
deemed as clinically significant by clinicians; biological 
hemolysis defined by a serum-free hemoglobin level 
higher than 100 mg/l; clinical hemolysis when associated to 
jaundice, hemoglobinuria, or impaired renal function; 
thrombosis, membrane clotting, and catheter infection. 
Clinically significant bleeding was defined by the need of 
RBC transfusion, whatever the number of RBC units, 
and/or need to stop continuous intravenous unfractionated 
heparin infusion, and/or need of surgery or any 
interventional procedure to control bleeding, and/or as-
sociation to hemodynamic instability. Membrane clot-
ting was defined as apparent membrane clotting after a 
daily visual inspection or suspected massive membrane 
clotting leading to ECCO2R cessation and further con-
firmed by analysis of the circuit.

Statistical analyses

The primary outcome is reported as median and ex-
treme values. Other continuous variables are reported as 
median (interquartile range) (IQR) and categorical vari-
ables are reported as count and proportion. Categorical 
variables were compared using the Fisher exact test. Be-
tween-group comparisons of continuous variables were 
performed using the chi-square test. All analyses were 
made on R software (R version 3.3.2). All p values less 
than 0.05 were considered significant.

Results

Seventy patients were treated by ECCO2R during the 2-
year study period. Median monthly utilization rate by 
center was 0.19 patients (min 0.04; max 1.2). During the 
period, the median ICU admission rates of ARDS and 
AE-COPD patients were 8.16 (min 5.00; max 9.91) and 
2.19 (min 1.50; max 6.79), respectively. Fifty-three pa-
ients were treated with the Hemolung device and 17 
with the iLA Activve device.

Baseline demographic characteristics of the patients 
are reported in Table 1. The severity of patients at ICU 
admission was assessed by a median SAPS II of 43 (35– 
45). Main indications for ECCO2R were ultraprotective 
ventilation in 24 (34%) ARDS patients; shortening the 
duration of IMV in 21 (30%) COPD patients; preventing 
intubation in 9 (13%) COPD patients who failed non-
invasive ventilation (NIV); and controlling hypercapnia 
and dynamic hyperinflation in mechanically ventilated 
patients with severe acute asthma (n = 6; 9%). Etiology of 
ARDS was pneumonia in 19 patients, acute exacerbation 
of interstitial lung diseases in 3, lung toxicity of chemo-
therapy in 1, and smoke inhalation in 1. Table 2 
indicates baseline demographics in the two main indica-
tions: ARDS and AE-COPD. Other 10 indications were 
acute exacerbation of interstitial lung disease without 
ARDS criteria (n = 2), bronchiolitis (n = 2), bridge to lung 
transplantation, post-extubation laryngeal edema, unilat-
eral pneumonia, malignant tracheal obstruction, acute 
exacerbation of chronic restrictive pulmonary disease, 
and difficult IMV weaning outside chronic respiratory 
insufficiency (n = 1 each). Nineteen patients (11 ARDS 
and 8 AE-COPD) were treated by ECCO2R as part of a 
registered interventional clinical trial.

The median time between ICU admission and 
ECCO2R initiation was 3 days [1–9]. For IMV patients, 
the median IMV duration before ECCO2R initiation was 
2 days [1–5]. Table 3 indicates the technical settings and 
medical conditions in relation to the two medical 
devices.

Table 2 indicates the changes in ventilator parameters 
at day 1 after starting ECCO2R in AE-COPD and ARDS 
patients. A significant reduction in median V\textsubscript{T} was 
observed in ARDS patients from 5.9 to 4.1 ml/kg (predicted 
body weight, PBW), in line with an ultra-protective ven-
tilation strategy. A significant reduction in PaCO\textsubscript{2} values was 
observed in AE-COPD patients.

| Table 1 Baseline characteristics of the population |
|-----------------------------------------------|
| Age (years) | 65 (61–74) |
| Male patients | 41 (59%) |
| BMI (kg/m\textsuperscript{2}) | 25.3 (22.0–32.3) |
| Comorbidities |
| Chronic respiratory disease | 30 (43%) |
| Chronic cardiac disease | 11 (16%) |
| Chronic kidney disease | 8 (11%) |
| Diabetes | 12 (17%) |
| SAPS II | 43 (35–45) |
| pH | 7.28 (7.22–7.32) |
| PaCO\textsubscript{2} (mmHg) | 64 (56–73) |
| VT (ml/kg PBW) | 6.2 (5.9–7.9) |
| Respiratory setting |
| IMV | 59 (84%) |
| NIV | 11 (16%) |
| Concomitant treatments |
| Vasopressors | 27 (39%) |
| Renal replacement therapy | 8 (11%) |
| Neuromuscular blockade | 37 (53%) |
| Steroids | 16 (23%) |
| Prone positioning | 4 (6%) |

Results are expressed as median (IQR) for continuous variables and count and proportion for categorical variables

Abbreviations: BMI body mass index, SAPS Simplified Acute Physiology Score, VT tidal volume, PBW predicted body weight, IMV invasive mechanical ventilation, NIV non-invasive ventilation
Median ECCO$_2$R duration was 5 days [3–8] without difference between the two medical devices ($p = 0.812$). Main reasons for ECCO$_2$R discontinuation were improvement in clinical condition in 33 patients, ECCO$_2$R-related adverse events in 18 patients, limitation of life-sustaining therapies or measures decision in 10 patients, and death in 9 patients (Table 4). No patient among the 33 patients who weaned from ECCO$_2$R because of improvement died in ICU. Twenty-eight patients among the 59 under IMV when starting ECCO$_2$R were weaned from IMV. Among the 11 patients under NIV when starting ECCO$_2$R, 1 needed to be intubated and 5 were successfully weaned from NIV. There was no transition to ECMO for any patient. Thirty-five patients

### Table 2 Demographics, ventilator course, and clinical course according to the two main indications of ECCO$_2$R

|                      | AE-COPD ($n = 30$) | ARDS ($n = 24$) |
|----------------------|--------------------|-----------------|
| Age (years)          | 66 (61–72)         | 66 (63–77)      |
| Male: $n$ (%)        | 12 (40%)           | 17 (71%)        |
| FEV1 (L)             | 0.97 (0.69–1.2)    | NA              |
| FEV1 (%)             | 35% (29.5–53)      | NA              |
| PaO$_2$/FiO$_2$ (mmHg)| NA                | 131 (100–190)   |
| SAPS II              | 36 (32–50)         | 48 (43–62)      |
| Use of vasopressors: $n$ (%) | 10 (33%)         | 14 (58%)       |
| Type of ventilatory support |                 |                 |
| IMV: $n$ (%)        | 21 (70%)           | 24 (100%)       |
| NIV: $n$ (%)        | 9 (30%)            | NA              |
| IMV settings before ECCO$_2$R: |                 |                 |
| $V_t$ (ml/kg PBW)    | 8.0 (7.8–8.1)      | 5.9 (5.5–6.0)   |
| Applied PEEP (cmH$_2$O) | 0 (0–0)           | 10 (5–15.5)     |
| FiO$_2$ (%)          | 35 (30–38)         | 60 (50–70)      |
| Measured parameters under IMV before ECCO$_2$R: |       |                 |
| Plateau pressure (cmH$_2$O) | NA              | 28 (27–29)      |
| Total PEEP (cmH$_2$O) | 9 (7–11)          | NA              |
| pH                   | 7.30 (7.25–7.32)   | 7.24            |
| PaCO$_2$ (mmHg)      | 67.5 (60.75–73.25) | 58.0 (48.0–65.0) |
| ECCO$_2$R device     |                    |                 |
| iLa Activve: $n$ (%) | 5 (17%)           | 6 (25%)         |
| Hemolung: $n$ (%)    | 25 (83%)           | 18 (75%)        |
| IMV settings and measured parameters at day 1 after starting ECCO$_2$R: |       |                 |
| $V_t$ (ml/kg PBW)    | 7.98 (7.70–8.10)   | 4.1 (3.9–4.8)*  |
| pH                   | 7.39 (7.26–7.42)*  | 7.31 (7.24–7.36)** |
| PaCO$_2$ (mmHg)      | 51.0 (45.5–56.0)*  | 51.0 (44.5–55.7) |
| ECCO$_2$R duration (days): | 6.5 (3.25–8)       | 4 (2–6)         |
| IMV duration (days)  | 10 (4.75–15.25)    | 8.5 (5.5–14.25) |
| Course of ventilator support |                |                 |
| IMV weaning success (IMV patients) | 16 (76%) | 7 (29%) |
| Intubation (NIV patients) | 1 (11%)  | NA             |
| Mortality: $n$ (%)   | 10 (31%)           | 17 (71%)        |
| Linked to ECCO$_2$R  | 2 (7%)             | 1 (4%)          |

Results are expressed as median (IQR) for continuous variables and count and proportion for categorical variables

**Abbreviations:** FEV1 forced expiratory volume in 1 s, BMI body mass index, SAPS Simplified Acute Physiology Score, IMV invasive mechanical ventilation, NIV non-invasive ventilation, $V_t$ tidal volume, PBW predicted body weight, PEEP positive end-expiratory pressure

* $p < 0.01$ as compared to values before ECCO$_2$R

** $p < 0.05$ as compared to values before ECCO$_2$R
died in the ICU. In-hospital mortality was 51.5% (36 deceased patients, 6 missing data mainly due to transfer to another institution). Three deaths were judged as ECCO2R-related by clinicians in charge (2 intra-cranial bleedings without heparin overdosing and 1 cardiac tamponade following a right jugular vein catheterization).

At least one ECCO2R-related adverse event was reported in 38 patients (Table 5). Hemolysis was reported in 21 patients all treated with the Hemolung device and led to ECCO2R discontinuation in 6 patients. Lung membrane clotting was reported in 11 patients leading to ECCO2R discontinuation in 6. Clinically significant bleeding was reported in 17 patients, 7 of whom needed RBC transfusion and 3 needed specific treatments (catheter-selective embolization in 3, with a further need for surgery in 1). Bleeding was the reason for ECCO2R discontinuation in 6 patients.

Device malfunction leading to ECCO2R discontinuation was reported in 6 patients. Software was involved in 3 of the 4 Hemolung malfunctions, 1 malfunction being not investigated. Air in the circuit was reported in 2 patients treated with the iLa Activve device.

### Discussion

Our study describes a collaborative institutional multicenter process for implementation of new ECCO2R medical devices in a large metropolis area, with the aim to establish a registry, in accordance with national recommendations [16]. Despite a low rate of utilization, mainly in COPD and ARDS patients, we were able to report a confirmed physiological efficacy and different safety profiles between the devices.

At least one ECCO2R-related adverse event was reported in 38 patients (Table 5). Hemolysis was reported in 21 patients all treated with the Hemolung device and led to ECCO2R discontinuation in 6 patients. Lung membrane clotting was reported in 11 patients leading to ECCO2R discontinuation in 6. Clinically significant bleeding was reported in 17 patients, 7 of whom needed RBC transfusion and 3 needed specific treatments (catheter-selective embolization in 3, with a further need for surgery in 1). Bleeding was the reason for ECCO2R discontinuation in 6 patients.

Device malfunction leading to ECCO2R discontinuation was reported in 6 patients. Software was involved in 3 of the 4 Hemolung malfunctions, 1 malfunction being not investigated. Air in the circuit was reported in 2 patients treated with the iLa Activve device.

### Discussion

Our study describes a collaborative institutional multicenter process for implementation of new ECCO2R medical devices in a large metropolis area, with the aim to establish a registry, in accordance with national recommendations [16]. Despite a low rate of utilization, mainly in COPD and ARDS patients, we were able to report a confirmed physiological efficacy and different safety profiles between the devices.

Primary end-point was the rate of utilization during a first 2-year period. We report a low rate of use, predominantly in AE-COPD and ARDS patients, with a maximal value of 1.2 patients/month/center. Altogether, ECCO2R was used in less than 2% of ARDS and AE-COPD patients during the corresponding period. Such a result is in line with a previous national survey in 239 ICUs and probably illustrates the lack of formally demonstrated strong outcome benefit of such expensive medical devices [18]. Nevertheless, our study is one of the largest ECCO2R multicenter initiatives and permitted to confirm and/or to extend efficacy and safety information as well as to introduce ECCO2R as a therapeutic option in selected centers.

As expected, we report a preferential ECCO2R use in ARDS and AE-COPD patients. Contrary to other reports, we observed a higher number of AE-COPD patients as compared to ARDS patients, most of them being treated by ECCO2R while on IMV [6, 18]. Interestingly, we observed that ECCO2R was used, as the third main indication, in acute severe asthma patients while

### Table 3

| Catheter size: n (%) | Hemolung | iLa Activve |
|----------------------|----------|------------|
| 15.5 F               | 53 (100) | 9 (53)     |
| 18 F                 |          | 8 (47)     |

| Canula site: n (%)  | 0.539    |
|---------------------|----------|
| Right internal jugular vein | 32 (60) |
| Femoral vein        | 21 (40)  |

| Respiratory support: n (%) | 0.895 |
|---------------------------|-------|
| IMV                       | 44 (83) |
| NIV                       | 9 (9)   |

| ECCO2R duration (days)    | 5 (3–8) |
|---------------------------|---------|
| Number of membrane lung per patient | 1       |

Results are expressed as count and proportion for categorical variables.

### Table 4

| Type of ventilatory support when starting ECCO2R | IMV | NIV |
|--------------------------------------------------|-----|-----|
| n (%)                                            | 59 (84%) | 11 (16%) |

| Reasons for stopping ECCO2R                     | IMV | NIV |
|-------------------------------------------------|-----|-----|
| Success                                         | 28 (47%) | 5 (45%) |
| Adverse events                                  | 17 (29%) | 1 (9%) |
| Transition to ECMO                              | 0 (0%) | 0 (0%) |
| Death                                           | 7 (12%) | 2 (18%) |
| Limitation of life-sustaining therapy decision | 7 (12%) | 3 (27%) |

| IMV weaning                                      | 28 (47%) | NA |
| NIV weaning                                      | NA       | 5 (45%) |
| Tracheal intubation                              | NA       | 1 (9%) |
| In-ICU mortality                                 | 27 (46%) | 7 (64%) |

Results are expressed as count and proportion for categorical variables.

Abbreviations: IMV invasive mechanical ventilation, NIV non-invasive ventilation

| ECCO2R-related adverse events | Hemolung | iLa Activve | p     |
|-------------------------------|----------|------------|-------|
| Catheterization failure       | 2 (4%)   | 1 (4%)     | 1     |
| Biological hemolysis          | 15 (28%) | 0 (0%)     | 0.033 |
| Clinically significant hemolysis | 6 (11%) | 0 (0%)     | 0.147 |
| Bleeding                      | 16 (30%) | 1 (6%)     | 0.042 |
| Membrane clotting             | 4 (8%)   | 7 (41%)    | <0.001|
| Catheter infection            | 0 (0%)   | 1 (6%)     | 0.075 |
| Device malfunction            | 4 (8%)   | 2 (12%)    | 0.638 |
| ECCO2R-related death          | 3 (6%)   | 0 (0%)     | 0.316 |

Results are expressed as counts and proportions. Biological hemolysis was defined by at least one measurement of serum-free hemoglobin higher than 100 mg/l without clinically significant hemolysis.

Augy et al. Journal of Intensive Care (2019) 7:45 Page 5 of 8
on IMV, despite the scarcity of data [19–21]. ECCO2R indication in asthma was probably driven by a strong physiopathological rational, aiming at both limiting the levels of hypercapnia and of dynamic hyperinflation.

The physiological efficacy of ECCO2R was confirmed by the respiratory parameters observed at day 1. A significant reduction in median $V_T$ was observed in ARDS patients from 5.9 to 4.1 ml/kg (PBW); in line with an ultra-protective ventilation strategy. However, our results are limited by the lack of systematic recordings of respiratory rate and plateau pressure after initiation of ECCO2R in ARDS patients. As a consequence, we cannot precisely address these additional components of an ultraprotective ventilation strategy. A significant reduction in PaCO2 values was observed in AE-COPD patients, with no modification in median $V_T$. No systematic assessment of dynamic hyperinflation and/or work of breathing was planned in the study and accordingly recorded in the dedicated form, and no specific recommendations were made for respiratory setting adjustments under ECCO2R, so we cannot indicate to what extent improvements in such important parameters were also observed in AE-COPD patients. The median ECCO2R duration was of 5 days whatever the device, which is less than the maximal duration of use indicated by the firms.

We observed a 50% ICU mortality rate. Such a high mortality rate could be explained by the inclusion of very severe patients (as illustrated by the number of limitation of life-sustaining therapies or measure decisions), by the inclusion of patients with very severe conditions outside the main ECCO2R indications (possibly of poorer prognosis), and by a learning curve in the majority of the centers, therefore possibly minimizing ECCO2R benefits. The number of limitation of life-sustaining therapies or measure decisions could be explained mainly by the inclusion of ARDS patients, in which such decisions are frequent during the course of the disease [22]. Another explanation for the observed high mortality rate could be the lack of inclusion of trauma patients in the ARDS group. Indeed, trauma is a condition generally associated with a better short-term prognosis than for other ARDS etiologies [23]. We observed 3 (4%) ECCO2R-related deaths, which seem higher than in previous reports [6, 8, 24] and higher than the treatment-related mortality hypothesis retained in a physiological precision medicine study, aiming to identify the best ARDS candidates for inclusion in a randomized trial on ultra-protective ventilation [25].

Bleeding was reported in 17 (24%) patients, more frequently associated with the Hemolung device, despite a similar heparin regimen. One explanation could be a more frequent occurrence of an acquired Willebrand disease, as recently suggested with the Hemolung device [26]. Further studies are needed to explore such a hypothesis. Such results also highlight the need to optimize an anticoagulation regimen in ECCO2R patients. Membrane clotting was more frequently reported with the iLA Activve and led to ECCO2R discontinuation in nearly half of the cases. It seems possible that the higher rate of membrane clotting could be explained by easier membrane visualization for the iLA Activve circuit. Biological hemolysis was reported only in patients treated with the Hemolung device. An explanation could be in link with the different configuration of the devices, with different velocity profiles in pumps and membranes. The lack of pressure monitoring could also be involved, since very negative drainage pressures could have been more easily detected with the iLA Activve device. However, the clinical signification of a pure biological hemolysis as defined in the study remains to be established, especially if transient. Nevertheless, there was also a trend to more frequent clinical hemolysis in patients treated with the Hemolung device.

The limits of the study are those of a register, with differences between centers according to indications, learning curves, and frequency of utilization. Indeed, there were no precisely defined criteria for ECCO2R initiation, outside the general proposal of initiating ECCO2R for achieving ultraprotective ventilation in ARDS patients and to prevent NIV failure or to shorten the duration of intubation in AE-COPD patients. There were a higher number of patients treated with the Hemolung device, which was available prior to the iLA Activve device. Since the choice between devices was not randomized, any comparisons between devices must be considered with caution. Indications outside ARDS, AE-COPD, and asthma were too scarce to infer valuable conclusions (even preliminary) about the efficacy of ECCO2R in such settings.

**Conclusion**

We report the feasibility of an ECCO2R registry in a large metropolitan area. Based on the first 70 patients, we report a lower than expected rate of ECCO2R device utilization, mainly in severe COPD and ARDS patients. Physiological efficacy was confirmed in these two populations. We also confirmed safety concerns such as hemolysis, bleeding, and thrombosis with different profiles between the devices. Our results could help to design future studies aiming to enhance safety, to demonstrate a still-lacking strong clinical benefit of ECCO2R, and to guide the choice between the different devices. In the meantime, use of ECCO2R should be limited to clinical trials and/or registries, due to an uncertain benefit-risk ratio.
Abbreviations
AE-COPD: Chronic obstructive pulmonary disease acute exacerbation; AE: Adverse event; AGEPS: Assistance Publique–Hôpitaux de Paris Institutional Pharmacy Agency; AP-HP: Assistance Publique–Hôpitaux de Paris; ARDS: Acute respiratory distress syndrome; CO2: Carbon dioxide; COPD: Chronic obstructive pulmonary disease; EECO2R: Extracorporeal carbon dioxide removal; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; IV: Non-invasive ventilation; PaCO2: Carbon dioxide arterial pressure; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; RBC: Red blood cells; RCT: Randomized clinical trial; SAE: Serious adverse event; SAPS II: Simplified acute physiology score II; Vt: Tidal volume; Xa: Clotting factor X activated

Acknowledgements
Not applicable.

Authors’ contributions
JLD, CR, EM, MF, AMD, JDC, SG, AC, BM, EC, SH, and MP contributed to the study design. JLA, NA, RP, NA, CB, YC, SV, AD, JLD, CR, EM, MF, AMD, JDC, SG, AC, and BM collected the data. JLA, NA, and JLD analyzed the data. JLD, CR, EM, MF, AMD, JDC, SG, AC, BM, EC, SH, and MP interpreted the data. JLA, NA, and JLD prepared the report. All authors read and approved the final manuscript.

Funding
No specific funding was provided for the study.

Availability of data and materials
Datasets are available in the coordinating center.

Ethics approval and consent to participate
The study was approved by the Ethical Committee of the French Intensive Care Society and by the “Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé,” a governmental committee on the use of information in the health domain. A written information form was given and orally explained to patients or proxies, who had the possibility to decline the utilization of data.

Consent for publication
Not applicable.

Competing interests
Dr. Diehl reported receiving research support and personal fees from Alung and Novakings/Venics.

Author details
1Service de Médecine Intensive Réanimation, AP-HP, Hôpital Européen Georges Pompidou, Paris, France. 2Service de Médecine Intensive Réanimation, AP-HP, Hôpital de Bicêtre, Le Kremlin Bicêtre, France. 3Service de Médecine Intensive Réanimation, AP-HP, Hôpital Saint-Antoine, Paris, France. 4Service de Réanimation Polyvalente, AP-HP, Hôpital Tenon, Paris, France. 5Service de Médecine Intensive Réanimation, AP-HP, Hôpital Henri Mondor, Créteil, France. 6Service de Réanimation Polyvalente, Centre Hospitalier de Longjumeau, Longjumeau, France. 7Service de Réanimation Polyvalente, AP-HP, Hôpital Avicenne, Bobigny, France. 8Service de Médecine Intensive Réanimation, AP-HP, Hôpital Cochin, Paris, France. 9Service de Réanimation Polyvalente, AP-HP, Hôpital Louis Mourié, Colombes, France. 10Service de Médecine Intensive Réanimation, AP-HP, Hôpital Lariboisière, Paris, France. 11AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation, Département R3S, Sorbonne Université, INSERM, UMR1158 Neurophysiologie Respiratoire Experimentionelle et Clinique, Paris, France. 12Service de Médecine Intensive Réanimation, AP-HP, Hôpital Pitié-Salpêtrière, Institut de Cardiologie, Paris, France. 13AP-HP, Office du Transfert de Technologie et des Partenariats Industriels, Paris, France. 14AP-HP, Agence Générale des Equipements et des Produits de Santé, Paris, France. 15Faculty of Pharmacy, INSERM UMR-S1140, Paris Descartes University, Paris, France.

Received: 22 March 2019 Accepted: 12 August 2019
Published online: 20 August 2019

References
1. Taccone FS, Maflertheiner MV, Ferrari F, Di Nardo M, Swol J, Breman LM, et al. Extracorporeal CO2 removal in critically ill patients: a systematic review. Minerva Anestesiologica. 2017;83:762–72.
2. Morelli A, Del Sorbo L, Pensiati A, Ranieri VM, Fan E. Extracorporeal carbon dioxide removal (ECCO2R) in patients with acute respiratory failure. Intensive Care Med. 2017;43:59–30.
3. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Briccoco A, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology. 2009;111:826–35.
4. Fanelli V, Ranieri MV, Mancebo J, Moerter O, Quintet M, Morley S, 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.
5. Schmidt M, Jaber S, Zoghbi E, Godet T, Capellier G, Combos A. 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. Crit Care. 2018;22:122.
6. Winiszewski H, Aptel F, Belon F, Belin N, Chaignat C, Patry C, et al. Daily use of extracorporeal CO2 removal in a critical care unit: indications and results. J Intensive Care. 2018;6:36.
7. Bein T, Weber-Canterns S, Goldmann A, Müller T, Staudinger T, Bredelaur J, et al. Lower tidal volume strategy (4–6 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;39:847–56.
8. On behalf of the European Society of Intensive Care Medicine Trials Group and the “Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS” (SUPERNOVA) investigators, Combos A, Fanelli V, Pham T, Ranieri VM. Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. Intensive Care Med. 2019;45:592–600.
9. Grasso S, Stripoli T, Mazzone P, Pezzuto M, LaCignola L, Centonze P, et al. Low respiratory rate plus minimally invasive extracorporeal CO2 removal decreases systemic and pulmonary inflammatory mediators in experimental acute respiratory distress syndrome. Crit Care Med. 2014;42:e451–60.
10. Burki NK, Mani RK, Herth FJF, Schmidt W, Teshchler H, Bonin F, et al. A novel extracorporeal CO2 removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest. 2013;143:78–86.
11. Kluge S, Braune SA, Engel M, Nierhaus A, Frings D, Ebel H, et al. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med. 2012;38:1632–9.
12. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, 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;43:120–7.
13. Braune S, Sieweke A, Blettner F, Staedtling T, Joannidis M, Verbrugge S, et al. 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;42:1347–44.
14. Dehl JL, Piquilloud L, Richard J-CM, Mancebo J, Mercart A. Effects of extracorporeal carbon dioxide removal on work of breathing in patients with chronic obstructive pulmonary disease. Intensive Care Med. 2016;42:951–2.
15. Boyle AJ, Sklar MC, McNamme JJ, Brodie D, Slusky AS, Birchard L, et al. Extracorporeal carbon dioxide removal for lowering the risk of mechanical ventilation: research questions and clinical potential for the future. Lancet Respir Med. 2018;6:874–84.
16. Richard C, Argaud L, Blet A, Boulian T, Contentin L, Dechartres A, et al. Assistance extracorporelle au cours du syndrome de détresse respiratoire aiguë chez l’adulte et l’enfant (à l’exclusion du nouveau-né). Conférence de consensus organisée par la Société de réanimation de langue française. Réanimation. 2013;22:548–66.
17. Epuration extracorporelle du CO2. Avis du CEDIT Juin 2014 http://cedit.aphhp.fr/hospital-based-hta-evaluation-de-technologies-de-sante-a-l-hotelier/epuration-extra-corporelle-du-co2/. Accessed 07 July 2019.
18. Deniau B, Ricard JD, Messika J, Dreyfuss D, Gaudry S. Use of extracorporeal carbon dioxide removal (ECCO2R) in 239 intensive care units: results from a French national survey. Intensive Care Med. 2016;42:624–5.
19. Schneider T-M, Bence T, Brettner F. “Awake” ECCO2R supersedes intubation in a near-fatal asthma attack. J Intensive Care. 2017;5:53.
20. Brenner K, Abrams DC, Agerstrand CL, Brodie D. Extracorporeal carbon dioxide removal for refractory status asthmaticus: experience in distinct exacerbation phenotypes. Perfusion. 2014;29:26–8.
21. Pavot A, Mallat J, Vangrunderbeeck N, Thevenin D, Lemyze M. Rescue therapeutic strategy combining ultra-protective mechanical ventilation with extracorporeal CO2 removal membrane in near-fatal asthma with severe pulmonary barotraumas: a case report. Medicine (Baltimore). 2017;96:e8248.
22. The LUNG SAFE Investigators and the ESICM Trials Group, Laffey JG, Bellani G, Pham T, Fan E, Madotto F, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med. 2016;42:1865–76.
23. El-Haddad H, Jang H, Chen W, Soubani AO. Effect of ARDS severity and etiology on short-term outcomes. Respir Care. 2017;62:1178–85.
24. Sklar MC, Beloncle F, Katsios CM, Brochard L, Friedrich JO. Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. Intensive Care Med. 2015;41:1752–62.
25. Goligher EC, Amato MBP, Slutsky AS. Applying precision medicine to trial design using physiology: Extracorporeal CO2 removal for acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;196:558–68.
26. Kalbhen J, Neuffer N, Zieger B, Schmutz A. Is extracorporeal CO2 removal really “safe” and “less invasive”? Observation of blood injury and coagulation impairment during ECCO2R. ASAIO J Am Soc Artif Intern Organs. 2017;63:666–71.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.