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A 2-year multicenter, observational, prospective, cohort study on extracorporeal CO_2 removal in a large metropolis area

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Abstract

Background: Extracorporeal carbon dioxide removal ($ECCO_2R$) 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 $ECCO_2R$ 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). $ECCO_2R$ 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 Activve 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 V_T was observed in ARDS patients from 5.9 to 4.1 ml/kg (p <0.001). A reduction in $PaCO_2$ values was observed in AE-COPD patients from 67.5 to 51 mmHg (p< 0.001). Median duration of $ECCO_2R$ was 5 days (IQR 3–8). Reasons for $ECCO_2R$ discontinuation were improvement ($n = 33$), $ECCO_2R$-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 $ECCO_2R$-related.

Conclusions: Based on a registry, we report a low rate of $ECCO_2R$ 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 $ECCO_2R$, and to guide the choice between different devices.

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

Keywords: Extracorporeal CO_2 removal, Acute respiratory distress syndrome, COPD exacerbation, Safety

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Introduction

Extracorporeal CO_2 removal ($ECCO_2R$) 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 $ECCO_2R$ in ARDS is to implement an ultra-protective 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 $ECCO_2R$ within clinical trials and/or to contribute to data registries [1, 2, 15, 16].

Accordingly, within the great Paris area, the use of the $ECCO_2R$ 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 $ECCO_2R$ activity, to authorize the use of $ECCO_2R$ in selected voluntary centers, to organize a systematic recording of the activity on an individual basis, and to reassess periodically the $ECCO_2R$ 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 $ECCO_2R$ patient and to strictly follow user's guides developed by the firms.

$ECCO_2R$ 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 $ECCO_2R$ 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 $ECCO_2R$, type of $ECCO_2R$ device, type and site of veno-venous $ECCO_2R$ catheter, type of ventilatory support, concomitant treatments, adverse events (AE) and serious adverse events (SAE), reason for $ECCO_2R$ discontinuation, and respiratory and general follow-up until ICU discharge or death.

Endpoints

The primary outcome was the number of patients treated by $ECCO_2R$ 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 $ECCO_2R$ 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 association to hemodynamic instability. Membrane clotting was defined as apparent membrane clotting after a daily visual inspection or suspected massive membrane clotting leading to $ECCO_2R$ cessation and further confirmed by analysis of the circuit.

Statistical analyses

The primary outcome is reported as median and extreme values. Other continuous variables are reported as median (interquartile range) (IQR) and categorical variables are reported as count and proportion. Categorical variables were compared using the Fisher exact test. Between-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 $ECCO_2R$ 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 patients 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 $ECCO_2R$ 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 chemotherapy in 1, and smoke inhalation in 1. Table 2 indicates baseline demographics in the two main indications: 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, unilateral 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 $ECCO_2R$ as part of a registered interventional clinical trial.

Table 1 Baseline characteristics of the population

Age (years)	65 (61–74)
Male patients	41 (59%)
BMI (kg/m^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)
$PaCO_2$ (mmHg)	64 (56–73)
V_T (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, V_T tidal volume, *PBW* predicted body weight, *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation

The median time between ICU admission and $ECCO_2R$ initiation was 3 days [1–9]. For IMV patients, the median IMV duration before $ECCO_2R$ 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 $ECCO_2R$ in AE-COPD and ARDS patients. A significant reduction in median V_T was observed in ARDS patients from 5.9 to 4.1 ml/kg (predicted body weight, PBW), in line with an ultra-protective ventilation strategy. A significant reduction in $PaCO_2$ values was observed in AE-COPD patients.

Table 2 Demographics, ventilator course, and clinical course according to the two main indications of $ECCO_2R$

	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 $ECCO_2R$:		
V_T (ml/kg PBW)	8.0 (7.8–8.1)	5.9 (5.5–6.0)
Applied PEEP (cmH_2O)	0 (0–0)	10 (5–15.5)
FiO_2 (%)	35 (30–38)	60 (50–70)
Measured parameters under IMV before $ECCO_2R$:		
Plateau pressure (cmH_2O)	NA	28 (27–29)
Total PEEP (cmH_2O)	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)
$ECCO_2R$ device		
iLa Activve: *n* (%)	5 (17%)	6 (25%)
Hemolung: *n* (%)	25 (83%)	18 (75%)
IMV settings and measured parameters at day 1 after starting $ECCO_2R$:		
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)
$ECCO_2R$ 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 $ECCO_2R$	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 $ECCO_2R$
**$p < 0.05$ as compared to values before $ECCO_2R$

Median $ECCO_2R$ duration was 5 days [3–8] without difference between the two medical devices ($p = 0.812$). Main reasons for $ECCO_2R$ discontinuation were improvement in clinical condition in 33 patients, $ECCO_2R$-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 $ECCO_2R$ because of improvement died in ICU. Twenty-eight patients among the 59 under IMV when starting $ECCO_2R$ were weaned from IMV. Among the 11 patients under NIV when starting $ECCO_2R$, 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 3 Technical settings and medical conditions according to the use of the two medical devices

	Hemolung $n = 53$	iLa Activve $n = 17$	p
Catheter size: *n* (%)			
15.5 F	53 (100)		
18 F		9 (53)	
24 F		8 (47)	
Canula site: *n* (%)			0.539
Right internal jugular vein	32 (60)	9 (53)	
Femoral vein	21 (40)	8 (47)	
Respiratory support: *n* (%)			0.895
IMV	44 (83)	15 (88)	
NIV	9 (9)	2 (6)	
$ECCO_2R$ duration (days)	5 (3–8)	5 (3–9)	0.812
Number of membrane lung per patient	1	1	1

Results are expressed as count and proportion for categorical variables

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 $ECCO_2R$-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 $ECCO_2R$-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 $ECCO_2R$ discontinuation in 6 patients. Lung membrane clotting was reported in 11 patients leading to $ECCO_2R$ 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 $ECCO_2R$ discontinuation in 6 patients.

Table 4 Clinical course after ECCO2R initiation depending on the initial ventilatory support

Type of ventilatory support when starting $ECCO_2R$	IMV	NIV
n (%)	59 (84%)	11 (16%)
Reasons for stopping $ECCO_2R$		
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

Table 5 $ECCO_2R$-related adverse events

n (%)	Hemolung $n = 53$	iLa Activve $n = 17$	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
$ECCO_2R$-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

Device malfunction leading to $ECCO_2R$ 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 $ECCO_2R$ 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, $ECCO_2R$ 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 $ECCO_2R$ multicenter initiatives and permitted to confirm and/or to extend efficacy and safety information as well as to introduce $ECCO_2R$ as a therapeutic option in selected centers.

As expected, we report a preferential $ECCO_2R$ 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 $ECCO_2R$ while on IMV [6, 18]. Interestingly, we observed that $ECCO_2R$ was used, as the third main indication, in acute severe asthma patients while

on IMV, despite the scarcity of data [19–21]. $ECCO_2R$ 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 $ECCO_2R$ 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 $ECCO_2R$ in ARDS patients. As a consequence, we cannot precisely address these additional components of an ultraprotective ventilation strategy. A significant reduction in $PaCO_2$ 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 $ECCO_2R$, so we cannot indicate to what extent improvements in such important parameters were also observed in AE-COPD patients. The median $ECCO_2R$ 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 $ECCO_2R$ indications (possibly of poorer prognosis), and by a learning curve in the majority of the centers, therefore possibly minimizing $ECCO_2R$ 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%) $ECCO_2R$-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 $ECCO_2R$ patients. Membrane clotting was more frequently reported with the iLA Activve and led to $ECCO_2R$ 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 $ECCO_2R$ initiation, outside the general proposal of initiating $ECCO_2R$ 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 $ECCO_2R$ in such settings.

Conclusion

We report the feasibility of an $ECCO_2R$ registry in a large metropolis area. Based on the first 70 patients, we report a lower than expected rate of $ECCO_2R$ 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 $ECCO_2R$, and to guide the choice between the different devices. In the meantime, use of $ECCO_2R$ 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; CO_2: Carbon dioxide; COPD: Chronic obstructive pulmonary disease; $ECCO_2R$: Extracorporeal carbon dioxide removal; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; NIV: Non-invasive ventilation; $PaCO_2$: 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; V_T: Tidal volume; Xa: Clotting factor X activated

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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.

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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 Novalung/Xenios.

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