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Extracorporeal CO_2 removal in acute exacerbation of COPD unresponsive to non-invasive ventilation

Mathilde Azzi ,[1] Jerome Aboab,[1] Sophie Alviset,[1] Daria Ushmorova,[1] Luis Ferreira,[1] Vincent Ioos ,[1] Nathalie Memain,[1] Tazime Issoufaly,[1] Mathilde Lermuzeaux,[1] Laurent Laine,[1] Rita Serbouti,[2] Daniel Silva[1]

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[1]Service de Médecine Intensive Réanimation, Centre Hospitalier de Saint Denis, Saint Denis, France
[2]Medical Affairs, Fresenius Medical Care France SAS, Fresnes, Île-de-France, France

Correspondence to
Dr Mathilde Azzi;
mathilde.azzi@ch-stdenis.fr

ABSTRACT

Background The gold-standard treatment for acute exacerbation of chronic obstructive pulmonary disease (ae-COPD) is non-invasive ventilation (NIV). However, NIV failures may be observed, and invasive mechanical ventilation (IMV) is required. Extracorporeal CO_2 removal ($ECCO_2R$) devices can be an alternative to intubation. The aim of the study was to assess $ECCO_2R$ effectiveness and safety.

Methods Patients with consecutive ae-COPD who experienced NIV failure were retrospectively assessed over two periods of time: before and after $ECCO_2R$ device implementation in our ICU in 2015 (Xenios AG).

Results Both groups ($ECCO_2R$: n=26, control group: n=25) were comparable at baseline, except for BMI, which was significantly higher in the $ECCO_2R$ group (30 kg/m² vs 25 kg/m²). pH and $PaCO_2$ significantly improved in both groups. The mean time on $ECCO_2R$ was 5.4 days versus 27 days for IMV in the control group. Four patients required IMV in the $ECCO_2R$ group, of whom three received IMV after $ECCO_2R$ weaning. Seven major bleeding events were observed with $ECCO_2R$, but only three led to premature discontinuation of $ECCO_2R$. Eight cases of ventilator-associated pneumonia were observed in the control group. Mean time spent in the ICU and mean hospital stay in the $ECCO_2R$ and control groups were, respectively, 18 vs 30 days, 29 vs 49 days, and the 90-day mortality rates were 15% vs 28%.

Conclusions $ECCO_2R$ was associated with significant improvement of pH and $PaCO_2$ in patients with ae-COPD failing NIV therapy. It also led to avoiding intubation in 85% of cases, with low complication rates.

Trial registration number ClinicalTrials.gov, NCT04882410. Date of registration 12 May 2021, retrospectively registered. https://www.clinicaltrials.gov/ct2/show/NCT04882410.

Key messages

- The key question: extracorporeal CO_2 removal ($ECCO_2R$) effectiveness and safety
- We observed a much better clinical response compared with previous studies, leading to avoiding intubation in 85% of cases despite including severe patients with chronic obstructive pulmonary disease (COPD), some of them receiving long-term oxygen therapy or NIV at home (which were excluded in previous studies). Indeed, only four patients of the $ECCO_2R$ group had to be intubated. For all but one, intubation occurred after $ECCO_2R$ weaning.
- We observed a much lower rate of major bleeding complications compared with previous studies. Just over 20% of patients with $ECCO_2R$ (six patients) experienced significant bleeding complications and only three led to premature discontinuation of $ECCO_2R$ (despite patients being obese and thus more difficult to cannulate). In the ÉCLAIR study (by Braune *et al*[15]), 11 major bleeding events occurred among the 25 patients treated with the same $ECCO_2R$ device.
- Good results and low complication rate are likely to revive the discussion about the role of $ECCO_2R$ in the therapeutic arsenal of COPD acute decompensation.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a frequent pathology. It is commonly complicated by acute exacerbations (ae-COPD), which are associated with a significant increase in mortality.[1]

Independently of the aetiologic treatment of exacerbations, non-invasive ventilation (NIV) has significantly improved the prognosis of these exacerbations. Nevertheless, nearly 20% of NIV-treated patients require invasive mechanical ventilation (IMV).[2 3] IMV initiation is unquestionably considered a failure and is associated with significant mortality,[4 5] particularly due to ventilator-associated pneumonia.[6]

The extracorporeal CO_2 removal ($ECCO_2R$) device eliminates a portion of CO_2 through extracorporeal circulation but cannot oxygenate the blood because of the low flow system. Advances in technology and a better knowledge of the technique have enabled its use in patients with ae-COPD.[7] Combined with NIV, the use of $ECCO_2R$ in patients with ae-COPD may enhance CO_2

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removal effectiveness, lowering the respiratory rate and, thus, minimising dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP). Thus, work of breathing can be reduced and CO_2 production from respiratory muscles lowered.[8] The absence of sedation allows patients to receive active physiotherapy preventing muscle deconditioning.

Two potential benefits for patients with ae-COPD are currently being investigated, that is, to avoid the use of IMV in case of NIV failure and to facilitate IMV weaning.[9–12] Studies assessing $ECCO_2R$ in patients with ae-COPD are scarce and all had a small study sample.

Besides potential benefits, $ECCO_2R$ is associated with adverse effects. This technique requires inserting intravascular cannulas and administering anticoagulant therapy, which expose patients to major bleeding risks. A benefit-risk approach is, therefore, necessary before offering this treatment on a larger scale.

The study objective was to confirm the effectiveness of this technique in a selected population of patients with COPD for whom NIV proved insufficient to improve clinical condition (both alveolar ventilation and work of breathing). The primary endpoint was to record $ECCO_2R$ failure (IMV or death by day 90). Secondary endpoints were effectiveness, safety and observational data.

METHODS

Study design

We performed an observational, single centre (Centre Hospitalier de Saint-Denis, Saint-Denis, France), retrospective study. Successive patients with ae-COPD with NIV failure were assessed over two periods of time: before and after $ECCO_2R$ device implementation.

Criteria used to include patients in both groups were: no improvement or worsening of respiratory acidosis after NIV treatment, and no improvement of respiratory distress signs or decreased level of consciousness. Exclusion criteria were severe hypoxaemia (F_IO_2 >40% for an oxygen saturation ≥90% with NIV), contraindications to anticoagulant therapy, contraindications to continuation of active treatment for reasons of futility.

In the control group, intubation criteria were the same as the inclusion criteria mentioned above for defining NIV failure. In the $ECCO_2R$ group, patients underwent intubation during/after $ECCO_2R$ treatment using the same criteria to which we added agitation potentially leading to self-inflicted dislocation of $ECCO_2R$ cannulas, deteriorating neurological status with loss of airway protective reflexes, development of unmanageable copious pulmonary secretions or progressive hypoxemia.

From January 2010 to February 2015—before implementation of the $ECCO_2R$ device in the ward—67 of 206 patients with ae-COPD required invasive ventilatory support. After applying the exclusion criteria, 25 patients were included in the control group (figure 1). From February 2015 to February 2020, 32 of 354 patients with ae-COPD were treated with $ECCO_2R$ (without invasive ventilation weaning). After applying the exclusion criteria, 26 patients were included in the $ECCO_2R$ group (figure 1).

NIV management

NIV was performed with Respironics V60 Ventilator (Philips Respironics: USA) in S/T mode, as recommended in our unit protocol: the pressure support was increased by 2 cmH_2O steps depending on the patient's tolerance, up to a maximum of 20 cmH_2O to reach a tidal volume of 8 mL/kg of ideal body weight. The expiratory positive airway pressure was between 5 cmH_2O and 10 cmH_2O. The FiO_2 was adapted to reach an oxygen saturation of 90%–92%. The interface was a full-face mask (PerformaTrak, Philips Respironics).

$ECCO_2R$ device

$ECCO_2R$ was performed with the Xenios console, iLA active iLA kit (Xenios AG, Heilbronn, Germany). The membrane used for every patient had a gas exchange area of 1.3 m^2. Anticoagulant therapy was maintained with continuous intravenous unfractionated heparin with anti-Xa monitoring. The anticoagulant therapy target was 0.3 IU anti-Xa/mL. Most patients had femoral cannulation with Novaport twin 24 Fr (on the right side, except for one patient). Only two patients had jugular cannulation (18 and 22 Fr). Targeted blood flow through the circuit was 1 L/min. Initiation of $ECCO_2R$ was medically and collectively decided, and cannulation was performed by a medical doctor.

IMV and sedation management

A protocol was developed for the ventilation weaning strategy and the sedation withdrawal strategy. Sedation was systematically adjusted by the nursing staff to ensure the patients' comfort and safety according to the ward's protocol, using the Richmond agitation sedation scale (RASS) score. As for weaning from mechanical ventilation and according to pre-established criteria, pressure support was reduced until patients were considered ready for extubation.

Data collection

Data collected (patient characteristics, arterial blood gas, report of $ECCO_2R$ adverse effects, outcomes, and duration) during the two periods (before and after ECCO2R device implementation in the ward) were extracted from each patient's electronic health record. A first request including the inclusion criteria allowed identification of each patient. Data were then exported to a single anonymised datasheet from the various databases containing texts, treatments, biological results and various dates to calculate duration of hospitalisation, etc. Analyses were then carried out using this material.

Blood gas tests were performed at various time points: 6 hours before intervention ($ECCO_2R$ or endotracheal

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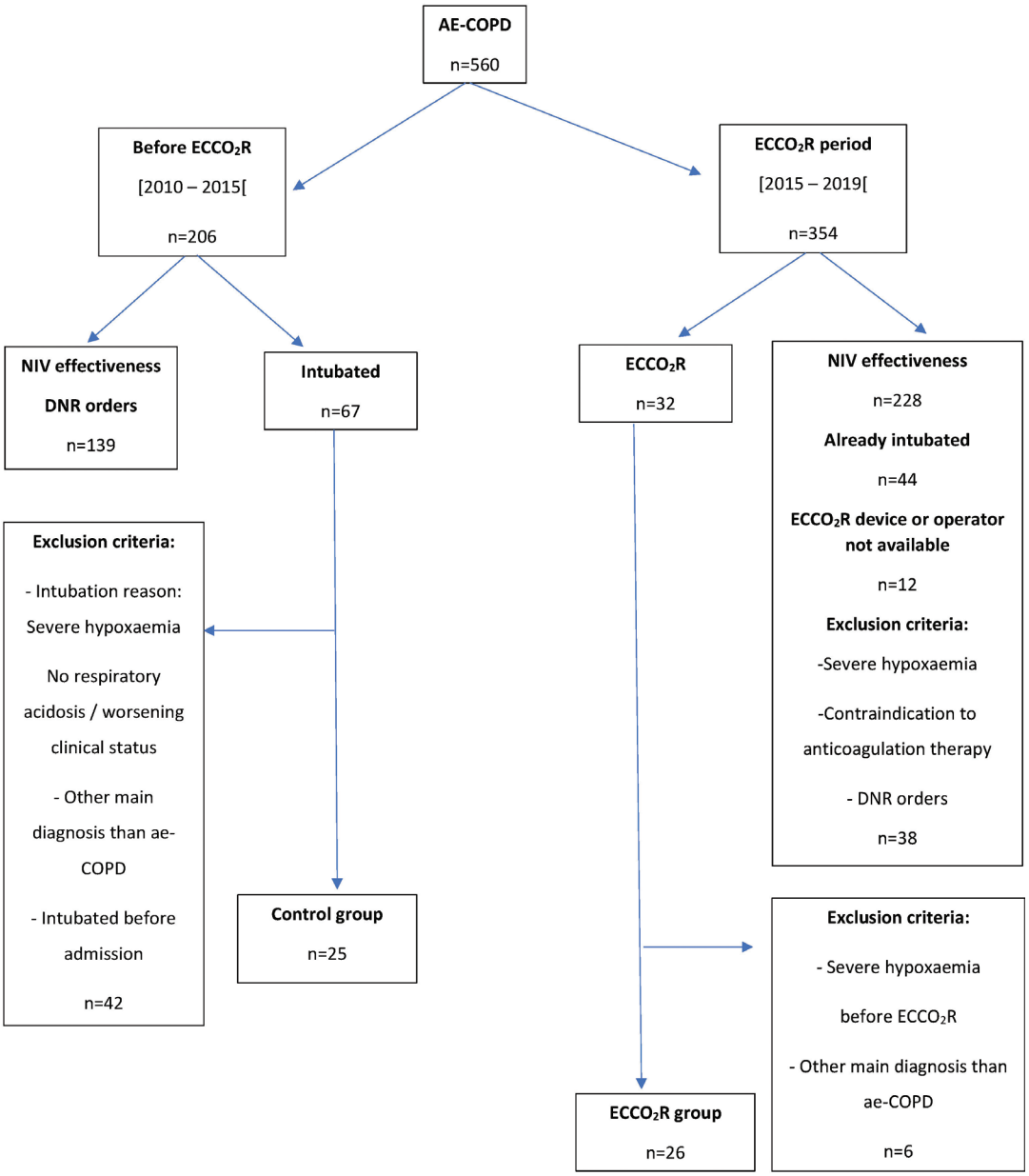

Figure 1 Flow chart. Ae-COPD, acute exacerbation of chronic obstructive pulmonary disease; DNR, do not resuscitate order; $ECCO_2R$, extracorporeal CO_2 removal; NIV, non-invasive ventilation.

intubation), 2 hours before intervention, 6 hours after intervention, 24 hours after intervention and before decannulation or extubation. Major bleedings were defined by fatal bleeding or symptomatic bleeding in a critical site or fall in haemoglobin level of more than 2 g/dL or bleeding leading to transfusion of two or more units of packed red blood cells.[13] Thrombocytopenia was defined by a blood platelet count below 100 G/L with more than half of the baseline count. Haemodynamic instability was defined by the need for catecholamine administration.

Statistical analysis

The R Studio software (V.1.2.1335 2009–2019 RStudio) was used for analyses. Variables are reported as mean±SD for quantitative data and number (percentage) for categorical data. Population distribution was tested with the Shapiro-Wilk normality test. Quantitative variables were compared with t test or paired t test with a 95% CI and with Welch's two-sample t test when the two populations had unequal variances. As one of the variables was not following a normal distribution, we used Wilcoxon rank sum test with continuity correction. Qualitative variables were compared with Pearson's χ^2 test, with or without Yates' continuity correction, depending on the theoretical distribution of variables. The analyses were conducted at a two-sided alpha level of 5%.

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Patient and public involvement

Patients with ae-COPD experiencing NIV failure require mechanical ventilation, preventing them from talking and moving. One of our motivations was to find an alternative for them to regain some autonomy during the hospital stay.

We performed a non-randomised study with a before/after design. Patients were not involved in the study design, neither were they involved in the recruitment or conduct of the study.

The study results will be disseminated to study participants on request, in accordance with French law. They will also be published on the hospital website.

Ethics

Individual patient information, collective information within the facility, opposition possibility and a data protection strategy were, thus, required. Patients were informed by individual letters of the use of their anonymous data, with the possibility to object to their participation in the study.

The database was declared to the French Data Protection Authority (CNIL, 'Commission nationale de l'informatique et des libertés'). Data processing was conducted on an anonymised datasheet.

RESULTS

Patient characteristics

Patients were mostly men (72%) with a mean±SD age of 69±11 years. Both groups ($ECCO_2R$ group: n=26, IMV group: n=25) were comparable at baseline, except for BMI, which was significantly higher in the $ECCO_2R$ group (30 kg/m² vs 25 kg/m²) (table 1). Comorbidities were similar in both groups (hypertension, diabetes, heart failure, coronary heart disease, atrial fibrillation, stroke). In the $ECCO_2R$ group, 11 (42%) and 7 (27%) patients, respectively, received long-term oxygen therapy (LTOT) and NIV prior to hospitalisation. No significant difference was observed compared with the IMV group. Four patients (15%) had an exacerbation related to influenza in the $ECCO_2R$ group, whereas none of them in the IMV group.

Arterial blood gas tests (pH, $PaCO_2$, PaO_2 and HCO_3) carried out 6 hours before intervention did not differ between both groups. All patients had pH <7.35 and $PaCO_2$ >45 mm Hg. In the $ECCO_2R$ group, 19 patients (73%) had a $PaCO_2$ > 75 mm Hg and 15 patients (58%) had a pH <7.25 before intervention.

Table 1 Baseline patient characteristics

Patient characteristics	$ECCO_2R$ group (n=26)	Control group (n=25)	P value
Demographic data			
Gender (male)	20 (77)	17 (68)	0.48
Age (years)	67±12	72±11	0.08
BMI (kg/m²)	**30±9**	**25±7**	**0.035**
SAPS II	49±14	50±15	0.81
Glasgow	13±3	12,4±3,6	0.62
Comorbidities			
Hypertension	13 (50)	16 (64)	0.31
Diabetes	8 (31)	10 (40)	0.49
Renal failure	4 (15)	1 (4)	0.37
Heart failure	6 (23)	7 (28)	0.69
Coronary heart disease	6 (23)	6 (24)	0.94
Atrial fibrillation	3 (12)	6 (24)	0.42
Stroke	2 (8)	2 (8)	1
Sleep apnoea	5 (19)	2 (8)	0.45
Asthma	1 (4)	2 (8)	0.97
Cancer <5 years	2 (8)	6 (24)	0.22
Systemic corticosteroid	1 (4)	3 (12)	0.57
LTOT	11 (42)	10 (40)	0.87
NIV	7 (27)	4 (16)	0.34
Causes of exacerbation			
Influenza A	4 (15)	0	0.13
Bronchitis	15 (58)	9 (36)	0.34
Heart failure	9 (35)	6 (24)	0.41
None identified	4 (15)	10 (40)	0.09
Arterial blood gases 6 hours before			
pH	7,24±0,05	7,23±0,13	0.91
$PaCO_2$ (mm Hg)	86±21	82±24	0.64
PaO_2 (mm Hg)	69±28	78±31	0.43
Bicarbonates (mmol/L)	36±9	37±9	0.75

Values are presented as mean±SD or number (%).
BMI, body mass index; $ECCO_2R$, extracorporeal carbon dioxide removal; LTOT, long-term oxygen therapy; N/A, not applicable; NIV, non-invasive ventilation; SAPS II, Simplified Acute Physiology Score II.

Main objective

The primary endpoint was to record $ECCO_2R$ failure (IMV or death) by day 90. Five patients (19%) experienced $ECCO_2R$ failure: four patients (15%) were intubated in the $ECCO_2R$ group, among whom, three patients were no longer alive at day 90. One patient died without being intubated due to multiple organ failure.

Among these four patients requiring IMV, intubation occurred after $ECCO_2R$ weaning due to recurrent hypercapnia for three of them. Only one patient required IMV during the $ECCO_2R$ procedure, due to a haemothorax (jugular cannulation). Duration between $ECCO_2R$ weaning and IMV was 3,2±4 days (mean).

Four patients (15%) died by day 90 in the $ECCO_2R$ group compared with seven patients (28%) in the IMV group. For two patients of the $ECCO_2R$ group, death occurred after ICU discharge (table 2) (figures 2 and 3).

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Table 2 Main objective

	$ECCO_2R$ group (n=26)	Control group (n=25)	P value
$ECCO_2R$ failure (intubation OR 90-day mortality)	5 (19)	25 (100)	<0001
Intubation rate	4 (15)	25 (100)	<0001
Due to $ECCO_2R$ complication	1 (3)	–	
Due to hypoxemia	0	–	
After $ECCO_2R$ weaning	3 (11)	–	
Days between $ECCO_2R$ weaning and OTI	3,2±4	–	
90-day mortality	4 (15)	7 (28)	0.26
With/after intubation period	3 (11)	7 (28)	
With $ECCO_2R$ device	1 (4)	–	
After ICU discharge	2 (8)	0	

Values are presented as mean±SD or number (%).
$ECCO_2R$, extracorporeal carbon dioxide removal; ICU, intensive care unit; OTI, orotracheal intubation.

Effectiveness

pH and $PaCO_2$ values quickly improved in both groups without any significant difference between them (figure 4).

The pH value was significantly lower 6 hours before $ECCO_2R$ (7.24±0.05) compared with time of decannulation (7.41±0.06) (p<0.001). Likewise, the $PaCO_2$ value 6 hours before $ECCO_2R$ was significantly higher (86±21 mm Hg) than at the time of decannulation (53±10 mm Hg) (p<0.001). In the IMV group, the mean arterial blood pH value 6 hours before intubation was 7.23±0.13 and increased to 7.39±0.06 before extubation (p<0.001). The mean $PaCO_2$ value 6 hours before IMV was 82±24 mm Hg and decreased to 52±13 mm Hg before extubation (p<0.001).

The ICU length of stay in the $ECCO_2R$ group was 18±14 days compared with 30±43 days in the IMV group. The length of hospital stay was 29±22 days in the $ECCO_2R$ group compared with 49±53 days in the IMV group. No significant difference was identified for these parameters, nor for the 28-day or 90-day mortality. The 90-day mortality rate was, respectively, 15% and 28% in the $ECCO_2R$ and IMV groups (table 3).

Safety

Complications in the $ECCO_2R$ group

Seven major bleeding events occurred in six patients (23%) of the $ECCO_2R$ group.

$ECCO_2R$ was discontinued due to bleeding for 11% of patients (three patients): one patient underwent haemorrhagic shock and respiratory distress due to haemothorax during jugular cannula insertion (18 French) complicated by cardiac arrest requiring emergency intubation (the patient was still alive at day 90); another patient experienced recurrent bleeding at the cannula insertion femoral site with rectus abdominis muscle haematoma; the remaining patient had an haematoma of the right pectoral muscle (jugular insertion 22 French cannula). Of seven major bleeding events, four occurred with anti-Xa ≥0.60 IU/mL (figure 5). There were six minor bleeding episodes (minor Scarpa's fascia bleeding, epistaxis, haematuria) in five patients (20%). No cerebral or digestive bleeding event was observed (table 4).

Three patients (11%) had haemolysis due to $ECCO_2R$. Six patients had thrombocytopenia <100 G/L. Three cases of circuit thrombosis were observed, all leading to premature discontinuation of $ECCO_2R$. They occurred at 4.8 days (mean) of $ECCO_2R$. One of these patients never received the adequate dosing (under dosed) (figure 6). Anti-Xa control was usually performed two times a day.

No patient of the $ECCO_2R$ group developed pneumonia.

Complications in the IMV group

Eight patients (32%) experienced ventilator associated pneumonia (VAP). Most of these cases were late pneumonia. Twenty-five haemodynamic instability events with catecholamine administration requirement occurred in 19 patients (76%). Self-extubation was observed in six patients: all but one required reintubation (table 5).

Three patients (12%) died due to IMV-related complications: one patient had a pneumomediastinum following reintubation (self-extubation) consequently to a high intrinsic PEEP; another patient was discovered disconnected from the respiratory device; the remaining patient died due to haemorrhagic shock and respiratory distress after tracheotomy-related massive bleeding.

Observational data

Therapy initiation (IMV or $ECCO_2R$) seems to have been started earlier in the IMV group than in the $ECCO_2R$ group: respectively 20±35 hours and 42±69 hours from NIV initiation (p=0.15).

Thirteen (50%) cannulations were performed during the night shift (between 19:00 and 08:00).

NIV was continued for 18 patients (69%) of the $ECCO_2R$ group. Nine patients (35%) had high-flow nasal oxygen therapy during $ECCO_2R$ treatment because of mild hypoxemia.

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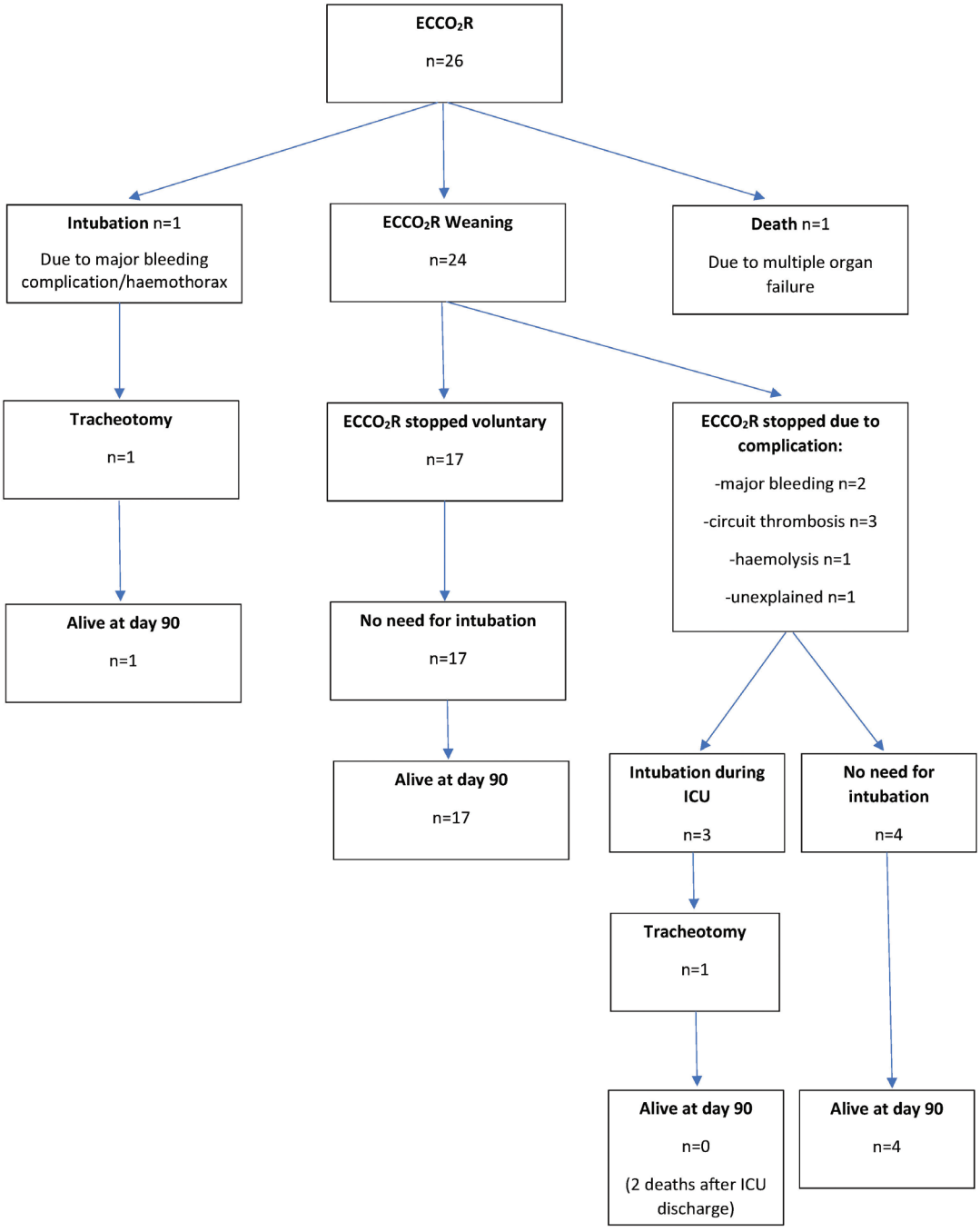

Figure 2 $ECCO_2R$ group outcomes. $ECCO_2R$, extracorporeal CO_2 removal; ICU, intensive care unit.

$ECCO_2R$ and IMV interventions lasted 5.4±4 and 27±43 days (p=0.019), respectively. Seven patients (28%) required neuromuscular blocking agent after intubation because of high intrinsic PEEP. The rate of tracheotomy in the IMV group was 20% (five patients) and 8% (two patients) in the $ECCO_2R$ group (table 6).

DISCUSSION

This study has numerous limitations. It is a retrospective, monocentric and observational study. The before/after design of the study and the extended study period may also have altered the results. However, treatments were protocolised, thus minimising the impact on our results. International recommendations on NIV, invasive ventilation and sedation were followed. These strategies are likely to homogenise the historical group of patients treated with IMV. In addition, analysed data are mostly objective numerical data that are not affected by the retrospective design. Finally, we aimed to document the feasibility of $ECCO_2R$ and not to compare $ECCO_2R$ with IMV, which is associated with different adverse effects and for which we already know the consequences in patients with COPD.

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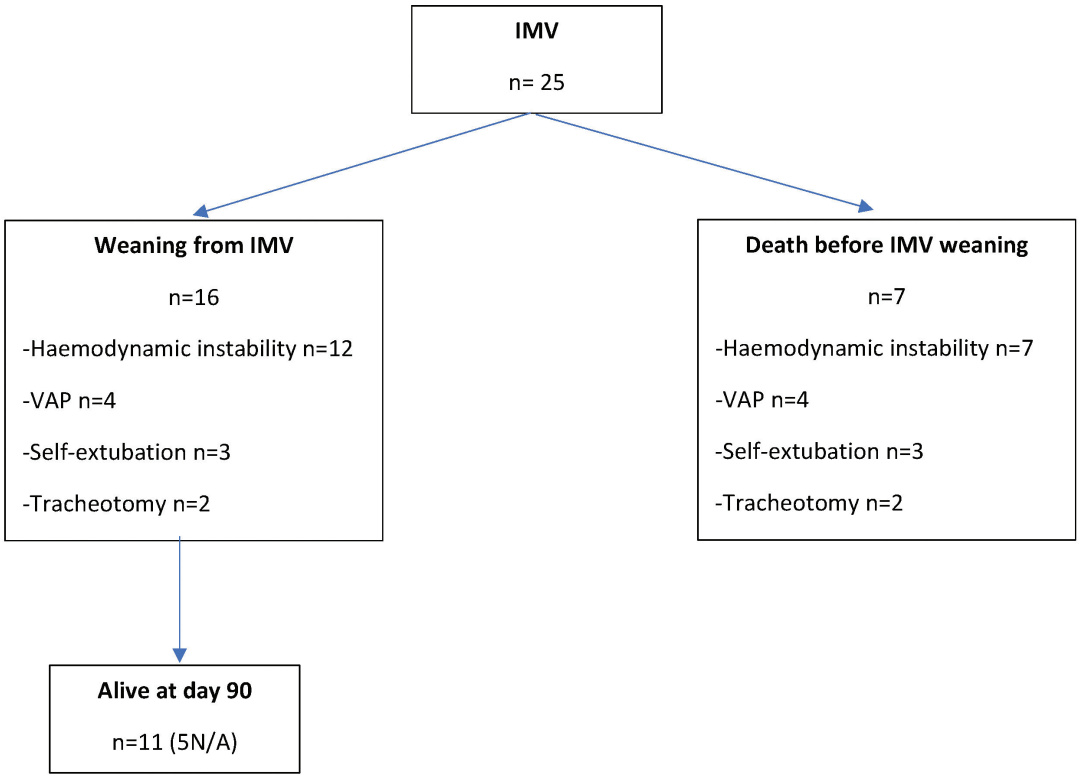

Figure 3 IMV group outcomes. IMV, invasive mechanical ventilation; N/A, non-available; VAP, ventilator-associated pneumonia. *With catecholamine administration required.

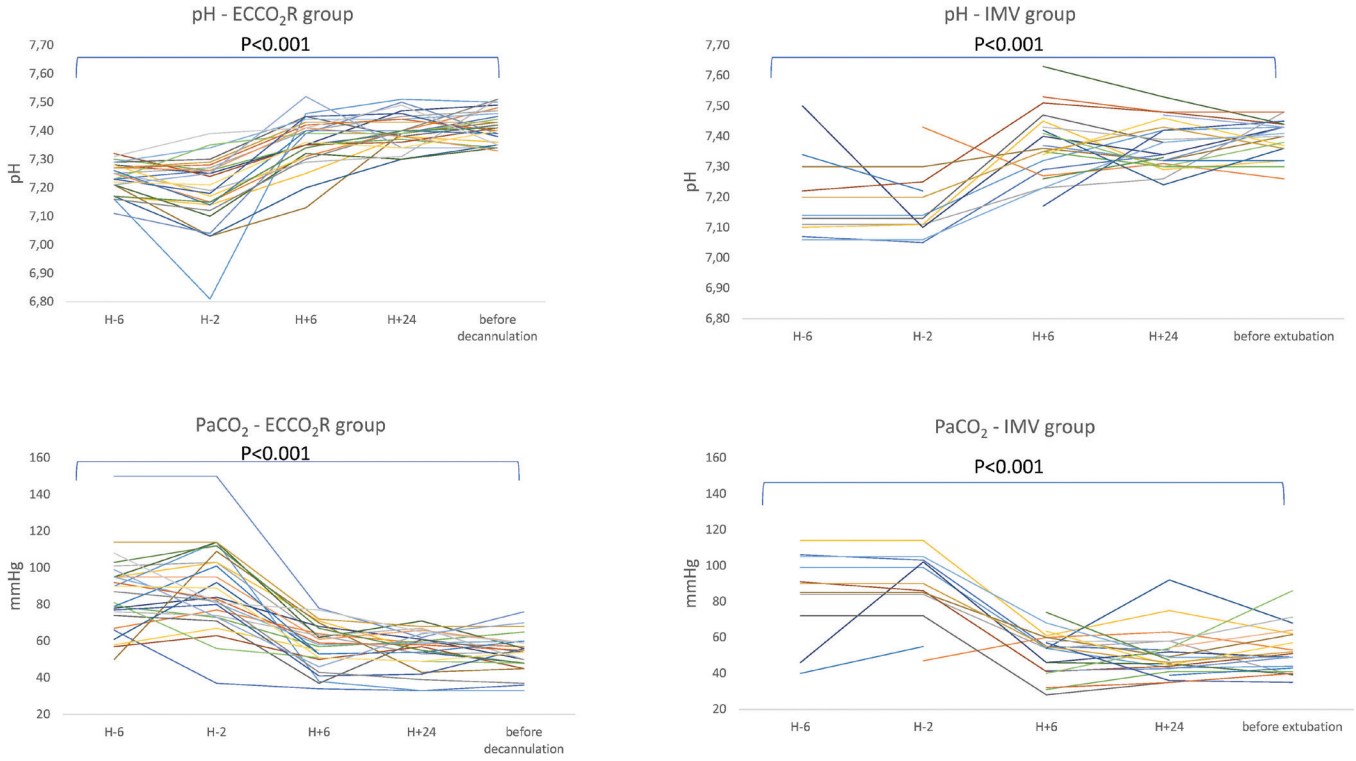

Figure 4 Evolution of pH and carbon dioxide arterial pressure ($PaCO_2$) from 6 hours before cannulation or intubation until before weaning. $ECCO_2R$, extracorporeal CO_2 removal; IMV, invasive mechanical ventilation.

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Table 3 Effectiveness

	$ECCO_2R$ group (n=26)	Control group (n=25)	P value
Length of stay			
Days in ICU	18±14	30±43	0.18
Days in hospital	29±22	49±53	0.54
Mortality			
During ICU	2 (8)	7 (28)	0.12
28-day mortality	3 (12)	4 (16)	0.63
90-day mortality	4 (15)	7 (28)	0.26

Values are presented as mean±SD or number of events.
$ECCO_2R$, extracorporeal CO_2 removal; ICU, intensive care unit.

Numerous spirometric data are missing to acquire better knowledge of our population because most patients were managed outside the hospital. However, most of them suffered from long-term illness and had full insurance coverage, which requires a diagnosis based on spirometric data because of their oxygen or NIV home need.

This $ECCO_2R$ device is associated with significant improvement of pH and $PaCO_2$ values in patients with ae-COPD (figure 1). However, the objective was not to normalise arterial blood gases, which can be deleterious, but to achieve both an improvement in alveolar ventilation and in work of breathing. Some very low-flow systems may not be able to remove sufficient CO_2 to significantly improve the respiratory rate and intrinsic PEEP.[14] Due to the retrospective design of the study, we could not collect information about pulmonary mechanics evolution such as the respiratory rate or the oesophageal pressure, which reflect inspiratory work. Gasometric improvement was comparable to that produced by IMV.

IMV was avoided in 85% of patients treated with $ECCO_2R$ (15% of $ECCO_2R$ patients had to be intubated). This result is very encouraging given that our patients

Table 4 $ECCO_2R$-associated adverse effects

Adverse effects (n)	$ECCO_2R$ group
Major bleeding	7
Scarpa's fascia (cannula insertion site)	3
During cannula removal	1
Retroperitoneal haematoma (psoas)	1
Haemothorax	1
Pectoral bleeding	2
Cerebral bleeding	0
Digestive bleeding	0
>Two globular transfusions	7
Time to onset from cannulation (days)	4±3,7
Leading to premature discontinuation of $ECCO_2R$	3
Minor bleeding	6
Scarpa's fascia (cannula insertion site)	3
During cannula removal	3
Epistaxis	1
Haematuria	2
Device-related complications	15
Circuit thrombosis	3
Unexplained device discontinuation	1
Slow decrease in $PaCO_2$ value	2
Haemolysis	3
Thrombocytopenia<100 G/L	6
Causes of premature discontinuation of $ECCO_2R$	9
Major bleeding	3
Circuit thrombosis	3
Unexplained device discontinuation	1
Haemolysis	1
Death	1

Values are presented as mean±SD or number of events.
ECCO2R, extracorporeal CO_2 removal.

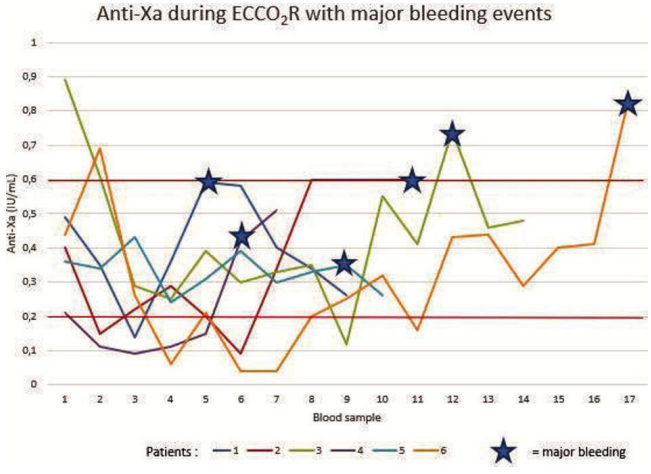

Figure 5 Anti-Xa in $ECCO_2$ patients with major bleeding events.

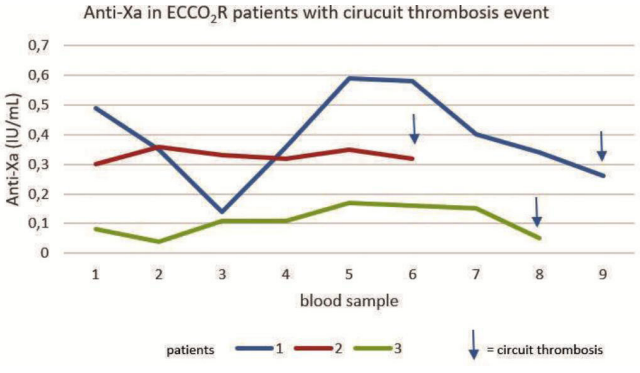

Figure 6 Anti-Xa in $ECCO_2R$ patients with circuit thrombosis event.

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Table 5 IMV-associated adverse effects

Adverse effects (n)	Control group
VAP	8
Time since intubation (days)	18±16
Early pneumonia (<7 days postintubation)	2
Haemodynamic instability*	25
Postintubation	16
Catecholamine >24 hours	12
Due to VAP septic shock	4
Catecholamine >24 hours	3
Pneumothorax due to high intrinsic PEEP	1
Self-extubation	6
Reintubation	5
Death due to IMV complication	3

Values are presented as mean±SD or number of events.
*With catecholamine administration required.
ICU, intensive care unit; IMV, invasive mechanical ventilation; VAP, ventilator-associated pneumonia.

were highly severe patients with COPD with, for many of them, LTOT or NIV at home (which were excluded in the ÉCLAIR study by Braune *et al*[15]). All but one $ECCO_2R$ failures were due to recurrent hypercapnia occurring after a premature discontinuation of ECCO2R due to a complication, suggesting that decannulation was performed too early. The only intubation performed during $ECCO_2R$ was due to cardiac arrest caused by jugular cannulation complicated by haemothorax.

Caution should be exercised with hypoxemic patients, in whom $ECCO_2R$ failure seems to be more frequent in other studies.[15 16] The ÉCLAIR study reported 11 patients (44%) requiring intubation in the $ECCO_2R$ group, including seven for hypoxemia. More than 90% of intubation cases reported in the ÉCLAIR study occurred during the $ECCO_2R$ treatment. Indeed, during spontaneous ventilation, excessive CO_2 removal leads to a decrease in the tidal volume with increased risk of atelectasis and decrease in alveolar PO_2.[17]

Although we used the same definition for major bleeding[13] and despite our $ECCO_2R$ group patients being more obese with associated difficulties in cannulation, just over 20% of our $ECCO_2R$ patients experienced significant bleeding complications while 36% (nine patients) or 11 major bleeding events occurred in the ÉCLAIR study.[15] The ÉCLAIR study may have made a higher use of jugular cannulation than we did. As patients with jugular cannulation experienced serious haemorrhagic and pulmonary complications, we should further study the site of cannulation in these patients who often present with significant pulmonary hypertension and emphysema. Furthermore, jugular cannulation requires patients to be placed in supine position while experiencing respiratory distress. Based on our acquired expertise, we stopped cannulating in jugular sites. We also learnt to target the low anti-Xa range although all major bleeding events do not occur because of heparin overdose. Other factors are probably involved in these phenomena.[18]

Despite a low anti-Xa target, we only observed three cases of circuit thrombosis. They all led to premature

Table 6 Observational data

Observational data	$ECCO_2R$ group (n=26)	Control group (n=25)	P value
Duration between NIV and $ECCO_2R$ or IMV (hours)	42±69	20±35	0.15
Days on $ECCO_2R$	5,4±4	N/A	
Days on IMV	N/A	27±43	
Curarisation	N/A	7 (28)	
Prone position or NO	N/A	0	
IMV rate	4 (15)	N/A	
Tracheotomy	2 (8)	5 (20)	0.38
NIV during $ECCO_2R$	18 (69)	N/A	
HFNOT during $ECCO_2R$	7 (27)	N/A	
Haemodynamic instability*	3 (12)	16 (64)	**0.0001**
RRT	3 (12)	3 (12)	1
HIT	0	1 (4)	0.98
Pulmonary embolism	2 (8)	1 (4)	1
Weaning from successful $ECCO_2R$ or IMV	17 (65)	16 (64)	0.91

Values are presented as mean±SD or number (%).
*With catecholamine administration required.
$ECCO_2R$, extracorporeal CO_2 removal; HFNOT, high flow nasal oxygen therapy; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; IMV, invasive mechanical ventilation; N/A, not applicable; NIV, non-invasive ventilation; NO, nitrogen monoxide; RRT, renal replacement therapy.

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discontinuation of $ECCO_2R$ but only one patient required IMV. We did not measure plasma-free haemoglobin nor did we notice urine coloration, which can help to anticipate this complication.[19] Other studies reported rates of nearly 25%.[20] The higher mean blood flow throughout the circuit, therefore, seems to play a role in decreasing the circuit thrombosis occurrence. This complication, together with bleeding issue, highlights the importance of an anticoagulant strategy and of trained staff.

CONCLUSION

This study reveals that ae-COPD patients with NIV failure could be treated with $ECCO_2R$. Findings show that intubation can be avoided, especially in the absence of significant hypoxemia. However, it is important to consider the adverse effects of $ECCO_2R$ treatment, especially haemorrhagic complications. Such treatment requires constant monitoring and team training. It is, therefore, important to identify the subset of patients and, when in the disease course, patients could most benefit from this technique. Finally, this article also raises the question of the optimal time of $ECCO_2R$ weaning. Prospective randomised studies are required. Technical progress may facilitate the management of this emerging technique in the near future.

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ORCID iDs
Mathilde Azzi http://orcid.org/0000-0002-8269-2332
Vincent loos http://orcid.org/0000-0001-6959-5602

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