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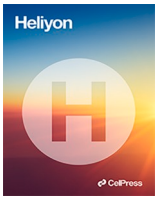

Low-flow $ECCO_2R$ conjoined with renal replacement therapy platform to manage pulmonary vascular dysfunction with refractory hypercapnia in ARDS

Armand Mekontso Dessap [a,b,c,*], François Bagate [a,b,c], Xavier Repesse [d], Clarisse Blayau [e], Muriel Fartoukh [e], Florence Canoui-Poitrine [f], Nicolas de Prost [a,b,c], Antoine Vieillard-Baron [d]

[a] AP-HP, Hôpitaux Universitaires Henri-Mondor, Service de Médecine Intensive Réanimation, F-94010, Créteil, France
[b] Univ Paris Est Créteil, CARMAS, Créteil, F-94010, France
[c] Univ Paris Est Créteil, INSERM, IMRB, Créteil, F-94010, France
[d] AP-HP, Hôpital Ambroise Paré, Service de Médecine Intensive Réanimation, Boulogne Billancourt, Créteil, France
[e] AP-HP, Hôpital Tenon, Service de Médecine Intensive Réanimation, Paris, France
[f] AP-HP, Hôpitaux Universitaires Henri-Mondor, Service de Santé Publique, F-94010, Créteil, France

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ABSTRACT

Background: Hypercapnia worsens lung vascular dysfunction during acute respiratory distress syndrome (ARDS). We tested whether an extracorporeal carbon dioxide removal ($ECCO_2R$) device based on a renal replacement therapy platform (Prismalung®) may reduce $PaCO_2$ and alleviate lung vascular dysfunction in ARDS patients with refractory hypercapnia.

Methods: We planned to prospectively include 20 patients with moderate-to-severe ARDS, pulmonary vascular dysfunction on echocardiography, and $PaCO_2 \geq 48$ mmHg despite instrumental dead space reduction and the increase in respiratory rate. Hemodynamics, echocardiography, respiratory mechanics, and arterial blood gases were recorded at 2 (H2), 6 (H6) and 24 (H24) hours as $ECCO_2R$ treatment was continued for at least 24 h.

Results: Only eight patients were included, and the study was stopped due to worldwide shortage of $ECCO_2R$ membranes and the pandemic. Only one patient fulfilled the primary endpoint criterion (decrease in $PaCO_2$ of more than 20 %) at H2, but this objective was achieved in half of patients (n = 4) at H6. The percentage of patients with a $PaCO_2$ value < 48 mmHg increased with time, from 0/8 (0 %) at H0, to 3/8 (37.5 %) at H2 and 4/8 (50 %) at H6 (p = 0.04). There was no major change in hemodynamic and echocardiographic variables with $ECCO_2R$, except for a significant decrease in heart rate. $ECCO_2R$ was prematurely discontinued before H24 in five (62.5 %) patients, due to membrane clotting in all cases.

Conclusions: This pilot study testing showed a narrow efficacy and high rate of membrane thrombosis with the first version of the system. Improved versions should be tested in future trials.

Trial registration: Registered at clinicaltrials.gov, identifier: NCT03303807, Registered: October 6, 2017, https://clinicaltrials.gov/ct2/show/NCT03303807.

* Corresponding author. AP-HP, Hôpitaux Universitaires Henri-Mondor, Service de Médecine Intensive Réanimation, F-94010, Créteil, France.
E-mail addresses: armand.dessap@aphp.fr (A. Mekontso Dessap), francois.babate@aphp.fr (F. Bagate).

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1. Introduction

Acute respiratory distress syndrome (ARDS) complicated by pulmonary hypertension was first reported in the 1970s by Zapol and Snider [1]. The condition is generated by an increase in the pulmonary vascular resistance, whilst patients are on respirator support, that progressively leads to right ventricular (RV) failure and ultimately to acute cor pulmonale and refractory circulatory failure [1]. Pulmonary vascular dysfunction and RV failure are common in moderate-to-severe ARDS (up to 70 % of patients develop pulmonary hypertension) and had often been associated with a worse outcome before the wide-scale introduction of low-tidal volume ventilation [2–6]. The use of protective mechanical ventilation has not remarkably changed the landscape since several pulmonary vascular dysfunction markers are still documented as independent predictors of mortality in ARDS patients, such as blood (e.g., angiopoietin-2/angiopoietin-1 ratio) [7], respiratory (e.g., dead-space fraction) [8], or hemodynamic (e.g., the level of central venous pressure or transpulmonary gradient surpasses that of pulmonary artery occlusion pressure) [9,10] parameters. Acute cor pulmonale is still common in the era of protective mechanical ventilation (20 % of patients with moderate-to-severe ARDS) and is often associated with a worse outcome [11,12], unless specific measures aiming at correcting it are implemented [13,14].

ARDS-related pulmonary vascular dysfunction is mediated by several factors, including mechanical compression (by interstitial edema and injurious mechanical ventilation) [15,16], vaso-occlusion (by microvascular thromboemboli) [17], and vasoconstriction. The latest mechanism is probably central, with a role for circulating mediators, hypoxic vasoconstriction [18], and most importantly, hypercapnia [19].

Carbon dioxide removal is a novel and appealing strategy to reduce partial pressure of carbon dioxide ($PaCO_2$) and to alleviate pulmonary vascular dysfunction, with the potential of improving ARDS outcome. For such, various extracorporeal CO_2 removal ($ECCO_2R$) devices have been developed, of which a device that functions with renal replacement therapy (RRT) Prismaflex® platform (Prismalung®) [20]. We hypothesized that this device may prove useful in reducing $PaCO_2$ in ARDS patients with refractory hypercapnia in order to alleviate lung vascular dysfunction and RV failure.

2. Method

2.1. Study design and procedure

This pilot study was run in three intensive care units (ICUs) with high skills for ARDS and $ECCO_2$-R management, from January 2018 to February 2019. This clinical trial was approved by the concerned ethical committee: *Comité de Protection des Personnes Ile-de-France XI, Paris, France* (no 2016-A01689-42), and registered on www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT03303807).

2.2. Patients

Patients were included if met all of the following criteria: i) moderate-to-severe ARDS according to Berlin criteria (respiratory failure within one week of a known clinical insult or new or worsening respiratory symptoms; with bilateral chest opacities not fully explained by effusions or lobar/lung collapse or nodule, and not fully explained by cardiac failure or fluid overload; and an arterial oxygen tension to fraction of inspired oxygen ratio (PaO_2/FiO_2) $\leq$200 mmHg with a positive end-expiratory pressure (PEEP) $\geq$ 5 cmH_2O) [21]; pulmonary vascular dysfunction on echocardiography, as defined by at least one of the following: ii) pulmonary hypertension (pulmonary artery systolic pressure >40 mmHg), a dilated right ventricle (end-diastolic RV/left ventricle (LV) area ratio >0.6), or interventricular septal dyskinesia [11]; iii) refractory hypercapnia, as defined by an arterial $PaCO_2 \geq$ 48 mmHg despite instrumental dead space reduction (use of a heated humidifier) and the increase in respiratory rate (RR) without inducing intrinsic positive end-expiratory pressure [12]. Patients were excluded if presented at least one of the following criteria: age <18 years, pregnancy, lactation, contra-indication to curative anticoagulation, thrombopenia <50 G/L, heparin-induced thrombopenia, allergy to heparin, and refractory hypoxemia with an indication to extracorporeal membrane oxygenation (ECMO), namely $PaO_2/FiO_2 <$ 50 mmHg with $FiO_2 \geq$ 80 % for >3 h, despite optimization of mechanical ventilation (tidal volume-V_T set at 6 mL/kg and trial of PEEP $\geq$10 cm H_2O), and despite the use of adjunctive therapies (including neuromuscular blocking agents, prone position and/or inhaled nitric oxide) [22].

2.3. $ECCO_2R$ system

A low-flow CO_2 removal device (Prismalung®, Baxter) was used with a conventional RRT platform (Prismaflex®, Baxter), using a hemopurification kit (HP-X®, Baxter). In patients already treated with continuous RRT for renal failure or metabolic acidosis, a decarboxylation gas exchanger membrane was integrated into the RRT circuit (HF1400®, Baxter). For this purpose, standard tubes and Luer-lock system were used to connect the hollow fiber, polymethylpentene-made, 0.23 m^2-surface area, gas exchange membrane to the extracorporeal circuit. In case a patient had not already been equipped with a dialysis catheter, a 13-Fr hemodialysis venous catheter (Gamcath™®; Gambro-Baxter) was aseptically and percutaneously threaded through the right jugular or femoral vein under ultrasonographic guidance. Systemic curative anticoagulation with sodium heparin was set throughout the CO_2 removal process to maintain anti Xa activity at 0.2–0.5 IU/mL. Our team relied on the Prismaflex® platform to continuously monitor venous, arterial line, and filter pressures.

2.4. Study protocol

All patients were sedated, paralyzed, and ventilated with a target V_T of 6 mL/kg (predicted body weight) and a target plateau pressure below 30 cmH_2O. After priming, the patient was put on the Prismaflex® platform where the extracorporeal blood flow was gradually increased to attain a target value between 200 and 400 mL/min. Gas flow through the gas exchanger was set to 10 L/min, with an oxygen concentration between 0.21 and 1. Each attending physician could manage refractory hypoxemia and/or hypercapnia with nitric oxide, prone positioning and/or ECMO, at their discretion. The $ECCO_2R$ treatment was continued for at least 24 h (unless dysfunction) and for a maximum of 72 h. The potential for weaning off $ECCO_2R$ was assessed daily if the following criteria were all present: i) resolution of pulmonary vascular dysfunction on echocardiography, with a pulmonary artery systolic pressure $\leq$40 mmHg, an end-diastolic RV/LV area ratio $\leq$0.6, and normal kinetics of interventricular septum; ii) an arterial $PaCO_2 \leq 40$ mmHg with a RR $<$ 25/min, not inducing intrinsic positive end-expiratory pressure; iii) a PaO_2/FiO_2 ratio $>$200 mmHg. $ECCO_2R$ weaning was initiated by changing the MV parameters following the conventional ARDSnet settings ($V_T = 6$ mL/kg, PEEP = 5–10 cmH_2O, RR $<$ 25 breaths/min without inducing intrinsic PEEP, $FiO_2 = 40$ %) and by stopping the sweep-gas flow through the $ECCO_2R$ device. If the patient condition remained unchanged for at least 2 h after initiating the weaning, i.e., with no worsening of hypoxemia, no hypercapnia, nor pulmonary vascular dysfunction, the $ECCO_2R$ device was removed. According to the manufacturer of Prismalung® device, the maximum duration of the membrane is estimated at 72 h.

2.5. Data collection

The following parameters were recorded at baseline (H0), 2 h (H2), 6 h (H6), and 24 h (H24) after the initiation of CO_2 removal: i) hemodynamics: blood pressure, heart rate, catecholamine dose; ii) echocardiography: RV size (RV/LV area ratio), LV shape (eccentricity index), tricuspid regurgitant jet velocity, tricuspid annular plane systolic excursion, and aortic velocity time index [11]; iii) arterial blood gases with PaO_2, $PaCO_2$, bicarbonates, and lactate; iv) respiratory mechanics: plateau pressure, total PEEP, RR, tidal volume.

The primary endpoint was the percentage of patients with hypercapnia reduction (defined as a 20 % decrease in $PaCO_2$ at H2 of $ECCO_2R$ initiation). Secondary endpoints included: i) the change in $PaCO_2$, hemodynamic, and echocardiographic variables; ii) the percentage of patients with a $PaCO_2$ value $<$ 48 mmHg at various time points; iii) $ECCO_2R$ discontinuation and adverse events. Serious adverse events were a priori defined and prospectively collected as: any clinical event causing death, representing immediate life-threat, bringing along permanent disability/severe incapacity, or requiring long hospital stay; OR any event that may put the patient at risk and necessitates medical or surgical intervention to halt one of these outcomes; AND any event judged clinical trial-induced by the attending physician. An adverse event was defined as: study related if it could be linked to a study procedure; or non-study related if was initially related to the underlying disease or to ARDS and its complications. Other adverse events that did not

Table 1
Clinical characteristics of eight included patients with acute respiratory distress syndrome, pulmonary vascular dysfunction and refractory hypercapnia.

Characteristics	Value, N = 8
Sex (male/female)	5/3
Age (years)	59 [37–81]
Body mass index (kg/m^2)	29 [27–44]
SAPS II	46 [44–51]
SOFA score at $ECCO_2R$ insertion	8 [6–12]
ARDS risk factor	
Pneumonia	6 (75)
Aspiration	1 (13)
Other	1 (13)
Pre-$ECCO_2R$ therapy	
Vasopressors	1 (38)
Dialysis	2 (25)
Steroids	3 (38)
Neuromuscular blockade	7 (88)
Prone positioning	4 (50)
Nitric oxide	1 (13)
Recruitment maneuvers	0 (0)
ECMO	0 (0)
Time from intubation to $ECCO_2R$ initiation (days)	1.9 [1.7–6.5]
Outcome	
Mechanical ventilation duration (days)	24 [16–33]
ICU length of stay (days)*	24 [18–34]
Day-28 mortality	3 (38)

Data are median (Quartile 1- Quartile3) or n (%). SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, $ECCO_2R$: extracorporeal carbon dioxide removal, ICU: intensive care unit. *28 days if the patient is not yet discharged at day 28.

meet these definitions were recorded in the patients' healthcare file. After $ECCO_2R$ weaning, patients were followed up for adverse events until ICU discharge or day 28 after enrollment, whichever comes first.

2.6. Statistical analyses

Data were analyzed using the IBM SPSS Statistics 24 statistical software package (IBM Corp, Armonk, New York, USA) and R 2.15.2 environment (The R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as median (25th–75th percentiles) and compared using the Friedman test. Categorical variables, expressed as percentages, were evaluated using the Cochran Q test. Two-sided p values less than 0.05 were considered significant.

The number of patients to be included was estimated based on the following assumptions. We expected a mean arterial $PaCO_2$ of at least 48 ± 15 mmHg at the initiation of CO_2 removal [11,13,14]. Based on data available at the time of the protocol writing [20] we anticipated a success rate (reduction in arterial $PaCO_2$ of 20 % or more after 4 h of therapy with the Prismalung®) in at least 20 % of patients (the strategy would be considered insufficiently effective below this threshold). We postulated a success rate of 50 % above which the strategy would be considered sufficiently effective with a beta risk of 10 % (power of 90 %). With these hypotheses, we needed to include 19 patients with a one-step Fleming plan. If eight successes were observed on 19 patients, the alternate efficacy hypothesis would not be rejected. We decided to include a total of 20 patients.

3. Results

The study was stopped in February 2019 and could not be prolonged further due to worldwide shortage of $ECCO_2R$ membranes. Only eight patients were included, with moderate (n = 5) or severe (n = 3) ARDS. Two patients underwent jugular cannulation and six femoral cannulation. Patients' baseline characteristics are shown in Table 1.

Prior to inclusion, seven patients were given neuromuscular blocking agents and four were put in prone position. Ventilatory, hemodynamic and echocardiographic parameters during the protocol are presented in Table 2.

Ventilatory settings were in accordance with protective ventilation and did not change during the protocol. There was a trend towards a decrease in $PaCO_2$ from 53.5 [52–56.5] at H0, to 52 [46.5–58.5] at H2 and 48.5 [41–55] mmHg at H6 (p = 0.09), while

Table 2
Ventilatory, hemodynamic and echocardiographic parameters during extracorporeal carbon dioxide removal in eight patients with acute respiratory distress syndrome, pulmonary vascular dysfunction and refractory hypercapnia.

Parameters	Baseline (Hour 0)	Hour 2	Hour 6	P value*
Ventilation				
V_T (ml/kg PBW)[b]	5.95 [5.68–6.13]	5.95 [5.37–6.38]	6.00 [5.82–6.14]	0.71
RR (breaths/min)	27.5 [23.5–33.5]	27.5 [24.5–33.5]	25 [23.5–32.5]	0.87
PEEP (cmH_2O)[b]	12.5 [8–13]	11.5 [9–16]	11 [9.5–12]	0.42
P_{plat} (cmH_2O)[b]	23.5 [19.5–26]	23.5 [19–29.5]	22 [18.5–27]	0.94
Blood gases				
pH	7.28 [7.21–7.30]	7.31 [7.24–7.35]	7.33 [7.26–7.36]	0.13
PaO_2/FiO_2 (mmHg)	111 [79–173]	123 [96–155]	154 [109–156]	0.96
$PaCO_2$ (mmHg)[b]	53.5 [52–56.5]	52 [46.5–58.5]	48.5 [41–55]	0.09
HCO_3 (mmol/L)	24.7 [21.8–29.4]	24.5 [20.9–28.2]	24 [21.3–27.4]	0.07
Lactate (mmol/L)	1.2 [1.0–1.9]	1.5 [1.1–2.0]	1.6 [1.1–2.4]	0.37
Temperature (°C)	37.6 [36.7–38.2]	37.4 [36.2–38.3]	36.1 [36.1–37.0]	0.04
Patients on $ECCO_2R$	8/8 (100 %)	6/8 (75 %)	6/8 (75 %)	0.26
Patients with $PaCO_2$ < 48 mmHg	0/8 (0 %)	3/8 (37.5 %)	4/8 (50 %)	0.04
$ECCO_2R$				
Blood flow (ml/min)	300 [275–300]	300 [250–350]	300 [250–320]	0.61
Sweep-gas flow (L/min)	10 [9.5–10]	10 [10–10]	10 [9,10]	0.22
Hemodynamics				
Mean arterial pressure (mmHg)	72 [66–77]	81 [76–92]	87 [85–95]	0.10
Heart rate (beats/min)	108 [93–124]	86 [80–122]	83 [71–95]	<0.01
Shock (need for vasopressor)	4/8 (50 %)	4/8 (50 %)	4/8 (50 %)	>0.99
Norepinephrine dose (mg./h)*	1.95 [1.15–6.7]	1.75 [1.15–6]	1 [0.95–3.75]	0.53
Echocardiography				
TR jet velocity (m/s)	2.9 [2.7–3.2]	2.6 [2.5–2.8]	2.7 [2–2.8]	0.45
TAPSE (mm)	19 [18–23]	21 [20–22]	22 [19–23]	0.39
RV/LV ratio	0.74 [0.72–0.78]	0.75 [0.68–1.01]	0.65 [0.56–0.82]	0.21
LV eccentricity index	1.02 [0.97–1.21]	1.13 [1.07–1.15]	1.02 [0.99–1.14]	0.85
VTI LVOT (cm)	20.1 [16–23.6]	17 [16–21.6]	17.5 [17–22.5]	0.16

Values presented as median (1st-3rd quartile) or n (%) for continuous and categorical data, respectively; *p values are derived from Friedman test for continuous variables and Cochran Q test for categorical variables. V_T: tidal volume; PBW: predicted body weight; RR: respiratory rate; PEEP: end-expiratory positive pressure; P_{plat}: plateau pressure; PaO_2: partial alveolar oxygen pressure; FiO_2: fraction of inspired oxygen; $PaCO_2$: partial alveolar carbon dioxide pressure; HCO_3-: bicarbonate; $ECCO_2R$: extracorporeal carbon-dioxide removal; TR: tricuspid regurgitant; TAPSE: Tricuspid annular plane systolic excursion; LV: left ventricle; VTI LVOT: velocity-time integral of left ventricular outflow tract. *in patients receiving norepinephrine.

PaO_2/FiO_2 did not change. Only one patient fulfilled the primary endpoint criterion (decrease in $PaCO_2$ of more than 20 %) at H2, but this objective was achieved by half of patients (n = 4) at H6. There was no major change in hemodynamic and echocardiographic variables, except for a significant decrease in heart rate. The percentage of patients with a $PaCO_2$ value < 48 mmHg increased with time, from 0/8 (0 %) at H0, to 3/8 (37.5 %) at H2 and 4/8 (50 %) at H6 (p = 0.04).

Overall median duration of $ECCO_2R$ was 16.5 [1.4–37.5] hours. Median value of anti-Xa activity was 0.2 international units (IU)/mL [0.2–0.6] at H6 and 0.2 IU/mL [0.2–2] at H24. $ECCO_2R$ was prematurely discontinued before H24 in five (62.5 %) patients, in relation to membrane clotting in all cases. Other adverse events included one cannulation-related complication and one resolutive hypothermia. The overall day-28 mortality was 37.5 % (n = 3 deaths).

4. Discussion

Our pilot study demonstrated that the use of a low-flow $ECCO_2R$ device mounted on an RRT platform to reduce $PaCO_2$ in ARDS patients with refractory hypercapnia and lung vascular dysfunction was feasible, with encouraging, albeit perfectible results. A high rate of membrane thrombosis was observed in this selected critically-ill population.

4.1. Refractory hypercapnia and lung vascular dysfunction

We included a population of severe ARDS with refractory hypercapnia and lung vascular dysfunction. Low tidal volumes are more commonly used nowadays to provide pulmonary protective ventilation though often give rise to hypercapnia in the majority of ARDS patients [23]. Hypercapnia can exacerbate hypoxic vasoconstriction [24,25] and can also directly induce vasoconstriction of the pulmonary vasculature, as shown in experimental animals [26,27], young healthy volunteers [28], brain-dead patients subjected to apnea tests [29], cardiac-surgery patients [30], and patients with ARDS [31,32]. Patients with cor pulmonale exhibited higher $PaCO_2$ levels as compared to their counterparts in all published clinical studies assessing RV function by echocardiography during ARDS [11,13,33,34]. Acidosis and hypercapnia induced by tidal volume reduction were associated with impaired RV function and hemodynamics in a physiological clinical study of severe ARDS [35].

The pharmacological manipulation of pulmonary vascular tone (using inhaled nitric oxide) is possible in ARDS patients, though not proven beneficial in terms of mortality [36]. Another option to unload the RV may be prone position [37,38], but its routine implementation is not easy. Two technical solutions have been developed to mitigate hypercapnia in ARDS patients ventilated with low tidal volumes: i) increasing the RR (which is often limited by the occurrence of intrinsic positive end-expiratory pressure) [39]; ii) replacing the heat and moisture exchanger by a heated humidifier to reduce instrumental dead space and hence $PaCO_2$ [40]. However, normocapnia is rarely achieved with these strategies [35], as it was the case in our patients. In these patients with lung vascular dysfunction and refractory hypercapnia despite increased respiratory rate and reduced dead space, $ECCO_2R$ seems a valuable option to be tested.

4.2. Low-flow $ECCO_2R$ device mounted on an RRT platform

We chose to study a low-flow $ECCO_2R$ device mounted on an RRT platform as we believe that it has several advantages, including the use of moderate-sized catheters, and the dual implementation with RRT. However, we observed moderate efficacy of the system. Although half of patients reached hypercapnia control after H6, only one patient fulfilled the primary endpoint at H2. This moderate efficacy is in line with other human studies using this technology [41]. Apparently, the CO_2-removal rate achieved by this device is lower than that achieved by other systems operating with similar blood flows [42,43], perhaps because of its smaller membrane oxygenation surface.

In our study, $ECCO_2R$ was prematurely discontinued before H24 in 62.5 % of patients, in relation to membrane clotting in all cases. These results are in line with another similar report where membrane clotting occurred in half of the patients [41]. This high rate of clotting despite adequate anticoagulation may be favored by factors linked to the technique (e.g., low flow rate) and/or the patient (e.g., enhanced coagulopathy in ARDS patients with lung vascular dysfunction). Technical improvements in future systems may include strategies of regional circuit anticoagulation, higher blood flows and/or membranes with lower biological interactions.

4.3. Limitations

Our study has several limitations. The main limitation is the very small sample size and premature end. We could not resume inclusions due to the COVID-19 pandemic and the evolutions of the Prismalung platform. Future studies are warranted to compare this new platform to other $ECCO_2R$ devices. However, to our knowledge, this is the only study addressing the role of $ECCO_2R$ in patients with lung vascular dysfunction and refractory hypercapnia. To date, the vast majority of $ECCO_2R$ studies focuses on ultraprotective ventilation. Second, we could not analyze oxygenator membranes after their use with regard to clotting. This important point warrants further research to scrutinize the precise origin of clotting in this platform. Third, we did not record transmembrane pressures and could not assess their role in membrane thrombosis.

5. Conclusions

In conclusion, our study tested the feasibility of CO_2 removal using an RRT platform-mounted low-flow $ECCO_2R$ device in ARDS

patients with lung vascular dysfunction, and showed a narrow efficacy and high rate of membrane thrombosis with the first version of the system. Improved versions should be tested in future trials.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The protocol was approved by appropriate legal and ethics authorities (Comité de Protection des Personnes Ile-de-France XI, Paris, France; no 2016-A01689-42). The clinical trial protocol was registered with www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT03303807).

Consent for publication

Not applicable.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository and data will be made available on request.

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CRediT authorship contribution statement

Armand Mekontso Dessap: Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **François Bagate:** Writing – review & editing, Investigation, Formal analysis. **Xavier Repesse:** Writing – review & editing, Investigation, Formal analysis. **Clarisse Blayau:** Writing – review & editing, Investigation. **Muriel Fartoukh:** Writing – review & editing, Investigation, Formal analysis. **Florence Canoui-Poitrine:** Writing – review & editing, Methodology. **Nicolas de Prost:** Writing – review & editing, Investigation, Formal analysis. **Antoine Vieillard-Baron:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Pr Armand Mekontso Dessap reports financial support and equipment, drugs, or supplies were provided by Baxter.

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Abbreviations

ARDS	acute respiratory distress syndrome
RV	right ventricle
$PaCO_2$	partial pressure of carbon dioxide
$ECCO_2R$	extracorporeal carbon dioxide removal
RRT	renal replacement therapy
ICU	intensive care unit
PaO_2/FiO_2	arterial oxygen tension to fraction of inspired oxygen ratio
PEEP	positive end-expiratory pressure
LV	left ventricle
RR	respiratory rate
ECMO	extracorporeal membrane oxygenation
V_T	tidal volume

References

[1] W.M. Zapol, M.T. Snider, Pulmonary hypertension in severe acute respiratory failure, N. Engl. J. Med. 296 (1977) 476–480.
[2] M. Monchi, F. Bellenfant, A. Cariou, L.M. Joly, D. Thebert, I. Laurent, J.F. Dhainaut, F. Brunet, Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis, Am. J. Respir. Crit. Care Med. 158 (1998) 1076–1081, https://doi.org/10.1164/ajrccm.158.4.9802009.
[3] P.J. Sloane, M.H. Gee, J.E. Gottlieb, K.H. Albertine, S.P. Peters, J.R. Burns, G. Machiedo, J.E. Fish, A multicenter registry of patients with acute respiratory distress syndrome. Physiology and outcome, Am. Rev. Respir. Dis. 146 (1992) 419–426, https://doi.org/10.1164/ajrccm/146.2.419.
[4] P. Squara, J.F. Dhainaut, A. Artigas, J. Carlet, Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study, Intensive Care Med. 24 (1998) 1018–1028.
[5] J. Villar, M.A. Blazquez, S. Lubillo, J. Quintana, J.L. Manzano, Pulmonary hypertension in acute respiratory failure, Crit. Care Med. 17 (1989) 523–526.
[6] W.M. Zapol, R. Jones, Vascular components of ARDS. Clinical pulmonary hemodynamics and morphology, Am. Rev. Respir. Dis. 136 (1987) 471–474.
[7] T. Ong, D.E. McClintock, R.H. Kallet, L.B. Ware, M.A. Matthay, K.D. Liu, Ratio of angiopoietin-2 to angiopoietin-1 as a predictor of mortality in acute lung injury patients, Crit. Care Med. 38 (2010) 1845–1851, https://doi.org/10.1097/CCM.0b013e3181eaa5bf.
[8] T.J. Nuckton, J.A. Alonso, R.H. Kallet, B.M. Daniel, J.-F. Pittet, M.D. Eisner, M.A. Matthay, Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome, N. Engl. J. Med. 346 (2002) 1281–1286, https://doi.org/10.1056/NEJMoa012835.
[9] D. Osman, X. Monnet, V. Castelain, N. Anguel, J. Warszawski, J. Teboul, C. Richard, Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome, Intensive Care Med. 35 (2009) 69–76.
[10] T.M. Bull, B. Clark, K. McFann, M. Moss, National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network, Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury, Am. J. Respir. Crit. Care Med. 182 (2010) 1123–1128, https://doi.org/10.1164/rccm.201002-0250OC.
[11] F. Boissier, S. Katsahian, K. Razazi, A. Thille, F. Roche-Campo, R. Leon, E. Vivier, L. Brochard, A. Vieillard-Baron, C. Brun-Buisson, A. Mekontso Dessap, Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome, Intensive Care Med. 39 (2013) 1725–1733.
[12] A. Mekontso Dessap, F. Boissier, C. Charron, E. Bégot, X. Repessé, A. Legras, C. Brun-Buisson, P. Vignon, A. Vieillard-Baron, Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact, Intensive Care Med. 42 (2016) 862–870, https://doi.org/10.1007/s00134-015-4141-2.
[13] G. Lhéritier, A. Legras, A. Caille, T. Lherm, A. Mathonnet, J.-P. Frat, A. Courte, L. Martin-Lefèvre, J.-P. Gouëllo, J.-B. Amiel, D. Garot, P. Vignon, Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study, Intensive Care Med. 39 (2013) 1734–1742, https://doi.org/10.1007/s00134-013-3017-6.
[14] A. Vieillard-Baron, B. Page, R. Augarde, S. Prin, S. Qanadli, A. Beauchet, O. Dubourg, F. Jardin, Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate, Intensive Care Med. 27 (2001) 1481–1486.
[15] A. Vieillard-Baron, K. Chergui, R. Augarde, S. Prin, B. Page, A. Beauchet, F. Jardin, Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography, Am. J. Respir. Crit. Care Med. 168 (2003) 671–676.
[16] A. Mekontso Dessap, G. Voiriot, T. Zhou, E. Marcos, S. Dudek, J. Jacobson, R. Machado, S. Adnot, L. Brochard, B. Maitre, J. Garcia, Conflicting physiological and genomic cardiopulmonary effects of recruitment maneuvers in murine acute lung injury, Am. J. Respir. Cell Mol. Biol. 46 (2012) 541–550.
[17] J.F. Tomashefski, P. Davies, C. Boggis, R. Greene, W.M. Zapol, L.M. Reid, The pulmonary vascular lesions of the adult respiratory distress syndrome, Am. J. Pathol. 112 (1983) 112–126.
[18] A. Benzing, G. Mols, T. Brieschal, K. Geiger, Hypoxic pulmonary vasoconstriction in nonventilated lung areas contributes to differences in hemodynamic and gas exchange responses to inhalation of nitric oxide, Anesthesiology 86 (1997) 1254–1261.
[19] A. Mekontso Dessap, C. Charron, J. Devaquet, J. Aboab, F. Jardin, L. Brochard, A. Vieillard-Baron, Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome, Intensive Care Med. 35 (2009) 1850–1858, https://doi.org/10.1007/s00134-009-1569-2.
[20] T. Godet, A. Combes, E. Zogheib, M. Jabaudon, E. Futier, A.S. Slutsky, J.-M. Constantin, Novel CO2 removal device driven by a renal-replacement system without hemofilter. A first step experimental validation, Anaesth. Crit. Care Pain Med. 34 (2015) 135–140, https://doi.org/10.1016/j.accpm.2014.08.006.
[21] Acute respiratory distress syndrome: the Berlin definition, JAMA 307 (2012), https://doi.org/10.1001/jama.2012.5669.
[22] A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N. Ferguson, E. Fan, A. Slutsky, D. Brodie, A. Mercat, Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome, N. Engl. J. Med. 378 (2018) 1965–1975, https://doi.org/10.1056/NEJMoa1800385.
[23] A. Esteban, N. Ferguson, M. Meade, F. Frutos-Vivar, C. Apezteguia, L. Brochard, K. Raymondos, N. Nin, J. Hurtado, V. Tomicic, M. González, J. Elizalde, P. Nightingale, F. Abroug, P. Pelosi, Y. Arabi, R. Moreno, M. Jibaja, G. D'Empaire, F. Sandi, D. Matamis, A. Montañez, A. Anzueto, Evolution of mechanical ventilation in response to clinical research, Am. J. Respir. Crit. Care Med. 177 (2008) 170–177.
[24] W.H. Noble, J.C. Kay, J.A. Fisher, The effect of PCO2 on hypoxic pulmonary vasoconstriction, Can. Anaesth. Soc. J. 28 (1981) 422–430.
[25] Y. Yamamoto, H. Nakano, H. Ide, T. Ogasa, T. Takahashi, S. Osanai, K. Kikuchi, J. Iwamoto, Role of airway nitric oxide on the regulation of pulmonary circulation by carbon dioxide, J. Appl. Physiol. Bethesda Md 91 (2001) (1985) 1121–1130.
[26] C.E. Rose, K. Van Benthuysen, J.T. Jackson, C.E. Tucker, D.L. Kaiser, R.F. Grover, J.V. Weil, Right ventricular performance during increased afterload impaired by hypercapnic acidosis in conscious dogs, Circ. Res. 52 (1983) 76–84.
[27] G. Zobel, S. Rödl, B. Urlesberger, D. Dacar, W. Schwinger, M. Bermoser, Effects of inhaled nitric oxide during permissive hypercapnia in acute respiratory failure in piglets, Crit. Care Med. 26 (1998) 1231–1237.
[28] D.G. Kiely, R.I. Cargill, B.J. Lipworth, Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans, Chest 109 (1996) 1215–1221.
[29] J.C. Combes, F. Nicolas, F. Lenfant, N. Cros, P. D'Athis, M. Freysz, [Hemodynamic changes induced by apnea test in patients with brain death], Ann. Fr. Anesthèsie Rèanimation. 15 (1996) 1173–1177.
[30] A.C. Chang, H.A. Zucker, P.R. Hickey, D.L. Wessel, Pulmonary vascular resistance in infants after cardiac surgery: role of carbon dioxide and hydrogen ion, Crit. Care Med. 23 (1995) 568–574.
[31] L. Puybasset, T. Stewart, J.J. Rouby, P. Cluzel, E. Mourgeon, M.F. Belin, M. Arthaud, C. Landault, P. Viars, Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome, Anesthesiology 80 (1994) 1254–1267.
[32] V.M. Ranieri, L. Mascia, T. Fiore, F. Bruno, A. Brienza, R. Giuliani, Cardiorespiratory effects of positive end-expiratory pressure during progressive tidal volume reduction (permissive hypercapnia) in patients with acute respiratory distress syndrome, Anesthesiology 83 (1995) 710–720.
[33] A. Vieillard-Baron, J.M. Schmitt, R. Augarde, J.L. Fellahi, S. Prin, B. Page, A. Beauchet, F. Jardin, Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis, Crit. Care Med. 29 (2001) 1551–1555.
[34] A. Mekontso Dessap, F. Boissier, C. Charron, E. Bégot, X. Repessé, A. Legras, C. Brun-Buisson, P. Vignon, A. Vieillard-Baron, Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact, Intensive Care Med. 42 (5) (2015) 862–870, https://doi.org/10.1007/s00134-015-4141-2. Epub 2015 Dec 9.
[35] A. Mekontso Dessap, C. Charron, J. Devaquet, J. Aboab, F. Jardin, L. Brochard, A. Vieillard-Baron, Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome, Intensive Care Med. 35 (2009) 1850–1858.
[36] A. Afshari, J. Brok, A.M. Møller, J. Wetterslev, Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults, Cochrane Database Syst. Rev. (2010), CD002787, https://doi.org/10.1002/14651858.CD002787.pub2.
[37] A. Vieillard-Baron, C. Charron, V. Caille, G. Belliard, B. Page, F. Jardin, Prone positioning unloads the right ventricle in severe ARDS, Chest 132 (2007) 1440–1446.

[38] M. Jozwiak, J.L. Teboul, N. Anguel, R. Persichini, S. Silva, D. Chemla, C. Richard, X. Monnet, Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 188 (2013) 1428–1433.

[39] A. Vieillard-Baron, S. Prin, R. Augarde, P. Desfonds, B. Page, A. Beauchet, F. Jardin, Increasing respiratory rate to improve CO2 clearance during mechanical ventilation is not a panacea in acute respiratory failure, Crit. Care Med. 30 (2002) 1407–1412.

[40] S. Prin, K. Chergui, R. Augarde, B. Page, F. Jardin, A. Vieillard-Baron, Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS, Intensive Care Med. 28 (2002) 1756–1760, https://doi.org/10.1007/s00134-002-1520-2.

[41] M. Schmidt, S. Jaber, E. Zogheib, T. Godet, G. Capellier, A. Combes, 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 22 (2018), https://doi.org/10.1186/s13054-018-2038-5.

[42] J. Allardet-Servent, M. Castanier, T. Signouret, R. Soundaravelou, A. Lepidi, J.-M. Seghboyan, Safety and efficacy of combined extracorporeal CO2 removal and renal replacement therapy in patients with acute respiratory distress syndrome and acute kidney injury: the pulmonary and renal support in acute respiratory distress syndrome study, Crit. Care Med. 43 (2015) 2570–2581, https://doi.org/10.1097/CCM.0000000000001296.

[43] V. Fanelli, M.V. Ranieri, J. Mancebo, O. Moerer, M. Quintel, S. Morley, I. Moran, F. Parrilla, A. Costamagna, M. Gaudiosi, A. Combes, 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 20 (2016), https://doi.org/10.1186/s13054-016-1211-y.