

RESEARCH

Open Access



Ultraprotective ventilation allowed by extracorporeal CO₂ removal improves the right ventricular function in acute respiratory distress syndrome patients: a quasi-experimental pilot study

Suzanne Goursaud^{1,2*} , Xavier Valette¹, Julien Dupeyrat¹, Cédric Daubin¹ and Damien du Cheyron¹

Abstract

Background: Right ventricular (RV) failure is a common complication in moderate-to-severe acute respiratory distress syndrome (ARDS). RV failure is exacerbated by hypercapnic acidosis and overdistension induced by mechanical ventilation. Venovenous extracorporeal CO₂ removal (ECCO₂R) might allow ultraprotective ventilation with lower tidal volume (V_T) and plateau pressure (P_{plat}). This study investigated whether ECCO₂R therapy could affect RV function.

Methods: This was a quasi-experimental prospective observational pilot study performed in a French medical ICU. Patients with moderate-to-severe ARDS with PaO₂/FiO₂ ratio between 80 and 150 mmHg were enrolled. An ultraprotective ventilation strategy was used with V_T at 4 mL/kg of predicted body weight during the 24 h following the start of a low-flow ECCO₂R device. RV function was assessed by transthoracic echocardiography (TTE) during the study protocol.

Results: The efficacy of ECCO₂R facilitated an ultraprotective strategy in all 18 patients included. We observed a significant improvement in RV systolic function parameters. Tricuspid annular plane systolic excursion (TAPSE) increased significantly under ultraprotective ventilation compared to baseline (from 22.8 to 25.4 mm; $p < 0.05$). Systolic excursion velocity (S' wave) also increased after the 1-day protocol (from 13.8 m/s to 15.1 m/s; $p < 0.05$). A significant improvement in the aortic velocity time integral (VTIAo) under ultraprotective ventilation settings was observed ($p = 0.05$). There were no significant differences in the values of systolic pulmonary arterial pressure (sPAP) and RV preload.

Conclusion: Low-flow ECCO₂R facilitates an ultraprotective ventilation strategy that would improve RV function in moderate-to-severe ARDS patients. Improvement in RV contractility appears to be mainly due to a decrease in intrathoracic pressure allowed by ultraprotective ventilation, rather than a reduction of PaCO₂.

Keywords: Acute respiratory distress syndrome, Extracorporeal CO₂ removal, Protective mechanical ventilation, Right ventricular dysfunction, Critical care echocardiography

Background

Although the current guidelines recommend a protective ventilation strategy [1] and adjuvant therapeutics such as prone positioning and neuromuscular blockade [2, 3], acute respiratory distress syndrome (ARDS) remains associated with significant mortality [4–6].

*Correspondence: goursaud-s@chu-caen.fr

¹ CHU de Caen Normandie, Service de Réanimation Médicale, Av côte de Nacre, 14000 Caen, France

Full list of author information is available at the end of the article

This is partly due to hyperinflation, which may promote ventilator-induced lung injury (VILI) [7–9]. It is now well established that pulmonary capillary lesions are associated with alveolar lesions, that specifically lead to pulmonary hypertension [10], worsened by local hypoxic vasoconstriction. Pulmonary hypertension may be associated with right ventricular (RV) dysfunction and/or acute cor pulmonale in 20 to 50% of patients with ARDS ventilated with a protective strategy [11]. Right ventricular failure has a deleterious impact on ARDS prognosis [12, 13], and experts recommend a systematic echocardiography assessment to evaluate RV function in patients with ARDS [14].

Many studies have shown that respiratory settings in ARDS patients are associated with RV function by several pathophysiological mechanisms. First, the deleterious effect of positive pressure correlated with tidal volume (V_T) on the right ventricle is well demonstrated. A study showed that the incidence of RV failure was related to plateau pressure (P_{plat}) [12]. Second, the application of high positive end-expiratory pressure (PEEP), which is actually recommended in ARDS, may also overload the right ventricle [13, 15]. Third, it was suggested that decreased V_T and P_{plat} could decrease driving pressure, which was recently identified as a risk factor for mortality in ARDS [16]. However, this strategy can lead to hypercapnia and acidosis, which may worsen RV overload and ultimately RV function [17]. Therefore, it is now important to consider an RV-protective approach. The goal of this strategy is to limit P_{plat} , titrate PEEP, and ultimately limit hypercapnia. This theoretical approach to preserving RV function in ARDS patients is sometimes difficult to implement in clinical practice. Additional measures as prone positioning could improve RV function [18]. While no strong recommendations routinely support this device in ARDS, veno-venous extracorporeal CO_2 removal (ECCO₂R) is actually used to facilitate ultraprotective ventilation while avoiding risks of hypercapnia, acidosis and injurious ventilator settings [19–23]. Currently, main indications for ECCO₂R in French intensive care units are ultraprotective ventilation for ARDS patients, shortening the duration of invasive mechanical ventilation in chronic obstructive pulmonary disease (COPD) patients, preventing intubation in COPD patients, and controlling hypercapnia and dynamic hyperinflation in mechanically ventilated patients with severe acute asthma [24, 25].

Despite an interesting physiological approach, no study has investigated the potentially beneficial role of ECCO₂R in RV function. Therefore, the aim of the current quasi-experimental pilot study was to assess the impact of an ultraprotective ventilation strategy facilitated by low-flow

veno-venous ECCO₂R on RV function in patients with moderate-to-severe ARDS.

Methods

Study design and procedure

This quasi-experimental observational prospective pilot study was conducted between January 2017 and March 2019 in a French intensive care unit (ICU) of an academic hospital. The protocol was approved by appropriate legal and ethics authorities (Comité de Protection des Personnes Ile-de-France 6, Paris, France; no. 17032, June 29, 2017). Informed consent was obtained from patients or legally authorized surrogates.

Patients

The inclusion criteria were as follows: severe-to-moderate ARDS with $\text{PaO}_2/\text{FiO}_2$ between 80–150 mmHg with fraction of inspired oxygen (FiO_2) $\geq 60\%$; under protective invasive mechanical ventilation and sedation; and ARDS of pulmonary origin to have a homogeneous patient cohort. Exclusion criteria were age < 18 years, pregnancy, contraindication for systemic anticoagulation, platelet count < 50 Giga/L, moribund patients or those with treatment-limitation decisions, pre-existing severe treated pulmonary arterial hypertension, significant mitral valvulopathy, ARDS from extra-pulmonary cause and poor echogenicity, making the echocardiography assessment impossible.

ECCO₂R system

ECCO₂R was provided by a low-flow CO_2 -removal device (Prismalung[®]; Gambro-Baxter) integrated into the renal replacement therapy (RRT) platform (PrismaFlex[®]; Gambro-Baxter). Of note, this device is currently unavailable, pending the new Prismalung Plus device (Gambro-Baxter). The polymethylpentene, hollow fiber, and gas-exchanger membrane (surface area 0.32 m²) was connected to the extracorporeal circuit. When RRT was required, both techniques were performed simultaneously. A 13 or 14-Fr double-lumen hemodialysis catheter (Gamcath[®]; Gambro-Baxter) was aseptically and percutaneously inserted under ultrasonography guidance into the internal jugular or femoral vein. Systemic anticoagulation was started after catheter insertion. We performed a priming with unfractionated heparin, and maintained systemic continued heparinization with the goal of anti-Xa between 0.3 and 0.7 UI/mL.

Study protocol

The study protocol is described in Fig. 1. At inclusion, patients were sedated, paralyzed, and ventilated in accordance with the recommendations for protective ventilation in ARDS [26]: V_T at 6 mL/kg of predicted

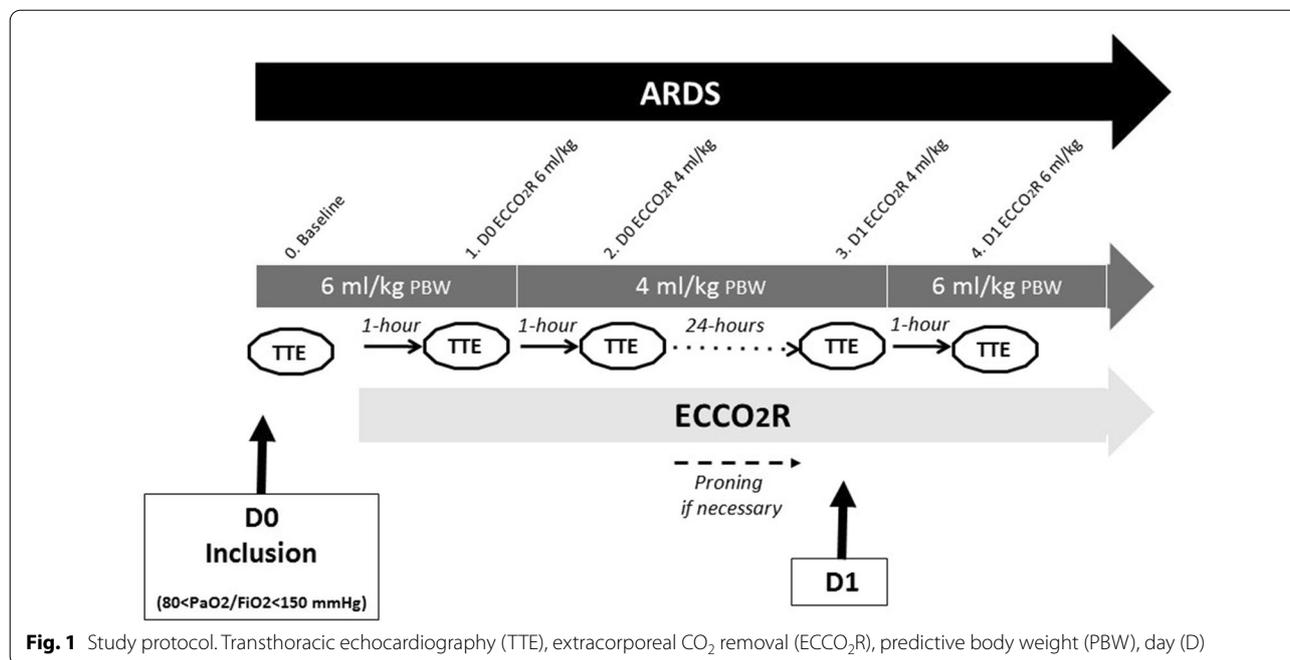


Fig. 1 Study protocol. Transthoracic echocardiography (TTE), extracorporeal CO₂ removal (ECCO₂R), predictive body weight (PBW), day (D)

body weight (PBW) and PEEP set to achieve a P_{plat} of 28–30 cm H₂O. Transthoracic echocardiography (TTE) and blood gas were performed at inclusion. Then, after priming anticoagulation, the ECCO₂R device was connected to the patient, and extracorporeal blood flow was progressively increased to 400 mL/min with sweep-gas flow through maintenance with 100% oxygen at 10 L/min during the entire protocol. After 1 h with ECCO₂R, TTE and blood gas were performed simultaneously. Then, V_T was reduced from 6 to 4 mL/kg PBW under the ECCO₂R device. After 1 h with these settings, TTE and blood gas were performed again. Then, the ECCO₂R device was maintained for 24 h with ultraprotective ventilation parameters (4 mL/kg PBW). During the protocol, severe hypercapnia, acidosis and/or hypoxemia could be managed at the attending clinician’s discretion with changes in respiratory rate (RR) and V_T and with prone positioning and/or switching to ECMO if necessary. After 24 h under V_T 4 mL/kg PBW and ECCO₂R, we also performed TTE and blood gas. After measurement, V_T was returned back to 6 mL/kg PBW with other settings adjusted according to the recommendations of protective ventilation. One hour later, under these standard conditions for the ventilatory management of patients with ARDS, TTE and blood gas were also performed. This last step allows the patient to be his or her own control in a quasi-experimental design. If, under these conditions, the patient remained stable, the ECCO₂R device could be maintained after the protocol. The manufacturer determined

the PrismaLung® membrane’s maximum duration to be 72 h.

Data collection

Demographic data collected included age, gender, primary admission diagnosis, cause of ARDS, comorbidities and documented microorganisms during ARDS. Ventilator settings (V_T , minute ventilation (VM), RR, PEEP, P_{plat} , FiO_2 , and driving pressure calculated as P_{plat} minus PEEP [16], hemodynamic parameters, arterial blood gas values (partial alveolar oxygen pressure (PaO₂), partial alveolar carbon dioxide pressure (PaCO₂), bicarbonate (HCO₃⁻), pH, lactate) were also collected. All TTE exams were made by two experienced physicians with specialized diploma in echocardiography to reduce the inter- and intra-observer variability. The TTE parameters evaluated were left ventricular ejection fraction (LVEF) at baseline, aortic velocity time integral (VTIAo), early diastolic mitral inflow velocity (E), atrial contraction mitral inflow velocity (A), E/A ratio, early diastolic mitral annular velocity (E'), RV systolic excursion velocity (S'), tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary arterial pressure (sPAP), right/left ventricular end-diastolic diameter (RV/LV) ratio, and right atrial (RA) pressure estimation [27]. Heparin dose, anti-Xa, and ECCO₂R parameters (blood flow, sweep-gas flow, characteristics of catheterization) were collected at baseline and then at the different times described previously. During the 24-h protocol, the need for prone positioning, nitric oxide, ECMO, and association with continuous RRT were

recorded. Blood chemistry data and urine volume were collected daily. Physiologic data collected during and after the end of the protocol included the need for renal replacement therapy, ICU mortality, length of ICU stay, length of mechanical ventilation and duration under the ECCO₂R system.

Patients were also monitored for severe adverse events until ICU discharge (clotting membrane, hemorrhagic complications, thrombocytopenia).

Statistical analysis

The primary end point of the study was RV systolic function, assessed first by contractility parameters with TAPSE and S' wave. Second, RV afterload (sPAP estimation), RV preload parameters (RV/LV ratio, RA pressure estimation, distensibility index), VTIAo (to assess cardiac output), and LV function (LVEF, LV end diastolic and systolic diameter, E velocity, E/A ratio, E' velocity, E/E' ratio) were evaluated. The number of subjects required for the study was not calculated because of a pilot study design. Qualitative variables were expressed as numbers and percentages. Quantitative variables were expressed as the median and interquartile range (IQR; 25–75%). Changes in values are expressed as the percentage with the median and IQR. Comparisons between data over time during the protocol were performed using analysis of variance (ANOVA) for repeated measures. Missing data were integrated in the calculation. The comparison of one variable in 2 groups, taking into account (or correcting for) the variability of other variables (called covariates), was performed using analysis of covariance (ANCOVA). Values obtained at different times were compared with those obtained at baseline by using paired Student's *t*-tests. The significance level was fixed at $p < 0.05$. Statistical analyses were performed using MedCalc Software (version 15.11.4).

Results

Eighteen patients with moderate-to-severe ARDS were included in the study. The baseline characteristics of the patients at inclusion are shown in Table 1. The ECCO₂R device was implemented in the early phase of ARDS (median time from intubation to ECCO₂R start, 2 days). Neuromuscular blockade and prone positioning were applied before inclusion in 17 and 8 patients, respectively. In the 24 h following ECCO₂R initiation, 6 patients received prone positioning. Four patients were under RRT at inclusion without additional patients thereafter. Two patients required vvECMO for worsening hypoxemia after the 24-h protocol. The operational characteristics of ECCO₂R are summarized in Additional file 1: Table S1.

Table 1 Baseline characteristics of the 18 patients at study inclusion

Variables (units)	Median (IQR)
Sex (male/female)	13/5
Age (years)	64 (57–76)
Body mass index (kg/m ²)	28 (24–31)
SAPS II at admission	42 (39–45)
SOFA score at ECCO ₂ R insertion	6 (5–8)
PaO ₂ /FiO ₂ (mmHg) at ECCO ₂ R initiation	117 (100–136)
Comorbidities, <i>n</i> (%)	
Arterial hypertension	6 (33.3)
Chronic heart failure	6 (33.3)
Diabetes	5 (27.8)
Chronic renal impairment	2 (11.1)
Chronic obstructive pulmonary disease	0 (0)
Cause of ARDS, <i>n</i> (%)	
Pneumonia	15 (83.3)
Documented germs	12 (66.7)
Influenza	7 (38.9)
Others	5 (27.8)
Pulmonary contusion	1 (5.5)
Drug-induced pneumonia	1 (5.5)
Neoplastic lung disease	1 (5.5)
Pre-ECCO ₂ R adjuvant therapy, <i>n</i> (%)	
Neuromuscular blockade	17 (94.4)
Prone positioning	8 (44.4)
Nitric oxide	0 (0)
Recruitment maneuvers	0 (0)
Time from ICU admission to ECCO ₂ R initiation (days)	2.5 (1–4)
Time from intubation to ECCO ₂ R initiation (days)	2 (1–3.8)

ARDS acute respiratory distress syndrome, ECCO₂R extracorporeal CO₂ removal, SOFA Sequential Organ Failure Assessment, SAPS Simplified Acute Physiologic Score, IQR interquartile range (25–75%)

Ventilation settings, blood gas analysis, and renal and hemodynamic parameters throughout the protocol are shown in Table 2. The initial stepwise reduction V_T was significant in all 18 patients at a mean of 4.04 (4–4.19) mL/kg PBW one hour after CO₂ removal began ($p < 0.001$). Initiation of ECCO₂R resulted in a reduction in PaCO₂ from 43.1 to 37.7 mmHg, a change of 13% from baseline (Fig. 2). There was a significant change in PaCO₂ throughout the protocol ($p = 0.001$). Twenty-four hours after the ultraprotective ventilation strategy with ECCO₂R, PaCO₂ and pH were maintained at 52.5 mmHg (44.2–64) and 7.31 (7.27–7.33), respectively. The reduction in V_T was associated with a significant reduction in P_{Plat} from 25.5 (24–28) at baseline to 21.5 (20–25.8) cm H₂O (D0 ECCO₂R 4 ml/kg). The evolution of P_{Plat} remained significant throughout the study protocol ($p = 0.04$). V_T and P_{Plat} reduction with ECCO₂R were not associated with a significant change in the PaO₂/FiO₂

Table 2 Ventilation, arterial blood gases, renal and hemodynamic parameters during the study period

	ECCO ₂ R					Analysis of variance <i>p</i>
	V _T 6 mL/kg (n = 18)		V _T 4 mL/kg (n = 16)			
	Day 0	Day 1	V _T 6 mL/kg (n = 18)	V _T 4 mL/kg (n = 16)	V _T 6 mL/kg (n = 17)	
Ventilation variable						
V _T (mL/kg PBW)	6.06 (6–6.35)	6.11 (6–6.30)	4.04 (4–4.19)*	4.13 (4–4.28)*	6.09 (5.83–6.48)	< 0.001
VM (L/min)	10.7 (10.1–12.2)	10.8 (10.1–12.2)	7 (6.4–8.4)*	7.8 (6.5–8.7)*	11 (10.1–12.2)	< 0.001
RR (breaths/min)	28 (25–30)	28 (25–30)	29 (25–30)	30 (27.5–32)	28 (26–30)	0.7
PEEP (cm H ₂ O)	11.5 (9.3–14.8)	11.5 (10–15)	12 (10–14.8)	13 (9.5–15.3)	13 (10–16)	0.9
P _{plat} (cm H ₂ O)	25.5 (24–28)	26 (22.3–28.8)	21.5 (20–25.8)*	22.5 (19.8–25.3)*	24 (22–28)	0.04
Driving pressure (cm H ₂ O)	11.5 (10–17.8)	11 (10–17)	9 (8–10)	8.5 (6–11.5)	11 (9–16)	0.2
PaO ₂ /FiO ₂ (mmHg)	108.5 (96.5–136.3)	109.5 (85.3–143)	116 (83.3–161)	113.5 (81.9–142)	112 (69–131)	0.9
Blood gases						
PaO ₂ (mmHg)	79.9 (68.3–88.7)	70.7 (64.7–87.8)	81.8 (70.7–110.4)	72.8 (68.3–95.1)	65.6 (58.3–79.4)*	0.4
PaCO ₂ (mmHg)	43.1 (38.2–57.9)	37.7 (33.5–48.3)*	50 (45.1–58.6)*	52.5 (44.2–64)*	39 (35.7–46.9)	0.001
Patients with PaCO ₂ > 50 mmHg at baseline (n, %)	7 (39)					
FiO ₂ (%)	70 (60–88.8)	70 (60–90)	80 (61.3–100)	85 (57.5–100)	75 (50–100)	0.8
pH	7.38 (7.34–7.42)	7.42 (7.38–7.44)*	7.31 (7.26–7.35)*	7.31 (7.27–7.33)*	7.41 (7.36–7.44)	< 0.001
Lactate (mmol/l)	1.2 (0.9–1.4)	1.2 (1–1.7)	1.2 (0.9–1.4)	1.2 (1–1.5)	1.2 (1–1.6)	0.6
HCO ₃ ⁻ (mmol/l)	23.6 (22.9–27.9)	22.6 (21.6–27.3)	23.4 (22.8–27.3)	25.2 (22.2–30)	24.9 (20.9–26.8)	0.8
Renal function						
Diuresis (ml)	860 (325–1191)		1700 (351–2050)			0.06
Creatinine (μmol/l)	72 (56–137)		81 (58–176)			0.9
Patients with CRRT (n, %)	4 (22)		4 (22)			0.9
Hemodynamic						
Mean arterial pressure (mmHg)	75 (70–80)	87 (79–95)*	84 (73–97)*	80 (73–87)	86 (68–87)*	0.4
Heart rate (beats/min)	84 (65–100)	75 (56–91)*	95 (57–100)*	86 (71–95)	76 (70–95)	0.8
Patients on norepinephrine, n (%)	4 (22.2)	4 (22.2)	2 (22.2)	4 (25)	5 (29.4)	
Norepinephrine dose (μg/kg/min)	0.25 (0.20–0.27)	0.21 (0.12–0.44)	0.11 (0.29–0.43)	0.24 (0.41–0.54)	0.19 (0.38–0.44)	0.6
Patients on dobutamine	1 (5.6)	1 (5.6)	1 (5.6)	1 (6.3)	1 (5.9)	
Total fluid resuscitation (ml)	250 (0–750)					
Prone positioning during protocol (n, %)	6 (33)					

Values presented as median and IQR, interquartile range (25–75%)

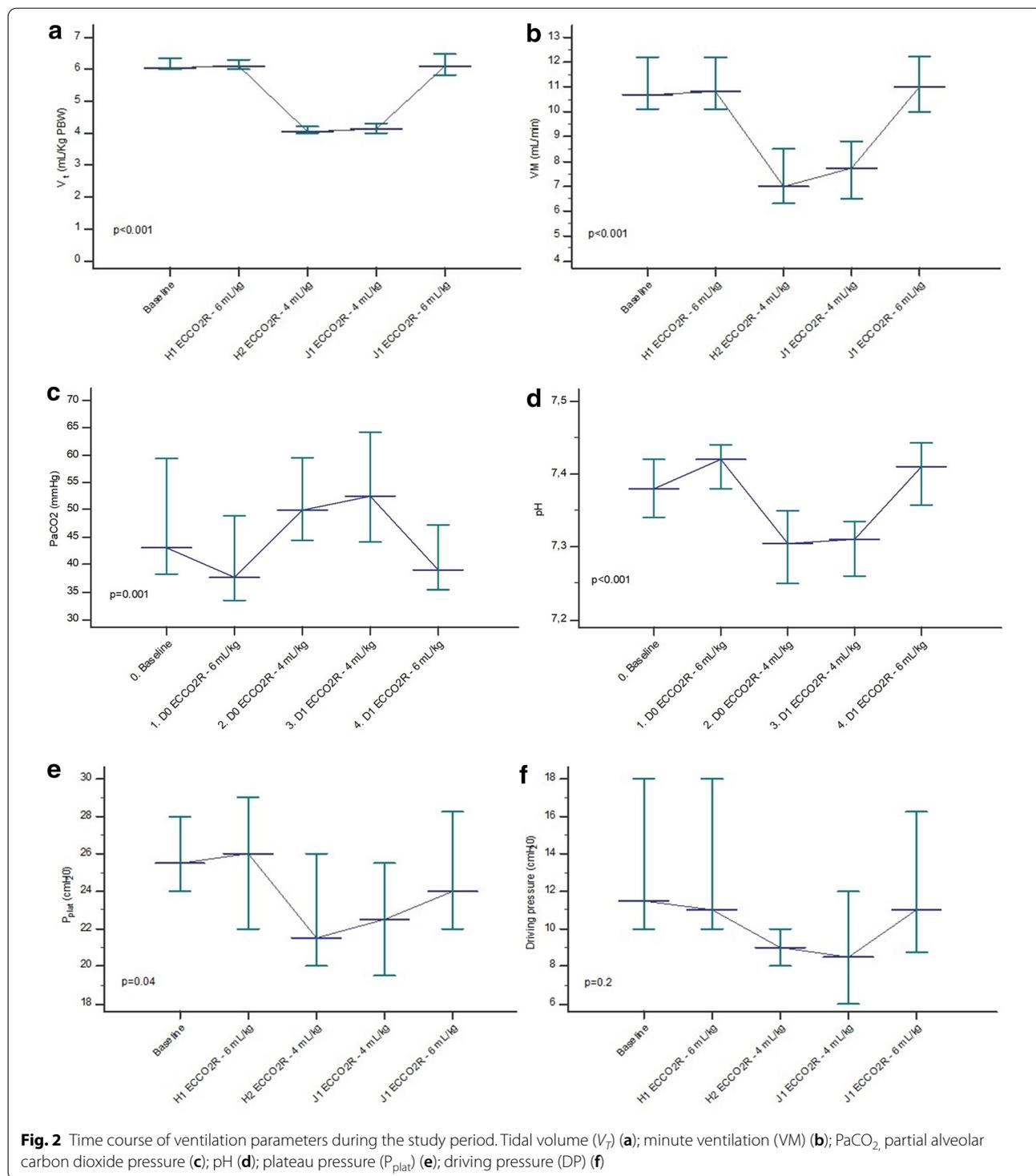
PBW predicted body weight, ECCO₂R extracorporeal CO₂ removal, V_T, tidal volume, VM minute ventilation, RR respiratory rate, PEEP positive end-expiratory pressure, P_{plat} plateau pressure, PaO₂ partial alveolar oxygen pressure, FiO₂ fraction of inspired oxygen, PaCO₂ partial alveolar carbon dioxide pressure, HCO₃⁻ bicarbonate, CRRT continuous renal replacement therapy

**p* < 0.05 vs baseline

ratio. All the renal and hemodynamic parameters did not differ significantly during ECCO₂R therapy (Table 2).

Echocardiographic characteristics are described in Table 3. Regarding RV systolic function, TAPSE changed significantly during the protocol with ECCO₂R

(*p* = 0.02), as illustrated in Fig. 3. More specifically, we observed a significant increase in TAPSE after initiation of the ultraprotective strategy with ECCO₂R at day 0 (25.4 mm) compared to baseline (22.9 mm) (*p* = 0.02) (Additional file 1: Fig. S1). Individual data focused on



RV parameters for patients who needed rescue therapies are given in Table 4. Assessment of correlation coefficient between TAPSE on the one hand, and V_T and $PaCO_2$ on the other hand, found a significant ($r = -0.23$; $p = 0.03$) and a non-significant ($r = -0.12$; $p = 0.26$)

inverse correlation for V_T and $PaCO_2$, respectively. When we separated all 18 patients in two groups with normocapnia ($PaCO_2 < 50$ mmHg; $n = 11$) and hypercapnia ($PaCO_2 > 50$ mmHg; $n = 7$) at baseline, we observed a poorer TAPSE value in the hypercapnic patients than

Table 3 Time course of echocardiographic parameters during the study protocol

Parameter	ECCO ₂ R					Analysis of variance <i>p</i>
	<i>V_T</i> 6 mL/kg (n = 18)		<i>V_T</i> 4 mL/kg (n = 16)			
	Day 0	Day 1	Day 0	Day 1	Day 1	
Left ventricular function						
LVEF at baseline	57.5 (50–60.8)					
VTIAo (cm)	18.3 (15.7–22.1)	20.3 (16.6–22.9)	21.9 (16.2–24)	22.1 (19–25.4)*	20.8 (16.5–24.9)	0.03
LV end-diastolic diameter (cm)	4.8 (3.8–5.9)	4.7 (4–5.4)	4.8 (4–5.9)	4.4 (4–4.7)	4.5 (4–5.6)	0.6
LV end-systolic diameter (cm)	3.3 (2.9–4.2)	3.2 (2.8–4.3)	3.7 (2.9–4.2)	2.9 (2.8–3.5)	3.5 (2.8–4.1)	0.6
Left ventricular filling pressures estimation						
<i>E</i> velocity (m/s)	77.6 (61.4–91.5)	73.7 (64.9–101.3)	79.7 (69.8–100.8)	78.6 (66.9–95.4)	78 (63.6–96.6)	0.9
<i>E/A</i> ratio	1.02 (0.95–1.24)	1.04 (0.89–1.24)	1.11 (0.94–1.43)	1 (0.89–1.18)	0.98 (0.86–1.25)	0.7
<i>E'</i> velocity (m/s)	8.43 (7.92–9.86)	10 (7.67–12.3)	9.72 (8.04–11.7)	9.63 (6.91–11.2)	9.32 (7.47–10.7)	0.9
<i>E'/E</i> ratio	8.47 (7.28–11.05)	8.51 (7.28–11.3)	8.58 (6.74–11.12)	7.49 (7.15–9.47)	8.19 (7.13–9.88)	0.9
Right ventricular function						
<i>S'</i> velocity (cm/s)	13.8 (12.5–15.3)	13.1 (12–14.2)	14.8 (12–15.9)	15.1 (14.3–17.2)*	14.7 (11.5–16.6)	0.1
TAPSE (mm)	22.9 (19.2–24.3)	25 (19.8–27)	25.4 (21.4–27.9)*	24.1 (21.4–26.9)	23.8 (20.8–26)	0.02
Paradoxical septal motion (n)	0	0	0	0	0	–
Tricuspid regurgitation gradient (mmHg)	27 (24–34)	29 (24–33)	33 (28–37)	30 (27–40)	29 (24–37)	0.7
sPAP estimation (mmHg)	44 (40–52)	43 (38–49)	42 (38–51)	46 (40–56)	44 (42–53)	0.7
Right ventricular preload						
RV/LV ratio	0.74 (0.57–0.79)	0.71 (0.61–0.77)	0.68 (0.62–0.74)	0.64 (0.59–0.81)	0.73 (0.61–0.79)	0.8
RA pressure estimation (mmHg)	15 (15–19)	15 (10–19)	15 (10–15)	15 (14–15)	15 (15–20)	0.2
Distensibility index	11.2 (5.2–20.8)	12.4 (5.4–25.1)	10.7 (6.8–22.3)	10.6 (6.5–16.9)	9.5 (6.1–14)	0.6

LVEF left ventricular ejection fraction, VTIAo aortic velocity time integral, *E* early diastolic mitral inflow velocity; *E'* early diastolic septal mitral annular velocity, *A*: atrial contraction mitral inflow velocity, *S'* right ventricle systolic excursion velocity, TAPSE tricuspid annular plane systolic excursion, sPAP systolic pulmonary arterial pressure, RV/LV ratio right/left ventricular end-diastolic diameter (RV/LV) ratio, RA right atrial

**p* < 0.05 vs baseline

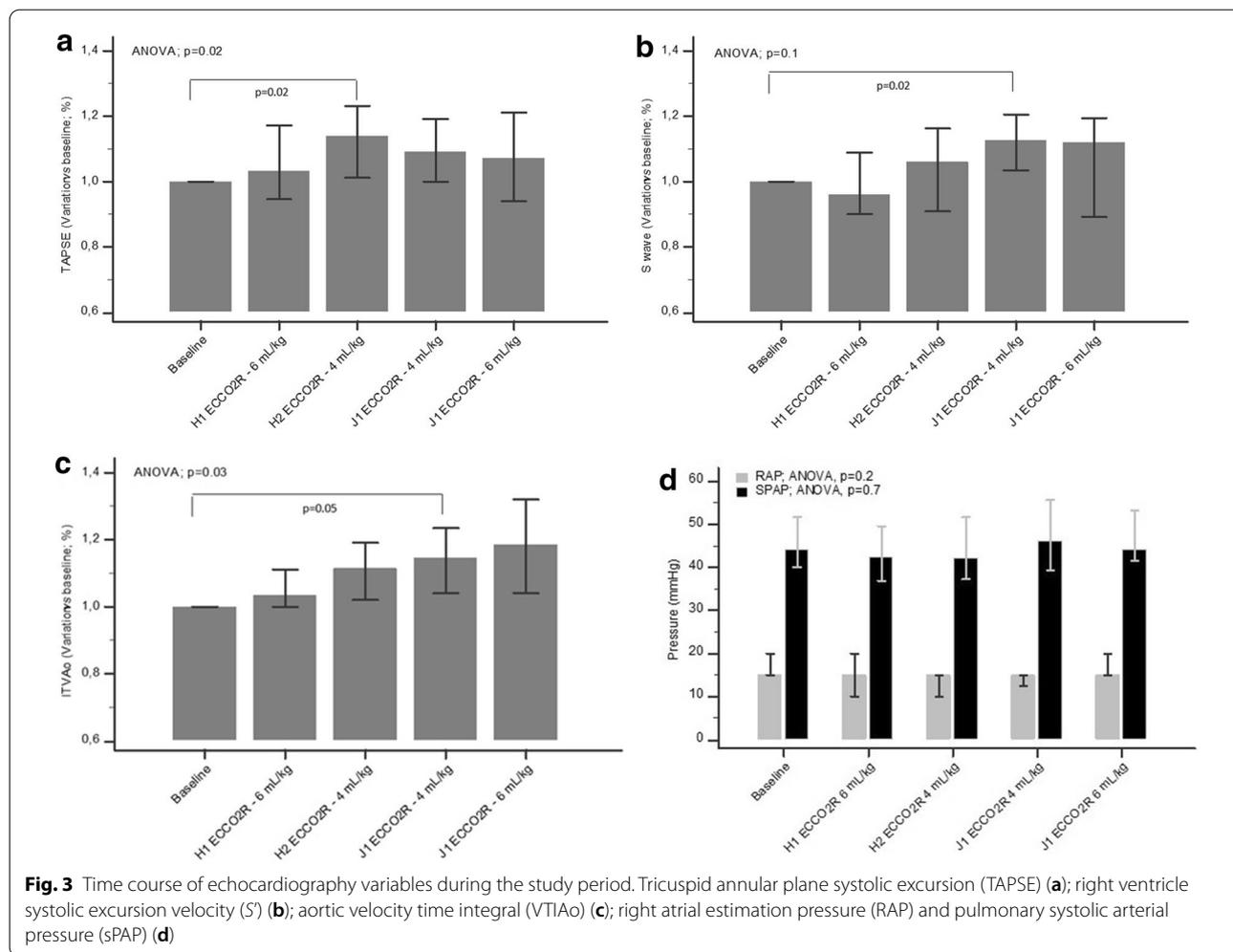
in the normocapnic patients but a significant improvement in TAPSE in both groups associated with low *V_T* at 4 mL/kg PBW (ANCOVA, *p* = 0.04) (Additional file 1: Fig. S2). *S'* wave values did not change significantly overall throughout the study, but we observed a significant evolution between day 1, with a *V_T* reduced at 4 mL/kg PBW with ECCO₂R, and the *S'* wave median at baseline (15.1 versus 13.8 cm/s, respectively; *p* = 0.02). There was no significant difference in the other echocardiographic parameters reflecting RV function and RV preload. Regarding left ventricular systolic and diastolic function, parameters did not differ significantly throughout the study, whereas interestingly, we observed a significant increase in VTIAo values from 18.3 cm at baseline to 22.1 cm at day 1 ECCO₂R 4 mL/kg (*p* = 0.05). Of note, RV variables of interest (TAPSE and *S'* wave velocity) returned at day 1 to a value close to the baseline value of

day 0, after recovering standard conditions of ventilation with 6 mL/Kg *V_T*.

Regarding the ECCO₂R-related adverse events, we observed 5 (28%) membrane lung clotting events (Additional file 1: Table S2). Of note, 3 of the 5 clots of membrane were observed in the first patients included in the study, before HNF priming was increased from 25 to 50 UI/Kg. One severe adverse event occurred with a fatal intracerebral hemorrhage 24 h after the end of protocol, when the patient had been switched from the ECCO₂R device to vvECMO because of worsening ARDS.

Discussion

The results of this quasi-experimental pilot study showed that a low-flow ECCO₂R device improves RV systolic function through the application of an early ultraprotective ventilation strategy, which reduces intrathoracic pressure during mechanical ventilation



in moderate-to-severe ARDS patients. As previously described, the concept of the RV-protective approach was to limit P_{plat} to decrease RV afterload [28]. On the other end, the RV approach also includes a limitation of hypercapnia. These two goals are allowed by the ECCO₂R system. We could highlight a significant improvement in the RV contractility measured by TAPSE and S' wave velocity associated with a reduction in tidal volume. From our study, it seems that improvement in RV contractility is mainly due to a “mechanic” effect with the decrease in intrathoracic pressure rather than a “metabolic” effect with PaCO₂ and pH changes, but this question cannot be answered more precisely because of the study design and limitations. Interestingly, we showed that the improvement in RV systolic function is associated with increased VTIAo (cause or consequence; In fact, it is possible that changes in RV parameters we observed was related to increased VTIAo due to decreases in intrathoracic pressure and

LV afterload [29]), without any changes in systolic or diastolic LV parameters. However, pathophysiology of RV function during ARDS with or without ECCO₂R is complex, and many confounding factors (i.e., lung stress, PaCO₂, pH, hemodynamics, etc.) could explain the observed variation of TAPSE, S' wave velocity and VTIAo in our study.

Concerning the other RV parameters, we failed to highlight a significant modification of RV preload including RV/LV ratio, and afterload (sPAP) measures during the protocol period. RV function depends on preload, contractility and afterload, in particular through ventricular interdependence. No changes in RV preload (RA pressure estimation, distensibility index and RV dilatation) reflect constant and adequate volaemia. Consequently, our results support that RV preload did not affect directly change in TAPSE and VTIAo under ultraprotective ventilation, despite the lack of power of the study. Furthermore, no changes in RV afterload parameters suggest

Table 4 Individual ventilation parameters, RV echocardiographic parameters and outcomes of patients who required rescue therapies

Patient	Etiology of ARDS	PaO ₂ /FiO ₂ ratio at inclusion	Driving pressure at inclusion (cm H ₂ O)	RV echocardiographic parameters										Pa O ₂ / FiO ₂ ratio before rescue therapy	ECMO position	Outcomes (at 28 days)			
				TAPSE (mm)					S' velocity (cm/s)								Prone position		
				ECCO ₂ R		ECCO ₂ R		ECCO ₂ R		ECCO ₂ R		ECCO ₂ R						DO	D1
				V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg						
1	Toxic pneumonia	133	8	269	198	212	27	27	107	103	112	141	147		Alive				
2	Documented bacterial pneumonia	137	17	245	26	28	21	242	154	139	151	18	12		Alive				
3	Documented bacterial pneumonia	144	10	168	156	172	214	21	151	136	163	15	169		Alive				
4	Non documented interstitial pneumonia	132	8	254	25	25	248	237	136	131	148	162	16		Alive				
5	Documented bacterial pneumonia (immuno-compromised)	141	18	188	293	225	268	22	114	18	159	146	141		Alive				
6	Toxic	134	19	28	288	351	333	254	127	142	135	141	109		Alive				
7	Non documented pneumonia	98	10	204	198	224	-	194	143	12	12	-	115	80	Dead				
8	Malignant hemopathy	143	19	122	168	15	-	178	82	91	118	-	953		Dead				

Table 4 (continued)

Patient	Etiology of ARDS	PaO ₂ /FiO ₂ ratio at inclusion	Driving pressure at inclusion (cm H ₂ O)	RV echocardiographic parameters						S' velocity (cm/s)		Pa O ₂ / FiO ₂ ratio before rescue therapy	ECMO position	Outcomes (at 28 days)		
				TAPSE (mm)		ECCO ₂ R		ECCO ₂ R		ECCO ₂ R						
				V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg	V _T 6 mL/kg	V _T 4 mL/kg				V _T 6 mL/kg	V _T 4 mL/kg
9	Bacterial pneumonia	85	14	178	133	17	212	186	132	126	99	12	827	59	Alive	
10	H1N1 pneumonia	90	10	231	286	285	27	293	117	133	14	143	151	91	80	Dead
11	H1N1 pneumonia	111	22	234	27	293	256	268	167	163	16	187	187			Dead
12	H1N1 pneumonia	105	11	261	27	274	268	24	128	113	10	144	141			Alive
13	H1N1 pneumonia	123	10	214	301	317	234	238	124	125	157	134	112			Alive
14	H1N1 pneumonia	106	10	231	-	266	234	204	175	-	138	169	223	158		Dead
15	H1N1 pneumonia	149	13	236	244	258	343	26	142	153	163	164	166		79	Dead
16	Toxic pneumonia	105	32	225	255	174	225	-	163	171	152	151	-	131		Dead
17	H1N1 pneumonia	86	12	186	173	22	199	285	172	103	185	185	167			Dead
18	Traumatic	93	9	226	214	258	214	208	139	13	16	18	147	111		Alive

Missing data are presented with endash (-)

an improvement in RV contractility that arises with an ultraprotective ventilation strategy. However, our results for sPAP values should be treated with caution. Indeed, there is no specific agreement regarding the definition of pulmonary hypertension in ARDS. Using echocardiography, it is currently considered that a sPAP higher than 40 mmHg defines the presence of moderate pulmonary hypertension in ARDS [30]. The literature has shown a modest correlation between sPAP estimated from echocardiography and the gold-standard right-heart catheterization from mild-to-moderate pulmonary hypertension [31]. The sPAP could be influenced by several factors, such as hypercapnia, acidosis, hypoxia and mechanical ventilation. Moreover, applying high PEEP showed no effect in sPAP, while these manoeuvres induced an increase in RV area and pulmonary vascular resistance [32]. The relevance of the sPAP measure compared to the RV function itself in estimations of the RV overload in ARDS is therefore questionable. Consequently, caution should be exercised in the interpretation of these findings.

In our study, we demonstrated the efficacy of a low-flow device to implement an ultraprotective ventilation strategy in ARDS patients, as previously described [33]. During these settings, the PaO₂/FiO₂ ratio remained consistent, and we did not have to increase the PEEP level. Some studies have suggested that lowering V_T may be associated with derecruitment [34]. Similar to previous report of *Allardet-Servent* et al. using the same RRT platform with an ECCO₂R membrane [33], this was not the case in our study because our median PEEP levels close to 12 cmH₂O were probably sufficient to prevent alveolar collapse.

The magnitude of the 13% PaCO₂ reduction during the primary phase was lower than that observed in other studies [33, 35], which explains the gradual increase in PaCO₂ during the V_T reduction phase at 4 mL/kg PBW. This statement is related to the low-flow device that we used compared with the high-flow devices which provide with higher CO₂ extraction. However, in accordance with the recent literature, the V_T reduction phase at 4 mL/kg PBW was achievable in all cases [36], and hypercapnia and acidosis were not limiting factors during the protocol in our study. Because of the low level of decarboxylation allowed with a low-flow device ECCO₂R, we were unable to decrease respiratory rate with the risk of worsen PaCO₂ level and acidosis. Interestingly, we observed a deleterious effect of hypercapnia on RV function when we separated patients into normocapnic and hypercapnic patients with PaCO₂ > 50 mmHg at baseline. However, early ultraprotective ventilation allowed by the ECCO₂R device remains efficient on TAPSE in both groups.

The strengths of this study were its originality and design. To the best of our knowledge, no research has focused on the potential role of low-flow ECCO₂R associated with ultraprotective ventilation on RV function despite a strong pathophysiological rationale. In ARDS, single-center or multicentre studies have examined the feasibility of ultraprotective ventilation facilitated by ECCO₂R [21–23, 37, 38]. A case report described an improvement in RV function after one week of initiation of ECCO₂R in a severe ARDS patient with an acute cor pulmonale [39]. Regarding preclinical research, a study examined the implementation of ECCO₂R in a porcine model with experimental ARDS. The authors found a significant reduction in pulmonary arterial pressure [40]. However, it will be necessary to investigate more accurately on a larger scale, with multicentre studies, the potential place and utilization (i.e., timing) of ECCO₂R to allow ultraprotective ventilation in the improvement of RV function and to what extent its potential benefits lead to improved prognosis in ARDS patients. Focusing on the same purpose, further larger studies will be necessary to specifically assess the safety and the benefit–cost ratio of the ECCO₂R in the ARDS population.

Several limitations should be addressed in our study. First, because of the monocentric design and our small sample size (18 patients) which results in a lack of power, inferences from this quasi-experimental pilot study may be limited. Second, RV assessment with TTE could cause problems with reproducibility. The interrater reliability was not evaluated in our study, but previous studies found excellent results for right function valuation in echocardiography with low interobserver variability, particularly for the TAPSE [41]. Transoesophageal echocardiography (TEE) has been shown to be superior to TTE in diagnosing RV dysfunction in mechanically ventilated patients with moderate-to-severe ARDS [42], but is a more invasive tool. Third, in our study, the baseline values of TAPSE and S' velocity were 22.9 mm and 13.8 cm/s, respectively, which were much higher than the threshold values under which RV systolic dysfunction is usually defined (16 mm and 10 cm/s, respectively) [41]. In addition, change in TAPSE values were not very impressive, and the values change from a normal to a supra normal value. Thus, assessment of TAPSE with ECCO₂R in ARDS patients with RV dysfunction are now warranted. Moreover, our evaluation of RV function was not exhaustive. Other parameters, such as the right ventricular–vascular coupling (TAPSE/sPAP), or RV area, and RV wall thickness and RV outflow tract acceleration time, could also be measured. Similarly, for ventilator parameters, mean airway pressure was not monitored throughout the study protocol. Indeed, in accordance with the literature about ventilator factors influencing RV dysfunction,

we focused our data collection on P_{plat} , driving pressure, V_T and PEEP. Fourth, concerning our population study, we made the choice to exclude extra-pulmonary ARDS in order to have a small homogeneous group of ARDS patients. Our choice could be discussed because of in contrast to previous study [43], recent meta-analysis and large cohort study showed no difference about the prognosis between pulmonary and extra-pulmonary ARDS patients [44, 45]. Finally, there was a high degree of heterogeneity in the severity of our ARDS patients. Almost one-third of patients have engaged in prone positioning sessions during the protocol. This should be considered as an important confounding factor because it may significantly improve RV function [18].

Conclusion

This quasi-experimental study demonstrated that ultraprotective ventilation strategy facilitated by a low-flow ECCO₂R device could improve RV systolic function in moderate-to-severe ARDS patients. Similarly to prone positioning, ECCO₂R could become a strategy that enables the reconciliation of a lung protective approach with an RV-protective approach in ARDS patients. Large-scale clinical studies, including patients with severe RV dysfunction, are warranted to confirm these preliminary results and to assess the overall benefits of ECCO₂R ARDS patients.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-020-00784-3>.

Additional file 1: Table S1. Operational characteristics of extracorporeal CO₂ removal during the study period for the 18 patients. **Table S2.** Adverse events and outcomes of the 18 patients receiving ECCO₂R. **Figure S1.** Individual changes in TAPSE between baseline and 1-hour after reduction of VT at 4 mL/kg PBW with ECCO₂R. Tricuspid annular plane systolic excursion (TAPSE) increased from 22.9 mm (19.2–24.3) to 25.4 mm (21.4–27.9) ($p=0.02$). **Figure S2.** Time course of TAPSE in two groups of patients with PaCO₂ < 50 mmHg ($n=11$) and PaCO₂ > 50 mmHg ($n=7$) at baseline (ANCOVA, $p=0.04$).

Abbreviations

A: Atrial contraction mitral inflow velocity; ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; CRRT: Continuous renal replacement therapy; D: Day; E: Early diastolic mitral inflow velocity; E': Early diastolic mitral annular velocity; ECCO₂R: Extracorporeal CO₂ removal; FiO₂: Fraction of inspired oxygen; ICU: Intensive care unit; IQR: Interquartile range (25–75%); LVEF: Left ventricular ejection fraction; NIV: Non-invasive ventilation; PaCO₂: Partial alveolar carbon dioxide pressure; PaO₂: Partial alveolar oxygen pressure; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; P_{plat} : Plateau pressure; RA: Right atrial; RR: Respiratory rate; RRT: Renal replacement therapy; RV: Right ventricular; RV/LV ratio: Right/left ventricular end-diastolic diameter; S': RV systolic excursion velocity; SAPS: Simplified acute physiologic score; SOFA: Sequential organ failure assessment; sPAP: Systolic pulmonary arterial pressure; TAPSE: Tricuspid annular plane systolic excursion; TEE: Transoesophageal echocardiography; TTE: Transthoracic echocardiography; vECCMO: Veno-venous extracorporeal membrane oxygenation; VILI:

Ventilator-induced lung injury; VM: Minute ventilation; V_T: Tidal volume; VTIAo: Aortic velocity time integral.

Acknowledgements

The authors thank the nursing staff, residents and seniors of the intensive care units for their cooperation with the protocol.

Authors' contributions

SG and DdC initiated the study and the design. SG and DdC were involved in the interpretation of the results and statistical analysis. SG wrote the manuscript. DdC helped to draft the manuscript. SG, XV, JD, CD and DdC contributed to the realization of the study. All authors read and approved the final manuscript.

Authors' information

This work has been presented at the congress of the Société de Réanimation de Langue Française (SRLF) held in February 2020, Paris, France.

Funding

This study was funded by an unrestricted academic research grant from the Caen University Hospital.

Availability of data and materials

All data generated and analyzed during this study are not publicly available due to lack of consent of the participants for dataset publication, but can be made available by the corresponding author upon reasonable request.

Ethics approval and consent to participate

The protocol was approved by appropriate legal and ethics authorities (Comité de Protection des Personnes Ile-de-France 6, Paris, France; no. 17032). Informed consent was obtained from patients or legally authorized surrogates.

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

Author details

¹ CHU de Caen Normandie, Service de Réanimation Médicale, Av côte de Nacre, 14000 Caen, France. ² Normandie Univ, UNICAEN, INSERM, U1237, PhIND "Physiopathology and Imaging of Neurological Disorders", Institut Blood and Brain @ Caen-Normandie, Cycleron, 14000 Caen, France.

Received: 13 July 2020 Accepted: 25 November 2020

Published online: 07 January 2021

References

- ARDSNetwork. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301.
- Guérin C, Reigner J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013;368:2159–68.
- Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363:1107–16.
- Brun-buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. *Intensive Care Med.* 2004;30:51–61.
- Phua J, Badia JR, Adhikari NKJ, et al. Has mortality from acute respiratory distress syndrome decreased over time? A Systematic Review. *Am J Respir Crit Care Med.* 2009;179:220–7.
- Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* 2016;315:788–800.
- Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2007;175:160–6.

8. Grasso S, Stripoli T, Michele MD, et al. ARDSnet Ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176:761–7.
9. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369:2126–36.
10. Zapol WM, Kabayashi K, Snider MT, Greene R, Laver MB. Vascular obstruction causes pulmonary hypertension in severe acute respiratory failure. *Chest*. 1977;71:306–7.
11. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med*. 2016;42:862–70.
12. Jardin F, Vieillard-baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. *Intensive Care Med*. 2007;33:444–7.
13. Mekontso Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med*. 2009;35:1850–8.
14. Vieillard-Baron A, Matthay M, Teboul JL, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. *Intensive Care Med*. 2016;42:739–49.
15. Bouferrache K, Vieillard-baron A. Acute respiratory distress syndrome, mechanical ventilation, and right ventricular function. *Curr Opin Crit Care*. 2011;17:30–5.
16. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372:747–55.
17. Viitanen A, Salmenpera M, Heinonen J. Right ventricular response to hypercarbia after cardiac surgery. *Anesthesiology*. 1990;73:393–400.
18. Vieillard-baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest*. 2007;132:1440–6.
19. Richard C, Argaud L, Blet A, et al. Extracorporeal life support for patients with acute respiratory distress syndrome: report of a Consensus Conference. *Ann Intensive Care*. 2014;4:15.
20. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (3 ml / kg) combined with extracorporeal CO₂ removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39:847–56.
21. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml / kg enhances lung role of extracorporeal carbon dioxide removal. *Anesthesiology*. 2009;111:826–35.
22. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A. Feasibility and safety of low-flow extracorporeal CO₂ removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. *Crit Care*. 2018;22:122.
23. Combes A, Fanelli V, Pham T, Ranieri VM, et al. Feasibility and safety of extracorporeal CO₂ removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med*. 2019;45:592–600.
24. Augy JL, Aissaoui N, Richard C, et al. A 2-year multicenter, observational, prospective, cohort study on extracorporeal CO₂ removal in a large metropolis area. *J Intensive Care*. 2019;7:45.
25. Combes A, Auzinger G, Capellier G, et al. ECCO₂R therapy in the ICU: consensus of a European round table meeting. *Crit Care*. 2020;24:490.
26. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195:1253–63.
27. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol*. 1990;66:493–6.
28. Repesse X, Charron C, Vieillard-Baron A. Right ventricular failure in acute lung injury and acute respiratory distress syndrome. *Minerva Anestesiol*. 2012;78:941–8.
29. Lamia B, Teboul JL, Monnet X, Richard C, Chemla D. Relationship between the tricuspid annular plane systolic excursion and right and left ventricular function in critically ill patients. *Intensive Care Med*. 2007;33:2143–9.
30. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med*. 2013;39:1725–33.
31. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart*. 2011;97:612–22.
32. Fougères E, Teboul J, Richard C, Osman D, Chemla D, Monnet X. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med*. 2010;38:802–7.
33. Allardet-Servent J, Castanier M, Signouret T, Soudarvelou R, Lepidi A, Seghboyan J. 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*. 2015;43:2570–81.
34. Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L. Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med*. 2001;163:1609–13.
35. Forster C, Schriewer J, John S, Eckardt KU, Willam C. Low-flow CO₂ removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. *Crit Care*. 2013;17:R154.
36. Combes A, Tonetti T, Fanelli V, et al. Efficacy and safety of lower versus higher CO₂ extraction devices to allow ultraproductive ventilation: secondary analysis of the SUPERNOVA study. *Thorax*. 2019;74:1179–81.
37. Fanelli V, Ranieri MV, Mancebo J, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care*. 2016;20:36.
38. Winiszewski H, Aptel F, Belon F, et al. Daily use of extracorporeal CO₂ removal in a critical care unit: indications and results. *J Intensive Care*. 2018;6:36.
39. Cherpanath TGV, Landburg PP, Lagrand WK, Schultz MJ, Juffermans NP. Effect of extracorporeal CO₂ removal on right ventricular and hemodynamic parameters in a patient with acute respiratory distress syndrome. *Perfusion*. 2016;31:525–9.
40. Morimont P, Guiot J, Desai T, et al. Venovenous extracorporeal CO₂ removal improves pulmonary hemodynamics in a porcine ARDS model. *Acta Anaesthesiol Scand*. 2015;59:448–56.
41. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.
42. Lhéritier G, Legras A, Caille A, et al. 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*. 2013;39:1734–42.
43. Kim SJ, Oh BJ, Lee JS, et al. Recovery from lung injury in survivors of acute respiratory distress syndrome: difference between pulmonary and extrapulmonary subtypes. *Intensive Care Med*. 2004;30:1960–3.
44. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med*. 2016;42:1865–76.
45. Agarwal R, Srinivas R, Nath A, et al. Is the mortality higher in the pulmonary vs the extrapulmonary ARDS? A meta analysis. *Chest*. 2008;133:1463–73.

Publisher's Note

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