Efficacy and safety of lower versus higher CO_2 extraction devices to allow ultraprotective ventilation: secondary analysis of the SUPERNOVA study

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ABSTRACT

Retrospective analysis of the SUPERNOVA trial exploring the hypothesis that efficacy and safety of extracorporeal carbon dioxide removal ($ECCO_2R$) to facilitate reduction of tidal volume (V_T) to 4 mL/kg in patients with acute respiratory distress syndrome (ARDS) may differ between systems with *lower* (area of membrane length 0.59 m^2; blood flow 300–500 mL/min) and *higher* (membrane area 1.30 m^2; blood flow between 800 and 1000 mL/min) CO_2 extraction capacity. Ninety-five patients with moderate ARDS were included (33 patients treated with *lower* and 62 patients treated with *higher* CO_2 extraction devices). We found that (1) V_T of 4 mL/kg was reached by 55% and 64% of patients with the lower extraction versus 90% and 92% of patients with higher extraction devices at 8 and 24 hours from baseline, respectively (p<0.001), and (2) percentage of patients experiencing episodes of $ECCO_2R$-related haemolysis and bleeding was higher with *lower* than with *higher* extraction devices (21% vs 6%, p=0.045% and 27% vs 6%, p=0.010, respectively). Although V_T of 4 mL/kg could have been obtained with all devices, this was achieved frequently and with a lower rate of adverse events by devices with *higher* CO_2 extraction capacity.

INTRODUCTION

Reduction of tidal volume (V_T) to 3–4 mL/kg of predicted body weight (PBW) and of end-inspiratory plateau pressure (P_{PLAT}) to ≤25 cmH_2O integrated by extracorporeal carbon dioxide removal ($ECCO_2R$) has been proposed in patients with acute respiratory distress syndrome (ARDS).[1]

We recently reported results of the SUPERNOVA trial, a phase II study that assessed feasibility and safety of $ECCO_2R$ in patients with moderate ARDS.[2] The study was conducted using *lower* (cross-sectional area of membrane lung 0.59 m^2, blood flow 300–500 mL/min; Hemolung, ALung Technologies, Pittsburgh, Pennsylvania, USA) and *higher* (cross-sectional area of membrane lung 1.30 m^2, blood flow between 800 and 1000 mL/min; iLA, Novalung, Heilbronn, Germany and Cardiohelp, Getinge, Rastatt, Germany) CO_2 extraction devices.[2] We perform a retrospective analysis of the SUPERNOVA trial to explore the hypothesis that efficacy and safety of $ECCO_2R$ to allow V_T of 4 mL/kg and P_{PLAT} ≤25 of cmH_2O may vary between *lower* vs *higher* CO_2 extraction devices.

METHODS

Patients older than 18 years with moderate ARDS[3] were included. Inclusion and exclusion criteria have been previously reported.[2]

V_T and positive end-expiratory pressure (PEEP) were in September as previously described (baseline).[4] V_T was reduced to 4 mL/kg PBW, titrating PEEP to target P_{PLAT} of 23–25 cmH_2O and $ECCO_2R$ hence was initiated.

Effectiveness was assessed as the proportion of patients who achieved a V_T of 4 mL/kg with $PaCO_2$ not increasing more than 20% from baseline (with arterial pH >7.30). Safety was assessed as the number of patients experiencing severe and $ECCO_2R$-related adverse events. Physiological variables were recorded at baseline, 8 and 24 hours.

Proportions and continuous variables between *lower* and *higher* extracting devices were compared using χ^2, Fisher exact tests, Student t-test or Wilcoxon rank-sum test. Continuous variables assessed at 8 and 24 hours were compared with previously described statistical analysis plans.[2]

RESULTS

Thirty-three patients (35%) were treated with the *lower* and 62 patients (65%) with the *higher* CO_2 extraction devices. At baseline, values of PaO_2/FiO_2 were higher and use of recruiting manoeuvres was less frequent in patients on *lower* vs *higher* CO_2 extraction devices (table 1) (p<0.05).

A 15.5 Fr catheter was used with the *lower* extraction device; an 18 (18–20) Fr catheter was used in patients on *higher* extraction devices (p=0.0001). At 12 hours after inclusion, doses of heparin and activated partial thromboplastin time ratio were similar between lower and higher extraction devices (21 000 (18 000; 27 950) vs 20 000 (14 000; 26 400), p=0.425 and 49.1±14.9 vs 57.6±21.6, p=0.074, respectively).

Respiratory rate and minute ventilation were higher in patients on the *lower* versus *higher* extraction devices (p<0.001) (figure 1). Time course of ventilator and blood gas parameters are shown in table 1. Compared with baseline, P_{PLAT} decreased by 10%–20% in both *lower* and *higher* extraction groups (p<0.001), and at 24 hours was significantly lower in patients treated with *lower* than in patients with *higher* extraction devices (p=0.003). Compared with baseline, $PaCO_2$ decreased at 8 and 24 (p<0.01) hours in patients treated with the *higher* extraction devices while it increased at 8 hours in patients treated with

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Table 1 Time course of ventilator settings and blood gas analysis

	Baseline		8 hours		24 hours	
	Lower CO_2 extraction (N=33)	Higher CO_2 extraction (N=62)	Lower CO_2 extraction (N=33)	Higher CO_2 extraction (N=62)	Lower CO_2 extraction (N=33)	Higher CO_2 extraction (N=62)
P_{PLAT} (cmH_2O)	26.7±2.81	26.7±3.30	23.6±2.70†	24.3±3.96‡	21.9±3.15‡	24.4±4.03§
PEEP (cmH_2O)	13.58±3.73	13.55±3.77	13.84±3.11‡	14.54±3.88†	12.96±3.23	14.16±4.15†
Driving pressure (cmH_2O)	13.2±4.13	13.2±4.15	9.67±3.35‡	9.65±4.08‡	8.93±3.78†	10.4±4.49§
PaO_2/FiO_2	185±57.1	159±66.9*	197±66.2	154±61.5*	198±62.9	153±56.3*
$PaCO_2$ (mm Hg)	45.9±9.09	49.0±9.72	52.5±13.8†	44.8±9.28*†	49.0±13.6	45.5±8.33†
pH	7.33±0.09	7.35±0.09	7.30±0.09	7.40±0.08*†	7.35±0.08	7.41±0.07*†

Data are mean±SD.
*p<0.05 *lower* vs *higher* CO_2 extraction.
†p≤0.01 vs baseline.
‡8 missing values.
§5 missing values.
$PaCO_2$, arterial PCO_2; PaO_2/FiO_2, arterial to inspiratory O_2 fraction; P_{PLAT}, end-inspiratory plateau pressure; PEEP, positive end-expiratory pressure.

the lower extraction system (p=0.01). $PaCO_2$ at 8 hours was lower with the *higher* than with the *lower* extraction system (p=0.008).

Percentage of patients reaching a V_T of 4 mL/kg PBW was 55% and 64% with the *lower* versus 90% and 92% with *higher* extraction devices at 8 and 24 hours, respectively (p<0.001).

Two severe adverse events were attributed to $ECCO_2R$ (right frontal massive parenchymal haematoma with the *lower* and pneumothorax at insertion cannula in the internal jugular vein with the *higher* extraction devices). Percentage of patients experiencing $ECCO_2R$-related adverse events was 48% with the *lower* and 34% with the *higher* extraction devices (p=0.242). Percentage of patients experiencing episodes of haemolysis and bleeding was higher with *lower* than with *higher* extraction devices (p<0.05) (table 2).

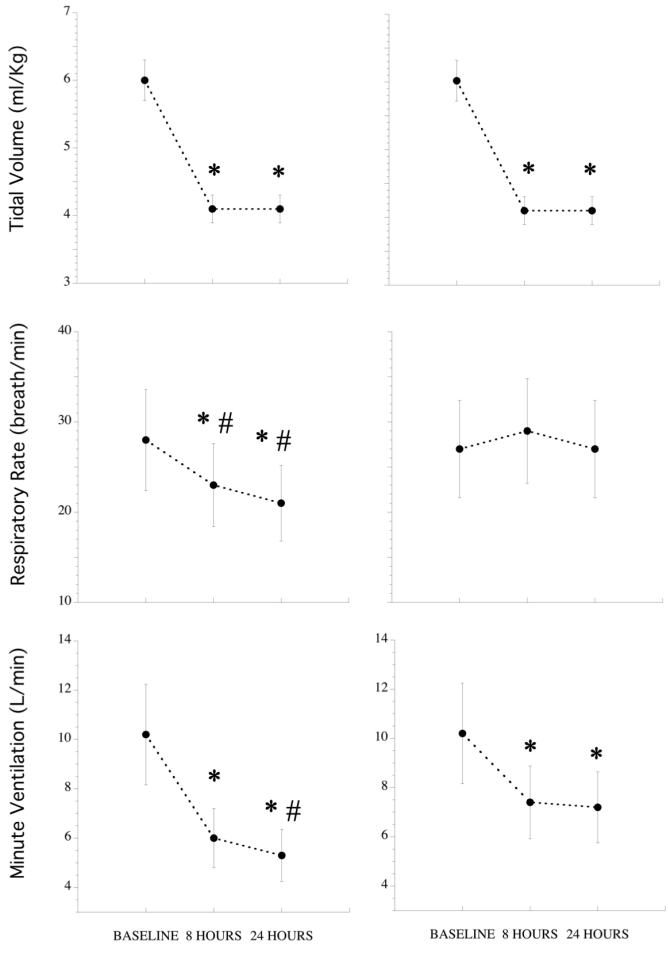

Figure 1 Time course of respiratory variables. *p<0.001 *lower* vs *higher* CO_2 extraction; #p<0.01 vs baseline.

DISCUSSION

Analysis of the SUPERNOVA trial suggests that systems using higher flow (800–1000 mL/min) and a larger membrane (1.30 m^2) are more effective in facilitating ultraprotective ventilator settings than using lower flow (<500 mL/min) and a smaller membrane (0.59 m^2). Since there is no evidence of a safe upper limit for

Table 2 Numbers of patients experiencing $ECCO_2R$-related adverse events occurring between enrolment and day 28

Patients experiencing $ECCO_2R$-related adverse events n (%)	Lower CO_2 extraction (N=33)	Higher CO_2 extraction (N=62)
Mechanical		
Lung clotting membranes	3 (9)	10 (16)
Leading to circuit change	1 (3)	5 (8)
Leading to $ECCO_2R$ discontinuation	2 (6)	5 (8)
Pump malfunction	2 (6)	1 (2)
Catheter displacement	2 (6)	0 (0)
Clinical		
Haemolysis	7 (21)	4 (6)*
Bleeding	9 (27)	4 (6)†
Related to cannula insertion	2 (6)	1 (2)
At cannula site	6 (18)	1 (2)*
Significant	3 (9)	3 (5)
Infectious complications	2 (6)	0 (0)
Thrombocytopenia	4 (12)	8 (13)
Hypofibrinogenemia	0 (0)	2 (3)

*p<0.05.
†p<0.01.
‡Haemolysis: serum-free haemoglobin ≥100 mg/L or haematocrit reduction not related to haemorrhage or other causes of blood loss, jaundice, haemoglobinuria, impaired renal function. Hypofibrinogenemia: fibrogen <1.5 g/L. Significant bleeding: any bleeding event requiring administration of 1 U of packed red cells. Thrombocytopenia: platelet count below $50*10^9$/L L.
$ECCO_2R$, extracorporeal carbon dioxide removal.

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protective ventilator settings,[5] outcomes may be improved by aggressively lowering V_T using devices that can remove more CO_2, allowing lower respiratory rates, which were shown to be lung protective[6] by decreasing mechanical power.[7] It should be acknowledged that clearance and total amount of CO_2 removed by $ECCO_2R$ with *lower* and *higher* extraction devices were not quantified.

Fitzgerald and coworkers recently performed a comprehensive systematic review that included 14 studies with 495 patients treated with $ECCO_2R$ and found that complication rates ranged from 0% to 25%.[8] Clotting/membrane malfunction, bleeding and increasing the requirement for blood transfusion were the most common complications.[8] We have found that, although the *lower* extraction device used smaller cannulas and lower blood flow than the ones used with *higher* extraction devices, the percentage of patients with haemolysis and bleeding episodes was significantly higher in the former (table 2). Moreover, it should be noted that heparose and activated partial thromboplastin time ratio were similar between *lower* and *higher* extraction devices. This observation may be particularly relevant since (1) the balance between excessive anticoagulation (bleeding, haemolysis) and insufficient anticoagulation (clotting) is crucial for the safety and feasibility of $ECCO_2R$, and (2) the importance of monitoring coagulation during $ECCO_2R$ is confirmed. Moreover, since in the present study contraindications for systemic anticoagulation and bleeding disorders were observed in 30% of patients,[2] feasibility and safety of randomised clinical trials using *lower* CO_2 extraction devices may be problematic.

In conclusion, these data suggest that reductions of V_T to 4 mL/kg and of P_{PLAT} to ≤25 of cmH_2O are consistently achievable only with the *higher* extraction devices. Future randomised clinical trials assessing the overall benefit and harm of ultraprotective ventilation should be carried out with $ECCO_2R$ devices equipped with a larger membrane lung and blood flows between 800 and 1000 mL/min.

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