EKSTRAKORPORAL CO2-FJERNELSE ECCO2R

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ARDS

ACUTE RESPIRATORY DISTRESS SYNDROM

VENTILATION-INDUCERET LUNGESKADE(VILI)

LUNGE-PROTEKTIV VENTILATION

MAX P_{PLAT} 30CM H2O OG V_T 6ML/KG

ULTRA LUNGEPROTEKTIV VENTILATION

PPLAT PÅ 25CM H2O ELLER LAVERE OG VT 4ML/KG

LAVERE GRAD AF INFLAMMATION I LUNGEVÆVET

HYPERKAPNI OG RESPIRATORISK ACIDOSE

Basale principper ved ECCO2R

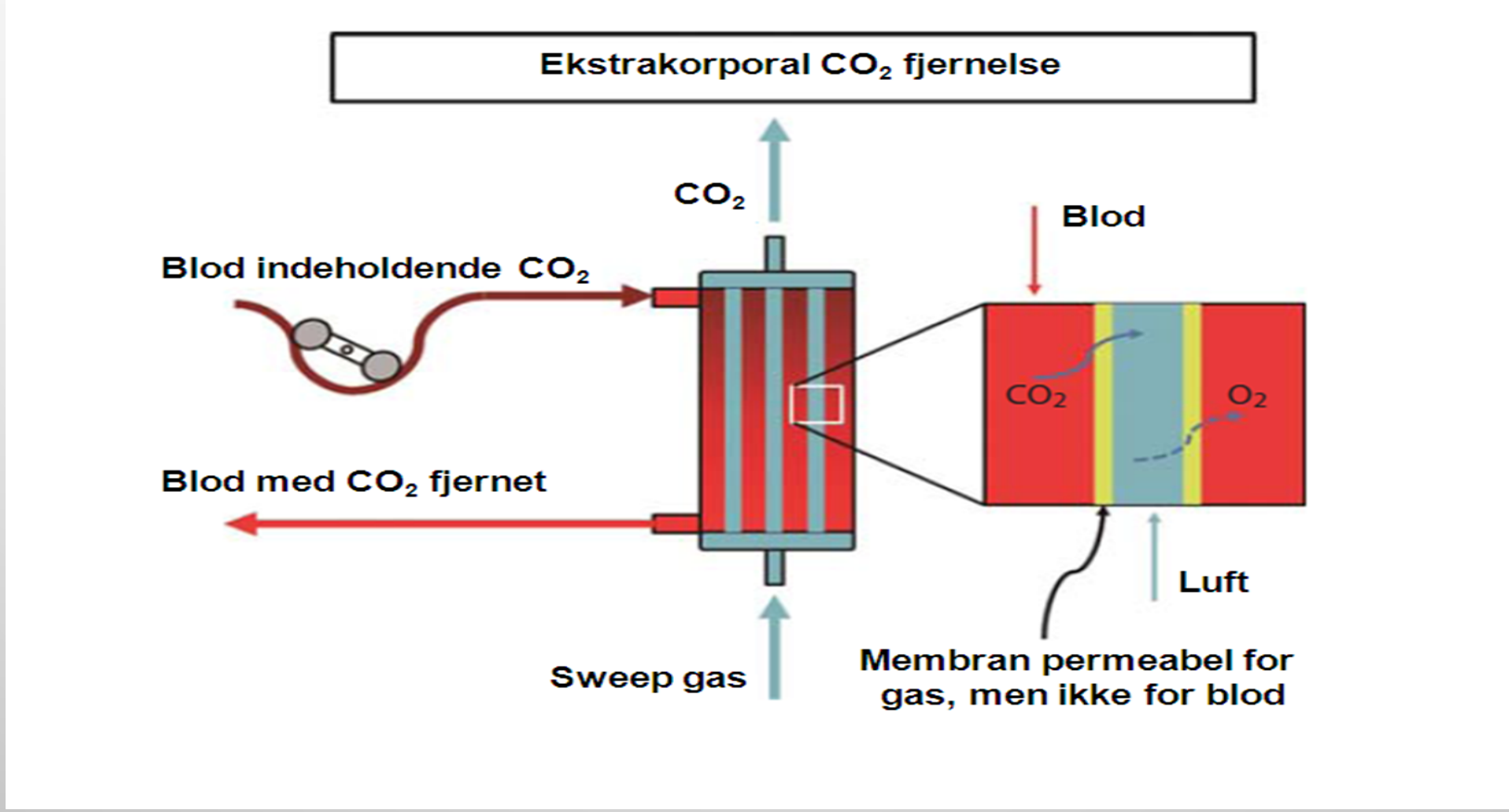
CO_2 har sammenlignet med O_2 en mere lineær dissociationskurve og fjernes derfor lettere fra blodet.

Da indholdet af CO_2 i venøst blod er højt kan man opnå betydelig udskillelse af CO_2 med blodflow $\leq$ 500 ml/min. gennem ECCO2R filter.

CO_2 har desuden en høj grad af diffusions-potentiale

I modsætning til oxygenering er CO_2-transport primært ventilation eller gas flow afhængig, og derfor kan effektiv CO_2 fjernelse finde sted ved anvendelse af relativt lavt blodflow.

ECCO2R


Ekstrakorporal CO_2 fjernelse
CO_2
Blod
Blod indeholdende CO_2
CO_2
O_2
Blod med CO_2 fjernet
Luft
Sweep gas
Membran permeabel for gas, men ikke for blod

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SEVEN-DAY PROFILE PUBLICATION

Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

Alain Combes[1], Vito Fanelli[2], Tai Pham[3], V. Marco Ranieri[4*] and On behalf of the European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators

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Abstract

Purpose: We assessed feasibility and safety of extracorporeal carbon dioxide removal ($ECCO_2R$) to facilitate ultra-protective ventilation (V_T 4 mL/kg and $P_{PLAT} \leq 25$ cmH_2O) in patients with moderate acute respiratory distress syndrome (ARDS).

Methods: Prospective multicenter international phase 2 study. Primary endpoint was the proportion of patients achieving ultra-protective ventilation with $PaCO_2$ not increasing more than 20% from baseline, and arterial pH > 7.30. Severe adverse events (SAE) and $ECCO_2R$-related adverse events ($ECCO_2R$-AE) were reported to an independent data and safety monitoring board. We used lower CO_2 extraction and higher CO_2 extraction devices (membrane lung cross-sectional area 0.59 vs. 1.30 m^2; flow 300–500 mL/min vs. 800–1000 mL/min, respectively).

Results: Ninety-five patients were enrolled. The proportion of patients who achieved ultra-protective settings by 8 h and 24 h was 78% (74 out of 95 patients; 95% confidence interval 68–89%) and 82% (78 out of 95 patients; 95% confidence interval 76–88%), respectively. $ECCO_2R$ was maintained for 5 [3–8] days. Six SAEs were reported; two of them were attributed to $ECCO_2R$ (brain hemorrhage and pneumothorax). $ECCO_2R$-AEs were reported in 39% of the patients. A total of 69 patients (73%) were alive at day 28. Fifty-nine patients (62%) were alive at hospital discharge.

Critical Care

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tensive care units:
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ane Gaudry[1,3*]

surgical ICUs). Response rate was 98.5 % with only refusals to participate. Based on responses to the e interview, 35 (15 %) ICUs had used ECCO2R at once during the period of interest, in a total of 303 nts. The median number of patients treated per ICU hree (interquartile range 1–8; minimum 1, maxi- 140). Responders used the iLA® device (Novalung H, Heilbronn, Germany) for 63 % of the ECCO2R dures and the Hemolung® (Alung Technologies, urgh, PA) for 37 %. Among the 35 ICUs using O2R, 18 used arteriovenous ECCO2R, ten used venous ECCO2R with double lumen catheter and used venovenous ECCO2R with two catheters (one r used both arteriovenous and venovenous with ble lumen catheter ECCO2R). The most frequent ation was ultra-protective ventilation for ARDS). Other indications included failure of non-invasive lation during chronic obstructive pulmonary disease rbation (30 %), weaning from invasive mechani- ntilation in chronic obstructive pulmonary disease nts (12 %) and miscellaneous (4 %). Among the par- ting ICUs, 22 (63 %) reported at least one compli- n, of which the most frequent were bleeding (45 %) membrane failure (18 %). Satisfaction rates were 2.4 for decarboxylation, 6.9 ± 2.6 for tolerance and 2.2 for overall satisfaction. The main reasons for sing ECCO2R were a lack of trained staff, unavail- y of the device and a lack of scientific evidence (for 9 and 17 % of responders, respectively). Among 201 not using ECCO2R, 20 (10 %) envisioned initiating O2R in the coming months.
s national survey shows that ECCO2R is not widely in French ICUs. In the ICUs using this technology, ique and expertise were heterogeneous. Lack of g scientific data on outcome is likdely the main rea- ehind the limited use of ECCO2R. Ongoing studies

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weaning off $ECCO_2R$

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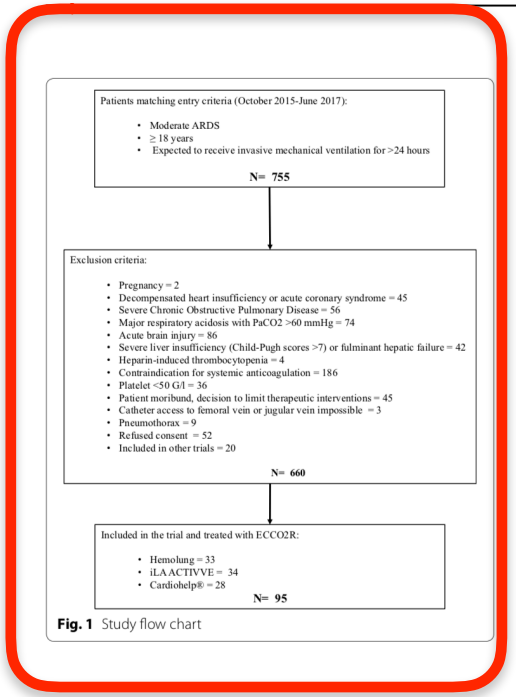

Fig. 1 Study flow chart

No assumptions were made for missing data. Statistical analyses were performed using R (version 3.5.1). All p values were two-sided and values < 0.05 were deemed significant. The statistical analysis plan is available online.

Results

Of the 483 patients matching entry criteria, 95 patients were enrolled between October 2015 and June 2017 at 23 centers in Europe and Canada. Thirty-three patients were treated with the Hemolung device at five sites. Ten sites used the iLA activve device and treated 34 patients; eight sites used the Cardiohelp® HLS 5.0 device and treated 28 patients (Fig. 1). The centers enrolled a median of 3 [1–5] patients. Baseline characteristics and concomitant treatments at inclusion are shown in Table 1. No patient was lost to follow-up.

The proportion of patients who achieved ultra-protective settings by 8 h and 24 h was 78% (confidence interval 68–89%) (74 out of 95) and 82% (confidence interval 76–88%) (78 out of 95), respectively. $ECCO_2R$ was maintained for 5 [3–8] days.

Cannulation was performed through the internal jugular vein in 57% and through the femoral vein in 43% of patients. Catheter size was 15.5 Fr in patients on the Hemolung device and 18 [18–20] Fr in patients on the iLA activve and Cardiohelp® HLS 5.0 devices ($p < 0.001$).

Table 1 Characteristics of patients at study inclusion

Age (years)	60.2 ± 14.0
Female (*n*, %)	31 (32.6%)
BMI (kg/m^2)	29.2 ± 8.79
SAPS II	45.9 ± 15.5
SOFA score	7.42 ± 3.22
Cause of ARDS (*n*, %)	
Pneumonia	78 (82.1%)
Non-pulmonary sepsis	3 (3.2%)
Pancreatitis	2 (2.1%)
Pulmonary contusion	2 (2.1%)
Other	10 (10.5%)
Ventilatory settings	
V_T (mL/kg)	6.0 ± 0.2
RR (breaths/min)	27.3 ± 4.8
V_E (L/min)	10.2 ± 2.3
PEEP (cmH_2O)	15.5 [10.0;16.0]
P_{PLAT} (breaths/min)	26.6 ± 3.0
ΔP (cmH_2O)	13.2 ± 4.3
$PaCO_2$ (mmHg)	47.8 ± 9.4
pH	7.34 ± 0.08
FiO_2	0.57 [0.50;0.70]
PaO_2 (mmHg)	101.2 ± 34.5
PaO_2/FiO_2	173 ± 61
Adjunctive treatments before inclusion (*n*, %)	
Muscle paralysis	80 (84.2%)
Prone position	23 (24.2%)
Pulmonary vasodilator	8 (8.42%)
Recruitment maneuvers	26 (27.4%)

Data are mean (standard deviation) or median [interquartile range]

BMI body mass index, *SAPS* simplified acute physiological score, *SOFA* sequential organ failure assessment, V_T tidal volume, *RR* respiratory rate, V_E minute ventilation, P_{PLAT} end-inspiratory plateau pressure, *PEEP* positive end-expiratory pressure, ΔP delta pressure ($\Delta P = P_{PLAT}$ minus PEEP), $PaCO_2$ partial pressure of arterial CO_2, PaO_2 arterial oxygen fraction, FiO_2 inspiratory oxygen fraction, PaO_2/FiO_2 ratio of arterial-to-inspiratory oxygen fraction

Operational characteristics of $ECCO_2R$ are shown in Table 2.

The time course of the respiratory variables in the first 24 h is reported in Fig. 2. V_T, respiratory rate, minute ventilation, P_{PLAT}, and ΔP were significantly lower at 8 h and 24 h compared to baseline ($p = 0.001$). Compared to baseline, $PaCO_2$ and PaO_2/FiO_2 ratio remained stable, while pH significantly increased at 8 h ($p < 0.05$) and 24 h ($p < 0.001$). Trend of respiratory variables until $ECCO_2R$ discontinuation was consistent with the one observed in the first 24 h (Table 1_online supplement).

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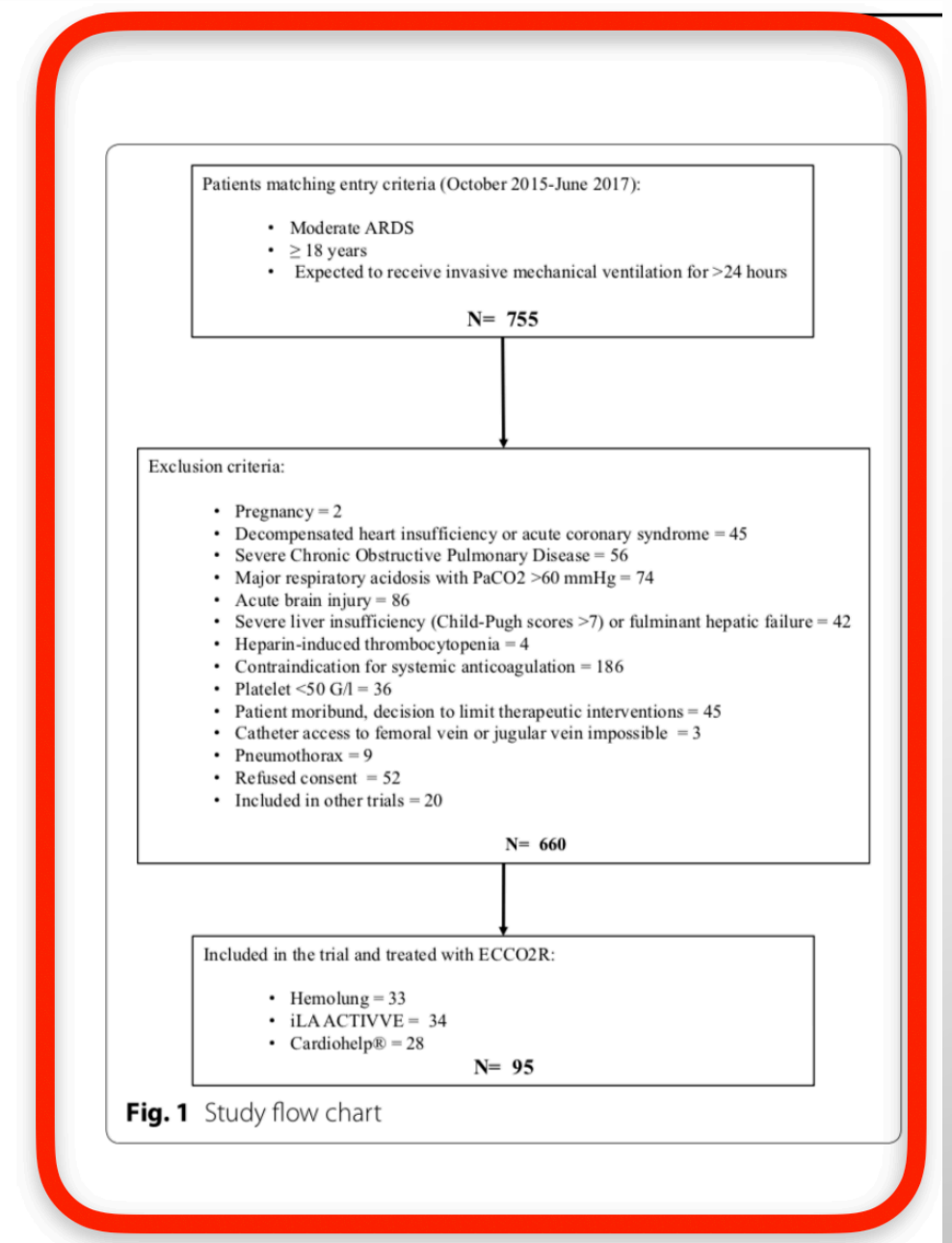

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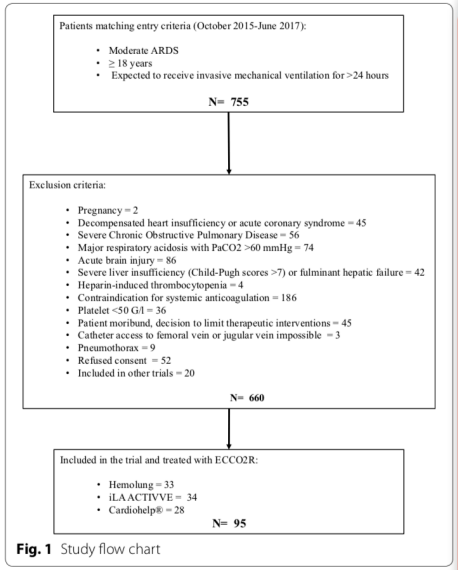

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Table 2 Operational characteristics of extracorporeal CO_2 removal

	Blood flow (mL/min)		Sweep gas flow (L/min)		Heparin (IU/kg/day)		Activated partial thromboplastin time	
	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)	Lower extraction (*N* = 33)	Higher extraction (*N* = 62)
8 h	440 [410;465]	970 [800;1000]*	10.0 [10.0;10.0]	6.00 [3.00;10.0]*	21,000 [18,000;27,950]	20,000 [14,000;26,400]	48.4 ± 18.5	55.0 ± 21.3
24 h	440 [430;480]	960 [800;1000]*	10.0 [10.0;10.0]	8.00 [5.00;10.0]*	20,000 [12,750;26,000]	20,160 [16,000;29,000]	49.1 ± 14.9	57.6 ± 21.6

Data are mean (standard deviation) or median [interquartile range]

*$p < 0.05$ lower vs. higher CO_2 extraction

Table 3 Numbers of patients experiencing $ECCO_2R$-related adverse events occurring between enrollment and day 28

$ECCO_2R$-related adverse events	Patients experiencing $ECCO_2R$-related adverse events, *n* (%)
Mechanical	
Membrane lung clotting	13 (14)
Leading to circuit change	6 (6)
Leading to $ECCO_2R$ discontinuation	7 (7)
Pump malfunction	3 (3)
Catheter displacement	2 (2)
Clinical	
Hemolysis	11 (12)
Bleeding	13 (14)
Related to cannula insertion	3 (3)
At cannula site	7 (7)
Significant	6 (6)
Infectious complications	2 (2)
Thrombocytopenia	12 (13)
Hypofibrinogenemia	2 (2)

$ECCO_2R$ extracorporeal carbon dioxide removal. *Hemolysis*: serum free hemoglobin ≥ 100 mg/L or hematocrit reduction not related to hemorrhage or other causes of blood loss, jaundice, hemoglobinuria, impaired renal function; *significant bleeding*: any bleeding event requiring administration of 1 unit of packed red cells; *thrombocytopenia*: platelet count below 50,000 per microliter; *hypofibrinogenemia*: fibrinogen < 1.5 g/L

internal jugular vein). Two SAEs (massive right frontal parenchymal hematoma and pneumothorax at cannula insertion in the internal jugular vein) were considered attributable to $ECCO_2R$. $ECCO_2R$-AE were reported in 37 patients (39%). Adverse events occurred in the first 24 h of $ECCO_2R$ in 26 patients (Table 3).

Duration of invasive mechanical ventilation was 17 [11–29] days. A total of 69 patients (73%) were alive at day 28. Fifty-nine patients (62%) were alive at hospital discharge. Ventilator-free days were 11 [0–17] days.

Discussion

This study shows that $ECCO_2R$ can be used to minimize respiratory acidosis while applying an ultra-protective ventilatory strategy in patients with moderate ARDS. However, the relatively high numbers of observed adverse events confirm the need for randomized clinical trial(s) to assess if benefits outweigh the risks.

A number of lung protective strategies such as decreasing P_{PLAT}, driving pressure, power, respiratory rate, or tidal volume have been suggested to decrease VILI. These approaches are often associated with hypercapnia and respiratory acidosis [18]. Although hypercapnia may be well tolerated [19], there are a number of important side effects [20, 21], and recent data suggest an association between values of $PaCO_2 > 50$ mmHg and increased mortality [22]. In the present study we tested the efficacy of $ECCO_2R$ to decrease tidal volume below 6 mL/kg because it is the variable most commonly associated with lung protective strategies, has a clear physiologic linkage to CO_2 removal, and has been studied in previous studies [6, 8, 9, 11].

Recent data have demonstrated that there is no safe upper limit for P_{PLAT} or ΔP [13, 23]. For example, the mortality rate in ARDS patients with ΔP values ≤ 14 cmH_2O is still as high as 20% [13, 23]. Patient outcomes may therefore be improved by aggressively lowering ventilatory variables such as V_T, P_{PLAT}, or ΔP as facilitated by $ECCO_2R$ devices that remove CO_2. In addition, $ECCO_2R$ might further decrease VILI by allowing lower respiratory rates, which have been shown to be lung protective [12], perhaps by decreasing mechanical power delivered to the lungs [14].

A few studies have examined the feasibility of ultra-protective ventilation facilitated by $ECCO_2R$. Two studies were single-center studies and included small numbers of patients [6, 10]. Other multicenter observational [8, 9] or randomized [11] studies treated patients with a single device. A survey of 239 French intensive care units found that 15% of the units used $ECCO_2R$ at least once (total

In conclusion, this study demonstrates that ultra-protective ventilation facilitated by $ECCO_2R$ is feasible, mitigating respiratory acidosis in patients with moderate ARDS. A randomized clinical trial is required to assess overall benefits and harms.

Indikationer for ECCO2R

- Mekanisk ventilation med forventet varighed >1 døgn
- Svær hypoxæmi ; $PaO_2/FiO_2 < 26$ kPa ved PEEP ≥ 15cm H_2O eller Pmean > 25 cmH_2O ved APRV modus
- Hyperkapni med pH < 7,30
- Forventet reversibel tilstand
- Patienten er allerede i CRRT behandling

Alle ovennævnte kriterier skal være opfyldt.

Kontraindikationer

- Alder<18
- Graviditet
- Akut hjerneskade
- Heparin induceret trombocytopeni
- Trombocytter < 50
- Tilstande hvor ECCO2R skønnes udsigtsløs
- Relativ kontraindikationer for Heparin-behandling: Trombocytopeni (< 80), traume eller nyopereret, koagulopati

- 5 PATIENTER INKLUDERET
- ALLE ALLEREDE I CRRT
- MULTIORGANSVIGT
- 4 DØDE EFTER KORT OPHOLD PÅ INTENSIV. MEN ECCO2R VAR EFFEKTIV; FALDENDE PCO2 OG STIGENDE PH

DEN SIDSTE PATIENT:

NDLAGT MED MULTIRESISTENT PSEUDOMONAS PNEUMONI

DAG 7: EFTER OVERFLYTTET TIL INTENSIV OG INTUBERET

DAG 10: AKI OG BEHOV FOR CRRT, ECCO2R. PH 7,09, PCO2 10,6KPA

DAG 11: PH 7,28 OG PCO2 5,4KPA

DAG 18 : UDSKREVET FRA INTENSIV OG 5 UGER EFTER UDSKREVET FRA HOSPITAL