Low-flow extracorporeal CO$_2$ removal in patients with moderate ARDS to enhance lung protective ventilation

*Pilot feasibility and safety study*

Promoter: European Society of Intensive Care Medicine (ESICM)

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**INTRODUCTION AND JUSTIFICATION OF THE RESEARCH PROJECT**

1.1. *Background information*

Over the past few decades, highly significant progress has been made in understanding the pathophysiology of the acute respiratory distress syndrome (ARDS). Recognition of ventilation-induced lung injuries (VILI) has led to the radical modification of the ventilatory management of these patients (1-4). The landmark trial by the ARDSnet trial group demonstrated in 2000 that ventilating ARDS patients with a low tidal volume ($V_T$) of 6 ml/kg (calculated from predicted body weight), and with a maximum end-inspiratory plateau pressure ($P_{plat}$) of 30 cmH$_2$O decreased mortality from 39.8% (in the conventional arm treated with a $V_T$ of 12 ml/kg PBW) to 31% (5). However, recent studies have shown that lung hyperinflation still occurs in approximately 30% of ARDS patients even though they are being ventilated using the ARDSNet strategy (6). Additionally, Hager and coworkers found that mortality decreased as $P_{plat}$ declined from high to low levels at all levels of $P_{plat}$ on the data collected by the “ARDSNet” trial group (7). Their analysis suggested a beneficial effect of $V_T$ reduction even for patients who already had $P_{plat}<$30 cm H$_2$O before $V_T$ reduction (7). Similar observation was also recently reported by Needham et al on a cohort of 485 patients with ARDS (8). Because $V_T$ reduction to <6 ml/kg to achieve very low $P_{plat}$ may induce severe hypercapnia and may cause elevated intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow, and the release of endogenous catecholamines, this strategy using “ultraprotective” MV settings is not possible for most patients on conventional mechanical ventilation for moderate to severe ARDS (9).

Extracorporeal carbon dioxide removal (ECCO$_2$R) may be used in association with mechanical ventilation to permit $V_T$ reduction to <6 ml/kg and to achieve very low $P_{plat}$ (20–25 cm H$_2$O). In an observational study conducted in the 80’s,Gattinoni showed that use of venovenous ECCO$_2$R at a flow of 1.5–2.5 l/min in addition to quasi apneic mechanical ventilation with peak inspiratory pressures limited to 35–45 cmH$_2$O and PEEP set at 15–25 cmH$_2$O resulted in lower than expected mortality in an observational cohort of severe ARDS patients (10). However, a randomized, controlled single-center study using that same technology and conducted in the 1990s by Morris’s group in Utah was stopped early for futility after only 40 patients had been enrolled and failed to
demonstrate a mortality benefit with this device (58% in the control group vs. 70% in the treatment group) (11).

In recent years, new-generation ECCO$_2$R devices have been developed. They offer lower resistance to blood flow, have small priming volumes and have much more effective gas exchange (12). With ECCO$_2$R the patient’s PaCO$_2$ is principally determined by the rate of fresh gas flow through the membrane lung (13) In an ECCO$_2$R animal model, CO$_2$ removal averaged 72±1.2 mL/min at blood flows of 450 mL/min, while CO$_2$ production by the lung decreased by 50% with reduction of minute ventilation from 5.6 L/min at baseline to 2.6 L/min after insertion of the device (14). Lastly, Terragni et al (15) demonstrated that ECCO$_2$R could improve pulmonary protection by allowing very low tidal volume ventilation (3.5-5 ml/kg of PBW) in a proof-of-concept study of ten patients with ARDS. This strategy was also associated with a significant decrease in pulmonary inflammatory biomarkers.

1.2. Rationale for ECCO$_2$R use in moderate ARDS patients

Pathophysiological, experimental and clinical data suggest that an “ultraprotective” mechanical ventilation strategy may further reduce VILI and ARDS-associated morbidity and mortality. Severe hypercapnia induced by $V_T$ reduction in this setting might be efficiently controlled by ECCO$_2$R devices. A proof-of-concept study conducted on a limited number of ARDS cases indicated that ECCO$_2$R allowing $V_T$ reduction to 3.5-5 ml/kg to achieve $P_{plat}<25$ cm H$_2$O may further reduce VILI.

2. STUDY OBJECTIVES

Extracorporeal CO$_2$ (ECCO2R) removal devices (HLS SET ADVANCED 5.0, MAQUET; ILA-active, NOVALUNG; Hemolung, ALung) allow $V_T$ and plateau pressure reduction in patients with moderate ARDS. This study will assess changes in pH/ $PaO_2$ /$PaCO_2$, Respiratory Rate and device CO$_2$ clearance in the first 24 hours of ECCO$_2$R following $V_T$ and plateau pressure reduction in patients with moderate ARDS. Safety variables during treatment will also be analyzed.

2.1. Research PROTOCOL

2.2. Study design
We plan to prospectively collect data on 100 patients during usual care in 21 centers.

2.3. **Study devices**

HLS SET ADVANCED 5.0®, MAQUET (Orléans, France); ILA-active®, NOVALUNG (Heilbronn, Germany); Hemolung®, ALung (Pittsburgh, USA). All devices are CE-marked in the European Union.

2.4. **Inclusion criteria:**

- Mechanical ventilation with expected duration of >24h
- Moderate ARDS according to the Berlin definition (16) 
  \[ \text{PaO}_2/\text{FiO}_2 \text{: 200-100 mmHg, with PEEP \geq 5 cmH}_2\text{O} \]

2.5. **Exclusion criteria:**

- Age <18 years
- Pregnancy
- Decompensated heart insufficiency or acute coronary syndrome
- Severe COPD
- Major respiratory acidosis \(\text{PaCO}_2>60\text{ mmHg}\)
- Acute brain injury
- Severe liver insufficiency (Child-Pugh scores >7) or fulminant hepatic failure
- Heparin-induced thrombocytopenia
- Contraindication for systemic anticoagulation
- Patient moribund, decision to limit therapeutic interventions
- Catheter access to femoral vein or jugular vein impossible
- Pneumothorax
- Platelet <50 G/l

2.6. **Study protocol**

2.6.1. Baseline ventilator settings will be established per the EXPRESS protocol:

- \(V_T = 6 \text{ mL/kg (ideal body weight)}\); inspiratory flow will be set at 50-70 L/min resulting in an end-inspiratory pause of 0.2-0.5 sec, I:E ratio 1:1 to 1:3, PEEP set so that the plateau pressure \(P_{\text{plat}}\), measured during the end-inspiratory pause of 0.2 to 0.5 s, will be within the following limits: 28 cm H\_2O \leq P_{\text{plat}} \leq 30 cm H\_2O; Set RR to 20-35 to maintain approximately the same minute ventilation as before study initiation.
2.6.2. Baseline ventilator settings will be maintained for a 2-hour run-in time (time to setup ECCO2R devices).

2.6.3. **Use heated humidifiers for gas humidification and minimize instrumental dead space.**

2.6.4. ECCO\textsubscript{2}R will be initiated during the 2-hour run-in time.

2.6.4.1. A single (15.5 to 19 Fr) veno-venous ECCO\textsubscript{2}R catheter will be inserted percutaneously (jugular vein strongly suggested).

2.6.4.2. Catheters should be rinsed with heparinized saline solution before insertion.

2.6.4.3. Once the catheter has been inserted each line will be filled with an heparinized saline solution before its connection to the extracorporeal circuit.

2.6.4.4. The ECCO\textsubscript{2}R circuit will be connected to the catheter and blood flow set, depending on the device, up to 1000 mL/min.

2.6.4.5. Initially, sweep gas flow through the ECCO\textsubscript{2}R device will be set at zero (0 LPM) such as to not initiate CO\textsubscript{2} removal through the device.

2.6.4.6. Anticoagulation will be maintained with unfractionated heparin to a target aPTT of 1.5 – 2.0X baseline. A bolus of heparin is suggested at the time of cannulation.

2.6.5. Patients will receive NMBA starting in the run-in period and continued for the first 24 hours and thereafter will be directed by the attending physician.

2.6.6. Following the 2-hour run-in time, V\textsubscript{T} will be reduced gradually to 5 mL/kg. Sweep gas initiated then V\textsubscript{T} decreased to 4.5 then 4 mL/kg and PEEP adjusted to reach 23 ≤ P\textsubscript{plat} ≤ 25 cm H\textsubscript{2}O.

2.6.7. EtCO\textsubscript{2} will be monitored for safety purposes. Blood gases will be analyzed 20-30 minutes after each V\textsubscript{T} reduction.

2.6.8. RR will be kept what it was at baseline.

2.6.9. The objective is to maintain PaCO\textsubscript{2} to its baseline value ± 20% of baseline settings obtained during 2 hour run-in (when V\textsubscript{T} = 6 mL/kg) provided that pH remain >7.30.

2.6.10. Sweep gas flow will be adapted to maintain the same EtCO\textsubscript{2}
2.6.11. If PaCO$_2$ > 75 mmHg and/or pH < 7.2, despite respiratory rate of 35/min and optimized ECCO$_2$R, $V_T$ will be increased to the last previously tolerated $V_T$.

2.6.12. If PaCO$_2$ remains within the target range, respiratory rate will be progressively decreased to a minimum of 15/ min and facilitated by increases in sweep flow.

2.7. **Troubleshooting**

2.7.1. If the patient experiences refractory hypoxemia and/or hypercapnia, treatment shall be at the discretion of the treating physician (e.g. VV-ECMO, prone, NO).

2.8. **The experimental protocol will be stopped and the device and catheter removed in the following situations**

- Air embolus in the extracorporeal circuit
- Circuit clotting leading to abrupt stop of extracorporeal blood flow
- Device malfunction leading to abrupt stop of extracorporeal blood flow
- Severe thrombopenia (<20 G/L)
- Fibrinogen <1 g/L or fibrinogen <1.5 g/L with diffuse bleeding
- At any time if the physician in charge believes that the protocol compromise patient’s outcome

2.9. **ECCO$_2$R weaning**

2.9.1. ECCO$_2$R and the “low volume - low pressure” MV strategy will be continued for at least 24 hours.

2.9.2. After 24 hours, ECCO$_2$R can be continued or not at the discretion of the attending physician; we recommend it be continued and the following weaning strategy be used:

2.9.2.1. The patient’s ability to tolerate conventional MV will be tested once daily if PaO$_2$/FiO$_2$ > 200 regardless of PEEP level (according to the EXPRESS trial standard)

2.9.2.1.1. $V_T$ will be set at 6 ml/kg IPBW
2.9.2.1.2. PEEP 5-10 cm H$_2$O
2.9.2.1.3. RR 20-30 /min
2.9.2.1.4. FiO$_2$ 40%
2.9.2.1.5. Gas flow on the ECCO$_2$R device will then be switched off
2.9.2.2. The ECCO2R device and the venous access catheter will be removed when the attending physician will judge it appropriate (a minimum of 12 hours of stability under the aforementioned MV settings is suggested).

2.9.3. Following discontinuation of ECCO2R, subjects will be monitored for adverse events until hospital discharge or Day 28 from enrollment, whichever is sooner.

2.10. Study endpoints

2.10.1. Primary endpoint:

Achievement of VT reduction to 4 mL/kg while maintaining pH and PaCO2 to ± 20% of baseline values obtained at VT of 6 mL/kg.

2.10.2. Secondary endpoints

- Assessment of the changes in pH/ PaO2 /PaCO2, and device CO2 clearance in the first 24 hours of ECCO2R following VT reduction from 6 mL/kg to 4 ml/kg.
- Assessment of changes in respiratory parameters (VT, Pplat, RR, and PEEP) and ABG
- Amount of CO2 removed by the ECCO2R device
  - During the first 12 hours (every hour)
  - Thereafter at least twice daily at 08:00 ± 2 hours and 20:00 ± 2 hours.
- Evaluation of lung recruitment/derecruitment (FRC measurement by the ventilator, ECHO-LUS...)
- Lifetime of the extracorporeal circulation
- Safety assessment

2.11. Measurements

2.11.1. Measurements will be performed at baseline and 5-10 minutes after reaching each state of equilibrium

2.11.2. Measurements will be performed at least twice a day for the time the ECCO2R device is functioning (as usual in these patients).

2.11.3. See Appendix 1 for full schedule of measurements.
2.12. **Safety Assessment**

2.12.1. The safety of enhancing lung protection with ECCO$_2$R will be assessed by measuring the frequency of serious adverse events (SAE).

2.12.2. A serious adverse event (SAE) in the trial will be defined as:

2.12.2.1. any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating or requires prolonged hospitalization **OR**

2.12.2.2. any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above **AND**

2.12.2.3. which the attending physician perceives may be directly related to enrollment in the clinical trial.

2.12.3. **Reportable adverse event**

A reportable adverse event will be defined as any clinically important untoward medical occurrence in a patient receiving ECCO2-R or undergoing study procedures which is different from what is expected in the clinical course of a patient with ARDS or any event thought to be associated with ECCO2-R. Examples of adverse events that are expected in the course of ARDS include transient hypoxemia, agitation, delirium, nosocomial infections, intolerance of gastric feeding, or skin breakdown. Such events, which are often the focus of prevention efforts as part of usual ICU care, will not be considered reportable adverse events unless the event is considered by the investigator to be associated ECCO2-R, or events that are unexpectedly severe or frequent for an individual patient with ALI. Examples of unexpectedly frequent adverse events would be repeated episodes of unexplained hypoxemia, in contrast to an isolated episode of transient hypoxemia (eg. Sp02 $\sim$85%), particularly if related to positioning of suctioning. This latter event would not be considered unexpected by nature, severity or frequency.

2.12.4. **Device-related mechanical events**
SUPERNova, Pilot trial, Jan 15

- Difficulties with insertion of the catheter to deliver ECCO2-R (i.e. need for >2 attempts at catheter insertion during primary placement procedure)
- Pump malfunction (i.e. need for > 2 consecutive interventions during the same treatment with the same blood circuit), regardless of the need for stopping the procedure or for replacement of the pump
- Membrane lung clotting (number/patient; number/day on ECCO2R)
- Catheter displacement
- Cannula thrombosis
- Air in the circuit
- Tubing rupture
- System leaks

2.12.5. Device-related clinical events

- Hemolysis (i.e. Hct reduction not related to hemorrhage or other causes of blood loss, jaundice, hemoglobinuria, impaired renal function)
- Vein perforation, significant bleeding (i.e. any bleeding event that required the administration of 1 unit of packed red cells)
- Hemodynamic instability (i.e. 80-90 mmHg increase or a 30-40 mmHg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs for at least two hours to maintain systolic blood pressure higher than 85 mmHg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias)
- Ischemic/gangrenous bowel, pneumothorax, renal complications (i.e. occurrence after initiation of carbon dioxide removal of creatinine > 1.5 mg/dL)
- Infectious complications (i.e. occurrence after initiation of carbon dioxide removal of culture proven new infection)
- Metabolic (i.e. occurrence after initiation of carbon dioxide removal of glucose ≥ 240 mg/dL or hyperbilirubinemia)
- Thromboembolic complications (i.e. occurrence after initiation of deep venous thrombosis or pulmonary embolus),
- Neurologic complications (i.e. occurrence after initiation of carbon
dioxide removal of cerebral infarction, or clinical seizure, or cerebral
hemorrhage or cerebral edema

2.12.6. An event will be considered to be unexpected for ECCO2-R if it is not
identified in the list above, or is unexpectedly severe or more frequent than
events described in the list above. Events will be recorded and analyzed as
frequency (n).

2.12.7. Investigators will report all serious, study-related and unexpected adverse
events to the Clinical Coordinating Center within 24 hours. The local
Institutional Review Board must also be notified within 72 hours. The
investigator will then submit a detailed written report to the Clinical
Coordinating Center and the Institutional Review Board no later than 5 days
after the investigator discovers the event. A written report will be sent to the
Data and Safety Monitoring Board within 15 calendar days and these reports
will be sent to investigators for submission to their respective Institutional
Review Boards. The Data and Safety Monitoring Board will also review all
adverse events during scheduled interim analyses. The Clinical Coordinating
Center will distribute the written summary of the Data and Safety Monitoring
Board periodic review of adverse events to investigators for submission to
their respective Institutional Review Boards

2.12.8. Follow-up Period: Following discontinuation of ECCO$_2$R, subjects will be
monitored for adverse events until hospital discharge or Day 28 from
enrollment, whichever is sooner.

- Device-related Gaseous Emboli
- Device-related Massive hemolysis (Serum Free Hb >1000 mg/dL)
- Device-related Massive hemorrhage (requiring >= 10 PRBC)
- Device-related Cardiac arrest
- Device-related Ischemic or Hemorrhagic stroke
- Bacteremia related to device-related infection
- Any other device-related complication that the investigator perceives as jeopardizing the patient.

2.13. **Statistical Analysis**

Data from this study will be analyzed using standard statistical comparisons such as averages, percentages, and absolute totals. This data will be summarized to draw conclusions on the purpose of the study and to identify meaningful clinical endpoints.

3. **FUTURE APPLICATION & DEVELOPMENT OF THE TECHNOLOGY TESTED IN THIS STUDY**

The strategy of enhanced lung-protective (low-volume, low-pressure) ventilation allowed by the ECCO₂R device might improve clinical outcomes (mortality, numbers of days under MV) compared with standard-of-care lung-protective ventilation in patients with moderate to severe ARDS. This hypothesis should later be tested on a large population of patients in this context.
REFERENCES


**SUPERNova, Pilot trial, Jan 15**

**Appendix: Measurement Table. Data to be recorded at all study sites.** All data collection per standard of care as usual in these patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>2 hr run-in (VT=6 ml/kg)</th>
<th>After Vent Change</th>
<th>Hourly Day 1 on ECCO₂R</th>
<th>Minimum Twice Daily on ECCO₂R</th>
<th>Daily on ECCO₂R</th>
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<tr>
<td><strong>Clinical Variables:</strong></td>
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<td>pH, PaO₂, PaCO₂, HCO₃, SaO₂, Lactate</td>
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<td>Transfusions (pRBC, platelets, fibrinogen, plasma)</td>
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<td>All patient related adverse events</td>
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