ECCO2R – EMERGING SUPPORT FOR ACUTE RESPIRATORY FAILURE

Ramiro Saavedra MD
Department of Critical Care Medicine
Director of Medical ECMO Program
Medical Director MICU/SICU

Abbott Northwestern Hospital

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AllinaHealth

Conflict of Interest

- PI : Vent-Avoid trial at ANW hospital
- No financial disclosure (I refuse to show my tax returns)

OBJECTIVES

- Learn what extracorporeal CO2 removal is (ECCO2R)
- Describe differences between ECMO and ECCO2R
- Possible applications of ECCO2R in ARDS
- Possible applications of ECCO2R in COPD

ECLS goals

To temporary replace lung function (oxygenation and/or CO2 removal)

Allow lung rest (minimize VILI)

Allow lung healing

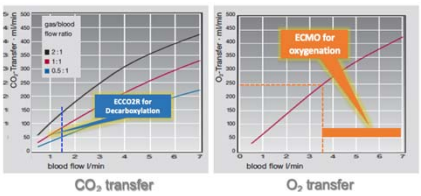
Not a new concept

Gattinoni 1978. BJA

TABLE III. *Comparative technical difficulty of haemodialysis, extracorporeal removal of carbon dioxide and extracorporeal oxygenation*

	Renal haemodialysis	Extracorporeal removal of carbon dioxide	Extracorporeal oxygenation
Extracorporeal blood flow (ml min^{-1})	200–300	500–1000	2000–4000
Blood pumping	optional	optional	required
Haemodynamic changes	small	small	major
Vascular access	A–V shunt or A–V fistula	A–V shunt or A–V fistula or V–V pumping	V–A or V–V
Surgical complexity	simple	simple	complex
Complexity of equipment	moderate	simple	advanced
Requirement for heparin	small	small	large

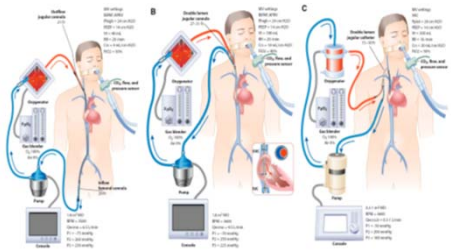
Membrane Lung Gas Transfer



CO_2 transfer O_2 transfer

ECMO Vs ECCO2R

- ECMO
  - Large cannulas
  - Need for high flow (>5000 ml/min)
  - Need for large membrane oxygenator
  - Full blood oxygenation
  - Full blood CO2 removal
- ECCO2R
  - Smaller double lumen catheter
  - Low flow (250-1000 ml/min)
  - Medium size membrane oxygenator
  - No blood oxygenator
  - Partial CO2 removal



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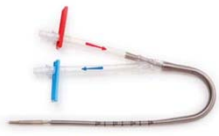
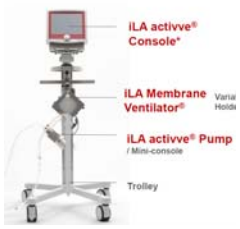
Low flow ECCO2R



Catheter

High Flow ECCO2R



ECCO2R in ARDS (VILI)

- Supportive mechanical ventilation is the cornerstone of treatment/support for respiratory failure
- MV although necessary it can aggravate or cause lung damage
  - High inflation transpulmonary pressures (barotrauma)
  - Alveolar overdistention (volutrauma)
  - Repetitive opening and closing of alveoli (atelectrauma)
- Factors inducing VILI could trigger inflammatory mediators resulting in local and systemic inflammatory response (biotrauma) leading to non-pulmonary organs that could result in multiple system organ dysfunction

ECCO2R in ARDS (VILI)

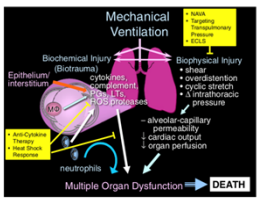
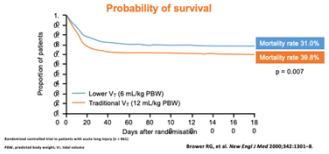


Figure 1 Mechanisms for VILI and potential targets for physiologic and non-physiologic interventions to minimize VILI. Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Slutsky AS, Tremblay LN. **Multiple system organ failure: is mechanical ventilation a contributing factor?** *Am J Resp Crit Care Med* 1998; **157**:1721–1725. ECLS, extracorporeal life support; LT, leukotrienes; MØ, macrophages; NAVA, neurally adjusted ventilatory assist; PG, prostaglandins; ROS, reactive oxygen species; VILI, ventilator-induced lung injury.

Fan, E., Gattinoni, L., Combes, A. et al. Intensive Care Med (2016) 42: 712.

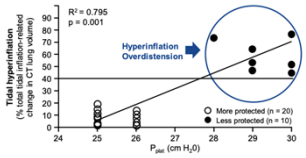
The ARDS Network trial – MV with lower versus traditional tidal volumes

Probability of survival



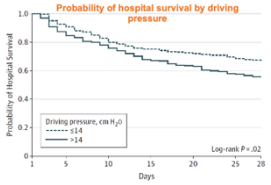
Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

Relationship between amount of tidal hyperinflation and plateau pressure

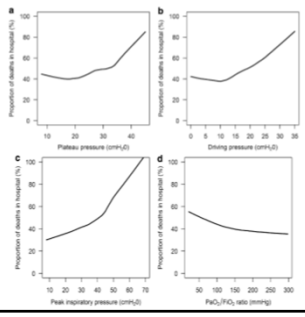


Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Probability of hospital survival by driving pressure



Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study

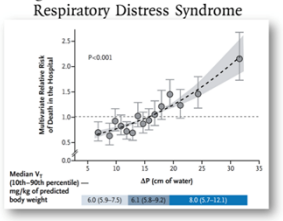


Laffey, Intensive Care Med 2016

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

SPECIAL ARTICLE

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015



ECCO2R in ARDS

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

Combes, A., Fanelli, V., Pham, T. et al. Intensive Care Med (2019) 45: 592.

ECCO2R in ARDS

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.

Conclusions: Use of $ECCO_2R$ to facilitate ultra-protective ventilation was feasible. A randomized clinical trial is required to assess the overall benefits and harms.

Clinicaltrials.gov: NCT02282657

Keywords: Acute respiratory distress syndrome, Mechanical ventilation, Extracorporeal carbon dioxide removal, Ventilator-induced lung injury

Combes, A., Fanelli, V., Pham, T. et al. Intensive Care Med (2019) 45: 592.

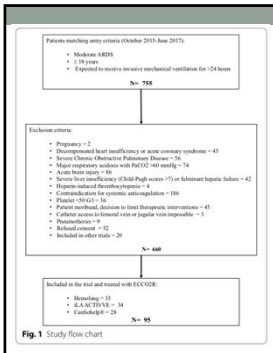


Fig. 1 Study flow chart

Table 1 Characteristics of patients at study inclusion

Age (years)	60.2 ± 14.0
Female (n, %)	31 (32.6%)
BMI (kg/m²)	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
PR (breaths/min)	27.3 ± 4.6
V_E (L/min)	10.2 ± 2.3
PEEP (cmH₂O)	15.3 (10.0-24.0)
F_{RESP} (breaths/min)	26.6 ± 3.0
ΔP (cmH₂O)	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
Ventilatory parameters 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 (ΔP = 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

Combes, A., Fanelli, V., Pham, T. et al. Intensive Care Med (2019) 45: 592.

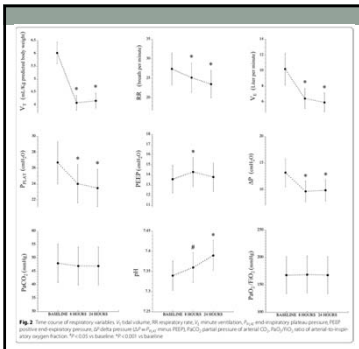


Fig. 2 Time course of respiratory variables. V_T tidal volume, RR respiratory rate, V_E minute ventilation, P_{PLAT} end-inspiratory plateau pressure, PEEP positive end-expiratory pressure, ΔP delta pressure (ΔP = P_{PLAT} minus PEEP), $PaCO_2$ partial pressure of arterial CO_2, PaO_2/FiO_2 ratio of arterial-to-inspiratory oxygen fraction. *P < 0.05 vs baseline; †P < 0.001 vs baseline

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 (%)
Any device	
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)
Blood	
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

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ECCO2R in COPD

- For acute COPD exacerbation
- Goals
  - Prevents need for invasive mechanical ventilation
  - Facilitate mechanical ventilation liberation
  - Allow ambulation and prevent deconditioning

ORIGINAL

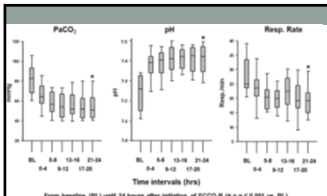
The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case–control study

Stephan Braune[1], Annekatrin Sieweke[1], Franz Brettner[2], Thomas Staudinger[3], Michael Joannidis[4], Serge Verbrugge[5], Daniel Frings[5], Axel Nierhaus[1], Karl Wegscheider[6] and Stefan Kluge[1]*

Methods: Case–control study. Patients with acute hypercapnic respiratory failure refractory to NIV being treated with a pump-driven veno-venous $ECCO_2R$ system (iLA-Activve®; Novalung, Heilbronn, Germany) were prospectively observed in five European intensive care units (ICU). Inclusion criteria were respiratory acidosis (pH ≤ 7.35, $PaCO_2$ > 45 mmHg) with predefined criteria for endotracheal intubation (ClinicalTrials.gov NCT01784367). The historical controls were patients with acute hypercapnic respiratory failure refractory to NIV who were treated with IMV. The matching criteria were main diagnosis, age, SAPS-II score and pH.

Results: Twenty-five cases (48.0 % male, mean age 67.3 years) were matched with 25 controls. Intubation was avoided in 14 patients (56.0 %) in the $ECCO_2R$ group with a mean extracorporeal blood flow of 1.3 L/min. Seven patients were intubated because of progressive hypoxaemia and four owing to ventilatory failure despite $ECCO_2R$ and NIV. Relevant $ECCO_2R$-associated adverse events were observed in 11 patients (44.0 %), of whom 9 (36.0 %) suffered major bleeding complications. The mean time on IMV, ICU stay and hospital stay in the case and control groups were 8.3 vs. 13.7, 28.9 vs. 24.0 and 36.9 vs. 37.0 days, respectively, and the 90-day mortality rates were 28.0 vs. 28.0 %.

Intensive Care Med (2016) 42:1437–1444



From baseline (BL) until 24 hours after initiation of $ECCO_2R$ (* = p ≤ 0.001 vs. BL)

Intensive Care Med (2016) 42:1437–1444

Clinical course	$ECCO_2R$ group (n = 25)	Control group (n = 25)	p value
Days on $ECCO_2R$	8.5 (1.0–27.0)	N/A	N/A
Days on IMV	8.3 (0–49.0)	13.7 (3.0–52.0)	0.02*
Tracheotomy	9.0 (36.0)	15.0 (60.0)	0.09*
Days on NIV during $ECCO_2R$	4.6 (0–22.0)	N/A	N/A
Mode of NIV used during $ECCO_2R$	A-NIV 12.0 % C-NIV 8.0 % Mix-NIV 44.0 %	N/A	N/A
Length of stay			
Days in ICU	28.9 (8.0–100.0)	24.0 (2.0–66.0)	0.09*
Days in hospital	36.9 (9.0–100.0)	37.0 (12.0–248.0)	0.49*
Mortality n (%)			
28-day mortality	4.0 (16.0)	3.0 (12.0)	0.68
Hospital mortality	6.0 (24.0)	3.0 (12.0)	0.28
90-day mortality	7.0 (28.0)	7.0 (28.0)	1.0

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Extracorporeal CO2 Removal With the Hemolung RAS for Mechanical Ventilation Avoidance During Acute Exacerbation of COPD (VENT-AVOID)

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	500 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Prospective, multi-center, randomized, controlled, two-arm, open-label, adaptive, two-strata, pivotal trial
Masking:	Single (Outcomes Assessor)
Masking Description:	Due to the nature of the interventional device and treatment, the study participants, care providers, and investigators will not be masked. However an independent Clinical Endpoint Committee will be masked for adjudication of the primary endpoint and serious adverse events. An independent Data and Safety Monitoring Board will make study continuation recommendations based on the statistical analysis plan and the overall safety and efficacy endpoints without masking.
Primary Purpose:	Treatment
Official Title:	A Prospective, Multi-Center, Randomized, Controlled, Pivotal Trial to Validate the Safety and Efficacy of the Hemolung® Respiratory Assist System for COPD Patients Experiencing an Acute Exacerbation Requiring Ventilatory Support
Actual Study Start Date :	February 18, 2018

ECCO2R in COPD

VENT-AVOID TRIAL

Primary Study Objective

To demonstrate the safety and efficacy of using the Hemolung RAS to provide low-flow ECCO2R as an alternative or adjunct to invasive mechanical ventilation versus standard of care invasive mechanical ventilation alone to increase ventilator-free days for COPD patients who require respiratory support due to an acute exacerbation of their COPD.

Patient Population

Patients with underlying COPD who are experiencing an acute exacerbation and require either noninvasive ventilatory support (Stratum 1) or immediate intubation and invasive mechanical ventilation (Stratum 2) due to Type II hypercapnic respiratory failure.

Primary Safety and Efficacy Endpoint

Ventilator-free days measured from randomization through 60 days following randomization (VFD-60).

Conclusions

- ECCO2R; Could be use for refractory hypercapnia where mechanical ventilation can cause VILI (If refractory hypoxia is present VV ECMO should be considered).
- Potential use in COPD exacerbation to avoid invasive mechanical ventilation and to help with rapid mechanical ventilation liberation
- Potential use for moderate to severe ARDS to minimize VILI by reducing Tvol, Pplat and driving pressure

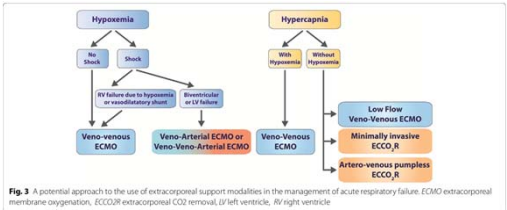
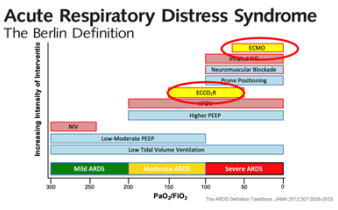


Fig. 3 A potential approach to the use of extracorporeal support modalities in the management of acute respiratory failure. *ECMO* extracorporeal membrane oxygenation, *ECCO2R* extracorporeal CO2 removal, *LV* left ventricle, *RV* right ventricle

Fan, E., Gattinoni, L., Combes, A. et al. Intensive Care Med (2016) 42: 712.



TO CONTACT ME

- Ramiro Saavedra
(Ramiro.SaavedraRomero@allina.com)

Allina Health