ECCO$_2$R...
What’s next?

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Disclosures

• Principal Investigator: EOLIA trial
  • VV ECMO in ARDS
  • NCT01470703
  • Sponsored by MAQUET, Getinge Group

• Received honoraria for lectures from
  • MAQUET, XENIOS, BAXTER
The rationale of ECCO2R...

For ARDS patients...

To decrease the intensity of MV?
MV in ARDS patients...

• MV harms the respiratory system
  • Ventilator-Induced Lung Injury
    • Pressure
    • Volume
    • Resp Rate
  • Inactivity of the diaphragm

• MV promotes VAP

• MV requires patients sedation/paralysis
Changes in the ultrastructural appearance of the alveolar-capillary barrier after MV

- Detachment of the thin part of the endothelial cell from the basement membrane
- Diffuse alveolar damage resulting from very severe changes in the alveolar-capillary barrier


Rat model

MV at 45 cm H₂O peak airway pressure
The ARDS Network trial – MV with lower versus traditional tidal volumes

Randomised controlled trial in patients with acute lung injury (n = 861)

PBW, predicted body weight; V\(_T\), tidal volume

Lung protective MV and two-year survival in patients with ALI


Adjusted HR of 1.18 (95% CI 1.07–1.31) indicated an 18% relative increase in mortality for each 1 mL/kg predicted body weight.

p-value shown for non-linear terms in cubic spline model
Prospective cohort study (n = 485)
ALI, acute lung injury
Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

Pier Paolo Terragni, Giulio Rosboch, Andrea Tealdi, Eleonora Corno, Eleonora Menaldo, Ottavio Davini, Giovanni Gandini, Peter Herrmann, Luciana Mascia, Michel Quintel, Arthur S. Slutsky, Luciano Gattinoni, and V. Marco Ranieri

Am J Respir Crit Care Med 2007;175:160-166.

Relationship between amount of tidal hyperinflation and plateau pressure

\[ R^2 = 0.795 \]
\[ p = 0.001 \]

Hyperinflation Overdistension

More protected (n = 20)

Less protected (n = 10)

Tidal hyperinflation (% total tidal inflation-related change in CT lung volume)

P_{plat} (cm H_2O)
Reduction in tidal volume in patients with ALI when plateau pressures are not high

Robust locally weighted regression and smoothing (Lowess) plot (bandwidth, 0.4) of mortality and Day 1 plateau pressure among patients enrolled in the ARDS Network study (n = 787)

Bivariate regression analysis: Lower $V_T$ strategy was associated with lower mortality vs higher $V_T$ strategy ($p = 0.02$)

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Median $V_T$ (10th–90th percentile) — mg/kg of predicted body weight

<table>
<thead>
<tr>
<th>$\Delta P$ (cm of water)</th>
<th>Median $V_T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.0 (5.9–7.5)</td>
</tr>
<tr>
<td>10</td>
<td>6.1 (5.8–9.2)</td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>8.0 (5.7–12.1)</td>
</tr>
</tbody>
</table>

$P<0.001$
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tâl Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MSc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

LUNG SAFE
Epidemiology of ARDS
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

Driving pressure, cm H$_2$O
- ≤14
- >14

Log-rank $P = .02$
Targeting Resp Rate?...
Factors associated with hospital mortality in MV patients \((n = 2377)\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Multivariate model ((n = 2091))</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>(1.03) (1.019–1.032)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active neoplasm</td>
<td>(1.83) (1.31–2.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Management factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR total (breaths/min)</td>
<td>(1.03) (1.01–1.04)</td>
<td>0.003</td>
</tr>
<tr>
<td>pH</td>
<td>(0.12) (0.05–0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\text{PaO}_2/\text{FiO}_2) ratio (mmHg)</td>
<td>(0.998) (0.997–1.000)</td>
<td>0.025</td>
</tr>
<tr>
<td>Non-pulmonary SOFA score adjusted</td>
<td>(1.12) (1.09–1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Management factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR total (breaths/min)</td>
<td>(1.03) (1.01–1.04)</td>
<td>0.003</td>
</tr>
<tr>
<td>PEEP ((\text{cmH}_2\text{O}))</td>
<td>(0.95) (0.92–0.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak inspiratory pressure ((\text{cmH}_2\text{O}))</td>
<td>(1.02) (1.01–1.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>CU organizational factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of beds</td>
<td>(0.99) (0.99–1.00)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Low Respiratory Rate Plus Minimally Invasive Extracorporeal CO₂ Removal Decreases Systemic and Pulmonary Inflammatory Mediators in Experimental Acute Respiratory Distress Syndrome

Grasso, Crit Care Med, 2014

Objective: The Acute Respiratory Distress Syndrome Network protocol recommends limiting tidal volume and plateau pressure; it also recommends increasing respiratory rate to prevent hypercapnia. We tested a strategy that combines the low tidal volume with lower respiratory rates and minimally invasive CO₂ removal.

Subjects: Ten lung-damaged pigs (instilled hydrochloride).

Interventions: Two conditions randomly applied in a crossover fashion: the Acute Respiratory Distress Syndrome Network protocol and the Acute Respiratory Distress Syndrome Network protocol plus lower respiratory rate plus minimally invasive CO₂ removal. A similar arterial CO₂ partial pressure was targeted in the two conditions.
Low Respiratory Rate Plus Minimally Invasive Extracorporeal CO₂ Removal Decreases Systemic and Pulmonary Inflammatory Mediators in Experimental Acute Respiratory Distress Syndrome

Grasso, Crit Care Med, 2014

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARDS Net</th>
<th>Low RR ECCO₂R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (mL)</td>
<td>345 ± 79</td>
<td>342 ± 73</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>30.5 ± 3.8</td>
<td>14.2 ± 3.5</td>
</tr>
<tr>
<td>Minute volume (L/min)</td>
<td>10.4 ± 1.6</td>
<td>4.9 ± 1.7</td>
</tr>
<tr>
<td>Inspiratory time (s)</td>
<td>0.68 ± 0.1</td>
<td>1.53 ± 0.5</td>
</tr>
<tr>
<td>Inspiratory flow (mL/s)</td>
<td>509 ± 97</td>
<td>243 ± 83</td>
</tr>
<tr>
<td>P_{Aa} (cm H₂O)</td>
<td>23.3 ± 3.6</td>
<td>23.2 ± 3.2</td>
</tr>
<tr>
<td>P_{Aa,AL} (cm H₂O)</td>
<td>15.4 ± 3.3</td>
<td>14.8 ± 2.7</td>
</tr>
<tr>
<td>Total positive end-expiratory pressure (cm H₂O)</td>
<td>10.5 ± 2.9</td>
<td>10.4 ± 2.6</td>
</tr>
<tr>
<td>Stress index</td>
<td>1.034 ± 0.023</td>
<td>1.028 ± 0.026</td>
</tr>
<tr>
<td>Static respiratory system elastance (cm H₂O/L)</td>
<td>41.6 ± 10.6</td>
<td>38.0 ± 11.7</td>
</tr>
<tr>
<td>Static lung elastance (cm H₂O/L)</td>
<td>34.3 ± 10.9</td>
<td>31.9 ± 11.7</td>
</tr>
<tr>
<td>Static chest wall elastance (cm H₂O/L)</td>
<td>7.5 ± 2.1</td>
<td>6.9 ± 2.8</td>
</tr>
<tr>
<td>PaCO₂/Fio₂</td>
<td>252 ± 75</td>
<td>231 ± 86</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>61.8 ± 11.6</td>
<td>61.9 ± 0.7</td>
</tr>
<tr>
<td>pH</td>
<td>7.381 ± 0.041</td>
<td>7.375 ± 0.054</td>
</tr>
<tr>
<td>Base excess</td>
<td>4.5 ± 1.5</td>
<td>4.8 ± 1.9</td>
</tr>
</tbody>
</table>

![Graph showing VCO₂ comparison between ARDS Net and LOW RR ECCO₂R](image-url)
Low Respiratory Rate Plus Minimally Invasive Extracorporeal CO₂ Removal Decreases Systemic and Pulmonary Inflammatory Mediators in Experimental Acute Respiratory Distress Syndrome

Grasso, Crit Care Med, 2014

Less pro-inflammatory Cytokines in Blood and BAL with Low RR
The evolving paradigm...

- ARDSnet strategy might not protect against tidal hyperinflation
  - When $P_{plat}$ remains >28-30 cm H$_2$O
- Further decrease of $V_t$ to reduce VILI
  - From 6 to 5, 4 or 3 ml/kg IBW
  - To decrease $P_{plat}$ <25 cm H$_2$O
  - With sufficient PEEP to prevent lung derecruitment
  - Resulting in a significant decrease in $\Delta P$
- To decrease RR to <20... <15... <10?????
- Induced Hypercapnia controlled by ECCO$_2$ removal
  - “CO$_2$ dialysis”
  - Low-flow devices
Lower tidal volume strategy ($\approx 3 \text{ ml/kg}$) combined with extracorporeal $\text{CO}_2$ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS

The prospective randomized Xtravent-study
Lower tidal volume strategy ($\approx 3$ ml/kg) combined with extracorporeal CO$_2$ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS

The prospective randomized Xtravent-study

Thomas Bein
Steffen Weber-Carstens
Anton Goldmann

Intensive Care Med

Screening → 305 patients: acute respiratory failure $\text{PaO}_2/\text{FiO}_2 \leq 200$

\begin{itemize}
  \item Stabilization over 24 hrs:
  \begin{itemize}
    \item $V_t$ 6 ml/kg/IBW
    \item ARDSNet „high-PEEP“
    \item CVP 10 – 16 mmHg
    \item MAP ≥ 70 mmHg
    \item echocardiography
  \end{itemize}
\end{itemize}

103 patients: no inclusion criteria fulfilled

64 patients: no inclusion due to improvement $\text{PaO}_2/\text{FiO}_2 > 200$

50 patients: no inclusion due to deterioration $\text{PaO}_2/\text{FiO}_2 < 70 \rightarrow v\text{ECMO}$

4 patients: no inclusion due to death

5 patients: no informed consent

randomization → 79 patients

40 patients → avECCO$_2$R
\begin{itemize}
  \item $V_t$ 3 ml/kg/IBW
  \item ARDSNet „high-PEEP“
\end{itemize}

ventilation target:
\begin{itemize}
  \item $\text{PaO}_2 \geq 60$ mmHg
  \item art. pH ≥ 7.2
\end{itemize}

39 patients → control
\begin{itemize}
  \item $V_t$ 6 ml/kg/IBW
  \item ARDSNet „high-PEEP“
\end{itemize}

40 ECCO2R Strategy

39 Conventional Strategy
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

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>avECCO₂-R</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Ventilator-free-days-28</td>
<td>10.0 ± 8</td>
<td>9.3 ± 9</td>
<td>0.779</td>
</tr>
<tr>
<td>Ventilator-free-days-60</td>
<td>33.2 ± 20</td>
<td>29.2 ± 21</td>
<td>0.469</td>
</tr>
<tr>
<td>Non-pulmonary organ failure free days-60</td>
<td>21.0 ± 14</td>
<td>23.9 ± 15</td>
<td>0.447</td>
</tr>
<tr>
<td>Lung injury score on day 10</td>
<td>2.2 ± 0.6</td>
<td>2.1 ± 0.5</td>
<td>0.854</td>
</tr>
<tr>
<td>Length of stay in hospital (days)</td>
<td>46.7 ± 33</td>
<td>35.1 ± 17</td>
<td>0.113</td>
</tr>
<tr>
<td>Length of stay in ICU (days)</td>
<td>31.3 ± 23</td>
<td>22.9 ± 11</td>
<td>0.144</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7/40 (17.5 %)</td>
<td>6/39 (15.4 %)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Subgroup: PaO₂/FIO₂ &lt;150</th>
<th>avECCO₂-R</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free-days-28</td>
<td>11.3 ± 7.5</td>
<td>5.0 ± 6.3</td>
<td>0.033</td>
</tr>
<tr>
<td>Ventilator-free-days-60</td>
<td>40.9 ± 12.8</td>
<td>28.2 ± 16.4</td>
<td>0.033</td>
</tr>
<tr>
<td>Non-pulmonary organ failure free days-60</td>
<td>24.1 ± 7.5</td>
<td>29.0 ± 17.7</td>
<td>0.428</td>
</tr>
<tr>
<td>Lung injury score on day 10</td>
<td>2.3 ± 0.8</td>
<td>2.2 ± 0.5</td>
<td>0.601</td>
</tr>
<tr>
<td>Length of stay in hospital (days)</td>
<td>42.0 ± 16.6</td>
<td>40.3 ± 15.7</td>
<td>0.815</td>
</tr>
<tr>
<td>Length of stay in ICU (days)</td>
<td>25.9 ± 13.1</td>
<td>31.0 ± 12.7</td>
<td>0.258</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1/21 (4.8 %)</td>
<td>1/10 (10 %)</td>
<td>0.563</td>
</tr>
</tbody>
</table>

Thomas Bein
Steffen Weber-Carstens
Anton Goldmann

Intensive Care Med
Techniques of the 2010’s...
Low Flow ECCO2R...

Machine derived from CRRT devices
Amplya, Hemolung, PrismaLung, Decap...
Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate ARDS

Vito Fanelli1*, Marco V. Ranieri2, Jordi Mancebo3, Onnen Moerer4, Michael Quintel4, Scott Morley5, Indalecio Moran3, Francisco Parrilla3, Andrea Costamagna1, Marco Gaudiosi1 and Alain Combes6

Methods: In fifteen patients with moderate ARDS, $V_T$ was reduced from baseline to 4 mL/kg PBW while PEEP was increased to target a plateau pressure – ($P_{plat}$) between 23 and 25 cmH2O. Low-flow ECO2R was initiated when respiratory acidosis developed (pH < 7.25, $\text{PaCO}_2 > 60$ mmHg). Ventilation parameters ($V_T$, respiratory rate, PEEP), respiratory compliance ($C_{RS}$), driving pressure ($\Delta P = V_T/C_{RS}$), arterial blood gases, and ECO2R system operational characteristics were collected during the period of ultra-protective ventilation. Patients were weaned from ECO2R when $\text{PaO}_2/\text{FiO}_2$ was higher than 200 and could tolerate conventional ventilation settings. Complications, mortality at day 28, need for prone positioning and extracorporeal membrane oxygenation, and data on weaning from both MV and ECO2R were also collected.

Table 2 Time course of ventilation variables during the run-in phase

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>$V_T$ 5 mL/kg</th>
<th>$V_T$ 4.5 mL/kg</th>
<th>$V_T$ 4 mL/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_T$ (mL/kg)</td>
<td>6.2 ± 0.7</td>
<td>5.02 ± 0.1*</td>
<td>4.48 ± 0.1*</td>
<td>3.96 ± 0.1*</td>
</tr>
<tr>
<td>Respiratory rate (beats/minute)</td>
<td>28 ± 7</td>
<td>29 ± 4</td>
<td>30 ± 4*</td>
<td>30 ± 5*</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (cmH2O)</td>
<td>12 ± 3</td>
<td>13.8 ± 3</td>
<td>13.6 ± 4</td>
<td>13.0 ± 4.0</td>
</tr>
<tr>
<td>Plateau pressure (cmH2O)</td>
<td>27.7 ± 1.6</td>
<td>25.2 ± 1.6*</td>
<td>23.6 ± 1.3*</td>
<td>22.7 ± 1.8*</td>
</tr>
<tr>
<td>Patients who reached the pH threshold for ECO2R, n</td>
<td>0</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate ARDS

Vito Fanelli¹, Marco V. Ranieri², Jordi Mancebo³, Onnen Moerer⁴, Michael Quintel⁴, Scott Morley⁵, Indalecio Moran³, Francisco Parrilla³, Andrea Costamagna¹, Marco Gaudiosi¹ and Alain Combes⁵

Critical Care (2016) 20:36
Feasibility and safety of low-flow extracorporeal CO$_2$ removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS

Matthieu Schmidt$^{1,2}$, Samir Jaber$^3$, Elie Zogheib$^4$, Thomas Godet$^{5,6}$, Gilles Capellier$^{7,8}$ and Alain Combes$^{1,2}$
Results

Driving Pressure

PEEP
pRective vEntilation with venovenous lung assist in respiratory failure

REST Study

UK collaborative (NHS), Multicentre, RCT
PI: Danny McAuley & James McNamee

ECCO$_2$R for acute hypoxemic respiratory failure
Not just ARDS, P:F < 150

Pragmatic design, HEMOLUNG
Ongoing; 1,120 subjects planned
28 day mortality
Higher Flow ECCO2R...

Machine derived from ECMO devices
HLS 5.0, ILA-ACTIVE...
More to come...
A new paradigm...
Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Taskforce. JAMA 2012;307:2526-2533.
“In God we (may) trust; all others must bring data...”

W. Edwards Deming
(1900-1993)
International ECMONet

To promote research on ECMO
Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients

Alain Combes¹, Daniel Brodie², Robert Bartlett³, Laurent Brochard⁴, Roy Brower⁵, Steve Conrad⁶, Daniel Eddy Fan⁷, Niall Ferguson⁸, James Fortenberry⁹, John Fraser¹⁰, Luciano Gattinoni¹¹, William Lynch¹², Graeme MacLaren¹², Alain Mercat¹³, Thomas Mueller¹⁴, Mark Ogino¹⁵, Giles Peek¹⁶, Vince Pellegrino¹⁷, Antonio Pesenti¹⁸, Marco Ranieri¹⁹, Arthur Slutsky²⁰, and Alain Vuilsteke²⁰. The International ECMO Net (ECMOnet) American Journal of Respiratory and Critical Care Medicine Volume 190 Number 5 | September

Abstract

The use of extracorporeal membrane oxygenation for acute respiratory failure (ARF) is guided by recent advances in technology, evidence regarding the evidence justifying this high-risk, and costly modality, at centers with sufficient experience in its use safely. This position paper of an international group of physicians who have expertise in the treatment of patients with severe respiratory distress syndrome is intended to provide policy makers a description of the current use of ECMO programs for ARF in the intensive care unit. It is hoped that future observational and randomized controlled studies of this technique may be performed under the auspices of the ECMOnet. We encourage restraint in the publication of such data so that we have a better appreciation for the characteristics of the patients and the optimal techniques for their treatment.

Research

There is a clear need for further randomized, controlled trials and other high-level evidence with respect to the use of ECMO in ARF. These data will help guide clinicians with respect to specific indications and contraindications of the various techniques.
A **Strategy of UltraProtective** lung ventilation

With **Extracorporeal CO$_2$ Removal** for **New-Onset** moderate to severe **ARDS**

**The SUPERNOVA trial**
Pilot trial, RCT

• PILOT trial
  • Feasibility and safety
  • 95 patients
  • 3 devices (MAQUET, NOVALUNG, ALUNG)
  • ESICM trial group

• RCT
  • Will randomize up to 1000 patients
  • Adaptive design
  • Protocol will be finalized according to the results of the Pilot trial
Flow chart

95 in the analysis

MAQUET
N=28

NOVALUNG
N=34

ALUNG
N=33
PEEP INCREASED:
From 12±4 to 14±4 cmH$_2$O, $p<0.01$
(29±58 % baseline vs. 4 ml/Kg)
Driving Pressure

DeltaP decreased:
from 13±5 to 9±4 cmH₂O, p<0.01
33±16 % baseline vs. 4 ml/Kg
PaCO$_2$

NO SIGNIFICANT CHANGES

start run-in
end run-in
at 5ml/kg
at 4.5ml/kg
at 4 ml/kg
at 6h post 4ml/kg
at 12h post 4ml/kg
at D1
NO SIGNIFICANT CHANGES
PaO$_2$/FiO$_2$

NO SIGNIFICANT CHANGES
Survival at D28

69/95 = 73%
Probability of being on ECCO2R

ECCOR duration: 5 [3-8] days
CONCLUSIONS

THE SUPERNOVA “SUPER-PROTECTIVE” VENTILATORY STRATEGY IS:

• FEASIBLE

• SAFE
Precision Medicine...
Applying Precision Medicine to Trial Design Using Physiology
Extracorporeal CO$_2$ Removal for Acute Respiratory Distress Syndrome

Ewan C. Goligher$^{1,2}$, Marcelo B. P. Amato$^3$, and Arthur S. Slutsky$^{1,4}$

• Predictive enrichment
  • Enrolling patients with the greatest probability of responding
    • Better understanding of disease pathophysiology
    • Ex. Predict patients with greatest reduction in DeltaP post ECCO2R
  • To increase relative risk reduction
    • Further increases in absolute risk reduction
    • Apart from any change in baseline risk
Dead space and static compliance determine the effect of ECCO2R on driving pressure and mechanical power.

Applying Precision Medicine to Trial Design Using Physiology

Extracorporeal CO₂ Removal for Acute Respiratory Distress Syndrome

Ewan C. Goligher¹,², Marcelo B. P. Amato³, and Arthur S. Slutsky¹,⁴
Applying Precision Medicine to Trial Design Using Physiology: Extracorporeal CO₂ Removal for Acute Respiratory Distress Syndrome

Ewan C. Goligher¹,², Marcelo B. P. Amato³, and Arthur S. Slutsky¹,⁴

Dead space and static compliance determine the effect of ECCO2R on driving pressure and mechanical power. Might enable prediction of individual treatment responses to ECCO2R.
<table>
<thead>
<tr>
<th>Threshold for Inclusion</th>
<th>Patient Group (% of Sample)</th>
<th>Baseline P/F (Mean ± SD) (mm Hg)</th>
<th>Baseline Mortality Rate (%)</th>
<th>Median Predicted Decrease in ΔPaw* (cm H₂O)</th>
<th>Predicted Absolute Risk Reduction† (%)</th>
<th>Predicted Number Needed to Treat</th>
<th>Sample Size Requirement (80% Power)</th>
<th>Number of Patients to Screen</th>
<th>Predicted Serious Complications from ECCO₂R (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with ARDS</td>
<td>100%</td>
<td>145 ± 49</td>
<td>38</td>
<td>4.7</td>
<td>6.1</td>
<td>17</td>
<td>1,888</td>
<td>1,888</td>
<td>119</td>
</tr>
<tr>
<td>Baseline P/F ≤ 150 mm Hg</td>
<td>56%</td>
<td>109 ± 26</td>
<td>46</td>
<td>4.8</td>
<td>7.3</td>
<td>14</td>
<td>1,432</td>
<td>2,558</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>191 ± 27</td>
<td>29</td>
<td>4.7</td>
<td>4.8</td>
<td>21</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baseline P/F ≤ 100 mm Hg</td>
<td>21%</td>
<td>81 ± 14</td>
<td>56</td>
<td>4.9</td>
<td>8.4</td>
<td>12</td>
<td>1,100</td>
<td>5,239</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>79%</td>
<td>162 ± 39</td>
<td>34</td>
<td>4.7</td>
<td>5.6</td>
<td>18</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baseline ΔPaw ≥ 15 cm H₂O</td>
<td></td>
<td>143 ± 48</td>
<td>39</td>
<td>5.1</td>
<td>6.9</td>
<td>15</td>
<td>1,530</td>
<td>1,962</td>
<td>97</td>
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<tr>
<td></td>
<td>&lt;15 cm H₂O (22%)</td>
<td>153 ± 48</td>
<td>36</td>
<td>3.2</td>
<td>3.8</td>
<td>27</td>
<td>—</td>
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</tr>
<tr>
<td>Predicted decrease in ΔPaw ≥ 15 cm H₂O</td>
<td>Responders (66%)</td>
<td>144 ± 49</td>
<td>41</td>
<td>5.6</td>
<td>7.9</td>
<td>13</td>
<td>1,180</td>
<td>1,788</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Nonresponders (34%)</td>
<td>146 ± 50</td>
<td>32</td>
<td>3.3</td>
<td>3.5</td>
<td>29</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Predicted decrease in ΔPaw ≥ 5 cm H₂O</td>
<td>Responders (44%)</td>
<td>142 ± 47</td>
<td>44</td>
<td>6.4</td>
<td>9.5</td>
<td>11</td>
<td>822</td>
<td>1,869</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Nonresponders (56%)</td>
<td>147 ± 50</td>
<td>34</td>
<td>3.7</td>
<td>4.3</td>
<td>24</td>
<td>—</td>
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</tr>
<tr>
<td>Predicted decrease in ΔPaw ≥ 6 cm H₂O</td>
<td>Responders (27%)</td>
<td>143 ± 46</td>
<td>45</td>
<td>7.3</td>
<td>11.2</td>
<td>9</td>
<td>598</td>
<td>2,215</td>
<td>38</td>
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<tr>
<td></td>
<td>Nonresponders (73%)</td>
<td>145 ± 50</td>
<td>36</td>
<td>4.1</td>
<td>5.3</td>
<td>19</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Conclusion

• ExtraCorporeal CO₂ Removal
  • “Respiratory dialysis”, Not for refractory hypoxemia: VV-ECMO

• Potential for use for moderate to severe ARDS
  • To allow further reduction of Vt/Pplat/ΔP, to limit VILI,

• Before large diffusion, should be (re)tested in large clinical trials...
  • SUPERNOVA RCT...
La Pitié “International Diploma in ECMO & Short-Term Respiratory/Circulatory Support”

June 27-28, 2019

TCS - ECMO
International Congress

Program committee:
G. Montalescot – C. Mossadegh – C. Spaulding

www.paris-tcsecmo.org