# Lessons from EOLIA

## *ECMO* to rescue *Lung Injury* in severe *ARDS*

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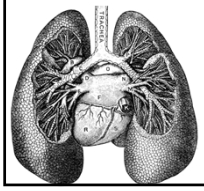
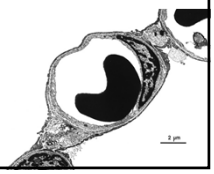
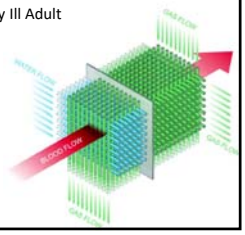




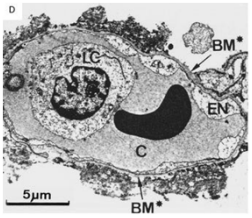
## Or lies, damned lies and statistics

Advanced Therapies for the Critically Ill Adult
May 17, 2019



## We should still care about a negative trial

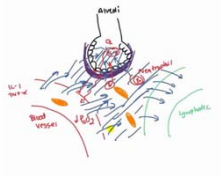
- Overview of the EOLIA trial
- Trial results
- Criticism/controversy




PMN in alveolar capillary

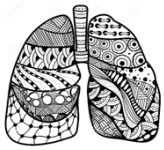
## Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

- Determine the effect of early initiation of ECMO in patients with the most severe forms of ARDS
- Intention to treat with goal 331 patients (ARR 20%)
- Primary endpoint: mortality at 60 days (40% ECMO, 60% control)
- Stopped for futility by the DSMB at 75% enrollment



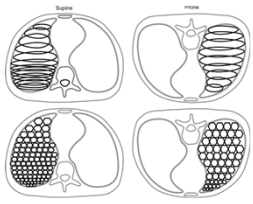
## Study Design

- Randomized, open label, controlled trial
- International, 64 centers
- 2011-2017; 249 patients
- Early ECMO vs conventional ventilation
- Standardized method of ventilation
- Crossover to ECMO allowed
- ECMO and non-ECMO centers (39%)



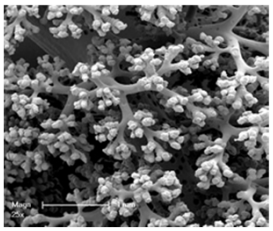
## Inclusion criteria

- Severe ARDS
- PaO2: FiO2 of less than 50 mm Hg for more than 3 hours
- PaO2: FiO2 of less than 80 mm Hg for more than 6 hours
- Arterial blood pH of less than 7.25 with PaCO2 of at least 60 mm Hg for more than 6 hours
- Mechanical ventilation < 7 d
- Prone positioning and neuromuscular blockade prior to randomization encouraged



## Patients

- Bacterial pneumonia 45%
- Viral pneumonia 18%
- Septic 78%
- Age 52; 70% male
- PEEP 12, pH 7.24, PaCO2 57, PaO2 69, compliance 25, plateau pressure 29, prone 60%
- Cause of death: MOF, resp failure, septic shock



## Treatment/complications

ECMO: 124 patients
- Bicaval cannulation within 3 hours of randomization
- Decreased force applied to the lungs and normalization of ABG
- ECMO average 16 d
- PTT 40-55
- More transfusions and severe thrombocytopenia

Control: 125 patients
- Vent strategy proven to improve outcome
- 90% prone
- 100% NMB
- Plateau pressure 28-30, PEEP 12
- 83% inhaled NO or prostacyclin
- 28% (35 patients) crossed over to ECMO

## Results: recruitment halted at 4th interim analysis

ECMO: 124 patients
- 60 day mortality 35% (44)
- Days without proning: 59
- Days free from cardiac failure: 48
- Days without RRT: 50

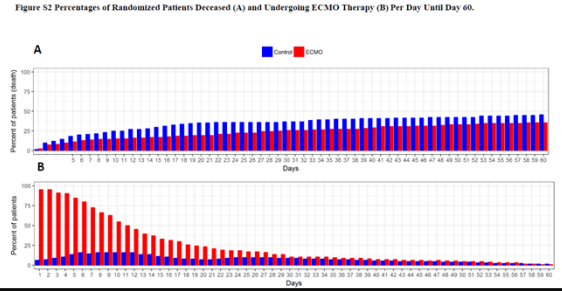
Control: 125 patients
- 60 day mortality 46% (57)
- Days without proning: 46
- Days free from cardiac failure: 41
- Days without RRT: 32

## Crossover patients: 15 survived (43%) and 20 died (57%)

- Refractory hypoxemia defined as SaO2 <80% for >6 hours, despite mandatory use of recruitment maneuvers, and inhaled NO/prostacyclin and if technically possible a test of prone position

- 35 patients (28%)
- Mean 6.5 days after randomization
- Discretion of investigator
- Median O2 sat 77%
- PaO2: FiO2 51 mm Hg
- Compliance 21
- 9 cardiac arrest
- 7 severe RV failure
- 11 renal failure requiring dialysis

## Percentages of randomized patients per day: A. Deceased B. On ECMO

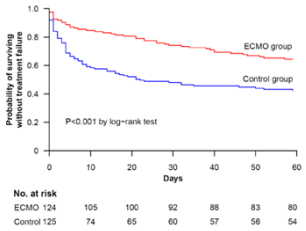



## Conclusions
## Primary Endpoint: 60 day mortality

- Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy.
- Cross-over dilutes ECMO effect

## Conclusions
## Key Secondary Endpoint: Treatment failure

- Defined as death in the ECMO group and cross-over to ECMO or death in the control group.
- Favored ECMO (bias against control)




## ECMO effect

- Cross-over results in underestimation of ECMO effect in primary end-point (60 d mortality)
- RPSFT: HR 0.51, P= 0.55 (from HR 0.7, P=0.07)
- Cross-over results in over-estimation of ECMO effect in secondary endpoint (treatment failure)

**Table S5. Post-Hoc Sensitivity Analysis of Treatment Failure at Day 60 Considering Different Survival Rates in Control Patients Crossed Over to ECMO**

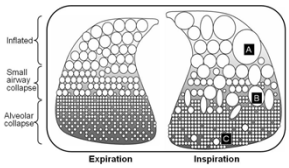
| Survival Rate in Control-Group Patients Crossed Over to ECMO | ECMO Group (N = 124) | Control Group (N = 125) | Relative Risk (95% CI) | P Value |
|---|---|---|---|---|
| 0% — no. (%) | 44 (35.5) | 72 (57.6) | 0.62 (0.47–0.82) | <0.001 |
| 10% — no. (%) | 44 (35.5) | 68 (54.4) | 0.65 (0.50–0.87) | 0.003 |
| 20% — no. (%) | 44 (35.5) | 65 (52.0) | 0.68 (0.51–0.91) | 0.009 |
| 33% — no. (%) | 44 (35.5) | 60 (48.0) | 0.74 (0.55–0.99) | 0.045 |

## Controversy/criticism

- Stopped for futility: secondary end-points and post-hoc analysis favored ECMO
- Underpowered and slow patient recruitment: 9 yrs to show a statistically significant difference in mortality
- Study design allowed crossover; can't do RCT with ECMO
- Statistical analysis was incorrect

## Significance

- Absolute mortality was 11% lower in the ECMO group
- 43% of cross-over patients survived
- The vent does harm that ECMO can ameliorate: 60% decrease in force applied to the lungs on ECMO




## Summary: ECMO for ARDS

- When ARDS is diagnosed, can't predict who will benefit from ECMO
- ECMO is a necessary part of the treatment algorithm for ARDS that still relies heavily on expertise and clinical judgement
- Early ECMO is better than late ECMO
- Future: WWBD?

## Bibliography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## Ventilator management

ECMO: 124 patients

- Venovenous ECMO will be started as rapidly as possible
- Mechanical ventilation settings:

Volume assist control mode, FiO2 30–60%, PEEP ≥10 cm H2O, VT lowered to obtain a plateau pressure 24 cm H2O, RR 10–30/minute or APRV mode with high pressure level 24 cm H2O an low pressure level ≥10 cm H2O

- ECMO weaning according to protocol

**Control: 125 patients**

- Conventional management of ARDS
- Ventilatory settings: volume-assist control mode, VT 6 ml/kg of ideal body weight and PEEP adapted so as not to exceed plateau pressure of 28–30 cm H2O
- In the case of refractory hypoxemia, the usual adjunctive therapies can be used: NO, prone position, HFO ventilation, almitrine
- Cross-over option to ECMO possible