Do we have enough evidence for ECMO in

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Faculty Disclosures
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• Maquet Cardiovascular
  – Research support
ECMO for Adult ARDS

Current state of the evidence?
1st Successful ECMO in an adult

1972

Hill DJ, et al. NEJM 1972
150 patients
ECMO for acute respiratory failure

1974
NHLBI–sponsored
Prospective RCT
Conventional MV alone vs. ECMO
with MV

Zapol WM, et al. JAMA
1979
9 centers
90 subjects
Venoarterial ECMO

Survival: no difference
9.5% ECMO
8.3% Conventional MV

1979

Zapol WM, et al. JAMA 1979
Criticisms

Small study
Lack of experience at some centers
Use of VA
High dose anticoagulation
Excessive bleeding

Outdated, injurious MV strategies

Antiquated ECMO technology

1979

Zapol WM, et al. JAMA 1979
“Rest the lung”

Extracorporeal CO$_2$ Removal (ECCO$_2$R)

1980

Low-Frequency Positive-Pressure Ventilation With Extracorporeal CO₂ Removal in Severe Acute Respiratory Failure

Luciano Gattinoni, MD; Antonio Pesenti, MD; Daniele Mascheroni, MD; Roberto Marcolin, MD; Roberto Fumagalli, MD; Francesca Rossi, MD; Gaetano Iapichino, MD; Giuliano Romagnoli, MD; Ljiljana Uziel, MD; Angelo Agostoni, MD; Theodor Kolobow, MD; Giorgio Damia, MD

ECCO₂R
P:F < 100
Rest Settings with “apneic oxygenation”
RR 3–5
PIP 35–40
PEEP 15–25

Survival 48.8%

1986
2nd RCT: Utah

ECCO$_2$R

40 patients

Severe ARDS

Conventional MV

vs.

PC–IRV then ECCO$_2$R with Low Frequency

Morris AH, et al. AJRCCM
1994;149:295
2nd RCT: Utah

No difference in survival
P = 0.8

42% Conventional MV

33% PC–IRV with ECCO$_2$R

Morris AH, et al. AJRCCM
1994;149:295
2\textsuperscript{nd} RCT: Utah

Small study

Single center

Inexperienced: only 2 prior patients
(Milan Fellow)

1994

2nd RCT: Utah

Criticisms

Outdated, injurious MV strategies
Mean PIP 45.4 with ECCO$_2$R

Two separate interventions (PC-IRV & ECCO$_2$R)

Excessive bleeding

Outdated ECMO technology

After 2 RCTs

Conclusion

ECMO for ARDS in adults does not work
Why are we here?
Observational studies
1990s
2000s
Observational studies

Survival with ECLS
47–66%

ECMO
ECCO$_2$R
AVCO$_2$R
2009 H1N1 Influenza Pandemic
Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome

15 ICUs in Australia & New Zealand
ECMO for H1N1–associated ARDS
68 patients
Median age 34.4
Median P:F 56

Survival 75%

Davies A, for the ANZ ECMO Influenza Investigators. JAMA 2009;302:1888

JAMA 2010;303:941
ELSO

Extracorporeal Life Support Organization

Adult H1N1 Registry
As of April 2011
238 cases
67% survival
Observational trials

Confounded by indication
Observational Trials

How do you compare severity?
No standard definition
“Severe” ARDS

How do you estimate what mortality should be?
P:F
ALIS
Secular Trends in Critical Care
Improvements in Outcomes

• Ventilator management
• Fluid management
• Prevention of infection (CLABSIs, VAPs, CAUTIs)
• Trauma management
• Sedation protocols
• Physical & occupational therapy
Mortality from ARDS
University of Washington
Is it the ECMO?
ICU in Utah
30 patients with H1N1–associated ARDS
Median age 34
Median P:F 61

Not treated with ECMO

Survival 73%
Is it the ECMO?
Reasons to believe it works

Rationale: buy time with “lung rest”

Advances in technology
Pumps
Oxygenators
Biocompatible circuits
Catheters

Improved techniques
Decreased anticoagulation
Miniaturized set ups
Improved lung rest

Greater experience
Is it the referral center doing the ECMO?
2009–2010 H1N1–related ARDS

“ECMO–referred patients” (80)
Transferred for ECMO
Any of 4 adult ECMO centers in the UK

Matched with...

“Non–ECMO–referred patients” (1756)
Swine Flu Triage Study

Concurrent, longitudinal, cohort study
Critically ill patients with H1N1
80 ECMO–referred
69 received ECMO (86.3%)
Hospital mortality 27.5%

59 matched pairs (individual matching)
23.7% ECMO–referred vs. 52.5%

75 matched pairs (propensity score matching)
24.0% ECMO–referred vs. 46.7%

75 matched pairs (GenMatch matching)
24.0% ECMO–referred vs. 50.7%

Noah et al. JAMA 2011
“Referral & transfer to an ECMO center was associated with lower hospital mortality compared with matched non-ECMO-referred patients”

Noah et al. JAMA 2011
Does ECMO improve clinical outcomes in severe ARDS?

Need a modern RCT

Modern technology
Modern techniques
180 adults
Severe but potentially reversible respiratory failure
Randomized...

CESAR
2009

Continued conventional management at a designated treatment center

Vs.

Consideration for treatment with ECMO

[75% received ECMO]

Death or severe disability at 6 months
53% conventional arm
37% consideration for treatment with ECMO
16% absolute reduction in primary endpoint

Criticism

Not a trial of MV vs. ECMO

Referral to a highly specialized center
With a standardized management protocol
Included consideration for treatment with ECMO

Wealth of ECMO experience

Advanced therapies
MARS in 17%

2009;374:1351
Criticism

Conventional MV arm not standardized
Only 70% received low-volume, low-pressure ventilation at any time
(Standard of care)

93% at Glenfield
Due to better care or because ECMO facilitated?
Do we need another modern RCT?
Clinical equipoise?

Miller FG, Joffe S. NEJM 2011;364:476
“To clinicians familiar with ECMO. . . the available data would seem to validate ECMO support as reasonable therapy for patients whose conditions do not respond to conventional care. To those who regard ECMO. . . as unproven or misguided, this study [CESAR] may reinforce the belief that there is little or no evidence to support its use.”

Dalton HJ, MacLaren G. CCM 2010;381:1484
“For the moment the use of this therapy will remain driven by enthusiasts. . . . Others will need more convincing.”

Clinical equipoise writ large
With or without equipoise

“When treatments are likely to be very expensive, and their clinical benefits are uncertain based on current knowledge, it becomes all the more important to develop sufficiently rigorous evidence about their risks and

Miller FG, Joffe S. NEJM 2011;364:476
“... evaluation in [RCTs] should be the default... before new treatments are approved and covered solely on the basis of evidence from uncontrolled trials.”

Miller FG, Joffe S. NEJM 2011;364:476
We need another RCT

What would a new RCT look like?
An ideal RCT?

Multiple ECMO centers
Standardized ECMO protocols
Strict enrollment criteria
Any transportation on ECMO

Standardized conventional MV
ARDSNet ARMA Express

NEJM 2000;342:1301
An ideal RCT?

A priori comparison of early vs. late initiation

Use of restrictive transfusion thresholds?
EOLIA

ECMO to Rescue Lung Injury in severe ARDS

Department de la Recherche Clinique et du Developpement
Assistnace Publique-Hopitaux de Paris

Professor Alain Combes
Institut de Cardiologie, Group Hospitalier Pitie-Salpetriere
Conclusion

ECMO likely has a role in severe ARDS

But... 

We need more evidence