Lung Track Summaries: The Evolution of Lung Support Devices Regulatory considerations in Lung Transplantation

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ECMO as a Bridge to Transplant Should be Exempt from 1 Year Mortality Outcomes in Lung Transplant

Charles Hoopes MD versus Duane Davis, MD MBA

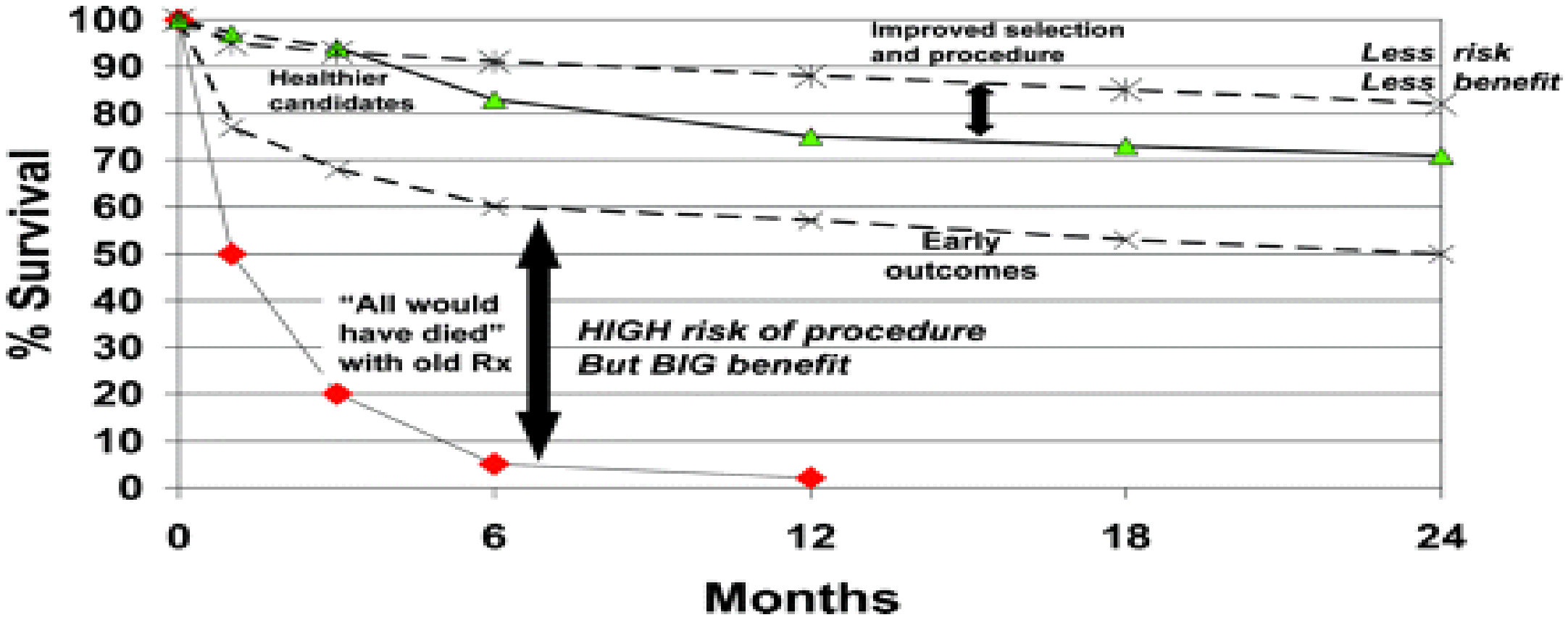
*“ … hospitals have become more **risk averse based on these metrics** with concerns about treating patients who are considered relatively at higher risk for survival”*

*“ … providing the optimal treatment option for patients with end-stage organ disease may place programs at **higher risk for punitive regulatory consequences**”*

*“ … **metrics should be applicable to assess performance … and most importantly directly align with what is in the best interest of the patient populatio**n”*

Approved by the AST Executive Committee on April 4, 2017

The “curve of downshifting risk”… surgical innovation and behavior



Stewart and Stevenson (2011) Circ

The Challenges in Predicting ECMO Survival, and a Path Forward

Marco Huesch*† and Christopher Brehm*‡

Summary of ECMO Adult Risk Models Since 2010

	Focus in Study on ECMO Therapy Configuration		
ECMO Indication in Study	Exclusively Veno-venous	Both Veno-venous and Veno-arterial, or Hybrid	Exclusively Veno-arterial
Exclusively respiratory failure		Huang *et al*., 2016 Klinzing *et al*., 2015 [PRESERVE] Schmidt *et al*., 2013 [RESP]	
Large majority respiratory failure		Schmidt *et al*., 2014 [RESP]	
Mixed respiratory and cardiogenic indications		Kim *et al*., 2015	Chen *et al*., 2016*
Large majority cardiogenic shock			Schmidt *et al*., 2015 [SAVE]
Exclusively cardiogenic shock			Muller *et al*., 2016 [ENCOURAGE] Burrell *et al*. 2015 Li *et al*. 2015 Hsu *et al*., 2010 Formica *et al*., 2010
Exclusively witnessed cardiac arrest			Mégarbane *et al*., 2015

"ECMO risk prediction has two key goals … (1) prospectively stratify the outcome risk and (2) measure risk-adjusted ECMO performance across all patients."

"Across these objectives, the different indications for ECMO, modalities, and characteristics of the infrastructure and practice patterns all matter. Accordingly, the ideal model would be customized along those dimensions, be constructed in large datasets and successfully validated in external datasets."

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ASAIO Journal (2017) 63:847–848

Balance between doing the right thing and doing the thing right

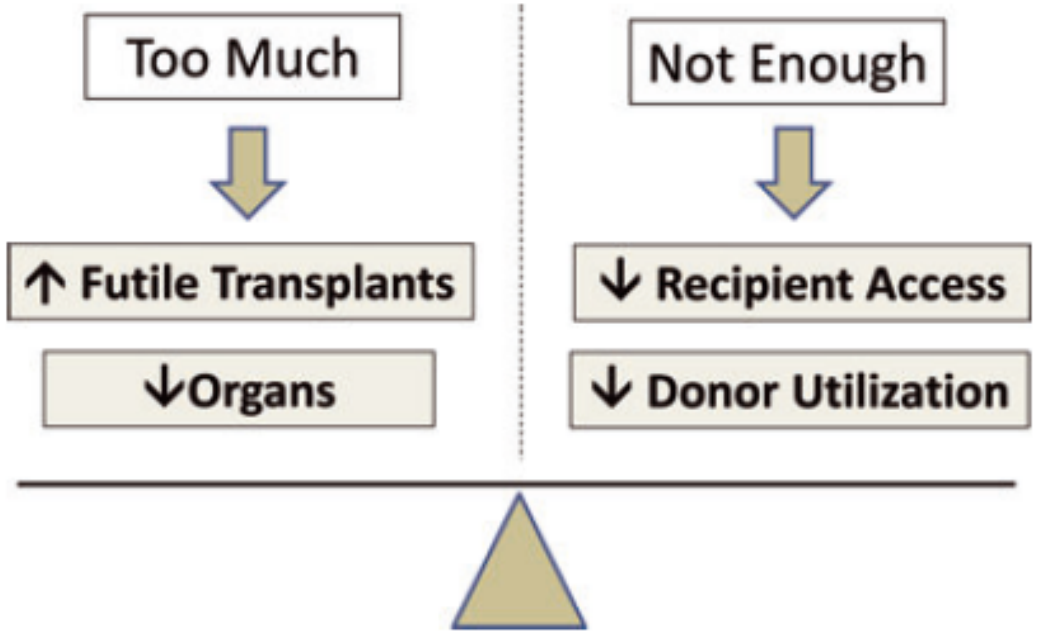


Figure 3: The right balance in adjusting program-specific outcomes for risk. "Too much" adjustment could forgive centers for performing futile transplants and wasting organs. "Not enough" adjustment could discourage centers from performing transplants in suitable high-risk candidates, and/or accepting high-risk donors.

American Journal of Transplantation 2012; 12: 1988–1996

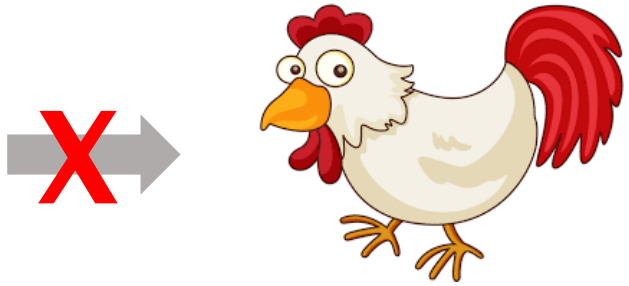
Ex Vivo Lung Perfusion is an Essential Tool for Donor Optimization

Shaf Keshavjee MD and Thomas Egan MD, MSc

EVLP Provides the Opportunity to Test Questionable Organs

- Different threshold of comfort to accept a “non-perfect” organ
- Retrieval by “unknown” retrieval surgeon
- If you are not sure/ not comfortable – check it out on EVLP
- A stable lung on EVLP will work after transplant
- Use more lungs SAFELY (no more “adventures” with “marginal lungs”

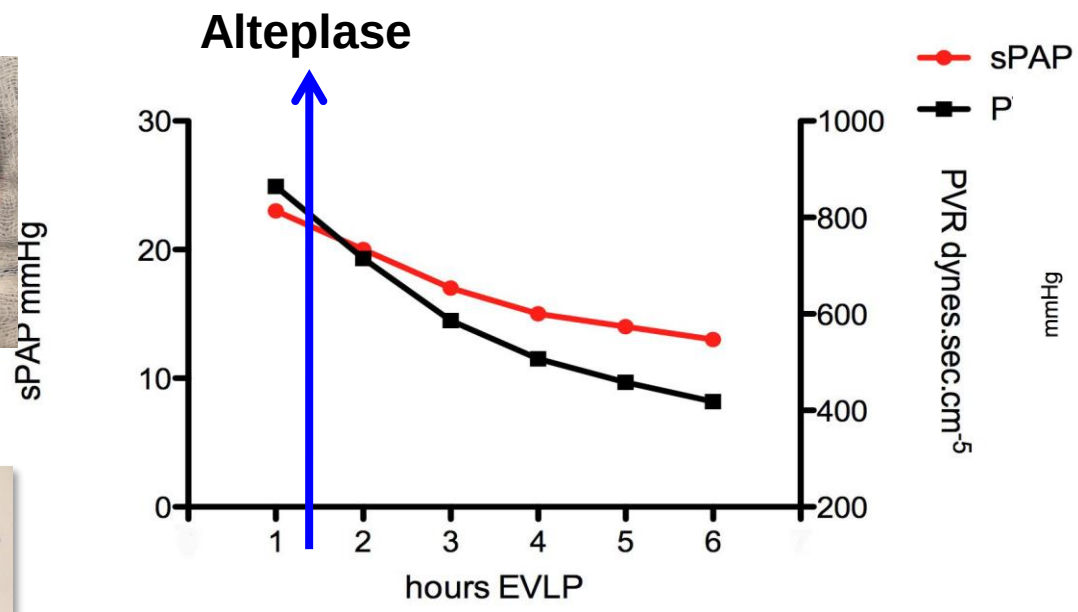
Decision Making - Experience

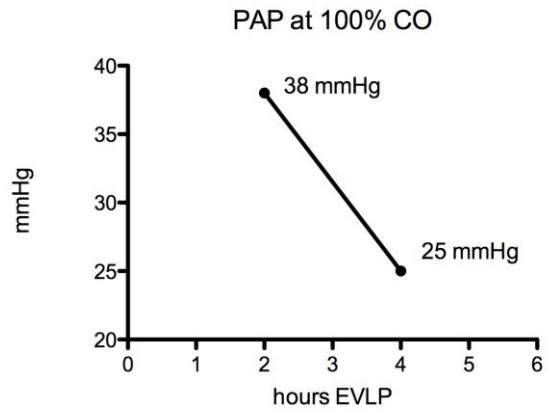


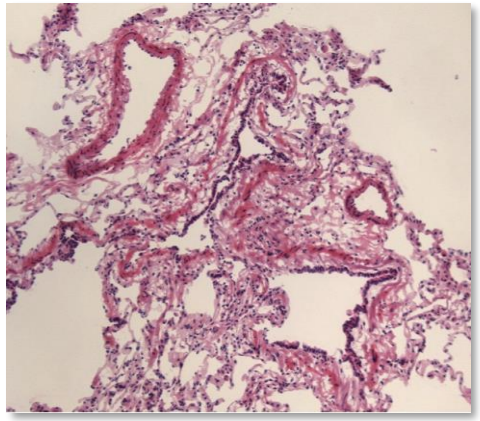
- Experienced team can make the decision together with the more junior team that went on recovery

You cannot make a chicken out of a fried egg!!

Donor with High PAP and PE: Significant Improvement of Pulmonary Hemodynamics after Treatment on EVLP



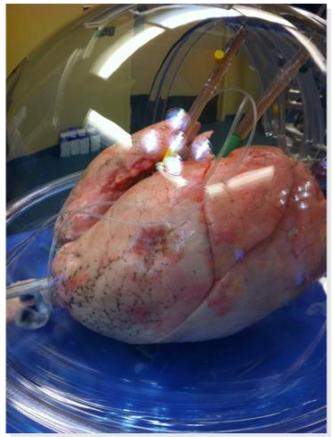




diagnosis

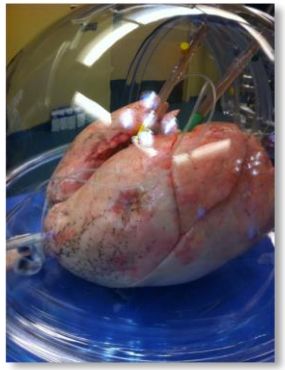
treatment

Response monitoring



EVLP Provides the Opportunity to Repair Donor Lungs

EVLP Treatment Strategies



- Perfusion
- Gene Therapy
- Drugs
- Cell Therapy
- Biological
- Immuno-cloaking
- Inhaled Gases

EVLP Impact on lung donor pool

- multiple publications attest to ↑ use of lungs after EVLP
- most of these lungs would not have been used
- most reports show equivalent early and late mortality
- does EVLP “recondition” lungs?
- if bad lungs become better, shoudn’t good lungs become even better?
-

Does EVLP make lungs better?

- lit search:

  human ex vivo lung perfusion
- 307 citations back to 1988 – some irrelevant
- not one citation showed better lung function or survival with EVLP alone

Conclusions

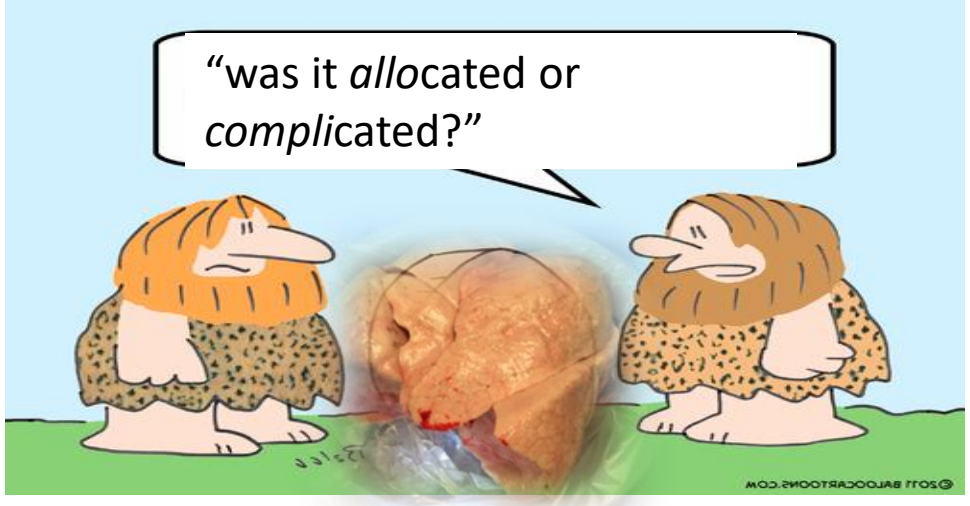
- EVLP is a useful tool to help evaluate lungs
  - absolutely necessary for uDCDD lungs
- EVLP will probably be very useful to treat lungs
- currently there is no evidence that EVLP should be performed on every set of lungs

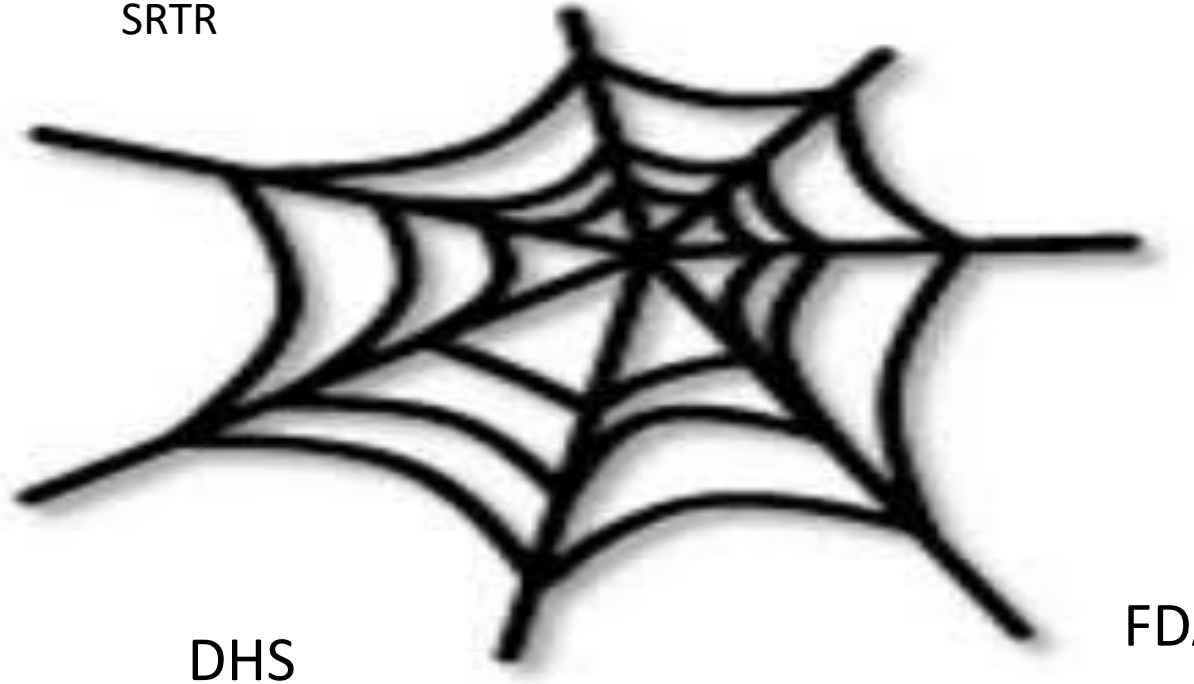
The Regulatory Imperative – Impact on the Practice of Lung Transplant

Christopher Wigfield MD

Examples of the regulatory imperative

1. *identify accountability*
2. *be enforceable*
3. *be easy to understand*
4. *have broad public support*
5. *be balanced and avoid knee-jerk reactions*
6. *reconcile contradictory policy objectives*
7. *balance risks, costs and benefits*
8. *avoid unintended consequences*
9. *be relevant to current conditions*




UNOS / OPTN
Private Payers
HC Networks
CMS
SRTR
Program / Public
representation
OPO
CDC
FDA
DHS
HRSA
Foundations
Economists
Ethics Comittee

Regulatory realities- Redefining Benefit of Lung Transplant in the Current Era

Gundeep Dhillon MD, MS

Since LAS implementation…

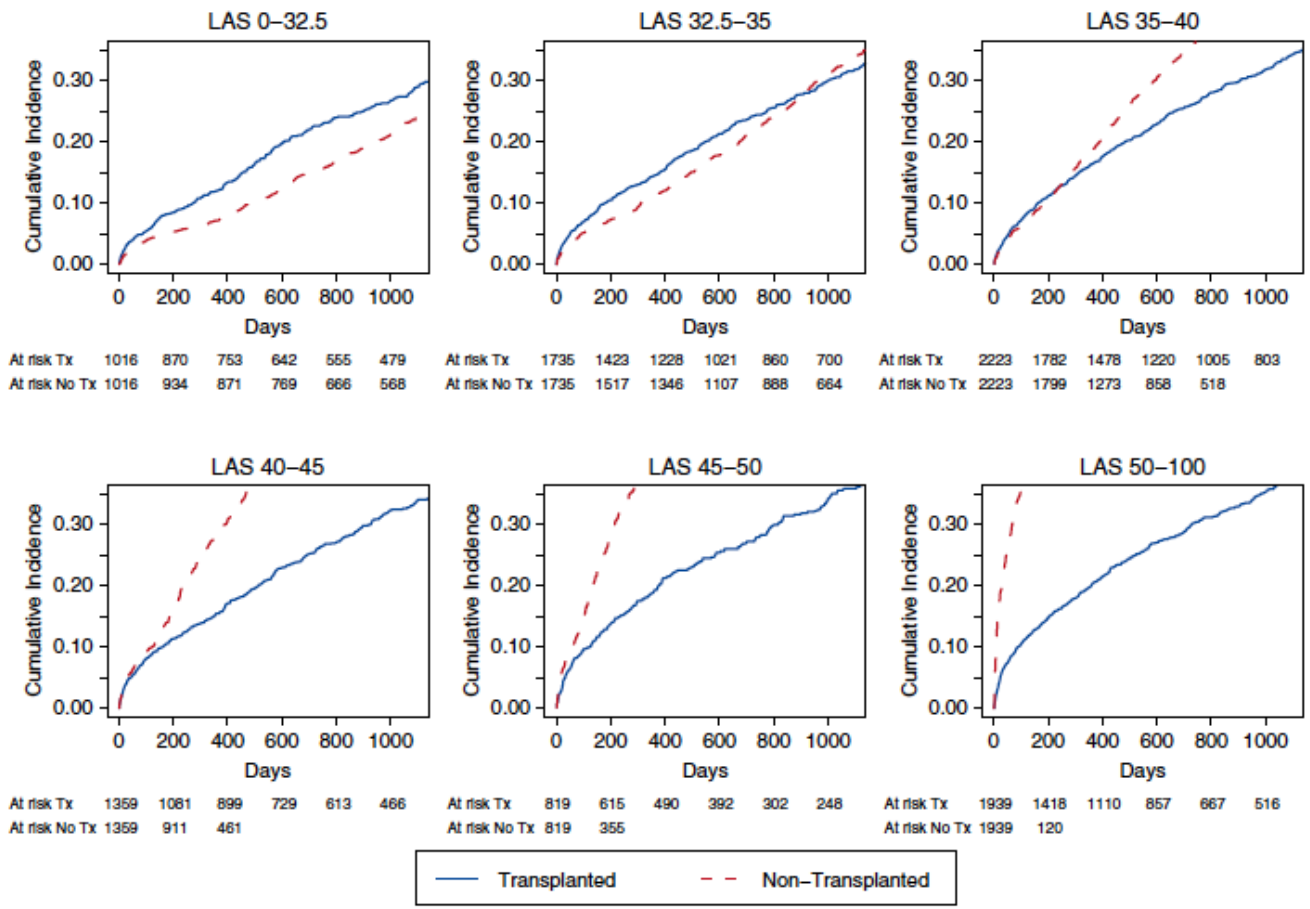
- Decreased number of wait list patients and waiting list time per patient
- Decreased waiting list mortality, initially, now increasing
- Recipient Characteristics Shift
  - Older patients
  - Sicker Patients
  - Group D / ILD recipient favored
- High LAS scores associated with increased post-transplant mortality
- But, No change in overall survival at 1 year

But …

- Long-term survival appears to have worsened
- Increased resource utilization
- Indirect evidence of increased morbidity

Survival Benefit of Lung Transplantation in the Modern Era of Lung Allocation

David M. Vock[1], Michael T. Durheim[2,3], Wayne M. Tsuang[4], C. Ashley Finlen Copeland[3], Anastasios A. Tsiatis[5], Marie Davidian[5], Megan L. Neely[2,6], David J. Lederer[7], and Scott M. Palmer[2,3]



Vock et al. Ann Am Thorac Soc Vol 14, No 2, pp 172–181, Feb 2017

Summary

- Implementation of LAS shifted the organs towards older & sicker patients
- Concurrent increase in regulatory pressures, probably led to:
  - Increased focus on 1-year survival
  - Worsening long term outcomes
  - Increased resource utilization to maintain 1-year outcomes
- Risk aversion leading to decreased number of transplants in the higher LAS groups

Cell Free DNA and Other Immune Monitoring Techniques in Lung Transplantation – Are We There Yet?

David Neujahr MD

Key Points (are these technologies ready for prime time?)

Dad, are we there yet?

NO!

When will new technologies be “there”?

- Cell free DNA is a technology without a well formulated question…yet
  - Artifact of using an existing technology for a separate purpose
  - Longitudinal studies are key
- Viral next-gen sequencing
  - Needs to be paired with other measures to be informative
  - Cost needs to come down
- Microvesicles/Exosomes
  - Too early to tell, but hot topic
  - Lots of abstracts at ATC!

Controlled Donation after Determination of Circulaory Death (cDCDD- Improving yield

Michael Smith MD

Improving Lung DCD Yield Summary

- DCD is an important resource to narrow donor shortage
- Controlled DCD criteria are similar to DBD
- Outcomes for Controlled DCD are comparable to DBD
- Challenges
  - Restricted donor/pt management
  - Alleviate “dry run” cost allocation issues
  - Graft risks
    - Aspiration
    - Prolonged WIT
  - EVLP for extended criteria controlled DCD
- Consider expansion of uncontrolled DCD programs
  - EVLP likely to improve outcomes

Xeno Lung Transplantation- The Path Forward

Agnes Azimzadeh PhD

The Path Forward

- Combine TBM and EPCR
- Evaluate TFPI
- Humanize pig vWF
- Target cellular adhesion pathways (selectins, CD11b/CD18/Mac-1 integrin)
- Target macrophages (clodronate liposomes, ASGR1, SIRP1a)
- Target sialidases

Extracorporeal Lung Support-A Bridge too far?

Jonathon D’Cunha MD

ECMO

- **Any patient with refractory hypoxemia or hypercapnia despite optimal ventilatory support and adjunctive medical management**

- **Often referred to as “bridge” therapy**

- **Bridge to what:**
  - **Recovery**
  - **Transplant**

Summary

- ECMO is a viable and dynamic option for failing patients

- Patients should be carefully selected
  - Center volume
  - Pulmonary Hypertension
  - Other Organ failure
  - Sensitization
  - Re-tx

Major Take Message

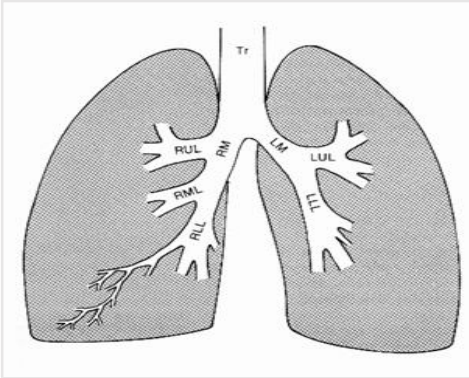
Timely implementation of ECMO translates to greatest benefit

The Artificial Lung- Can it be realized?

William Federspiel PhD

The Natural Lung Versus an Artificial Lung

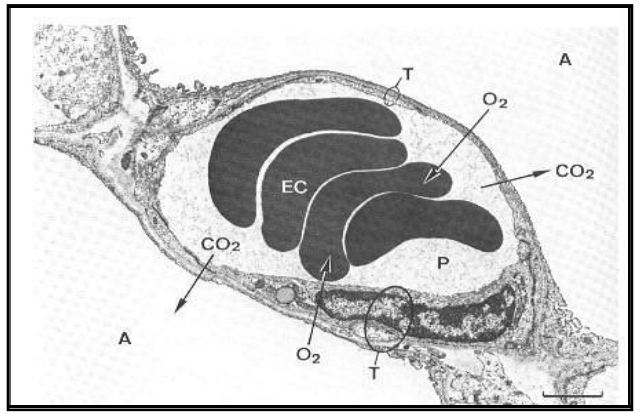
Nature's Technology



The natural lung is a remarkable organ for gas exchange

Vs

Alveolar-Capillary Microvascular Units



$A \sim 140\ m^2$
$A/V \sim 2900\ cm^{-1}$
$\delta \sim 1\ \mu m$
$VO_2 \sim 210 - 3200$ ml/min

"Our" Technology

Hollow Fiber Membrane Modules

$A \sim 2.5\ m^2$
$A/V \sim 28\ cm^{-1}$
$\delta \sim 10\text{-}30\ \mu m$
$VO_2 \sim 150 - 250$ ml/min

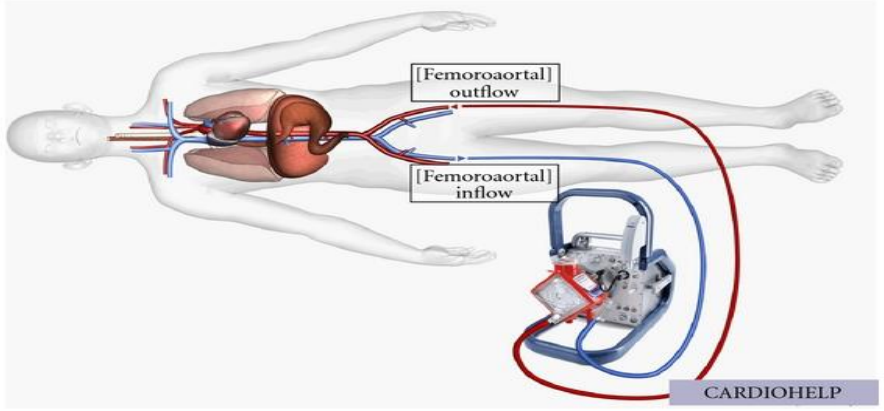
Medical Devices Laboratory
McGowan Institute of Regenerative Medicine

Current Artificial Lungs: ECMO Devices

MAQUET
GETINGE GROUP

CARDIOHELP System

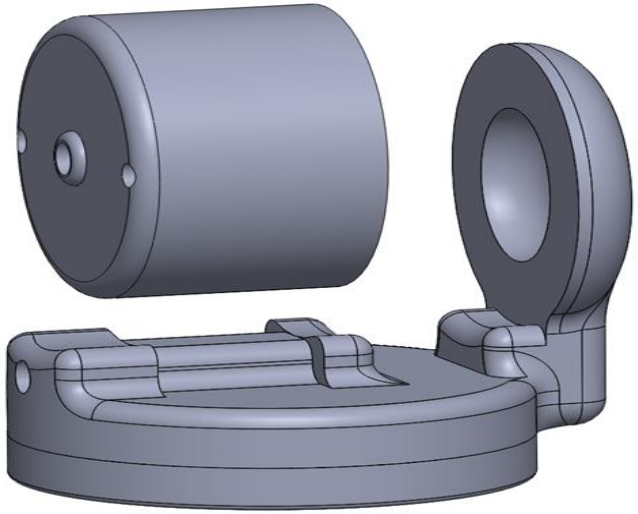
The world's smallest portable heart-lung support system.



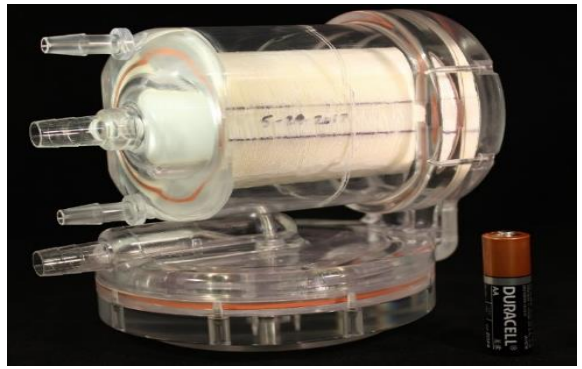
TANDEM | LIFE
LIFE SUPPORT SIMPLIFIED

A Comprehensive Solution: ModELAS*

*Modular Extracorporeal Lung Assist System:
"wearable" lung assist for adults and children



Pediatric
ModELAS
(P-ModELAS)



Adult
ModELAS
A-ModELAS

	Function	Blood Flowrate	Clinical Goal	Clinical Market (NA/EU)
P-ModELAS	Pediatric O_2 supply and CO_2 removal	1-2.5 Liters/min	Bridge to recovery (acute) or transplant (chronic)	200-500
A-ModELAS	Adult O_2 supply and CO_2 removal	2-3.5 Liters/min	Bridge to recovery (severe ARDS) or transplant (chronic)	20,000-50,000
A,P-ModELAS ECCO2R	Minimally invasive CO2 removal (respiratory dialysis)	200-500 mL/min	Bridge to recovery (ARDS, AE-COPD)	300,000-500,000

Medical Devices Laboratory
McGowan Institute of Regenerative Medicine

Conclusion: It can be realized but …

We are about 20-30 years behind VAD technology

	VADs	Artificial Lungs
Implantable working unit	Yes	No Extracorporeal
Reliability	Years	Days-Months
Destination Therapy	Yes	No ICU
Hemocompatibility	Very Good ~ cm^2 contact area	Challenge ~ m^2 contact area
Technology Platform	Mostly Perfected	In Infancy