Artificial Lungs: A New Inspiration

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Presenter Disclosure Information

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  Avalon Laboratories, LLC, Grand Rapids Mi
Introduction

• Respiratory failure is now the 3rd leading cause of death in the USA

• Despite advances, death from acute respiratory failure remains ~ 40%
VENOARTERIAL ECMO
ECMO: Complex, Labor Intensive, Expensive, Time Limited
VENOVOENOUS ECMO
Single, Double Lumen Cannula
For total gas exchange alone

Zwischenberger 1989
## ELSO Registry: 7/2009

<table>
<thead>
<tr>
<th>Category</th>
<th>Total #</th>
<th>% Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>23,191</td>
<td>85</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3,749</td>
<td>59</td>
</tr>
<tr>
<td>Pediatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>4,188</td>
<td>64</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4,564</td>
<td>62</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1,663</td>
<td>60</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1,059</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>40,195</td>
<td>74</td>
</tr>
</tbody>
</table>
Oxygen transfer
Carbon Dioxide Removal
AVCO$_2$R: Carbon Dioxide Removal (get the bad air out) with a low-resistance gas exchanger in a simple arterio-venous shunt

Zwischenberger 1996
AVCO$_2$R

CO$_2$ removal and O$_2$ transfer are uncoupled:

- CO$_2$ is transferred across the membrane gas exchanger
- Low Frequency Ventilation: O$_2$ diffuses across the native lungs

Ted Kolobow 1977
AVCO$_2$R: Sheep Studies

- Shunt flow to 30 % cardiac output did not alter organ blood flow.  
  *J Thorac Cardiovasc Surg* 1997;114:1107-1114.

- Percutaneous cannulas (10-12 F) allow near total CO$_2$ removal in adult sheep.  
  *ASAIO J* 1997;43:M817-M820.

- AVCO2R allows significant reductions in ventricular pressures and improves gas exchange.  

- AVCO$_2$R improves survival in a prospective randomized outcomes study over 96 hrs in a LD$_{50}$ ovine smoke/burn model of ARDS.  
AVCO$_2$R Outcome

- 5/5 completed 72 hr trial
- 3/5 Discharged
- 2 minor complications
  

- 8/8 completed 72 hr trial for ARDS with hypercapnia
- 5/8 Discharged
- No major complications
  
Arteriovenous CO$_2$ Removal
NOVALUNG (Europe)

percutaneous
cannulation
of femoral artery and vein
NOVALUNG Registry Data
100 protocol patients ( >3000 total)

[OVERALL SURVIVAL >70%]
Summary:

- iLA routinely normalizes CO$_2$ and pH, allows to dramatically reduce MV
- Limb Ischemia reduced with small catheters
- Early use (less than 2 days on mechanical ventilation) might improve outcomes
AVCO$_2$R for Transport
Schema

Smoke/Burn Injury

Volume Controlled Mechanical Ventilation (24-36 hrs)

Meet Entry Criteria (P/F <200)

Randomize

AVCO₂R (n=7)

High Frequency Percussive Ventilation (HFPV) (n=9)

LTV (N=9)
AVCO$_2$R has significantly better survival than LTV 96 h post-injury, 72 h post criteria (p = 0.05)
Impact of CO$_2$ Homeostasis

CO$_2$ flux is greatly reduced by AVCO$_2$R, and may be important in:

- organ tissue neutrophil apoptosis
- resolution of inflammation
- maintaining a normal alveolar milieu
Clinical Trials at Novalung

- **Registry**: Novalung Clinical Specialist Team

- **European Xtravent trial (ARDS)**
  ECMO for lung protection in severe ARDS – a prospective randomized multicentre study

- **Toronto Lung Transplantation Trial**
  iLA as a Bridge to Lung Transplant and Recovery

- **iLA in exacerbated COPD**
  Single-Center, open study using iLA in COPD
## Toronto Novalung Experience

(8 patients, 9 devices)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge To Transplant (BTT)*</td>
<td>N =4</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Bridge To Recovery (BTR)**</td>
<td>N =4</td>
<td>2/4 (50%)</td>
</tr>
</tbody>
</table>

* Includes 1 pt BTR +BTT; ** Includes 1 pt non Tx
Alung® Technologies

HEMOLUNG System:
- Percutaneous (15 Fr)
- Low Flow (400-500 ml/min)
- Veno Venous ECMO for primarily CO₂ removal
Human Data – Rapid ABG Normalization

### Preliminary Results – First 4 Patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Hemolung &lt; 6 hr</th>
<th>Hemolung 3-7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO₂ (mmHg)</td>
<td>87.5 ± 16.8</td>
<td>67.7 ± 7.5</td>
<td>62.4 ± 3.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.24 ± 0.07</td>
<td>7.34 ± 0.04</td>
<td>7.35 ± 0.04</td>
</tr>
</tbody>
</table>

**Patient 01-01**

**Patient 01-02**
The Paracorporeal Artificial Lung (PAL) As a Bridge to Lung Recovery or Transplant
Paracorporeal Artificial Lung: PA-PA Configuration

- 100% flow through device
- Full lung metabolic function
- No risk of stroke or R→L shunt
  - High right heart power requirement

Right Heart Failure!!
Assisted RA-PA Artificial Lung

1. Right ventricular assist device (RA-PA) 100% of cardiac output through the Paracorporeal Artificial Lung to prevent right heart failure

2. Requires only one PA anastomosis

3. Insertion without CPB

4. Spares pulmonary hilum for subsequent transplant

ASAIO 2006 – Wang/Zwischenberger
Total respiratory and right heart support
2 weeks: No sedation, stable Hemodynamics

Zwischenberger/Wang ASAIO 2006
Ambulatory, Compact, and Paracorporeal Successful to 4 weeks

Artificial Lung

Outlet Cannula

Inlet Cannula

Pump Driver

MicroMed Pump

Zwischenberger/Wang STSA 2006
Problem: RA access and PA anastomosis too delicate for ambulation

Goal: To develop a minimally invasive double lumen cannula for a Paracorporeal Artificial Lung to:
  – Avoid Thoracotomy
  – Avoid Major Vessel Central Access
  – Avoid recirculation

Based on VV ECMO cannulation
VENOVENOUS ECMO
Single, Double Lumen Cannula
For total gas exchange alone

Zwischenberger/Drake 1989
The higher pump flow, the more recirculation (♦)
Effective flow (■) no longer increases
as pump flow increases
VV Triple site cannulation

- Minimizes recirculation
- Maximizes venous drainage
- Improves gas exchange

2003
Wang-Zwische DLC
Bicaval cannulation to separate flow
W-Z DLC ➔ Avalon Elite®: Key Elements

- Ultra-thin membrane reinfusion lumen
- Anti-kink stainless steel reinforced catheter with ultra-thin wall
- Reinforced reinfusion port
- Extended tip introducer
Our DLC show only 2% recirculation at flow of 2 l/min. DLC tip dislodgement made recirculation jump to 50%.
Survival Study

- 26 Fr DLC in 37 kg Sheep
- General anesthesia
- Cannulation with ACT 180-250 s
- Pump to Elite DLC attachment
- Animal free access to food and water
DLC/Artificial Lung Blood Flow

Blood Flow (l/min)

2 L/min

day 28
Artificial Lung Gas Exchange

- **Oxygen Transfer**
- **CO₂ Removal**

**Gas Exchange (ml/min)**

- 0
- 50
- 100
- 150
- 200

**Day 28**

- 125 ml/min
- 150 ml/min
Conclusion

The Avalon Elite Bicaval Double Lumen Catheter (26 F)

- 2 l/min Blood Flow
- Total CO$_2$ Removal
- Up to 190 ml/min O$_2$ Transfer
- Ambulation
Avalon Elite® Bicaval Cannula
USA release date 1/15/2009
Newborn with Meconium Aspiration on Avalon Elite® VVSDL ECMO 6 days

Blue blood out → Red blood in
Inflow jet directed toward tricuspid valve without recirculation
ECMO- Then and Now

Old Circuit: Complicated  New Circuit: Simplified
ECMO- Then and Now

VENTILATORS Impose Risk!!

• Inhibit ambulation
• Patient/ventilator dysynchrony leads to more hyperinflation and increased need for sedation
• In sepsis, ventilators incite inflammation
• In COPD, ventilators
  – lead to diaphragmatic and generalized muscle atrophy
Ventilator Pressure versus Mortality

Day 1 Plateau Pressure (cm H₂O)

Mortality Proportion

CESAR-Trial

- Randomized controlled trial of Adult ECMO versus standard management
- 766 patients screened, 180 enrolled
- 90 randomized to control and managed in local hospital
- 90 randomized to ECMO and transferred to Glenfield hospital for management
- 16% survival advantage without severe disability in the ECMO group (Mortality: 37% ECMO; 53% Conv)

Not so fast ..... 

• When only the patients placed on ECMO are compared to the control group - no survival benefit
• 5 deaths (~5%) related to transfer
• Dedicated team and capital equipment costs considerable
• Study provided ammunition for both sides of debate

Extracorporeal Membrane Oxygenation for 2009 Influenza A (H1N1) Acute Respiratory Distress Syndrome

- Observational study from 6/1 - 8/31 2009
- 68 adults placed on ECMO for influenza related ARDS (61 H1N1, 7 suspected H1N1)
- 54/68 survived to “off ECMO” (~80%)
- No published comorbidities or follow-up

Australia and New Zealand ECMO Influenza Investigators
JAMA-EXPRESS JAMA 2009;302:17
ELSO H1N1 Registry: 2010

• 72 ECMO centers
• 238 cases (293 hrs average on ECMO)
  – 128 alive (~55% survival off ECMO)
  – 79 died
• Age group
  – 144 adult
  – 87 pediatric
  – 7 neonatal
Goal: Ambulatory Paracorporeal Artificial Lung
Alert 3-3-09 Chuck Hoopes (UCSF): the first Ambulatory Lung Assist patient using Avalon Cannula, Quadrox and Centrimag!!

Total gas exchange - no recirculation
ECMO as bridge to lung Transplant
Cleveland Clinic Experience n=7

2 - non intubated resp failure (ambulatory)
5 - intubated with inadequate ventilation

6/7 lung transplant, 1/7 died on wait list

1 single, 5 double lung transplant all weaned from ECMO within 24 hrs
1 death day 26, 5 survivors 1-16 mo

Yun et al ISHLT 2010
30 Day RA-PA Sheep Trials
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Utilizing CPA Systolic Arterial Pressure (SAP) Returned to Physiological level
CPA normalized CVP and PAP immediately and throughout the two hour experiment. Total CP assistance is demonstrated by a higher PAP than CVP.