Transplantation for the Patient with Pulmonary Hypertension

*Stanford Medicine Pulmonary Hypertension Grand Rounds*

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Disclosures

- Sub investigator in clinical trial through United Therapeutics
- Otherwise no relevant financial conflicts of interest
Outline

- Challenges of Organ Transplantation for PAH
- Lung Transplant vs Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
- Perioperative management of transplant in PAH
Case Presentation
Case Presentation: HPI

- 57 yo F with a history of scleroderma, interstitial lung disease (ILD), and pulmonary arterial hypertension (PAH)
- Diagnosed with ILD after developing symptoms of dyspnea
- One year later she had hand swelling
  - Connective tissue disease serologies sent
- Diagnosed with scleroderma
- Underwent right heart catheterization and was diagnosed with PAH

Case •• Challenges •• Type •• ECMO •• Perioperative
Case Presentation: HPI

- Initially started on sildenafil, ambrisentan, lasix, spironolactone
- Clinically worsened and five years later she was started on Remodulin
- Remodulin was titrated up to 30 ng/kg/min
- Presented to UCSF from Chicago for lung transplant evaluation
Case Presentation: HPI

- Dyspnea with 50 feet
- Required 4-5 L of oxygen with exertion
Case Presentation: Physical Exam

- Vitals: Blood pressure 97/65; **Pulse 121**; Temp: 36.6 °C; RR: 20, **SpO2 90 % on 5L NC**
- PULM: **Bibasilar crackles**, moving air, **bronchial breath sounds**
- CV: **JVD elevated, RV Lift noted, Accentuated P2, 2/6 SEM**
- Ext: **2+ edema** up to knees bilaterally
Case Presentation: Labs

- WBC 4.7
- Hct 37.9
- PLT 161

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<tr>
<th>Parameter</th>
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<tr>
<td>PO2</td>
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Case Presentation: Baseline ECHO
Case Presentation: Right Heart Catheterization

Pressures:
- RA Pressure: 14
- RV Pressure: 59/2 (16)
- PA Pressure: 62/27 (41)
- PCW Pressure: 11
- PVR: 6.25 woods units

Cardiac Output:
- Fick: 4.8 L/min
- Thermodilution: 4.45 L/min

Cardiac Index
- Fick: 2.5 L/min/m²
- Thermodilution: 2.32 L/min/m²
Case Presentation: Next Steps

- Determined to be a candidate for work up
- Recommended diuresis and relocation
- Two weeks later moved to San Mateo to initiate lung transplant evaluation
- Directly admitted for IV diuresis and expedited work up
Challenges of Organ Transplantation for PAH
Outline

- Challenges of Organ Transplantation for PAH
- Lung Transplant vs Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
- Perioperative management of transplant in PAH
Lung Transplantation in PAH

- Lung transplant is a viable option in PAH to improve life expectancy and quality of life
- Double lung transplant is preferred
  - Improved outcomes when compared to single lung transplant recipients
  - Risk of recurrence of PAH after single lung transplant
- Some patients require heart-lung transplantation when they have severe RV failure or anatomical abnormalities
Lung Transplantation in PAH: Numbers

- January 2004-June 2015 ISHLT Registry had 32,237 lung transplant recipients
  - 897 of them were IPAH and 276 PH-not IPAH (3.6% of lung transplants)
- January 2004-June 2015 ISHLT Registry had 812 combined heart-lung transplant recipients
  - 222 IPAH (27.3% of combined heart-lung transplant recipients)
- Thus, 4.1% of all lung or heart-lung transplant recipients have pulmonary hypertension as primary diagnosis
Adult Lung Transplants - Kaplan-Meier Survival by Diagnosis - January 1990-June 2014

Survival (%)

- CTD (N=294)
- ILD-CTD (N=255)
- IPAH (N=1,658)
- LAM/tuberous sclerosis (N=496)
- OB (N=429)
- Sarcoidosis (N=1,222)

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Lung Transplantation in PAH: Survival

- Early survival is worse than in other diagnostic groups
  - Possibly due to increased likelihood of early complications (e.g. primary graft dysfunction)
  - Possibly due to patients being further along in disease progression relative to patients listed with other diagnoses
Lung Allocation History

- In United States donor lung allocation occurs through the Organ Procurement and Transplantation Network (OTPN)
  - Operated by United Network for Organ Sharing (UNOS)
- Prior to 2005, time on waiting list was used to determine priority
- High waiting list mortality for certain diagnoses (e.g. IPF)
In May 2005 the OPTN introduced the Lung Allocation Score (LAS)

- Calculated score by need based on clinical parameters
  - (e.g. FVC, age, 6MWD, oxygen requirements)
- Goal to maximize transplant benefit and minimize risk of wait list death
- Score ranges 0 to 100 with higher numbers representing sicker patients

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<th>25&lt;sup&gt;th&lt;/sup&gt; percentile</th>
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<tr>
<td>Current Iteration</td>
<td>33.3</td>
<td>35.5</td>
<td>39.9</td>
<td>47.2</td>
<td>85.6</td>
</tr>
</tbody>
</table>
Lung Allocation History: Kozower et al. 2008

  - Multicenter retrospective cohort from 5 academic medical centers
- LAS reduced the waiting time for transplant recipients
  - 680.9 days pre LAS vs 445.6 days post LAS; P < .001
### Lung Allocation History: Kozower et al. 2008

<table>
<thead>
<tr>
<th>Etiology of end-stage lung disease</th>
<th>Pre-LAS (n = 170)</th>
<th>LAS (n = 171)</th>
<th>P value</th>
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<tbody>
<tr>
<td>COPD</td>
<td>78 (45.9%)</td>
<td>58 (33.9%)</td>
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</tr>
<tr>
<td>Cystic fibrosis</td>
<td>39 (22.9%)</td>
<td>22 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>25 (14.7%)</td>
<td>42 (24.6%)</td>
<td>.002</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>7 (4.1%)</td>
<td>4 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21 (12.4%)</td>
<td>45 (26.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*LAS, Lung allocation score; COPD, chronic obstructive pulmonary disease.*
<table>
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<tr>
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<th>PAH</th>
<th>IPF</th>
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<tr>
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<tr>
<td>Assistance</td>
<td>Some</td>
<td>Some</td>
<td>Total</td>
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</tr>
<tr>
<td>Diabetes</td>
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<td>Oxygen Use</td>
<td>6L at rest</td>
<td>4L at rest</td>
<td>100% on VA ECMO Circuit</td>
<td>100% on tracheostomy</td>
</tr>
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<td>% FVC</td>
<td>4.45 (95% predicted)</td>
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<td>Could not obtain</td>
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<td>ECMO and ventilator and triple therapy with IV epoprostenol</td>
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| LAS Score     | 32.6076     | 39.5996     | 37.1235     | 94.3824     |
Lung Allocation History: Chen et al. 2009

- Chen et al. Am J Respir Crit Care Med 2009
- 7,952 adults listed for transplant through UNOS between 2002-2008
  - Excluded Heart-Lung Transplant listings
- Compared transplantation, waiting list mortality
Lung Allocation History: Chen et al. 2009

Case •• Challenges: Allocation •• Type •• ECMO •• Perioperative
Lung Allocation History: Chen et al. 2009

Idiopathic pulmonary arterial hypertension (solid line).
Idiopathic pulmonary fibrosis (dashed line).
Chronic obstructive pulmonary disease (gray line).
Cystic fibrosis (dotted line).
Lung Allocation History: Chen et al. 2009

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Case •• Challenges: Allocation •• Type •• ECMO •• Perioperative
Lung Allocation History: Chen et al. 2009

- Likelihood of transplantation improved for all diagnosis after LAS implementation
- IPAH was the only diagnosis for which wait list mortality did not improve
Lung Allocation History: Exceptions

- In 2006 UNOS started sending out letters to programs for PAH exception
  - Candidates with pulmonary hypertension who are deteriorating on optimal therapy AND have RAP >15 mmHg or CI <1.8 L/min/m²
  - Placed at 90\textsuperscript{th} percentile of National Average

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Lung Allocation History: Exceptions

- Many programs started asking for exceptions to get higher score for patients
- Willie et al. J Heart Lung Transplant. 2017 reviewed all exception requests between 2006-2014
  - PAH is the most common diagnostic category for which requests are made
  - Demonstrated more frequent exception requests over time
  - 22 PAH requests in 2006 rose to 118 PAH requests in 2014
Lung Allocation History: Schaffer et al. 2013

- Schaffer JM et al. Circulation 2013
- 1430 adults listed for lung alone or heart-lung transplant for IPAH
  - 80 months before and after implementation of LAS
  - Analyzed data through 2011 (three years after Chen et al.)
- Evaluated in a competing-outcomes analysis the cumulative incidence of transplantation and mortality on waitlist
- Also evaluated post transplant survival
Lung Transplants

Heart-Lung Transplants

Case • Challenges: Allocation • Type • ECMO • Perioperative

UCSF
Lung Allocation History: Schaffer et al. 2013

Case •• Challenges: Allocation •• Type •• ECMO •• Perioperative

Lung Transplant

Heart-Lung Transplant

P=0.04, by Wilcoxon test
- Received double lung transplant, pre-LAS era (DLTPRE)
- Received double lung transplant, post-LAS era (DLTPOS)

P=0.52, by Wilcoxon test
- Received heart-lung transplant, pre-LAS era (HLTPRE)
- Received heart-lung transplant, post-LAS era (HLTPOS)
Lung Allocation History: Schaffer et al. 2013

- Incidence of transplantation has increased after LAS for IPAH
- Wait list mortality has now decreased in patients with IPAH after LAS
  - Later time period than Chen et al.
- Despite transplantation of a sicker cohort of patients (based on need) early post-transplant survival has improved
Can LAS be modified? Benza et al. 2010

- Benza et al. Transplantation 2010
- 2327 Patients in REVEAL registry
- Compared predicted mortality by LAS to observed mortality in REVEAL
- Sought to identify key parameters independently associated with death
  - Identified 6MWD and mean right atrial pressure (mRAP)
- Created alternative LAS using 6MWD and mRAP
Can LAS be modified? Benza et al. 2010

Case •• Challenges: Allocation •• Type •• ECMO •• Perioperative
Can LAS be modified? Benza et al. 2010
Can LAS be modified? Gomberg-Maitland et al. 2013

- Gomberg-Maitland et al. J Heart Lung Transplant 2013
  - Created a new equation using 6MWD, cardiac output and resting O2 requirement
  - Outperformed LAS to predict 1 year survival
2015 LAS Revision

- Revision to LAS was made on February 19, 2015
  - Now used Cardiac Index and CVP in algorithm
    - Previous collected but not used
  - Total Bilirubin was added to algorithm
  - Adjusted 6MWD cut offs for impact on score

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| LAS Score | 32.607 | 37.1235 | 39.5996 | 94.3824 |
| LAS Score after revision | 43.6503 | 36.7965 | 76.4832 | 89.2568 |
Challenges in Transplant for PAH: HRQL

Table 5: Effect of lung transplantation on HRQL by disease category

<table>
<thead>
<tr>
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<th>Early change</th>
<th>Test of difference</th>
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<tr>
<td>SF12-PCS (MCID = 5)</td>
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<tr>
<td>Group A (COPD)</td>
<td>15.9 (11.5, 20.3)</td>
<td>p &lt; 0.001</td>
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<td>Group B (PAH)</td>
<td>7.9 (1.0, 14.7)</td>
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<tr>
<td>Group C (CF)</td>
<td>23.8 (19.5, 28.1)</td>
<td></td>
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<tr>
<td>Group D (PF)</td>
<td>13.8 (11.9, 15.8)</td>
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<tr>
<td>SF12-MCS (MCID = 5)</td>
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<tr>
<td>Group A (COPD)</td>
<td>2.7 (−0.9, 6.4)</td>
<td>p = 0.020</td>
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<tr>
<td>Group B (PAH)</td>
<td>0.1 (−5.6, 5.7)</td>
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<td>Group C (CF)</td>
<td>10.3 (6.4, 14.1)</td>
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<td>Group D (PF)</td>
<td>4.8 (3.1, 6.6)</td>
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<td>AQ26-R (MCID = 1.75)</td>
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<td>Group A (COPD)</td>
<td>7.7 (6.4, 9.1)</td>
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<td>Group B (PAH)</td>
<td>4.5 (2.1, 6.9)</td>
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<td>Group C (CF)</td>
<td>9.4 (8.2, 10.5)</td>
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<td>Group D (PF)</td>
<td>7.9 (7.3, 8.6)</td>
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<td>EQ6D (MCID = 0.66)</td>
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<tr>
<td>Group A (COPD)</td>
<td>0.16 (0.09, 0.21)</td>
<td>p = 0.003</td>
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<td>Group B (PAH)</td>
<td>0.04 (−0.05, 0.19)</td>
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<tr>
<td>Group C (CF)</td>
<td>0.30 (0.22, 0.39)</td>
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</tr>
<tr>
<td>Group D (PF)</td>
<td>0.16 (0.13, 0.19)</td>
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<td>EQVAT (MCID = 10)</td>
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<td>Group A (COPD)</td>
<td>23.3 (16.2, 30.5)</td>
<td>p = 0.003</td>
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<tr>
<td>Group B (PAH)</td>
<td>18.4 (2.6, 34.2)</td>
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<tr>
<td>Group C (CF)</td>
<td>43.0 (36.8, 49.3)</td>
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<td>Group D (PF)</td>
<td>30.8 (27.4, 34.3)</td>
<td></td>
</tr>
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Singer LG et al. Am J Respir Crit Care Med 2015

Lung Transplant vs Heart-Lung Transplant
Outline

- Challenges of Organ Transplantation for PAH
- Lung Transplant vs Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
- Perioperative management of transplant in PAH
Case Presentation

- Patient admitted to hospital and initiated on IV diuresis, TAPSE was 1.2 cm
- Remodulin increased to 32 ng/kg/min
- Sildenafil increased to 80 mg TID
- Repeat ECHO demonstrates TAPSE down to 0.9 cm

- Faced with decision: Which organ transplant should she be offered?
Type of Organ Transplant: Single vs Double

- 15 PAH lung transplant recipients at Johns Hopkins
Type of Organ Transplant: Single vs Double

- Consensus became that double lung transplantation was preferred to single
  - Risk of recurrence of PAH
  - Better long term outcomes
Type of Organ Transplant: SLT vs DLT vs HLT

- 59 PAH patients undergoing transplant at Pittsburgh
Challenges of Organ Transplantation in PAH: Allocation

Lung Transplants Over Time

Heart-Lung Transplants Over Time

- Bilateral
- Single Lung
Type of Organ Transplant: Lung vs Heart-Lung

  - Paris-Sud University, Paris, France
  - 219 patients
- Decision for Heart-Lung when
  - Systemic to Pulmonary Shunts or RV failure
  - Severe RV enlargement
  - Cardiac index lower than 2.2 L/min/m²
  - Preoperative renal failure
Type of Organ Transplant: Lung vs Heart-Lung

![Graph showing survival rates over months for HLT and DLT with p-value of 0.458]
Type of Organ Transplant: Lung vs Heart-Lung

- 79 patients with Pulmonary Hypertension in Toronto
Type of Organ Transplant: Lung vs Heart-Lung

- Historical Studies demonstrated survival benefit of double lung transplant over combined heart-lung transplant
- Not seen in more contemporary studies
Type of Organ Transplant: Lung vs Heart-Lung

- 2014 ISHLT Consensus Document for Selection of lung transplant recipients
  - "Irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH are considered for heart-lung transplantation"
  - "In the absence of objective assessment of infarcts or fibrotic changes of the right ventricle, heart-lung transplantation is usually not indicated"
Case Presentation

- Repeat ECHO demonstrates TAPSE down to 0.9 cm
  - How to tell if reversible myocardial dysfunction?
- Performed Dobutamine ECHO
  - RV function improved and TAPSE went up to 1.6 cm with dobutamine
- Patient listed for Lung Transplant
Case Presentation

- Patient becomes hypotensive and requires initiation of dobutamine
- Worsening hypotension, patient started on epinephrine
- Despite dobutamine and epinephrine RV function continued to decline
  - Repeat ECHO had TAPSE 0.8 cm
Case Presentation: ECHO on Dobutamine/Epi
Case Presentation

- Decision to list for heart-lung transplant
  - Removed from lung transplant waiting list
- Patient deteriorates further and becomes more hypoxemia and hypotensive

- Faced with decision: How to support the patient further?
Use of ECMO in Patients with PAH
Outline

- Challenges of Organ Transplantation for PAH
- Lung Transplant vs Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
- Perioperative management of transplant in PAH
Extracorporeal Membrane Oxygenation

- Device which pumps blood out of body through an oxygenator and then back into the body
  - Takes oxygen-poor blood and converts it to oxygen-rich blood
  - Acts as a pump to improve circulation
  - Scavenges carbon dioxide
ECMO Strategy: Sorokin V. et al. 2017

- Sorokin V. et al. Eur J Heart Fail 2017 reviewed Extracorporeal Life Support Organization Registry
Veno-venous ECMO

Venous blood comes out of body

Passed through oxygenator

Entered back into body in venous system
Extracorporeal Membrane Oxygenation: Peripheral VV

- **Pro:**
  - Less bleeding risk
  - Low stroke risk
  - Can detect improvements by monitoring ABG

- **Con:**
  - Venous stasis from two cannulas in the IVC
  - Limits mobility
  - Limited use in PAH
Venous blood comes out of SVC and IVC.

Passes through oxygenator.

Entered back into body through port directed to tricuspid valve.

Avalon Catheter ECMO
Extracorporeal Membrane Oxygenation: Avalon

- **Pro:**
  - Allows for mobilization
  - Circulation through natural pattern

- **Con:**
  - No cardiac support
  - Limited use in PAH

Case •• Challenges •• Type •• ECMO •• Perioperative
Veno-arterial ECMO

Venous blood comes out of body via femoral vein

Passes through oxygenator

Entered back into body in femoral artery
Extracorporeal Membrane Oxygenation: Peripheral VA

**Pro:**
- Allows for cardiac support via arterial system
- No problem with overwhelming the RV

**Con:**
- Limits Mobility
- Impaired venous return from contralateral leg
- Higher risk of stroke than VV ECMO
- Harlequin Syndrome from unequal arterial oxygenation
  - Most deoxygenated blood goes to coronaries and cerebral flow

Case Challenges Type ECMO Perioperative
Central Veno-arterial ECMO

Venous blood comes out of Right Atrium

Passes through oxygenator

Entered back into body via aorta
Extracorporeal Membrane Oxygenation: Central VA

- **Pro:**
  - Very effective mode of ECMO
  - No Harlequin Syndrome
  - Can mobilize
  - Can be used if peripheral arteries diseased

- **Con:**
  - Higher risk of complications from bleeding/infection
  - Have to leave chest open
  - Higher risk of stroke
Venous blood comes out of Right Atrium
Passes through oxygenator
Entered back into body via pulmonary artery
Venous blood comes out of Right Atrium
Extracorporeal Membrane Oxygenation: ProtekDuo

- **Pro:**
  - Can mobilize in patients with RV failure
  - More physiologic circulation
  - Acts as RV Assist Device

- **Con:**
  - High rates of hemolysis
  - Can flip into RV if cannula is too short
  - Very complex placement
Extracorporeal Membrane Oxygenation: Center Practice

- Generally prefer Avalon (dual lumen VV) in all patients
  - Do not use in PAH
- Typically use VA ECMO in patients with PAH
- Have tried the Protek catheter a few times but have had limited success
Other Bridging Techniques

- Novalung – pumpless ECMO, not approved by FDA
- Atrial Septostomy
  - Creation of inter-atrial right-to-left shunt
- Transcatheter Potts Shunt
  - Connect the left pulmonary artery to the descending aorta

Corris & Degano Eur Respir Rev. 2014
Case Presentation

- Patient deteriorates further and becomes more hypoxemia and hypotensive while on dobutamine and epinephrine
- Decision to place patient on VA ECMO
- Patient gets offer for Heart-Lung Transplantation
Perioperative Management of PAH Undergoing Lung Transplant
Outline

- Challenges of Organ Transplantation for PAH
- Lung Transplant vs Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
- Perioperative management of transplant in PAH
Perioperative Management: General Principles

- Patients with PAH are susceptible to hypotension and cardiac arrest during transplant surgery
  - Anesthetic drugs reduce sympathetic tone
  - Positive pressure ventilation alters venous return
  - Mobilization of lungs can impair venous return
- Risk factors for hemodynamic compromise
  - History of syncope, NYHA Class IV, low 6MWD, RV failure

Castillo M. Curr Opin Anaesthesiol. 2011
Schlisler T. Semin Cardiothorac Vasc Anesth. 2017
Perioperative Management: Induction

- Induction is high risk for hemodynamic compromise
  - Venodilation by anesthesia
  - Reduced venous return by positive pressure ventilation
  - Reduced RV stroke volume by paralysis

Case Challenges Type ECMO Perioperative
Perioperative Management: Induction

- Tools for management
  - Vasoactive drugs on standby
  - Rapid Sequence Intubation
  - Prophylactic awake ECMO
    - First described in 2001 in case series of thoracic organ transplants

Reference:
- de Boer WJ. Ann Thorac Surg. 2001
- Schlisler T. Semin Cardiothorac Vasc Anesth. 2017
Perioperative Management: Intraoperative

- Patients converted to central ECMO during procedure
- Intraoperative monitoring with TEE
- Can utilize iNO during procedure to decrease pulmonary artery pressure
  - Some centers use milrinone or inhaled prostacycline
Perioperative Management: Primary Graft Dysfunction

- After anastamosis the lung is inflated and PA clamp is released
- Reperfusion injury can occur – Primary Graft Dysfunction
  - Impaired gas exchange, increased capillary permeability
  - Worsened by loss of lymphatic drainage

Diamond JM. et al. Am J Respir Crit Care Med 2013
Perioperative Management: Primary Graft Dysfunction

- Primary Graft Dysfunction has long term effects
  - Increased duration of mechanical ventilation
  - Longer ICU Stay time
  - Increased risk of BOS
  - Increased risk of mortality in first year

Diamond JM. et al. Am J Respir Crit Care Med 2013
Perioperative Management: Primary Graft Dysfunction

Diamond JM. et al. Am J Respir Crit Care Med 2013
Perioperative Management: ICU Care Post Surgery

- When PGD is occurring
  - Typically utilize low volume ventilation to minimize further barotrauma
  - Diuresis to help keep lungs less edematous
- Standard ICU Care
  - Typically utilize dobutamine and iNO
  - Wean off as patient tolerates
Case Presentation

- Patient undergoes combined Heart-Lung Transplant
- Three weeks later she was discharged from hospital
- 6/20/2017: Patient was just seen in clinic and continues to do well
Summary

- Challenges of Organ Transplantation for PAH
  - PAH patients negatively impacted by LAS
  - Hopefully improving after 2015 revision
- Lung Transplant vs Heart-Lung Transplant
  - Prefer double lung transplant
  - Selected patients undergo combined Heart-Lung Transplant
- Deploying ECMO in the setting of PAH
  - VA ECMO is means of choice
  - ProtekDuo is conceptually ideal, more experience needed
- Perioperative management of PAH
  - Minimizing risks
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