Evolution of Surgical Therapies for End-Stage Cardiopulmonary Failure

Heart Failure at the Shoe XI
October 5, 2012

Robert S.D. Higgins, MD, MSHA
Executive Director, Comprehensive Transplant Center

Improving People's Lives
through innovations in personalized health care
Evolution of Surgical Therapies for Cardiopulmonary Failure

- Since 1900, therapies to treat cardiac and pulmonary failure have been evolving to address a critical problem.

- Alexis Carrel, Nobel laureate in 1912, performed heart and lung transplants in the dog (1907).

- In 1951, Demikhov performed successful heart-lung transplants in the dog.

- Clinical heart-lung transplantation began in 1981 with the advent of cyclosporine immunosuppression in a patient with primary pulmonary hypertension.
Transplant History

Fantastic Firsts in Our field

Source: www.UNOS.org
Development of Heart Transplantation

Figure 1–8. Norman Shumway, regarded by most investigators as the major contributor to successful heart transplantation, is shown here in 1968, soon after his initial human heart transplant procedure.

Figure 1–5. Principals in the experimental laboratory at Stanford University in 1960. Norman Shumway (left), Richard Lower (right), and Raymond Strofer (right lower) with a long-term surviving dog heart transplant patient.

reality at the University of Capetown in South Africa.
Figure 12–8. The implantation procedure is begun with the left atrial anastomosis.
Louis Washkansky, recipient of the historic transplant, smiles after regaining consciousness.
Heart Transplantation

A HUMAN CARDIAC TRANSPLANT: AN INTERIM REPORT OF A SUCCESSFUL OPERATION PERFORMED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN

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On 3 December 1967, a heart from a cadaver was successfully transplanted into a 54-year-old man to replace a heart irreparably damaged by repeated myocardial infarction.

As soon as it had become obvious that, despite therapy, death was imminent in the donor, the recipient was anaesthetized and the saphenous vein and common femoral
TRANSPLANTATION - Quality and Quantity of LIFE
Why Start Over?
“ I can’t catch my breath”

- 58 year old woman with progressive Dyspnea and shortness of breath
- FEV1<25% of predicted
- Supplemental Oxygen, steroids
- Secondary osteoporosis, infections
- Underwent right lung transplant- October 1994
- Survived 11 years off oxygen
Who will benefit?

**Chronic respiratory illness-Burden of Disease**

- Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease that interferes with normal breathing – it is more than a “smoker’s cough”.
- An estimated 64 million people have COPD worldwide in 2004.¹
- More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year.
- Almost 90% of COPD deaths occur in low- and middle-income countries.
- The primary cause of COPD is tobacco smoke (through tobacco use or second-hand smoke).
- COPD is not curable, but treatment can slow the progress of the disease.
- Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke.
Disease-Specific Classification of End Stage Lung Disease

- Group A – obstructive pulmonary disease (COPD, Emphysema, α-1-antitrypsin)
- Group B - pulmonary vascular disease (PPH, Eisenmenger’s disease)
- Group C – immunodeficiency disorder (cystic fibrosis, hypogammaglobulinemia)
- Group D – restrictive lung disease (IPF, sarcoidosis)
Other Chronic Respiratory Illnesses

- Bronchiectasis
- Pulmonary hypertension
- Cystic Fibrosis

Inflammatory lung disease
- sarcoidosis
- idiopathic pulmonary fibrosis
- bronchiolitis obliterans
- histiocytosis X
- chronic eosinophilic pneumonia
- collagen vascular disease
- granulomatous vasculitis
- Goodpasture's syndrome
- pulmonary alveolar proteinosis
How Can We Make it Work?  
Lung Transplantation 2012

Program requirements

- Physician/surgeon experience
- Multidisciplinary team including nursing, respiratory, ID, critical care, social work, coordinators, anesthesia, pharmacy
- Institutional commitment
- Administrative leadership
- OPO relationship and support
- Quality assurance/Process improvement program
<table>
<thead>
<tr>
<th>Rank</th>
<th>Center</th>
<th>2009 Volume</th>
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<tbody>
<tr>
<td>0</td>
<td>All Lung Centers (n=152)</td>
<td>1599</td>
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<tr>
<td>1</td>
<td>OHCC-TX1 Cleveland Clinic Foundation</td>
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<tr>
<td>2</td>
<td>PAPT-TX1 Univ of Pittsburgh Med Ctr</td>
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<td>4</td>
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<td>5</td>
<td>MOBH-TX1 Barnes-Jewish Hospital</td>
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<td>6</td>
<td>NYCP-TX1 New York-Presbyterian/Columbia</td>
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<td>7</td>
<td>CAUC-TX1 UCLA Medical Center</td>
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<td>8</td>
<td>PAUP-TX1 The Hosp of the Univ of PA</td>
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<td>9</td>
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<td>10</td>
<td>FLSL-TX1 Mayo Clinic Florida</td>
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<td>11</td>
<td>ILLU-TX1 Loyola Univ Med Center</td>
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<td>12</td>
<td>FLTG-TX1 Tampa General Hospital</td>
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<td>13</td>
<td>CASU-TX1 Stanford Univ Med Ctr</td>
<td>37</td>
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<td>14</td>
<td>WIUW-TX1 Univ of Wisconsin Hosp and Clinics</td>
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<td>15</td>
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<td>16</td>
<td>MIUM-TX1 Univ of Michigan Med Ctr</td>
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<tr>
<td>17</td>
<td>MDUM-TX1 Univ of Maryland Med System</td>
<td>34</td>
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<td>18</td>
<td>CASF-TX1 Univ of CA San Francisco Med Ctr</td>
<td>32</td>
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<td>19</td>
<td>FLUF-TX1 Shands Hosp at Univ of FL</td>
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<tr>
<td>20</td>
<td>MAPB-TX1 Brigham and Womens Hosp</td>
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<td>54</td>
<td>OHUH-TX1 University Hosp of Cleveland</td>
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<tr>
<td>58</td>
<td>OHCH-TX1 Nationwide Childrens Hospital</td>
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<tr>
<td>59</td>
<td>OHOU-TX1 Ohio State Univ Med Ctr</td>
<td>2</td>
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</table>
ADULT LUNG TRANSPLANTATION: Indications for Single Lung Transplants
(Transplants: January 1995 - June 2010)

*Other includes:
- Pulmonary Fibrosis, Other: 3.4%
- Sarcoidosis: 1.9%
- Bronchiectasis: 0.4%
- Congenital Heart Disease: 0.3%
- LAM: 0.8%
- Connective Tissue Disease: 1.0%
- OB (non-ReTx): 0.6%
- Miscellaneous: 0.9%
ADULT LUNG TRANSPLANTATION: Indications for Bilateral/Double Lung Transplants
(Transplants: January 1995 - June 2010)

*Other includes:
- Pulmonary Fibrosis, Other: 2.9%
- Sarcoidosis: 3.0%
- Bronchiectasis: 4.4%
- Congenital Heart Disease: 1.2%
- LAM: 1.1%
- Connective Tissue Disease: 1.3%
- OB (non-ReTx): 1.3%
- Miscellaneous: 1.7%

**ISHLT**

*J Heart Lung Transplant. 2011 Oct; 30 (10): 1071-1132*
Contraindications

- Age >70
- Obesity (BMI >35) or severe malnutrition
- Current tobacco, alcohol, or illicit drug abuse
- Active or recent malignancy
- AIDS
- Pulmonary hypertension (fixed)
- Severe end-organ complications from diabetes mellitus
- Major chronic debilitating illness (COPD, neurologic disorders)
- Severe peripheral vascular disease
- Social issues (lack of support)
- Medical non-compliance
Therapeutic Options

- Lung Volume reduction
- Pulmonary Thromboendarterectomy
  - Atrial septostomy
- Medical alternatives
  - Pulmonary Vasodilators
  - Palliative Care
A Randomized Trial Comparing Lung-Volume-Reduction Surgery with Medical Therapy for Severe Emphysema

N Engl J Med
Volume 348;21:2059-2073
May 22, 2003
Table 2. Mortality among All Patients and in Subgroups.†

<table>
<thead>
<tr>
<th>Patients</th>
<th>90-Day Mortality</th>
<th>Total Mortality</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Surgery Group</td>
<td>Medical-Therapy Group</td>
</tr>
<tr>
<td></td>
<td>no. of deaths/total no. (% [95% CI])</td>
<td>no. of deaths/total no. (% [95% CI])</td>
</tr>
<tr>
<td>All patients</td>
<td>48/608 (7.9 [5.9–10.3])</td>
<td>8/610 (1.3 [0.6–2.6])</td>
</tr>
<tr>
<td>High-risk†</td>
<td>20/770 (26.6 [18.4–40.6])</td>
<td>0/770 (0 [0–3.1])</td>
</tr>
<tr>
<td>Other</td>
<td>28/538 (5.3 [3.3–7.4])</td>
<td>8/540 (1.5 [0.6–2.9])</td>
</tr>
</tbody>
</table>

Subgroups‡:
- Patients with predominantly upper-lobe emphysema
  - Low exercise capacity: 4/139 (2.9 [1.8–7.2]) vs 5/151 (3.3 [1.1–7.6])
  - High exercise capacity: 2/206 (1.0 [0.1–3.4])
- Patients with predominantly non-upper-lobe emphysema
  - Low exercise capacity: 7/119 (6.3 [3.4–16.4]) vs 0/63 (0 [0–5.5])
  - High exercise capacity: 11/110 (10.0 [5.1–17.3]) vs 1/111 (0.9 [0.02–4.9])

† Mortality was measured from the date of randomization in both treatment groups. Total mortality rates are based on a mean follow-up of 29.2 months. P values were calculated by Fisher’s exact test. Risk ratios are for the risk in the surgery group as compared with the risk in the medical-therapy group. A low baseline exercise capacity was defined as a postrehabilitation baseline maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men); a high-exercise capacity was defined as a workload above this threshold. CI denotes confidence interval.

‡ High-risk patients were defined as those with a forced expiratory volume in one second (FEV₁) that was 20 percent or less of the predicted value and either homogeneous or heterogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value.

§ High-risk patients were excluded from the subgroup analyses. For total mortality, P for interaction=0.004; this P value was derived from binary logistic regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the base-line FEV₁, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation in one minute to carbon dioxide excretion in one minute, distribution of emphysema (homogeneous vs. heterogeneous), perfusion ratio, score for health-related quality of life, and Quality of Well-Being score; age, race or ethnic group, and sex.
Conclusion

- Overall, lung-volume-reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy.
- It does yield a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity.
- Patients previously reported to be at high risk and those with non-upper-lobe emphysema and high base-line exercise capacity are poor candidates for lung-volume-reduction surgery, because of increased mortality and negligible functional gain.
Surgical Options

Lung Volume Reduction

- Complications
  - Prolonged air leakage is the most common complication after LVRS. Approximately 40% of patients will have this problem. Some patients will actually go home with a chest drain in place for a few days to help manage this.
  - Pneumonia (15%) can occur in emphysema patients, especially in patients who have a history of recurrent bouts
  - Bleeding (2-5%)
  - Stroke (<1%)
  - Heart attack (1%)
  - Death: The chance of dying after LVRS is approximately 3-8%
## World Health Organization (WHO) functional classification for pulmonary hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>WHO functional classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.</td>
</tr>
</tbody>
</table>

### Characteristics of medications used in the treatment of pulmonary hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose range, adult</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol*</td>
<td>Continuous IV</td>
<td>1 to 20 ng/kg/min</td>
<td>3 to 5 min</td>
</tr>
<tr>
<td>Treprostinil*</td>
<td>Continuous SC/IV</td>
<td>0.625 to 1.25 ng/kg/min</td>
<td>4 to 5 hr</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Inhaled</td>
<td>2.5 to 5 mcg, 6 to 9 times/day</td>
<td>1 to 2 hr</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Inhaled</td>
<td>6-13 mcg, 4 times daily</td>
<td>4 hr</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Oral</td>
<td>62.5 to 125 mg, 2 times/day</td>
<td>5 hr</td>
</tr>
<tr>
<td>Ambrisertan</td>
<td>Oral</td>
<td>5 to 10 mg/day</td>
<td>9 hr</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Oral</td>
<td>20 mg, 3 times/day</td>
<td>4 hr</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Oral</td>
<td>40 mg/day</td>
<td>35 hr</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>Oral</td>
<td>30 to 240 mg/day</td>
<td>2 to 5 hr</td>
</tr>
<tr>
<td>Diltiazem*</td>
<td>Oral</td>
<td>120 to 900 mg/day</td>
<td>2 to 4.5 hr</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Oral</td>
<td>2.5 to 20 mg/day</td>
<td>30 to 50 hr</td>
</tr>
</tbody>
</table>

* The dose range shown is for a short-term infusion; higher doses are required for long-term infusions (range often exceeds 100 to 150 ng per kg per minute).
* The half-life shown refers to immediate-release preparations; however, sustained-release preparations that can be administered once daily are available and preferred for maintenance.
Mean change (±SE) in six-minute walking distance from baseline to week 16 in the placebo and bosentan groups

![Graph showing changes in six-minute walking distance over weeks for placebo and different bosentan doses.]

P<0.01 for the comparison between the 125-mg dose of bosentan and placebo, and P<0.001 for the comparison between the 250-mg dose and placebo by the Mann-Whitney U test. There was no significant difference between the two bosentan groups (P=0.18 by the Mann-Whitney U test).

Primary Pulmonary Hypertension

Atrial Septostomy

- performed in some patients with syncope or severe right heart failure in an attempt to increase systemic blood flow by bypassing the pulmonary vascular obstruction
- The right-to-left shunting and consequent arterial desaturation offset in some patients by increased cardiac output and augmentation of systemic oxygen delivery by up to 27 percent
- procedure-related mortality may be as high as 15 to 20 percent It is difficult to predict which patients will benefit and which will deteriorate after this therapy.
- considered in individuals with refractory severe pulmonary arterial hypertension (PAH) and right heart failure; it may also be considered in patients who have signs of impaired systemic blood flow (such as syncope) due to reduced left heart filling. Stepwise balloon dilatation is the procedure of choice
- Patients with the most advanced PAH appear more likely to die or get worse with atrial septostomy
Pioneering Lung Transplant

FIGURE 1.10 - Joel Cooper led the Toronto Lung Transplant Team that began single-lung transplantation in the cyclosporine era. His work emphasized the need for bronchial revascularization with omentum. He later established Washington University in St. Louis as a major lung transplantation center.
Lung Transplantation

Guidelines when to refer a patient for transplant evaluation are as follows:

- **World Health Organization (WHO) functional class III or IV**
- **Mean right atrial pressure >10 mmHg**
- **Mean pulmonary arterial pressure >50 mmHg**
- **Cardiac index <2.5 L/min per m²**
- **Failure to improve functionally despite medical therapy**
- **Rapidly progressive disease**

**Figure 9.1** - Management of primary pulmonary hypertension. PGI₂, prostacyclin (epoprostenol); GBDAS, graded balloon dilatation atrial septostomy.
Lung Allocation Score (LAS) – introduced in 2005

Depends on many factors including probability of survival in the next year without a transplant, how long that survival would be, the probability of survival following a transplant, and the projected length of survival post-transplant. The patient data points that are included are below:

Attention: The lung allocation score may change on a daily basis due to age. The actual lung allocation score provided to a candidate is calculated by UNet\textsuperscript{SM} based solely on the data that is entered by the transplant center. The score produced by the LAS Calculator on this website is for your informational use only.
The Transplant Procedure

- Single lung ventilation
- Clamshell vs bilateral sequential incision
- Bronchus, Pulmonary artery, Left atrial anastomosis
- Reperfusion
- Positive pressure ventilation
- Bronchoscopy
Organ Perfusion Systems

OCS Cardiac resuscitation system
High-risk donor lungs can now be safely used for transplant due to the Toronto XVIVO Lung Perfusion System

- September 2008 to January 2010, 136 lung transplants were performed
- Toronto technique maintains donor lungs at a normal body temperature of 37 degrees Celsius, allowing for future organ repair and gene and cell therapy
- Twenty (20) high-risk donor lungs with impaired function and chest x-ray, abnormalities, which were treated and tested for four hours with the Toronto XVIVO Lung Perfusion System were transplanted
- Equivalent outcomes - 30-day mortality, ICU and hospital stay and length of mechanical ventilation.
During the study period from September 2008 to January 2010, 136 lung transplants were performed. Twenty (20) high-risk donor lungs with impaired function and chest x-ray abnormalities, which were treated and tested for 30 different antigens, were explanted and perfused with the Toronto XVIVO Lung Perfusion System. Donor lungs were chosen sequentially, via usual criteria such as blood type and size of the organ, and consented to the study protocol. The major endpoint was primary graft dysfunction (acute lung injury after transplantation), which is defined as ARDS or moderate to severe dyspnea. Patients with primary graft dysfunction 72 hours after transplant have more complications, higher organ rejection and mortality rates.
NUMBER OF LUNG TRANSPLANTS REPORTED
BY YEAR AND PROCEDURE TYPE

NOTE: This figure includes only the lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide.

ISHLT 2011

LUNG TRANSPLANTS:
Transplant Recipient Age by Year of Transplant
Transplants: January 1, 1987 – June 30, 2010

[Bar chart showing age distribution for lung transplant recipients from 1987 to 2009.]

ISHLT
2011

J. Heart Lung Transplant. 2011 Oct; 30 (10): 1071-1132
Thoracic Transplantation

Complications - Early
- Primary graft dysfunction
- Bronchial complications

Late
- Infection
- Rejection (acute and chronic)
- Cancer
  - solid tumors
  - lymphoma
ADULT LUNG TRANSPLANT RECIPIENTS:
Relative Incidence of Leading Causes of Death
(Deaths: January 1992 - June 2010)

- Bronchiolitis
- Infection (non-CMV)
- Malignancy (non-Lymph/PTLD)
- Graft Failure
- Cardiovascular

Lung function after Transplantation

Fig 2. Comparing the (A) peak forced expiratory volume in 1 second (FEV₁) and (B) peak percent-predicted FEV₁ values for patients with extracorporeal membrane oxygenation (ECMO) and without ECMO (No ECMO) demonstrates a significant decrement in allograft spirometric values. The error bars show the standard error of the mean.
Figure 1 Cut-points on the donor bronchus

(a) The donor bronchus should be cut back as close to the upper lobe bronchus origin as possible in an oblique plane with special attention to keep peribronchial tissues undisturbed; (b) if donor bronchus is cut at this level, there will be a risk zone for bronchial ischemia (gray zone). Reproduced with permission from [27*].
Bronchiolitis Obliterans (BOS)

- Progressive fibrosing process of airways and vasculature secondary to rejection
BOS Therapy

Therapeutic options for bronchiolitis obliterans following lung transplantation

- High dose parenteral corticosteroids
- Azithromycin
- Cytolytic therapy: OKT3, MALG, ATG
- Substitution of Tacrolimus (FK506) for cyclosporine
- Inhaled cyclosporine
- Total lymphoid irradiation
- Plasmapheresis
- Photopheresis
- Retransplantation
### ADULT LUNG TRANSPLANTATION

Kaplan-Meier Survival By Diagnosis Conditional on Survival to 1 Year (Transplants: January 1990 – June 2005)

<table>
<thead>
<tr>
<th>Year</th>
<th>ALPHA-1 (N=1,343)</th>
<th>CF (N=2,178)</th>
<th>COPD (N=5,378)</th>
<th>IPF (N=2,178)</th>
<th>PPH (N=573)</th>
<th>SARCOIDOSIS (273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100.0</td>
<td>99.9</td>
<td>100.0</td>
<td>100.0</td>
<td>99.8</td>
<td>100.0</td>
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<td>3</td>
<td>81.7</td>
<td>80.3</td>
<td>78.5</td>
<td>78.7</td>
<td>84.5</td>
<td>80.4</td>
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<td>67.5</td>
<td>60.1</td>
<td>61.4</td>
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<td>71.8</td>
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<td>7</td>
<td>55.9</td>
<td>57.9</td>
<td>44.4</td>
<td>46.6</td>
<td>60.5</td>
<td>62.9</td>
</tr>
<tr>
<td>10</td>
<td>40.1</td>
<td>45.0</td>
<td>25.2</td>
<td>27.4</td>
<td>43.2</td>
<td>48.9</td>
</tr>
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</table>

**Survival comparisons**
- Alpha-1 vs. IPF: p < 0.0001
- CF vs. COPD: p < 0.0001
- PPH vs. COPD: p < 0.0001
- COPD vs. Sarcoidosis: p < 0.0001

**Alpha-1 vs. COPD**: p < 0.0001
**CF vs. IPF**: p < 0.0001
**PPH vs. IPF**: p < 0.0001
**COPD vs. Sarcoidosis**: p = 0.0002

**Note:** Other comparisons are not statistically different.

*ISHLT 2007*

J Heart Lung Transplant 2007,26: 782-795
Evolving therapies for Cardiopulmonary Failure

- Innovative therapies have been the foundation for the treatment of end stage cardiopulmonary failure.
- Optimization of reversible pulmonary hypertension utilizing pulmonary vasodilators offers the best promise for long term improvements in quality of life and survival until a renewable donor pool can be developed.
- Extended criteria donors may be on the horizon with innovative ex-vivo perfusion and resuscitation techniques.