Transplant Cardiology 2013

Paul Rosenberg, MD
Heart Failure Symposium
DUMC
October, 5 2013
Historical Perspective on Heart Transplant

- **1960**: Surgical technique of heart transplantation pioneered by Normand Shumway
- **1967**: Christiaan Barnard performs the first human to human heart transplantation
- **1969**: Denten Cooley uses first total artificial heart as a bridge to transplant
- **1973**: Philip Caves develops technique of endomyocardial biopsy. Margaret Billingham develops a system for reading specimens
- **1983**: Cyclosporine approved by the FDA
- **1984**: First successful use of a ventricular assist device
- **1991**: Sievers develops the bivacaval technique for orthotopic heart transplantation
- **1990s**: Introduction of MMF and tacrolimus
- **Late 1990s**: Trials with sirolimus and everolimus. Introduced clinically early 2000 (everolimus not yet FDA approved in the USA)
- **Expected Advances**: Expected advances in organ preservation, immune monitoring, and immunosuppression

- **1960s**: 1 week
- **1970s**: 1 year
- **1980s**: 5 years
- **1990s**: 9.5 years
- **2000**: 10.3 years

Time to 50% Survival
• Improve late allograft outcomes
• Expand Donor pool
• Characterize and address pre-txp comorbidities
• Characterize and understand Antibody mediated rejection
Greater efforts should be focused on developing optimal practices that individualize immunosuppression therapies and manage the long-term effects of these drugs. In addition, research strategies need to address the non-immune complications of immunosuppression, such as diabetes mellitus, hypertension, obesity, the metabolic syndrome, chronic kidney disease, and malignancies.
# Adult Heart Transplant Recipients: Cause of Death (Deaths: January 1992 - June 2010)

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>0-30 Days (N = 4,094)</th>
<th>31 Days – 1 Year (N = 4,028)</th>
<th>&gt;1 Year – 3 Years (N = 3,166)</th>
<th>&gt;3 Years – 5 Years (N = 2,674)</th>
<th>&gt;5 Years – 10 Years (N = 6,273)</th>
<th>&gt;10 Years – 15 Years (N = 3,616)</th>
<th>&gt;15 Years (N = 1,753)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Allograft Vasculopathy</td>
<td>78 (1.9%)</td>
<td>195 (4.8%)</td>
<td>458 (14.5%)</td>
<td>428 (16.0%)</td>
<td>944 (15.0%)</td>
<td>521 (14.4%)</td>
<td>232 (13.2%)</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td>256 (6.3%)</td>
<td>474 (11.8%)</td>
<td>323 (10.2%)</td>
<td>122 (4.6%)</td>
<td>116 (1.8%)</td>
<td>36 (1.0%)</td>
<td>31 (1.8%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3 (0.1%)</td>
<td>76 (1.9%)</td>
<td>110 (3.5%)</td>
<td>110 (4.1%)</td>
<td>271 (4.3%)</td>
<td>146 (4.0%)</td>
<td>61 (3.5%)</td>
</tr>
<tr>
<td>Malignancy, Other</td>
<td>3 (0.1%)</td>
<td>106 (2.6%)</td>
<td>360 (11.4%)</td>
<td>489 (18.3%)</td>
<td>1,202 (19.2%)</td>
<td>723 (20.0%)</td>
<td>293 (16.7%)</td>
</tr>
<tr>
<td>CMV</td>
<td>4 (0.1%)</td>
<td>45 (1.1%)</td>
<td>18 (0.6%)</td>
<td>5 (0.2%)</td>
<td>6 (0.1%)</td>
<td>1 (0.0%)</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Infection, Non-CMV</td>
<td>539 (13.2%)</td>
<td>1,203 (29.9%)</td>
<td>392 (12.4%)</td>
<td>268 (10.0%)</td>
<td>684 (10.9%)</td>
<td>373 (10.3%)</td>
<td>260 (14.8%)</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>1,643 (40.1%)</td>
<td>723 (17.9%)</td>
<td>732 (23.1%)</td>
<td>544 (20.3%)</td>
<td>1,112 (17.7%)</td>
<td>582 (16.1%)</td>
<td>246 (14.0%)</td>
</tr>
<tr>
<td>Technical</td>
<td>300 (7.3%)</td>
<td>54 (1.3%)</td>
<td>36 (1.1%)</td>
<td>27 (1.0%)</td>
<td>59 (0.9%)</td>
<td>39 (1.1%)</td>
<td>38 (2.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>201 (4.9%)</td>
<td>312 (7.7%)</td>
<td>289 (9.1%)</td>
<td>208 (7.8%)</td>
<td>535 (8.5%)</td>
<td>296 (8.2%)</td>
<td>157 (9.0%)</td>
</tr>
<tr>
<td>Multiple Organ Failure</td>
<td>591 (14.4%)</td>
<td>460 (11.4%)</td>
<td>152 (4.8%)</td>
<td>150 (5.6%)</td>
<td>441 (7.0%)</td>
<td>289 (8.0%)</td>
<td>144 (8.2%)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>24 (0.6%)</td>
<td>41 (1.0%)</td>
<td>55 (1.7%)</td>
<td>95 (3.6%)</td>
<td>371 (5.9%)</td>
<td>298 (8.2%)</td>
<td>133 (7.6%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>164 (4.0%)</td>
<td>160 (4.0%)</td>
<td>123 (3.9%)</td>
<td>126 (4.7%)</td>
<td>257 (4.1%)</td>
<td>150 (4.1%)</td>
<td>77 (4.4%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>288 (7.0%)</td>
<td>179 (4.4%)</td>
<td>118 (3.7%)</td>
<td>102 (3.8%)</td>
<td>275 (4.4%)</td>
<td>162 (4.5%)</td>
<td>77 (4.4%)</td>
</tr>
</tbody>
</table>

Percentages represent % of deaths in the respective time period.

ISHLT
Exercise intolerance after cardiac transplant

Years Post TXP

% survival, Post OHT

Group 1
Vo2>50%

Group 2
Vo2<50%

Rosenberg PB JHLT 2000
Risk Factors for 5 Year Mortality
Conditional on Survival to 1 Year

<table>
<thead>
<tr>
<th>Continuous Factors (see figures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
</tr>
<tr>
<td>Donor age</td>
</tr>
<tr>
<td>Recipient BMI</td>
</tr>
<tr>
<td>Serum creatinine</td>
</tr>
<tr>
<td>PVR</td>
</tr>
<tr>
<td>Transplant center volume (borderline)</td>
</tr>
</tbody>
</table>

(N=9,189)
Metabolic Syndrome after cardiac transplant

Abdominal obesity, given as waist circumference

- **Men**: >102 cm (>40 in)
- **Women**: >88 cm (>35 in)

Triglycerides

- **≥150 mg/dL**

HDL cholesterol

- **Men**: <40 mg/dL
- **Women**: <50 mg/dL

Blood pressure

- ≥130/≥85 mm Hg

Fasting glucose

- ≥110 mg/dL

Cordero Fort, 2006 JHLT 25 (10) 1192
Exponential increase in the risk of mortality after heart transplantation with an increasing number of risk factors.

Kilac, Annal of Th Surgery 2012
Maintenance therapy

- Calcineurin inhibitors (CNIs)
  - FK506/Tacrolimus (Prograf®)
  - Cyclosporine (Neoral®, Sandimmune®)

- Anti-metabolites
  - Mycophenolate Mofetil (CellCept®)
  - Azathioprine (Imuran®)
  - mTOR inhibitors Everlimus and Sirolimus

- Corticosteroids
## Immunosuppressive drugs cause metabolic syndrome

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK506 (Prograf®/Tacrolimus)</td>
<td>Renal toxicity, Tremor, Headaches, Diabetes mellitus</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Renal toxicity, Hirsutism, Gingival hyperplasia, Hypertension</td>
</tr>
<tr>
<td>Mycophenolate Mofetil (CellCept®)</td>
<td>GI intolerance, Leukopenia</td>
</tr>
<tr>
<td>Azathioprine (Imuran®)</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Steroids</td>
<td>Cushingoid features, Cataracts, Diabetes, Weight gain</td>
</tr>
</tbody>
</table>
T-Cell Receptor signaling
T-Cell Receptor signaling
STIM1 Mutation Associated with a Syndrome of Immunodeficiency and Autoimmunity

Capucine Picard, M.D., Ph.D., Christie-Ann McCarl, B.S., Alexander Papilos, B.S., Sara Khalil, B.S., Kevin Lüthy, Claire Hivroz, Ph.D., Françoise LeDeist, M.D., Ph.D., Frédéric Rieux-Laucat, Ph.D., Gideon Rechavi, M.D., Anjana Rao, Ph.D., Alain Fischer, M.D., Ph.D., and Stefan Feske, M.D.
Orai1 mutations and immunodeficiency

Severe combined immunodeficiency
Skeletal Myopathy
Ectodermal Dysplasia
Neonatal hypoglycemia
Calcium, muscle function and exercise
Calcium, muscle function and exercise
SOCE, muscle function and exercise
STIM1 and metabolic syndrome

**Graphs**

1. **Body Mass (g)**: A box plot comparing body mass between WT and SM-STIM1 +/- genotypes.

2. **Serum Glucose Level (g/dL)**: Two line graphs showing serum glucose levels over time after insulin injection (left) and glucose injection (right), with data points for WT and SM-STIM1 +/- genotypes.
STIM1 and exercise in humans
STRIDDE study

$R^2 = 0.81458$
STIM1 and exercise in humans
STRIDDE study

p=0.1158

p=0.0434
A CONTROLLED TRIAL OF EXERCISE REHABILITATION AFTER HEART TRANSPLANTATION

JON A. KOBASHIGAWA, M.D., DAVID A. LEAF, M.D., NANCY LEE, P.T., MICHAEL P. GLEESON, B.S., HONGHU LIU, PH.D., MICHELE A. HAMILTON, M.D., JAIME D. MORIGUCHI, M.D., NOBUYUKI KAWATA, M.D., KIM EINHORN, B.S., ELISE HERLIHY, R.N., AND HILLEL LAKS, M.D.

### Table 3. Changes from Baseline to Six Months in Cardiopulmonary Exercise-Test Results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Group (N=14)</th>
<th>Control Group (N=13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BASE LINE</td>
<td>6 MONTHS</td>
<td></td>
</tr>
<tr>
<td>Peak oxygen consumption (ml/kg/min)</td>
<td>9.2</td>
<td>13.6</td>
<td>+4.4 (+49)</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>59</td>
<td>94</td>
<td>+35 (+59)</td>
</tr>
<tr>
<td>Ventilatory equivalent for carbon dioxide</td>
<td>66</td>
<td>53</td>
<td>-13 (-20)</td>
</tr>
<tr>
<td>Ventilatory equivalent for oxygen</td>
<td>79</td>
<td>67</td>
<td>-12 (-15)</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>6.9</td>
<td>9.0</td>
<td>+2.1 (+30)</td>
</tr>
<tr>
<td>Time to estimated lactic acidosis threshold (min)</td>
<td>1.8</td>
<td>3.3</td>
<td>+1.5 (+83)</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>90</td>
<td>109</td>
<td>+10 (+11)</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>102</td>
<td>125</td>
<td>+23 (+23)</td>
</tr>
<tr>
<td>Systolic blood pressure at rest (mm Hg)</td>
<td>126</td>
<td>121</td>
<td>-5 (-4)</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
<td>141</td>
<td>148</td>
<td>+7 (+5)</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>38</td>
<td>45</td>
<td>+7 (+18)</td>
</tr>
<tr>
<td>Sitting-to-standing rate (no./min)‡</td>
<td>10.6</td>
<td>23.9</td>
<td>+13.3 (+125)</td>
</tr>
</tbody>
</table>
Benefits of Exercise after heart transplant: Interval Training
Benefits of Exercise after heart transplant: TCAV
Benefits of Exercise after heart transplant:
Weight reduction

A

Change in leg lean tissue mass (kg)

0.78 (0.31 - 1.3)

NT

SET

B

Change in total lean tissue mass (kg)

1.34 (0.34 - 2.3)

NT

SET
Benefits of Exercise after heart transplant: Muscle Strength
Preventing the metabolic syndrome associated with transplant: A Transplant STRIDDE?

BB is a 40 M with CM S/P OHT 2005

- viral CM dx 2004
- TXP 2005
- Rapidly tapered from corticosteroids
- maintained on FK506, MMF
- no significant cellular rejection
- 2007-08 8 medals in US TXP games
- 2009 represented the US in the international TXP games. 3 Silver medals, 1 Bronze.
Summary

• Commonly used immunosuppressive therapy causes/worsens metabolic syndrome in patients post-transplant

• Presence of the metabolic syndrome is a major determinant of post-transplant survival

• Exercise therapy can mitigate the effects of metabolic syndrome
Can SNPs in Orai1 and STIM1 predict immunosuppressant need after CTXP

Future Strategies

STIM1

Mechanistic studies

High TP screening for activating and inhibiting peptides
Novel therapeutic targets for immunosuppression