Primary Graft Dysfunction after Heart Transplant: Incidence, Predictors and Management

AATS 2015
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Duke University
Disclosures

- Discussion of Organ Care System, product of Transmedics Inc., which is not FDA.
RADIAL score European review - Primary Graft Failure

Incidence 22%
Definition: high dose inotropes or new MCS
Incidence of PGD following Heart Transplant

- 47 centers responded to survey
- 9,901 heart transplant procedures
- Definition: need for new MCS
- Incidence of PGD 7.4%
- 30 day mortality 30%
- Majority of centers considered retransplant potential options for PGD

Incidence of PGD following Heart Transplant

- UNOS review 1999-2007
- Identified cases as PGD resulting in death or retransplant
- Incidence 2.5%

Russo MJ, Iribarne A, Hong KN. Transplantation 2010;90:444-50
Barriers to Understanding PGD

- Reports are predominantly single center
- Until 2014, lack of consensus definition
- UNOS and STS have not rigorously maintained data on this adverse event
- General reluctance to examine negative outcome
Is the cardiac transplant practice changing relative to PGD?

• Donor issues
  – More prolonged support of brain dead donor to enable maximal organ placement
  – Circulatory support with escalating doses of levofed and T4
• Preservation strategies
  – 3 major preservation solutions for cold static storage
  – Advent of perfusion storage
• Recipient issues
  – Disease etiology
  – Increasing utilization of implantable LVAD for bridging
  – Over the last decade, LVAD bridging has increased from 10 to 50% of cases
  – Amiodarone in recipient negatively impacts reperfusion process after transplant
Duke Heart Transplant Recipients supported on Durable Mechanical Circulatory Support

- 1995: 10%
- 2000: 20%
- 2010: 50%
- 2015: 60%

Red bar: durable MCS
ISHLT Consensus Definition

• Distinguishes PGD from secondary causes of graft failure such as increased pulmonary vascular resistance, antibody mediated rejection and excessive bleeding
• Requires PGD manifest within 24 hours of procedure
• Distinguishes between PGD-RV and PGD-LV

ISHLT 2014 Conference on PGD after Heart Transplant
Consensus Categories and Definition

- PGD-RV
- PGD-LV
  - mild
  - moderate
  - severe

PGD defined on the basis of echocardiographic data, hemodynamics and type of MCS

### Definition of Severity Scale for Primary Graft Dysfunction (PGD)

<table>
<thead>
<tr>
<th>1. PGD-Left ventricle (PGD-LV):</th>
<th>Mild PGD-LV: One of the following criteria must be met:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEF ≤ 40% by echocardiography, or</td>
</tr>
<tr>
<td></td>
<td>Hemodynamics with RAP &gt; 15 mm Hg, PCWP &gt; 20 mm Hg,</td>
</tr>
<tr>
<td></td>
<td>CI &lt; 2.0 L/min/m² (lasting more than 1 hour) requiring low-dose inotropes</td>
</tr>
<tr>
<td>Moderate PGD-LV: Must meet one criterion from I and another criterion from II:</td>
<td>I. One criteria from the following:</td>
</tr>
<tr>
<td></td>
<td>Left ventricular ejection fraction ≤ 40%, or</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic compromise with RAP &gt; 15 mm Hg, PCWP &gt; 20 mm Hg, CI &lt; 2.0 L/min/m², hypotension with MAP &lt; 70 mm Hg (lasting more than 1 hour)</td>
</tr>
<tr>
<td></td>
<td>II. One criteria from the following:</td>
</tr>
<tr>
<td></td>
<td>i. High-dose inotropes—Inotrope score &gt; 10³ or</td>
</tr>
<tr>
<td></td>
<td>ii. Newly placed IABP (regardless of inotropes)</td>
</tr>
<tr>
<td>Severe PGD-LV</td>
<td>Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. PGD-right ventricle (PGD-RV):</th>
<th>Diagnosis requires either both i and ii, or iii alone:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i. Hemodynamics with RAP &gt; 15 mm Hg, PCWP &lt; 15 mm Hg, CI &lt; 2.0 L/min/m²</td>
</tr>
<tr>
<td></td>
<td>ii. TPG &lt; 15 mm Hg and/or pulmonary artery systolic pressure &lt; 50 mm Hg, or</td>
</tr>
<tr>
<td></td>
<td>iii. Need for RVAD</td>
</tr>
</tbody>
</table>
Risk Factors for PGD
Radial Score
Review of 621 tpx, 9% incidence PGD

- Donor age ≥ 30 years
- Ischemic time ≥ 240 mins
- Recipient age ≥ 60
- Recipient diabetes mellitus
- Recipient RAP ≥ 10
- Recipient inotrope therapy
- Recipient MCS
Risk Factors for PGD
UNOS Review
16,716 tpx, incidence PGF 2.5%

• Female donor into male recipient
• Lung donation
• Prolonged Ischemic time (> 240 minutes)
• Short Ischemic time (< 60 minutes)
• Center volume
• ECMO, extracorporeal VAD, intracorporeal VAD
• Congenital etiology
Surgical Strategies to reduce PGD

- perform some of the anastomoses after reperfusion
- cardioplegia during implant
- cooling strategy during implant
- vent LV to prevent rewarming and avoid distension after reperfusion
- Leukocyte filtration on CPB prior to reperfusion
- Inhaled NO
- Preoperative cyclosporine
- T3 administration prior to reperfusion
Cold Preservation vs. Warm Perfusion

- Cold static storage allows for injury due to cold and ischemia
- No capability for optimizing organ condition
- No means of assessing organ function
- Limits organ utilization
- Results in compromised clinical outcomes

- Warm, functioning/living preservation
- Organ condition can be optimized ex-vivo
- Online organ viability/function assessment
- No time limitation
- Expands organ utilization
- Improves clinical outcomes
The OCS Heart Technology Platform

OCS Heart Device
Heart Perfusion Module
Maintenance Solution Set
OCS Heart Cannulation Process

1. 
2. 
3. 
4.
Final Cannulation
PROCEED II Trial Profile
Non-inferiority End point

143 patients screened
13 excluded after secondary screening
4 ineligible*
7 withdrew consent
3 donor hearts ineligible*

130 randomly assigned

67 assigned to the Organ Care System group
63 assigned to the standard cold storage group

67 included in intention-to-treat analysis
63 included in intention-to-treat analysis

62 included in as-treated analysis
66 included in as-treated analysis

2 protocol deviations¶
5 protocol deviations¶

60 included in per-protocol analysis
61 included in per-protocol analysis

The Lancet, published online April 15, 2015

# Donor and Recipient Characteristics (intention to treat population)

## Recipient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organ Care System group (n=67)</th>
<th>Standard cold storage group (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (20-75)</td>
<td>57 (20-76)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55 (82%)</td>
<td>45 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (18%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (53-125)</td>
<td>69 (40-113)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (145-195)</td>
<td>173 (152-191)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25 (17-41)</td>
<td>23 (16-38)</td>
</tr>
<tr>
<td>Diagnosis of cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>25 (38%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>30 (45%)</td>
<td>30 (48%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (12%)</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>On ventricular assist device</td>
<td>18 (27%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>Clinical history of diabetes</td>
<td>19 (28%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>United Network Organ Sharing status 1A†</td>
<td>45 (67%)</td>
<td>50 (79%)</td>
</tr>
</tbody>
</table>

## Donor characteristics

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<thead>
<tr>
<th>Characteristic</th>
<th>Organ Care System group (n=67)</th>
<th>Standard cold storage group (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (18-58)</td>
<td>34 (13-60)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (66%)</td>
<td>45 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (34%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (48-143)</td>
<td>77 (51-133)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (150-198)</td>
<td>173 (152-198)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>27 (18-44)</td>
<td>26 (15-45)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anoxia</td>
<td>15 (22%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Stroke or cerebrovascular accident</td>
<td>18 (27%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>26 (39%)</td>
<td>28 (45%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (9%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Female donor to male recipient</td>
<td>13 (19%)</td>
<td>11 (18%)</td>
</tr>
</tbody>
</table>

*Data are median (range) or n (%). *One recipient in the Organ Care System group did not have information about medical history and was excluded from analyses of diagnosis of cardiomyopathy, ventricular assist device, clinical history of diabetes, and United Network Organ Sharing status. †Most urgent status for heart transplant candidates.
Mean Changes in Organ Care System Perfusion Measures (A) And Lactate Trends (B) for Transplanted Hearts

(error bar shows SDs)

Cold Ischemia Time and Perfusion Time for Donor Hearts Preserved with Organ Care System

Mean Total Preservation (out-of-body) Time (A) and Total Cold Ischemia Time (B) in the Organ Care System Versus the Standard Cold Storage Group

**A**

<table>
<thead>
<tr>
<th></th>
<th>Standard cold storage</th>
<th>Organ Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total preservation time (min)</td>
<td>180</td>
<td>360</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th></th>
<th>Standard cold storage</th>
<th>Organ Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold ischemia time (min)</td>
<td>180</td>
<td>60</td>
</tr>
</tbody>
</table>

p < 0.0001

Outcomes of Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Organ Care System group</th>
<th>Standard cold storage group</th>
<th>Between-group difference (one-sided 95% UCB or 95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(30 day patient and graft survival)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>63/67 (94%)</td>
<td>61/63 (97%)</td>
<td>2.8 (8.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>As-treated</td>
<td>58/62 (94%)</td>
<td>64/66 (97%)</td>
<td>3.5 (9.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Per-protocol</td>
<td>56/60 (93%)</td>
<td>59/61 (97%)</td>
<td>3.4 (9.9)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(as-treated population)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with cardiac-related serious adverse events</td>
<td>8 (13%)</td>
<td>9 (14%)</td>
<td>1 (-12 to 11)</td>
<td>0.90</td>
</tr>
<tr>
<td>Incidence of severe rejection</td>
<td>11 (18%)</td>
<td>9 (14%)</td>
<td>4 (-8 to 17)</td>
<td>0.52</td>
</tr>
<tr>
<td>Median ICU length of stay (h)</td>
<td>147 (107-212)</td>
<td>137 (97-197)</td>
<td>10 (-10 to 42)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are n/N (%) or n (%), or median (IQR), unless otherwise indicated. UCB=upper confidence bound. ICU=intensive-care unit.
List of Cardiac-related Serious Adverse Events (as-treated population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Organ Care System group (n=62)</th>
<th>Standard cold storage group (n=66)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular dysfunction</td>
<td>5 (8%)</td>
<td>4 (6%)</td>
<td>0.657</td>
</tr>
<tr>
<td>Right ventricular dysfunction</td>
<td>2 (3%)</td>
<td>6 (9%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Graft failure</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.330</td>
</tr>
</tbody>
</table>

Data are n (%). We defined left ventricular dysfunction as a left atrial pressure greater than 18 mm Hg with a cardiac index less than 2.0 L/min per m², requiring implantation of a left ventricular assist device or inotropic treatment for more than 7 days. We defined right ventricular dysfunction as central venous pressure greater than 18 mm Hg with a cardiac index less than 2.0 L/min per m², in absence of left atrial pressure greater than 18 mm Hg, requiring implantation of a right ventricular assist device or inotropic treatment for more than 7 days. We defined graft failure as heart dysfunction requiring sustained (>30 days) assist devices or relisting for transplantation. Numbers in this table differ from those in table 2, because this table depicts the number of events.

Table 3: List of cardiac-related serious adverse events (as-treated population)

The Lancet, published online April 15, 2015
Successful clinical series of Extended Criteria Hearts using OCS Heart Platform

- Harefield Hospital, UK: to-date >50 successful transplants from:
  - LVH donor hearts;
  - Long cross clamp time;
  - >45 Yo donors;
  - Questionable EF and CAD donors
Evaluation of the Organ Care System in Heart Transplantation with an Adverse Donor/Recipient Profile

- 30 donor hearts supported on OCS of which 26 were transplanted
- High risk donor characteristics
  - cardiac arrest, decreased LVEF and LVH
- High risk recipient characteristics
  - Increased PVR and MCS

Evaluation of Organ Care System in Heart Transplantation with an Adverse Donor/Recipient Profile.

- Mean cold ischemic time 85 minutes
- OCS perfusion time $284\pm 90$ minutes
- Overall mortality 3.8% at 9 months
- One death after ECMO support
- 3 cases required IABP
- 5 cases required prolonged inotropes or inhaled NO for RV dysfunction
Recognizing and Treating PGD

• The only thing worse than PGD is PGD which is ignored and not properly supported.
  – Unexpected outcome
  – Exhaustion
  – Compromised monitoring with TEE and SG catheter
  – Risks associated with application of MCS

Develop a protocol for when to apply MCS
# Mechanical Support options for PGD after heart transplant

<table>
<thead>
<tr>
<th>Device</th>
<th>advantages</th>
<th>disadvantages/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IABP</td>
<td>simple to insert and remove, increases coronary blood flow and systemic pressure</td>
<td>May not support RV and requires LV ejection</td>
</tr>
<tr>
<td>RVAD (RA and PA cannulation)</td>
<td>Provides RV replacement</td>
<td>May induce pulmonary edema. May be a source for pulmonary emboli. Requires surgery to remove</td>
</tr>
<tr>
<td>Percutaneous RVAD</td>
<td>Does not require reopening of sternotomy for installation or removal</td>
<td>Immobilizes patient, may become mispositioned. Hemolysis</td>
</tr>
<tr>
<td>Temporary BIVAD</td>
<td>Provides biventricular replacement</td>
<td>Higher rate of stroke</td>
</tr>
<tr>
<td>ECMO</td>
<td>Provides biventricular and pulmonary replacement</td>
<td>Higher stroke rate, prone to ventricular thrombus</td>
</tr>
</tbody>
</table>
Percutaneous RVAD

RECOVER RIGHT
The use of Impella RP Support System in Patients with Right Heart Failure:
A Clinical Safety and Probable Benefit Study
Percutaneous RVAD IJ Approach

Protek Duo. Cardioassist Inc.
When to retransplant?

• 50% of PGDs demonstrate improvement during the first week or two
• Early retransplant is associated with reduced survival outcomes
• Avoid other end organ dysfunction
• Avoid infection
• Understand immunological barriers
Conclusion - PGD

- Important to adopt ISHLT definition
- In cases of stable recipients, avoid risk factors
- OCS may represent mechanism to reduce injury associated with ischemia and cold storage
- Consider protocol for institution of MCS
- Infrequent need for retransplant