Ex-Vivo Heart Perfusion and DCD Heart Donation

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Conflict of Interest Disclosure

- Organ Care System and Vivoline are not approved by FDA
- I served as the Chair of the Steering Committee for PROCEED II Trial
- There is no Financial Conflict of Interest
The Cape Argus Newspaper after the First Human Heart Transplant
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2013)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05.

JHLT. 2015 Oct; 34(10): 1244-1254
Cold Static Preservation
Risk Factors For 1 Year Mortality with 95% Confidence Limits

Ischemia Time

Hazard Ratio of 1 Year Mortality

p < 0.0001

(N = 10,739)

2014

JHLT. 2014 Oct; 33(10): 996-1008
Cold Ischemia Time and Mortality


<table>
<thead>
<tr>
<th>IT (mins)</th>
<th>Number at risk at day 0</th>
<th>% survival estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;155</td>
<td>305</td>
<td>93</td>
<td>90 – 96</td>
</tr>
<tr>
<td>155-189</td>
<td>284</td>
<td>91</td>
<td>87 – 94</td>
</tr>
<tr>
<td>190-229</td>
<td>332</td>
<td>87</td>
<td>83 – 90</td>
</tr>
<tr>
<td>≥230</td>
<td>332</td>
<td>84</td>
<td>79 – 87</td>
</tr>
</tbody>
</table>
Alternative to Cold Ischemic Preservation

- Ex Vivo Organ Perfusion
  - Platform to perfuse the donor organs
Ex-vivo Organ Perfusion

- Machine perfusion of Kidneys
  - Reduction of DGF
  - Improved 1 year graft outcome

- Ex-vivo perfusion of Liver
  - 2016, pilot trial
  - Pilot clinical use of several Portable platforms
Ex-vivo Lung Perfusion

- XPS (Xvivo)
- Vivoline LS1 (Vivoline)
- OCS (TransMedics)
Ex-vivo Heart Perfusion-Organ Care System
How does it work?
How to assess the donor heart on OCS?

• Hemodynamic parameters:
  – Aortic pressure (goal: 65-90 mm Hg)
  – Coronary blood flow (goal: 650-900 mL/min)

• Perfusate Lactate level
  – Arterio-venous difference
  – Absolute lactate level (goal: <5 mmol/L)

• Visual Inspection
The Organ Care System (OCS) Heart

- Physiologic preservation
  - Improve quality of donor organs
  - Reduce Cold Ischemia Time
  - Expand Time & Distance

- Resuscitative capabilities
  - Expand the donor pool

- Metabolically active platform
  - Modification of the donor heart
PROCEED II Trial Overview

**Design:** Prospective, Randomized (1:1), Multi-center, Non-Inferiority Trial Comparing the Safety & Efficacy of OCS to Cold Storage of Donor Hearts

**Primary Endpoint:** 30-Day Patient & Graft Survival

**Secondary Endpoints:**
- Incidence of Cardiac-related SAEs
- Incidence of Bx. Proven ISHLT Grade 2R or 3R Rejection
- ICU Time
<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 (30 day patient and graft survival)</strong></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 (as-treated population)</strong></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.

Table 2: Outcomes of primary and secondary endpoints
COLD Ischemia Time

![Graph showing comparison between OCS and Control groups in Cold Ischemia Time with p<0.001 significance level.]

- **OCS**
- **Control**
PROCEED II Findings

- 30 day patient and graft survival are similar when the donor heart preserved on OCS vs on ice
- No different in secondary endpoints of cardiac –related SAE, Rejection, ICU stay
- Cold ischemia time significantly shorter, despite longer total preservation time
New Technology Improvements
OCS Heart Device
Optimization of Perfusion

Addition of Compliance at AO Root

Optimizing Coronary Filling Time
New Aorta Cannula Design

Simplified & User Friendly Cannula Design
Automated Hemodynamic Management

Integrated and Automated IV infusion Pump to Regulates AOP Based On Set Target by User
Ex-vivo Donor Heart Perfusion (OCS)

- Expand the donor pool
  - Resuscitate donor hearts
  - Assess suitability for transplantation: DCD hearts
Organ Donation after Circulatory Death

- Widely accepted in kidney, liver, and lung transplantation
- Pediatric heart transplantation with donor hearts after circulatory death
- No adult heart transplantation with DCD hearts in modern era
- Concerns:
  - Warm ischemia, how long?
  - Inability to assess the donor heart prior to implantation
Australian DCD Heart Transplantation
DCD Heart Donation

- Young donors (<40 yrs of age), Warm ischemia time of <30 min
- Transfer to OR
- Very rapid blood retrieval. Transect RAA and insert dual-stage cannula. This will allow better drainage and decompress abdominal organs- heparin in the bag only
- During blood collection, clamp descending aorta
- Antegrade Perfusion: St. Thomas cardioplegia- 1L
- OCS instrumentation

DCD HTX - CASE #1

<table>
<thead>
<tr>
<th>WITHDRAWAL TO CIRCULATORY ARREST</th>
<th>WARM ISCHAEMIC TIME</th>
<th>START A-V LACTATE</th>
<th>END A-V LACTATE</th>
<th>TOTAL OCS PERFUSION</th>
<th>TOTAL ISCHAEMIC TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>28</td>
<td>8.2</td>
<td>3.8</td>
<td>257</td>
<td>90</td>
</tr>
</tbody>
</table>
Worldwide DCD Adult Donor Heart Experience (1/15/16)

- Sydney, Australia
  - 8 runs, 6 implants

- Harefield, UK
  - 4 implants

- Papworth, UK
  - 12 implants
EXPAND-Heart Trial

**Trial Design:** prospective, pivotal, single arm trial

**Non-standard Donor Hearts:** Age>55, LVH>1.3 cm, Ischemia time>6 hours

**Primary Endpoint**
A composite endpoint of patient survival at Day-30 post transplant and absence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation.

**Secondary Endpoints**
- Patient survival at day-30 post transplantation
- Incidence of severe primary heart graft dysfunction (PGD)
- Rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS heart device
Final Thoughts

• Ex-vivo heart perfusion technology is evolving
• Improvements in the platform will enhance donor heart perfusion, ease of use
• Ex-vivo heart perfusion may be considered in prolonged cold ischemia times, assessment or improvement of non-standard donor hearts, or resuscitation of DCD hearts
References