Heart Transplant: State of the Art

Dr Nick Banner
Heart Transplantation

• What is achieved
• Current challenges
  – Donor scarcity
  – More complex recipients
• Long-term limitations
  – Non-specific Pharmacological Immunosuppression
  – The versatile immune system
Heart Transplantation

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• Current challenges
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Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2013)

Survival (%)

Years

1992-2001 (N=39,368)
2002-2008 (N=24,023)
2009-6/2013 (N=16,200)

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

Median survival (years):
Adult Heart Transplants
Kaplan-Meier Survival by Era Conditional on Survival to 1 Year (Transplants: January 1982 – June 2013)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05 except 1992-2001 vs. 2009-6/2013.
Benefit of transplantation

- Relative risk of death following transplantation

<table>
<thead>
<tr>
<th></th>
<th>Risk less than on the waiting list after (days (95% CI))</th>
<th>Net benefit after (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent (non-ambulatory)</td>
<td>7 (0 to 46)</td>
<td>15</td>
</tr>
<tr>
<td>High risk</td>
<td>31 (16 to 46)</td>
<td>122</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>64 (41 to 82)</td>
<td>289</td>
</tr>
<tr>
<td>Low risk</td>
<td>95 (54 to 136)</td>
<td>729</td>
</tr>
</tbody>
</table>
Quality of life of patients in UK heart transplant pathway: EQ-5D dimensions.

Medical assessment
Medical list
LVAD
Heart Transplant

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Adult and Pediatric Heart Transplants
Number of Transplants by Year

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
Methods of heart donation

**Donation after circulatory death (DCD)**
- The method used for the first heart transplants
- Death certified on the basis of standard somatic criteria
- Family discussion must be anticipatory
- Donation procedure reactive
- Potential for hypoxic cardiac injury during the apnoeic period
- Injury may be potentiated by subsequent ischaemia
- Heart assessment limited

**Donation after brain-stem death (DBD)**
- The standard method once BSD criteria were established
- Family discussion based on a firm diagnosis
- Potential cardiac injury during BSD
- Subsequent loss of donor homeostatic functions
- Donation procedure fully controlled
- Heart Function assessed fully before donation
Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series

Kumud K Dhillon, Arjun Iyer, Mark Connellan, Hong C Chew, Ling Gao, Aoife Doyle, Mark Hicks, Gayathri Kumaraesinghe, Claude Sota, Andrew Dinale, Bruce Cartwright, Priya Nair, Emily Granger, Paul Jansz, Andrew Jabbour, Eugene Kotlyar, Anne Keogh, Christopher Hayward, Robert Graham, Phillip Sprott, Peter MacDonald

Summary
Background Orthotopic heart transplantation is the gold-standard long-term treatment for medically refractive end-stage heart failure. However, suitable cardiac donors are scarce. Although donation after circulatory death has been used for kidney, liver, and lung transplantation, it is not used for heart transplantation. We report a case series of heart transplantations from donors after circulatory death.

Methods The recipients were patients at St Vincent’s Hospital, Sydney, Australia. They received Maastricht category III controlled hearts donated after circulatory death from people younger than 40 years and with a maximum warm ischaemic time of 30 min. We retrieved four hearts through initial myocardial protection with supplemented cardioplegia and transferred to an Organ Care System (Transmedics) for preservation, resuscitation, and transportation to the recipient hospital.

Findings Three recipients (two men, one woman; mean age 52 years) with low transpulmonary gradients (<8 mm Hg) and without previous cardiac surgery received the transplants. Donor heart warm ischaemic times were 28 min, 25 min, and 22 min, with ex-vivo Organ Care System perfusion times of 257 min, 260 min, and 245 min. Arteriovenous lactate values at the start of perfusion were 8–3–8–1 mmol/L for patient 1, 6.79–6.48 mmol/L for patient 2, and 7.6–7.4 mmol/L for patient 3. End of perfusion lactate values were 3.6–3.6 mmol/L, 2.8–2.3 mmol/L, and 2.69–2.54 mmol/L, respectively, showing favourable lactate uptake. Two patients needed temporary mechanical support. All three recipients had normal cardiac function within a week of transplantation and are making a good recovery at 176, 91, and 77 days after transplantation.

Interpretation Strict limitations on donor eligibility, optimised myocardial protection, and use of a portable ex vivo organ perfusion platform can enable successful, distantly procured orthotopic transplantation of hearts donated after circulatory death.

Funding NHMRC, John T Reid Charitable Trust, EVOS Trust Fund, Harry Windsor Trust Fund.
Source of adult heart transplant donors in UK

Source NHSBT, courtesy of Dr Mehew
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support* by Year and Device Type

2005 2006 2007 2008 2009 2010 2011 2012 2013

% of Patients

Year of Transplant

ECMO  VAD+ECMO  TAH  LVAD+RVAD  RVAD  LVAD

* LVAD, RVAD, TAH, ECMO
All pair-wise comparisons with ECMO were significant at $p < 0.05$. Continuous flow vs. Pulsatile flow and No LVAD / Inotropes vs. Pulsatile flow were significant at $p < 0.05$. No other pair-wise comparisons were significant at $p < 0.05$. 

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JHLT. 2014 Oct; 33(10): 996-1008

JHLT. 2015 Oct; 34(10): 1244-1254
Adult Heart Transplants
Kaplan-Meier Survival Within 1 Year by Diagnosis
(Transplants: January 1982 – June 2013)

All pair-wise comparisons were significant at $p < 0.01$ except congenital vs. valvular.

For some retransplants, a diagnosis other than retransplant is reported, so the total number of retransplants may be greater.
Adult Heart Transplants
Kaplan-Meier Survival by Diagnosis Conditional on Survival to 1 Year (Transplants: January 1982 – June 2013)

Median survival (years):
- Cardiomyopathy=14.1
- CAD=11.7
- Congenital=20.2
- Retransplant=11.0
- Valvular=14.3

All pair-wise comparisons were significant at p < 0.0001 except cardiomyopathy vs. valvular and CAD vs. retransplant.

For some retransplants, a diagnosis other than retransplant is reported, so the total number of retransplants may be greater.
30-day patient survival by IT

<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;150</td>
<td>414</td>
<td>92</td>
<td>88 – 94</td>
</tr>
<tr>
<td>150-189</td>
<td>413</td>
<td>90</td>
<td>87 – 93</td>
</tr>
<tr>
<td>190-229</td>
<td>408</td>
<td>87</td>
<td>83 – 90</td>
</tr>
<tr>
<td>&gt;=230</td>
<td>400</td>
<td>84</td>
<td>79 - 87</td>
</tr>
</tbody>
</table>

Log-Rank p=0.002

Transplantation 2008; 86:542-7
Potential advantages of OCS for DCD donation

- Active heart resuscitation during normothermic perfusion
- Ischemia time minimised
- Functional assessment of the donor heart during ex-vivo perfusion
- Removal of time-pressure in the complex recipient
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Mechanisms of acute allograft rejection

Central role of the CD4+ T-cell
Clinical Immunosuppression: History and Mechanisms of Action

Effects on the T-cell activation cascade

1960
- azathioprine
- corticosteroids

1970
- antilymphocyte globulin

1980
- ciclosporin
- [muromonab-CD3]

1990
- tacrolimus
- mycophenolate
- basiliximab/ [daclizumab]

2000
- sirolimus
- everolimus
ISHLT CONSENSUS

Report from a consensus conference on antibody-mediated rejection in heart transplantation

Jon Kobashigawa, MD, Maria G. Crespo-Leiro, MD, Stephan M. Ensminger, MD, Hermann Reichenspurner, MD, PhD, Annalisa Angelini, MD, Gerald Berry, MD, Margaret Burke, MD, Lawrence Czer, MD, Nicola Hiemann, MD, Abdallah G. Kfoury, MD, Donna Mancini, MD, Paul Mohacsi, MD, Jignesh Patel, MD, PhD, Naveen Pereira, MD, Jeffrey L. Platt, MD, Elaine F. Reed, PhD, Nancy Reinsmoen, PhD, E. Rene Rodriguez, MD, Marlene L. Rose, PhD, Stuart D. Russell, MD, Randy Starling, MD, MPH, Nicole Suciu-Foca, PhD, Jose Tallaj, MD, David O. Taylor, MD, Adrian Van Bakel, MD, PhD, Lori West, MD, Adriana Zeevi, PhD, and Andreas Zuckermann, MD, on behalf of the Consensus Conference Participants

Conceptual framework and diagnostic criteria for AMR

Applied to Heart Transplantation

Stage
4
3
2
1

Donor Specific Antibody
Antibody binding to capillaries
Histological evidence of AMR
Allograft dysfunction

Clinical Acute AMR
Subclinical AMR
Silent
? Pre-rejection
? accommodation
Latent

Takemoto SK et al. Am J Transplant 2004:4; 1033
Influence of de-novo donor specific HLA antibody formation on survival following heart transplantation

Predicted survival curve for the time dependent variable de novo DSA from fitted Cox model for patients producing DSA at the outset (-----) and patients with no detectable DSA at any time point (—) following cardiac transplantation.

Smith JD et al. Am J Transplant 2011; 11: 312
Adult Heart Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 1994 – June 2014)

Since only leading causes of death are shown, the sum of percentages for each time period is less than 100%.
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