Heart Transplantation and VAD Therapy

J N Townend
Queen Elizabeth Hospital Birmingham
1967

Died at day 18 of rejection
Heart Transplantation
This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as evidence that the number of hearts transplanted worldwide has declined in recent years.
Heart Transplantation at QEHB

• Programme commenced 1992
• 556 transplants (273 hearts, heart lung and lung)
• Now providing ECMO, short term bed-side LVAD, long term LVAD as well as transplantation
• Multi-organ transplant
• Only UK centre offering heart and ASCT for amyloid
Referrals by Financial Year for Thoracic Organ Transplantation at QEHB
Heart Transplantation for Wales

- 49 Welsh recipients, 25 alive
- Longest survivor from Wales transplanted heart and kidney 1994 aged 20
From IABP to the IOW

Carry the card
Heart transplantation gives a second chance of life
Heartlung Transplantation Programme Birmingham, UK.
QEHB Transplant Team

- Director Prof RS Bonser
- 4 consultant surgeons
- 2 associate specialist surgeons
- 2 consultant transplant cardiologists
- 3 Senior Nurse Recipient co-ordinators
- ...

Referral

1. Contact us
   - Letter, E-mail or telephone
   - We will request detailed letter, simple pro-forma completion, imaging results on CD

2. If patient is ambulant we will see in the transplant assessment clinic (JNT or SL)
   - Clinical, Bloods, CXR, ECG, BNP, CPEX, Echo

3. Part 2 – in-patient 2 day stay, co-morbidity, RHC, immunology, social issues...

4. If urgent, ring and arrange transfer to CCU/ITU
HEART TRANSPLANTATION

Half-life = 10.0 years
Conditional Half-life = 13.0 years

N=74,267
ADULT HEART TRANSPLANTATION

All comparisons significant at p < 0.0001


J Heart Lung Transplant 2008;27: 937-983
UK Heart Transplant Activity

Figure 6.1  Deceased donor heart programme in the UK, 1 April 2000 - 31 March 2010
Number of donors, transplants and patients on the active transplant list at 31 March
### UK Adult Heart Transplants 2009-2010 (2008-2009)

<table>
<thead>
<tr>
<th></th>
<th>Non-urgent</th>
<th>Urgent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birmingham</td>
<td>10 (10)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Glasgow</td>
<td>0 (0)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Great Ormond Street</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Harefield</td>
<td>9 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Manchester</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Newcastle</td>
<td>10 (10)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Papworth</td>
<td>13 (21)</td>
<td>10 (10)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>49 (54(^1))</td>
<td>37 (42)</td>
</tr>
</tbody>
</table>
Prevalence of Heart Failure

Cowie et al. Hillingdon Heart Failure Study 1999
Heart Transplantation

An ‘epidemiological irrelevance’
UK Median Waiting Times for Adult Heart Transplant 1999-2003

- A 81 days (95% CI: 67 to 114)
- AB 76 days (95% CI: 52 to 178)
- O 214 days (95% CI: 162 to 308)
- B 174 days (95% CI: 78 to 249)

NB Influence of size: patients over 81kg waited a median of 271 days compared with those under 70kg who waited 95 days

Hussey et al. JHLT 2007
Heart Transplantation: The First Year

• Surgical mortality 10%
  – Primary graft failure
    • Donor organ cold ischaemia time is only 4 hours
  – RV failure (pulmonary hypertension)
  – Acute renal failure (pre-op renal dysfunction)

• First 12 months 5-10% mortality
  – Rejection
  – Infection
Long Term Management

- Immuno-suppression
  - Prednisolone 60 mg tapering to 10 mg by year 1
  - CNI
  - MMF
- Surveillance biopsies at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 32, 40, 52
Long Term Problems

- Rejection
  - Cellular
  - Humoral
  - Allograft vasculopathy
- Infection
- Renal dysfunction (CNI toxicity)
  - ESRF in 10% at 8 years
- PTLD
  - 15% at 5 years, mainly SCC and PTLD
- Medical problems
  - Hypertension
  - Gout
  - Steroid related
ESRD risk reaches 4.5% risk per year by the sixth post-transplant year.

Transplantation. 1998 66:1763-1770
Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single centre

From Bad Oeynhausen, Eur J Cardiothorac Surg 2008
Assessment for Heart Transplantation

• Primary questions
  1. Is there need?
     • One year prognosis < 50%
  2. Will it work?
     • Is the chance of a successful outcome in this patient good?

• Secondary question
  – Is this an appropriate use of a scarce donor organ?
Contra-Indications to Heart Transplant

• Absolute contra-indications
  – Elevated PVR
  – Malignancy (absolute unless ‘cured’)
  – Renal function GFR <40
    • Combined heart and renal transplant?
  – Recent major PE
  – Active sepsis

• Relative contra-indications
  – Age >70
  – Obesity
  – Diabetes with end organ damage
Other issues 2

– Tobacco use
– Alcohol and substance abuse
– Blindness and deafness
– Home circumstances
  • Homeless
  • No carer
  • In care/prison
– Pyscho-social
  • Learning disability
  • Compliance
Evaluation
ISHLTLT Guidelines 2006

• Assessment of heart failure severity
  – CPX
  – Echo
  – RH catheter data
• Evaluation of multi-organ function
  – Bloods, urinalysis, GFR, CXR, PFT, ABG, abdo USS, Carotid Dopplers (diabetic or >50), DEXA (steroids, >50), ophthalmic exam if diabetic
• Infectious serology
  – HBV, HIV, HSV, EBV, CMV, Tox, Flu vac,
• Screen for malignancy
  – Clinical, mammography, FOBs, PSA, abdo USS
• Social, financial, psychiatric…
Heart Failure Prognostic Markers

- Clinical
  - Effort tolerance
  - Rate of decline
  - Admissions
  - Arrhythmia including chronic AF
  - Wt loss
  - Signs: JVP, 3rd sound, hypotension
- CPEX
- LV dimensions on echo
- RV function
- Plasma noradrenaline (not used)
- BNP
- Serum sodium
- Renal and hepatic dysfunction
- Cardiac index
- Pulmonary hypertension
Cardiopulmonary Exercise Testing

- Provides information on level and cause of effort intolerance
  - RER
  - Peak VO$_2$
  - Anaerobic threshold
  - VE/VCO$_2$ slope

- Results only useful if on maximal therapy, well compensated and RER>1.05 and AT achieved
Peak VO$_2$

- Measure of peak exercise performance
  - If peak exercise, motivation, AT obtained
- Corrected for body mass and expressed as ml/Kg/min
- Average value in young adults c. 40 for females and 45 for males
- Olympian value 70-80
Peak VO$_2$ <14 and Assessment for Heart Transplant

Gp 1 (n=35) peak VO$_2$<14  
Gp 2 (n=52) peak VO$_2$>14  
Gp 3 (n=27) peak VO$_2$<14, rejected for non-cardiac reasons

Mancini Circ 1991
Current CPX Criteria

• Peak VO$_2$ <10 – strong indication
• Peak VO$_2$ 10-14 – probable indication
• Peak VO$_2$ >14 – too well unless other adverse prognostic features
  – Arrhythmia, symptoms, admissions, Na$^+$ …
  – Adverse aetiology (eg amyloid)
  – Unusual aetiology or indication (eg Congenital)
Problems with Peak VO$_2$ in the Modern Era

- Many new treatments improve prognosis with little effect on peak exercise tolerance
  - ACE inhibitors
  - Beta blockers
  - Spironolactone
  - CRT
  - ICD
Adjusted 5 Year Survival in 2105 patients with CHF at Cleveland Clinic: Interaction between BB and Peak VO$_2$
Pulmonary Haemodynamics

- Right heart failure is a common cause of death and poor recovery post transplantation
- Accounts for about 20% of early deaths
- Recognised very early (Stanford)
- RH catheter data used for assessment from 1980s
- Elevated PVR is a continuous risk factor, no ‘safe’ cut-off levels
RH Catheter prior to Cardiac Transplantation

- Usually done by Swan-Ganz catheter as need CO measurement
- TPG = mean PAP - mean PAWP
- PVR = TPG/CO (Wood units)
- Theory of reactive (reversible) vs. fixed pulmonary hypertension
- Use of vasoactive drugs (SNP, dobutamine, GTN, prostacycllin) to determine reversibility
PVR Reversibility with SNP

• Influence of pre-transplant RH catheter data on outcome after transplantation analyzed in 293 of 301 consecutive patients

• 3 month mortality rates post transplant:
  
  - PVR > 2.5 17.9%
  - PVR < 2.5 6.9%
  - PVR > 2.5 but reversible* 3.8%
  - PVR > 2.5 irreversible 41%
  - PVR > 2.5 reversible, low sBP 28%

*< 2.5 units with a systemic systolic pressure > to 85 mm Hg

J Am Coll Cardiol, 1992; 19:48-54
PVR – can it be reversed by long term therapy?

• Reports of success with
  – Beta blockers
  – Pulmonary vasodilators
  – VAD (months)

• Elevated PVR is also an adverse prognostic sign, survival without transplant is poor
Which (if any) ambulant patients with heart failure should be transplanted?

- NYHA IV patients requiring inotropic/mechanical support are frequently referred
- Need not in doubt
- Results are as good as for ambulant patients
- Many centres ‘acute’ patients now account for about 70% of activity
- Can we justify transplanting ambulant patients and do scoring systems patients help?
The Heart Failure Survival Score (HFSS)

- Derived and validated in US for ambulant patients who were candidates for heart transplant 1986-1995
- Outcome was death on WL or 'urgent' transplantation
- Score is sum of
  - CAD =1, other =0. x 0.6931
  - IV conduction delay =1, none = 0. x 0.6083
  - LVEF% x -0.0464
  - HR x 0.0216
  - Serum sodium x -0.0470
  - Mean arterial pressure x -0.0255
  - Peak VO2 x -0.0546
- Defined 3 groups:
  - High one year survival 43%
  - Medium one year survival 72%
  - Low risk one year survival 93%

Circulation 1997
The Hospitalised Patient with End-Stage Heart failure

- Is this patient for intensive support with a view to transplant or is palliation the correct option?
- If for intensive support, treat intensively
  - Preservation of end organ function
- May take many weeks of inotropic/mechanical supportive therapy while waiting for transplantation
- Concept of not weaning inotropes is difficult!
LVADs

- Bridge to transplantation
- Bridge to recovery of fitness for transplantation
- Bridge to recovery of LV function (?)
- Destination therapy – no UK programme
LVAD Therapy for Reversal of PHT

• Severe PHT is an absolute CI to heart transplantation
• A high PA pressure is a marker of good RV function and thus of good prognosis with only left heart support
• Continued unloading of the LV leads to a fall in PHT and remodelling of the pulmonary vasculature
• LVAD for un-transplantable patients?
Short Term Devices: Levitronix CentriMag

extracorporeal ventricular assist device to support patients for periods of up to 30 days
First Generation LVADs
Pulsatile Devices

(HeartMate: self contained, pneumatically driven vented electric device)
REMATCH TRIAL

• Randomised trial of chronic LVAD (HeartMate I) vs. optimal medical management
• 129 patients with end stage NYHA class IV CHF ineligible for transplant
• Inotropes used in 70%
• Ineligibility for transplant mainly due to at least one of:
  – age>65
  – CKD (creat>221)
  – DM with end organ damage

N Engl J Med 2001
REMATCH

48% reduction in all cause death
One year - 52% vs. 25%
Two years -23% vs. 8%

28% device infection rate within 3 months
Bleeding 42% at 6 months
Device failure 35% at 2 years

N Engl J Med 2001
Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation

Heartmate II (Thoratec)

actuarial survival for patients continuing to receive pump support was 89% at 1 month, 75% at 6 months, and 68% at 12 months
• Prospective, multicenter study, 281 patients urgently listed for heart transplantation underwent implantation of a continuous-flow LVAD
• Survival and transplantation rates were assessed at 18 months
• Adverse events recorded throughout the study and quality of life, functional status, and organ function for 6 months

JACC 2009
Results

Actuarial survival at 18 months 72%

JACC 2009
Adverse events

Major causes of death:
- sepsis (4%)
- stroke (4%)
- right ventricular failure (3%)
- device-related deaths (3%)
- Multi-organ failure (2%)

77% of deaths occurred within the first 6 post-operative months

Adverse events:
- strokes (9%)
- localized device-related infections (30%)
- percutaneous lead infections (14%)
- right ventricular failure (19%)
- 59% patients had at least 1 post-operative surgical procedure but there were no failures of the mechanical pumping mechanism

JACC 2009
Outcomes of Left Ventricular Assist Device Implantation as Destination Therapy in the Post-REMATCH Era
Implications for Patient Selection

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Odds Ratio (CI)</th>
<th>P</th>
<th>Weighted Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count ≤148×10^3/μL</td>
<td>7.7 (3.0 to 19.4)</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>Serum albumin ≤3.3 g/dL</td>
<td>5.7 (1.7 to 13.1)</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>International normalization ratio &gt;1.1</td>
<td>5.4 (1.4 to 21.8)</td>
<td>0.01</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilator therapy</td>
<td>5.2 (1.9 to 14.0)</td>
<td>0.008</td>
<td>4</td>
</tr>
<tr>
<td>Mean pulmonary artery pressures ≤25 mm Hg</td>
<td>4.1 (1.5 to 11.2)</td>
<td>0.009</td>
<td>3</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;45 U/mL</td>
<td>2.6 (1.0 to 6.9)</td>
<td>0.002</td>
<td>2</td>
</tr>
<tr>
<td>Hematocrit ≤34 %</td>
<td>3.0 (1.1 to 7.6)</td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;51 U/dL</td>
<td>2.9 (1.1 to 8.0)</td>
<td>0.03</td>
<td>2</td>
</tr>
<tr>
<td>No intravenous inotropes</td>
<td>2.9 (1.1 to 7.7)</td>
<td>0.03</td>
<td>2</td>
</tr>
</tbody>
</table>
Selection for VAD

• A complex calculation that includes
  – Assessment of prognosis on non-mechanical support
    • IABP use, response to inotropes
  – RV function: echo, high RA and low PA pressures
  – End organ dysfunction
    • Early dysfunction is a marker of need
    • Severe dysfunction is a marker of a bad outcome on VAD
  – Chances of early transplantation?
    • Size
    • Blood group
    • Sensitisation
    • Local circumstances
Timing and Patient Selection:

Importance of the MDT
Contact

• 24hrs helpline: 07850233730

• Heart lung transplant team on call person: SAB or BH or HJ 07699704668

• Via QEHB switch: 0121 371 2000

• Fax: 0121 627 5702

• Email: sharon.beer@uhb.nhs.uk