Heart transplant: patient selection and transplant emergency

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And Chulalongkorn University
Goals of Treatment of Heart Failure

- Prolonged life
- Improved QOL and functional capacity
HF-REF: The building blocks of therapy

- Digoxin
- CABG
- Beta-blocker
- ACEI/ARB
- MRA
- Ivabradine
- H-ISDN
- Tx
- VAD
- CRT
- ICD
- ARNI?
Heart Transplant
Overall Survival

- CAVAL
- ATRIAL
- TOTAL

Event = death after transplant
$p < 0.0345$ (CAVAL vs. ATRIAL)

<table>
<thead>
<tr>
<th># Subjects at Risk</th>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRIAL 11,343</td>
<td>8,125</td>
<td>6,204</td>
<td>4,138</td>
<td>2,197</td>
<td>413</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAVAL 6,673</td>
<td>3,946</td>
<td>2,152</td>
<td>876</td>
<td>100</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL 551</td>
<td>334</td>
<td>206</td>
<td>87</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Thailand: Recipient shortage
Heart transplantation activities at King Chulalongkorn Memorial Hospital

Total n = 138
King Chulalongkorn Memorial Hospital

- **138** Heart Transplants
- **6** HEARTMATE Ventricular Assist Devices (LVADs)
- **30+** Years of experiences

King Chulalongkorn Memorial Hospital
Survival of heart transplant recipients

1 year survival 89%
5 year survival 70%
Median survival 12 years
1 year survival = 86%

Kittipibul V and Puwanant S Unpublished
แพงไหม?

- 30 บาท จ่ายให้นะคะ
- ประกันสังคม - ยังไม่ครอบคลุมค่ะ
Indications

- Refractory **cardiogenic shock** requiring intra-aortic balloon pump counterpulsation or left ventricular assist device (LVAD); requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.);
- Peak VO$_2$ < 10 ml/kg/min **NYHA class of III or IV** despite maximized medical and resynchronization therapy;
- End-stage **congenital HF** with no evidence of pulmonary hypertension;
- Recurrent life-threatening left **ventricular arrhythmias** despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation;
- **Refractory angina** without potential medical or surgical therapeutic options.
Contraindications

- Advanced age (>65-70yr)
- Irreversible hepatic, renal, or pulmonary dysfx
- Active infection, AIDS,
- Systemic disease with life expectancy < 2 years despite transplant, Systemic disease (active SLE, amyloid)
- Recent, active cancer (within 5 yrs)
- Psych illness, poor compliance, Drug addiction
- Pulmonary hypertension with PVR
- > 6 Wood units or 3 Wood units after vasodilator
- Significant COPD (FEV1<1)
- Severe PAD or CVD
- Acute PE, Severe Obesity
- PRA (Panel Reactive Antibody) > 10%
Patient Selection

- Case based learning
a) RM
b) Transplant
c) OMT
Vo2 max = 12 ml/kg/min
Heart transplant (OHTX) evaluation

- RAP = 15
- PCWP = 28
- PAP = 65/30 (42)
- TPG = 42-28 = 14
- CO = 2.2
- PVR = 6.2

- RAP = 8
- PCWP = 20
- PAP = 45/22 (30)
- TPG = 30-20 = 10
- CO = 2.6
- PVR = 3.8

Choices
1) Pulm vasodilator test
2) Diuresis
3) HL transplant

Diuresis
## PH before heart transplant

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Normal value</th>
<th>Cut-off value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery systolic pressure</td>
<td>25 mm Hg</td>
<td>&lt;50 mm Hg</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>0.5–1.5 WU</td>
<td>≤6 WU at rest or &lt;3 WU</td>
</tr>
<tr>
<td>Transpulmonary gradient</td>
<td>5–7</td>
<td>with maximal vasodilatation 12–15 mm Hg</td>
</tr>
</tbody>
</table>
Few words about donor selection

- Perfect donor needed
- Clinical-Hemodynamics
- CXR ECG
- Echo
- Coronary Angiography
Life Post Heart Transplant

- Immunosuppressive agents: CNI, MMF, Steroid
- Rejection
- CMV Infection
- Non-CMV Infection
- Malignancy
Transplant Emergency Fellows should know

- Cardiac Allograft Rejection
Cardiac Allograft Rejection

- Acute Cellular Rejection
- Antibody-Mediated Rejection
- Coronary Artery Vasculopathy
Symptoms of rejection

- Symptoms of HF
  - Feeling tired or weak
  - Shortness of breath
  - Swelling of your feet, hands, or ankles
  - Sudden weight gain
  - Reduced amounts of urine
  - Nausea or loss of appetite
- Fever or chills
- Fast or irregular heartbeat
- Drop in blood pressure
- Flu-like aches and pains
- Dizziness or fainting
Endomyocardial Biopsy

- Biopsies are performed via a transjugular approach weekly and then every other week for several months.
- Monthly biopsies continue for 6 to 12 months in many programs and for years thereafter in some.
- Complication includes pericardial tamponade or tricuspid insufficiency.
<table>
<thead>
<tr>
<th>หลัง transplant</th>
<th>ความติ</th>
<th>จำนวนครั้ง</th>
<th>จำนวนครั้งรวม</th>
<th>ต่อปี</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>ตุ๊ก 1 สับปะรดจบกลับป่า</td>
<td>4 ครั้ง</td>
<td></td>
<td>12 ครั้ง/ปี</td>
</tr>
<tr>
<td></td>
<td>ตุ๊ก 2 สับปะรด</td>
<td>2 ครั้ง</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ตุ๊ก 3-6 สับปะรด</td>
<td>4 ครั้ง</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ตุ๊ก 7-12 เตือน</td>
<td>2 ครั้ง</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>ตุ๊ก 6 เตือน</td>
<td>2 ครั้ง</td>
<td></td>
<td>2 ครั้ง/ปี</td>
</tr>
<tr>
<td><strong>3, 4, 5</strong></td>
<td>ตุ๊ก 1 ปี</td>
<td></td>
<td>1 ครั้ง/ปี</td>
<td></td>
</tr>
<tr>
<td><strong>6-10</strong></td>
<td>พิจารณาเป็นรายๆไป</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acute Cellular Rejection

• common from the first week to several years after transplantation
• 40% of patients during the first year after surgery.
• T cell activation, moderated by interleukin-2, a cytokine. Interleukin-2 is produced by CD4^+ cells and to a lesser extent by CD8^+ cells and exerts both an autocrine and a paracrine response.
• Endomyocardial biopsy remains the gold standard for the diagnosis of acute rejection.
Grade 1R Rejection
Grade 1R Rejection
myocyte damage
Grade 1R with 1 focus of myocyte damage
2R rejection:
multi-local infiltrate +Myocyte damage
3R rejection
# Acute Cellular Rejection

<table>
<thead>
<tr>
<th>2004 System</th>
<th>1990 System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 0 R</strong></td>
<td>Grade 0</td>
</tr>
<tr>
<td>No rejection</td>
<td>No rejection</td>
</tr>
<tr>
<td></td>
<td>Grade 1, mild</td>
</tr>
<tr>
<td><strong>Grade 1 R, mild</strong></td>
<td><strong>A—focal</strong></td>
</tr>
<tr>
<td>Interstitial and/or</td>
<td>Focal perivascular and/or</td>
</tr>
<tr>
<td>perivascular infiltrate with</td>
<td>interstitial infiltrate</td>
</tr>
<tr>
<td>up to one focus of</td>
<td>without myocyte damage</td>
</tr>
<tr>
<td>myocyte damage</td>
<td><strong>B—diffuse</strong></td>
</tr>
<tr>
<td></td>
<td>Diffuse infiltrate without</td>
</tr>
<tr>
<td></td>
<td>myocyte damage</td>
</tr>
<tr>
<td><strong>Grade 2 R, moderate</strong></td>
<td>Grade 2, moderate (focal)</td>
</tr>
<tr>
<td>Two or more foci of</td>
<td>One focus of infiltrate</td>
</tr>
<tr>
<td>infiltrate with</td>
<td>with associated myocyte</td>
</tr>
<tr>
<td>associated myocyte</td>
<td>damage</td>
</tr>
<tr>
<td>damage</td>
<td><strong>Grade 3, moderate</strong></td>
</tr>
<tr>
<td></td>
<td>A—focal</td>
</tr>
<tr>
<td>Diffuse infiltrate</td>
<td>Multifocal infiltrate with</td>
</tr>
<tr>
<td>with multifocal</td>
<td>myocyte damage</td>
</tr>
<tr>
<td>myocyte damage</td>
<td><strong>B—diffuse</strong></td>
</tr>
<tr>
<td>± edema, ± hemorrhage, ± vasculitis</td>
<td>Diffuse infiltrate with myocyte damage</td>
</tr>
<tr>
<td><strong>Grade 3 R, severe</strong></td>
<td>Grade 4, severe</td>
</tr>
<tr>
<td></td>
<td>Diffuse, polymorphous</td>
</tr>
<tr>
<td></td>
<td>infiltrate with extensive</td>
</tr>
<tr>
<td></td>
<td>myocyte damage ± hemorrhage</td>
</tr>
<tr>
<td></td>
<td>± vasculitis</td>
</tr>
</tbody>
</table>
AMR: Antibody-mediated Rejection

<table>
<thead>
<tr>
<th>Immunopathology</th>
<th>-</th>
<th>+</th>
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</thead>
<tbody>
<tr>
<td>-</td>
<td>pAMR0</td>
<td>pAMR1i</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Suspicious</td>
</tr>
<tr>
<td>+</td>
<td>pAMR1h</td>
<td>pAMR2</td>
</tr>
<tr>
<td></td>
<td>Suspicious</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pAMR3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>
C4d stain
Immunofluorescence positivity for C4d in capillaries with “doughnut” appearance
Risk Factors for AMR

- Female
- Elevated pre-transplant panel-reactive antibodies (PRAs)
- Positive donor-specific crossmatch
- Prior sensitization to OKT3
- Cytomegalovirus (CMV) seropositivity
- Prior implantation of ventricular assist device
- Retransplantation
# Treatment of rejection

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic</th>
<th>Reduced EF</th>
<th>Heart Failure/Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular</td>
<td>Target higher CNI levels</td>
<td>Oral steroid bolus/taper or IV pulse steroids</td>
<td>IV pulse steroids</td>
</tr>
<tr>
<td></td>
<td>Oral steroid bolus + taper</td>
<td></td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>Humoral</td>
<td>No treatment?</td>
<td>Oral steroid bolus/taper or IV pulse steroids +/−</td>
<td>IV immune globulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inotropic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IABP or ECMO support</td>
</tr>
</tbody>
</table>
Coronary Artery Vasculopathy (CAV)

- After 3 years
- Before 1 year—early—poor prognosis
- 30% to 40% of heart transplant recipients within 5 years
- Rapidly progress
- Lack of Angina
- Detection of CAV: DSE (sens 80% spec 88%) vs. CAG + IVUS
- Rx: Statin+Everolimus
- Rx: Retransplant
Revascularization procedures for CAV are only palliative, no survival benefit

<table>
<thead>
<tr>
<th>Nonsurgical Revascularization</th>
<th>n</th>
<th>6 mo</th>
<th>12 mo</th>
<th>5 y</th>
<th>Death or Graft Loss (Time of Follow-Up)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td>33</td>
<td>41</td>
<td>53</td>
<td>68</td>
<td>NA</td>
<td>Simpson et al&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>67</td>
<td></td>
<td></td>
<td>NA</td>
<td>Redonnet et al&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td>39% (19 mo)</td>
<td>Halle et al&lt;sup&gt;115&lt;/sup&gt;</td>
</tr>
<tr>
<td>Angioplasty ± stenting</td>
<td>62</td>
<td>25</td>
<td>35</td>
<td>43</td>
<td>56% (60 mo)</td>
<td>Benza et al&lt;sup&gt;113&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>33</td>
<td></td>
<td></td>
<td>17% (14 mo)</td>
<td>Schnetzler et al&lt;sup&gt;116&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>48% (52 mo)</td>
<td>Doshi et al&lt;sup&gt;117&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td></td>
<td>36 (33 mo)</td>
<td></td>
<td>54% (24 mo)</td>
<td>Fernandez et al&lt;sup&gt;118&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stenting (BMS)</td>
<td>25</td>
<td></td>
<td>38</td>
<td></td>
<td>NA</td>
<td>Jonas et al&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>31</td>
<td>46</td>
<td>69</td>
<td>NA</td>
<td>Simpson et al&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>64</td>
<td></td>
<td></td>
<td>NA</td>
<td>Redonnet et al&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td>DES vs BMS</td>
<td>40</td>
<td></td>
<td>15% (DES) vs 31% (BMS) at 40-mo follow-up (P=0.27)</td>
<td></td>
<td>NA</td>
<td>Bader et al&lt;sup&gt;119&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NA indicates not available; BMS, bare-metal stent; and DES, drug-eluting stent.
Table 3. Long-Term Results of Surgical Revascularization Procedures After HTx

<table>
<thead>
<tr>
<th>Surgical Revascularization</th>
<th>n</th>
<th>1 y</th>
<th>3 y</th>
<th>5 y</th>
<th>7 y</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bypass grafting</td>
<td>12</td>
<td>58% (9 mo)</td>
<td></td>
<td></td>
<td></td>
<td>Halle et al\textsuperscript{115}</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td>Patel et al\textsuperscript{120}</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>25% to 35% Procedural mortality</td>
<td></td>
<td></td>
<td></td>
<td>Musci et al\textsuperscript{121}</td>
</tr>
<tr>
<td>Retransplantation</td>
<td>514</td>
<td>65%</td>
<td>55%</td>
<td></td>
<td></td>
<td>Srivastava et al\textsuperscript{122}</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>72%</td>
<td>66%</td>
<td>47%</td>
<td>41%</td>
<td>Topkara et al\textsuperscript{123}</td>
</tr>
</tbody>
</table>
Sample case

- A 36 yo M Post OHTX 2 years presented with HF at the ER. What should we do?
  - Diuresis and DC home after no HF
  - EMBx
  - CAV
  - Echo
Sample case

- A 17 yo M Post OHTX 6 Months presented with dyspnea and abd pain - acute cholecystitis and low BP. What should we do?
  - Review history
  - Meticulous Physical Exam
  - Echo
  - Steroid
  - MCS if needed
Sample case

- A 54 yo M Post OHTX 2 weeks at CVT ward presented with VT VF. What should we do?
  - Cardioversion
  - Amiodarone
  - Xylocaine
  - Review H and P (PRA, H/O rejection, Cyclo/FK levels, K, Mg, LVEF)
  - Steroid
  - MCS if needed
Conclusions

- Heart Transplant is one standard treatments for heart failure.
- Heart transplant improves survival, functional capacity, and QOL
- Disease exchange
- Pre-Peri-Post are all important steps for good transplant outcomes
- Cardiologist: Know how and when to refer; Know how to evaluate RHC, Know transplant Emergency

Case Referral : 081-383-9302
Thank you