Demystifying medicine: transplantation and replacement therapy for heart failure

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April 22, 2014
NIAID
## Pediatric Organ Transplantation* 2005

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transplants</th>
<th>Total transplants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>890</td>
<td>16,477 (5.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>569</td>
<td>6,443 (8.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>54</td>
<td>1,406 (3.8)</td>
</tr>
<tr>
<td>Intestine</td>
<td>96</td>
<td>178 (54)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>26</td>
<td>541 (4.8)</td>
</tr>
<tr>
<td>Heart</td>
<td>313</td>
<td>2,125 (14.7)</td>
</tr>
<tr>
<td>K/P</td>
<td>7</td>
<td>903 (0.8)</td>
</tr>
<tr>
<td>Heart/Lung</td>
<td>5</td>
<td>35 (14.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,960</strong></td>
<td><strong>28,108 (7%)</strong></td>
</tr>
</tbody>
</table>

*Children awaiting transplantation = 2,187/99,383 (2.2%)
<table>
<thead>
<tr>
<th>Organ</th>
<th>1-year graft survival (%)</th>
<th>1-year patient survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>Liver</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Heart</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Kidney + Pancreas</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Pancreas</td>
<td>78</td>
<td>95</td>
</tr>
<tr>
<td>Lungs</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>78</td>
<td>84</td>
</tr>
</tbody>
</table>

~85%                ~90%
## Solid Organ Transplantation
### Long-term failure

<table>
<thead>
<tr>
<th>Graft Survival (%)</th>
<th>1-year</th>
<th>3-year</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>92</td>
<td>82</td>
<td>68</td>
<td>38</td>
</tr>
<tr>
<td>Heart</td>
<td>87</td>
<td>79</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>Lung(s)</td>
<td>82</td>
<td>58</td>
<td>49</td>
<td>-</td>
</tr>
</tbody>
</table>
Pediatric Heart Transplants

Kaplan-Meier Survival (Transplants: January 1982 – June 2011)

- Median survival (years): <1 = 19.7; 1-5 = 16.8; 6-10 = 14.5; 11-17 = 12.4
- 6-10 vs. 11-17: p = 0.0192
- No other pair-wise comparisons were significant at p < 0.05
Persisting Pestering Problems

1) Supply/demand imbalance

2) Morbidity from immunosuppression (e.g., renal, cardiovascular, infectious, malignancy)

3) Chronic rejection/injury and graft loss

4) Competing and emerging therapeutics (e.g., mechanical circulatory assistance, xenotransplantation, stem cells, whole organ engineering)
Key knowledge gaps

1) How can we optimize and individualize therapies and improve late graft outcomes mediated by immune and non-immune factors

2) Expansion and optimization of the donor and recipient pool

3) Optimize and individualize IS therapies and improve late allograft outcomes mediated by immune and non-immune factors

4) Characterize and understand antibody mediated rejection
Figure 1–20. Joining blood vessels by suture anastomosis. This representation is adapted from the line drawing by Alexis Carrel published in Lyon Medical in 1902. The walls of the two blood vessels (here drawn as about 5 mm. in diameter) are held together by three holding sutures. Another is then used to sew over and over, with very fine needles ("aiguilles extrêmement fines"). This method of suture anastomosis, demonstrated initially by Carrel, is still used throughout surgery, and particularly in the transplantation of organs.
HYPOTHERMIA
ITS POSSIBLE ROLE IN CARDIAC SURGERY:
AN INVESTIGATION OF FACTORS GOVERNING SURVIVAL IN DOGS
AT LOW BODY TEMPERATURES*

W. G. BIGELOW, M.D., W. K. LINDSAY, M.D.,
AND W. F. GREENWOOD, M.D.

TORONTO, CANADA

THE USE OF HYPOTHERMIA as a form of anesthetic could conceivably
extend the scope of surgery in many new directions. A state in which the
body temperature is lowered and the oxygen requirements of tissues are
reduced to a small fraction of normal would allow exclusion of organs from
the circulation for prolonged periods. Such a technic might permit surgeons
to operate upon the "bloodless heart" without recourse to extra corporal
pumps, and perhaps allow transplantation of organs.

At the present time, pericardectomy as well as operations designed to
revascularize1, 2, 3 or repair4 the myocardium are in the process of develop-
ment; these involve the heart wall. Most so-called heart operations, however,
are restricted to the anastomosis of vessels about the heart, the most notable
in this category being the current operations for congenital heart disease6, 6
and a shunt7 for mitral stenosis. Intracardiac procedures upon human beings
are heroic technics designed to open a stenosed mitral valve and close8 or pro-
duce9 a septal defect in an intact heart with little or no visual control. All these
procedures represent advances in our knowledge, but the human heart until
now has resisted serious inroads by the surgeon. The shunt operations produce
a secondary, although less serious, defect and intracardiac operations under
direct vision are still not possible.

A bloodless heart excluded from the circulation is necessary before much
further progress can be made in the field of cardiac surgery. Methods to short
circ uit the heart by an extra corporal heart-lung pump have been under
experimental study in different centers10, 11, 12 for several years. We have used

* Financed in part by a Defence Board of Canada grant. Submitted for publication
November, 1949.
Fig. 1. Method of linking donor and patient for direct vision intracardiac surgery. a. Patient showing sites of arterial and venous cannulations. b. Donor showing sites of arterial (superficial femoral) and venous (saphena magna) cannulations. c. The pump assembly consisting of an electric motor, a speed changer, and the pumping unit. The pump consists of multiple cam operated metal fingers that massage the blood contained within the tubing. d. A magnified view of the patient's heart showing the plastic vena caval catheter which has been inserted through the internal jugular vein in the neck and positioned so that venous blood is withdrawn from both cavae during the interval of total cardiac by-pass. Note also the relative positions of the vena cavae excluding tapes for securing inflow stasis during the intracardiac procedure. The arterial blood from the donor is circulated to the patient's body via the catheter inserted into either the right or left subclavian artery.

Lillehei’s Cross-Circulation Diagram
Dad = heart-lung machine
Son = subject with hole in heart
John Heysham Gibbon and his wife
The Cape Argus Newspaper after the First Human Heart Transplant

Christiaan N. Barnard
Heart Transplantation

Diagram of extracorporeal circulation: superior and inferior venae cavae cannulated by catheters introduced, respectively, via internal jugular vein and subclavian vein, thus leaving operative field free.

Recipient’s thorax opened by midline sternum-splitting incision; pericardium incised longitudinally and stitched to wound edges; apex passed around upper corner of pericardium and tightened on patient is placed on extracorporeal circulation; aorta clamped. (Brown lines indicate levels for transection of aorta and pulmonary trunk.)
Heart Transplantation: Donor Heart

Heart removed from donor by severing superior and inferior vena cavae, pulmonary veins, aorta, and pulmonary trunk (viewed from rear). (Broken lines indicate incisions to connect caval orifices and vein orifices, thus opening the atria without dividing the septum.)

The flags created by the incisions indicated above have been turned out and drawn longitudinally by sutures, thus extending the septum and atrial walls to accommodate a larger heart of recipient.

Diagram to indicate successive continuous sutures to be employed in uniting donor heart to recipient.
Diagnosis of human cardiac allograft rejection by serial cardiac biopsy

Pathology of Transplantation

- Effects of immunosuppression
  - drug toxicity
  - infection
  - neoplasia
- Allograft rejection
  - humoral (antibody-mediated)
  - cellular
  - chronic injury
Therapy categories

**Induction** = therapy at start of transplant; typically consists of methylprednisolone and/or antibody preparations (lymphocyte depletion)

**Maintenance** = chronic therapy

**Desensitization** = therapies to reduce newly formed or pre-existing alloantibodies; IV Ig or Cyclophosphamide, Rituximab (anti-CD 20 antibody), Bortezomib, Eculizumab
## Basic Immunosuppression

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Basiliximab</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Daclizumab</td>
</tr>
<tr>
<td>Mycophenolate moftetil (MMF)</td>
<td>OKT3</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>ATGAM</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Thymoglobulin</td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
</tr>
<tr>
<td>Belatacept (FDA approved-2011)</td>
<td>Alemtuzumab (Campath-1H)</td>
</tr>
</tbody>
</table>
Side Effects of Chronic Immunosuppression

**Infectious**
- Viral
- Fungal
- Bacterial

**Malignant**
- Lymphoma
- Skin

**Toxic**
- Renal
- Cardiovascular (hypertension, hyperlipidemia)

**Metabolic**
- Diabetes
- Osteoporosis

**Cosmetic**
- Hirsutism
- Acne
Immunotherapy is a Balance

- Immunosuppression prevents rejection and is required indefinitely post-Tx
- Immunosuppression has risks: infection, malignancy, toxicity
- Finding the balance is an important task but there is no established objective measure of immunosuppression
Pediatric Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support* by Year (Transplants: January 2005 – December 2011)

* LVAD, RVAD, TAH, ECMO

JHLT. 2013 Oct; 32(10): 979-988
Pediatric Heart Transplants

All pair-wise comparisons were significant at p < 0.001 except No ECMO/VAD/TAH vs. VAD or TAH, no ECMO

ECMO, no VAD or TAH (N=172)
VAD or TAH, no ECMO (N=450)
No ECMO/VAD/TAH (N=2,063)

* LVAD, RVAD, TAH, ECMO

JHLT. 2013 Oct; 32(10): 979-988
Pediatric Heart Transplants
Freedom from Coronary Artery Vasculopathy by Age Group (Follow-ups: 2000 – June 2012)

% Free from CAV

Years

<1 Year (N = 834)
1-5 Years (N = 766)
6-10 Years (N = 473)
11-17 Years (N=1,196)

p < 0.0001

JHLT. 2013 Oct; 32(10): 979-988
# PEDIATRIC HEART TRANSPLANTS (2001-2010)

Risk Factors For 1 Year Mortality

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>P-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO</td>
<td>280</td>
<td>2.65</td>
<td>&lt;.0001</td>
<td>2.00-3.50</td>
</tr>
<tr>
<td>Retransplant</td>
<td>206</td>
<td>2.16</td>
<td>0.0003</td>
<td>1.42-3.27</td>
</tr>
<tr>
<td>Congenital diagnosis</td>
<td>1426</td>
<td>2.04</td>
<td>&lt;.0001</td>
<td>1.58-2.64</td>
</tr>
<tr>
<td>On dialysis</td>
<td>123</td>
<td>2.03</td>
<td>&lt;.0001</td>
<td>1.42-2.90</td>
</tr>
<tr>
<td>Donor cause of death = cerebrovascular/stroke vs. head trauma</td>
<td>327</td>
<td>1.53</td>
<td>0.009</td>
<td>1.11-2.11</td>
</tr>
<tr>
<td>Donor cause of death other than (head trauma, cerebrovascular/stroke, anoxia and CNS tumor) vs. head trauma</td>
<td>289</td>
<td>1.49</td>
<td>0.027</td>
<td>1.05-2.12</td>
</tr>
<tr>
<td>Male donor/female recip vs. male donor/male recip</td>
<td>913</td>
<td>1.44</td>
<td>0.006</td>
<td>1.11-1.88</td>
</tr>
<tr>
<td>Prior sternotomy</td>
<td>830</td>
<td>1.42</td>
<td>0.007</td>
<td>1.10-1.83</td>
</tr>
<tr>
<td>On ventilator</td>
<td>700</td>
<td>1.35</td>
<td>0.017</td>
<td>1.06-1.73</td>
</tr>
<tr>
<td>PRA &gt; 10%</td>
<td>311</td>
<td>1.35</td>
<td>0.05</td>
<td>1.00-1.81</td>
</tr>
<tr>
<td>Infection requiring IV drug therapy (within 2wk/TX)</td>
<td>610</td>
<td>1.32</td>
<td>0.027</td>
<td>1.03-1.69</td>
</tr>
<tr>
<td>Donor cause of death = anoxia vs. head trauma</td>
<td>902</td>
<td>0.75</td>
<td>0.026</td>
<td>0.58-0.97</td>
</tr>
</tbody>
</table>

Reference group = Cardiomyopathy, no devices

N = 3,516
Pathology of Rejection

- Hyperacute (antibody-mediated)

- Antibody-mediated rejection (humoral)

- Acute
  - cellular

- Chronic (OB, CAV, CAN, vanishing bile)
Heart transplant patient who died of humoral rejection. Macros show diffuse hemorrhage in both ventricles. Micros show intravascular macs and neutrophils. IF show capillary positivity for IgM, C1q and HLA-DR.
Hyperacute rejection

- < 1% incidence (role of cross-match)
- Minutes to days onset
- Abrupt organ dysfunction
- Preformed circulating Abs
  - complement activation
  - neutrophil recruitment
  - platelet aggregation
- Vascular thrombosis
AMR: Histology

A: No AMR
B: Borderline AMR
C: Severe AMR
D: Mild AMR
E: Moderate AMR

AMR: Immunopathology

A: IgG
B: C4d
C: HLA-DR
D: Fibrin
E: HLA-DR
F: Fibrin

Mild AMR
Moderate AMR
Severe AMR
The Spectrum of Antibody-mediated rejection
Cardiac Allograft Vasculopathy (CAV)

Histology: Chronic AMR?
Management of Antibody-mediated Rejection

“To fight the enemy, first know the enemy”

- **Removal of circulating anti-HLA antibodies**
  - Plasmapheresis, immune apheresis (adsorption)

- **Reduction in production/inhibition of anti-HLA antibodies**
  - Intravenous immune globulin (IVIG)
  - B-cell (anti-CD20 monoclonal antibody rituximab); plasma cell (proteasome inhib. bortezomib) depletion
  - Cytolytic therapy, tacrolimus/MMF, cyclophosphamide, TLI?, photopheresis?

- **Anti-complement therapy**
  - (eculizumab, anti-C5 monoclonal antibody)

- **High dose steroids, circulatory support, anticoagulation**
Chronic “rejection” (injury)

- Achilles heel (biologic constraint) of solid organ allotransplantation
- Months to years onset
- Insidious decline in organ function
- Chronic healing and scarring
- Vascular (or airway or biliary) dense fibrosis (ischemia)
- Rx-reTx (poor response to conventional immunotherapy)
How Technology Will Heal Your HEART

Patient Power on The Web
Made-to-Order Medicine
Robotic Surgery

The AbioCor implantable replacement heart
Advantages of Long-Term Mechanical Support

- nutritional status
- muscle mass and tone
- functional capabilities
- end-organ function
- better transplant candidates
Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system

Frazier et al.: Circulation. 2002;105:2855-2860
This report details the first case of cardiac xenotransplantation in a neonate. The recipient, a victim of hypoplastic left heart syndrome (HLHS), survived 20 days. Autopsy findings are documented. The cardiac graft showed only traces of cell-mediated rejection. Graft failure appears to have resulted from a progressive, potentially avoidable humoral response, unmodified by immunosuppression. Cardiac allotransplantation and selective baboon-to-human xenotransplantation deserve further exploration as investigational therapy for neonatal HLHS.

(JAMA 1985;254:3321-3329)
Animal and Human Models
Xenotransplantation

Galactose -alpha-1,3-galactose - main target for human preformed antibodies

1) With GRKO/HCD55 pigs to nonhuman primates (cardiac xenografts) have a median survival of 90 days

2) Further genetic modifications of pigs ongoing by introduction of human anticoagulant or antithrombotic protein-encoding genes (thrombomodulin, tissue factor pathway inhibitor) as well anti-inflammatory and anticoagulation genes will be needed for viable long-term outcome and organ function

3) Biosafety issues related to transmission porcine endogenous retroviruses (PERV)
Coronary Artery Disease
Organ Donor Management

International clinical trials of heart and lung organ management prior to implantation:

- PROCEED II
- NOVEL
- INSPIRE
Old and the New

1) Marginal donors (e.g., HIV+, HCV+, older, longer ischemic time, CAD, valvular disease, LVH)

2) Organ Care System (Transmedic) [Hearts and Lungs + pumping kidneys]

3) Cell therapy (e.g., stem cells, pluripotent cells, BMC)

4) Growth and generation of whole organs on various scaffolds
Donor – brain death

Leads to inflammatory response – in heart

- Increase levels of IL-6, IL-6 receptors, P-selectin, VCAM-1, TNF-α
- Higher levels in failing vs. non-failing hearts
- TNF-α elevation predicted poor outcome
Conclusions

- The first 60 years of organ transplantation has witnessed tremendous progress in management of acute rejection and one year graft survival approaches 90% for most organs.

- Attention is now refocused on improving long-term outcomes with attention focused on combating antibody and innate mediated injury, reducing renal and cardiovascular morbidities, donor organ management prior to implantation, and personalized immunosuppression.