History of Cardiac Transplantation

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HF in the US

~6.0 million Americans with HF (2.8% of adult US population)

- Lifetime risk at age 40 or 80 – 1 in 5
- 670,000 new cases/year
- Contributes to 281,000 annual deaths (1 in 8 death certificates mention HF)
- 1.1 million ADHF hospitalizations each year (~3M total)
  - 6.5 million hospital days; LOS 6.4 d
- 30 day readmission rate 25% (50% not seen by physician) – all cause penalized by Medicare to 1% of all reimbursement
- 1.8 million ambulatory visits
- Mortality 50% at 5 years; 34% at 1 year after a single hospitalization
- #1 reason for hospitalization of people > 65 yr. old
  - More costly than all forms of cancer combined
  - Largest federal Medicare (37¢/$1) and VA $ expenditure
- Cost $39.2 billion ($160 B by 2030)
  - $21B annual hospitalization costs
Chronic Heart Failure Care: We’ve come a long way...
Osler’s Recommendations for Heart Failure

“Special care should be taken of the bowels”
“A cold tub in the morning, if unsuccessful a lukewarm tub at night”
“Young people should be allowed plenty of sleep including an hour’s rest in the middle of the day”
“The question of marriage is always a distressing one”
“During the winter months a change in climate is most helpful”
“Moderation in all things should be the motto of the patient”
“More violent sports, such as football and hockey, should be interdicted”
“Golf is a particularly suitable game for young men”
“Gymnastic movements may be employed”
“Dancing is allowed in moderation for young girls with simple mitral lesions...and the apex beat not very far out”

Osler: The Principles and Practice of Medicine, 8th ed 1913
Hurst’s The Heart 1974

Treatment of HF

- Decreased physical activity
- Digitalis
- Thiazides plus potassium
- Change to furosemide if no response
ACCF/AHA 2013 HF Guidelines JACC 2013 5 June (E-Pub online)

**At Risk for Heart Failure**

**Stage A**
- At high risk for HF but without structural heart disease or symptoms of HF
  
  - e.g., Patients with:
    - HTN
    - Atherosclerotic disease
    - DM
    - Obesity
    - Metabolic syndrome
    - Patients using cardiotoxins
    - With family history of cardiomyopathy

**Stage B**
- Structural heart disease but without signs or symptoms of HF
  
  - e.g., Patients with:
    - Previous MI
    - LV remodeling including LVH and low EF
    - Asymptomatic valvular disease

**Stage C**
- Structural heart disease with prior or current symptoms of HF
  
  - e.g., Patients with:
    - Known structural heart disease and HF signs and symptoms

**Stage D**
- Refractory HF
  
  - e.g., Patients with:
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT

**Therapy**

**Stage A**
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities

- Drugs:
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate

**Stage B**
- Goals:
  - Prevent HF symptoms
  - Prevent further cardiac remodeling

- Drugs:
  - ACEI or ARB as appropriate

**Stage C**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality

- Drugs for routine use:
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists

**Stage D**
- Goals:
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality

- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic isotopes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

**Therapy**

**Stage A**
- In selected patients:
  - ICD
  - Revascularization or valvular surgery as appropriate

**Stage B**
- In selected patients:
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**Stage C**
- In selected patients:
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate
Two Year Survival of "Triple Therapy" in CHF

- Placebo
- Active
- Difference

- II
- 153 Lives Saved per 1,000 Treated

- III/IV
- 452 Lives Saved per 1,000 Treated
“Something’s just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty.”
What is Advanced Heart Failure?
(As Defined By the ESC and adopted by the ACCF/AHA for the 2013 Guidelines)

Despite maximal tolerated medical/device management:

- NYHA Cl III/IV symptoms
- Clinical signs of fluid retention and/or peripheral hypoperfusion
- Objective evidence of severe LV dysfunction
  - LVEF < 30%
  - Pseudonormal or restrictive mitral inflow pattern by Doppler
  - High left and/or right sided filling pressures
  - Elevated b-type natriuretic peptide
- Severe reduction in exercise capacity
  - 6 minute walk distance < 300 meters
  - Peak VO₂ < 12-14 ml/kg/min
  - > 1 hospitalization in last 6 mos
The Late Stage Heart Failure Patient

Severe exercise intolerance
Heart failure wasting syndrome
Cardiorenal syndrome
Right heart failure
Inotrope dependence

Courtesy of J. Rogers
Options for the Advanced Heart Failure Patient

• Optimize neurohormonal inhibition and device therapy
• High risk conventional cardiac surgery
• Heart transplantation
• Mechanical circulatory support
• Palliative care/hospice (chronic IV inotropes)
The “first” heart transplant using a chimpanzee as a donor

James Hardy

“This experience supports the scientific feasibility of heart transplantation in man”
“Observations...suggest that, if the Immunologic mechanisms were prevented from destroying the graft, in all likelihood it will continue to function adequately for the normal span of the animal”
CRISIS AFTER 7 DAYS

Louw tells of key factor in heart transplant

Thirty-two hours after his historic heart transplant in Groote Schuur Hospital, Mr. Louis Washkowsky is maintaining his satisfactory condition. Dr. J. C. Burger, Medical Superintendent of the hospital, said today.

The critical part in the heart transplantation would be in about a week’s time. Prof. J. H. Louw, head of the Department of Surgery at the University of Cape Town Medical School, said today.

Woman had no chance of survival

They will miss Denise...

And a surgeon took the pictures, too!

CHURCHMEN APPROVE

From a novel point of view the action of Groote Schuur Hospital to give a new heart to a patient has received support from the church.

MAN WITH A NEW HEART

Three years’ work on ‘op’
Moment in History

America's First Human Heart Transplantation

The Concept, the Planning, and the Furor

ADRIAN KANTROWITZ
EVERY SECOND COUNTS

The Race to Transplant the First Human Heart

DONALD McRAE
“The transplantation of organs will be assimilated into ordinary clinical practice...and there is no need to be philosophical about it. This will come about for the single and sufficient reason that people are so constituted that they would rather be alive than dead.”

Sir Peter Medawar, 1968
2nd Int Congress of The Transplantation Society
1960 Nobel Laureate for Transplantation Immunity
Heart Transplantation: Improvements Accounting for Improved Outcomes 1967-present

- Endomyocardial biopsy
- Immunosuppression to prevent rejection**
- Corticosteroid-free immunosuppression***
- Standardization of rejection definition*
- Identification and standardization of Antibody-mediated (Vascular) Rejection***
- Prevention of infection*
- Expansion of donor criteria*
- Study of cardiac allograft vasculopathy*

* Major contribution by UTAH Cardiac
1973: Philip K. Caves Develops the Bioptome for Endomyocardial Biopsy
“Come on, come on, come on, come on and take it...
Take another little piece of my heart now, Baby”

Janis Joplin at Woodstock
The Evolution of Immunosuppressive Therapy

1960’s
- Corticosteroids
- Polyclonal antibodies
- Azathioprine

1980’s
- Cyclosporine
- Monoclonal antibodies

1990’s
- Tacrolimus
- Mycophenolate mofetil
- Sirolimus
- IL2R Blockade

2000’s
- Everolimus
Adult and Pediatric Heart Transplants
Kaplan-Meier Survival
(Transplants: January 1982 – June 2015)

Median survival = 10.7 years;
Median survival conditional on surviving to 1 year = 13.3 years

N = 118,788
Erik Compton shares lead, steals show at Greenbrier Classic

USA Today 7/30/10

Heart transplant recipient at ages 12 and 28
Dale Shippam (11 Years Post Transplant) at the North Pole
Kelly Perkins Climbed 10 Teton Peaks in 4 Days at age 47 years (August 2009)

She received her heart transplant in 1995
Dick Cheney’s LVAD: BTT or DT??

TODAY Show 01/18/2011

“I haven't made a decision yet. The technology was originally developed to provide a transition. To take somebody who's reached the point where they needed a transplant but a transplant wouldn't immediately be available, so they put this in as a temporary measure.

What's happened over time is the technology's gotten better and better and we've gotten more and more experience with people living with this technology. So I'll have to make a decision at some point whether or not I want to go for a transplant. But we haven't addressed that yet.”
Heart Transplantation will never meet the demands
Even though transplants are considered the ‘gold standard’, the supply has been historically flat and limited

“Proposing heart transplantation to cure heart failure is analogous to proposing the lottery to cure poverty”
- LW Stevenson

4,147 await heart transplantation
(22 Aug, 2016)

1. UNOS Website: http://optn.transplant.hrsa.gov
2. O’Connell Advanced Heart Failure Therapies Forum Atlanta 2013
Transplant/Population Ratio

![Graph showing the Transplant/Population Ratio from 1988 to 2013. The ratio decreases over time, with a trend line indicating a downward trend.]
“Xenografting is the future ... and always will be.”

Norman Shumway

“I like pigs. Dogs look up to us; cats look down on us. Pigs are our equal”

Winston Churchill
“It’s been a pleasure to be able to help people and maybe you folks learned something” 1982
MED-LVAD 1966
Thoratec pvad in vfib
“When we have a totally implantable, inexhaustible, non-heat producing, noiseless power source and materials that neither cause blood clots nor deteriorate, we will have a better answer to the challenge of the total artificial heart. I suspect, however, that this new type of energy will be available initially in our automobiles and refrigerators long before it becomes a part of biology.”

N. Shumway, M.D.
Heart Transplantation 1983;3:3-5.
Continuous Flow LVAD
HeartMate II Improvements in BTT Survival From clinical trial to commercial Use

P < 0.001 log-rank test

Post-Trial (N=1496) 85%

Trial (N=486) 76%

John, Naka, Smedira et al Ann Thor Surgery 2011
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support*
(Transplants: January 2000 – December 2014)

Year of Transplant

% of Patients


* LVAD, RVAD, TAH, ECMO

JHLT. 2016 Oct; 35(10): 1149-1205
Summary of DT Outcomes

DT Post Approval (n=247)

- Months 0: 90 + 2%
- Months 6: 92 + 2%
- Months 12: 74 + 3%
- Months 18: 68 + 4%
- Months 24: 61 + 3%

Remaining at Risk:
- 247
- 192
- 169
- 151
- 130
- 133
- 95
- 82
- 69
- 62

DT Trial (n=133)¹

- Months 0: 90 + 2%
- Months 6: 92 + 3%
- Months 12: 92 + 2%
- Months 18: 90 + 2%

Remaining at Risk:
- 133
- 95
- 82
- 69
- 62

¹Slaughter, Rogers, Milano NEJM 2009;361:2241-51

LVAD Destination Therapy (HMII Post Approval Study)

Medical Management (REMATCH, NEJM 2001)

Jorde, ISHLT 2013
Yolanda walks the runway at the Georgia Transplant Association fashion show.
The HeartMate 3 LVAS (St. Jude Medical, Inc.) is a centrifugal, fully magnetically levitated, continuous-flow blood pump engineered to obviate thrombosis and shear stress on blood elements.
KM estimates for Event-free Survival (ITT)

Logrank Analysis P = 0.0298

no. at risk
HM3 152 146 138 135 130 128 127
HM II 142 125 119 116 110 106 103
“Better to put the device in 5 months too early than 5 minutes too late...”

Walter Dembitsky MD,
Cardiac Surgery
Sharp Memorial Hospital
San Diego
Young Once Immature Forever

Age 87 yrs

Age 90 yrs
1950’s

Provided by James Long MD
MCS – the Next Generation

Pump Technology

- Fully Magnetically Levitated Technology
- Designed to be the most hematologically compatible pump
- Continued commitment to Full MagLev™ technology
- Enhanced profile with full-support pump performance
- Designed to accommodate multiple access/incision strategies
That’s Not All...

You may be able to grow your own!!!!

Fig. 1 Generating patient-specific organs for transplantation

hES = human embryonic stem; iPSC = induced pluripotent stem cell

Taylor DA Texas Heart Inst J 2009 36:148-9
Tissue Engineered Autologous Bladders

7 p (age 4-19) with myelomeningocele
Urethral and muscle cells grown in culture from bladder biopsy and seeded on biogradable scaffold
Bladders functioned normally out to 46 months.

Atala et al. Lancet 2006; 367:1241-6
THE LAST THING YOU WANT TO HEAR ON YOUR NEXT TRIP TO THE HOSPITAL:

OH, WHAT THE HECK...
GET ME A JARVIK 7
WITH A COLD FUSION POWER UNIT...
The Vision: A Single Transplant Program in a VERY Competitive Market – It took Visionaries

UTAH Cardiac
Contributions of UTAH Cardiac

• Proved 3 very different hospitals could work together to provide a state of the art service to the entire state
• Could maintain comparable volume at two competing hospitals
• Incorporated private cardiology groups into the program as providers
• Became the second national VA program
• Incorporated a children’s hospital into an adult program
• Defined a national standard for program growth (highest volume program in US within three years) and relationship with community physicians
• A model of a comprehensive HF program utilizing APPs and made major contributions to HF drug development (beta blockers, PDE-3 inhibitors)
• Proved donors turned down by other programs could be very adequate
• Broke age barriers with both recipients and donors
• Defined risk profiles for rejection
• Major scientific contributions in areas of immunosuppression (OKT3, mycophenylate mofetil, corticosteroid immunosuppression, etc)
• Described vascular (AMR) rejection for the first time and characterized it’s clinical and immunopathologic implications
“Scientific purity is the temple of fools.”

Michael Bristow MD, 1993
U.T.A.H. Cardiac Transplant Program
Medical Director
John B. O’Connell, M.D.
Kent’s Contributions to Cardiac Transplantation

Great surgeon

- Original description of UTAH Cardiac
- Age and allograft rejection
- Sex and allograft rejection
- OKT3 prophylaxis
- Corticosteroid free immunosuppression and benefits (cholesterol, CAV)
- OKT3 treatment for rejection after prophylaxis
- Vascular (AMR) rejection – original description and relationship to CAV
- OKT3 sensitization
- Periop MCS
- Lymphoproliferative disease post OKT3
- First use of mycophenolate mofetil in cardiac transplants
This Hugh Hefner look alike:

- Taught Me a Left Handed Ute Loving Baseball player Could Really Operate