

2016

Part V:
Circulatory Support
& Transplantation

*Ain Shams Lecture Notes in
Cardiovascular & Thoracic Surgery*



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To My Students

You will remember

some of what you hear,

much of what you read,

more of what you see,

and

almost all of what you experience and understand fully.

'Happiness comes when you

believe in what you are doing,

know what you are doing,

and

love what you are doing'

Ezzeldin A. Mostafa, MD, PhD, MBA

Tell me.....and I will forget

Show me.....and I may remember

Involve me.....and I will understand

Confucius, 450 BC

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1. Low Cardiac Output & Circulatory Support

1.1. Cardiogenic Shock

1.1.1. Definition

BP systolic < 80 mmHg (or 30 mmHg below basal, BP mean <60 mmHg)
CI < 2 L/min/M² (with adequate filling)
LAP and/or RAP > 20 mmHg

1.1.2. Clinical Manifestations of Low C.O.

Decreased peripheral perfusion (pulses, cool, mottled)
Restlessness, confusion decreased mentation
UO < 20-30 ml/hr (adults)

1.1.3. Causes

MI, myocarditis, tamponade, arrhythmias, acute MR/AI
Massive pulmonary embolism, vena caval obstruction, tension pneumothorax
R/O hypovolemia, acidosis, anemia, sepsis

1.1.4. Determinants Of Cardiovascular Performance

Table 1: Determinants Of Cardiovascular Performance

Primary Determinants Of Cardiovascular Performance

Heart Rate & Rhythm

Sinus Rhythm vs Atrial Fibrillation, AVB; bradycardia; tachycardia

Preload (Ventricular filling)

Frank-Starling effect

Ventricular Compliance (Distensibility)

Effect of ischemia, injury, pericardial space
(Tamponade - decreased CO, BP, PP, increased LAP=RAP)

Ventricular Contractility

Inotropes

Sympathomimetic amines, phosphodiesterase inhibitors

Afterload (Vascular resistance)

Vasoactive therapy

Secondary Determinants Of Cardiovascular Performance

Oxygen delivery

O₂ carrying capacity (Hgb)
Oxygenation

Metabolic - acid/base status

Acidosis (effect on contractility)
Alkalosis (decreases release of O₂ from Hgb, Left shift oxygen-Hgb dissociation curve)

Metabolic stress/load

Fever, agitation, respiratory distress

1.1.5. Approach To Cardiogenic Shock

Table 2: Approach To Cardiogenic Shock

Medical Management of Reversible Causes
Primary Determinants of CV Performance
Rate & Rhythm, Preload, Compliance, Contractility, Afterload
Secondary Determinants of CV Performance
Oxygen delivery, Acid/base status, Metabolic load
Assisted Circulation
Intra-Aortic Balloon Pump (IABP)
Cardiopulmonary Support (CPS)
Ventricular Assist Device(s) (VAD's)
Total Artificial Heart (TAH's)

Intra-Aortic Balloon Pump (IABP)

Indications for Use

Failure to wean from CPB (49%)
Post-MI cardiogenic shock (22%)
Refractory myocardial ischemia (15%)
Post-op cardiogenic shock (7%)
MR or VSD (temporizing)
Ischemic arrhythmias
(Bridge to transplant)

Contraindications for Use

Aortic valve insufficiency
Severe peripheral vascular disease (?)

Complications

Limb ischemia (5-18%)
Insertion site hemorrhage (2-4%)
Infection (1-2%)
Aortic or iliac perforation (1-2%)
Aortic dissection (1%)
Renal artery embolism or thrombosis (1%)
Mesenteric infarction (1%)
Spinal cord injury (0.5-1%)
Gas embolization/rupture (0.5%)
CVA (0.5%)

Results

Post-cardiotomy Failure
75-85% weaned
55% survival
Post-MI Cardiogenic Shock
75% will improve hemodynamically
In post MI use, mortality is 85%
Post-MI + intervention - mortality = 40-50%

Advanced Mechanical Support

Indications

Post-cardiotomy cardiogenic shock
Post-MI cardiogenic shock
Post-transplant graft failure

- High-risk PTCA support
- Cardiopulmonary Resuscitation (CPR)
- Hypothermia rewarming
- Bridge-to-transplant (or recovery)
- Alternative to transplantation (future)

Post-Cardiotomy Mechanical Circulatory Support

Intraoperative Management

- Pharmacologic support
- Intra-aortic balloon pump
- Optimization (volume, metabolic, respiratory, drugs)
- Decision for VAD
- Patient selection
- Early intervention

Patient Selection

- Inclusion Criteria
 - Cardiogenic shock: CI <2 l/min/M², BP systolic <80 mmHg
 - LAP >20 and/or RAP >20 mmHg
 - (after medical optimization - pre/afterload, respiratory, metabolic)
 - (after pharmacologic support)

Exclusion Considerations

- Technically imperfect operation
- Perioperative MI (vs. stunned myocardium)
- Age
- Preoperative "emergency" status
- Massive bleeding
- Long CPB
- End-organ failure (renal, hepatic, pulmonary ..)
- Infection (i.e. endocarditis)

Intraoperative Management - Implementation of support

- Select VAD, cannulae
- Cannulate, implement VAD support
- Re-assess cardiac performance
- Secure hemostasis
- Wound handling (close vs. open)

Equipment

- Ventricular Assist Devices
 - (Considerations: cost, availability, familiarity, anticoagulation, blood trauma, monitoring)
 - Pulsatile, pneumatic
 - Centrifugal pumps
 - [Roller pumps]
- Cannulae
 - Uptake: R. side: 34-51 Fr; L.side: 28-36 Fr
 - Return: Ao and PA: 22 Fr

Management of VAD Support

- Observe for bi-ventricular failure
- Institute second VAD as needed
- Secure Hemostasis
 - Reverse Heparin
 - Fibrin Glue
- Wound Handling
 - Close sternum/skin
 - Close skin only, support sternum
 - Leave open (silastic or Esmark ...)

Postoperative - General

- Maximize Myocardial Recovery
 - Reduce Inotrope support
 - Keep heart decompressed
- Anticoagulation
 - Intraop - heparin is reversed
 - When CT output OK - ACT > 180
 - When weaning VAD - ACT > 220
- Maintain Pulsatile Perfusion (?)
 - Leave IABP in place

Postoperative - Weaning

- Time Course
 - At least 24 hours
 - But <10% survivorship after 7 days
- Follow Recovery
 - Reduce VAD flow (i.e. to 1L/min)
 - Observe LAP,RAP,AoP,PAP,SVO2
 - Observe cardiac function w/ TEE
- Remove VAD
 - With good hemodynamics at low VAD flow
- Wean IABP & drips as able

Problems

- Cardiovascular
 - RV failure with LVAD
 - decreased LAP, decreased VAD out, increased RAP
 - LV failure with RVAD
 - decreased RAP, decreased VAD out, increased LAP
 - Hypovolemia (decreased LAP/RAP decreased VAD out)
 - Cyanosis - shunting through PFO
- Device-Related
 - Thromboemboli
 - Cannula obstruction
 - increased LAP/RAP, decreased VAD out
 - Device failure
 - Hemolysis
- Systemic
 - Bleeding (30-45% return to OR)
 - End-organ failure (renal, respiratory, hepatic)
 - Infection

Results

Weaned - 50-60%

Survived - 25-50%

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1.2. Assisted Circulation

1.2.1. Advanced Mechanical Support

Indications

1. Post-cardiotomy cardiogenic shock
2. Post-MI cardiogenic shock
3. Post-transplant graft failure
4. High-risk PTCA support
5. Cardiopulmonary resuscitation (CPR)
6. Hypothermia rewarming
7. Alternative to transplantation (clinical trials)

1.2.2. Circulatory Support

Table 3: Circulatory Support

Mechanical cardiac assist
Intra-aortic balloon pump (IABP)
Ventricular assist devices (VAD)
Cardiopulmonary support (CPS, ECMO)
Mechanical cardiac replacement
Total artificial hearts (TAH)
Others
Biologic cardiac assist- cardiomyoplasty
Ventricular remodeling
Pacing

1.2.3. Mechanical Circulatory Support- Characterization

- Output hemodynamics
 - Pulsatile
 - Non-pulsatile
- Drive mechanism
 - Pneumatic; electric (hydraulic, mechanical)
- Configuration
 - TAH, BVAD, RVAD, LVAD
- Status/availability
 - Approved for market, IDE trials, in development

Placement position

- Orthotopic; heterotopic; extracorporeal
- Paracorporeal; transcutaneous
- Implantability
 - Fully; partially; not at all
- Application/ permanence
 - Temporary; bridge-to-transplant, cardiogenic shock; bridge-to-recovery
 - Permanent; alternative-to-transplantation

Table 4: Device Selection for Bridge-to-Transplantation

Criteria	LVAD	RVAD	BVAD	TAH
LV failure	++	--	--	+
RV failure	--	++	--	+
LV & BV failure	--	--	+	+
Unresectable trombus	--	--	--	+
S/P mechanical valve	--	--	--	+
AI (or PI)	--	--	--	+
Irreparable intracardiac shunts	--	--	--	+
Uncorrectable arrhythmias	?	?	+	+
Refractory ischemia, angina	--	--	--	+
Transplant heart rejection	--	--	--	+
Acute MI at cannula site	?	?	?	+
Unresectable cardiac tumor	--	--	--	?

1.2.4. Bridge-to-Transplant

- Problems
 - Cardiovascular
 - Failure on non-supported ventricle
 - Arrhythmias
 - Cyanosis/shunting with PFO
 - Ischemia/angina
 - Systemic
 - Hemorrhage
 - End-organ failure
 - Infection
 - Infection
 - Immune sensitization
 - Compromised quality of life
 - Device related

Thromboemboli
 Obstruction/compression
 Improper orientation
 Device infection
 Device failure
 Hemorrhage
 Air entrapment/embolus
 Hemolysis

Results

65-75% successfully bridged (90+% possible)
 90+% of those transplanted are discharged

Mechanical Circulatory Support– Issues for the future

Technological improvements

Size, biocompatibility, control, reliability, power and durability

Clinical effectiveness

Longevity, quality of life, complications, recovery, expertise

Cost-effectiveness

Of technology and implementation

Societal and ethical concerns

Allocation of resources; patient populations

Permanent Implantation– future NEED

By the year 2010

Number of patients: 35,000- 70,000 per year for long-term support

Devices: 10,000-20,000 TAH and 25,000-60,000 VAD

By the year 2020

Device reliability exceeds transplant

Number of patient may exceed 200,000 per year

(Ref. Institute of Medicine for NIH, NHLBI)

1.2.5. Total Artificial Heart

Table 5: Results– Bridge-to-transplant (Copeland et al)

	TAH		Control	
	N	%	N	%
Patients	27	--	18	--
Transplanted	25	93	8	44
Discharged home	28	89	7	39
Neurologic-embolic	9	33	--	--

Summary

- May be life saving in selected patients with end-stage heart disease
- Need for this intervention is increasing with decreasing donor availability
- May ultimately become an alternative to transplantation

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2. Cardiomyopathy / Cardiac Transplant Donor & Recipient Selection

Cardiomyopathy definition

Any myocardial disease process that leads to clinically significant myocardial dysfunction

Table 6: Cardiomyopathy classification

1. Dilated cardiomyopathy
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy
4. Arrhythmogenic right ventricular dysplasia

Dilated, characterized by dilation and impaired contraction of left or both ventricles

Idiopathic

Familial/genetic

Viral and/or immune

Alcoholic/toxic

Presentation with heart failure, often progressive, arrhythmias, thromboembolism, and sudden death

Hypertrophic, characterized by left and/or right ventricular hypertrophy

Usually asymmetric with normal or reduced LV volume

Systolic gradient common

Familial disease with predominantly autosomal dominant inheritance

Myocyte hypertrophy and disarray surrounding areas of increased loose connective tissue

Arrhythmias and premature sudden death are common

Restrictive, characterized by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near-normal systolic function and wall thickness

Idiopathic

Associated with other disease (amyloidosis; endomyocardial disease with or without eosinophilia)

Arrhythmogenic right ventricular dysplasia, characterized by progressive fibrofatty replacement of right ventricular myocardium, initially with typical regional and later global right and some left ventricular involvement with relative sparing of the septum

Familial disease common, autosomal dominant inheritance and incomplete penetrance

Presentation with arrhythmias and sudden death is common, particularly in the young

Specific cardiomyopathies: heart muscle diseases that are associated with specific cardiac or systemic disorders

Ischemic

Valvular

Hypertensive

Inflammatory (e.g., myocarditis, Chagas' disease, HIV, etc.)

Metabolic (e.g., thyrotoxicosis, hypothyroidism, storage diseases, etc.)

General system disease (e.g., SLE, sarcoidosis, etc.)

Muscular dystrophies (e.g., Duchenne, Becker-type, etc.)

Neuromuscular disorders (e.g., Friedreich's ataxia)

Sensitivity and toxic reactions (e.g., anthracyclines, irradiation, alcohol)

Peripartal

Table 7: Prognosis

Factor Possibly Predictive Not Predictive			
Factor	Predictive	Possibly Predictive	Not Predictive
Clinical	Symptoms	Acoholism, Peripartum, Family History	Age, Duration, Viral Illness
Hemodynamic	LVEF, CI	LV size, LAP, RAP	Viral Illness
Dysrhythmia	IVCD, Complex ectopy	AV block	Simple ectopy
Histologic		Myofibril volume	
Neuroendocrine	PI, NE, ANF, Serum Na		

Cumulative Mortality

Probability of Death

Probability of Survival

Pharmacological Treatment of Heart Failure

- Digoxin*
- Diuretics
- Afterload Reduction
- Isosorbine dinitrate/hydralazine**
- Angiotensin Converting Enzyme Inhibitors
- Enalapril**
- Captopril**
- Lisinopril

Angiotensin II Receptor Inhibitors

- Losartan

Calcium Channel Blockers

- Amlodipine

Beta Blockers

- Carvedilol**
- Metoprolol*

Inotropic Agents

Beta Agonists

- Dopamine
- Dobutamine

Phosphodiesterase Inhibitors

- Amrinone
- Milrinone

Anticoagulation

- *Decreases risk of hospitalization or decompensation
- **Decreases mortality

Table 8: Pharmacologic Treatment of Heart Failure

Improves Survival	Decreases Hospitalization	Decreases Survival
Enalapril	Digoxin	Dobutamine
Captopril	Metoprolol	Milrinone
Isosorbide dinitrate		Vesnarinone
Carvedilol		

Recipient Selection Process

- Inclusion criteria
- Exclusion criteria
- Ongoing re-evaluation process

Inclusion Criteria

- Absence of reversible or surgically amenable heart disease
- NYHA Class III - IV symptoms despite optimal medical management
- Maximal oxygen consumption < 14 ml/kg/minute
- Estimated 1 year survival without transplant < 50%

Insufficient Indications for Cardiac Transplantation

- Ejection fraction < 20%
- History of NYHA Class III - IV symptoms
- Low maximal oxygen consumption

Table 9: Candidate exclusion criteria

Criteria	High Risk	Moderate Risk
Pulmonary Hypertension		
PVR > 8 Wood Units, unresponsive to nitroprusside	X	
PVR > 8 Wood Units, decreasing in response to nitroprusside, but not below 3 Wood Units		X
Pulmonary artery systolic pressure > 70 mmHg despite nitroprusside	X	
Transpulmonary gradient > 15-20 mmHg (mean PAP - PCWP)		X
Infection - active, untreated	X	
Irreversible hepatic disease	X	
Irreversible renal disease	X	
Irreversible pulmonary disease		
FEV1 < 1 L	X	
FEV1 < 1.5 L		X
Recent pulmonary infarction		X
Age > 65 years	X	
Diabetes mellitus, Type 1, with significant end-organ damage		X
Cerebrovascular disease		
Symptomatic	X	
Asymptomatic		X
Peripheral vascular disease		
Symptomatic	X	
Peptic ulcer disease		
Active bleeding		X
Diverticulitis, recent	X	
Chronic Active Hepatitis		X
HIV positive		X
Malignancy, recent	X	
Malignancy, remote		X
Psychiatric disease		
Acute, unresolved	X	
Recent, resolved on treatment		X
Substance abuse		

Active, unresolved	X	
Recent, resolved		X

Panel Reactive Antibody (PRA) Screen

AKA: HLA antibody or white blood cell antibody screen

Technique: Recipient sera placed in 40-60 wells containing lymphocytes with a wide variety of HLA antigens

Use: Determine presence of preformed antibodies

If > 10%: Prospective crossmatch

Management of Transplant Candidate While Waiting

Close follow-up

Low threshold for hospitalization

IV diuretics

Inotropic support

Mechanical assistance

Ongoing re-evaluation of candidacy

Ongoing Re-evaluation for Candidacy

Periodic assessment for degree of illness (VO₂, EF, right heart pressures)

Periodic assessment of acceptability (development of a new or worsening of a pre-existing illness)

Periodic PRA determinations

Conditions Which Generally Preclude the Use of a Donor Heart

HIV positivity

Significant ventricular arrhythmia

Echocardiographic abnormalities

Significant global hypokinesis

Significant valvular abnormality

Significant coronary disease by arteriography or documented previous myocardial infarct

Any acute malignancy, except primary brain cancer

Inadequately treated systemic infection

HbsAG positive, unless recipient is also positive

Hepatitis C positivity, unless recipient is also positive

Death from carbon monoxide poisoning, with carboxyhemoglobin level > 20%

Significant cardiac contusion

Severe left ventricular hypertrophy by echo

History of intravenous drug use

Donor-recipient Matching

Size: Greater than 80% of recipient body weight

Blood type: Identical or compatible

HLA-matching: Generally not done

2.1. Cardiac Transplantation

2.1.1. Clinical Advances

- 1960 - Surgical technique reported
- 1967 - Successful human transplant
- 1970 - Recipient selection criteria standardized
- 1973 - Surveillance endocardial biopsy
- 1977 - Distant donor heart procurement
- 1980 - Cyclosporine A

Causes of Death
Transplant Volume

2.1.2. Etiology or End-Stage Heart Disease

Table 10: Etiology or End-Stage Heart Disease

Etiology	Percentage
Ischemia	44.8
Cardiomyopathy	46.2
Valvular	3.5
Congenital	1.8
Rejection	2.1
Other	1.6

2.1.3. Recipient Criteria

- Terminal heart disease
- Reasonable physiological
- No renal or hepatic dysfunction
- No acute infections
- No recurrent pulmonary infections
- Psychosocial stability
- No alcohol, tobacco or drug abuse

Contradictions

- Fixed pulmonary vascular resistance
- Peripheral vascular disease
- Acute malignancy
- COPD or chronic bronchitis
- Morbid obesity
- ABO incompatibility

2.1.4. Donor Criteria

- Brain death declared
- Age <45 (special exceptions)
- No re-existent heart disease
- Few CAD risk factors
- No untreated acute infections
- No systemic malignancy
- No cardiac trauma
- Normal ECG
- Normal echocardiogram
- Negative HIV and Hepatitis screen

2.1.5. Unique Features of Cardiac Recipient

Prone to infection (opportunistic)
Denervated heart physiology
Rejection at any time- few symptoms

2.1.6. Immunosuppressive Therapy

Cyclosporine A
Adrenocortical steroids
Azathioprine
OKT3
Anti-thymocyte globulin (ATG)

Immunosuppression

2.1.7. Rejection

Endomyocardial biopsy
Acute rejection
 Hospital
 Out-patient

2.1.8. Registry Database

Fifteenth Report- 1998
Total Transplants Reported- 45,993
Total Centers Reported- 257
Survival
 1 year- 79%
 Thereafter- 4% per year mortality

Total Survival
Survival by ERA
Survival by Age
Survival with Retransplant

2.1.9. Risk Factors(p value < 0.001)

Previous cardiac transplant
Ventricular support
Mechanical support (VAD)
Recipient < 5 years of age
Recipient > 60 years of age
Donor > 40 years of age
Donor female
Ischemic time >3.5 hours

2.1.10. Causes of Death after Transplantation

Rejection
Infection
Technical
CNS
Malignancy

Cause of Death Post Transplant

After First year

Graft Atherosclerosis
Infection
Malignancy- Lymphoma
Rejection

2.1.11. Improved Survival

Cyclosporine
Lower chronic steroid dose
Earlier diagnosis of rejection
Better patient selection
Diagnosis of infection
New antimicrobial agents
Medical and surgical experience

2.1.12. Functional Status Following Heart Transplant

Post Transplant Functional Status
Post Transplant Work Status
Post Transplant Rehospitalization

EXTENDED OUTLINE

Candidate Selection

- Most often from idiopathic dilated or ischemic cardiomyopathies
- “End stage...failure to respond to maximal therapy”; need to identify those who are likely to have sudden death or progressing heart failure
- Adequacy of therapy prior to evaluation is key
- Some guidelines for selection of candidates:
 - EF < 20%
 - Peak O₂ consumption (VO₂) < 10cc/kg/min

Cardiac Donor

- Only 10-20% of brain dead patients with suitable hearts become donors; cardiac transplantation is currently limited by donor availability
- Initial screening done by a local organ procurement agency
- Hep C generally OK
- Level of inotropic support
- Cardiovascular risk factors
- Substance abuse
- Ideally, donor body weight 80-120% of recipient's weight
- Age limits
- Intensive fluid management of the donor is important; often these people are hypovolemic from trauma or diabetes insipidus

Donor Cardiectomy

- Visualize/palpate the heart
- Divide the:
 - SVC
 - Left superior pulmonary vein
 - Incise IVC
- Clamp aorta

- Administer cardioplegia
- Avoid coronary sinus injury during liver procurement
- Divide aorta and pulmonary artery

Recipient Operation

- Open RA along the AV groove anteriorly
- Extend this incision to CS inferiorly and to the right atrial appendage posteriorly
- Aorta and main pulmonary artery are divide at the valve commissures
- Incise roof of the left atrium between the aorta and SVC
- Connect the atrial incisions and extend the incision to the left atrial appendage
- Incision is then extended along the AV groove posteriorly to the CS
- Check donor heart for PFO
- Donor pulmonary veins are connected to fashion a left atrial cuff
- Left atrial anastomosis is completed and a vent is placed
- Right atrial anastomosis is completed
- Great vessels are anastomosed; PA first
- Deair, pacing wires, chorotropic/inotropic support

Herotopic Cardiac Transplantation

Posttransplant Concerns

- Immunosuppression
 - as detailed previously
 - use of tacrolimus as both maintenance therapy and rescue therapy;
 - Pittsburgh group has evidence to prove that there are fewer repeat episodes of rejection and it is an effective agent for refractory rejection
- Transvenous myocardial biopsy
 - IJ approach
 - 3-5 specimens
 - weekly for the first 4 weeks
 - grading system developed by Billingham
- Coronary graft vasculopathy
- Infection
 - bacterial are most common followed by viruses, fungi, and protozoans
 - viral most common between months 1-6
 - fungal most common between months 1-2
 - protozoal infections peaked months 3-6
 - in the first 6 weeks of transplant, CMV, Herpes, or bacterial are equally likely; >2yrs is usually bacterial pneumonia is the most common infection
 - CMV can be cultured from almost all recipients; consider active infection in anyone with fever, fatigue, lymphocytosis, elevated LFT's , neutropenia, and thrombocytopenia; 25% will develop invasive GI or pulmonary disease; most severe infections seen in those seronegative prior to operation; Gangcyclovir is used to treat, but its use should be prophylactic
 - HSV usually causes mucocutaneous infections
 - EBstein-Barr infection seems to be related to the development of posttransplant proliferative disorder; most effective treatment appears to be reduction of immunosuppression
 - Candidiasis is the most common severe fungal infection seen posttransplant; aspergillosis also has a significant cause of death
 - PCP usually presents with fever, dry cough and dyspnea and may be slow to respond to therapy; TMP-SMX or pentamidine prophylaxis can usually prevent it; diagnosis is usually confirmed by

methenamine silver stains on BAL fluid; rapid reduction in immunosuppression may exacerbate the process in the lung

Renal Failure

Most important side effect of cyclosporin—from afferent arteriolar vasoconstriction and direct tubular cell injury; is dose related to some extent and will improve with reduction in the Cyclosporin dose; oliguria occurs in the early form of renal failure—late nephrotoxicity is characterized by a slow rise in serum creatinine

Other

Hirsutism, tremor, gingival hyperplasia, gout, elevated cholesterol, hyperglycemia, osteoporosis, and abdominal surgical complications

Survival

One year: >80%

3-5 years: 70%

12 years: ~40%

bridge to transplant > 90% survival

risk factors: previous transplant, preoperative ventilator dependence, age <5 or >60 recipient)

risk factors: age >40, female sex, ischemic time >3.5 hours (donor) most common causes of early

death: cardiac complications (40%); rejection (19%); infection (16%).

Infection is the most significant factor in late deaths, accounting for 40%

2.2. Heart/Lung and Lung Transplantation

2.2.1. History

Alexis Carrel- 1907

Demikhov- 1940s

Lower/ Shumway- 1960s

Clinical heart/lung transplantation

Cooley- 1968

Lillehei- 1969

Barnhard- 1971

Modern- era- Reitz

1963- first human lung transplant

1983- Cooper- first successful lung transplant

1985- Cooper / Patterson- double lung transplant

2.2.2. Donor Selection

Age <60 years

No history of pulmonary disease

Smoking history < 20 packs/ year

Normal chest x-ray

Adequate gas exchange

Normal bronchoscopy
Acceptable sputum gram stain
Normal serology
ABO compatibility
Adequate size matching

2.2.3. Absolute Donor Criteria

Adequate gas exchange
 $PO_2 > 300$ on F_iO_2 1.0
 $PO_2 > 100$ on F_iO_2 0.4
Absence of significant infiltrates
Normal serology
ABO compatibility

2.2.4. Indications of Thoracic Transplantation

Single lung transplant
 Pulmonary fibrosis
 Emphysema
Primary pulmonary hypertension
Double lung transplants
 Septic lung disease
 Cystic fibrosis
 Bronchiectasis
Emphysema
 Primary pulmonary hypertension
Heart / Lung transplant
 Irreversible disease of both heart and lung

2.2.5. Recipient Selection

Age <65
Other disease processes
Previous surgery
Steroids
Smoking
Nutrition
Ventilator dependence
Timing of transplant
Psychosocial factors

2.2.6. Lung Preservation for Transplantation

Hypothermia
Lung inflation
Pulmonary artery vasodilation- PGE_1
Pulmonary artery flush- solutions include:
 Modified eurocollins solution
 Belzer's (Wisconsin) solution
 Low potassium Dextran
Low potassium, colloids, free radical scavengers

2.2.7. Early Complications of Lung Transplantation

Reperfusion pulmonary edema
Primary graft failure
Hemorrhage

Bronchial dehiscence
Non-infectious pleural space problems

2.2.8. Infection in Lung Transplantation

Transplanted organ exposed to external environment
Target organ for CMV
Bacterial, viral (CMV), fungal Protozoan (PCP)
Infection increases expression of
 HLA antigens
 Adhesion molecules (ICAM-1)
Can trigger rejection
Transbronchial biopsy / bronchoalveolar lavage to differentiate

2.2.9. Rejection in Lung Transplantation

Routine screening
Lung allografts more antigenic and more vulnerable to rejection
Symptoms: malaise, shortness of breath, lung infiltrate
Differentiating infection from rejection difficult
Transbronchial biopsy, bronchoalveolar lavage useful
Serial daily spirometry (FEV₁)

2.2.10. Bronchiolitis Obliterans

Primary factor limiting long-term survival
Exact etiology unknown (chronic rejection/infection)
Most important cause of mortality and morbidity after lung transplantation
Affects 50% of long-term survivors
50% will respond to enhanced immunosuppression
The remainder will have progressive deterioration of lung function

2.2.11. Pediatric Lung Transplantation

Higher incidence of bypass
May be more vulnerable to bronchiolitis obliterans
Immune advantage has not been clearly documented in pediatric population

Table 11: Survival after Lung Transplantation

By Diagnosis		
Diagnosis	30 Days	1 Year
Emphysema (SL)	93%	78%
A1A (SL)	90%	75%
Cystic fibrosis (BL)	90%	70%
Pulmonary fibrosis (SL)	82%	65%
Pulmonary htn. (BL)	80%	75%

By Transplant		
Transplant	1 Year	5 Years
Single (SL)	70%	40%
Bilateral (BL)	70%	48%

EXTENDED OUTLINE

Introduction

A. 1963-Hardy @ U Mississippi 1st human lung transplant à 18d survival

- B. 1963-83 - 44 lung transplants w/o success [bronchial anastomosis/MOF]
- C. 1983 - Toronto Lung Transplant Group @ 6-yr survival

End-Stage lung disease

- A. Obstructive lung disease
 - 1. Chronic elevation in airway resistance
 - a) Decreased exp flow rates (FEV1, FVC, FEV1/FVC)
 - b) Air trapping (TLC and FRC)
 - 2. Prognostic factors = **age, degree of airway obstruction** (FEV1)
 - 3. COPD
 - 4. Alpha-1 antitrypsin deficiency emphysema
 - a) Lack protection against neutrophil elastase in distal airways
 - b) Severe bullous emphysema by 4th or 5th decade
- B. Cystic fibrosis (CF) (1/2,000 live births)
 - 1. Most common end-stage obstructive disease 1st-3rd decades
 - 2. Thick secretions, poor ciliary fxn => mucus plugging, pulm sepsis
- C. Restrictive lung disease - idiopathic pulmonary fibrosis (IPF)
 - 1. Decreased Lung volumes and exp flow
 - 2. Decreased diffusing capacity
- D. Pulmonary hypertension
 - 1. Primary pulmonary hypertension (PPH):Mortality correlates w/CVP >10mmHg, PA(mean) >60mmHg, CI<2L/min
 - 2. Eisenmenger's syndrome:Ca-channel blockers may [increase or decrease??] PA pressures
- E. Others: sarcoidosis, chemo/RT-induced fibrosis, lymphangiomatosis

Recipient selection

- A. Mean waiting time 9-12 mo. (Wash U) 13.5 mo. (US)

Preoperative evaluation and management of recipients

- A. All pts enrolled in cardiopulmonary rehab

Choice of procedure

- A. Obstructive lung disease
 - 1. Early single lung transplant (SLT)àhyperinflating native lung, crowding, V/Q mismatch
 - a) Oversizing donor lung
 - b) Proper preservation technique
 - 2. **SLT** for: >55yo, high risk), prior surgery, asymmetric dz
 - 3. Bilateral lung transplant (**BLT**) for: younger,bilat dz,small donor
- B. CF (and other septic lung disease)=> **BLT** due to infection risk in native lung
- C. IPF
 - 1. **SLT** theoretically ideal- decrease compliance and PA pressures in native lung favor allograft ventilation and perfusion
 - 2. **BLT** for large individual, especially with nl lung volumes

D. PPH - Ht-lung transplant, traditionally

- 1. **SLT** has been successful

- a) Post-op management difficult, nearly all pulm flow to allograft
- b) Late graft problem=severe V/Q mismatch
- 2. **BLT** may provide better long-term result

Timing of transplantation

- A. Pts w/life expectancy 12-24 mo
- B. ~30% will receive transplant w/in 1 year
- C. Risk of dying on the waiting list:PPH, IPF, CF >>> COPD

Other criteria

- A. Age (not absolute): **BLT**=55, **SLT**=65
- B. Ventilatory support- no longer an absolute contraindication (already listed)
- C. Corticosteroid therapy - data suggest:
 - 1. low-dose prednisone does not airway complications
 - 2. low-dose steroids may allograft bronchial circulation
- D. Prior surgery - no longer a contraindication, in general

Criteria for donor lung suitability

- A. 20-25% of multiple organ donors have suitable lungs
- B. Size - TLC, VC estimated by height/weight - oversize 20% for **SLT**
- C. Donor lung scarcity
 - 1. Use "marginal" lungs
 - 2. Single lung assessment (2-lumen ETT, PA clamping)
 - 3. Living related donor (for pediatric CF patients)

Technique of Lung Preservation and Extraction

Lung preservation

- A. Prostaglandin E-1 before inflow occlusion (vasodilatation + other benefits)
- B. PA flush w/3L cold Euro-collins
- C. Extraction of lungs semi-inflated w/100% O₂ (grafts use it)
- D. Transport under hypothermia (0-1°C)
- E. Topical cooling during implantation

Donor lung extraction

- A. Median sternotomy, dissection
 - 1. Isolate SVC and IVC
 - 2. Separate aorta and PA-Cardiopleg. cannula in aorta, cannulate distal PA
 - 3. Incise posterior pericardium, exposing distal trachea
- B. Graft flushing
 - 1. Bolus PGE-1 (500 mg)
 - 2. Inflow occlusion (ligate SVC, clamp IVC)
 - 3. Vent **R** heart - transect IVC
 - 4. X-C aorta, administer cardioplegia
 - 5. Amputate tip of LA appendage, start lung flush
 - 6. Flood chest w/ iced saline, ventilate w/100% O₂
- C. Extract heart
 - 1. Transect caeve and aorta

2. LA incision is last, leaving a cuff of atrium

D. Extract lungs

1. Divide trachea between two firings of TA-30
2. (Divide esophagus superiorly and inferiorly)
3. Transect descending thoracic aorta
4. Transport on ice

Lung Transplantation Procedure

Anesthetic considerations

- A. PA catheter
- B. Left-sided 2-lumen ETT
- C. Initial bronchoscopy and aspiration for CF patients
- D. Avoid "pulmonary tamponade"
- E. CPB for:
 1. Hemodynamic instability
 2. Pulmonary vascular dz
 3. Poor allograft function in BLT

Technique

- A. Incision
 1. **SLT**-posterolateral thoracotomy
 2. **BLT** - bilateral transverse thoracosternotomy ("clamshell") {5th IC space for COPD, 4th for CF}
- B. Choice of side - avoid surgery, remove better lung - in **BLT**, worse lung transplanted 1st
- C. R/O PFO in PPH-intra-op TEE
- D. In **SLT**, CPB is selective - trial of PA clamping

Lung implantation

- A. Divide 1st PA branch between ligatures, the staple PA trunk
- B. Mobilize both pulmonary veins (PV) intrapericardially
- C. Transect bronchus-**R**=just proximal to RUL takeoff, **L**=1-2 rings above bifurcation- hemostasis
- D. Topical cooling - iced gauze around graft
- E. Bronchial anastomosis
 1. Continuous 4-0 mono-absorbable for membranous
 2. Telescope cartilaginous arches figure-of-8 interrupted sutures
 3. Ometopexy no longer used
- F. PA anastomosis - 5-0 mono-non
- G. LA anastomosis - 4-0 mono-non
- H. De-air
 1. Antegrade (release PA clamp)
 2. Retrograde (release LA clamp)
- I. Bronchoscopy

Post-operative Management

- A. ICU post-op - quantitative perfusion scan

- B. Pain control - epidural
- C. Ventilator
 1. **SLT**: COPD=no PEEP, PPH=10cm PEEP x 36h
 2. Weaning - PPH=sedated, paralyzed x 36h, others=early wean
- D. Postural drainage (lat x 24h), chest PT
- E. Hemodynamics: dopamine for diuresis, PGE-1
- F. Bronchoscopy - OR, POD1, pre-extubation, and prn
- G. Infection
 1. Abx prophylaxis: CF - per recipient cultures; others, per donor, or ancef x 3-4d
 2. HSV prophylaxis: acyclovir 200mg BID for ³ 2 yr
 3. PCP: Septra-DS - one bid q M-W-F
 4. Candida: nystatin
 5. CMV
 - a) Attempt to match, avoid CMV neg recip/CMV pos donor
 - b) Prophylaxis=gancyclovir
- H. Immunosuppression
 1. Triple regimen: cyclosporine, azathioprine, corticosteroids
 2. Antithymocyte globulin (ATGAM) x 8 days

Follow-up strategies

- A. Clinical f/u - remain in town x 3 months
- B. PFTs - primarily FEV1 - Monthly in 1st year
- C. CXR - schedule similar to PFT's + prn
- D. Bronchoscopy (FOB) with transbronchial bx (TBLB)
 1. 3-4wk post-op, 3mo, 6mo, 1yr, then annually
 2. Direct TBLB to areas w/infiltrates
- E. Open lung bx-when TBLB inconclusive in face of clinical, physiologic deterioration

Problems (clinical-pathologic entities encountered in the lung transplant recipient)

- A. Acute rejection -more common than other solid-organ allografts
 1. Incidence unknown - "virtually all" in 1st 3-4wks post-tx
 2. From 1st 3-5 days post-op to years later
 3. Clinical manifestation variable-malaise, mild dyspnea, fever, decreased FEV1, decreased PO2
 4. Dx: FOB, TBLB => 84% sens, 100% spec (Ht-lung tx)
 5. Tx: High-dose steroids, maintenance prednisone, ATGAM or OKT3 for refractory episodes
- B. CMV infection
 1. May mimic rejection
 2. Dx by TBLB
 3. Tx w/gancyclovir (documented infection)
- C. Chronic rejection/Bronchiolitis Obliterans syndrome (BOS)
 1. Inflammatory disorder of the small airways-histologically, dense fibrosis and scar obliterating bronchial wall and lumen
 2. Prevalence as high as 50%
 3. Dry or productive cough, dyspnea refractory to bronchodilators
 4. Airflow obstruction with progressive $\bar{\bar{}}$ in FEV1
 5. Tx: Immunosuppression (empiric)-most pts will progress
- D. Bronchial anastomotic complications
 1. Usually result from ischemia which =>
 - a) Air leak or mediastinal collection (early)
 - b) Stenosis or malacia (late)

2. New dyspnea, stridor or wheeze
3. W/U=CXR, FOB, chest CT
4. Tx:
 - a) Early (dehiscence) = drainage and conservative measures
 - b) Late (stricture or malacia) - stent

Results

- A. Survival
 1. 92% hospital survival
 2. 70% 1-yr, 43% 5-yr
 3. Small benefit of **BLT** vs **SLT** (not significant)
- B. Functional results
 1. FEV1, ABG, 6-minute walk improved
 2. FEV1, PaO2, significantly better after **BLT** vs **SLT**
 3. **BLT** associated w/ higher complication rate
- C. Pulmonary vascular dz
 1. Decreased PAS, CVP, PVRI
 2. NYHA class III-IV => I-II

2.3. Medical Complications of Cardiac Transplant

1. Cardiac

- Ventricular dysfunction
- Sinus node dysfunction
- Tricuspid regurgitation
- Allograft rejection
- Allograft coronary artery disease
- Decreased exercise tolerance

Infection

- Bacterial
- Viral
- Parasitic
- Fungal

Non-cardiac, Non-infectious

- Renal insufficiency
- Hypertension
- Osteoporosis
- Hyperlipidemia
- Malignancy
- Psychologic/behavioral/societal
- Glucose intolerance
- Pancreaticobiliary disease
- Obesity

2. Cardiac Allograft Rejection

Propensity decreases with time

Types

- Hyperacute
- Acute

- Chronic (ACAD)
- Cellular
- Vascular (Humoral)
- Diagnosis
 - Endomyocardial biopsy
 - Non-invasive
 - Clinical
- Treatment
 - Insertion of Biopptome

Table 12: International Society for Heart & Lung Transplantation Endomyocardial Biopsy Grading Scheme

Grade	Finding	Rejection Severity
0	No infiltrates	None
1A	Focal (perivascular of interstitial infiltrates without necrosis	Mild
1B	Diffuse but not sparse infiltrate without necrosis	Mild
2	One focus only with aggressive infiltrate and/or myocyte damage Focal	Moderate
3A	Multifocal addressive infiltrates and/or myocyte damage	Moderate
3B	Diffuse inflammatory infiltrates with necrosis	Borderline severe
4	Diffuse aggressive polymorphous infiltrate with edema, hemorhage and vasculitis, with necrosis	Severe

Cellular biopsy Cellular biopsy Cellular biopsy Angiogram Vascular biopsy

4. Allograft Coronary Artery Disease

Leading cause of death > 1 year after transplantation

Equivalent to:

- "Chronic rejection" in renal allografts
- "Vanishing bile ducts" in hepatic allografts
- "Bronchiolitis obliterans" in pulmonary allografts

Prevalence of angiographically detectable disease

- 1 year: 10-20%
- 5 years: 30-50%

Potential risk factors

Non-transplant specific

- Age
- Sex
- Family history
- Hypertension
- Diabetes mellitus
- Smoking
- Hyperlipidemia

Transplant specific

- HLA mismatch, at DR locus
- Immunosuppressant drugs

- CMV infection
- Donor age
- Symptomatic
 - Angina
 - Acute myocardial infarction
 - Sudden death
- Asymptomatic
 - Coronary angiography
 - Nuclear (thallium/sestamibi)
 - Dobutamine stress echocardiography
 - Intravascular ultrasound
- Vascular Lesion Survival post Angiogram Survival post Transplant Infection post Transplant

5. Infectious Complications

- Phases
- Early (< 1 month), Nosocomial Phase
 - Wound
 - Catheter-related
 - Hospital acquired pneumonia
- Middle (2-5 months), Opportunistic Phase
 - Toxoplasmosis
 - Herpes viruses (cytomegalovirus, herpes simplex)
 - Pneumocystis carinii
 - Nocardia
 - Fungi
- Late (> 6-12 months) , "Normal" Phase

Table 13: Infectious Prophylaxis

Pathogenic Organism	Prophylactic Agent
Cytomegalovirus	Gancyclovir, Acyclovir, IVIg
Herpes simplex	Acyclovir
Toxoplasmosis	Pyrimethamine and Leucovorin
Pneumocystis	TMP/SMX, Dapsone, Pentamidine
Oral candidiasis	Nystatin, Mycelex troches

Malignancy

7. Malignancy

- Incidence 1-2 %/year
- Cutaneous Malignancy
 - Squamous cell carcinoma
 - Basal cell carcinoma
- Lymphoma (PTLD)
 - Frequency: Most common tumor in cyclosporine-based immunosuppression
 - Timing: 12-18 months post transplant

Location: Intraabdominal most common
Etiology: B cell origin induced by Epstein-Barr virus
Treatment: Reduce immunosuppression
Acyclovir
Chemotherapy/radiation

8. Cyclosporine-induced Nephrotoxicity

Characteristics

- Major decline in renal function in first 6 months
- Disproportionate azotemia
- Hyperkalemia
- Increased uric acid levels
- Mild proteinuria
- Decreased fractional excretion of sodium

Pathogenesis

Renal vasoconstriction (afferent arterioles)
Prostaglandins
Endothelin
Direct effect on smooth muscle
Direct tubular toxicity

Hypertension and Renal Dysfunction

9. Cyclosporine-induced Hypertension

Incidence: 50-90% of heart transplant recipients
Occurrence: Weeks to months
Treatment goal: BP < 140/90 mmHg
Moderate limitation of salt intake
Maintenance of ideal body weight
Moderate exercise
ACE inhibitors (captopril, enalapril, lisinopril)
Calcium channel blockers (diltiazem, nifedipine, verapamil, amlodipine, and others)
Diuretics
Others (Clonidine, B-blockers, hydralazine, prazosin)

Hyperlipidemia and Diabetes

10. Hypercholesterolemia

Incidence: 60-80% of heart transplant recipients
Occurrence: - 8 months
Magnitude: Increase of 30-80 mg/dl
Positive relationship to:
Prior history of ischemic heart disease
Preexisting lipid abnormalities
Cumulative dose of corticosteroids
Cyclosporine
Treatment goals: Serum cholesterol > 240 mg/dl (or LDL cholesterol > 160 mg/dl)
Moderate limitation of fat intake

- Maintenance of ideal body weight
- Moderate exercise
- Minimize corticosteroid dose

Gemfibrozil

HMG-CoA reductase inhibitors

- Lovastatin

- Simvastatin

- Pravastatin

- Fluvastatin

Bile acid sequestrants (Cholestyramine, Colestipol)

- Nicotinic Acid

- Probucol

- Fish oil (Omega-3 Free Fatty Acids)

11. Osteoporosis

Incidence:

- 10% of heart transplant recipients

Risk factors:

- Corticosteroids

- Older age

- Lower bone mass before transplantation

- Low cardiac output states

- Prolonged use of loop diuretics

- Physical inactivity

- Cardiac cachexia

- Heparin administration

- Postmenopausal status

2.4. Transplant Immunology

Allograft Rejection

Th Cell Events

B & T Cell-Mediated Death

Phases of Immunosuppression

Early rejection prophylaxis

Maintenance rejection prophylaxis

Treatment of established rejection

Mechanism of Action of Immunosuppressive Agents

Inhibitors of Interleukin -2

Production

- Cyclosporine A

- Tacrolimus

Action

- Rapamycin (Sirolimus)

- SDZ RAD

- Interleukin-2 Receptor Blockers

Daclizumab

Basiliximab

Inhibitors of purine or pyrimidine biosynthesis

Purine

Azathioprine

Methotrexate

Mycophenolate mofetil

Mizoribine (bredinin)

Pyrimidine

Brequinar sodium

Leflunomide

Both purine and pyrimidine

Cyclophosphamide

Opsonization of lymphocytes

Murine monoclonal anti-CD-3 antibody (OKT3)

Polyclonal antibodies (horse, rabbit)

Multiple mechanisms or not clearly defined mechanisms

Adrenocorticosteroids

15-Deoxyspergualin

Murine Monoclonal CD-3 Antibody (OKT3)

Identification: IgG2a Murine Immunoglobulin

Mechanism: Inhibits signal transduction of antigen recognition, opsonizes CD-3 lymphocytes

Dose/route: 5-10 mg/day, IV

Side effects: First dose reactions, HAMA formation

Interactions: None

Use: Early rejection prophylaxis, treatment of rejection

Monitoring: CD-3 Counts, OKT3 levels

Total Lymphocytes

Polyclonal Antibodies

Identification: Horse (ATGAM) or rabbit (Thymoglobulin) immunoglobulin

Mechanism: RES-mediated removal of opsonized cells

Dose/route: ATGAM 10-20 mg/kg/day IV; Thymoglobulin 1.5mg/kg IV

Side effects: Leukopenia, thrombocytopenia, fever, arthralgias, serum sickness

Interactions: None

Use: Early rejection prophylaxis, treatment of rejection

Monitoring: CD-2 counts

Cyclosporine

Identification: Metabolite of tolypocladium inflatum gams

Mechanism: Inhibits m-RNA transcription of interleukin-2

Dose/route: 3-6 mg/kg/day orally; IV:Oral = 1:3

Side effects: Nephrotoxicity, hypertension, tremor, headache/paresthesias, hirsutism, gingival hyperplasia

Interactions: Increase clearance of cyclosporine

Rifampin

Isoniazid

Phenytoin

Phenobarbital
Decrease clearance of cyclosporine
Erythromycin
Ketoconazole
Diltiazem
Verapamil
Nicardipine
Cimetidine
Use: Maintenance immunosuppression
Monitoring: Blood or serum level determination

Table 14: Cyclosporine Formulations

1. Sandimmune Liquid	Liquid & Capsules
2. Neoral (microemulsion) Liquid	Liquid & Capsules
3. Sang CYA (microemulsion) Liquid	Liquid

Tacrolimus (FK-506)

Identification: Fermentation product of *Streptomyces tsukubaensis*
Mechanism: Inhibits mRNA transcription of interleukin-2
Dose/route: 0.05 - 0.075 mg/kg orally q 12 hours 0.03 mg/kg intravenously q 24 hours
Side-effects:
Nephrotoxicity
Hyperglycemia
Neurotoxicity
Hypertension

Interactions: Believed similar to cyclosporine
Use: Maintenance immunosuppression
Monitoring: Blood level determination

Azathioprine

Identification: Precursor to 6 mercaptopurine
Mechanism: Disrupts normal purine incorporation into ribonucleic acids
Dose/route: 1 - 4 mg/kg/day; IV:Oral = 1:1
Side effects: Hematologic, pancreatitis, cholestatic jaundice, hepatitis, interstitial pneumonitis
Interactions: Increased levels with allopurinol
Use: Maintenance immunosuppression
Monitoring: White blood cell count

Mycophenolate Mofetil (RS-61443)

Identification: Morpholinoethylester of mycophenolic acid, a fermentation product of *Penicillium* species
Mechanism: Inhibits inosine monophosphate dehydrogenase in the de novo pathway of guanine nucleotide biosynthesis
Dose/route: 1,000 - 1,500 mg orally q 12 hours
Side-effects: Leukopenia, Nausea, vomiting, diarrhea
Interactions: Probably with acyclovir
Use: Maintenance immunosuppression
Monitoring: None

Corticosteroids (Prednisone, hydrocortisone, methylprednisolone)

Mechanism:

Inhibit transcription of IL-1 and IL-6 encoding m-RNA in macrophages
Block antigen recognition, decrease IL-1 AND IL-6 driven effects
Redistribution of lymphocytes

Dose/route: Prednisone 1 mg = hydrocortisone 4 mg = methylprednisolone 0.8 mg

Side effects:

Cushing's syndrome, osteoporosis, myopathy, cataracts, peptic ulcers
Glucose intolerance, hypercholesterolemia, skin fragility, adrenal suppression

Interactions: None clinically significant

Use: Maintenance immunosuppression, rejection treatment

Immunosuppression: Early Rejection Prophylaxis

Standard Triple therapy

Preoperative

Cyclosporine: 2-6 mg/kg po based on renal function

Azathioprine: 4 mg/kg IV

Intraoperative

Methylprednisolone: 500 mg

Postoperative

Cyclosporine: 2-6 mg/kg po bid based on trough levels and renal function

Azathioprine: 2 mg/kg/day

Methylprednisolone: 125 mg IV every 8 hours for 3-4 doses, followed by prednisone

Prednisone: (beginning after Methylprednisolone) 1 mg/kg/day tapering over 1 week to 0.5 mg/kg/day, followed by further tapering over 2-3 months to 0.2-0.3 mg/kg/day

Quadruple Therapy- OKT3 *

Preoperative

Cyclosporine: None

Azathioprine: 4 mg/kg IV

Intraoperative

Methylprednisolone: 500 mg

OKT3: 5-10 mg (or administer first dose of OKT3, 5 mg IV 24-48 hours postoperatively)

Post operative

OKT3: 5 mg/day IV for 7-10 days post operative

Cyclosporine: Beginning on the fourth post operative day, 2-6 mg/kg po bid based on trough levels and renal function

Azathioprine: 2 mg/kg/day

Methylprednisolone: 25 mg IV every 8 hours for 3-4 doses, followed by prednisone

Prednisone: (beginning after Methylprednisolone) 0.25 mg/kg/day during the time of OKT3 administration. After OKT3 course completed, increase to 1 mg/kg/day for 7 days, then taper either completely off over 4 weeks or to 0.2-0.3 mg/kg/day by 1-3 months.

* OKT3 should be premedicated daily for three days with diphenhydramine 50 mg IV, acetaminophen 650 mg po or per rectum, and ranitidine 100 mg IV. OKT3 should be post-medicated every 6, 12, and 18 hours after the first 3 doses with diphenhydramine 25 mg IV, acetaminophen 650 mg po or per rectum, and ranitidine 50 mg IV.

Quadruple Therapy - ATG/ALG/ALS**

Preoperative

Cyclosporine: None

Azathioprine: 4 mg/kg IV

Intraoperative

Methylprednisolone: 500 mg

Post operative

ATG/ALG/ALS: Daily dosing for 7-10 days, Dose depends on preparation

Cyclosporine: Beginning on the second or third post-operative day, 2 - 6 mg/kg po bid based on trough levels and renal function

Azathioprine: 2 mg/kg/day

Methylprednisolone: 125 mg IV every 8 hours for 3-4 doses, followed by prednisone

Prednisone: (beginning after Methylprednisolone) 0.25mg/kg/day during the time of

ATG/ALG/ALS, followed by 1mg/kg/day for 7 days, then taper either completely off over 4 weeks or to 0.2-0.3 mg/kg/day by 1-3 months.

** ATG/ALG/ALS should be pre-medicated daily with diphenhydramine 25-50 mg IV and acetaminophen 650 mg po or per rectum

Maintenance Immunosuppression Goal

Lowest overall level of immunosuppression to prevent rejection

Cyclosporine levels

Low therapeutic after 1-2 years

Azathioprine

1-2 mg/kg/day after 1-2 years

Prednisone

0 - 0.1 mg/kg/day after 1 year

Treatment of Rejection - Considerations

Histologic grade of biopsy

Allograft function

Time after transplantation

Past rejection history

Concomitant immunosuppression

Optimize cyclosporine/azathioprine

Table 15: Treatment Of Rejection

GRADE	
Mild	None or oral corticosteroid augmentation
Moderate	Oral corticosteroid augmentation or IV corticosteroids
Severe	IV corticosteroids and ATG/ALG OR OKT3

Immunosuppression Flow-chart

Other options

Alteration of maintenance regimen

Change from cyclosporine to Tacrolimus

Change from azathioprine to mycophenolate mofetil

Change from azathioprine to cyclophosphamide (vascular rejection)

Methotrexate course (2.5 - 7.5 mg. Q 12 hrs x 3 doses/week for 8-12 weeks)

Plasmapheresis (vascular rejection)

Total lymphoid irradiation

Photopheresis

Re-transplantation

EXTENDED OUTLINE

Major Histocompatibility Complex (MHC)-prime physiologic role is to recognize "self" from "nonself"; in humans, this is known as the HLA system

HLA: class I—HLA-A, B, C; expressed on all cells of an organism. Class I molecules present antigenic peptides to activated T lymphocytes expressing CD8 phenotype

class II—DP, DQ, DR; expressed on antigen presenting cells, e.g., B cells, T cells, macrophages, dendritic cells, and endothelium. Present to T lymphocytes expressing the CD4 phenotype.

-Pivotal cells moderating rejection are the T cells expressing the CD4 complex. These T cells recognize foreign Class II antigens on antigen presenting cells (APCs)—these cells not only present, but also provide signals (lymphokines/adhesion molecules) for T cell activation (second signal). There are two pathways for this to occur—direct and indirect routes of sensitization

-Activated CD4 cells are divided into Th1 and Th2 populations: Th1 subpopulation produces: IL-2 (CD8 differentiation), INF (MHC class II differentiation), TNF (NO radicals/O₂/Prostaglandins) Th2: IL-4,5,10—augments B cell mediated responses

Effectors of Graft Rejection:

-CD8 activation is thought to involve recognition of class I antigen (first signal) in a setting of increased levels of IL-2 (second signal) secreted by activated CD4 cells. Graft destruction ensues.

-Hyperacute rejection is secondary to pre-existing blood group antibodies, anti-MHC antibodies, or natural antibodies which react with the endothelial antigens—complement, coagulation, and kallikrein/bradykinin cascades activated. Leads to graft edema, hemorrhage, and vascular thrombosis.

-Accelerated rejection from IgM/IgG antibodies formed in response to the donor graft. Biopsy shows vascular destruction with a paucity of cellular infiltrate.

-Hallmark of cellular rejection is graft infiltration:

leukocyte attachment to the endothelium

mediated by cell adhesion molecules: selectins (rolling effect), integrins (bind the attached molecules), immunoglobulin superfamily-related molecules. This is followed by diapedesis—ICAM-1 and LFA-1 interaction

transmigration through the vessel wall

migration within the graft

selective retention of activated cells in the graft

local proliferation of cells

Rejection Prevention

-MHC matching

-Immunosuppression

1. Cyclosporin (CyA) and FK506—inhibit lymphocyte proliferation and lymphokine production by binding to cytosolic intracellular receptors known as immunophilins (CyA-cyclophilins/FK506-FK506 proteins). These complexes inhibit calcineurin an intracellular protein phosphatase which plays a crucial role in the induction of lymphokine genes (IL-2). Side effects: renal dysfunction, GI, CNS, hypertension, and diabetes

2. Corticosteroids—negatively affecting the release of IL-1 and IL-6 from macrophages and thereby inhibiting IL-2 release. Side effects include hypertension, diabetes, cushingoid features, poor wound healing and aseptic bone necrosis

3. Azathioprine works non specifically by virtue of its antimetabolite effects to inhibit lymphocyte proliferation

4. OKT3—mouse monoclonal antibody against T cell receptor CD3 which nonspecifically suppresses all T cell functions. Use is generally in acute rejection episodes. Side effects: cytokine release causing fever, chills, and pulmonary edema; antibody production against the murine antibody which precludes future courses; dramatic increase in lymphoproliferative disorders.

5. Rapamycin—homolog of FK506, but does not inhibit calcineurin. Mode of action is unclear. Has prevented development of cardiac allograft vasculopathy in rat allografts
6. 15-Deoxyspergualin (DSG)—binds cytoplasmic protein Hsc70 and interferes with antigen presentation and T and B cell development. Good for pancreatic islet cell survival. Causes myelosuppression
7. Mycophenolate mofetil— inhibits inosine monophosphate dehydrogenase which blocks the de novo pathway for purine synthesis. This pathway is crucial for the proliferative response of T and B cell response. There is a low side effect profile.
8. Brequinar inhibits dihydroorotate dehydrogenase and blocks the de novo synthesis of pyrimidines. The proliferative response is attenuated.

Induction therapy

- its use is associated with a greater cumulative rejection frequency
- does not delay the onset of first rejection
- does not reduce the cumulative number of episodes of rejection

Tolerance

-refers to the elimination of the immune response to the antigens of the transplant while the immune response to all other antigens remains intact

Anergy—inactivation of cells reactive to the foreign antigen; thought to be the result of T cells binding specific antigen, but not receiving the appropriate second signal from APCs or CD4 cells. IL-2 experimentally has been shown to reverse this

Clonal deletion—elimination of cells reactive to the foreign antigen; occurs primarily in the thymus by a process known as negative selection

Suppression—suppression of cells responsive to the foreign antigens by another, regulatory immunologic process. Veto cell—inhibits the activity of T cells reactive with antigens on its surface thereby suppressing the activity of the attacking cells

Chronic Rejection

Cardiac allograft vasculopathy (CAV)

- is now the leading cause of death or graft failure after the first year.
- manifested by diffuse and accelerated form of coronary arteriosclerosis—often involves the full length of the artery.
- virtually all transplant recipients have these findings.
- rapidly progresses to vessel occlusion and MI
- pathologic finding is a diffuse intimal thickening and perivascular inflammation extending from large epicardial arteries into medium sized arteries and arterioles
 - the endothelial response to injury theory likely forms the common bond; stimulated endothelial and smooth muscle cells produce cytokines and growth factors causing cell proliferation and smooth muscle and macrophage migration to the intima resulting in concentric lipid-laden calcium-poor plaque. There is evidence to document an inflammatory stage prior to the smooth muscle cell proliferation and also an impairment of endothelial-derived relaxation factor.
 - immune mechanisms are probably at work because the vasculopathy is selective for the allograft which it effects diffusely; the cause of the presumed endothelial injury is unknown
 - Risk factors??—lipid levels, hypertension, smoking, diabetes, and a history of previous atherosclerosis have not correlated with an increased risk of CAV. Only CMV infection has shown a strong association with either death or retransplantation from CAV.
- use of dobutamine stress echocardiography to follow vs. angiography
- best addressed by repeat transplantation although this is associated with a 30% or greater lower rate of survival

Xenotransplantation

-widespread preformed antibodies in humans which are reactive for antigens of other species—e.g. pig to human transplant results in hyperacute rejection (discordant) [Concordant rejection is when closely related species reject transplants in a manner similar to allograft rejection]

-cells and organs from one species may not be able to function in a xenogenic environment

-cell mediated xenografic rejection may differ from allogeneic rejection and thus require different immunosuppression

-the future may lie in manipulating the donor organ endothelial system expression of complement inhibitory proteins and therefore mediate hyperacute rejection by preventing complement activation.

3. The Living & Dying (Myocardial) Cell

3.1. Apoptosis vs. Necrosis

Apoptosis vs. Necrosis

"LIFELESS" (since cells are dead):

Differences are in:

L: Leaky membranes

I: Inflammatory response

F: Fate

E: Extent

L: Laddering

E: Energy dependent

S: Swell or shrink

S: Stimulus

4. Cell Transplantation & Stem Cell Research

5. Gene Therapy in Cardiovascular Research

6. Cell Therapy & Tissue Engineering For Cardiac Surgery

6.1. Stem Cells

Definition: are undifferentiated or partly differentiated precursor cells possessing the inherent capacity to proliferate on demand and to differentiate to mature cell type(s).

Stem Cells Categories

According to potency & developmental origin

1. **Totipotent:** Cells from embryo less than 4 days old. They have total potential and can form a human being.
2. **Pluripotent:** Embryonic stem cells from embryo more than 4-5 days old. They have the potential to form any cell but can not form a human being.
3. **Multipotent:** Adult stem cells from a person (adult or child) or from the umbilical cord. They can form several kinds of cells but not all e.g Mesenchymal stem cells (MSC).
4. **Unipotent:** Adult stem cells or progenitors that can form only specific type of cells e.g Skeletal Myoplasts (SM), Endothelial precursor cells (EPC), Epidermal stem cells.

The multipotent bone marrow derived mesenchymal stem cells (MSC) are:

- * The body's natural tissue regenerators
 - * Tissue that is injured sends signals to these unspecialized , progenitor cells.
- Stem cell transplantation was initially employed to treat hematopoietic disorders. Recently, scientists and physicians have started to use the potential of stem cells for tissue-defect repair, as :
- * Scar healing in reconstructive surgery.
 - * Cartilage-defect repair in traumatology.
 - * Treatment of diabetes or neurological disorders.
 - * Combined with chemotherapy & radiotherapy treatment for cancer to re-create bone marrow.
 - * Myocardial regeneration, since human myocardium is not (or barely) able to replace ischemic defects with functional tissue

	Embryonic stem cells	Adult stem cells
Source	It originate from the inner cell mass of a blastocyst developed from the frozen stored extra fertilized eggs used for in vitro fertilization (IVF)	Peripheral blood, bone marrow, umbilical cord.
Advantages	Totipotent or pluripotent cells that generate any kind of cells, very easy to identify, can divide indefinitely, grow fast	No ethical problem, autologous (no rejection).
Disadvantages	Ethical problem, rejection (immune-suppressive drugs should be used), immortalized (dividing endlessly) simulating cancer cells	Multipotent (more mature cells) so, Cure limited number of diseases, very small amount, hard to identify, take long time to grow Potentials for cell therapy in cardiac surgery Advanced ihd with scarred myocardium End result heart failure → cellular cardiomyoplasty Angiogenesis to increase vascularity in ischemic areas Endothelialization (in vitro) by tissue culture for a prosthesis then implantation to the patient

The ideal cell type for cardiac stem cell transplantation should be:

1. capable of proliferation and differentiation into contractile cells
2. should connect to neighboring cells electromechanically.
3. should be easy to obtain in sufficient numbers.
4. should not be burdened with immunological or ethical problems.

However, no ideal stem cell type meeting these demands has been identified yet, but adult autologous stem cells are preferred in research.

Route of delivery

- A. Direct intramyocardial stem cell injection
- B. Intracoronary injection
- C. Intravenously infused progenitor cells
- D. Tissue-engineered constructs

Route of Delivery

A polyurethane scaffold (Artelon®, Artimplant, Sweden) was permanently implanted on the outer surface of a myocardial scar in rats. These highly porous (>90%) scaffolds were seeded with 5 million cultured skeletal myoblasts and incubated for 2 weeks prior to implantation to allow cell attachment and proliferation (Siepe et. al., 2005)

Autologous adult stem cells and their application for myocardial regeneration

1. Bone marrow-derived stem cells (BMSC)
2. Endothelial progenitor cells (EPCs)
3. Skeletal myoblasts (SM)

Future Perspectives

Cord blood cells were recently suggested to be a new source of immature cells for transplantation. It demonstrated a high-differentiation potential of cord blood stem cells, including transdifferentiation to cardiomyocyte.

The question arises whether cord blood cell banks should be established for autologous replacement purpose or if we can even use these stem cells heterologously.

Other techniques to regenerate the damaged myocardium have been proposed.

Gene therapy, growth factor application, and tissue engineering in combination with stem cell transplantation are thought to improve the effectiveness of stem cells.

By means of gene therapy, cells could be directed into cardiac differentiation in vitro (e.g. by transfecting skeletal myoblasts with connexin-43, to allow better functional integration into the myocardium).

Moreover, stem cells transfected with specific genes to augment cardiac function (β -adrenergic receptor kinase, for example) or angiogenesis (e.g. VEGF) can serve as a permanent delivery device for the gene products.

However, the uncontrolled expression of cytokines and growth factors could pose an additional risk for neoplastic transformation.

Vasculogenesis vs. Angiogenesis

"Vascu is new. Angi is pre":

Vasculogenesis is new vessels developing in situ from existing mesenchyme.

Angiogenesis is vessels develop from sprouting off pre-existing arteries.

7. Appendices
