Heart failure

- Refers to the syndrome of fluid retention and breathlessness, caused by cardiac disease
- Usually biventricular in children due to ventricular interdependence and child specific pathology
- Causes include:
  - left to right shunts,
  - valvu lar disease
  - myocardial dysfunction
  - high output heart failure (AVM’s, anaemia, hormonal disturbances)

Heart failure

- Cardiac changes include:
  - Decreased stroke volume and cardiac output
  - Increased end-diastolic pressure
  - Ventricular dilatation or hypertrophy
  - Impaired filling (diastolic dysfunction)
  - Reduced ejection fraction (systolic dysfunction)
- Vascular changes include:
  - Increased systemic vascular resistance
  - Decreased arterial pressure
  - Impaired organ perfusion
  - Decreased arterial compliance
  - Increased venous pressure
  - Increased blood volume

Compensatory mechanisms during heart failure

- Cardiac:
  - Frank-Starling mechanism
  - Ventricular dilatation or hypertrophy
  - Tachycardia
- Autonomic nerves:
  - Increased sympathetic adrenergic activity
  - Reduced vagal activity to the heart
- Neurohormonal activation:
  - Renin-angiotensin-aldosterone system
  - Vasopressin (antidiuretic hormone)
  - Circulating catecholamines
  - Natriuretic peptides

Frank-Starling curves

- Increasing afterload or decreasing inotropy
- Decreasing afterload or increasing inotropy

Sympathetic activation in chronic heart failure

Renin-angiotensin-aldosterone axis in heart failure
Norepinephrine concentrations and prognosis in chronic heart failure

Heart failure - a self perpetuating cycle

Cardiomyopathies

Dilated cardiomyopathy: overview

• Characterised by dilatation and impaired ventricular contraction
• May be genetic, post-viral, drug or toxin induced, metabolic, mitochondrial, connective tissue associated or due to HIV
• In infants, anomalous coronary origin from a pulmonary artery must be excluded
• Late histological findings are non-specific
• Usually presents with heart failure
• Accompanying diastolic dysfunction may include impaired ventricular relaxation and non-compliance

Effects of natriuretic peptides

Cardiomyopathies

Definition

• WHO definition (1996): "Diseases of the myocardium associated with cardiac dysfunction"
  - Dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Restrictive cardiomyopathy
  - Unclassified: Arrhythmogenic RV dysplasia, LV non-compaction
**Dilated cardiomyopathy**

- Up to 25% of dilated CM is caused by genetic mutations
- 1st gene identified was dystrophin (X-linked CM); others include actin, desmin and lamin A/C (dominant and recessive)
- Actin, desmin and dystrophin are cytoskeletal proteins with roles in force transmission, cytoskeletal stability, calcium homeostasis, myocyte differentiation, myofibrillogenesis
- Lamin is a nuclear protein; commonest mutation and is associated with conducting system disease
- Dystrophin, desmin and lamin mutations can be associated with skeletal muscle disease

**Dilated cardiomyopathy: viral disease**

- Common pathogenic viruses include adenovirus, enterovirus, CMV, influenza
- About 20% of subjects with dilated CM have virus by PCR
- In subjects with myocarditis, 35-40% viral yield
- Mechanisms of damage are both acute (dystrophin cleavage) and delayed (lymphocytic infiltrate)
- Adenovirus typically causes little lymphocytic infiltrate

**Myocarditis**

**Mitotic model**

- Acute myocarditis
- Subacute myocarditis
- Chronic myocarditis

<table>
<thead>
<tr>
<th>Viral infection</th>
<th>Myocyte necrosis</th>
<th>Macrophage activation</th>
<th>Infiltrating mononuclear cells</th>
<th>Cytokines</th>
<th>Fibrosis</th>
<th>Dilatation</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral clearing</td>
<td>Neutralising antibodies</td>
<td>Neutrophil infiltration</td>
<td>Lymphocytes</td>
<td>Mono macrophage infiltration</td>
<td>4 days</td>
<td>14 days</td>
<td>Viral absence</td>
</tr>
</tbody>
</table>

**Histologic variation**

- Diffuse mononuclear infiltrate
- Focal mononuclear infiltrate
- Myocardial oedema – no infiltrate
- Myocardial fibrosis and hypertrophy

**Mitochondrial function**

- Mitochondria are the power plants of cells
- They convert fat, sugar and proteins to ATP
- Other roles include gluconeogenesis, amino acid and steroid synthesis, ROS and apoptosis

**Mitochondrial diseases**

- Typical organ involvement
  - Brain: seizures, demenia, infarcts, leukoencephalopathy
  - Eye: optic atrophy, pigmentary degeneration, cataracts
  - Ear: deafness
  - Muscle: skeletal myopathy
  - Heart: cardiomyopathy (HCM, DCM), conduction defects
  - Kidney: tubular dysfunction
  - Liver: hepatic dysfunction, bile stasis
  - Bone marrow: pancytopenia, specific cell line failure
  - Blood, urine, CSF: increased lactate
Hypertrophic cardiomyopathy

- Primary cardiac disorder with a heterogeneous expression and diverse clinical course
- Characterised by left ventricular hypertrophy in the absence of dilatation, or conditions capable of producing LVH
- Non-obstructive in around 75% of cases
- Prevalence in the general population is around 0.2%

Hypertrophic cardiomyopathy: morphological characteristics

- Distribution of hypertrophy is usually asymmetric
- Any pattern possible but anterior ventricular septum predominantly involved
- Spontaneous LV remodeling with increase in wall thickness during adolescence, and a decrease in wall thickness with aging

Hypertrophic cardiomyopathy: genetic defects

- Mendelian trait with autosomal dominant inheritance
- Mutations involve genes that encode for sarcomeric proteins
- 10 different proteins implicated and >200 described mutations (allelic heterogeneity)
- Around 50% of cases represent spontaneous mutations
- Hypertrophy may be secondary to altered sensitivity to calcium and impaired contractility
Hypertrophic cardiomyopathy
contractile protein mutations

- Nimura et al; NEJM 1998

Cardiac beta-myosin heavy chain
Cardiac troponin T
Cardiac myosin-binding protein C

HCM - age related penetrance

0 10 20 30 40 50 60 70 80 90 100
10-19 20-29 30-39 40-49 50-59 >60

In adults, some mutations are associated with development of hypertrophy beyond middle life
Disease penetrance may be incomplete below 60 years of age
With some mutations there is variable disease expression within a kindred
Electrocardiographic abnormalities may precede development of overt hypertrophy

Paediatric HCM
aetiological considerations

- Contractile protein abnormality
- Syndromes: Noonan, Beckwith-Wiedemann, LEOPARD, Friedrich's ataxia
- Metabolic: Carnitine deficiency, Fatty acid oxidation defects, Glycogen storage disease, MPS, Mannosidosis, Fucosidosis, Lipodystrophy
- Mitochondrial myopathies
- Neonatal hyperinsulinaemia

Causes of sudden cardiac death in young people

- Congenital coronary anomalies (10%)
- Mildly increased cardiac mass (10%)
- Ruptured aorta (5%)
- Tunneled LAD (5%)
- Aortic stenosis (4%)
- Myocarditis (3%)
- ARVC (3%)
- MVP (2%)
- CAD (2%)
- Other (6%)

Paediatric HCM
morphological considerations

- Congenital heart disease and inappropriate hypertrophy
- Subpulmonary RV outflow obstruction
- Pulmonary valve stenosis (Noonan syndrome)
- Atrial septal defect or stretched PFO
- Subaortic membrane
- Anomalous mitral cord insertion into the IVS
- Anomalous papillary muscle insertion directly into the anterior mitral leaflet
Mortality in HCM
Maron et al; Circulation 2000

- Stroke
- Heart failure
- Sudden death

Age at Death or Most Recent Evaluation (years)

- Hypertrophic cardiomyopathy

- Disorganized cellular architecture
- Abnormal intramural coronary arteries with thickened walls and narrowed lumens
- Replacement fibrosis adjacent to intramural vessels

Maron BJ; Lancet 1997

Adult hypertrophic cardiomyopathy
Risk factors for sudden death

- Cardiac arrest/sustained VT
- Family history of sudden death
- Recurrent syncope
- Multiple-repetitive NSVT
- Exercise hypotension
- Massive LVH
- Malignant genotype?

Implantable defibrillator
Medical therapy (?)

Relation of wall thickness to sudden death
Spirito P et al, NEJM 2000

Maximal Left-Ventricular-Wall Thickness (mm)

- Incidence of Sudden Death (per 1000 person-years)

Restrictive cardiomyopathy

- Basic defect unknown
- Diastolic dysfunction with normal wall thickness and systolic function
- Primary: endomyocardial fibrosis, Loeffler’s, and primary RCM
- Infiltrative: irradiation, sarcode, amyloid
- Metabolic: Glycogen storage disease, Fabry’s disease, haemachromatosis
- Mixed HCM and RCM may be due to Troponin I mutation
- Relentless downhill course

Restrictive cardiomyopathy: echocardiogram
Arrhythmogenic right ventricular dysplasia

- Progressive fibro-fatty replacement of right ventricular myocardium with relative septal sparing
- May be autosomal dominant with incomplete penetrance or autosomal recessive
- Presentation with arrhythmias and sudden death is common, particularly in adolescents and young adults

Paediatric cardiomyopathy

- ECG, CXR, cardiac ultrasound
- Serum carnitine, pyruvate, lactate, urine metabolic screen
- Viral PCR and culture of available tissues/fluids
- Metabolic consults; consider liver and skeletal muscle biopsy
- Screen first degree relatives
- Genotype and skeletal muscle biopsy if no improvement

Alternatives to heart transplantation

- **ACE inhibitors, beta-blockers and aldosterone antagonists improve outcomes in adults with left ventricular dysfunction**
- Carvedilol and bisoprolol have been shown to reduce mortality, decrease cardiovascular hospitalisation, improve LV function and quality of life
- With current therapy, 5 year survival for patients who are NYHA III at presentation is comparable to that of transplantation
- Prospective, randomised studies are lacking in paediatric patients but retrospective and limited prospective data suggests a similar benefit in children with cardiomyopathy
- The impact of beta-blocker therapy on ventricular function in children with congenital heart disease remains uncertain

Alternatives to heart transplantation

- LBBB with ventricular dysynchrony is mechanically disadvantageous
- Cardiac resynchronisation therapy improved symptoms, exercise tolerance and quality of life in several randomised trials
- The traditional criteria for resynchronisation include:
  - optimal medical therapy
  - depressed LV ejection fraction
  - wide QRS duration complex (duration >120ms) with left bundle branch block morphology
- Not all patients respond and mechanical dysynchrony is not necessarily related to electrical dysynchrony
- More recently echocardiographic criteria for ventricular dyssynchrony have been proposed, including M-mode, difference in ventricular pre-ejection intervals, analysis of regional wall motion analysis and tissue Doppler

Alternatives to heart transplantation

- Data on efficacy of resynchronisation therapy in children and in subjects with CHD is limited
- We have placed biventricular pacemakers in 16 children with CM (7) and congenital heart disease (9), none of whom have so far required transplantation
- In those with dilated CM, the mean baseline LVEF was 36%, compared to 59% at latest follow-up

Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy

Decisions about the use of ICD’s need to be made within the context of other known risk factors

Wall thickness alone is not a good predictor of sudden death
Alternatives to heart transplantation

ICD therapy

- Some subjects with CM and CHD are mainly at risk of sudden death
- Decisions about ICD’s are usually made on the basis of the underlying disease, family history, symptoms, documentation of arrhythmias and the results of an EP study
- ICD therapy rather than cardiac transplantation should be considered for these patients
- We have placed 26 ICD’s in children with CM (12), CHD (3) and primary arrhythmias (11), one of whom has subsequently been transplanted

Pediatric cardiac transplantation

Indications

- Severe heart disease (CM, CHD, anthracycline toxicity) with depressed LV function, symptoms and anticipated poor 12 month survival, despite optimal medical therapy
- Patients with palliated cardiac malformations who have a poor quality of life

Freedom from death/transplant

Survival probability

- HCM
- DCM
- LVNC
- RCM

Recipient assessment

- Try and make a firm diagnosis: genotyping, mitochondrial work-up and storage of DNA
- Quantify ventricular function and PVRI
- Consider any other available therapies
- Assess arrhythmic potential
- Neuro-psychometric assessment
- Let family meet team members (surgeons, ICU physician, transplant coordinator, social worker, psychologist) and other transplant families
- Allow several detailed conversations before canvassing a decision
- Discuss issues life support and extended ICU therapy in advance
- Periodically reassess the patient first-hand

Recipient assessment

Risk factors

- Children with palliated single ventricles
  - multiple previous sternotomies and transfusions
  - acquired aorto-pulmonary collaterals
  - additional surgery required at time of transplantation
  - long cardio-pulmonary bypass times
- Elevated pulmonary vascular resistance with reactivity
- Considerable deconditioning prior to transplantation
- On ventilator or mechanical support at time of transplantation
- Lack of a social support system

Pediatric cardiac transplantation

Contraindications

- Active neoplasm
- Inadequate pulmonary arteries
- Degenerative CNS, neuromuscular or metabolic disease
- Severe elevation of pulmonary vascular resistance without acute reactivity
Venous and arterial reconstruction at time of transplant

Donor assessment
- Check donor story and clinical status with appropriate physician
- ABO and lymphocyte cross-match
- Size matching (donor:recipient weight of up to 3.5:1)
- Check donor inotrope requirements once DI and hypovolaemia corrected
- Consider potential ischaemic time in light of:
  - Recipient characteristics
  - Donor function (always get an echo & ECG on remote donors)
  - Clinical urgency

Mechanisms of rejection and drug therapy

Acute cellular rejection
Occurs in 40-70% of patients
T cell mediated and most common within the first 3-6 months
Diagnosis requires endomyocardial biopsy
Graded on a scale according to extent and severity
Moderate rejection usually treated with steroids, antibodies (ATGAM or OKT3) or change in background therapy

Acute humoral rejection
Occurs in 7% of patients within days to weeks of transplantation
Due to alloantibodies against HLA or endothelial antigens
More common if high PRA levels or positive cross-match
Diagnosis made by endomyocardial biopsy with staining for complement
Requires therapy to remove or modulate antibody production
Associated with late coronary disease

Chronic rejection (coronary allograft vasculopathy)
Occurs within months to years
Poorly understood — immune mediated on background of donor and recipient characteristics
Often diffuse and involves small vessels, difficult to diagnose early
Occurs in up to 50% of adults and 10-15% of children within 5 years
Major cause of late mortality after transplantation
Therapy involves prevention (risk factors) and coronary intervention (if focal) or re-transplantation
Immunosuppressive therapies

Cyclosporine

- CSA enters T cells via diffusion and binds to immunophilin
- The complex binds to calcineurin and inhibits transcription of IL-2 and other cytokines
- The introduction of CSA in 1982 increased 3-year survival from 40% to 70%
- Long list of adverse effects includes nephrotoxicity, hypertension, hyperlipidaemia, type I diabetes, neurotoxicity and cholestasis
- Hypertrichosis and gingival overgrowth are prominent in young patients

Cyclosporin induced hirsutism

Cyclosporine induced gingival overgrowth

Immunosuppressive therapies

Tacrolimus

- Inhibits calcineurin through a pathway similar to that of CSA
- Prospectively compared with CSA in 3 small randomised trials: no difference in short-term survival, or frequency & severity of rejection
- Lower incidence of hypertension and hyperlipidaemia
- Type I diabetes probably more common
- No cosmetic side effects

Immunosuppressive therapies

Azathioprine

- Antimetabolite
- Converted into a purine analogue and incorporated into DNA, inhibiting proliferation of T and B cells
- Used as maintenance therapy in combination with steroids and a calcineurin inhibitor
- Major side effect is myelosuppression which can affect all cell lines
- Pancreatitis and hepatitis are rare side effects
**Immunosuppressive therapies**

**Mycophenolate mofetil**
- Noncompetitive inhibitor of de novo guanine nucleotide synthesis
- Selective inhibitor of lymphocyte proliferation with less myelosuppression than AZA
- Tested in a large, prospective randomised study: 3-year survival 88.2% compared to 81.7% for AZA
- Opportunistic infections more common
- Main side effects are gastrointestinal (nausea, vomiting and diarrhoea)

**Sirolimus**
- Similar structure to Tacrolimus
- Disrupts a kinase which connects signals from growth factor receptors to cell nucleus, leading to growth and proliferation of T and B lymphocytes
- Also inhibits smooth muscle and endothelial cell proliferation
- Tested against AZA in a prospective randomised study: reduced acute cellular rejection and prevented graft vasculopathy at 2 years post-transplant
- No inherent nephrotoxicity; may cause thrombocytopaenia
- Role in immunosuppressive regimens is still unclear

**Routine post transplant therapy**
- Triple therapy with tapering steroids
- Diltiazem for antihypertensive and CSA/TAC sparing effects
- Routine pneumocystis prophylaxis with cotrimoxazole
- Pravastatin for prevention of post-transplant coronary disease in recipients >10 years

**Endomyocardial biopsy**
- Conventional echo parameters are insensitive markers for the presence of mild-moderate cellular rejection
- Biopsies are not a gold standard - they are subject to differences in observer interpretation and there may be little to see in someone with rapidly progressive rejection
- Biopsies are of low risk and often add useful information
- Children older than 12 months have a biopsy based protocol with around 12 surveillance biopsies during the first year
- Children younger than 1 year have periodic but less frequent biopsies
- Try and avoid biopsies in haemodynamically unstable patients and in very young infants

**Immunosuppressive strategies**
- Cyclosporine used initially for all children
- Unacceptable cosmetic side-effects: consider a change to Tacrolimus (according to EBV status)
- Frequent or persisting cellular rejection: change to Tacrolimus or Mycophenolate Mofetil
- Renal dysfunction: reduce the dose of Cyclosporine/Tacrolimus or change to Sirolimus
- Coronary disease: optimise risk factors and add Sirolimus

**Diagnosis in Pediatric Heart Transplant Recipients (Age: < 1 Year)**

- Myopathy: 81%
- Congenital: 2%
- Other: 2%
- ReTX: 1%
- Myopathy: 69%

**Graph**
- 1988-1995: 15%
- 1996-2004: 29%
- Bar chart showing percentage of cases by year and diagnosis
Lymphoproliferative disease

- PTLD is the primary post-transplant malignancy in children
- Usually polymorphic, of B cell origin and EBV driven
- Incidence 9% within 7 years; 3 year 70% survival
- Options include reduction or cessation of therapy, or chemotherapy (for refractory or monomorphic disease)
- Relationship to Tacrolimus is unclear

Late follow-up

- Regular review in a clinic setting
- Coronary angiography yearly in adolescents and 2nd yearly in younger patients
- Additional biopsies if changes in therapy, low drug levels or evidence of non-compliance
- Annual measurement of glomerular filtration rate
- Dental review
- Regular contact with a psychologist

Adolescent non-compliance warning features

- Missed appointments without explanation
- Clinic attendance without parents
- Unstable social circumstances
- Low CSA levels without changes to therapy
- No routine for taking therapy
- Patient/family unfamiliar with drugs or doses
- Unexpected late rejection
- Previous non-compliance

Adolescent non-compliance minimising the risk

- Regular clinical review with non-invasive cardiac assessment and CSA levels
- Patient or family asked to list medications at each visit
- Pill-box
- Clinical psychologist on the team sees patients separately
- Biopsy based follow-up protocol for those with late rejection

Future directions

- Cardiac transplantation is a palliative procedure. Post-transplant survival and outcomes are acceptable and continue to gradually improve
- New immunosuppressive regimens have lowered the rates of acute rejection but have had relatively little impact on the incidence of chronic rejection.
- The ultimate goal is to induce a state of donor-specific tolerance, wherein the recipient will accept the allograft indefinitely without the need for long-term immunosuppression.
- Medical and surgical alternatives to heart transplantation should be explored and applied