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,
  - valvular 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
- Neurohormal activation:
  - Renin-angiotensin-aldosterone system
  - Vasopressin (antidiuretic hormone)
  - Circulating catecholamines
  - Natriuretic peptides

Frank-Starling curves

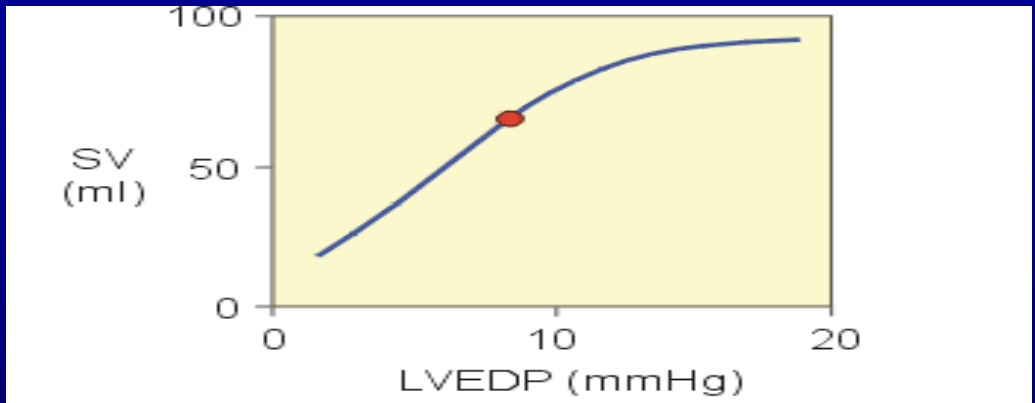
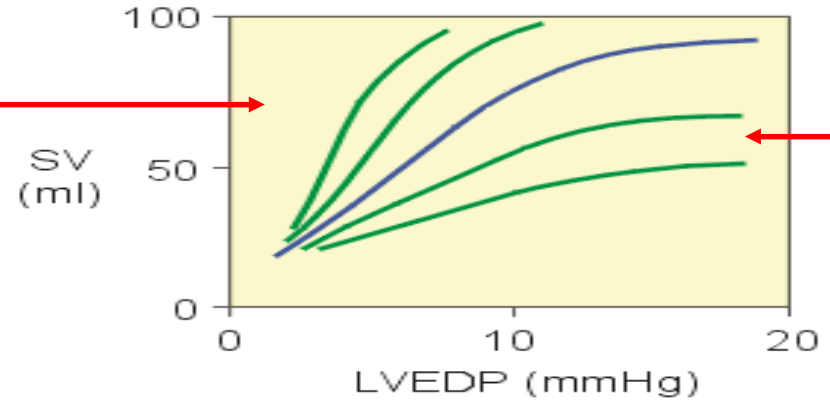


Figure 1. Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The "normal" operating point is at a LVEDP of ~8 mmHg and a SV of ~70 ml/beat.

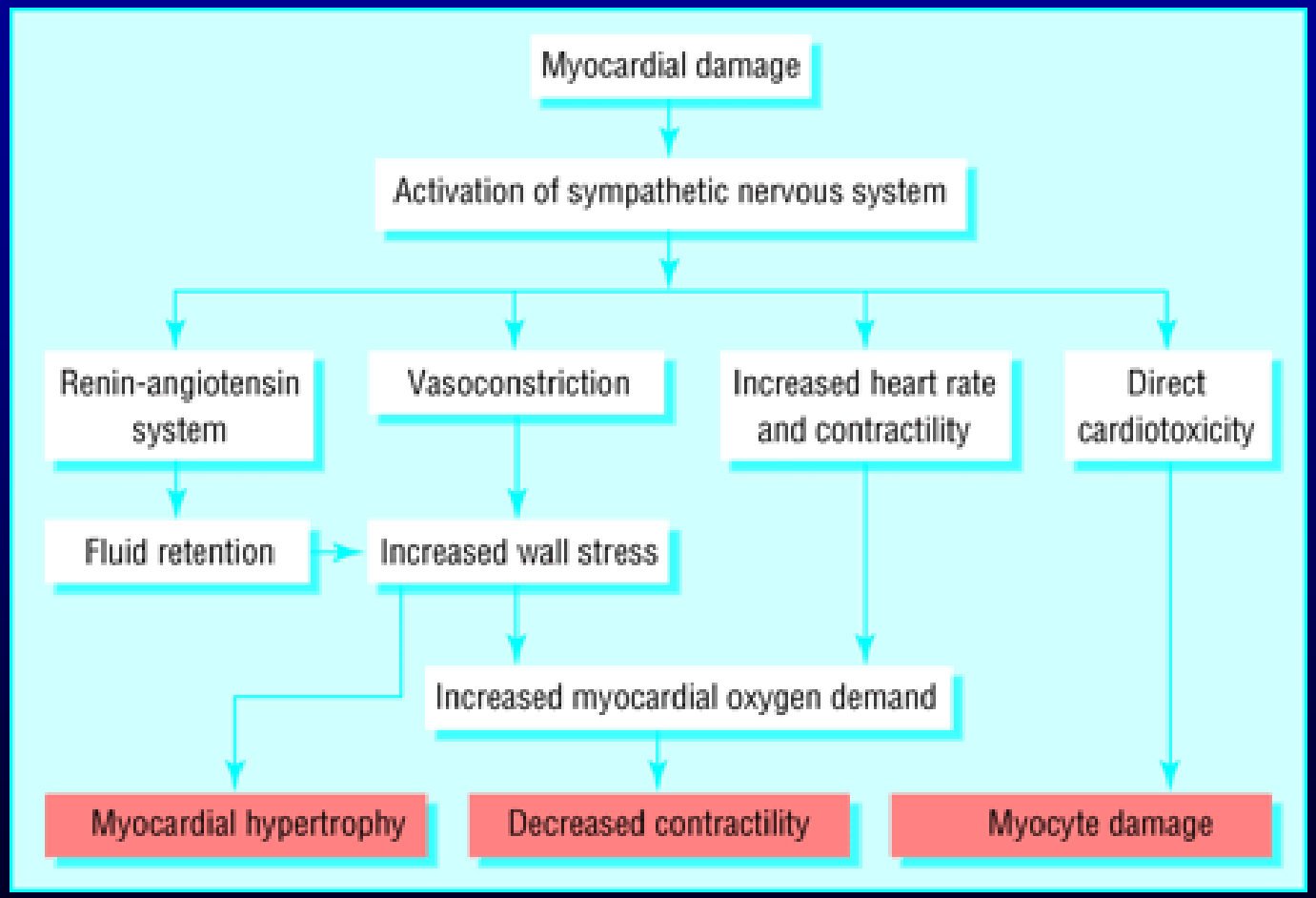
Decreasing afterload or increasing inotropy



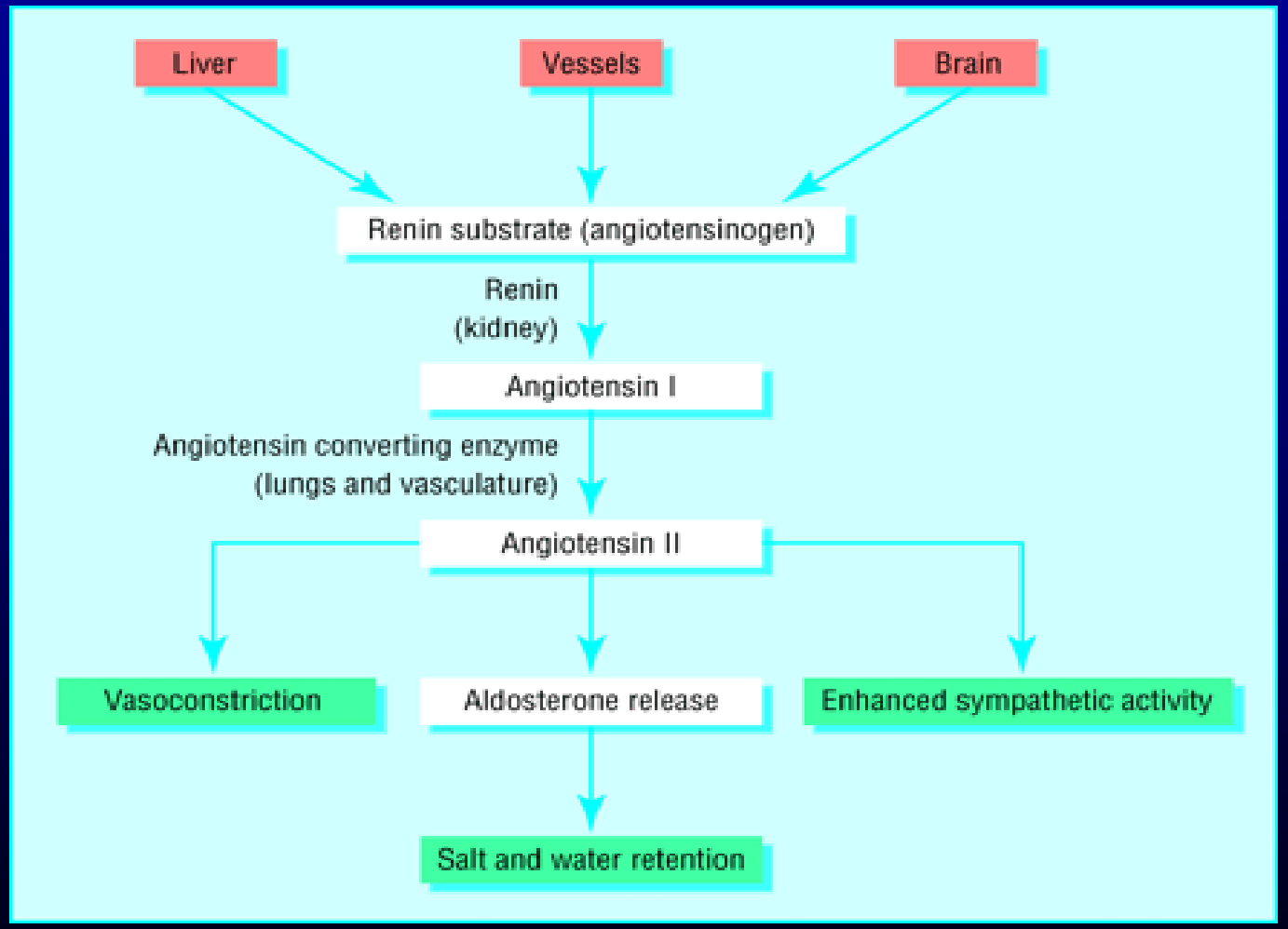
Increasing afterload or decreasing inotropy

Figure 2. Family of Frank-Starling curves. Changes in afterload and inotropy shift the Frank-Starling curve up or down.

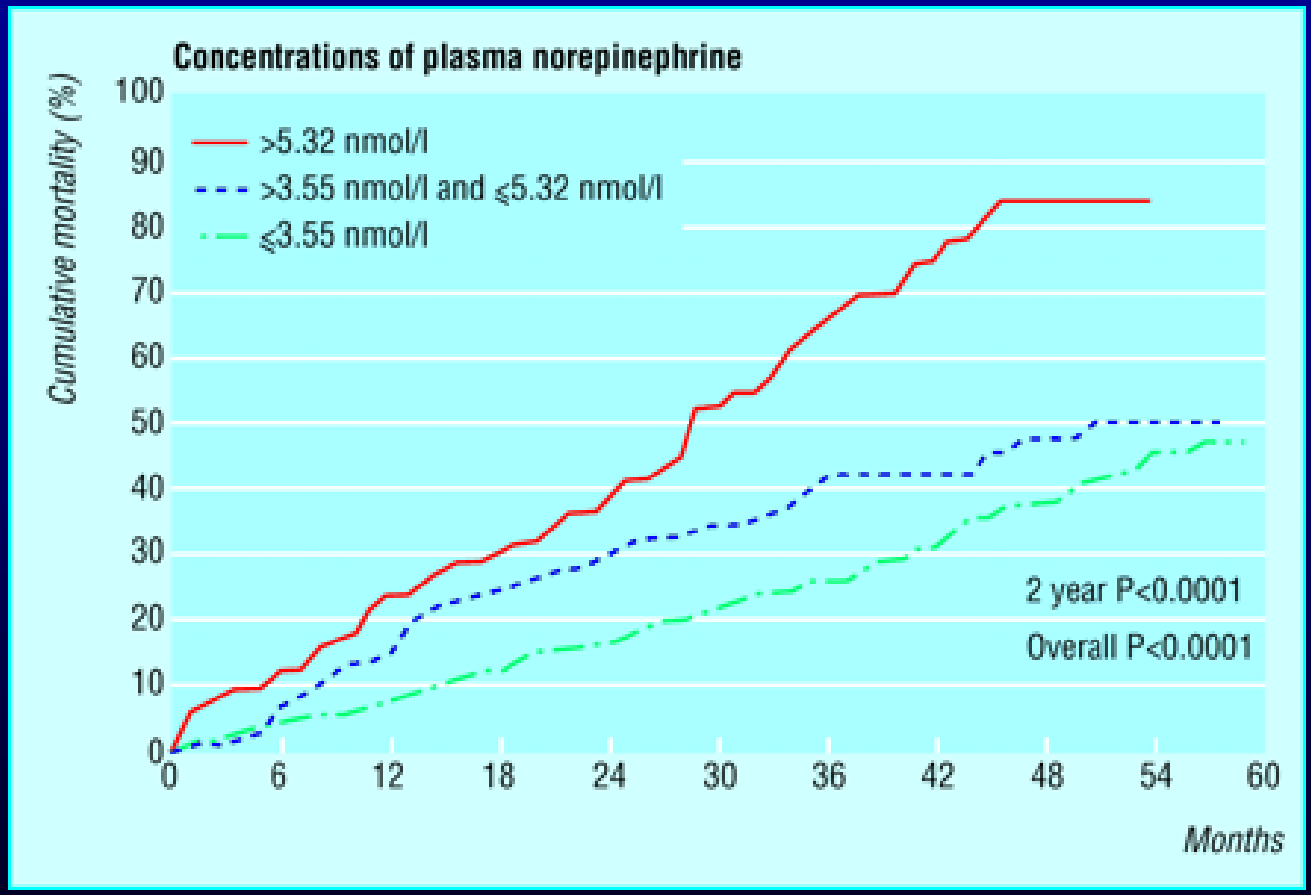
Sympathetic activation in chronic heart failure



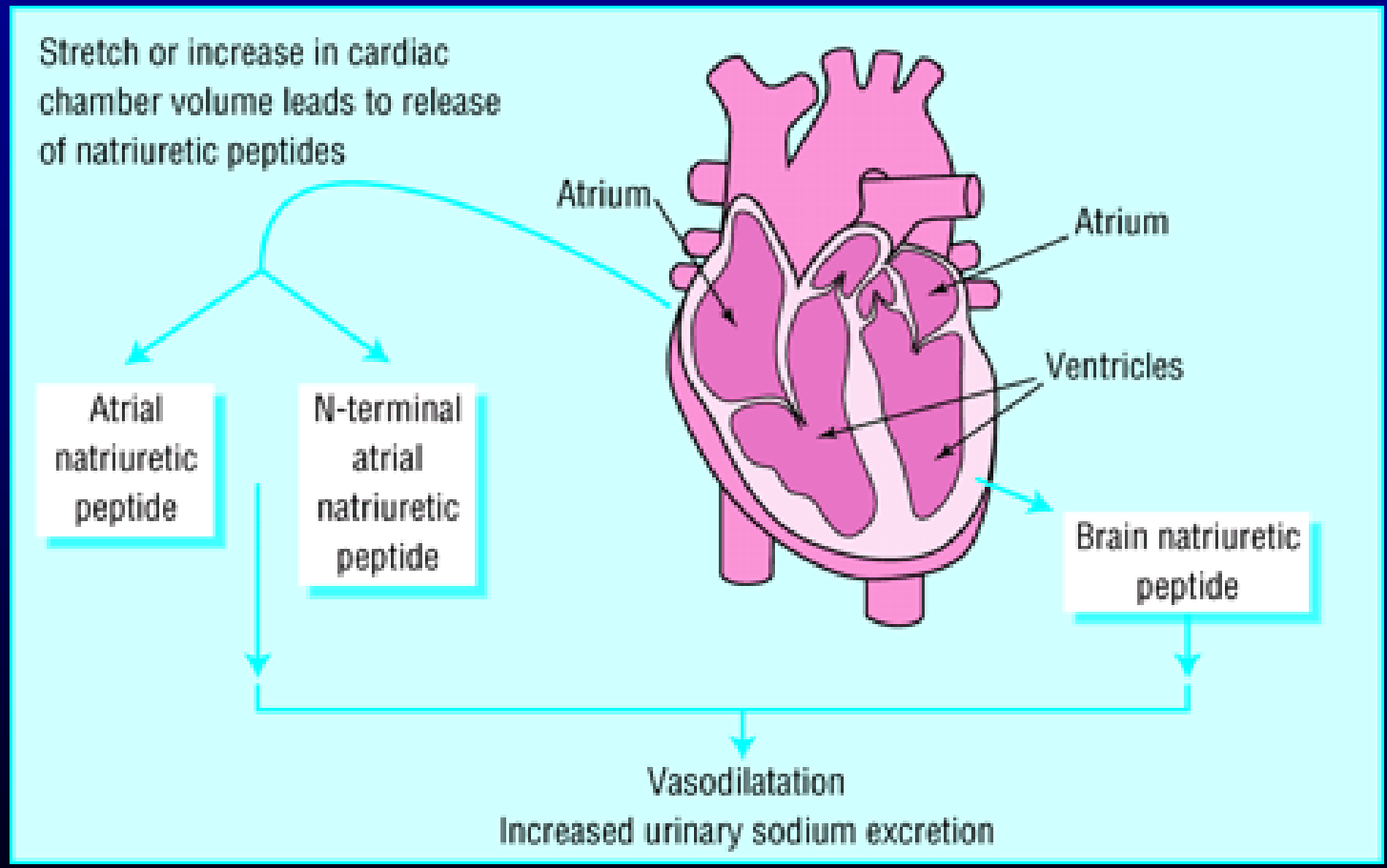
Renin-angiotensin-aldosterone axis in heart failure



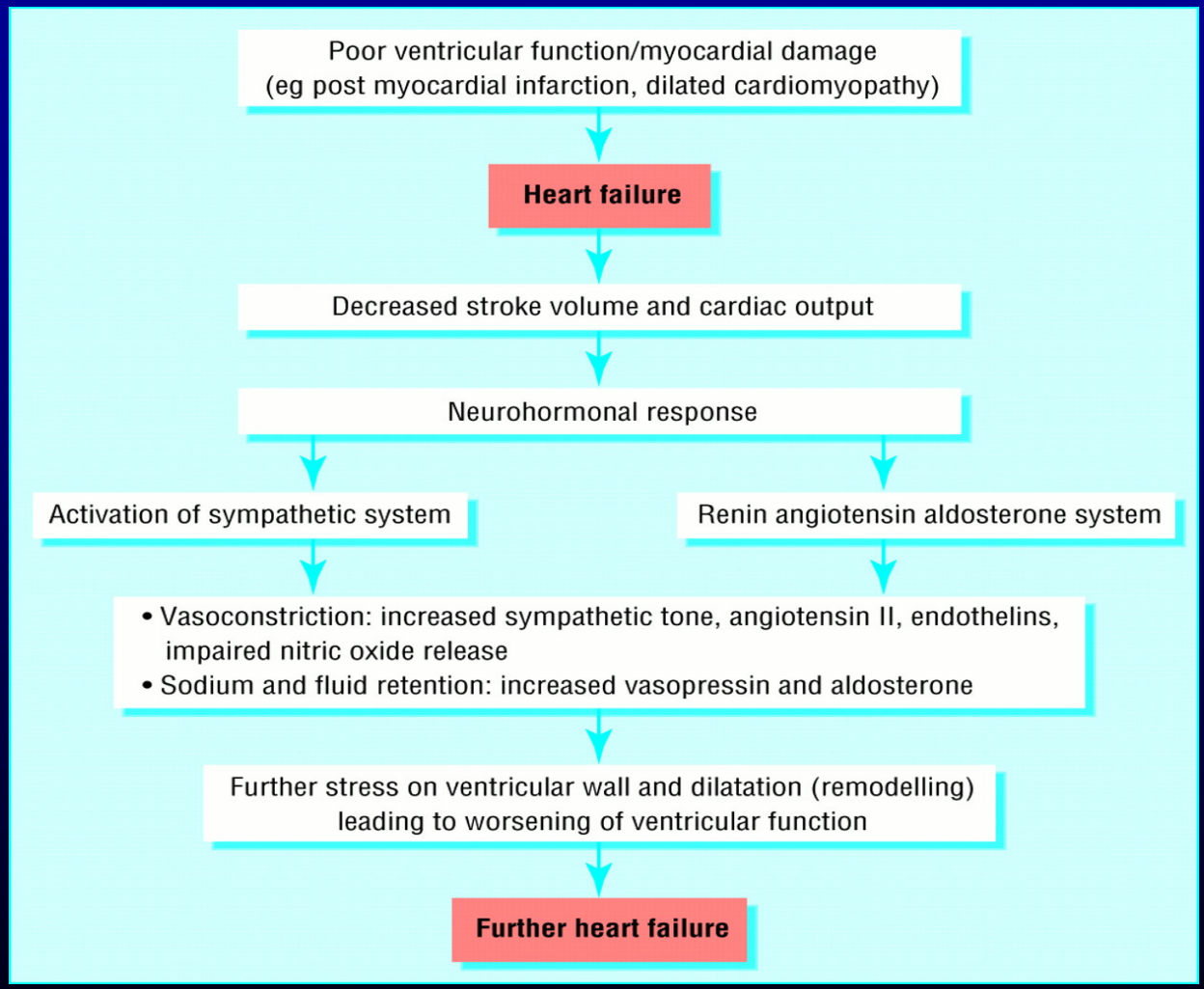
Norepinephrine concentrations and prognosis in chronic heart failure



Effects of natriuretic peptides



Heart failure – a self perpetuating cycle



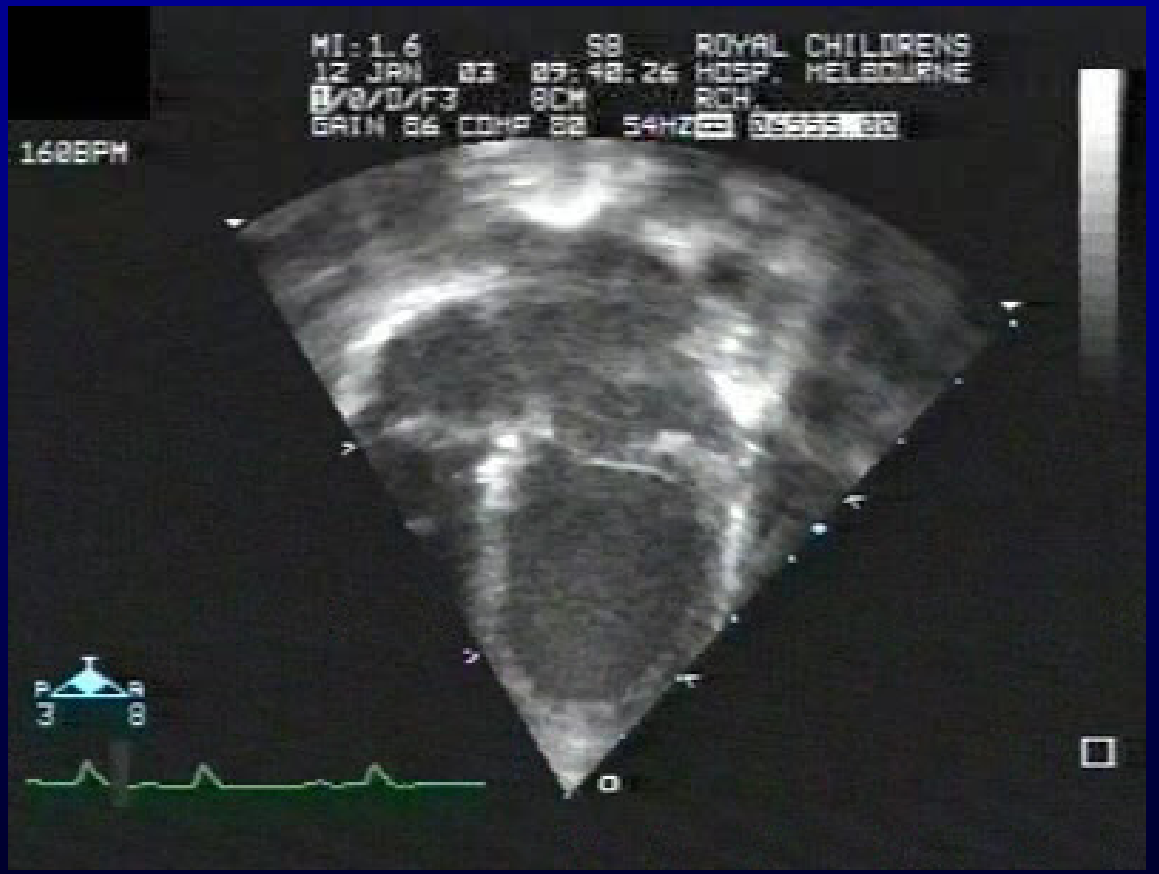
Cardiomyopathies
Definition

- 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:
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

Dilated cardiomyopathy:
echocardiogram



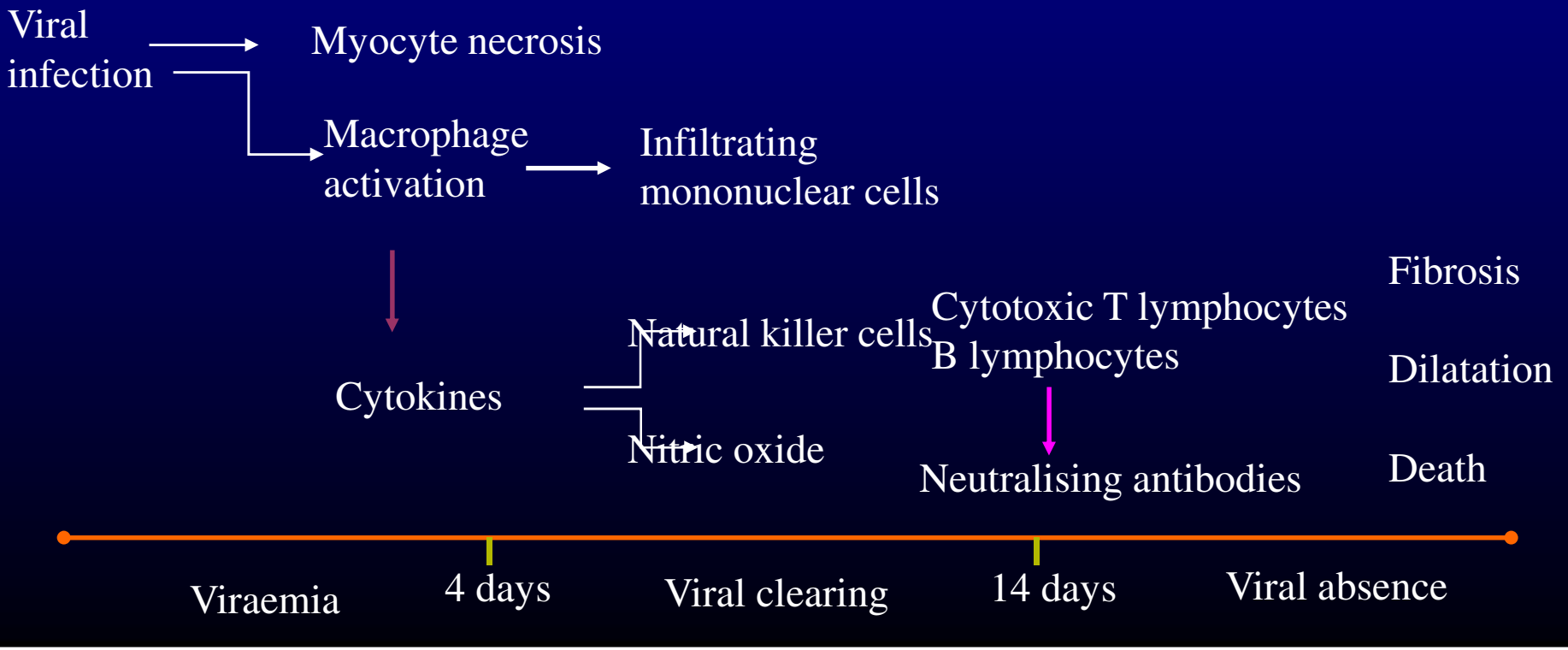
Dilated cardiomyopathy
genetic mutations

- 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

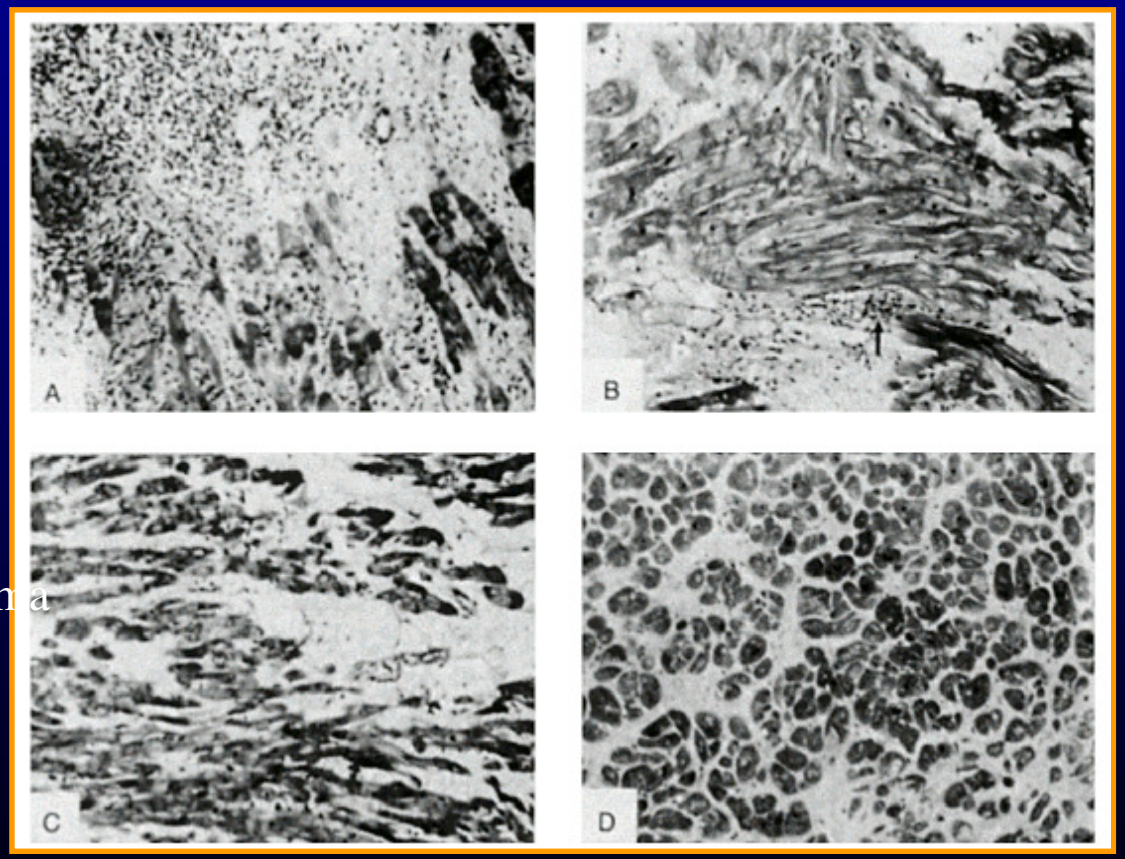
Myocarditis:
mouse model



Myocarditis – histologic variation

Diffuse mononuclear infiltrate

Myocardial oedema – no infiltrate

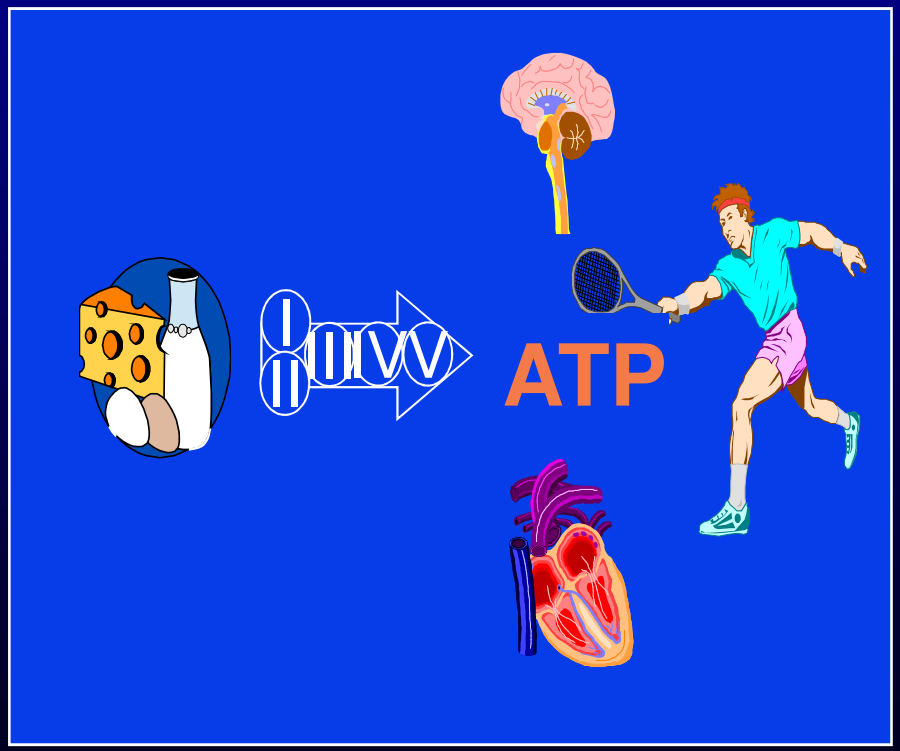


Focal mononuclear infiltrate

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, dementia, infarcts, leukoencephalopathy

Eye: optic atrophy, pigmentary degeneration, cataracts

Ear: deafness

Muscle: skeletal myopathy

Heart: cardiomyopathy (HCM, DCM), conduction defects

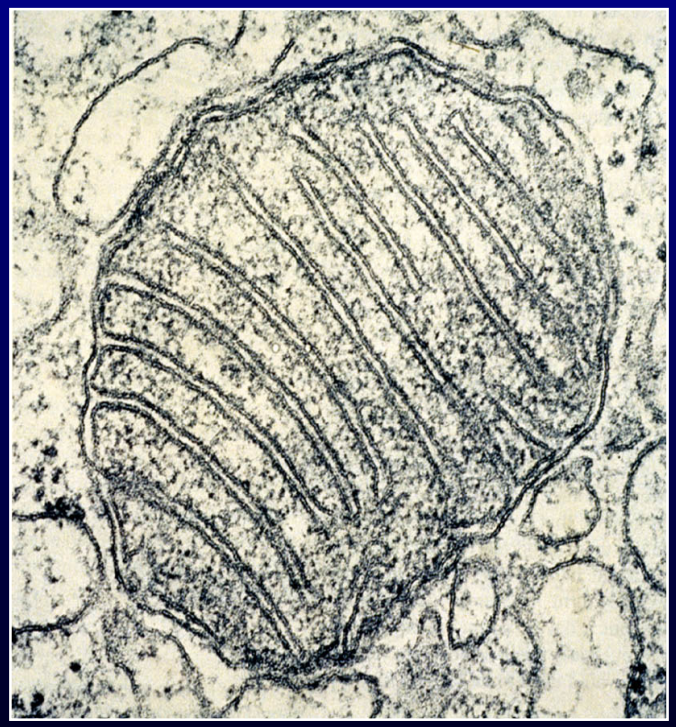
Kidney: tubular dysfunction

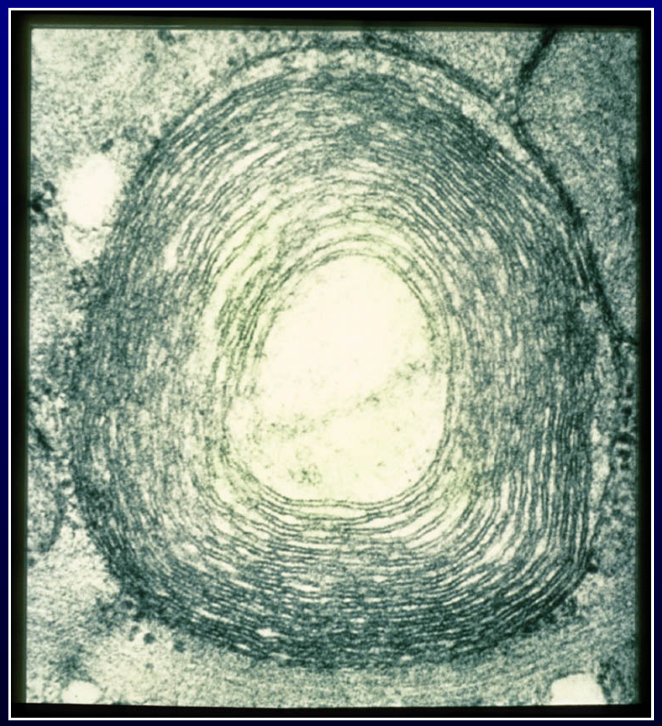
Liver: hepatic dysfunction, bile stasis

Bone marrow: pancytopaenia, specific cell line failure

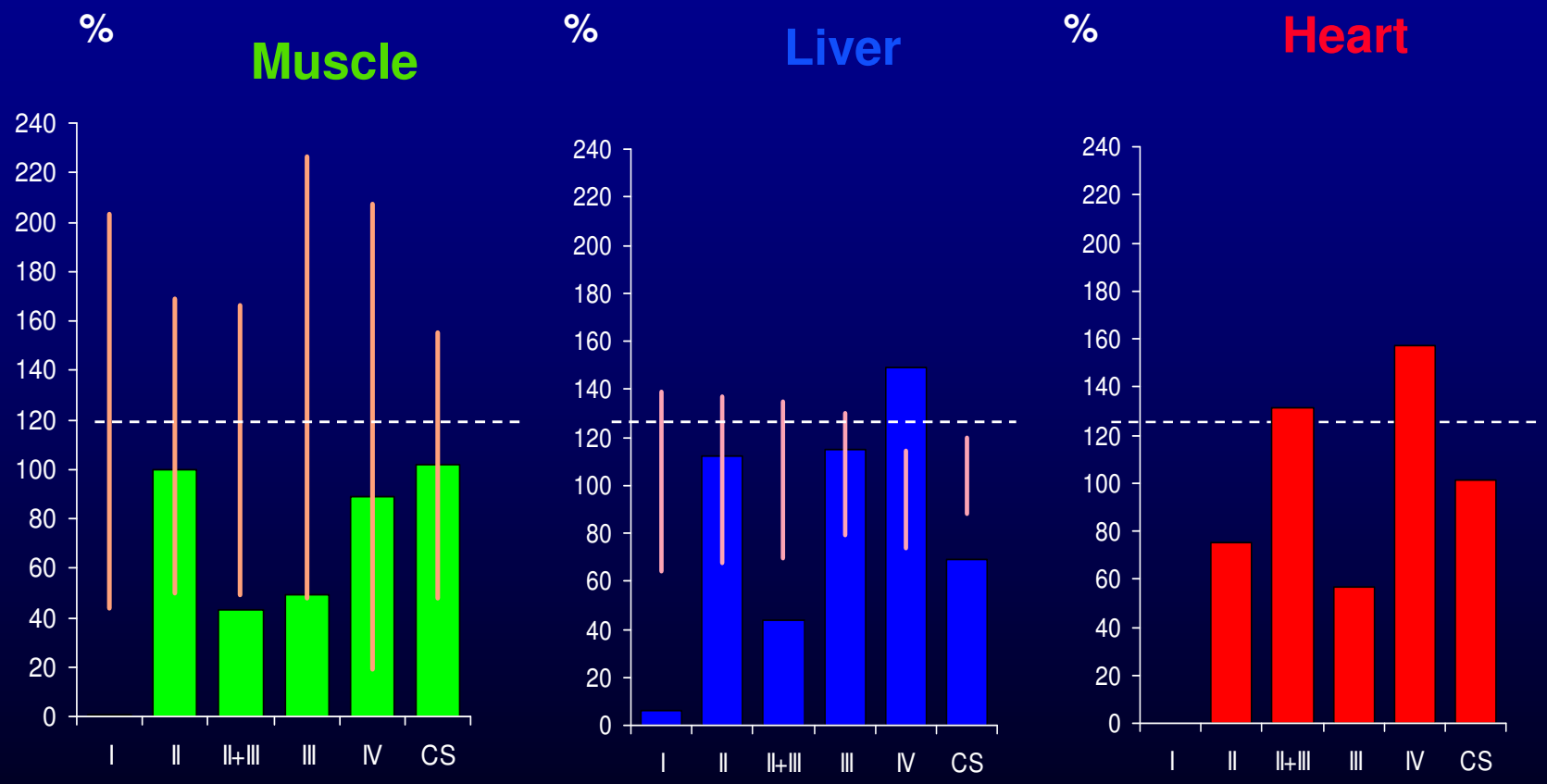
Blood, urine, CSF: increased lactate

Mitochondrial diseases





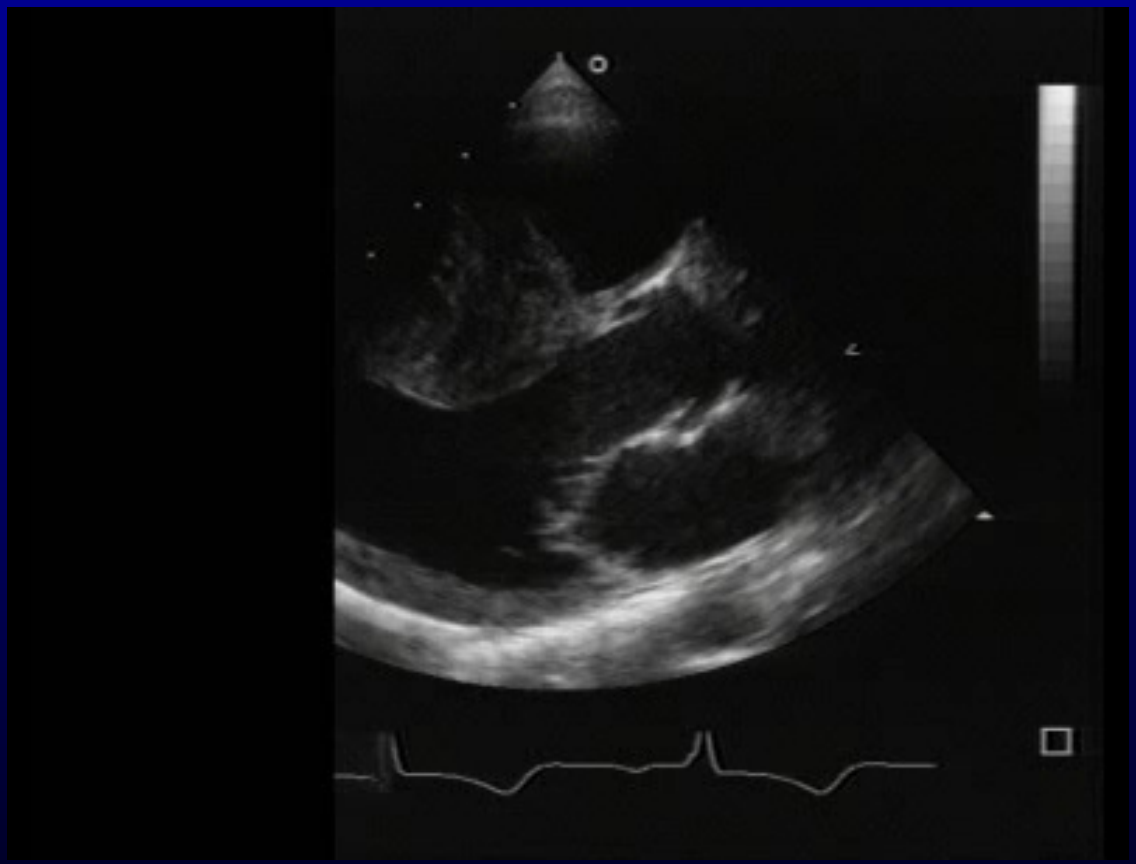
Respiratory chain Complex 1 deficiency
cardiomyopathy



Hypertrophic cardiomyopathy

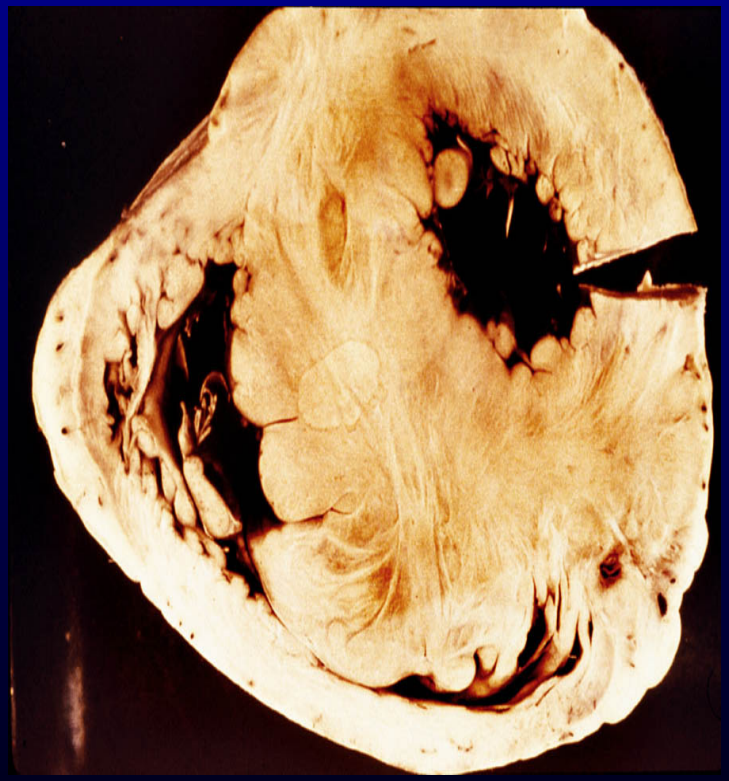
- Primary cardiac disorder with a heterogeneous expression and diverse clinical course
- Characterised by left ventricular hypertrophy in the absence of dilatation, or conditions capable of producing LVH
- Non-obstructive in around 75% of cases
- Prevalence in the general population is around 0.2%

Hypertrophic cardiomyopathy:
echocardiogram



Hypertrophic cardiomyopathy
morphological characteristics

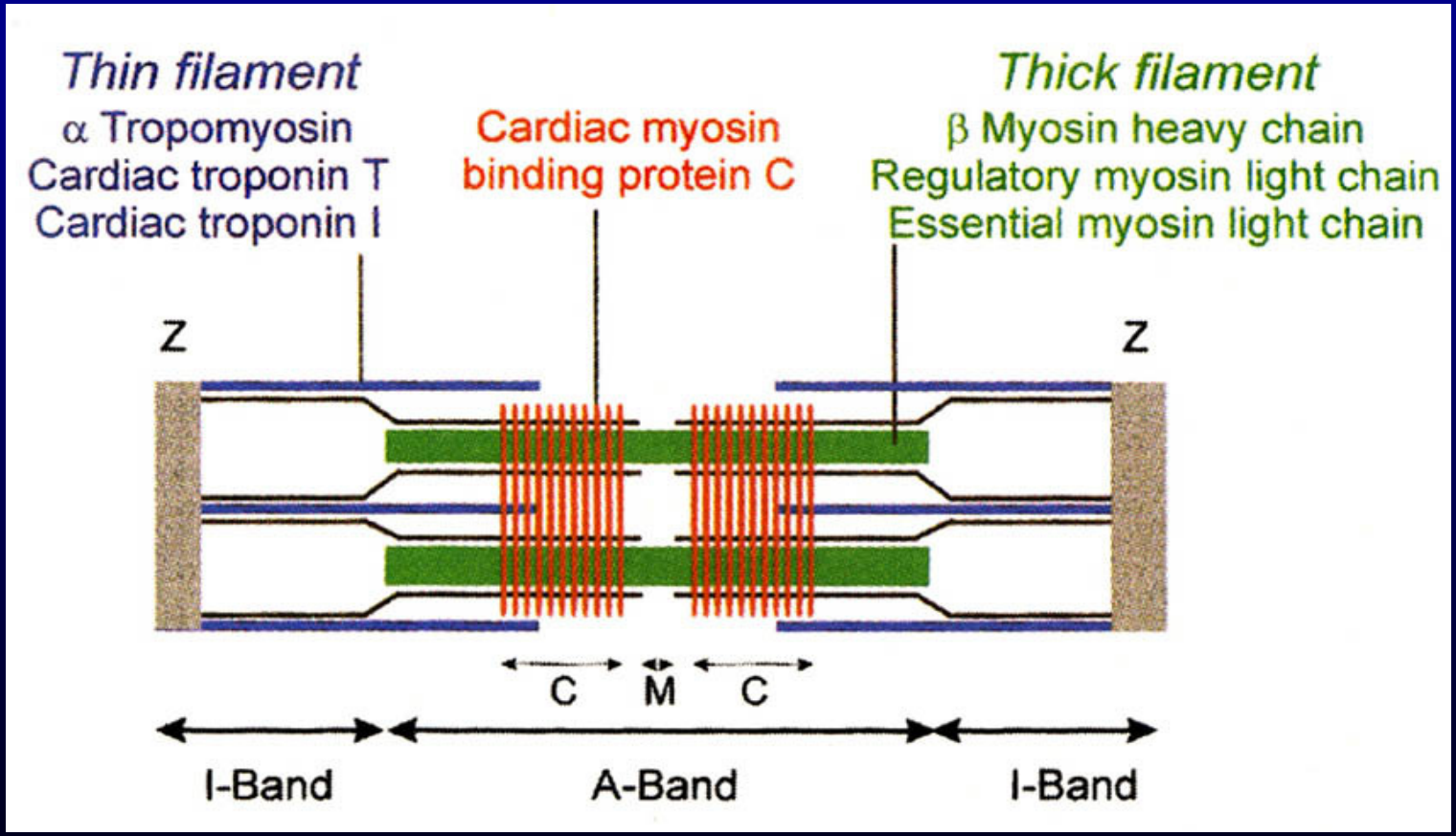
- Distribution of hypertrophy is usually asymmetric
- Any pattern possible but anterior ventricular septum predominantly involved
- Spontaneous LV remodeling with increase in wall thickness during adolescence, and a decrease in wall thickness with aging



Hypertrophic cardiomyopathy
genetic defects

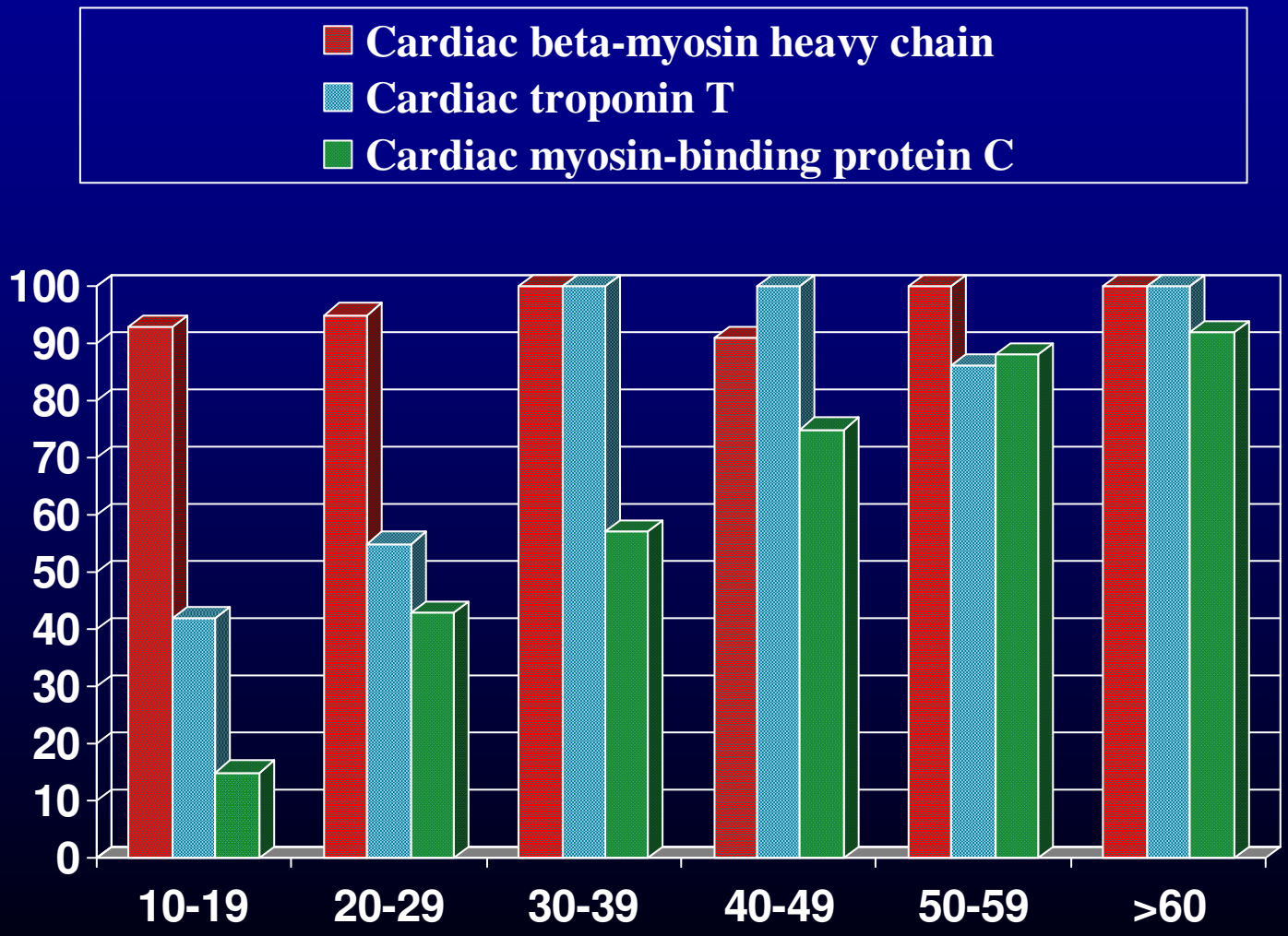
- Mendelian trait with autosomal dominant inheritance
- Mutations involve genes that encode for sarcomeric proteins
- 10 different proteins implicated and >200 described mutations (allelic heterogeneity)
- Around 50% of cases represent spontaneous mutations
- Hypertrophy may be secondary to altered sensitivity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

Hypertrophic cardiomyopathy
contractile protein mutations



HCM - age related penetrance

Nimura et al; NEJM 1998



Hypertrophic cardiomyopathy
clinical considerations

- 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

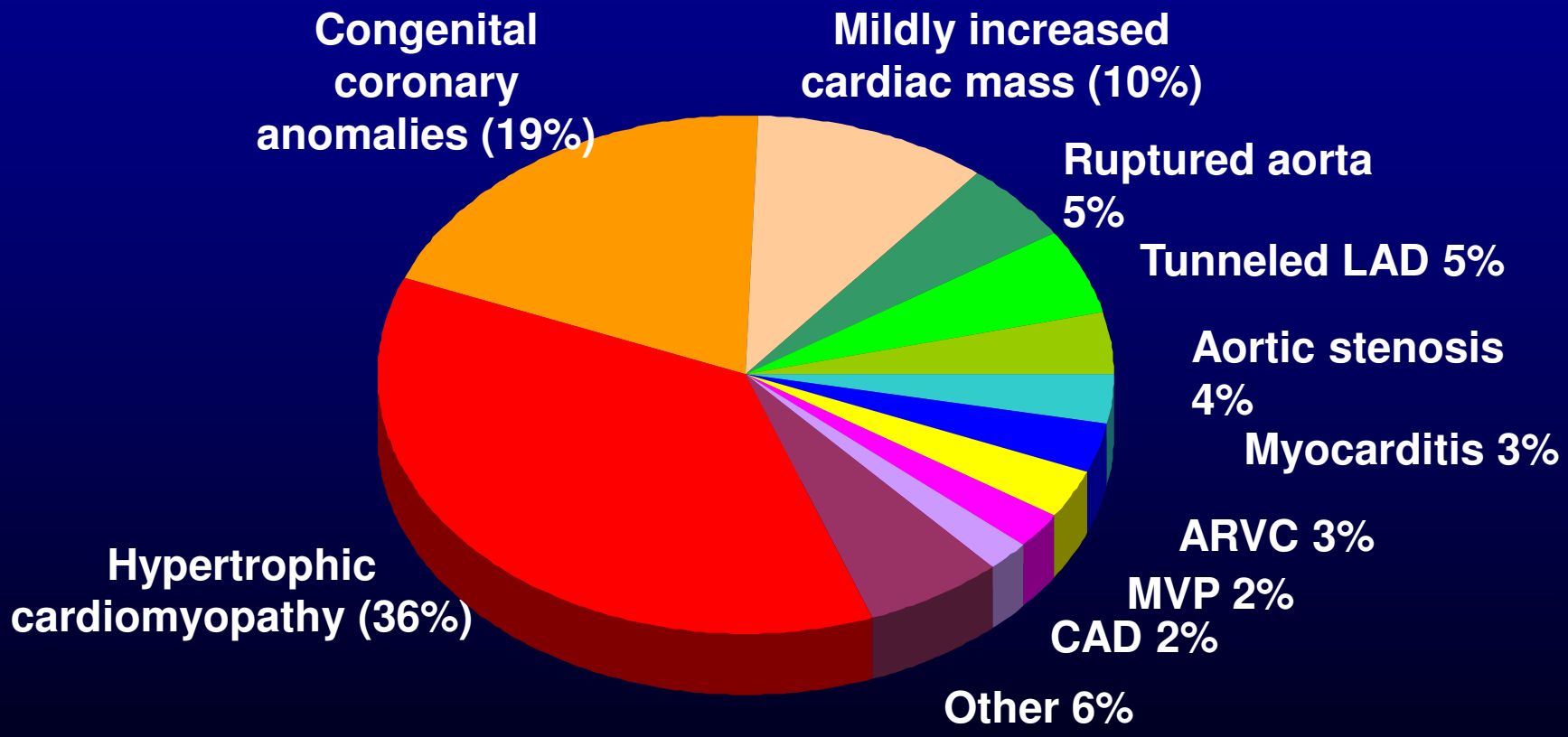
- Contractile protein abnormality
- Syndromes: Noonan, Beckwith-Wiedemann, LEOPARD, Friedreich's ataxia
- Metabolic: Carnitine deficiency, Fatty acid oxidation defects, Glycogen storage disease, MPS, Mannosidosis, Fucosidosis, lipodystrophy
- Mitochondrial myopathies
- Neonatal hyperinsulinaemia

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

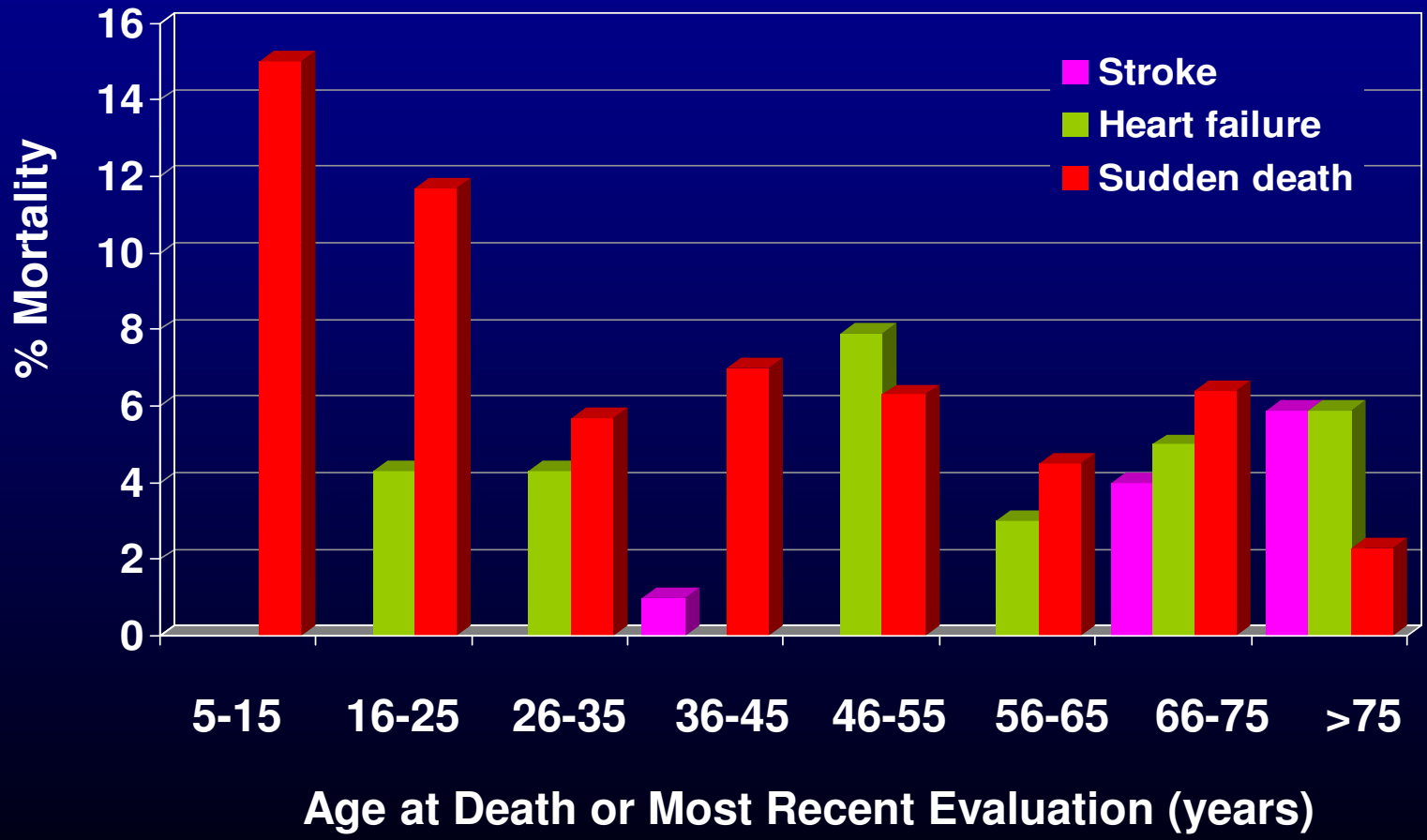
Causes of sudden cardiac death in young people

Maron BJ et al. *Circulation.* 1996;94:850-56.



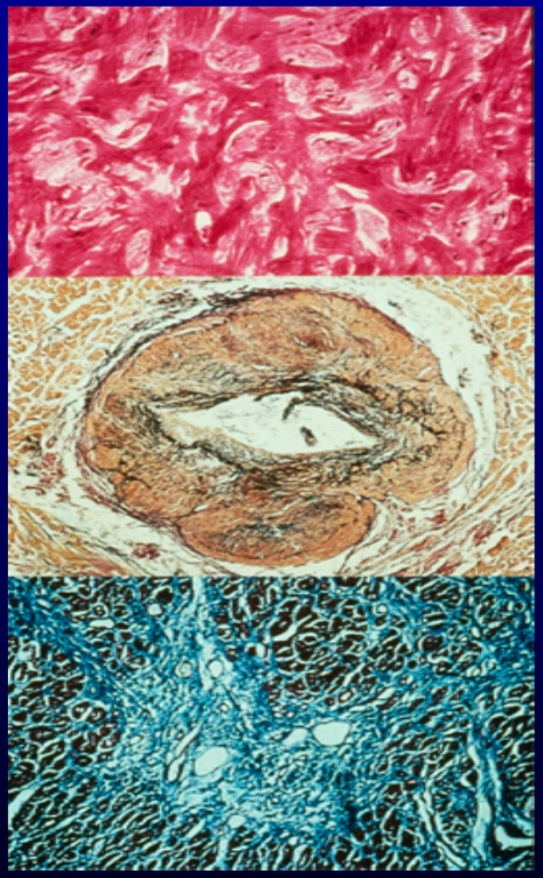
Mortality in HCM

Maron et al; Circulation 2000



Hypertrophic cardiomyopathy
substrate for SCD

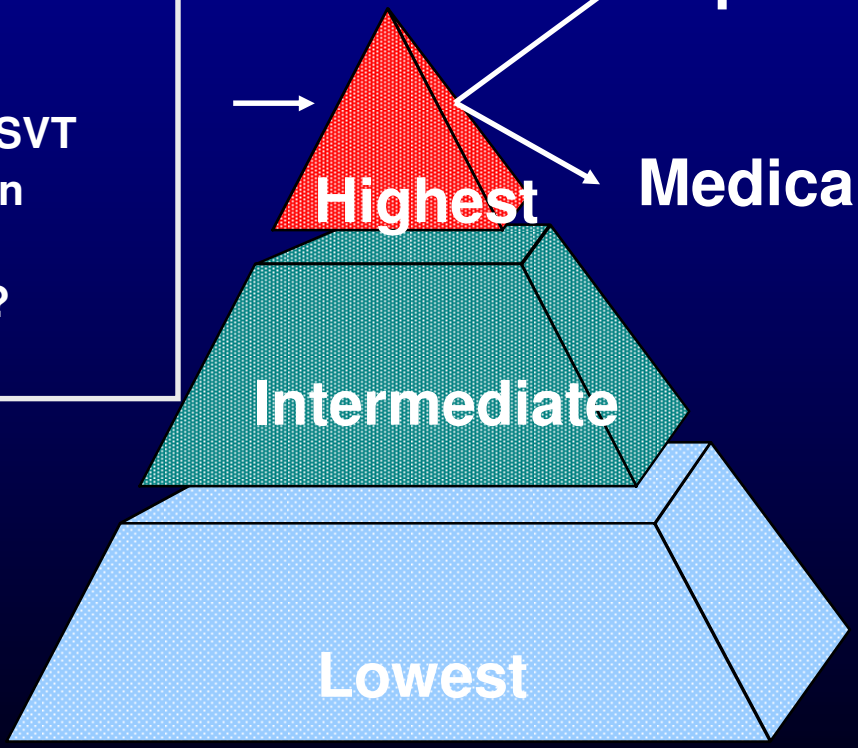
- Disorganised cellular architecture
- Abnormal intramural coronary arteries with thickened walls and narrow lumens
- Replacement fibrosis adjacent adjacent to intramural vessels



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?

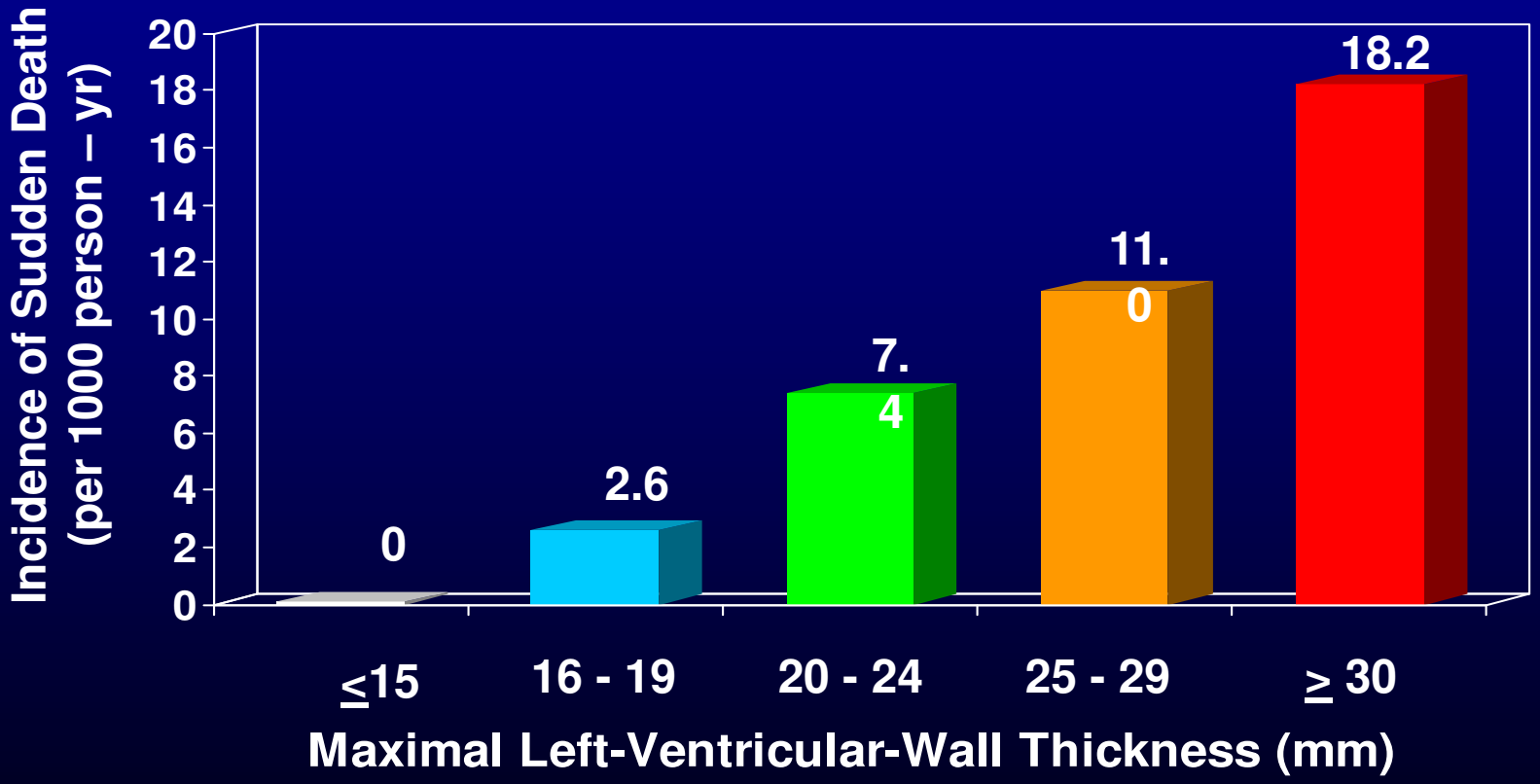


Implantable defibrillator

Medical therapy (?)

Relation of wall thickness to sudden death

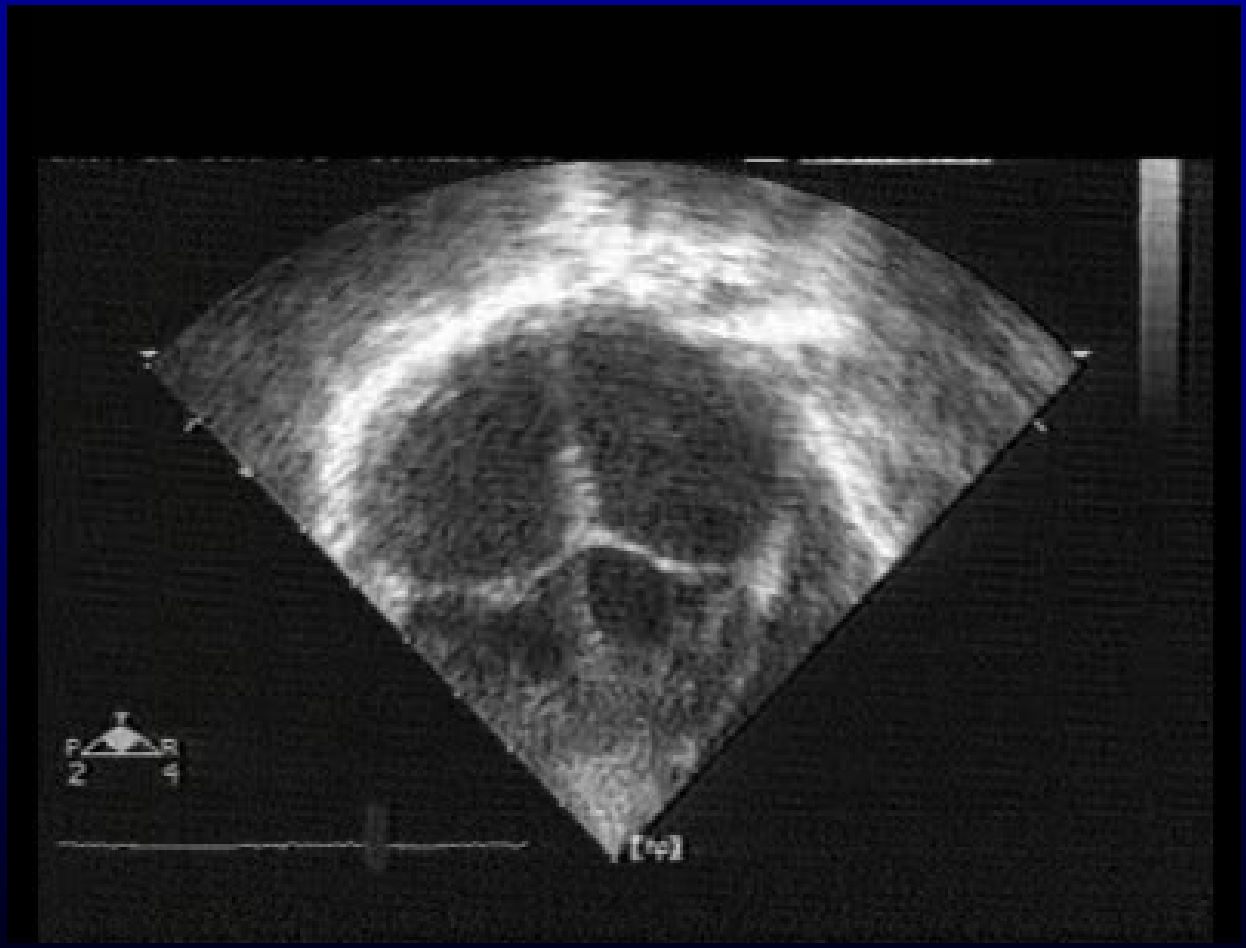
Spirito P et al, NEJM 2000



Restrictive cardiomyopathy

- Basic defect unknown
- Diastolic dysfunction with normal wall thickness and systolic function
- Primary: endomyocardial fibrosis, Loeffler's, and primary RCM
- Infiltrative: Irradiation, sarcoid, amyloid
- Metabolic: Glyocogen 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
investigations

- 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
medical therapy

- 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

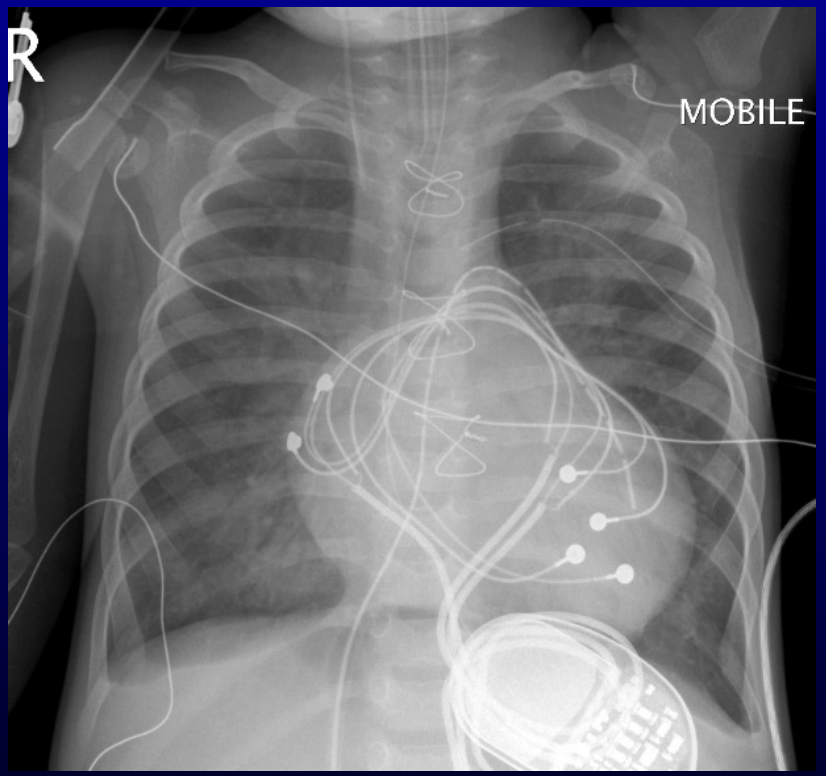
Alternatives to heart transplantation
cardiac resynchronisation

- LBBB with ventricular dyssynchrony 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 dyssynchrony is not necessarily related to electrical dyssynchrony
- 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

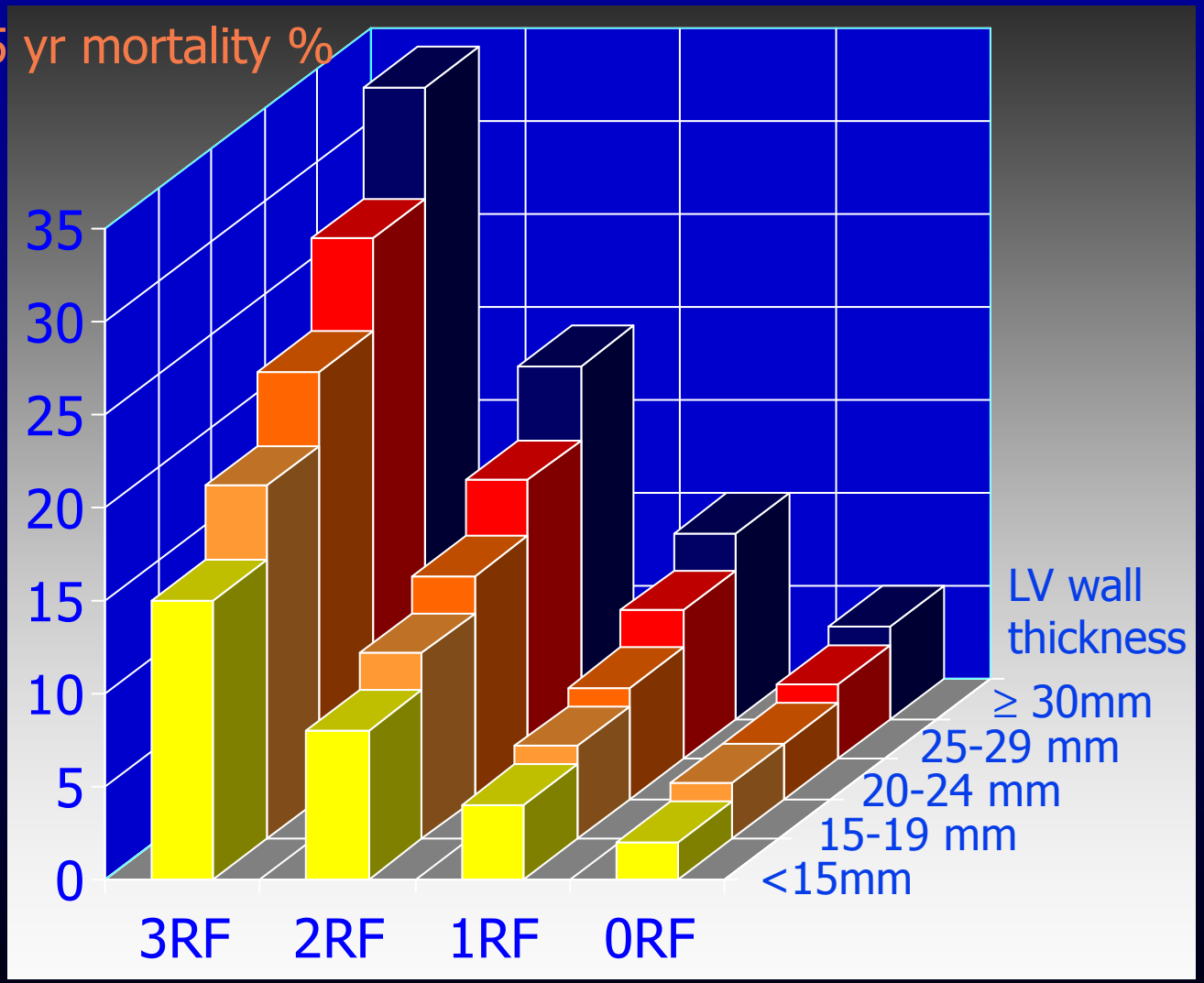
Cardiac resynchronisation

- 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

Perry M Elliott, Juan R Gimeno Blanes, Niall G Mahon, Jan D Poloniecki, William J McKenna Lancet 357 2001



Wall thickness alone is not a god predictor of sudden death

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

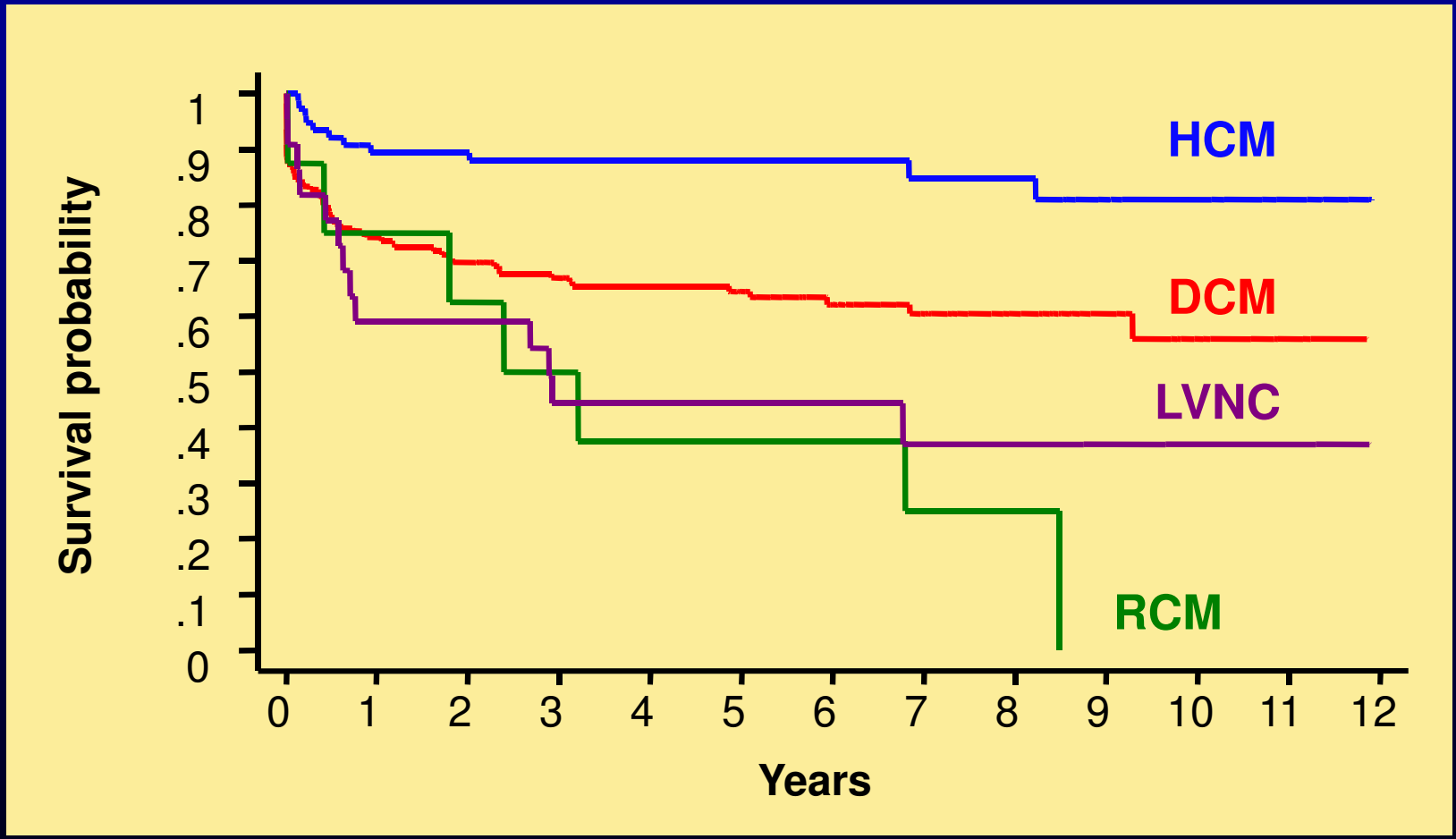
Alternatives to heart transplantation
ICD therapy

- 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

Paediatric 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



Paediatric cardiac transplantation contraindications

- Active neoplasm
- Inadequate pulmonary arteries
- Degenerative CNS, neuromuscular or metabolic disease
- Severe elevation of pulmonary vascular resistance without acute reactivity

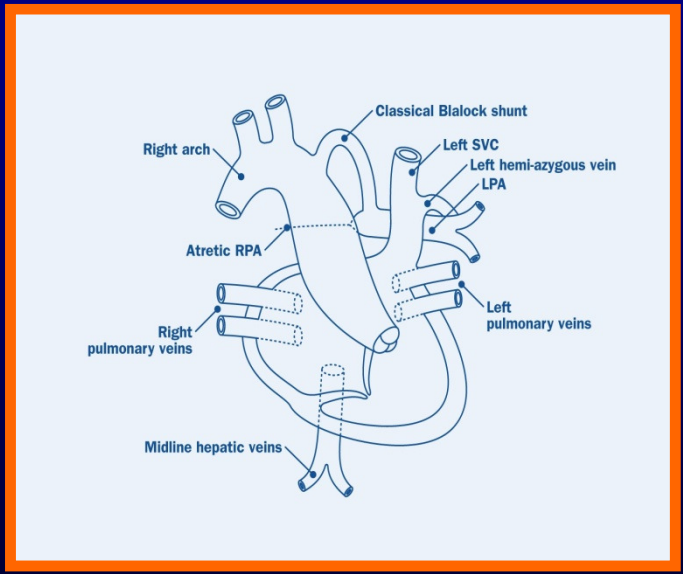
Recipient assessment

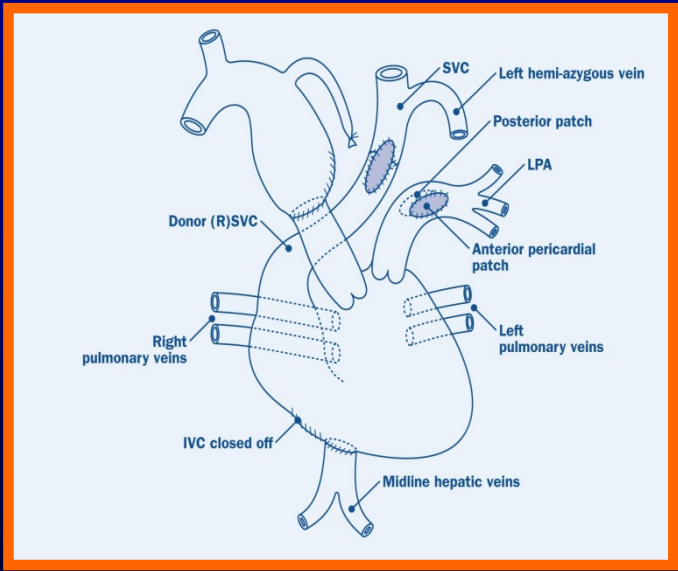
- Try and make a firm diagnosis: genotyping, mitochondrial work-up and storage of DNA
- Quantify ventricular function and PVRI
- Consider any other available therapies
- Assess arrhythmic potential
- Neuro-psychometric assessment
- Let family meet team members (surgeons, ICU physician, transplant coordinator, 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

Venous and arterial reconstruction at time of transplant

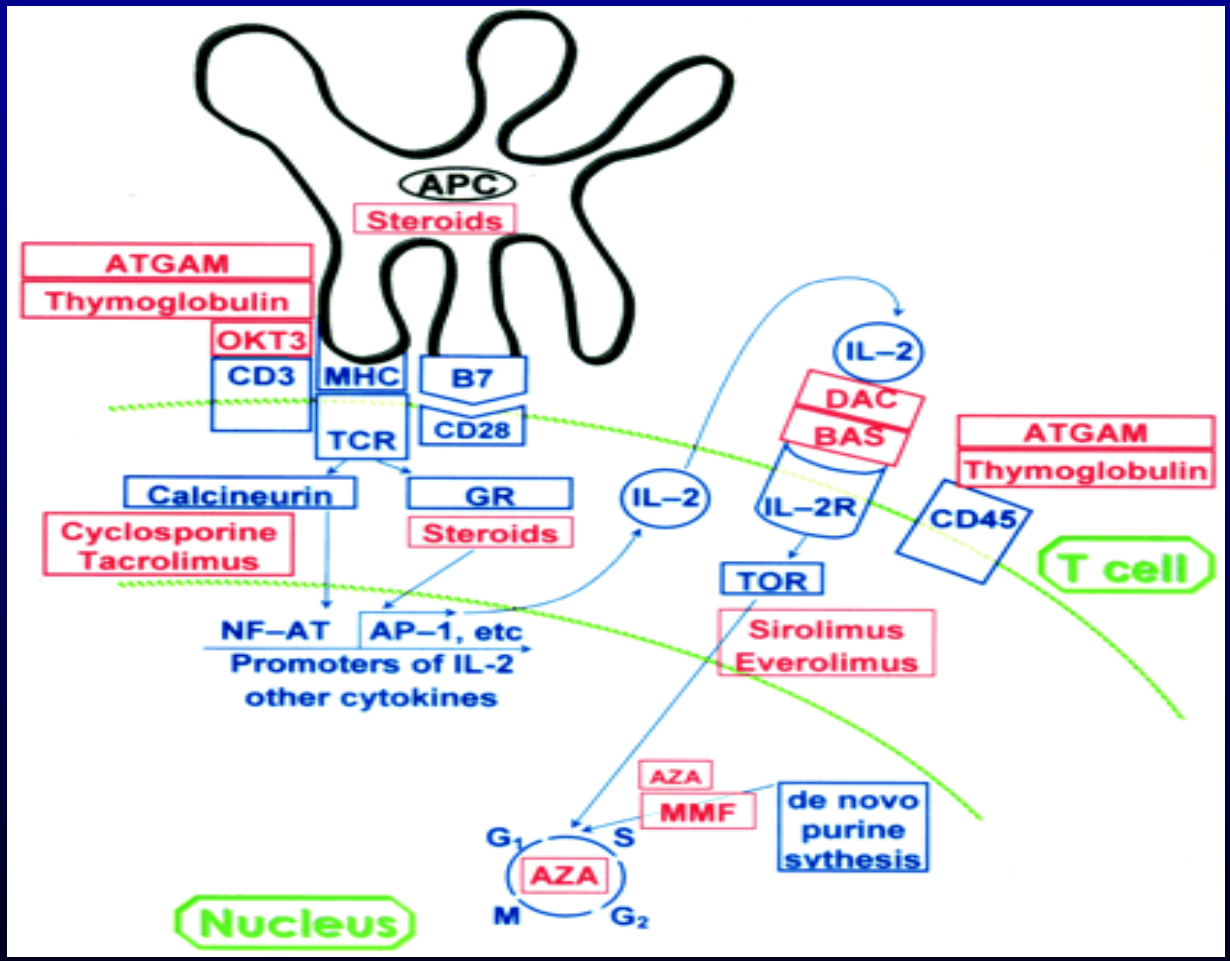




Donor assessment

- 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

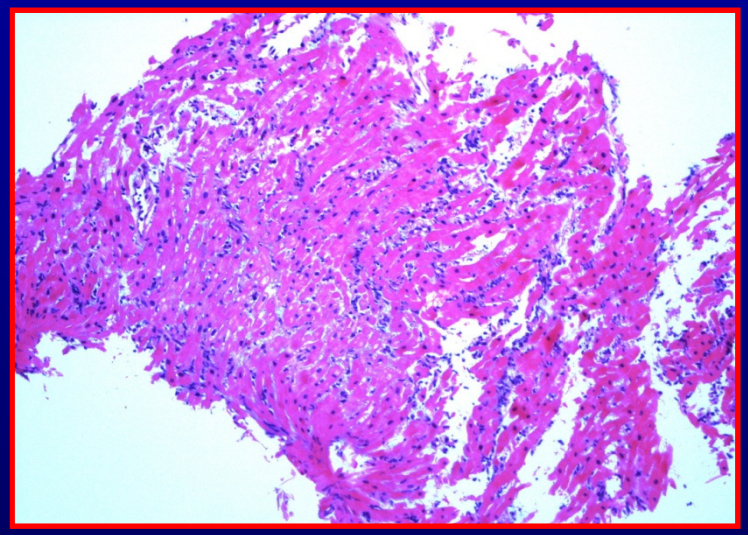
Occurs in 40-70% of patients

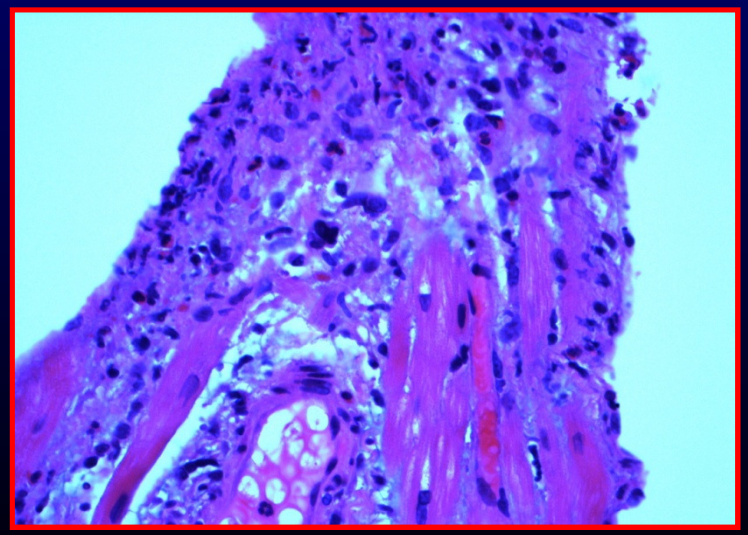
T cell mediated and most common within the first 3-6 months

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

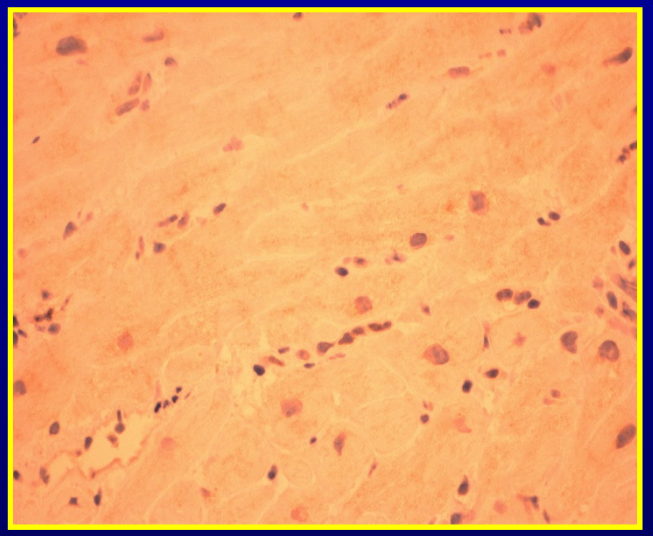
Due to alloantibodies against HLA or endothelial antigens

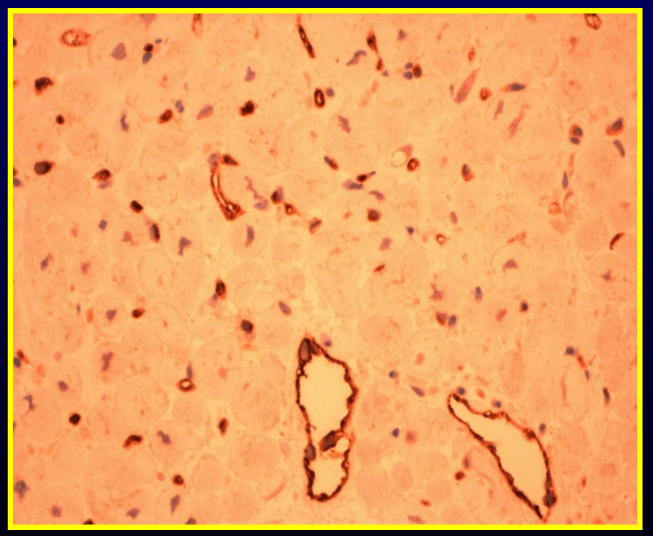
More common if high PRA levels or positive cross-match

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

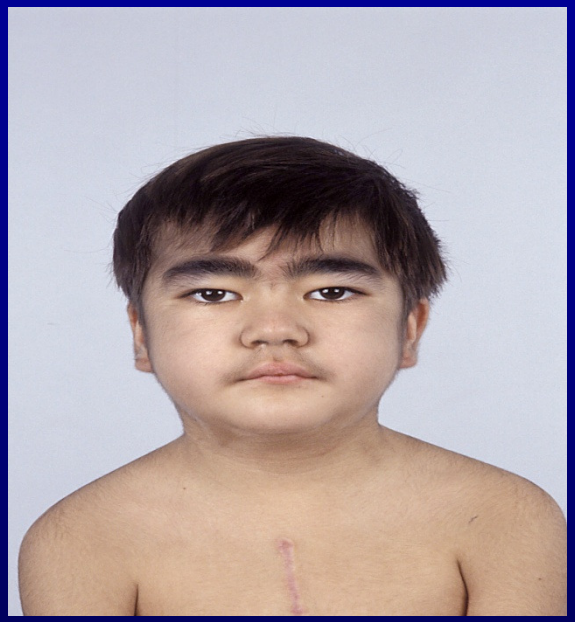
Major cause of late mortality after transplantation

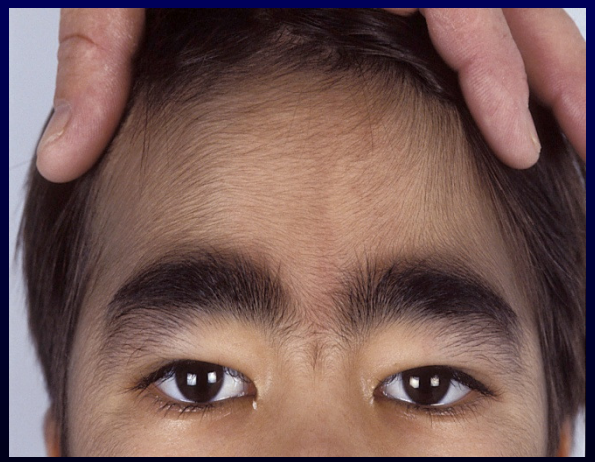
Therapy involves prevention (risk factors) and coronary intervention (if focal) and re-transplantation

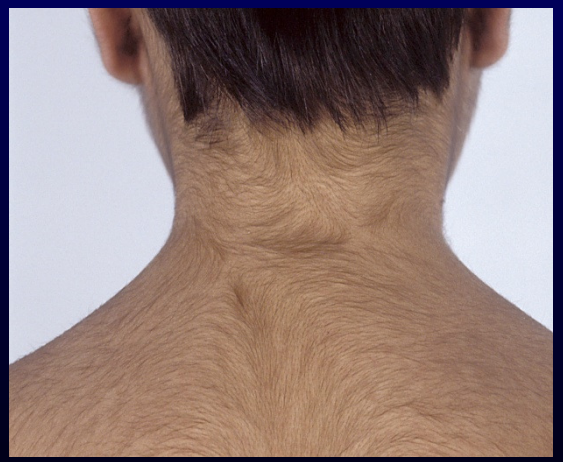
Immunosuppressive therapies
Cyclosporine

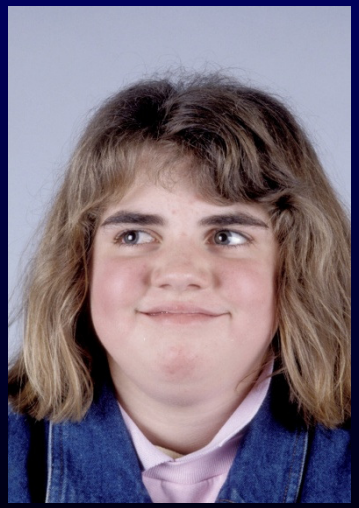
- CSA enters T cells via diffusion and binds to immunophilin
- The complex binds to calcineurin and inhibits transcription of IL-2 and other cytokines
- The introduction of CSA in 1982 increased 3-year survival from 40% to 70%
- Long list of adverse effects includes nephrotoxicity, hypertension, hyperlipidaemia,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

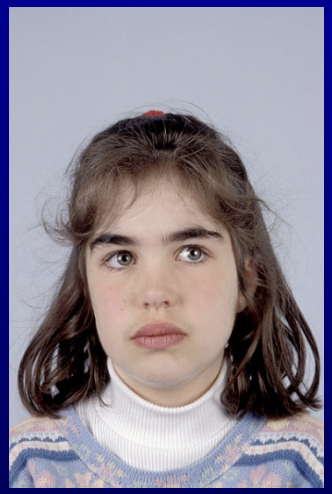
Cyclosporin induced hirsutism

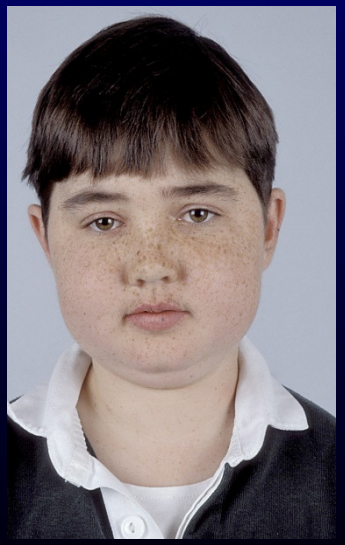




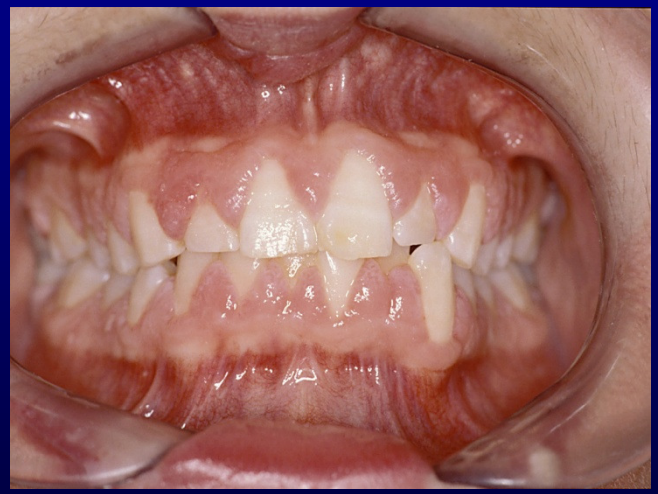


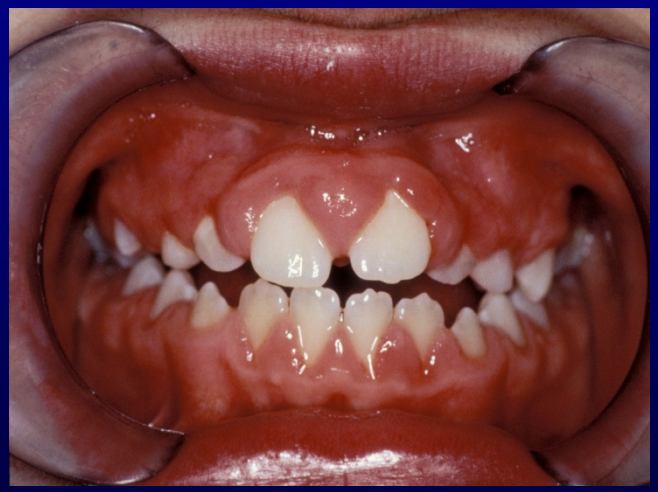






Cyclosporine induced gingival overgrowth





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)

Immunosuppressive therapies
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 lymphovctes
- 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

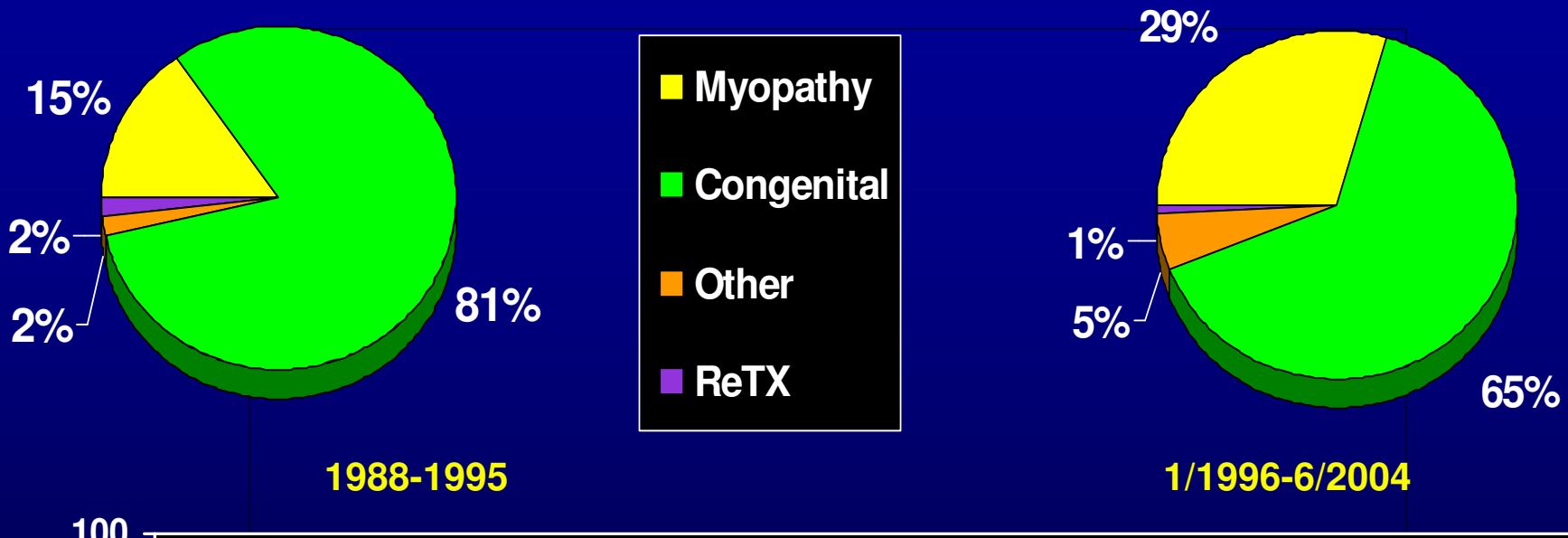
Endomyocardial biopsy

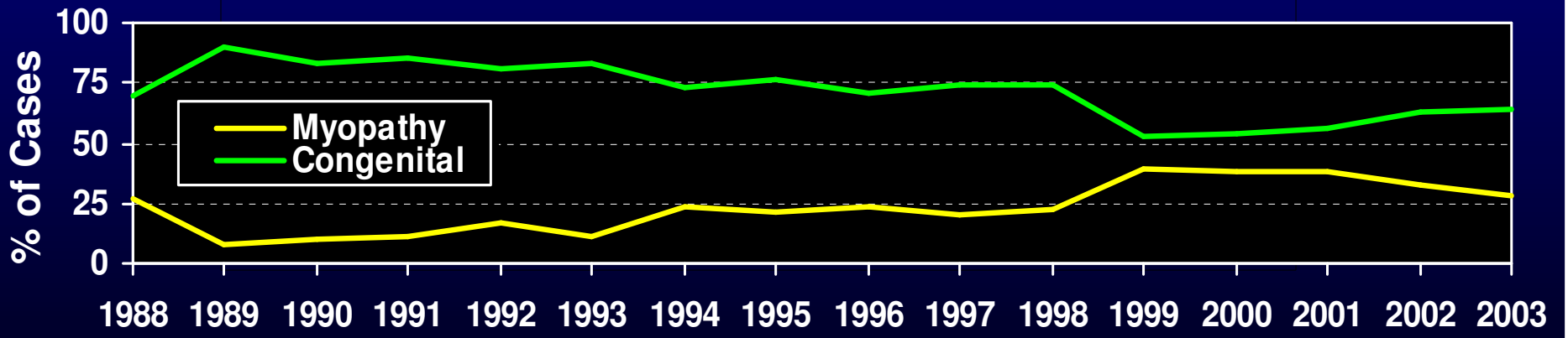
- Conventional echo parameters are insensitive markers for the presence of mild-moderate cellular rejection
- Biopsies are not a gold standard - they are subject to differences in observer interpretation and there may be little to see in someone with rapidly progressive rejection
- Biopsies are of low 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)

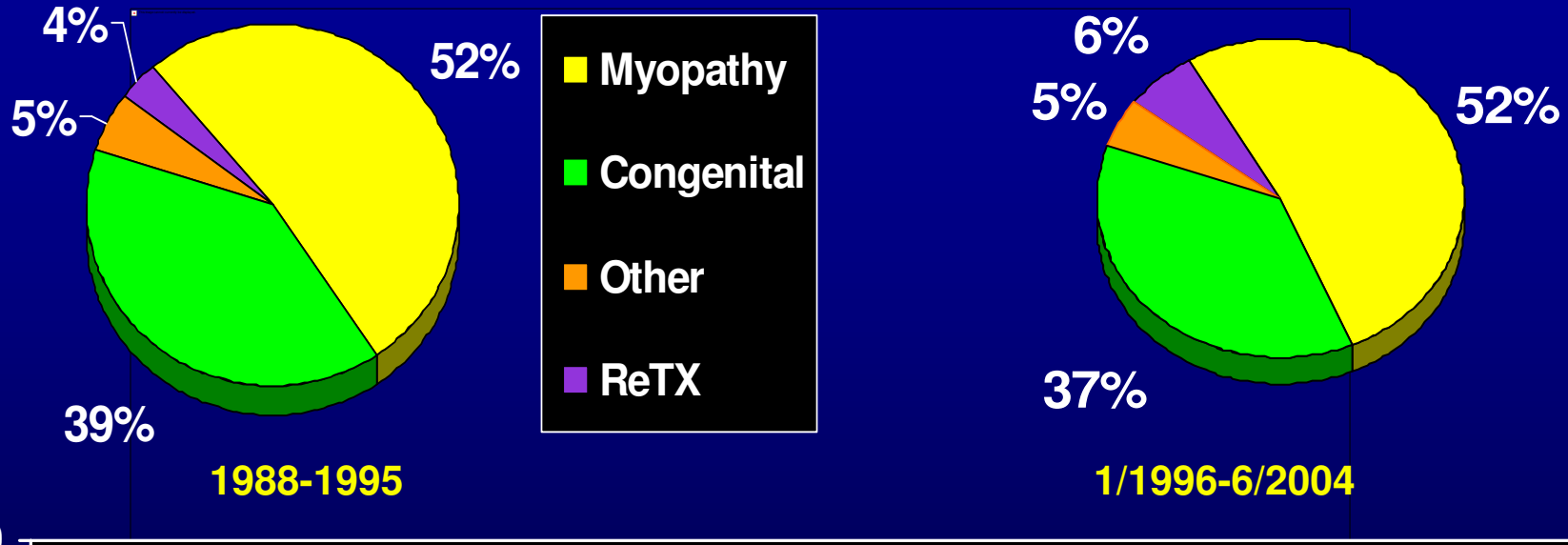


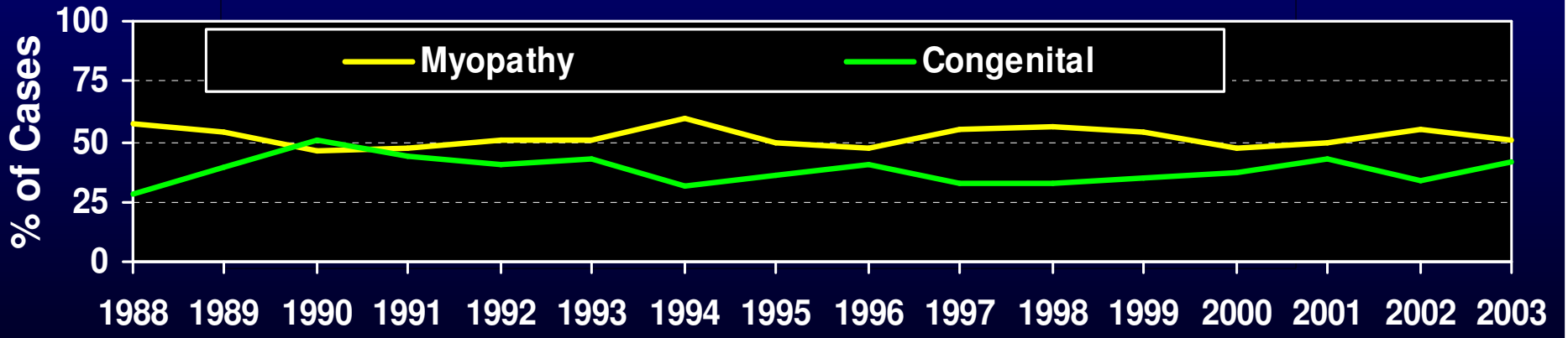


2005

J Heart Lung Transplant 2005;24: 945-982

DIAGNOSIS IN PEDIATRIC HEART TRANSPLANT RECIPIENTS (Age: 1-10 Years)

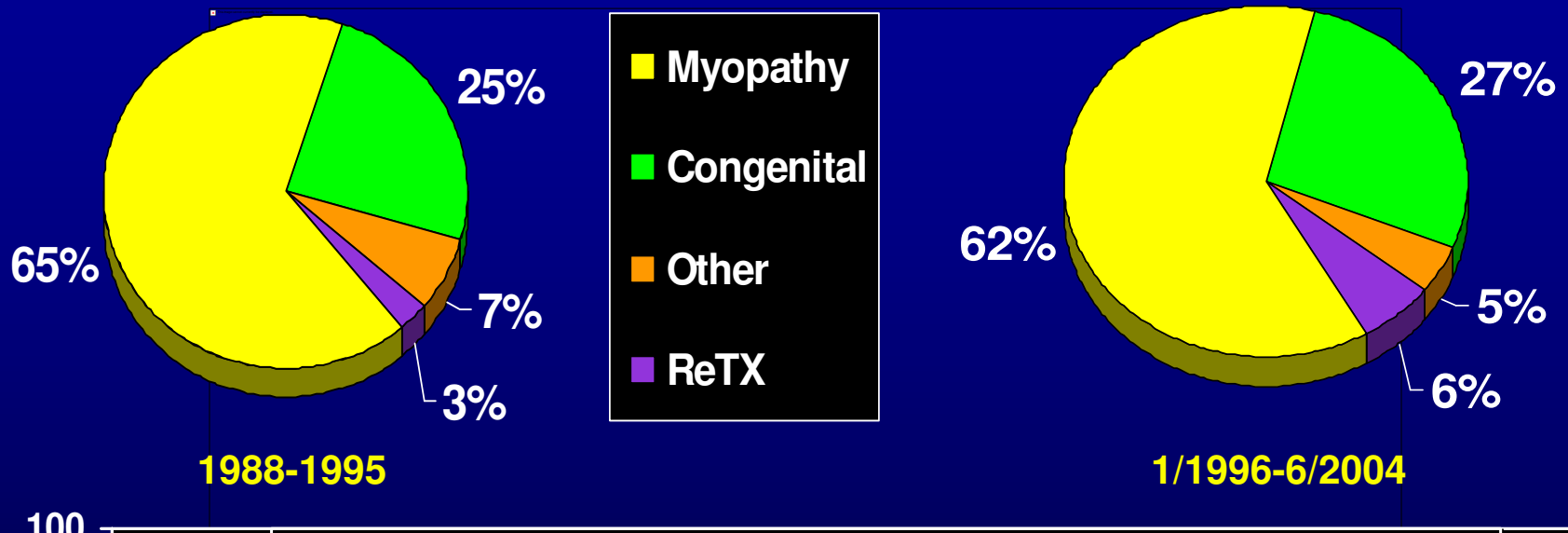


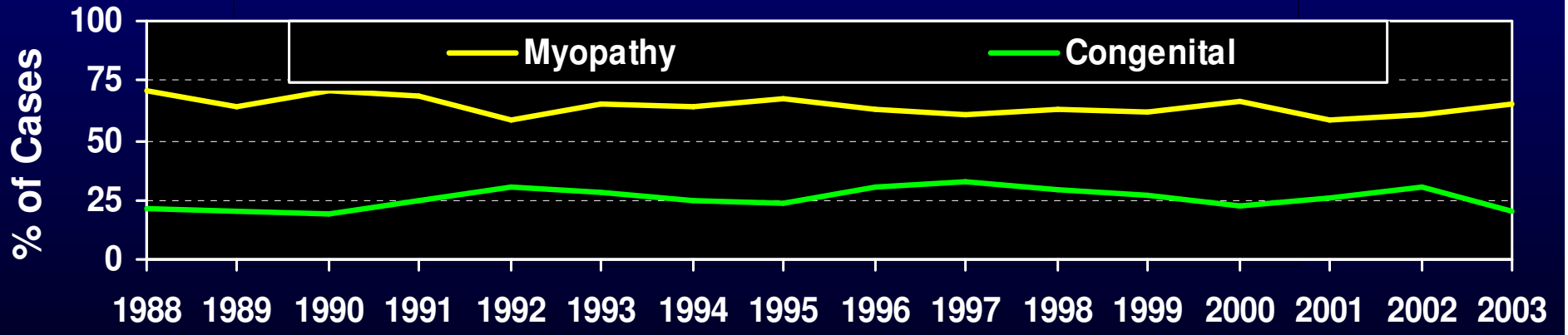


2005

J Heart Lung Transplant 2005;24: 945-982

DIAGNOSIS IN PEDIATRIC HEART TRANSPLANT RECIPIENTS (Age: 11-17 Years)





2005

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PEDIATRIC HEART TRANSPLANTS (1/1995-6/2003)

Risk Factors For 1 Year Mortality

VARIABLE	*N*	*Relative Risk*	*P-value*	*95% Confidence Interval*
Congenital diagnosis, on ECMO	69	4.16	<0.0001	2.66 -6.51
Congenital diagnosis, no ECMO	974	2.19	<0.0001	1.74 -2.77
ECMO, diagnosis other than congenital	68	1.9	0.0211	1.10 -3.28
Year of Transplant: 1995 vs. 1998	362	1.9	0.001	1.30 -2.77
Hospitalized (including ICU)	2132	1.55	0.0007	1.20 -2.00
On ventilator	448	1.35	0.0239	1.04 -1.76
Female recipient	1300	1.22	0.0409	1.01 -1.48
Donor age		Cont. variable		

N=3,014

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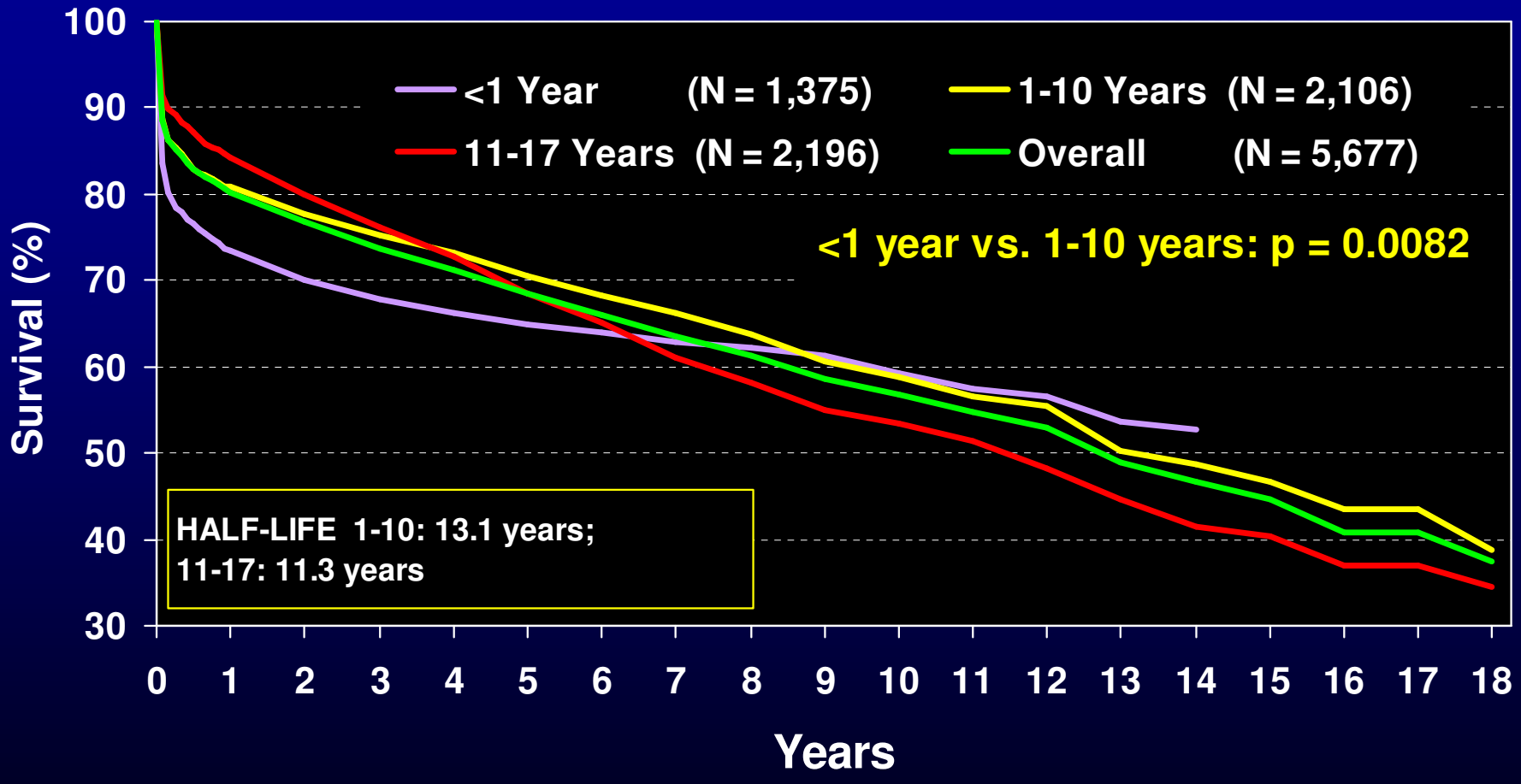
PEDIATRIC HEART TRANSPLANTATION

Kaplan-Meier Survival (1/1982-6/2003)



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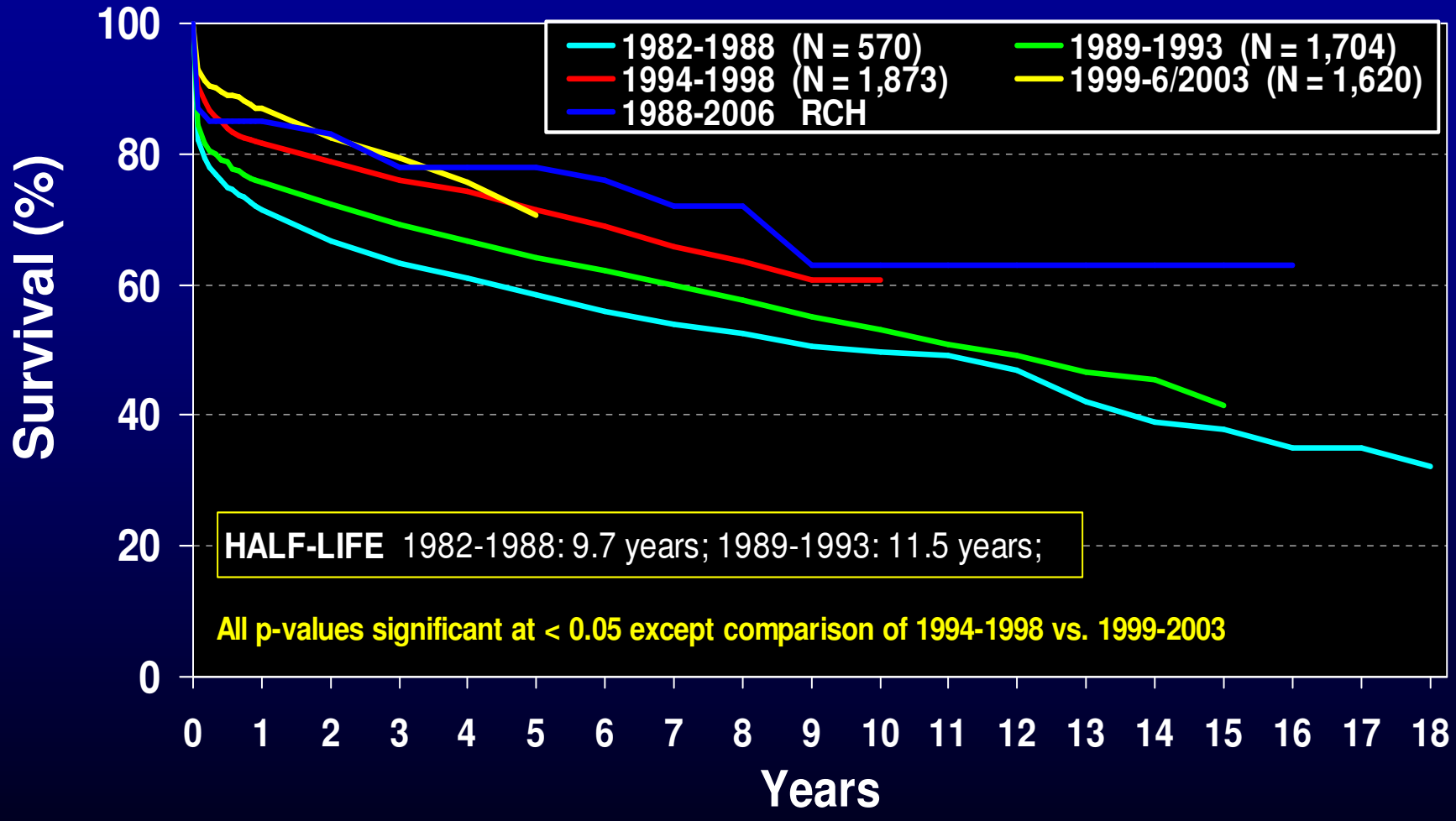
PEDIATRIC HEART TRANSPLANTATION

Kaplan-Meier Survival by Era (1/1982-6/2003)



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PEDIATRIC HEART TRANSPLANT RECIPIENTS:
Cause of Death (Deaths: January 1992 - June 2004)

CAUSE OF DEATH	0-30 Days (N = 335)	31 Days - 1 Year (N = 281)	>5 Years (N = 252)
CORONARY ARTERY VASCULOPATHY	3 (0.9%)	26 (9.3%)	72 (28.6%)
ACUTE REJECTION	27 (8.1%)	76 (27.0%)	32 (12.7%)
LYMPHOMA		6 (2.1%)	21 (8.3%)
INFECTION, NON-CMV	47 (14.0%)	46 (16.4%)	16 (6.3%)
PRIMARY FAILURE	58 (17.3%)	11 (3.9%)	12 (4.8%)
GRAFT FAILURE	79 (23.6%)	31 (11.0%)	49 (19.4%)
TECHNICAL	21 (6.3%)	2 (0.7%)	1 (0.4%)
OTHER	15 (4.5%)	16 (5.7%)	24 (9.5%)
MULTIPLE ORGAN FAILURE	36 (10.7%)	29 (10.3%)	6 (2.4%)
RENAL FAILURE	1 (0.3%)	4 (1.4%)	
PULMONARY	24 (7.2%)	16 (5.7%)	7 (2.8%)
CEREBROVASCULAR	23 (6.9%)	7 (2.5%)	3 (1.2%)

2005

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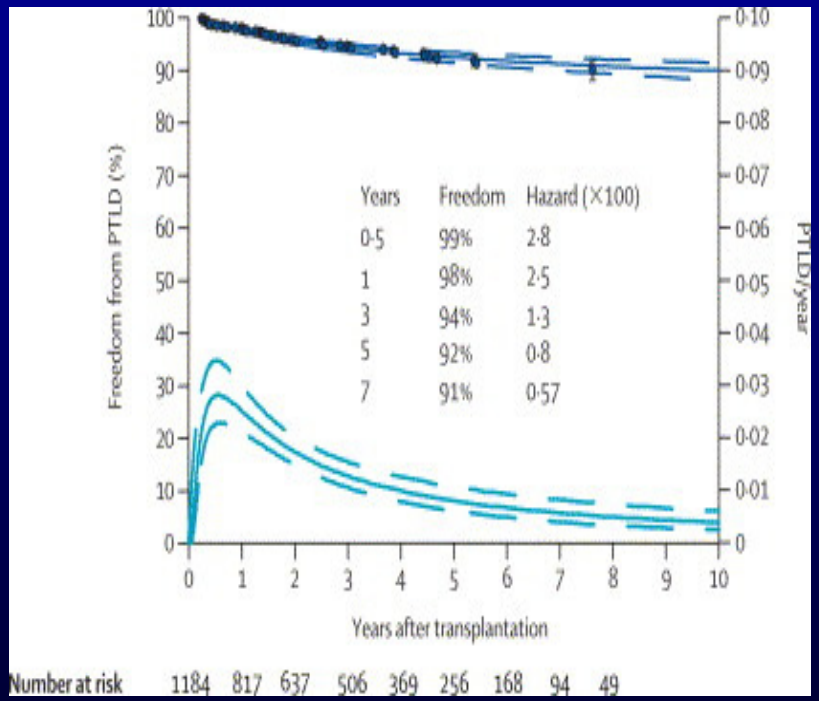
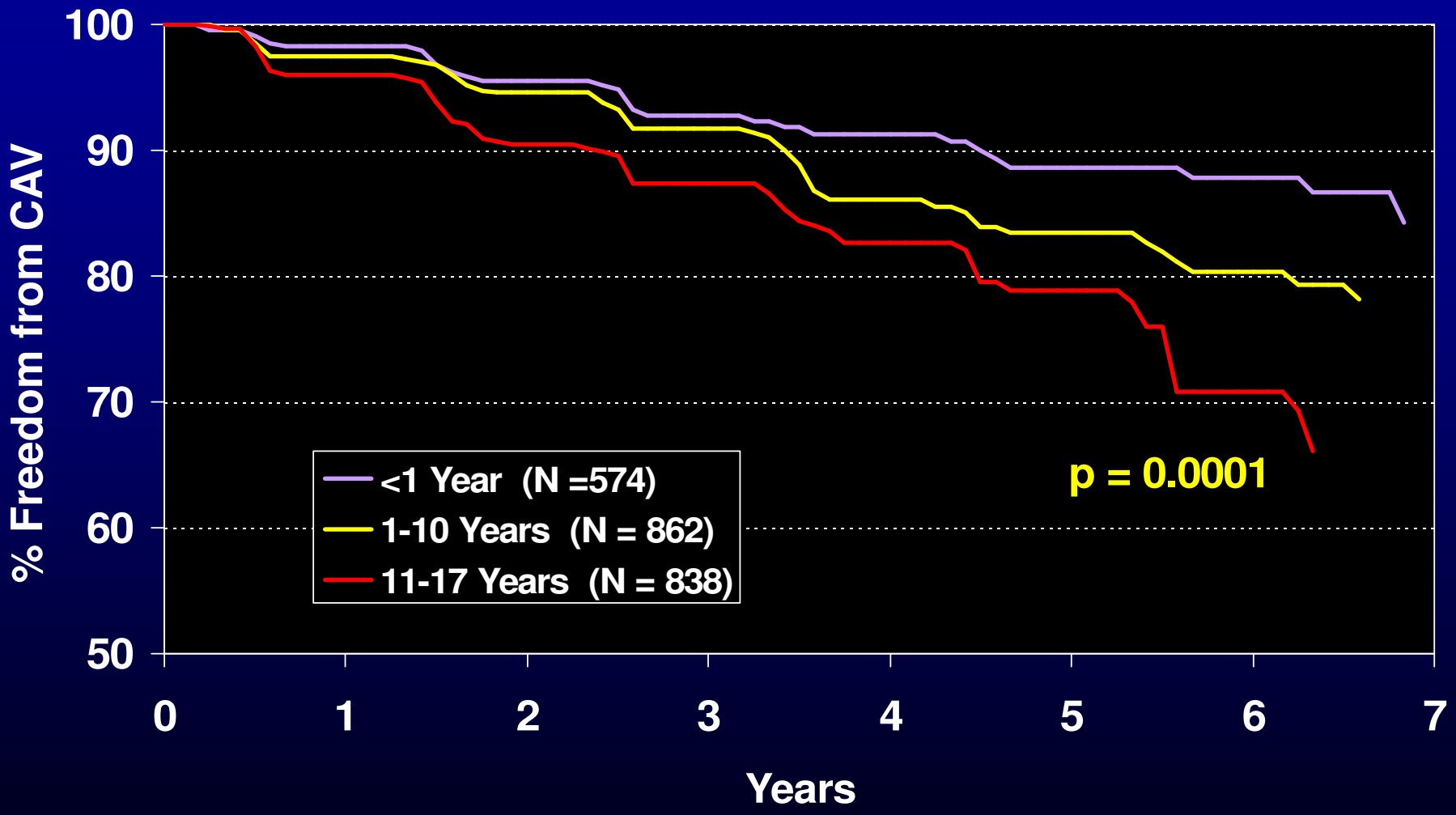
Lymphoproliferative disease

- 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



FREEDOM FROM CORONARY ARTERY VASCULOPATHY

April 1994 - June 2004; Stratified by Age Group



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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