

Congenital atrioventricular block in structurally normal heart.

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Introduction

CAVB



Complex CHD

- Heterotaxia
- Corrected TGA

...

Normal heart (~80%)

- Autoimmune mediated (~85%)
- Myocarditis
- Myocardial tumor
- Genetic abnormalities
 - LQTS
 - Kearn-Sayre syndrome

CAVB: Congenital atrioventricular block

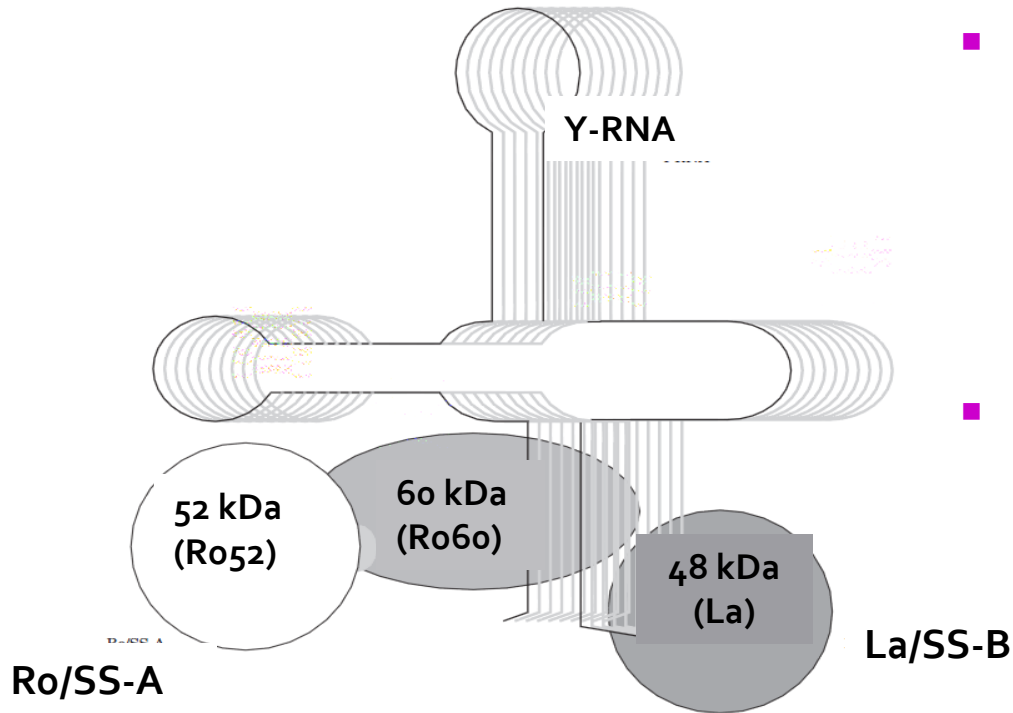
Introduction

- CAVB is a rare, potentially lethal disease
- Estimated incidence: 1 / 15,000 ~ 25,000 live births
- Recent ↑ incidence :1 /25,000 to 1/11,000
 - enhanced neonatal care
 - better diagnostic methods
 - more antenatal diagnosis
 - ↑ No of mothers with connective tissue disease
- Diagnosis can be made *in utero*
 - As early as 16 ~ 28 week of gestation age

Etiology

- Transplacental passage of
 - Maternal anti-SS-A/Ro , anti-SSB/La ribonucleoprotein Ab
- Damage to fetal myocardium & conduction system cells(Ro Ag)
 - Mother
 - completely asymptomatic in presence of auto Ab
 - collagen vascular disease (eg, SLE, Sjögren syndrome etc)
- Unclear
 - **What triggers** the maternal Ab interaction with the fetal Ro in a small percentage of Ab exposed babies
 - Why this affects in **particular the mid-gestational** fetus

Ro/SS-A and La/SS-B antigens in a small cytoplasmic RNP particle.



Critical role

- prevention of autoimmunity
- Involve in cell survival

■ Ro60 protein

- quality control of the intracellular metabolism of newly synthesized mRNA to prevent release of misfolded 5sRNAs

■ Ro52 protein

- regulation of cell Growth,
- apoptosis , down regulates pro-inflammatory cytokine production

■ La/SS-B protein

RNP= ribonucleoprotein

Circulation. 1996;93:1424-1438.)

Frequency of antibodies in various autoimmune diseases

Author		SLE (%)	CHB (%)	RA (%)	SS (%)	MCTD (%)	PSS (%)
Smeenk	anti-Ro/SS-A	40		5	70	50	30
	anti-La/SS-B	15		1	60	0	5
Mierau	anti-Ro/SS-A	24–60	95–100	15	70–100		
	anti-La/SS-B	9~35	75	5	40~94		
Tsay	anti-Ro/SS-A	30			74		
	anti-La/SS-B	41			65		
Wang	anti-Ro/SS-A	36					
	anti-La/SS-B	8					
Taylor	anti-Ro/SS-A		97				
	anti-La/SS-B		82.5				
Scott	anti-Ro/SS-A	50	100		70	50	
	anti-La/SS-B	15	100		40~50		
Buyon	anti-Ro/SS-A		100				
	anti-La/SS-B		90				
Julkunen	anti-Ro/SS-A		90				
	anti-La/SS-B		42				

SLE=systemic lupus erythematosus; CHB=congenital heart block; RA=rheumatoid arthritis; SS=Sjögren's syndrome; MCTD=mixed connective tissue disease; PSS=progressive systemic sclerosis.

Histologic Findings

- Myocardial biopsy: not routinely performed
 - various stages of fibrosis of the AV conduction area
 - (depending on the timing of the specimen)
 - Immune deposition
 - Frequent
- The mechanism of cell death and fibrosis : unclear.
- Hypotheses :
 - alloimmune-mediated inflammatory responses
 - immune-triggered apoptosis.

A proposed pathologic cascade leading from inflammation to fibrosis

Initiating event

Necessary factors

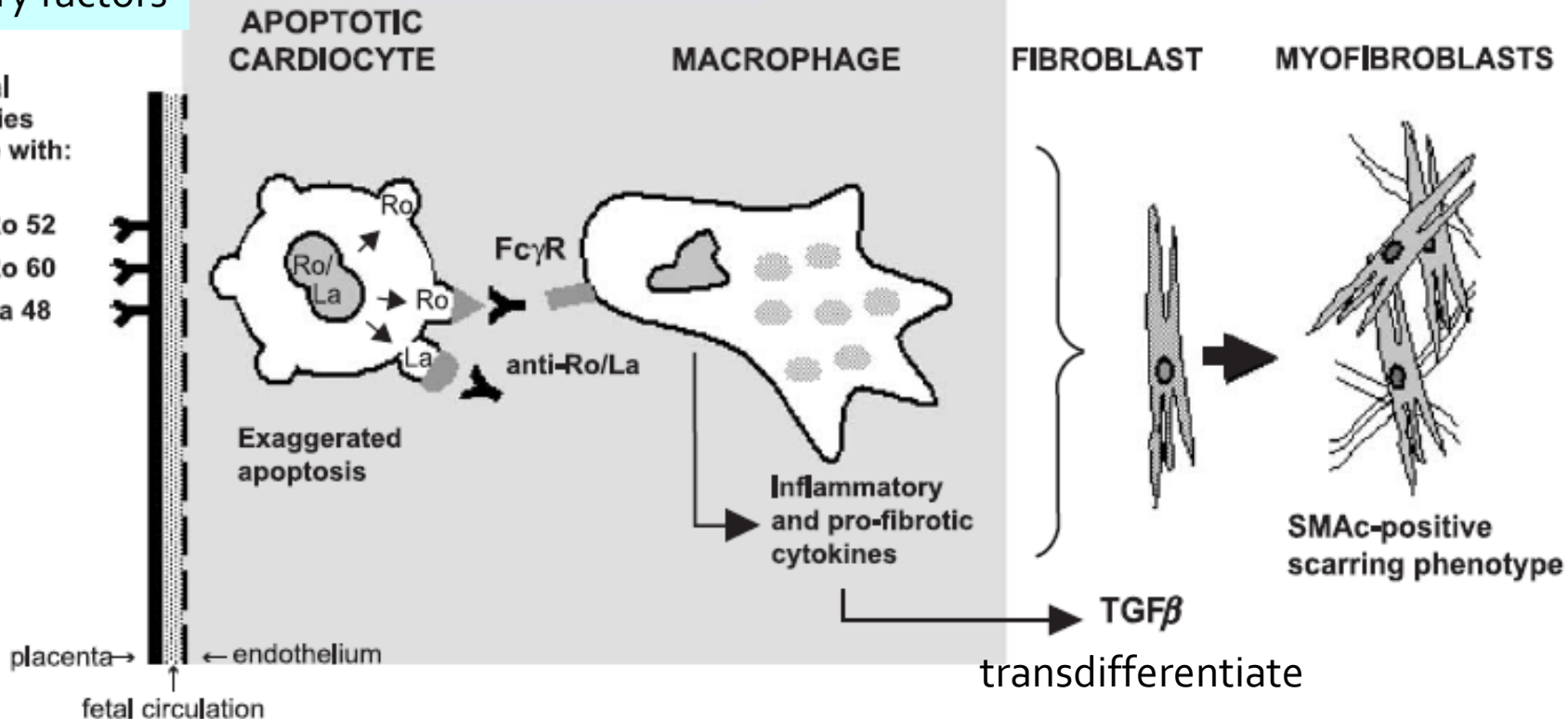
Cellular response
Of Target Tissue

Candidate Fetal Factors

Final sequence
Leading to fibrosis

Maternal antibodies reactive with:

Ro 52
Ro 60
La 48



Cardiac damage

Inflammation, fibrotic scarring, calcification in the conducting system

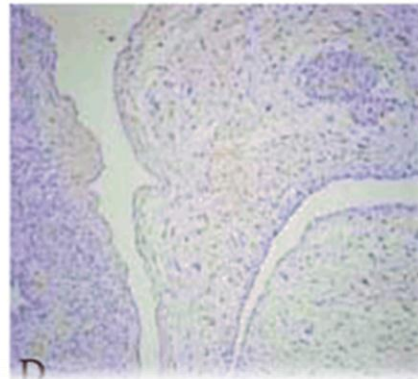
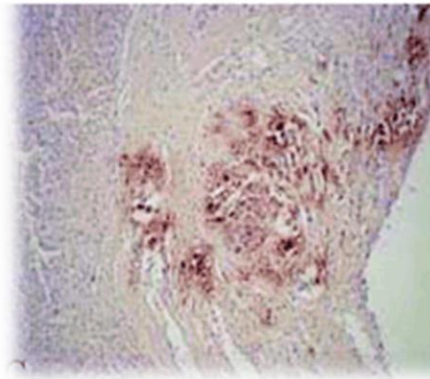
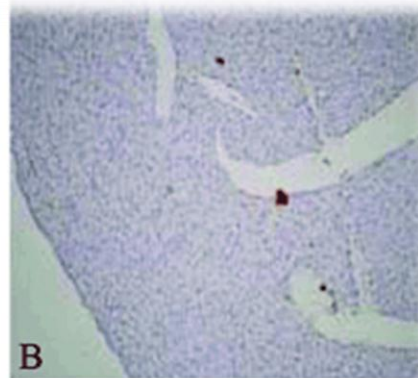
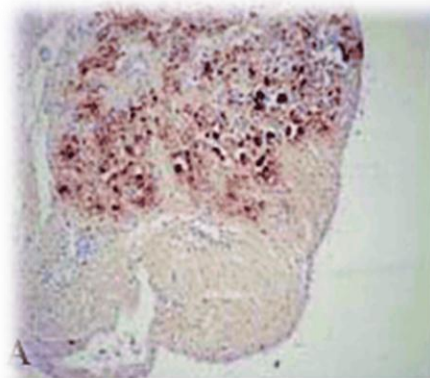
👉 **Heart block** and/or **endocardial fibroelastosis**

TNF- α mRNA expression in conduction tissue of fetus with CAVB and control.

20-wk fetus with CAVB

23-wk fetus with control

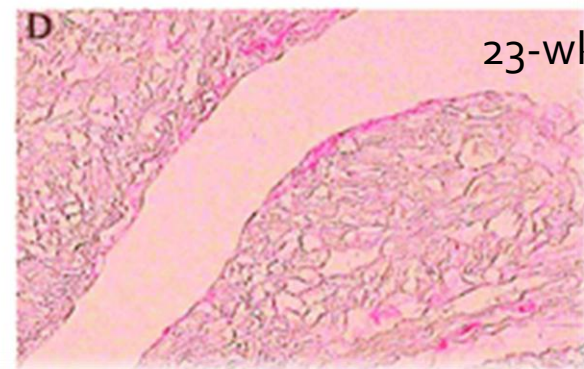
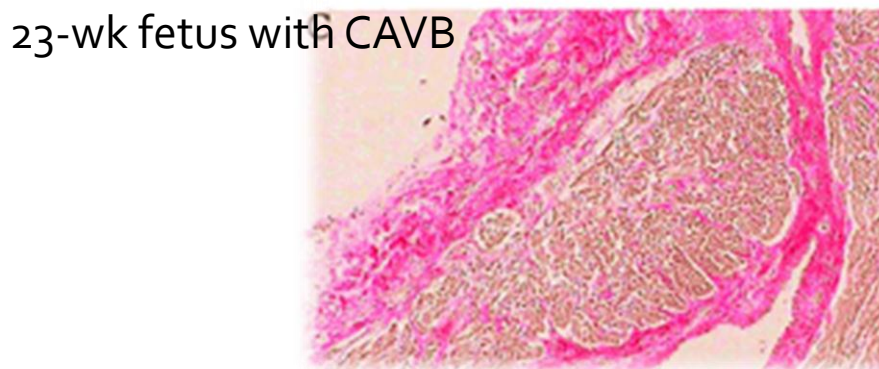
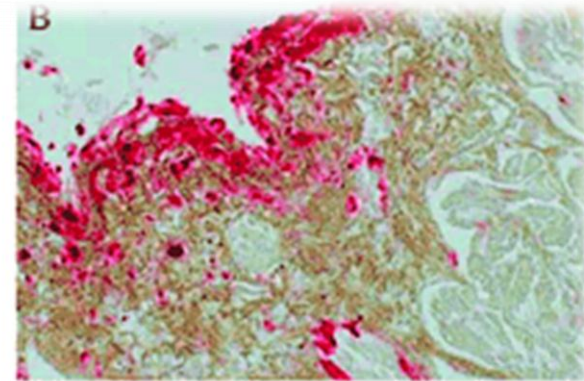
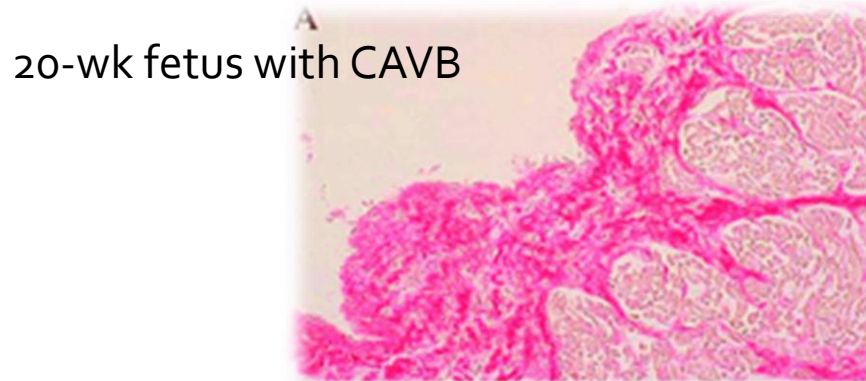
demonstrated localized to a region near the AV groove at a site enriched in mononuclear cells



no detectable expression of TNF- α in the control heart

Oligonucleotide in situ hybridization using the sense and antisense TNF- α digoxigenin-labeled probes. mRNA is reported using peroxidase-conjugated anti-digoxigenin.

Histological evidence of increased fibrosis in conduction tissue and colocalization with TGF- and myofibroblasts in CAVB.



- Picrosirius stain was used to identify collagen (red).
- Enhanced fibrosis is detected in the fetuses with CAVB, but not healthy control. *B*,
- A section adjacent to that represented in *A* was double stained with anti-human TGF- (peroxidase) and anti-SMAc (alkaline phosphatase) to demonstrate the proximity of TGF-, myofibroblasts, and fibrosis.

Pathological changes

- Fetal myocarditis, haemorrhage, necrosis, degeneration
- Fibrous replacement of the conducting tissue, myocardium
- Widespread dystrophic calcifications

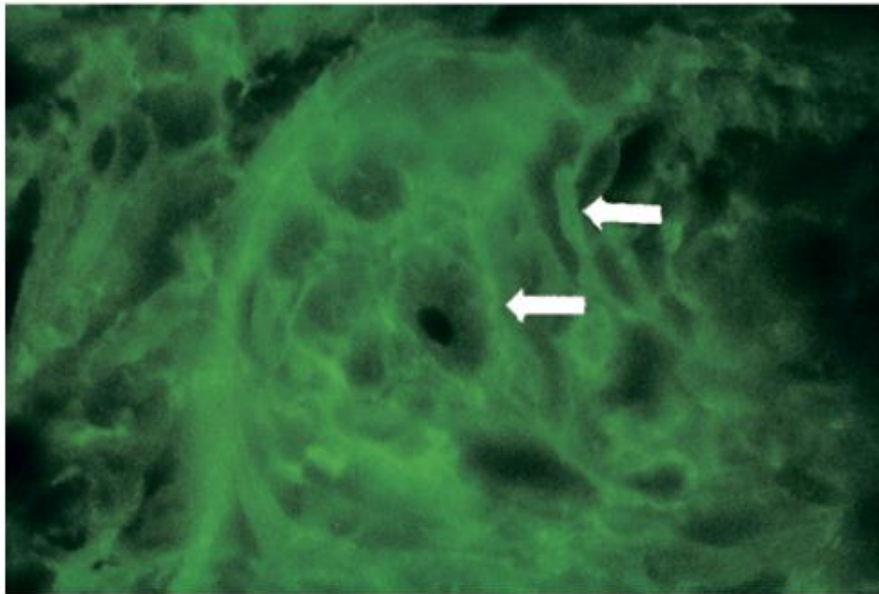
- Caused by failure of the AV conduction system to connect
 - discontinuity btw atrial musculature & AV node or His bundle

- Exaggerated apoptosis and macrophage infiltrates
 - ⇒ progressive scarring.

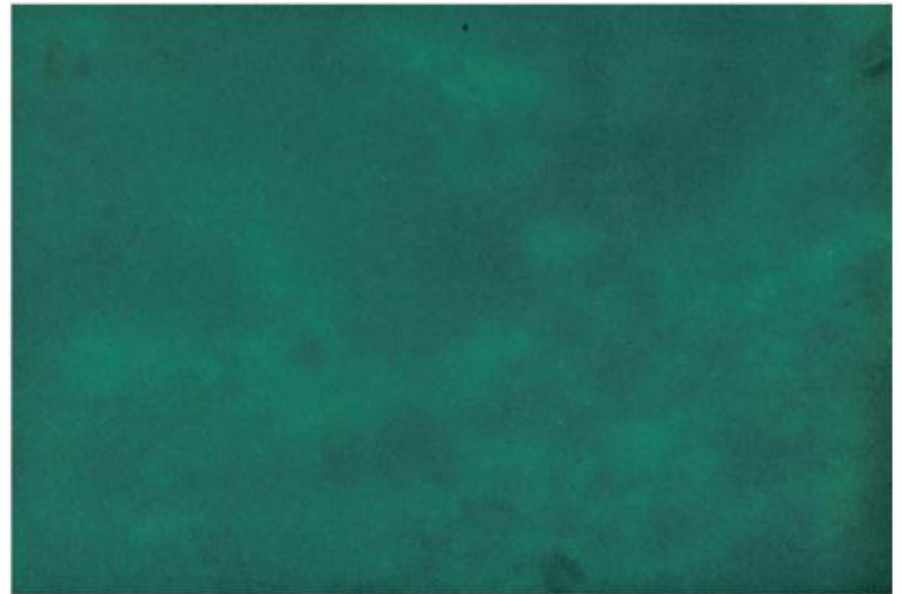
- Mechanisms by which maternal antibodies initiate and finally eventuate the fibrotic transformation are not clear

Antibodies against the human AV node & corresponding negative controls

cAVB

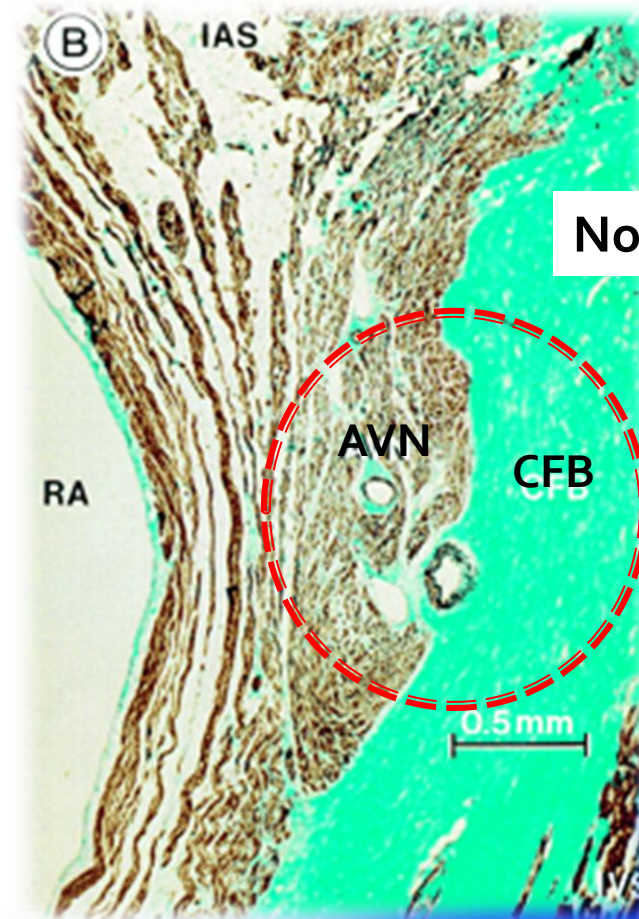
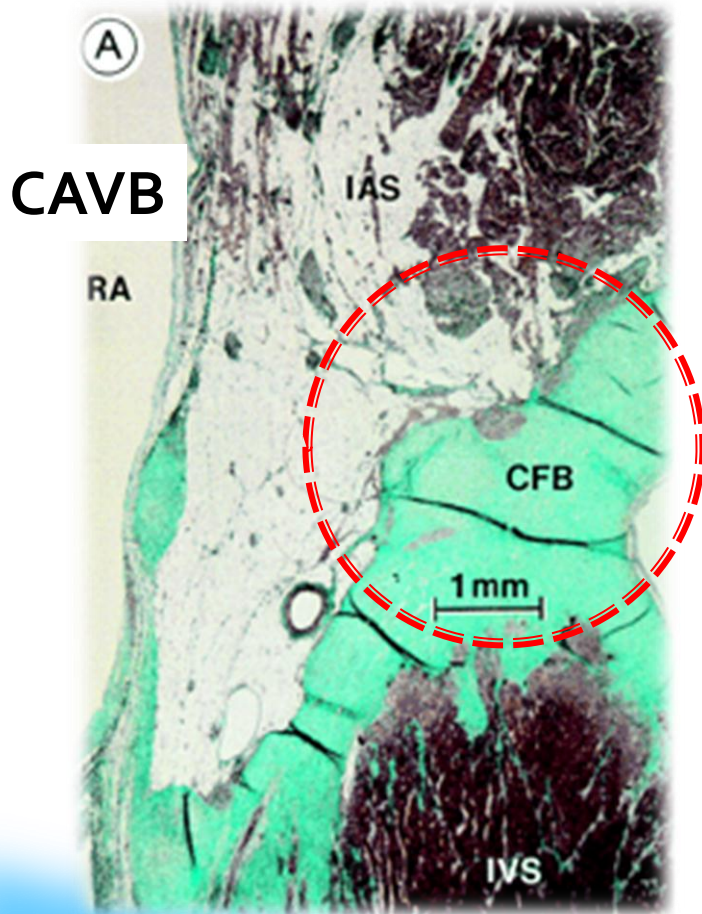


control



- immunofluorescent staining with FITC-labelled monoclonal antihuman mouse Ab; F(ab)₂-IgG fragment staining=white arrowsX800.
- F(ab)₂-IgG fragment staining avoids non-specific IgG-binding

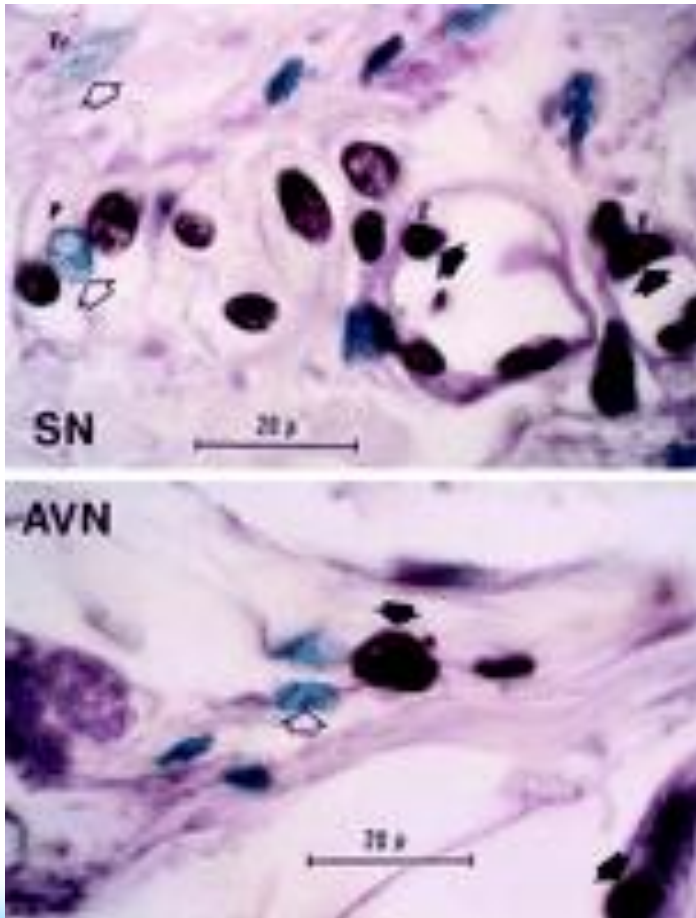
- **A: Absence of the AV node**
- Note the pocket in the central fibrous body in A in which the AV node was most likely located earlier in his life. Also note the normally patent AV node artery in A.



CFB, central fibrous body

Circulation. 1996;93:1424-1438.)

Apoptotic cells from both the sinus node (SN) and AV node (AVN)



Round or ovoid nuclei are typical of P cells normally present in both the sinus node and AV node of human hearts
both apoptotic (black arrows) and nonapoptotic (open arrows) cells are indicated in both the sinus node and AV node.

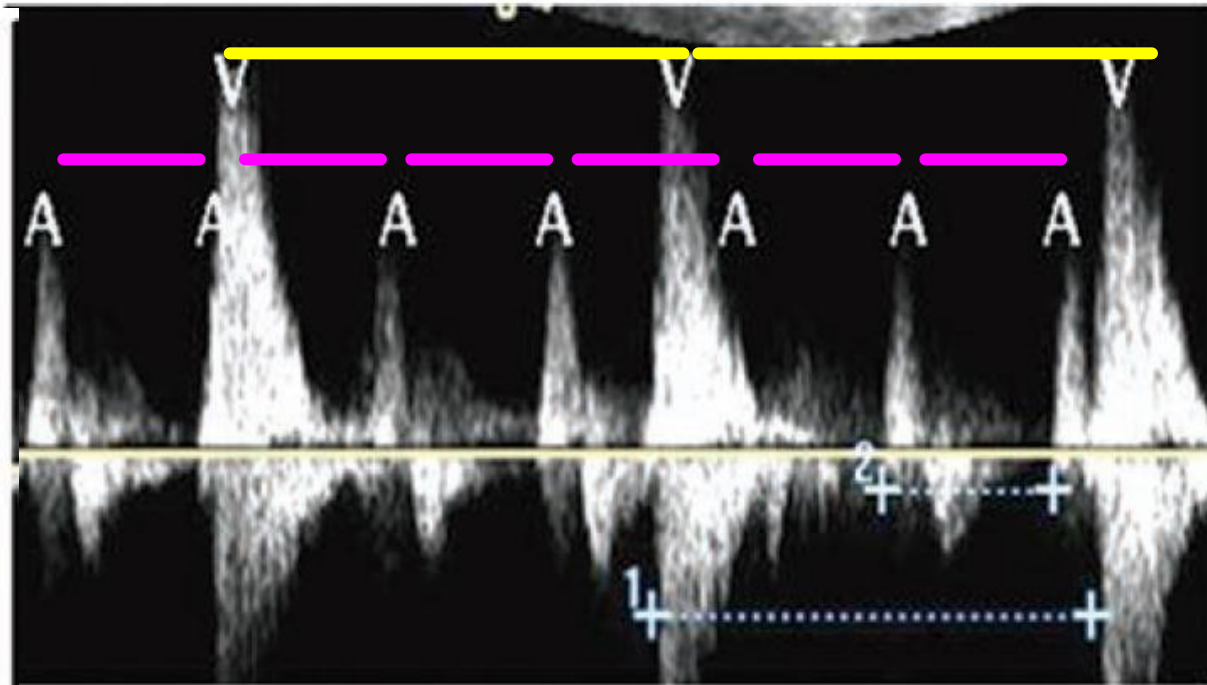
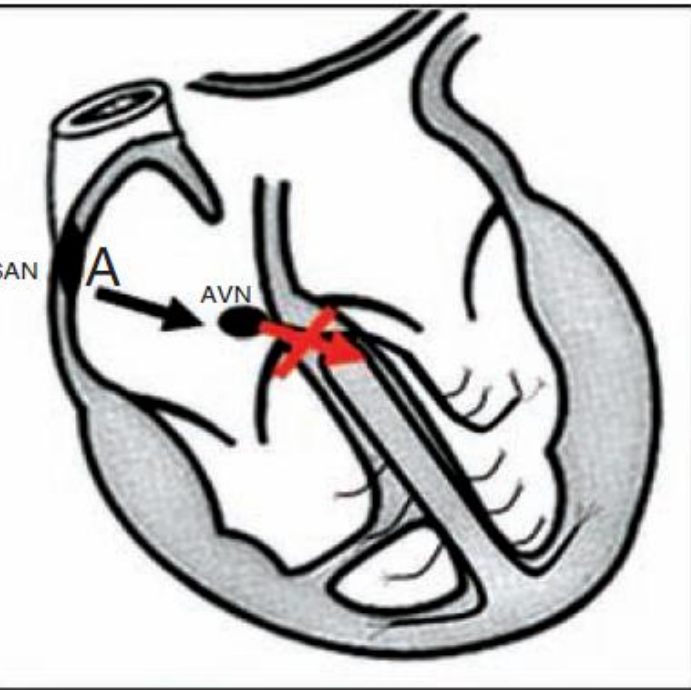
Neonatal Lupus syndrome

- Mothers who have SLE/ Sjögren's synd(SS)/undifferentiated connective tissue disease
- In utero heart block with normal heart
 - > 85 % : maternal autoAb to SSA/Ro or SSB/La Ribonucleoproteins regardless maternal Sx
- **Cardiac injury (CAVB/ myocarditis/endocarditis)**
 - MC IUP 16~ 28 weeks of gestation
 - 3rd-degree heart block : irreversible.
 - substantial mortality rate (20%)
 - morbidity ⇒ need permanent pacing

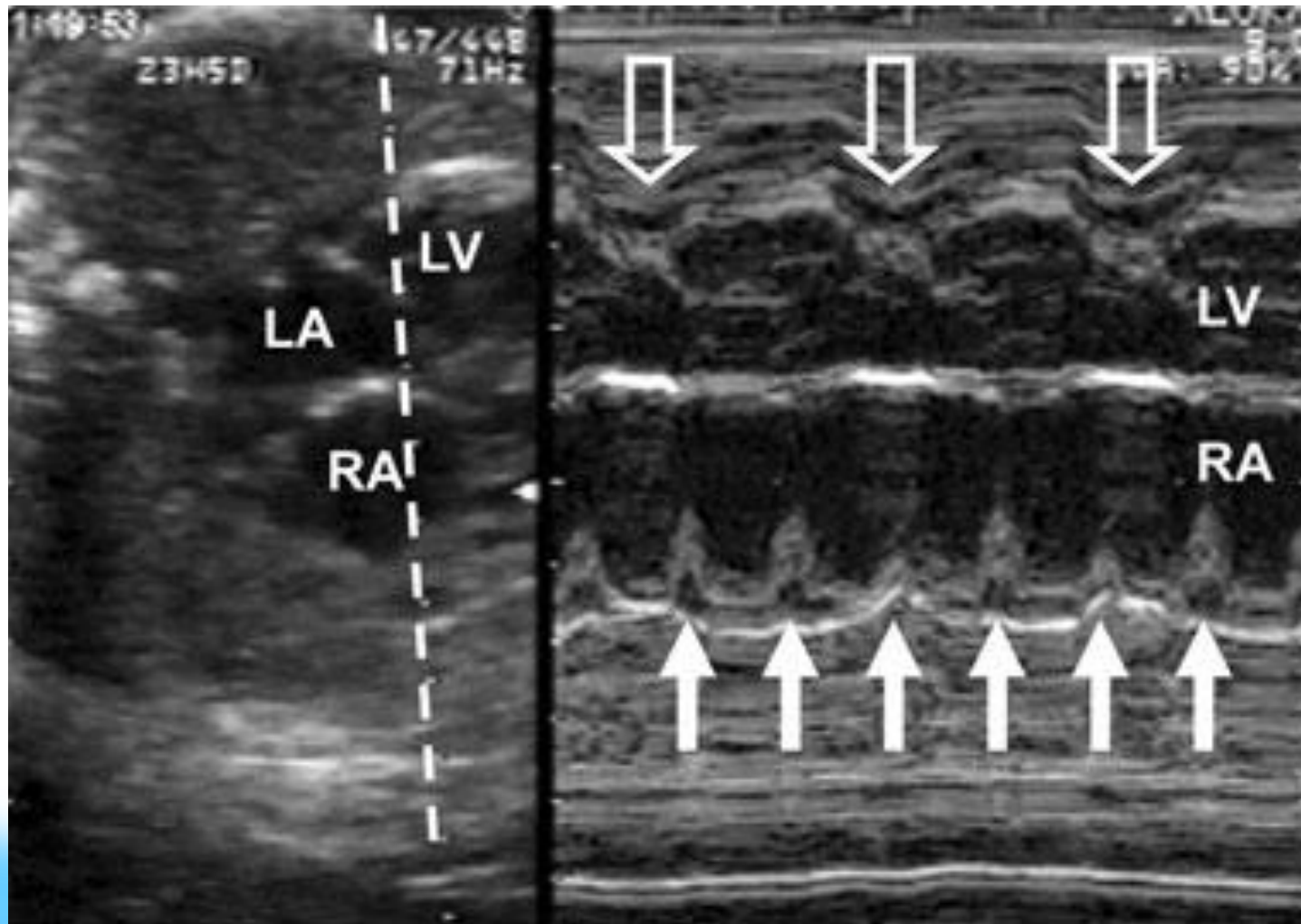
Neonatal Lupus syndrome

- Other manifestations of Neonatal SLE (hematologic/ skin...)
 - **Transient**
 - Parallel with maternal Ab titer in the fetal and neonatal circulation
 - Disappear with the clearance of the maternal Ab by 6~8 Mo of age
 - Continual regeneration

Fetal SVC/aorta Doppler tracing of complete AV block



**complete AV block of atrial & ventricular contraction
(ventricular rate =60 bpm)**



Ventricle

Atrium

Sex & Age

- **Sex**
 - females > males.
- **Age**
 - Fetuses or newborn
 - more serious course require earlier pacing
 - Later in childhood.

Clinical Manifestations

■ Fetus

- hydrops fetalis -high mortality rate.
- Bradycardia / fetal distress
- history of recurrent fetal loss
- recurrence for heart block in subsequent siblings is 17-22%.

■ Newborn

- Low C.O
- Asymptomatic- not likely to be identified
- Associated discoid skin lesions.

■ Older infants or children

- Asymptomatic
- Low C.O.
 - pallor, mottling, lethargy, exercise intolerance, palpitations, dizziness, or syncope, sudden death
 - night terrors, tiredness with frequent naps, and irritability

Physical examinations

- Low heart rate for age
- Junctional escape rhythm- regular at 60-80/min
- Variable S₁ (AV asynchrony)
- Cool skin, mottling, or cyanosis.
- Tachypnea and hepatomegaly (CHF)
- Complex of hydrops fetalis.

Lab Studies

- anti-Ro and anti-La antibody levels(ELISA)
 - Baby
 - Mother
- Assessment for other organ and/or tissue damage
 - Platelet (R/O thrombocytopenia)
 - Liver enzymes (R/O alloimmune hepatitis)

Clinical considerations

pregnancy in women with anti-Ro/La antibodies

- All women with autoimmune Sx
 - Early first Δ screening: reactivity to Ro and La
 - F/U immunoblot fine specificity of anti-Ro reactivity
(anti-52 kD, 60-kD Ro)
- **If anti-La (+), anti-Ro52 or Ro60 (+)**
 - High risk for development of CAVB in the fetus.
 - Monitor the fetal PR interval (by Echo)
 - weekly (16 ~ 26 weeks' GA)
 - biweekly (26 ~ 32 weeks' GA)

Imaging Studies

■ Echocardiography

- Assess ventricular function and size
- R/O congenital or acquired cardiac malformations
- Valve dysfunction.

■ ECG (confirm)

- P waves and QRS complexes have no constant relationship
- Prolonged QRS duration or normal

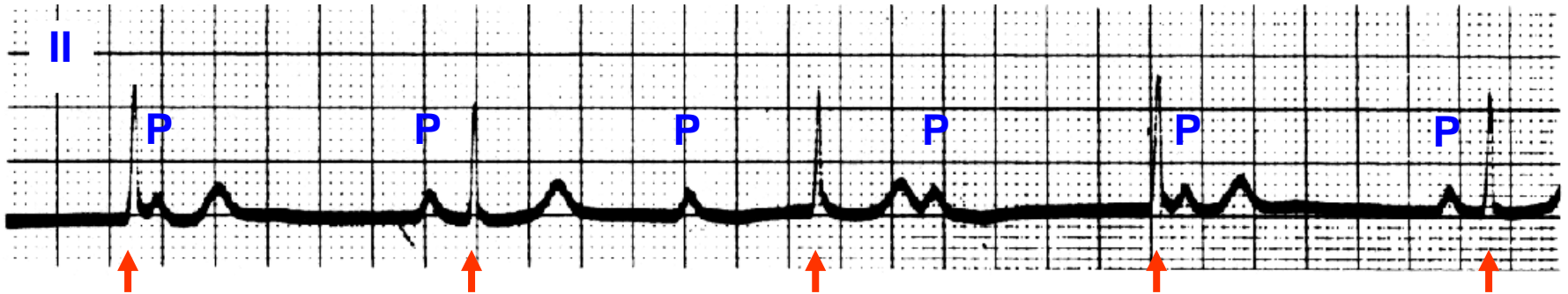
■ Holter ambulatory ECG monitoring

■ Exercise testing (>7 yrs)

■ Electrophysiologic test:

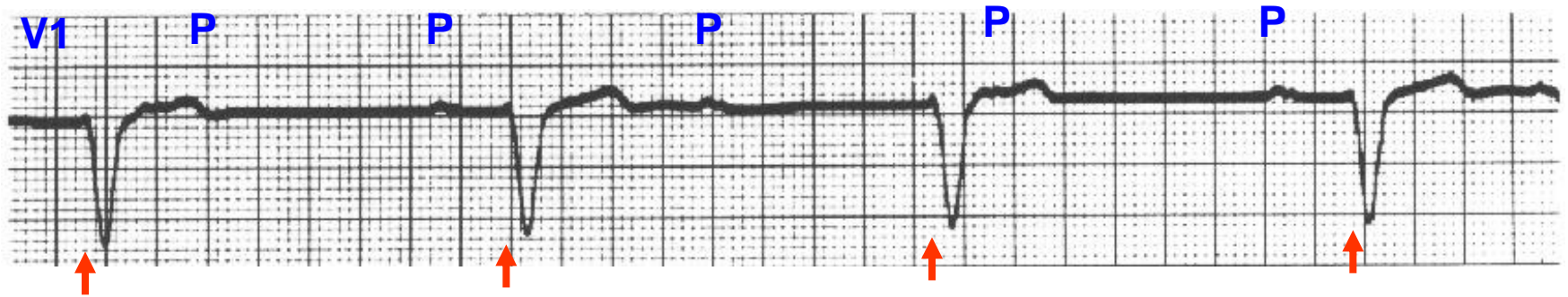
- Not routinely performed
- But provide information regarding pathophysiology & prognosis

Complete AV Block



- P waves: at 60 bpm
- QRS complexes (junctional escape rhythm) :45 bpm
- Atrial and ventricular activity are completely *unrelated*
- Junctional escape rhythm suggests *AV nodal site of block*

Complete AV Block



- P waves at 50-60 bpm
- QRS complexes (ventricular escape rhythm): 35 bpm
- Atrial and ventricular activity are completely *unrelated*
- Ventricular escape rhythm suggests *His-Purkinje site of block*



Treatment


Prenatal management approach still very much unresolved

- Anti-inflammatory fluorinated steroids
- Intravenous immune-globulins (IVIg)
- Plasmapheresis
- Augmentation in the fetal heart rate
 - direct fetal pacing
 - β -inotropic agent

Maternal oral fluorinated steroid (dexamethasone or betamethasone) Tx

- Efficacy and risks are questionable.
- No differences
 - in mortality, prematurity, degree of final block, or need for pacemaker between fetuses treated or not.
- Benefit: pericardial or pleural effusions, ascites, hydrops
- Suggestion: reversal of less-advanced block
- Potential risks
 - Fetal neurological development, growth retardation, oligohydramnios
 - Potential maternal side effects
- Dose
 - daily fetal dexamethasone exposure: does not exceed 0.05 mg/kg BW (based on a maximal 8 mg/kg/day maternal dose and a cord-to-maternal drug ratio of 30%),

Beta-sympathomimetics salbutamol & terbutaline

- β 1-adrenergic actions of the bronchodilators
- \uparrow heart rate , \downarrow systemic vascular resistance
- Recommendation
 - fetal heart rates $< 50-55$ bpm
 - significantly reduced cardiac contractility.
- Dose (orally to the mother)
 - Salbutamol (10 mg q 8 h; maximal: 40 mg/day)
 - Terbutalin (2.5–7.5 mg q 4–6 h; maximal 30 mg/day)
 -  \uparrow ventricular rate by 5–10 bpm.
- Possible maternal side effect

The Hospital for Sick Children, Toronto

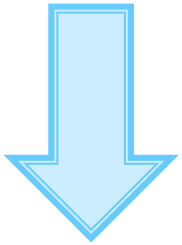
Treatment Guideline



overall survival rate
to birth of >95% !!

Dexamethasone

8mg/kg/d



4mg/kg/d



2mg/kg/d



Maternal IVIG

70g q 2~3wk

salbutamol

No Tx

If significant ventricular
Endocardial fibroelastosis.

If HR < 50–55 bpm
or cardiac dysfunction .

If uncomplicated case:

Treatment Protocol

At Dx of Fetal isolated AV Block

- HR > 55 bpm + Normal ventricular function : **Dexa**
- HR < 55 bpm + Abnormal ventricular function : **Dexa + β -inotropic**



Pregnant F/U

Weekly-biweekly: Obstetric assessment
Weekly-biweekly: Fetal Echocardiogram



Delivery at tertiary center

- Uneventful course: c/sec (or vaginal del) at about **37 week**
- **Progressive hydrops:** (paracentesis)+c/sec+immediate pacing

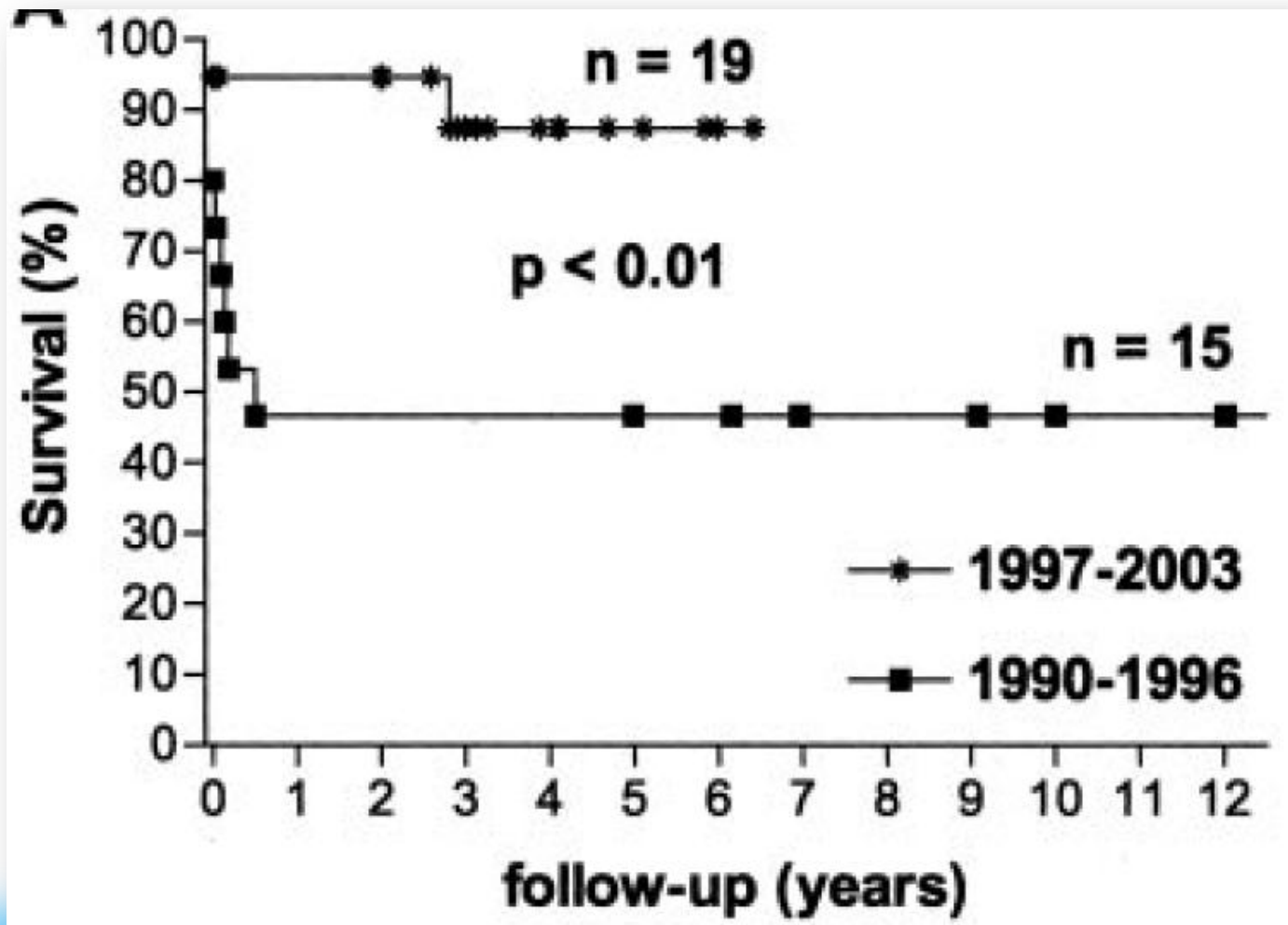


Neonatal critical care Management

- **Low C.O:** isoprenaline, pacing etc
- **Neonatal lupus:** oral prednosolone
- **Endocardial fibroelastosis:** IVIG

Era of diagnosis of fetal isolated CAVB and freedom from death.

Toronto, Texas
Treatment Protocol

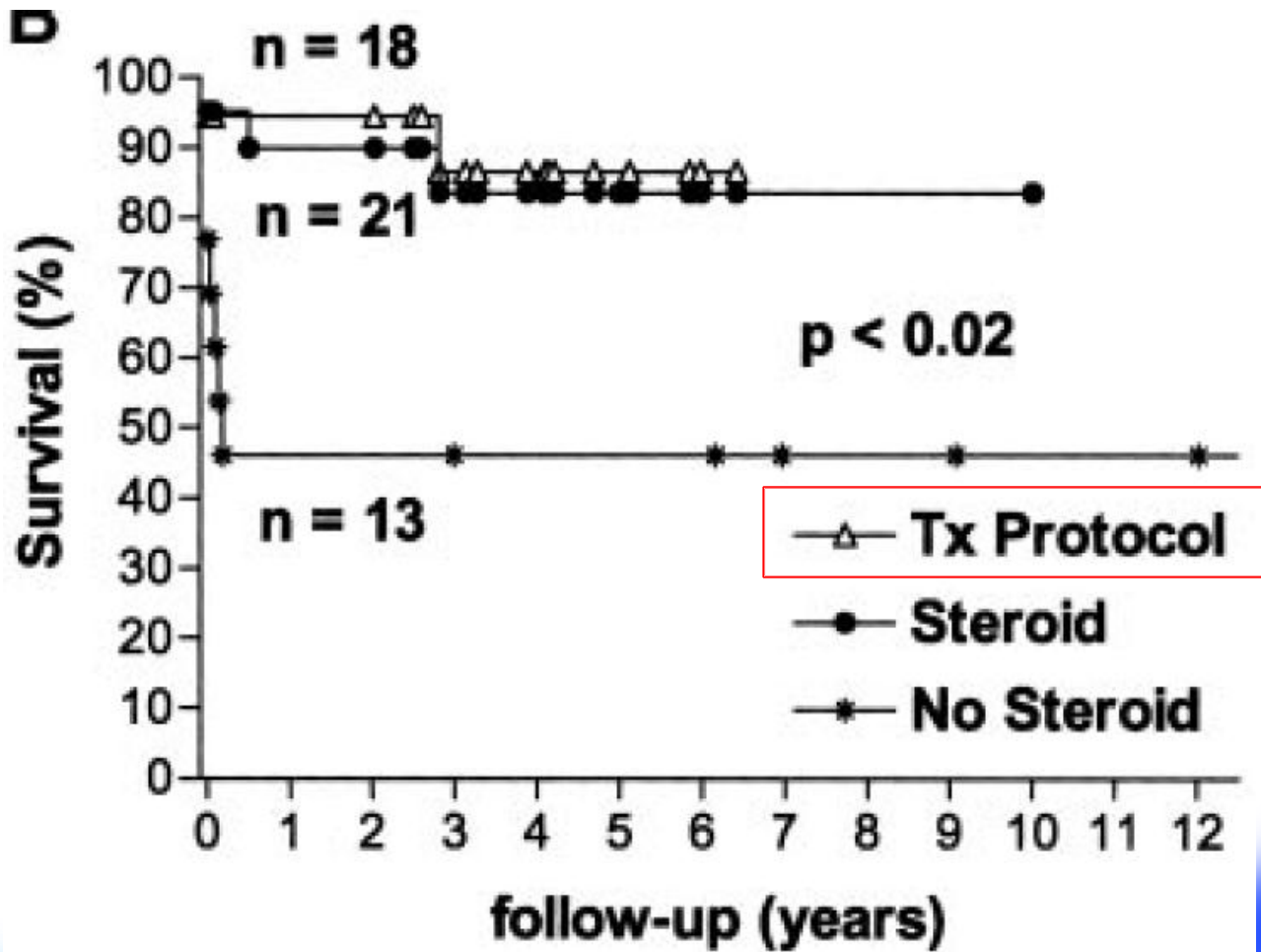


Transplacental fetal treatment

& freedom from death

Toronto, Texas

Treatment Protocol



Postnatal Treatment

Medical

- Medications are not necessary
- Chronotropic / inotropics :temporal until pacemaker
 - Isoproterenol, atropine, or epinephrine
 - May be helpful in fetuses and newborns
 - hydrops fetalis
 - congestive heart failure
 - low cardiac output.
- Immunosuppressive agents in fetuses and newborns
 - potentially slow or halt progressive in **utero** AV block.
- Steroid: little evidence
- **Currently focused on identifying the optimal timing of pacemaker !!**

Postnatal Treatment

Surgical -Indication for pacing

- **Major criteria for pacing based on ECG or Holter**

- Severe symptoms (eg, syncope)
- Average HR < 50 bpm. Sleeping HR < 45 bpm
- Pauses 2' heart block > 3 seconds.

- **Borderline major criteria**

- Cardiomegaly(dCMP)
- High atrial rate
- Junctional instability (eg, junctional exit block)
- Broad complex escape rhythm
- ↓ ventricular response to exercise
- QT prolongation :(mortality 7~22%)
- Complex ventricular ectopy.

Pacemaker

- **Transthoracic epicardial leads**
 - neonates, prematures
 - especially steroid-eluting epicardial leads
 - longevity and a better threshold.
- **Transvenous approach**
 - safe in children (>4-5 Yr) with weight >10-20kg



Prognosis

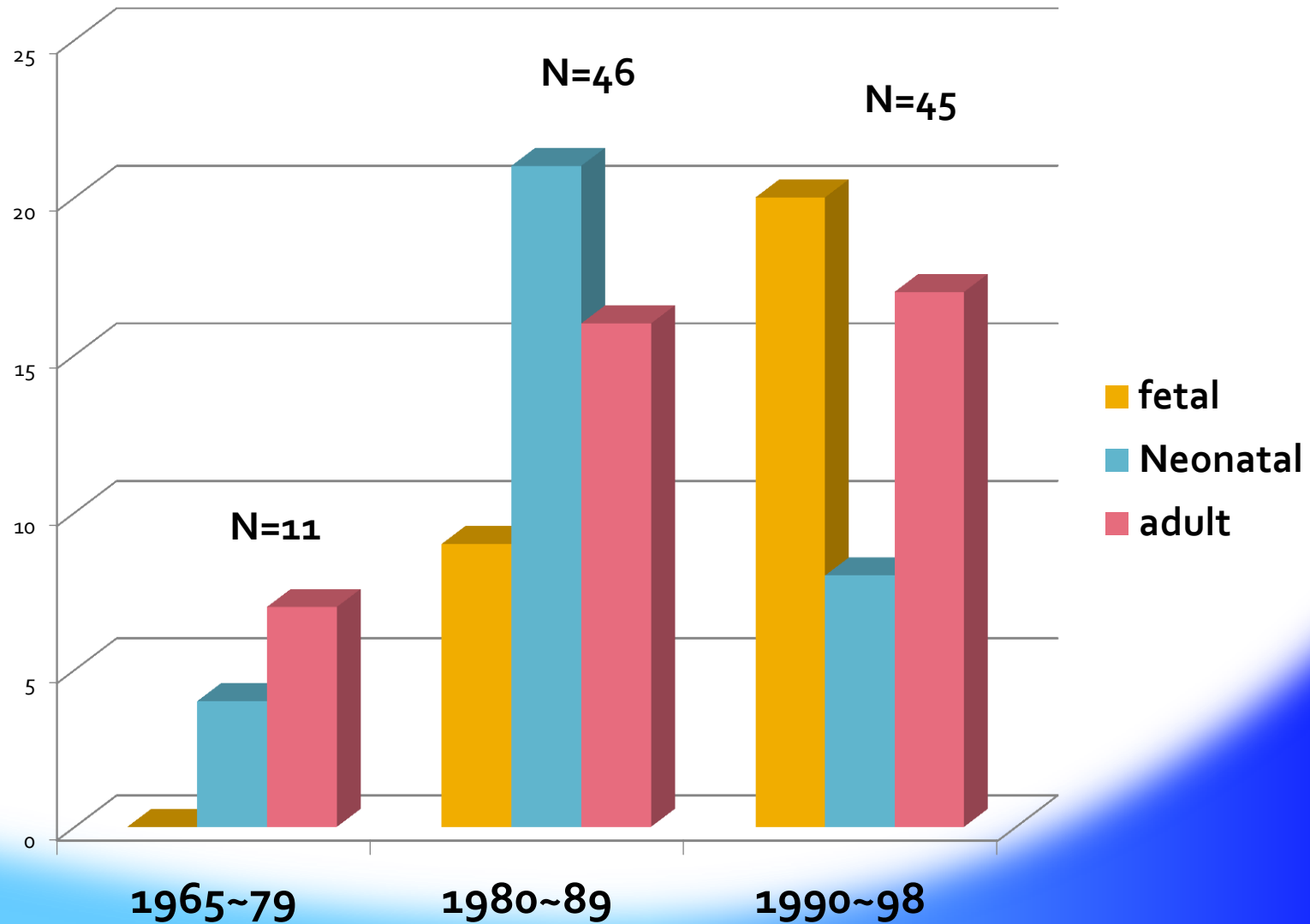
Fetal CAVB

Risk factors for worse outcome

- Fetal diagnosis
- Presence of hydrops fetalis
- Delivery at < 32weeks gestation
- Ventricular rate <55 bpm in early pregnancy
- Hydrops fetalis
- Endocardial fibroelastosis (strong predictor)
- Prolonged QTc

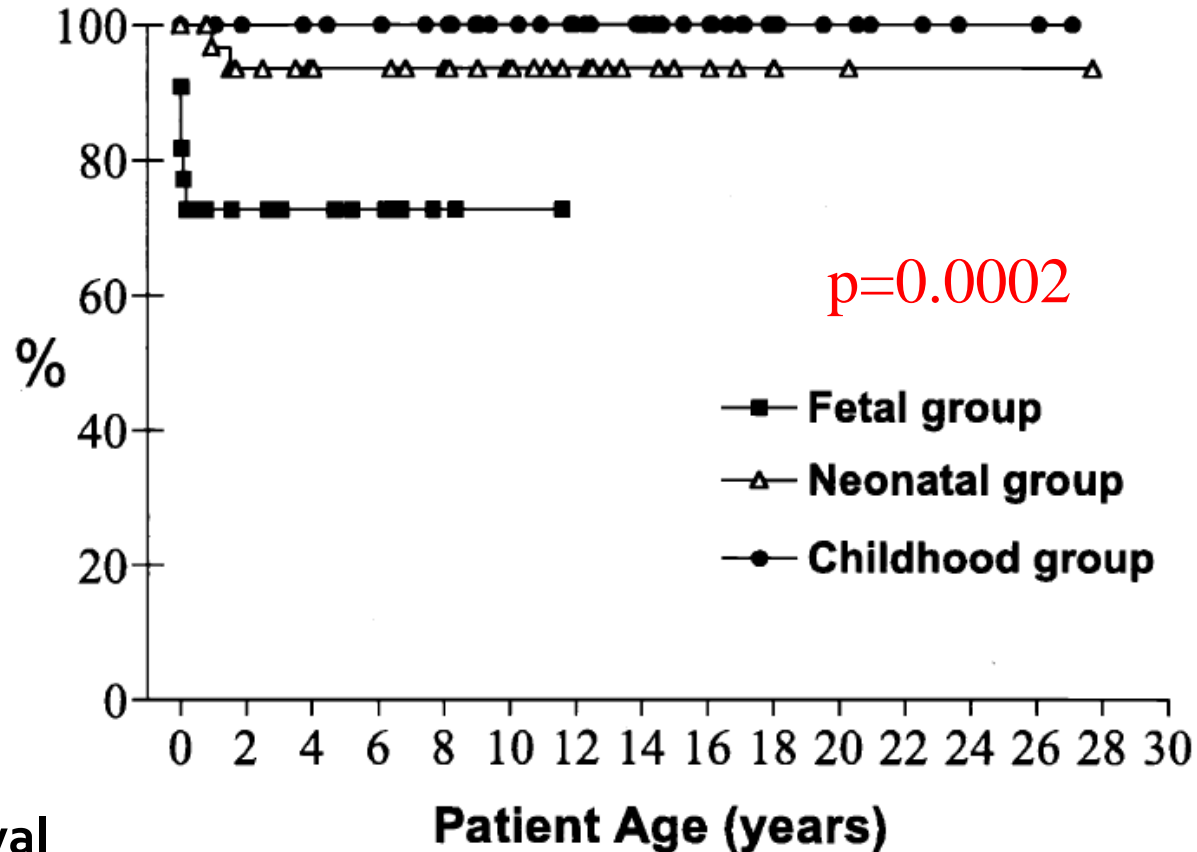
No of new cases with isolated CAVB -different time periods.

A Single Institution's Experience of 30 Years



Kaplan-Meier **survival** of CAVB diagnosed comparing age group

A Single Institution's Experience of 30 Years



- **Survival**

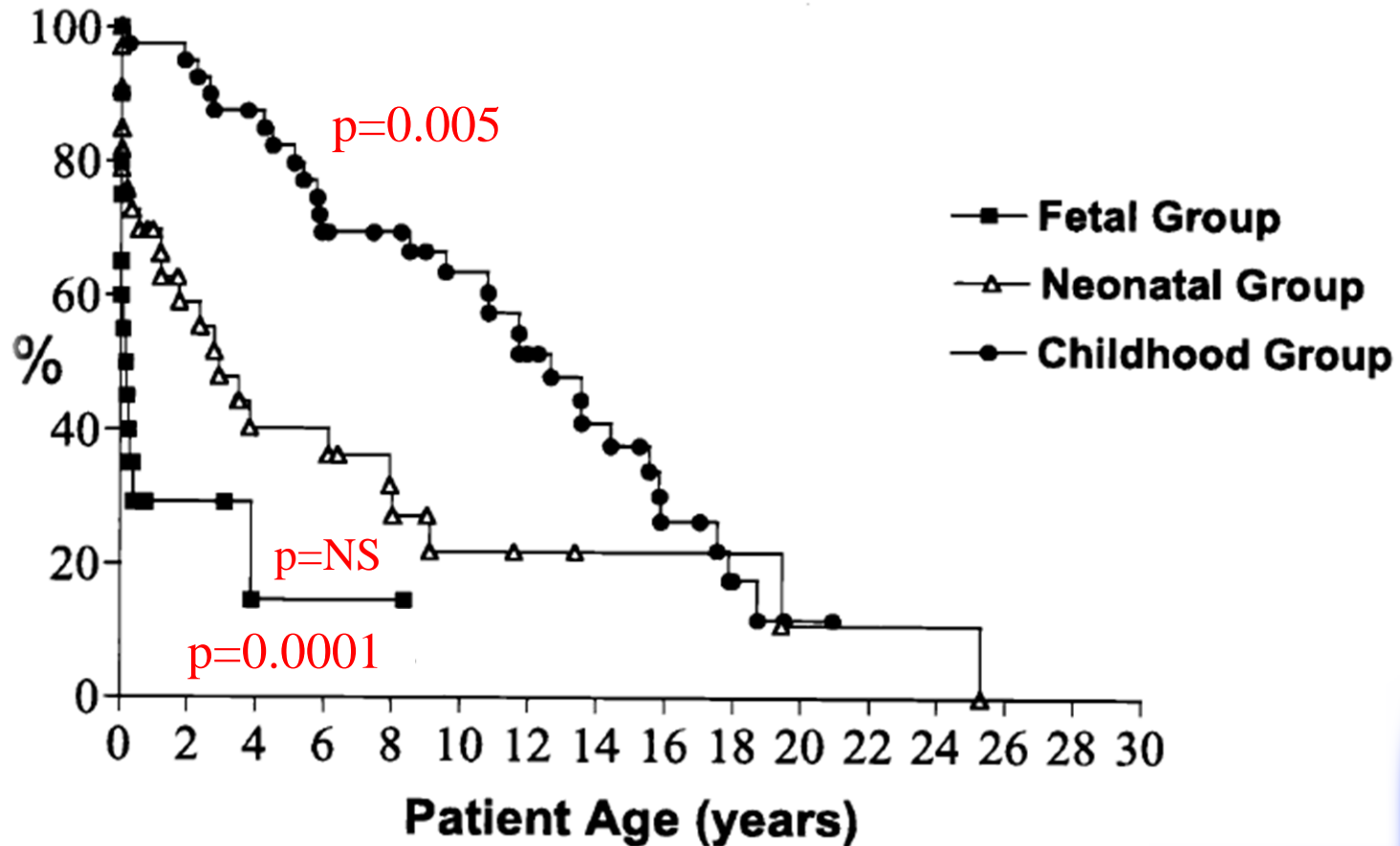
- **Fetal:70%**

- **Neonatal : 94%,**

- **childhood : 100%.**

Kaplan-Meier **freedom of pacemaker** implantation comparing age group of CAVB.

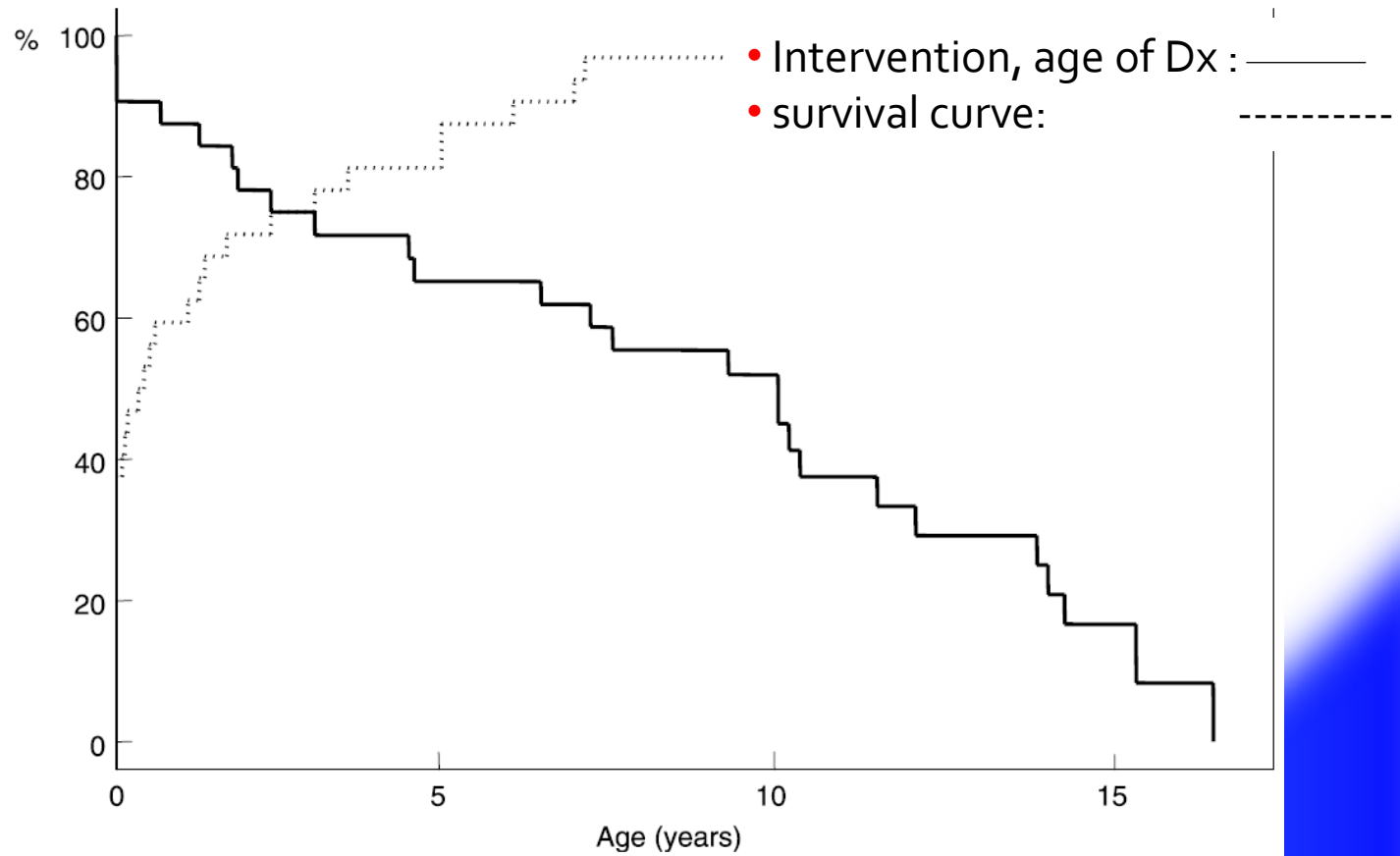
A Single Institution's Experience of 30 Years



Mortality/Morbidity

- Early infancy: greatest risk of death
- Beyond the neonatal period: significantly lower
- Children : 8 ~ 16%
- Adults : 4 ~ 8% in
- Overall morbidity : 17%
- dilated CMP: 75%

Free from intervention (solid line) and age at time of diagnosis (dotted line) expressed as survival curves (Kaplan Meier);

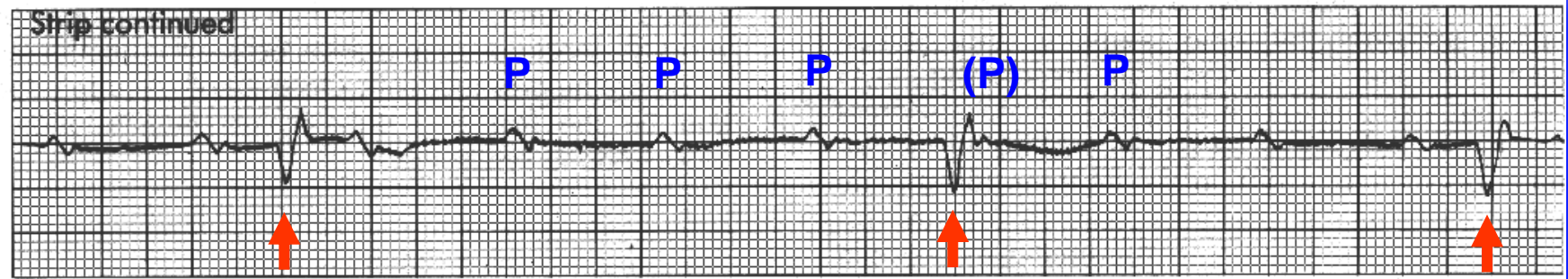
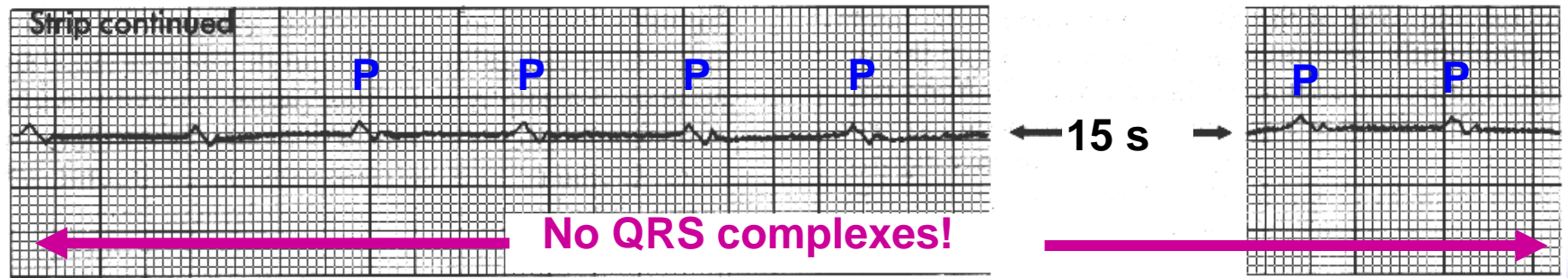
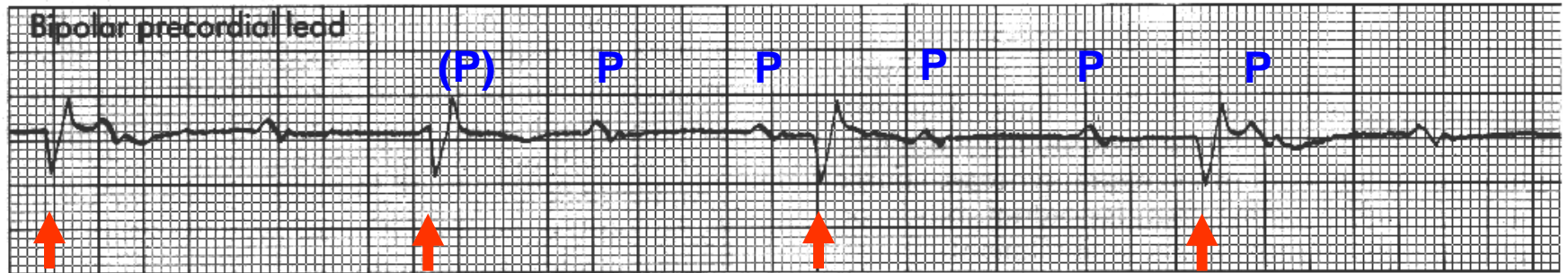


n=32; 6 censored data in the free from intervention-curve.

Prognosis:

- Usually favorable
- Progressive symptomatic
- Should consider pacemaker implantation
 - Exercise intolerance/Dizziness
 - Syncope (Stokes-Adams attacks)
 - Progressive cardiac enlargement (dCMP)
 - Prolonged pauses
 - Frequent episodes of junctional exit block
 - Flat junctional response
 - Tachyarrhythmias
 - Awake HR < 50 beats/min (syncope, sudden death risk).

Unreliability of Ventricular Escape Rhythm in CAVB



Consultations

- To Rheumatologist
 - Mother: monitoring for possible autoimmunedisease.
 - Infant: particularly if other manifestations of neonatal SLE
- Activity restriction
 - Patients with permanent pacing systems should be restricted
 - Avoid repeated intentional trauma to the pacemaker area
 - Exposure to high magnetic fields, such as direct MRI

Conclusions

- Overall prognosis in CAVB is relatively good but may be influenced by the patient's age at presentation.
- CAVB diagnosed after the newborn period carries relatively lower mortality and morbidity.
- Possibility of progressive dilated CMP should be taken into consideration when evaluating patients
- Regular echocardiographic monitoring is indicated in all children and young adults with CAVB.

- **Thank you for your attention!**

