PEDIATRIC PULMONARY HYPERTENSION

Recent Updates & Indian Scenario!

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MODERATOR:

MAITRI CHAUDHURI(MD, FNB)

EXPERTS:

- **MUNESH TOMAR (MD, FNB,FACC)**
- **HETAL MEHTA (American board certified in pediatrics and pediatric cardiology)**

Dedicated To Children Of India!

Pediatric PH – Underdiagnosed, Cryptic &The New Rays of Hope

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Why Special?

- Subtle Symptoms
- Multiple Aetiologies
- Late Referrals and Diagnosis
- Treatment Extrapolated From Adults
- Multi-disciplinary Teamwork
- Right Heart Cath not always feasible
- Uncorrected ,5 yr survival 60-75%.

CONSENSUS STATEMENT

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

2018 Latest Classification, NICE

Definitions	Characteristics	Clinical groups#
Pre-capillary PH	mPAP >20 mmHg	1, 3, 4 and 5
	PAWP ≤15 mmHg	
	PVR ≥3 WU	
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR <3 WU	
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg	2 and 5
	PAWP >15 mmHg	
	PVR ≥3 WU	

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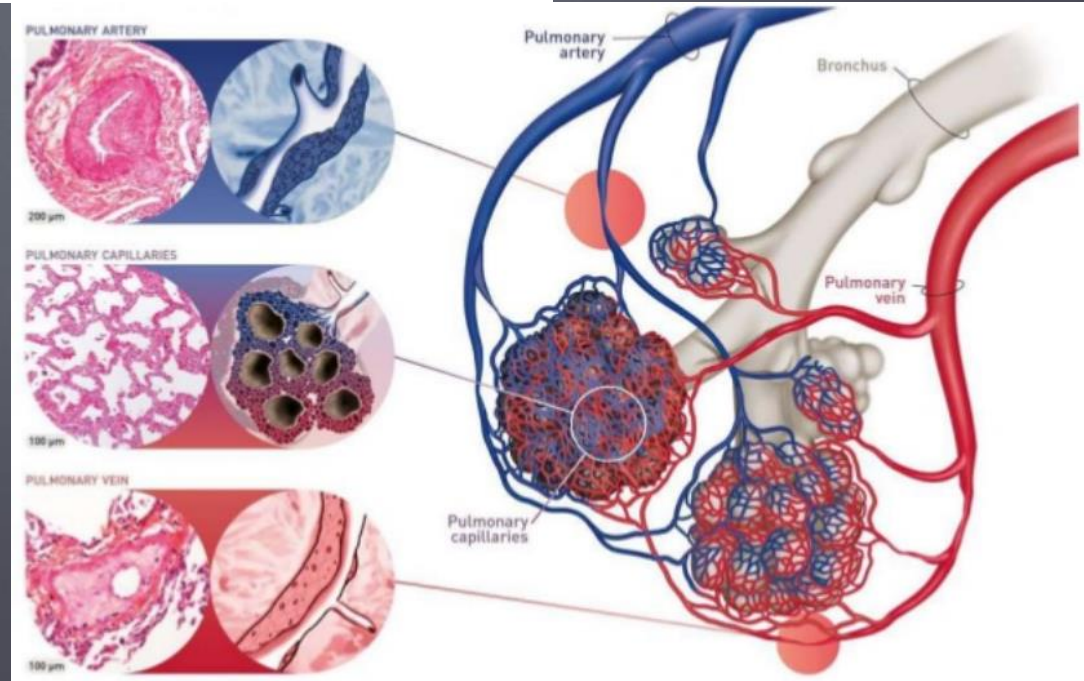
Valid from Age ≥ 3 Mo

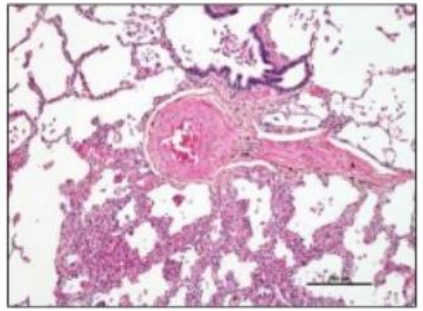
Define PAH

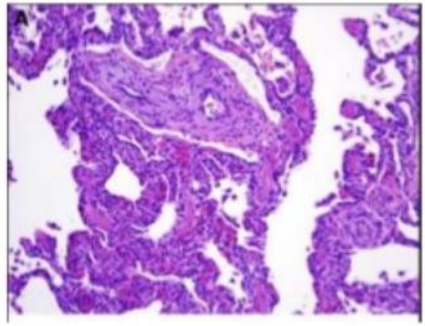
Change : Cut Off of ↑ Mean PAP Reduced From 25 to 20 mm Hg
20-24 is *grey zone*

Remember Echo Usually Tells PA Systolic Pressure

Normal mean PAP = 14.8 ±2 SD







1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

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6th World Symposium on PAH, NICE, 2018

A. Most Common Causes in Children :
1. **Cardiac**
2. **Lung (eg BPD, CDH, Hypoplastic)**

B. Distinguish whether Transient Or Permanent

C. PI. Focus on the RV , The End -Organ

CASE # 1

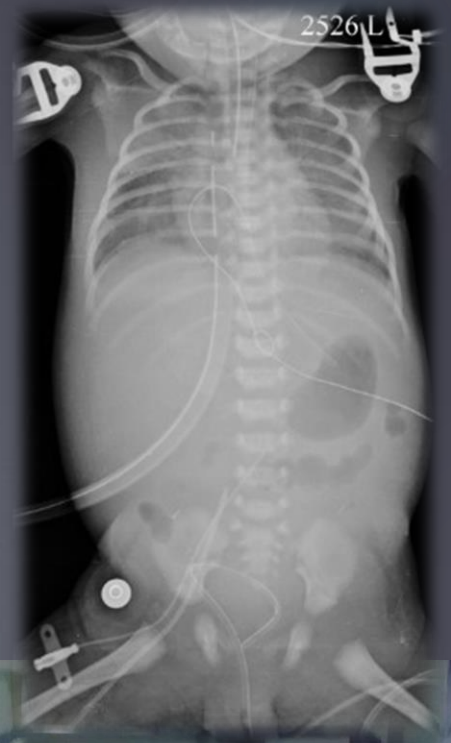
2 Days Newborn, Term, LSCS

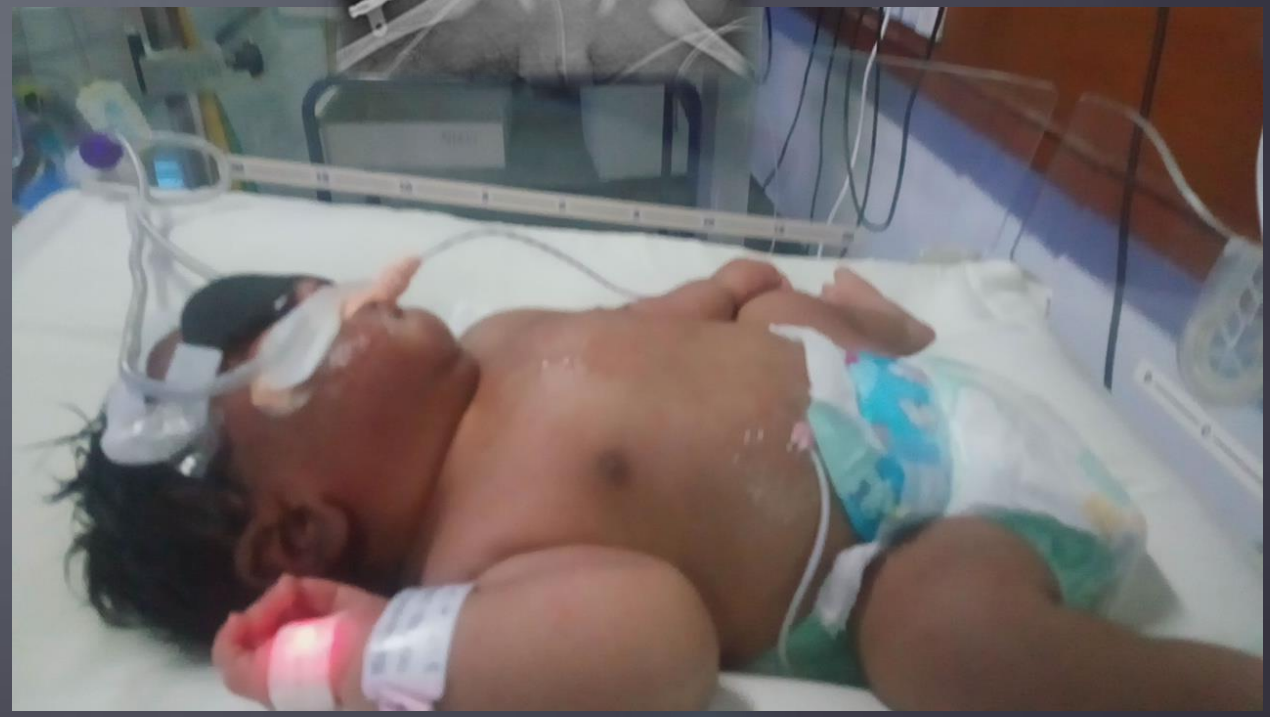
Infant of Diabetic Mother(HbA1c=9)

Weight 3.9 Kg, MAS +, NST +ve

Respiratory Distress from Birth

Pre& Post ductal Sats -76%





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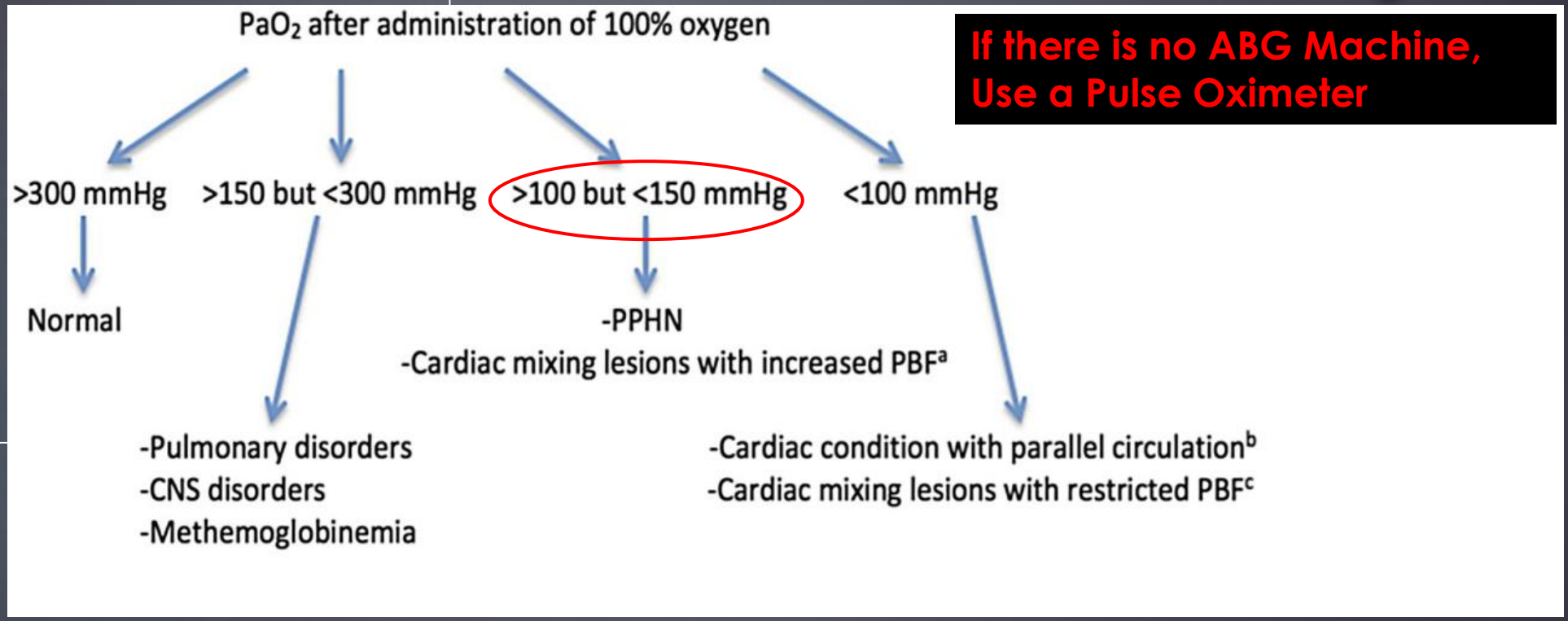
Possibilities:

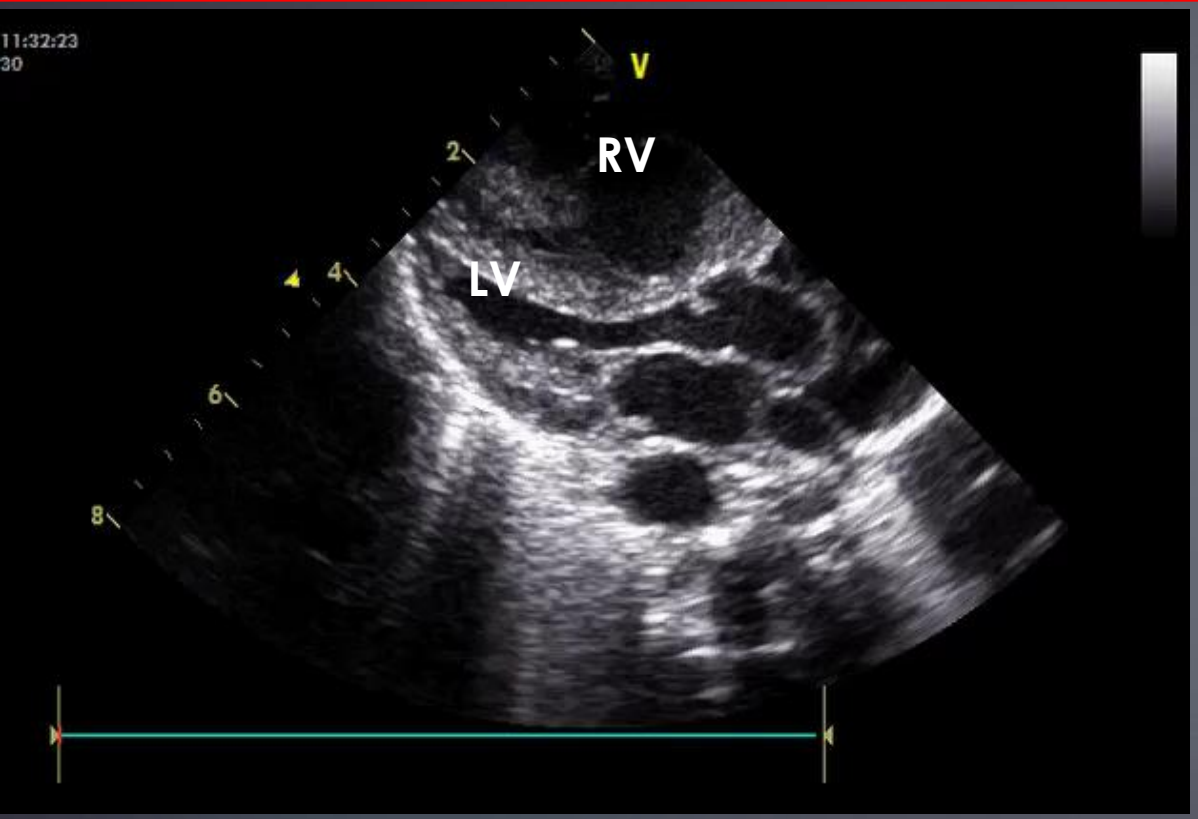
- PPHN
- Cardiac
- Respiratory
- Sepsis

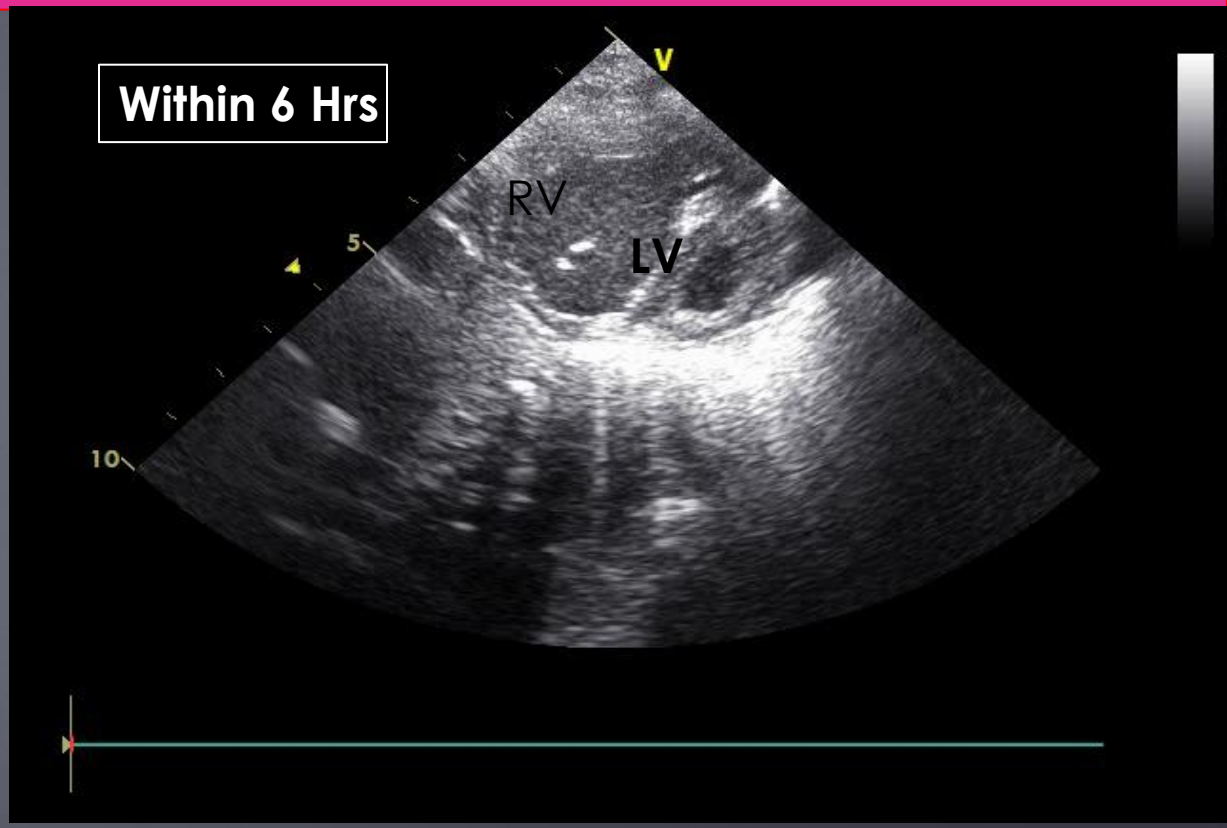
HYPEROXIA TEST



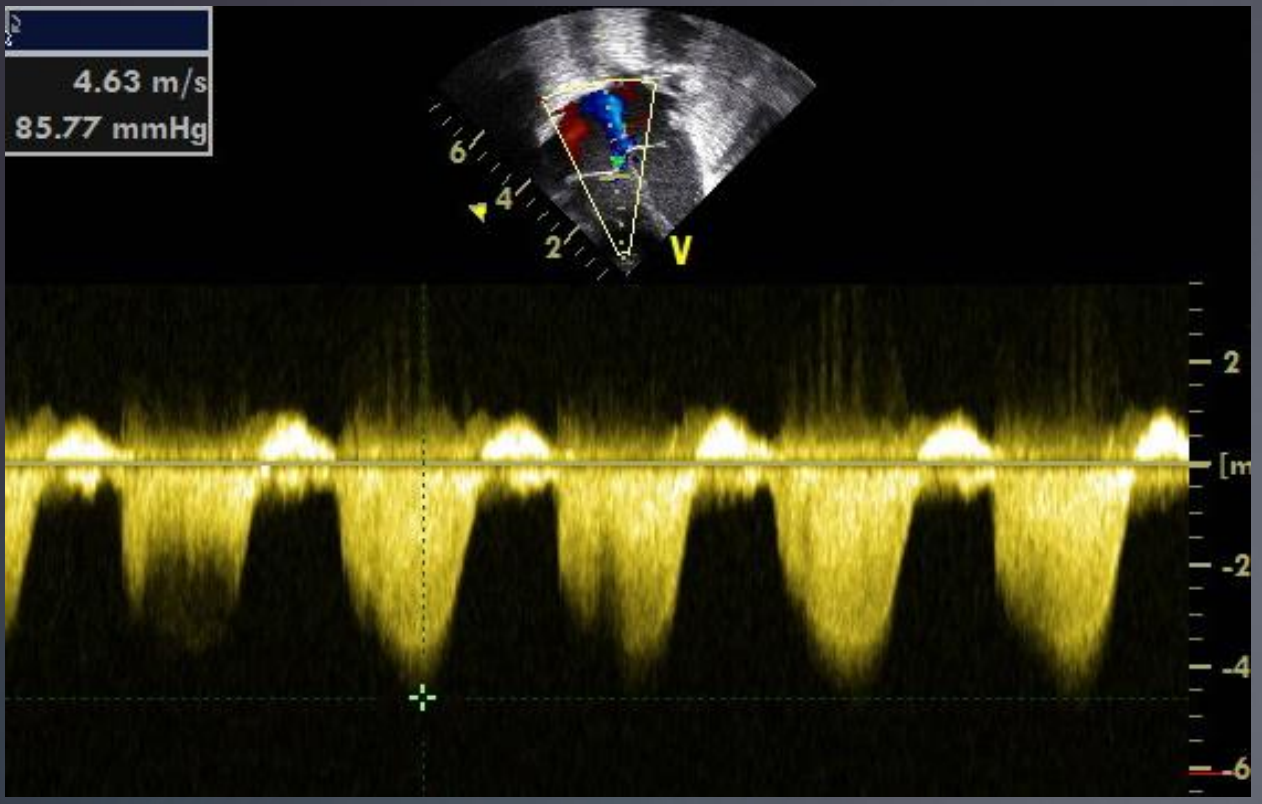
- A,B,C ..... As per NRP/NALS
- CXR : Cardiomegaly, Hazy Lungs, Comment On Pulmonary Vascularity
- Hypoglycemia, Hypothermia, Metabolic Correction
- Think About the operative hemodynamics from all angles
- Head box /HFNC not adequate Here , Mechanical Ventilation Required
- Keep an eye on vitals and color of baby, Pre-ductal & Post –Ductal Sats Difference <5-6%
- ? Surfactant, Next What

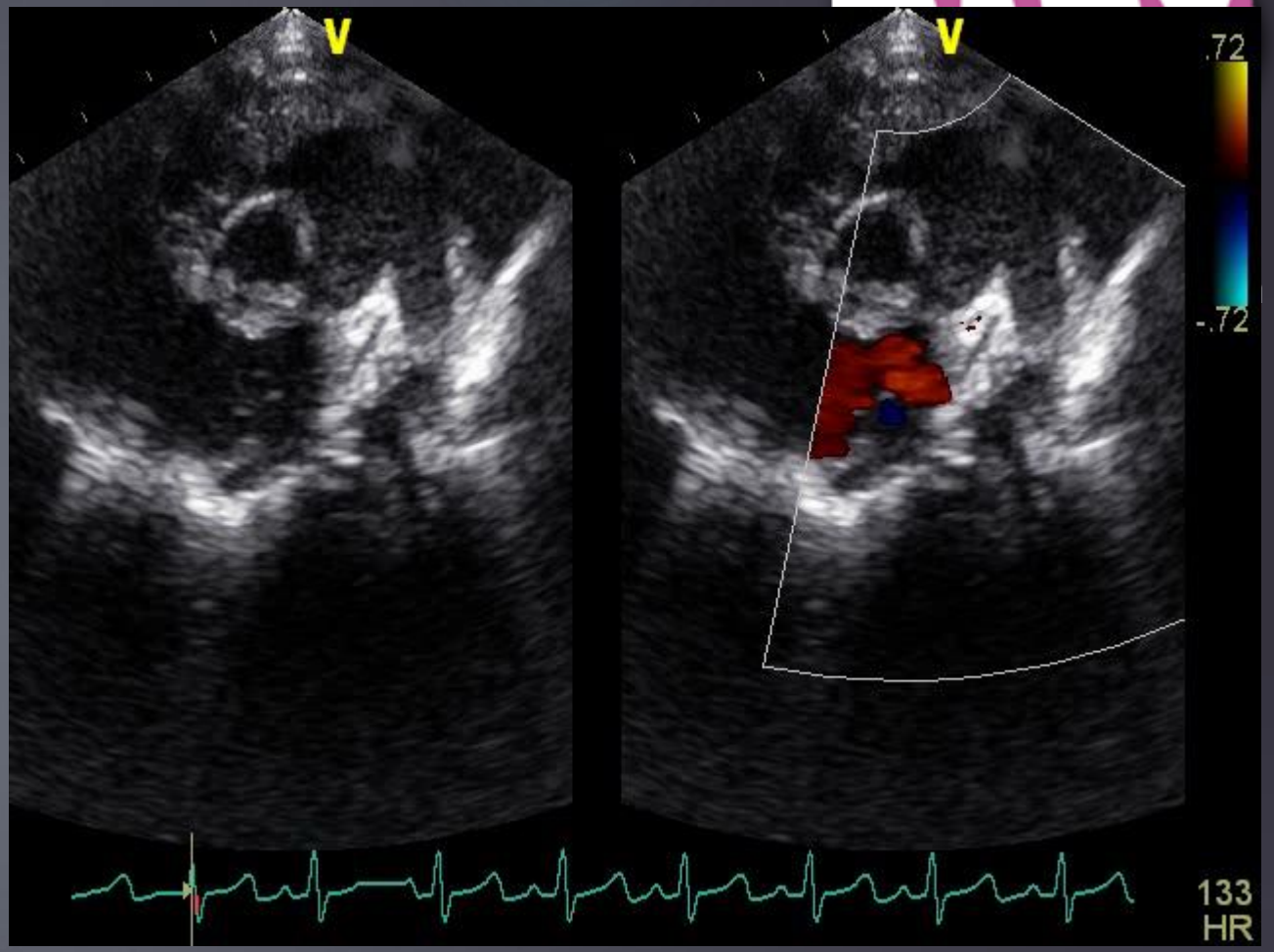
Functional Echocardiography in 1st Hospital





Midline IVS, D Shaped LV





Severe PH , PA Systolic Pressure =85mm Hg, Mean BP =40 mm Hg

Suprasystemic PAH , PDA R>Lshunt

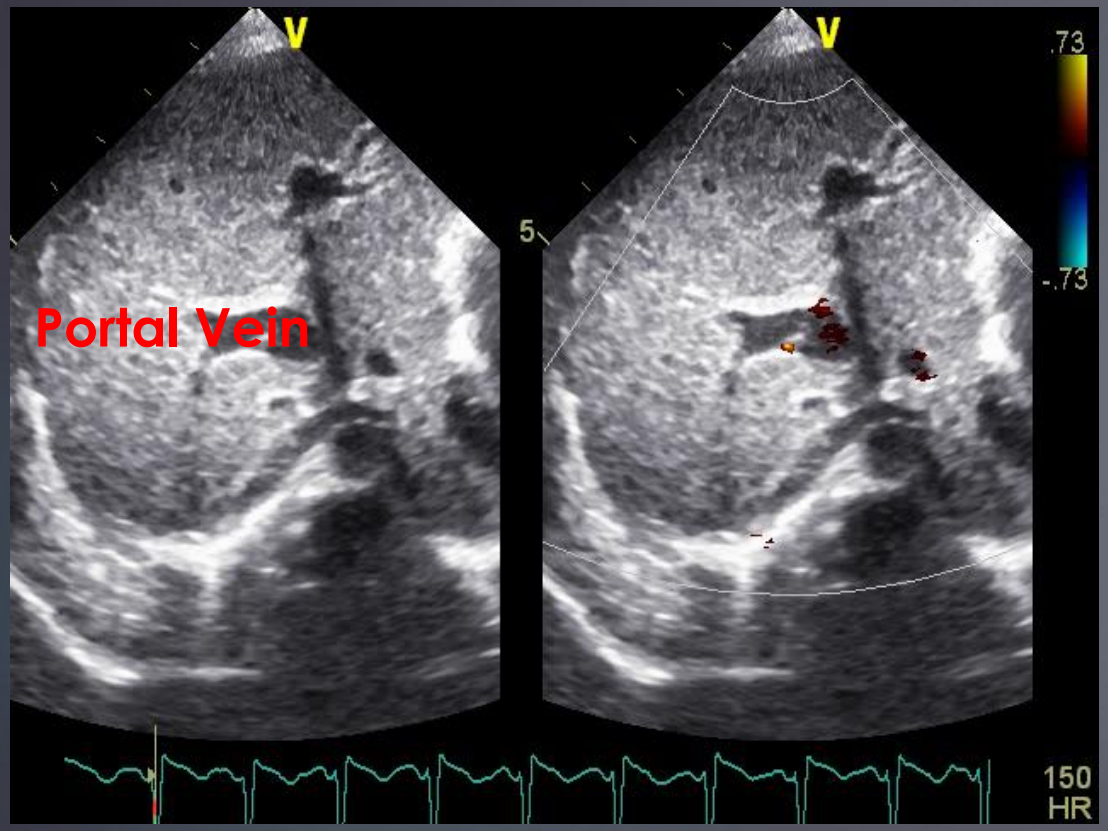
What Next?

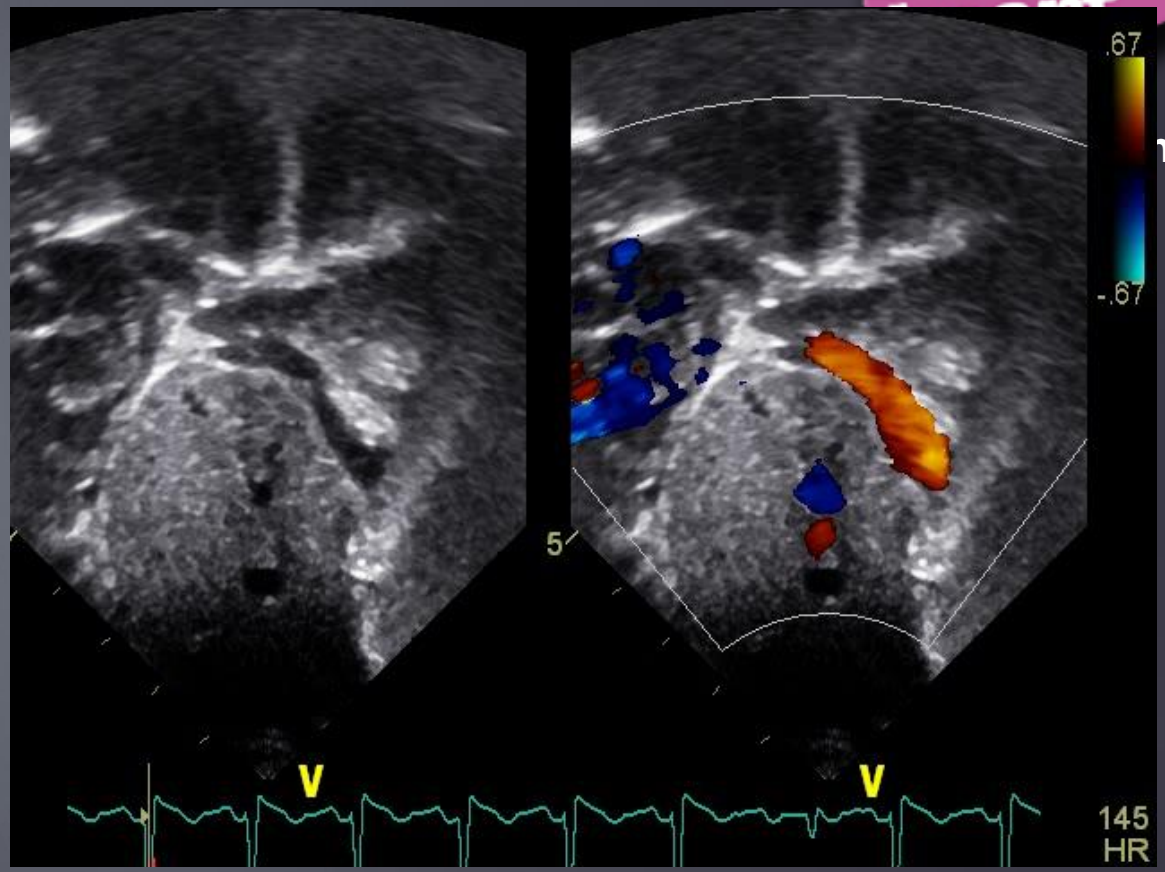
High Frequency Oscillatory Ventilation
Inhaled Nitric Oxide

Cheaper Alternatives: A,B,C(PIP/PEEP)

1. IV Sildenafil (if LVEF normal, normotensive)
2. IV Dobutamine
3. IV Milrinone
4. Avoid hypoxia, acidosis
5. Minimal Handling, Minimal Pain to Baby
6. NTG nebulization @25-50 mcg/kg /min for 10 Minutes

Review Echo Segment by Segment ~ Infracardiac TAPVC

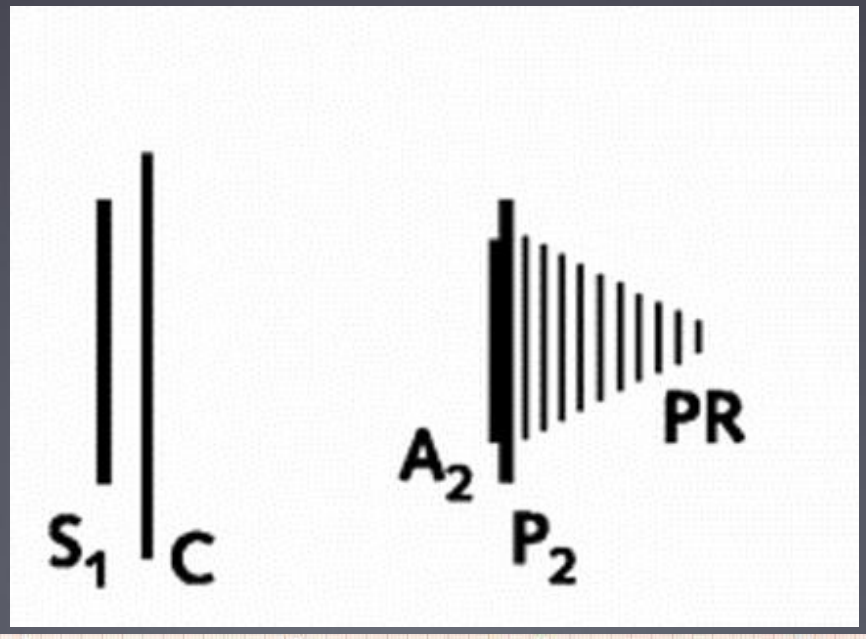


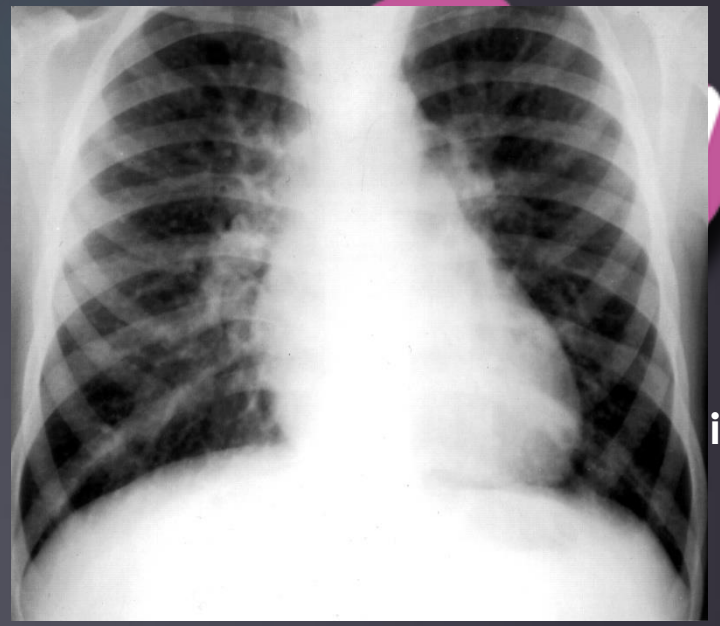


Always Exclude Heart Disease in PPHN Neonates
Management: emergency cardiac surgery!

CASE # 2

17 Y F, VSD Diagnosed at 6 M





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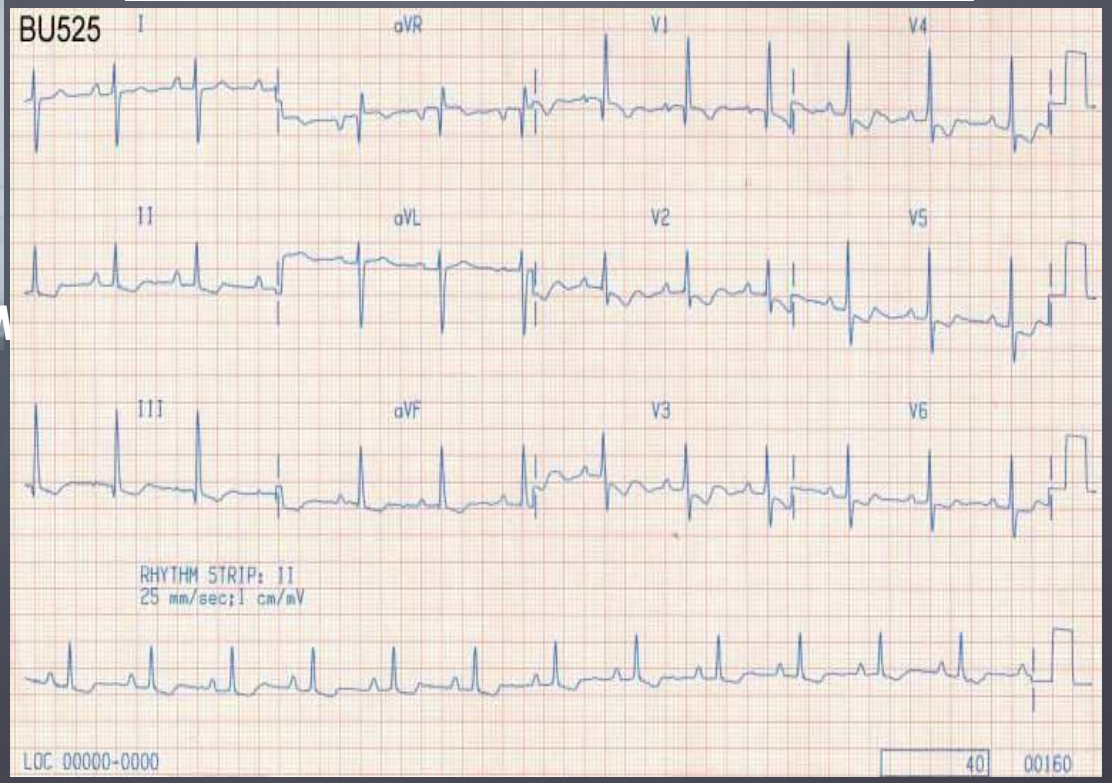

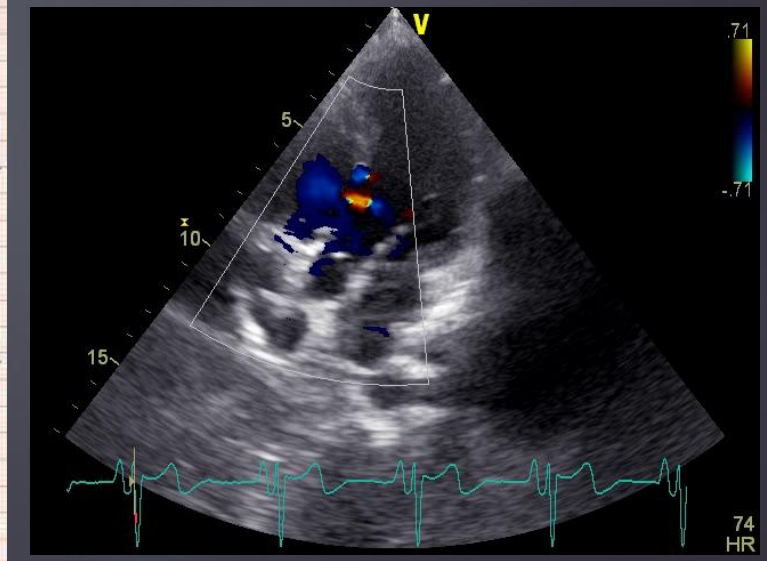

TOO LATE , STRIKE THE IRON ONLY WHEN HOT”

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Heath-Edwards Classification

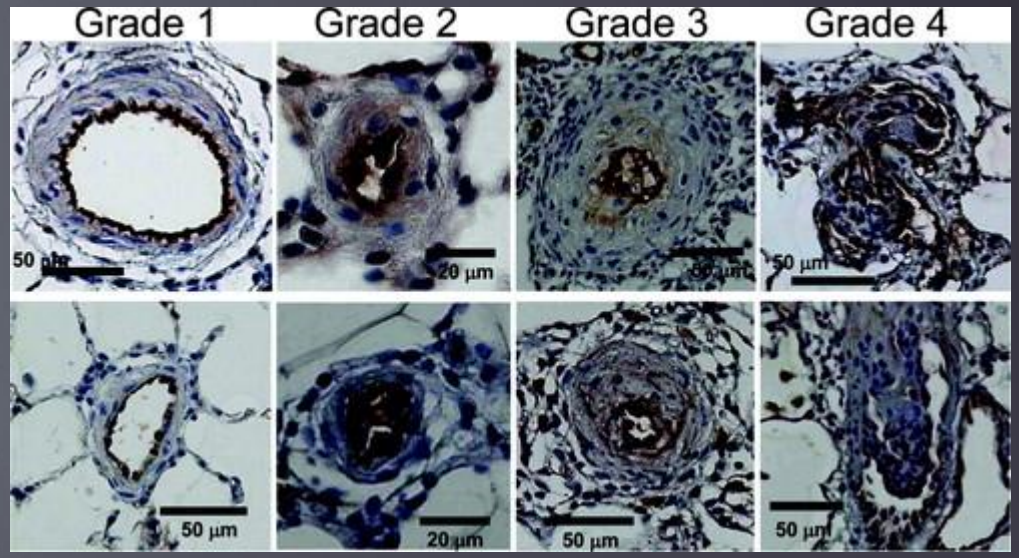
Reversible

- Stage I - Medial hypertrophy (reversible)
- Stage II - Cellular Intimal hyperplasia in a abnormally muscular artery (reversible)
- Stage III - Lumen occlusion from intimal hyperplasia of fibroelastic tissue (partially reversible)

Irreversible

- Stage IV - Arteriolar dilation and medial thinning (irreversible)
- Stage V - Plexiform lesion, which is an angiomatoid formation (terminal and irreversible)
- Stage VI - Fibrinoid/necrotizing arteritis (terminal and irreversible

Regular Ped cardio FU
Operate Early Within 6 Months

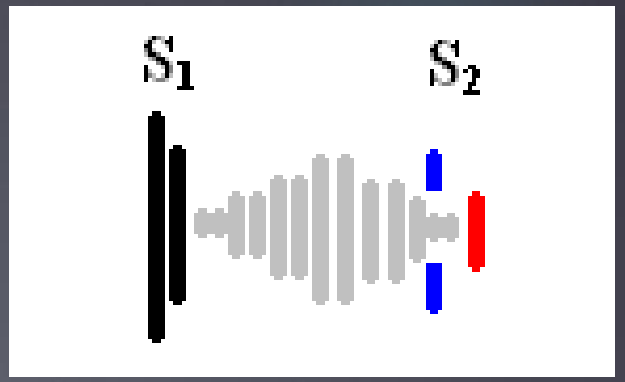


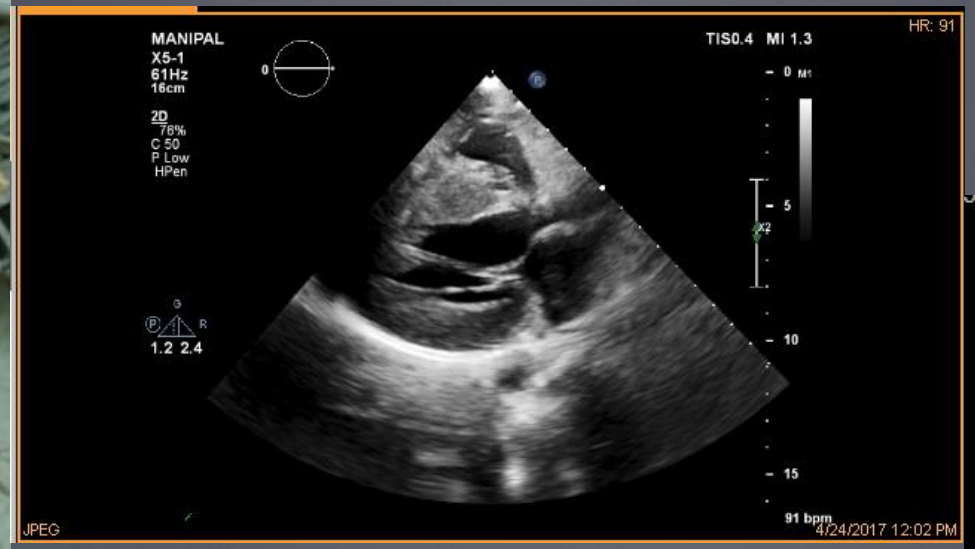
Pulmonary Hypertensive Vascular Disease/
Pulmonary Vascular Occlusive Disease

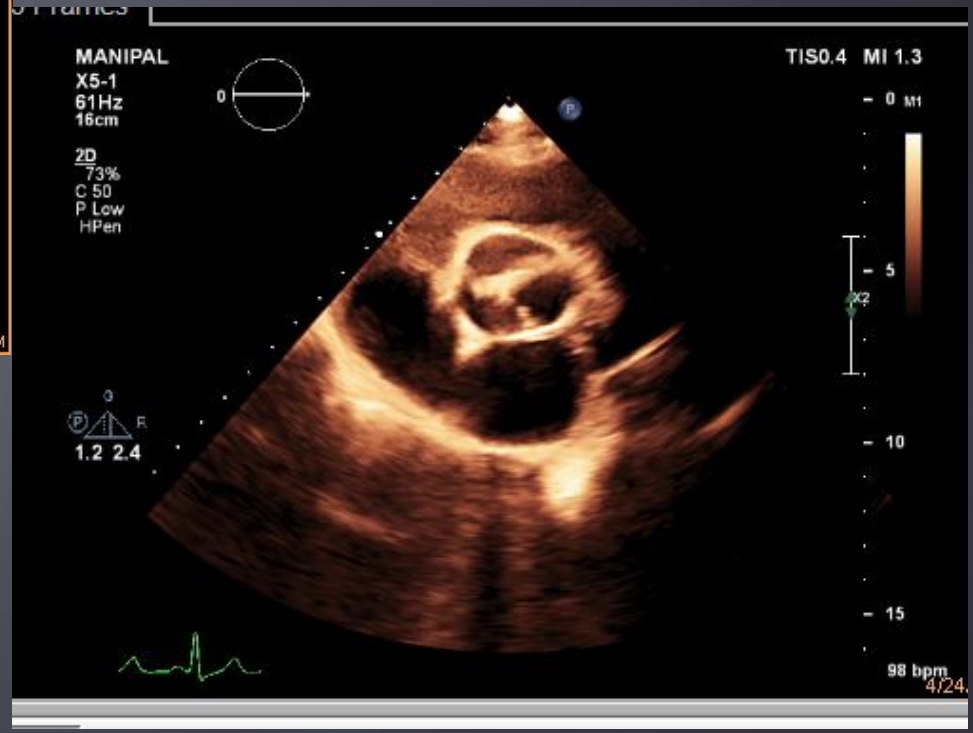
Eisenmenger Syndrome

- How To Manage?
- Expected Survival Rates?

CASE #3







- 19 Yr F,
- 7 mo Pregnant
- Lady notices “pulsation in neck”

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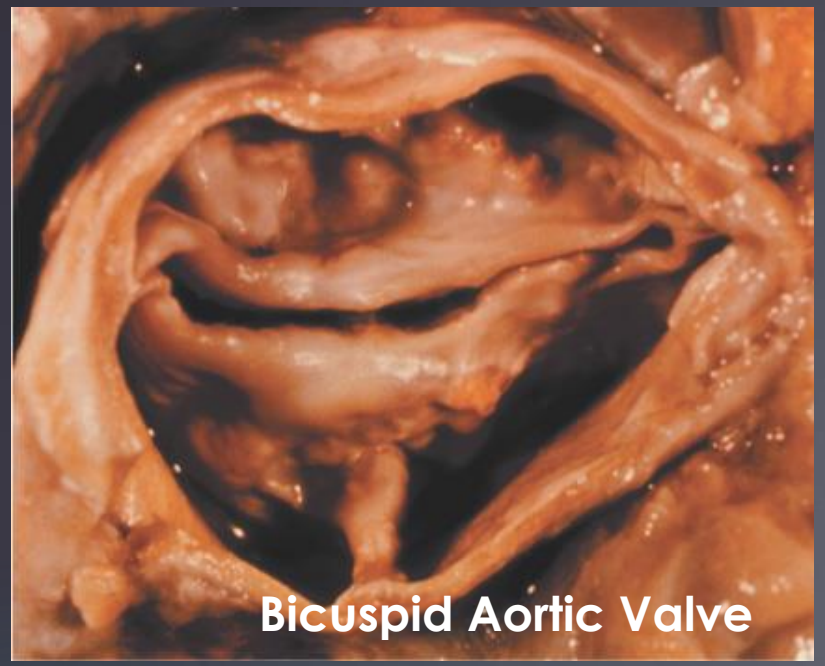

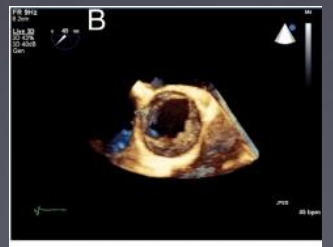

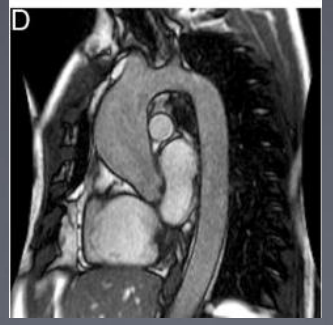

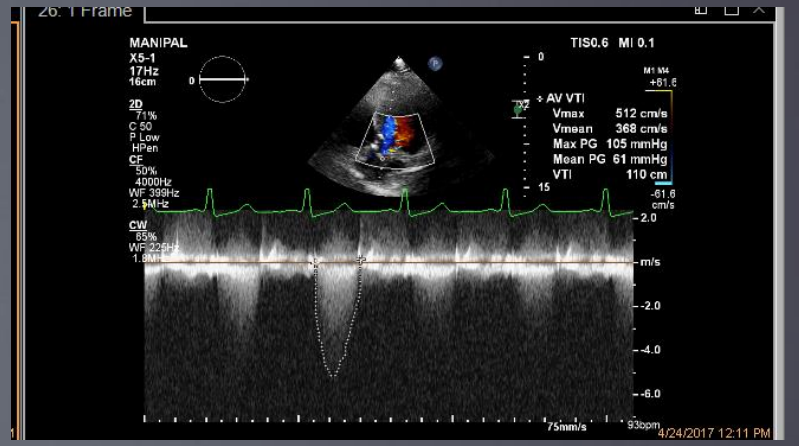

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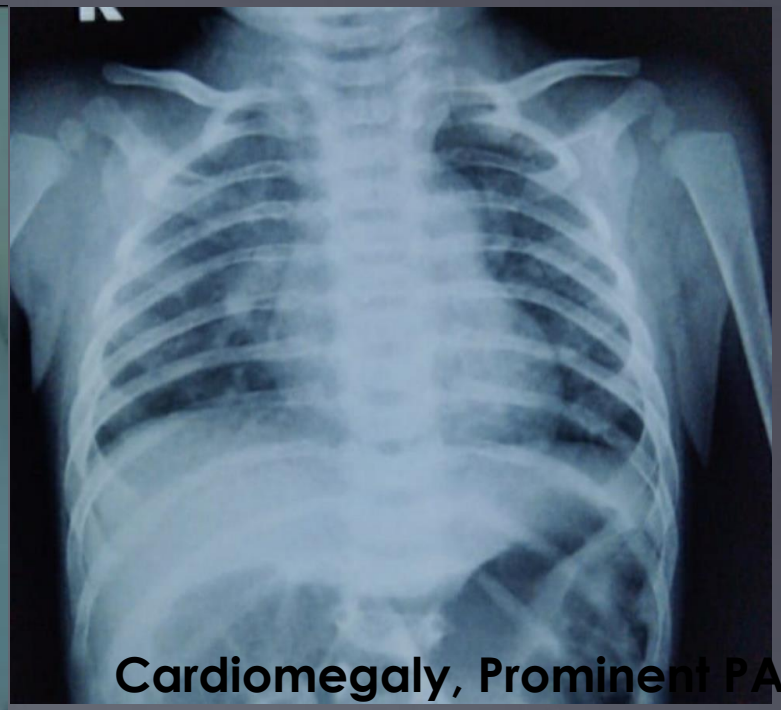
Category II : PH due to Left Heart Disease

Identify and Treat The Former, Do Not Chase PAH

CASE #4



Cardiomegaly, Prominent PA

PE: Normal Air entry

crepts/rub/wheeze/stridor nil

Echo : Severe PAH

TR Peak PG =64 mm Hg

No CHD

Lactate 18, PH -7.2,

HCO3- 11.5, PCO2 28,

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2.5 Mo, 3.8 Kg, Exclusively Breast Fed, Resp. Distress & Crying Episodes X 1 Week, CHF, Tachycardia, Sats >90%

The Missing Clue: Diet

Rx: IV Thiamine 100 mg/kg till normalization

followed by @2.5-5 mg daily X 4-6 Wks

"Prompt Response To Thiamine Is The Clue"

MALNUTRITION CAUSING PAH

ELSEVIER

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Shoshin beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India

Javeed Iqbal Bhat [a,*], Hilal Ahmad Rather [b], Ambreen Ali Ahangar [c], Umar Amin Qureshi [d], Parvez Dar [e], Qazi Iqbal Ahmed [a], Bashir Ahmed Charoo [a], Syed Wajid Ali [a]

[a] Department of Pediatrics, SKIMS Srinagar, J&K, India
[b] Department of Cardiology, SKIMS Srinagar, J&K, India
[c] Department of Anesthesiology and Critical Care, GMC Srinagar, J&K, India
[d] GB Panth Hospital Srinagar, J&K, India
[e] GB Panth Hospital Srinagar, J&K, India

ARTICLE INFO

Article history:
Received 10 March 2016
Accepted 27 July 2016
Available online 2 August 2016

Keywords:
Thiamine
Beriberi
Pulmonary hypertension

ABSTRACT

Objective: To study the effect of thiamine administration on the resolution of pulmonary hypertension in exclusively breastfed infants.
Design: Prospective cohort study.
Setting: Hospital based study of a tertiary care hospital.
Patients: A total of 29 infants with 17 males (58.6%) and 12 females (41.4%) were included in the study.
Intervention: In addition to the management of shock, right heart failure and renal failure, patients received intravenous thiamine 100 mg/kg IV followed by 10 mg/day till introduction of supplementary feeds.
Main outcomes measures: Resolution of shock, metabolic complications and pulmonary hypertension.
Results: Mean age at presentation was 78.45 ± 30.7 days. All infants were exclusively breastfed. 86.2% of mothers were on customary dietary restrictions. Biventricular failure and tachycardia was commonly present. There were four deaths in our series. Acute metabolic acidosis was a universal feature with a mean pH of 7.21 ± 0.15. Pulmonary hypertension was present in all patients on admission. Intravenous thiamine 100 mg/kg IV stat was given immediately after documenting pulmonary hypertension. Repeat echocardiography showed complete resolution of pulmonary hypertension.
Conclusion: Many infants present to us with Shoshin beriberi with unusually high pulmonary pressures. These patients respond to thiamine challenge with prompt resolution of metabolic complications and

Mechanically Milled Rice
Multiple Washing of Rice
Exclusive Rice Eating Mothers

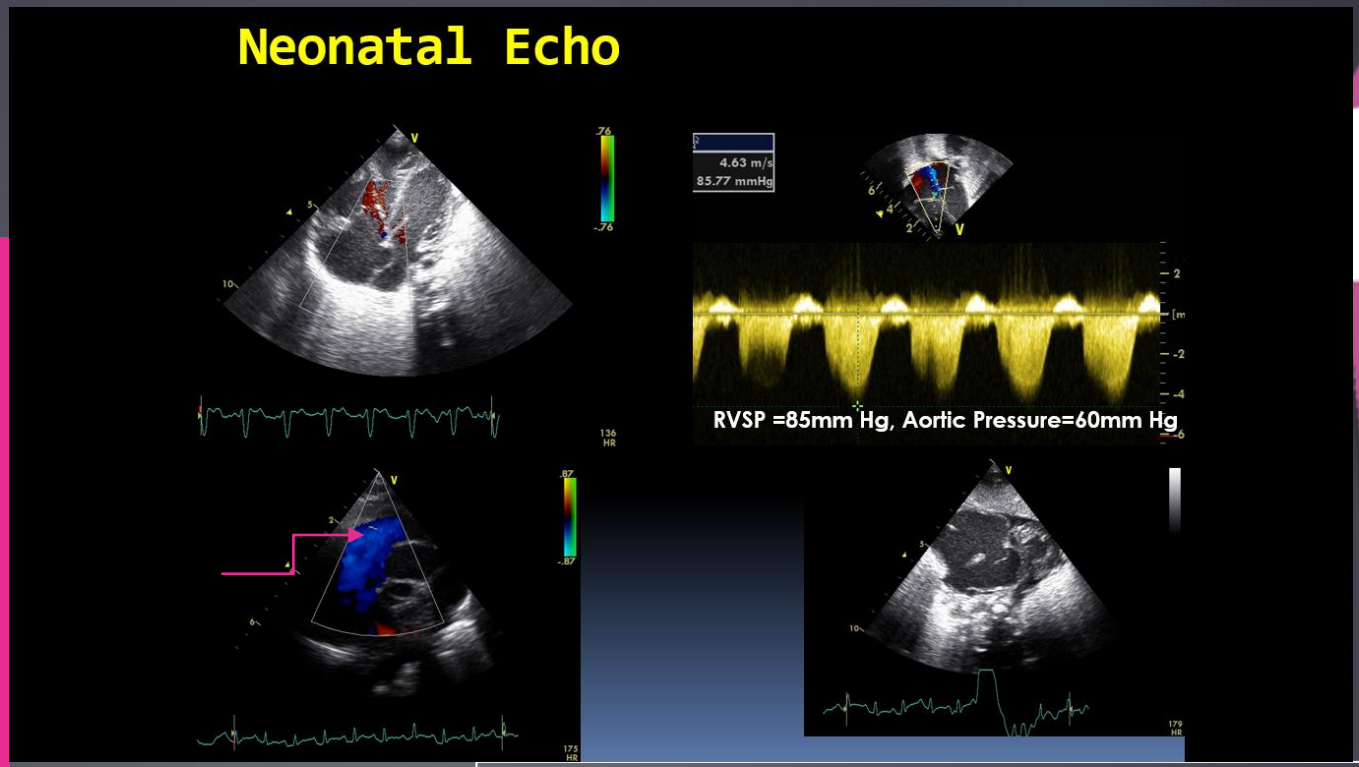
CASE # 5

16 Days Old Neonate

PE: CCF, Sats 85%

Possibilities:

1. Sepsis
2. Duct Dependent lesions
3. IEM
4. ??



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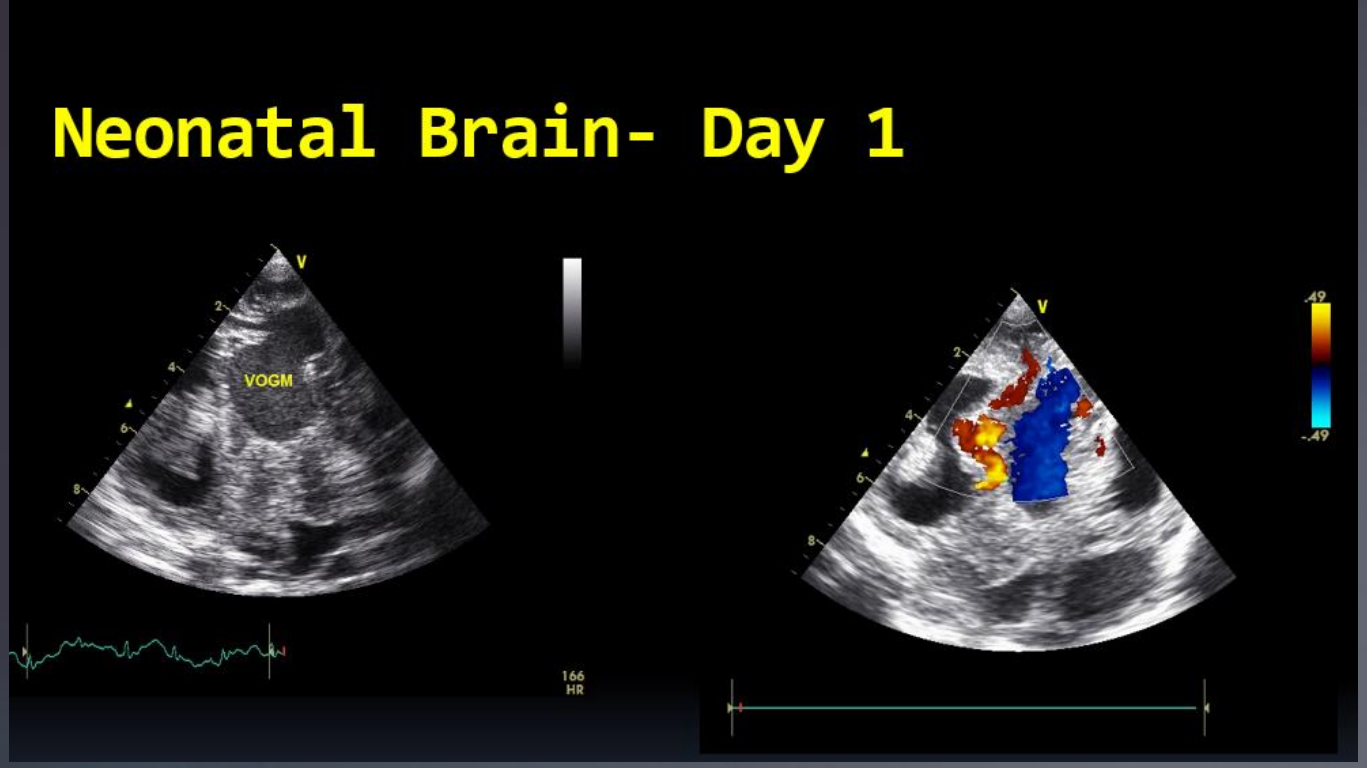
- Echo: Severe PAH, But Why?
- SVC is Unusually Dilated
- No Supracardiac TAPVC

Neonatal Brain- Day 1



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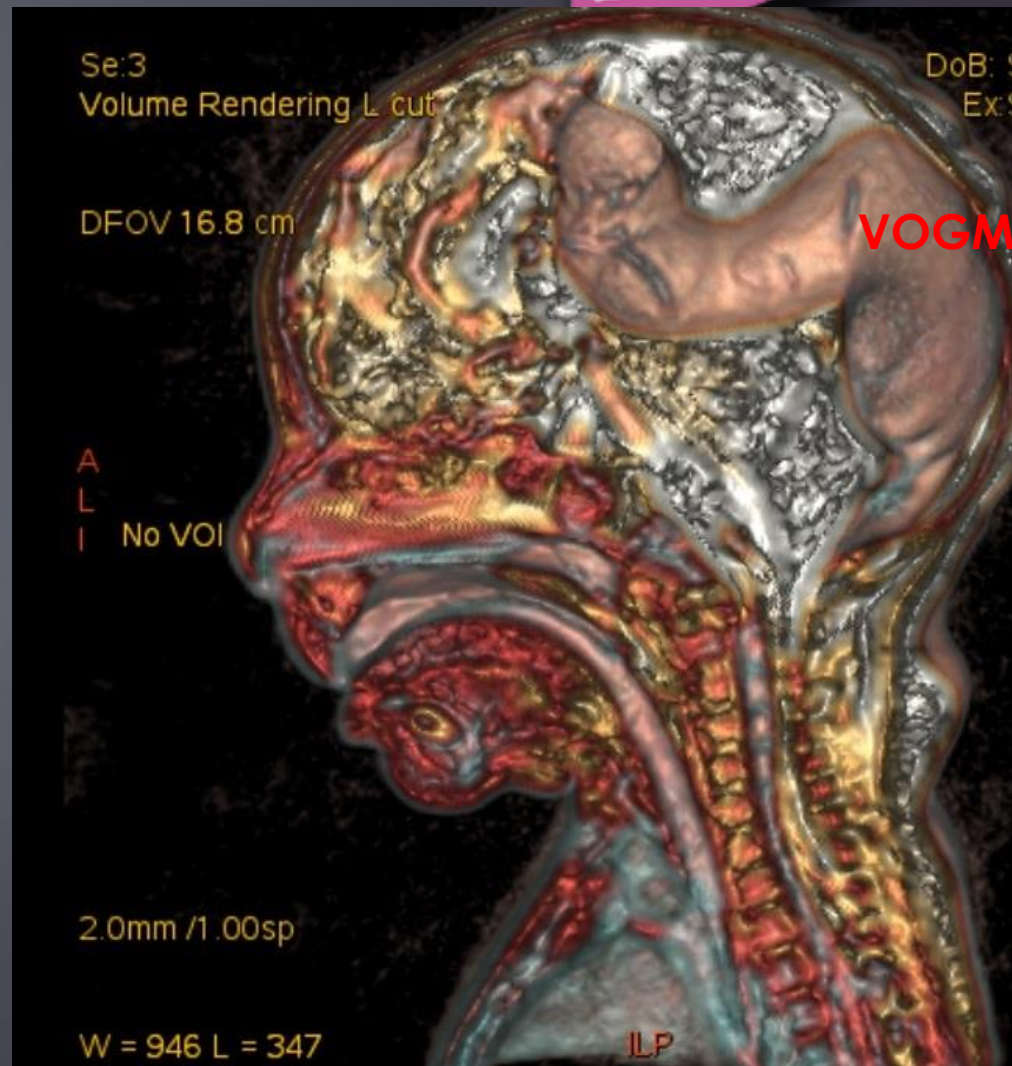

VEIN OF GALEN MALFORMATION WITH CCF & PAH
Grp . 5
Rx: Stabilization and Coiling
Extensive Feeders: Radio -ablation

Take Home Message: R/O AV Malformations in Unexplained PH.

CASE # 6

3 Yrs F/ Apparently Doing Well

H/o 2 Syncope While Jumping on Bed

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Pediatric Opinion : ? vasovagal

How To Approach?

Pediatric Exam: Normal

Neuro – Normal

CVS: P2 Loud, Slight Precordial Bulge

ECG – Sinus Rhythm, Normal QTc, RVH

+

Echo : OMG >> Severe PAH

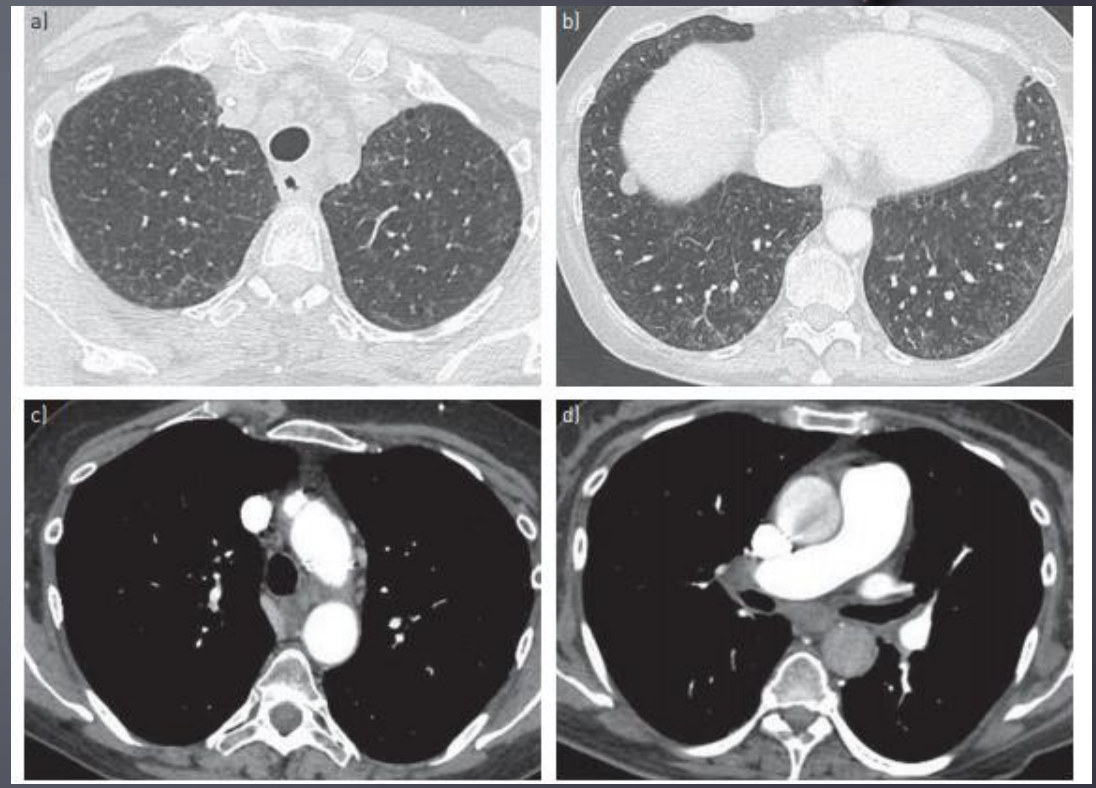
Structurally Normal Heart

Mild RV dysfunction

What next:

PFT: FEV1, FVC, TLC Normal

Pulmonary Vasodilators Started!



HRCT : PVOD

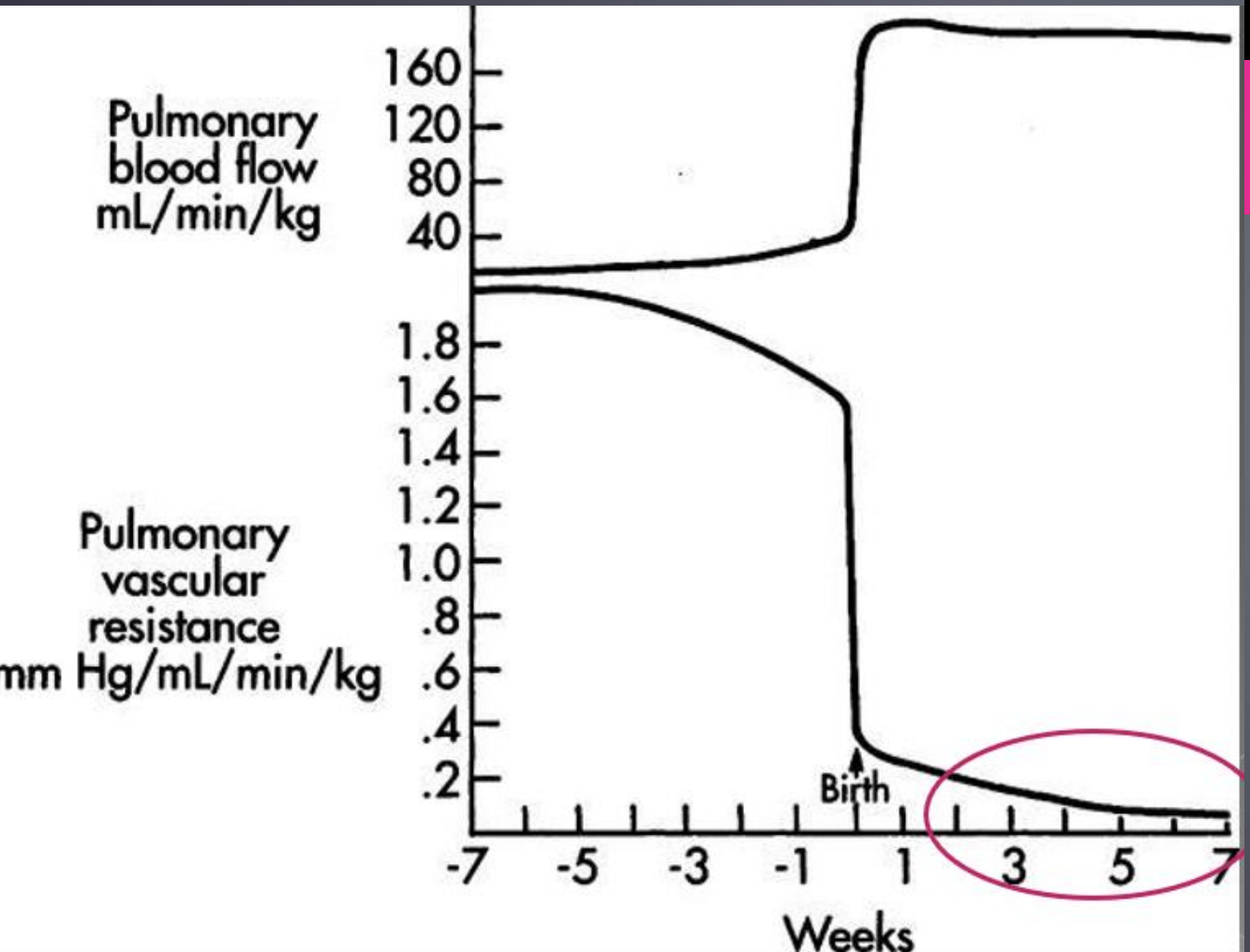
How To Approach?

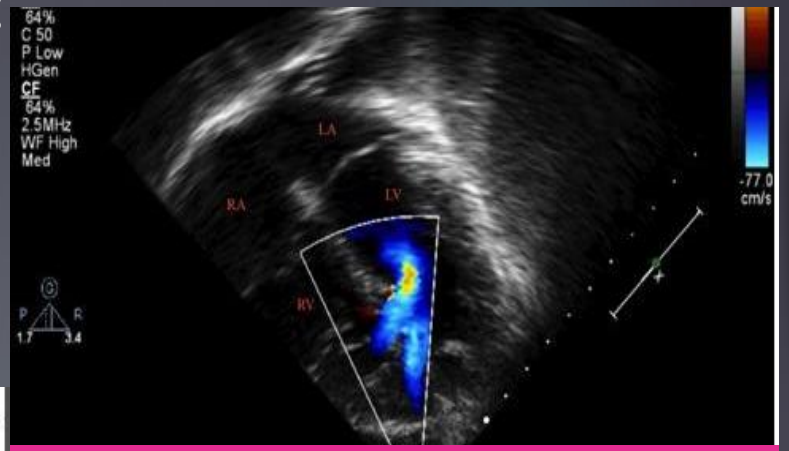
PVOD

- #3 diagnostic features:
- Centrilobular ground glass opacity
- Prominent Mediastinal Nodes
- Thickening of interlobular septa
- Predominantly involves small venules.
- Genetic Assessment. EIF2AK4. Autosomal Recessive Transmission.
- 1-year mortality 72%.
- Vasodilators Contra indicated
- Management: Bilateral Lung transplant, immunosupresive Rx, Supplemental oxygen &

CASE # 7

Term Baby, Murmur After 7 Days: VSD diagnosed , Tachypneic Frusemide Started Locally Delay Due to COVID, Reaches Us at 2 Mo of Age





Multiple Muscular VSD

Right to Left Shunt Why?

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Term Baby, Normal Anomaly Scan

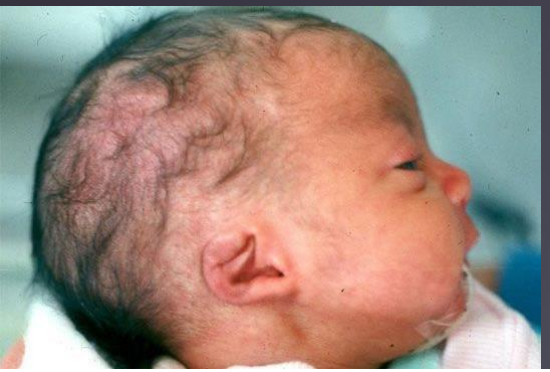
No Antenatal/Perinatal Event

Never in NICU

No Upper/Lower Airway Issues

Clinically not Down's Phenotype

No other hidden shunts



Genetic aetiology : Grp 1. 1.2

25-30% of IPAH are actually heritable PAH

Detailed Genetic counselling required

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Table 7 Recommendations on the Use of Genetic Testing and Biomarkers in Children with PH

Recommendations	COR	LOE
Genetic counseling is recommended for families with children diagnosed with IPAH or HPAH. (S7-1—S7-5)	I	B
Genetic counseling, if indicated, should be performed by a qualified individual with training in genetics and should precede genetic testing. Information on the disease and possible treatment options, prognosis, and psychosocial issues should be addressed. (S7-6)	I	C
Families of patients with syndromes associated with PAH should be educated on the symptoms of PAH. It is recommended to seek clinical evaluation if the child should develop symptoms of PAH.	I	C
Genetic testing for PAH-associated genes such as *ACVRL1*, *ABCC8*, *BMPR2*, *CAV1*, *ENG*, *TBX4*, *KCNK3*, and *EIF2AK4* can be useful in children with PAH of unknown cause to allow definition of PAH etiology, estimation of prognosis, and identification of family members at risk. (S7-2,S7-5—S7-10)	IIa	B
Genetic testing for the PAH-associated genes *NOTCH3*, *SMAD9*, *GDF2*, *AQP1*, *SMAD8*, *SOX17*, and *ATP13A3* may be useful in children with PAH of unknown cause and identification of family members at risk, although further evidence is needed to confirm pathogenicity of these mutations. (S7-1), (S7-11)	IIb	B
Children who are asymptomatic PAH mutation carriers should be screened with echocardiograms every 1—3 years for the presence of elevated RV pressure, and subsequently undergo additional diagnostic evaluation if clinically indicated.	I	C
Genetic testing of first-degree relatives of an index patient with PAH and a known disease-causing mutation is indicated for risk stratification and rationalizing surveillance.	I	C
Asymptomatic first-degree relatives of patients with HPAH without an identified PAH-associated gene mutation should be screened with serial echocardiograms for the presence of elevated RV pressure, and subsequently undergo additional diagnostic evaluation if clinically indicated.	I	C

NT OF MEDICAL GENETICS

MICROARRAY ANALYSIS REPORT

Referral Hospital	Manipal Hospitals
Sample Collection Date	27-04-2020
Sample Received Date	27-04-2020
Report Date	21-05-2020
Specimen	Peripheral Blood

ES / HISTORY:

ia and low set small cupped ears

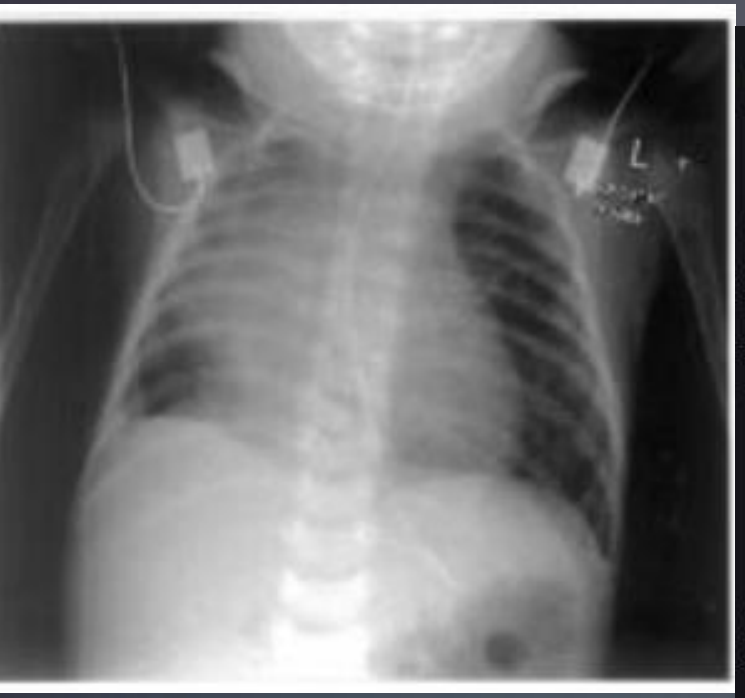
RESULT

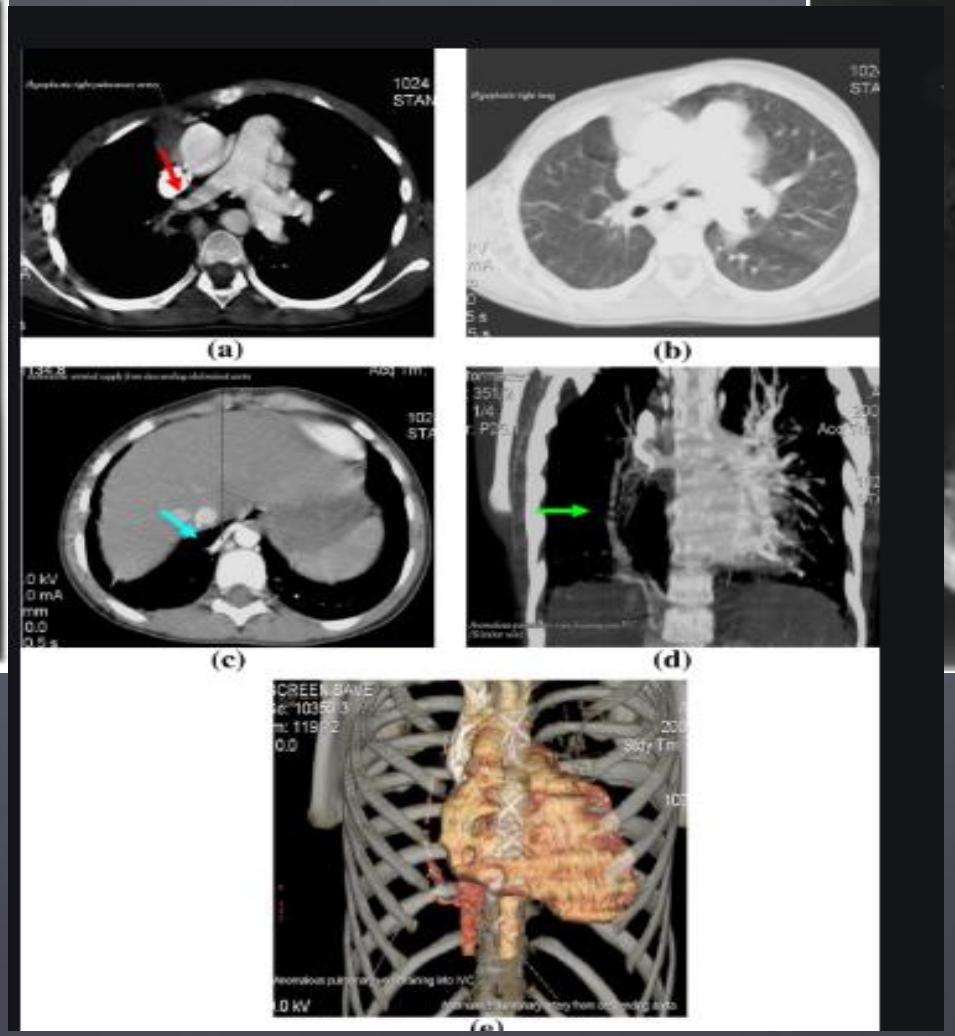
arr [hg19] 1p31.3 - p22.2 (66421418-90570894)x1

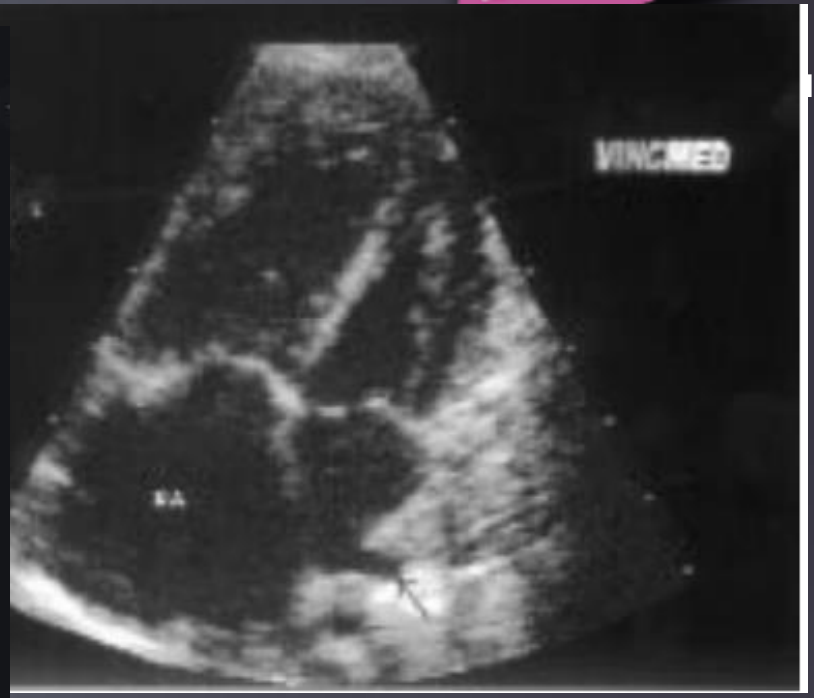
CN State	CNV Type	Cytoband	Size (KB)	Chr. Coordinates	Classification
1	Loss	1p31.3 - p22.2	24149.477	chr1:66421418-90570894	Pathogenic

CASE # 8

9 Days F/Term/SGA/Admitted with Respiratory Distress, On HFNC Sats =88%, Afebrile, ↓ Air Entry Right Side, ? Heart Sounds More On Right



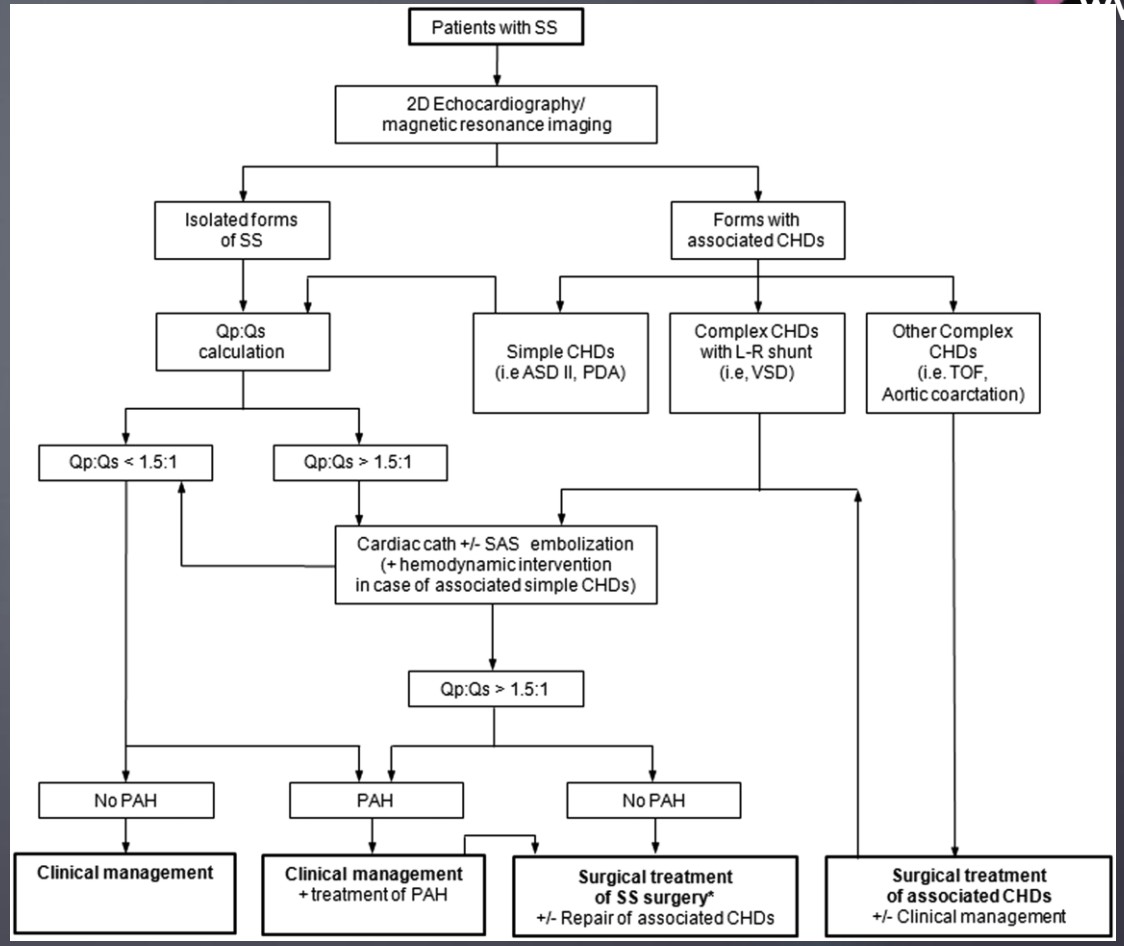




Diagnosis : Scimitar Syndrome

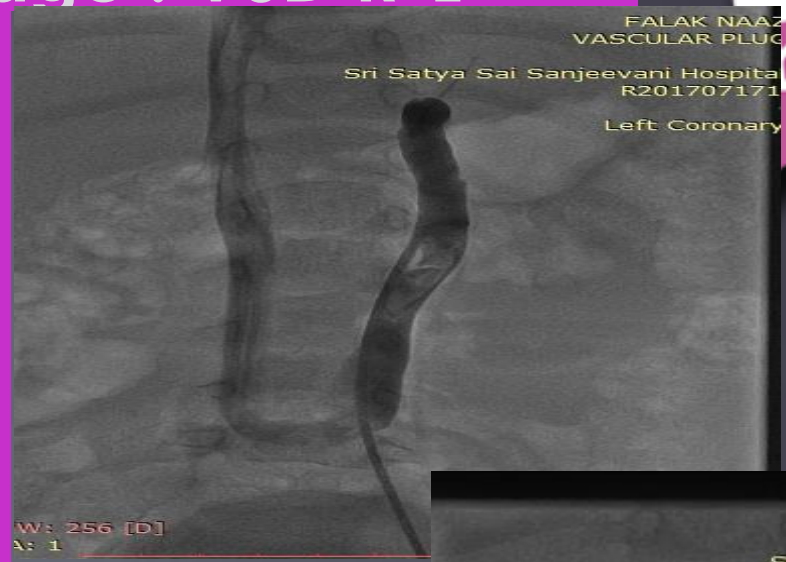
Survival poor in infantile presentation, associated CHD & PAH
Late Stenosis of Pulmonary vein to be looked. Adult survival `80%, Mortality 18.8% infancy

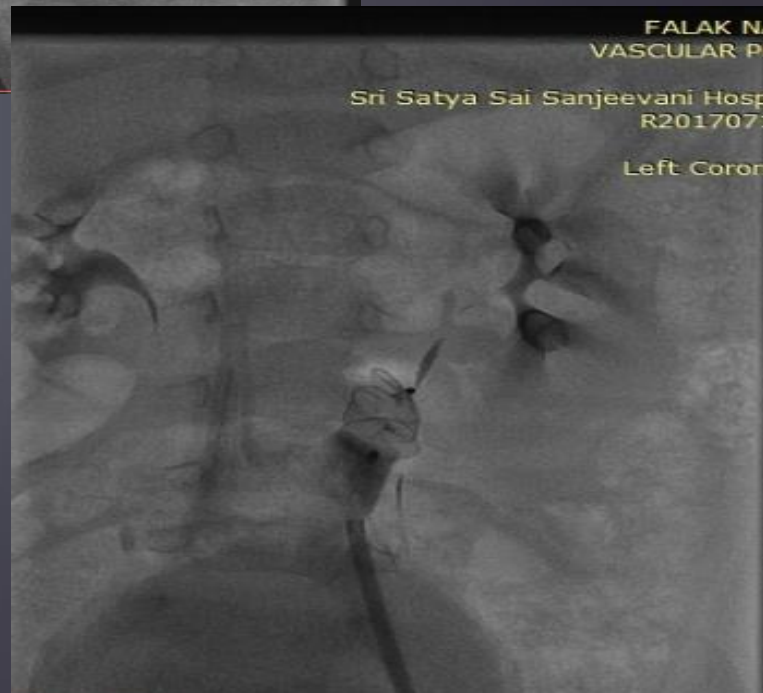
- Anomalous venous drainage of part /whole of right lung to IVC
- Right lung hypoplasia
- Aorto-pulmonary collaterals
- Associated CHD
- Presentation from neonates> Infants>adolescents>adults
- Symptoms: respiratory & cardiac predominant (CCF , PAH)



CASE # 9

8 month old ,Wt 6 kg
CHF with PAH,cyanosis (SpO2 78%)
Outside echo at 2months of age : VSD R-L





BABY heart

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CXR: cardiomegaly with increased PBF

Repeat echo:

large Perimembranous VSD+mid muscular VSD, ASD ,

Dominant R-L shunt, severe PAH,

"Suspicion of abnormal hepatic venous channel seen " in

subcostal imaging in liver tissue: Also seen in Abdominal

Doppler

CT angiography : large Type II Abernathy malformation

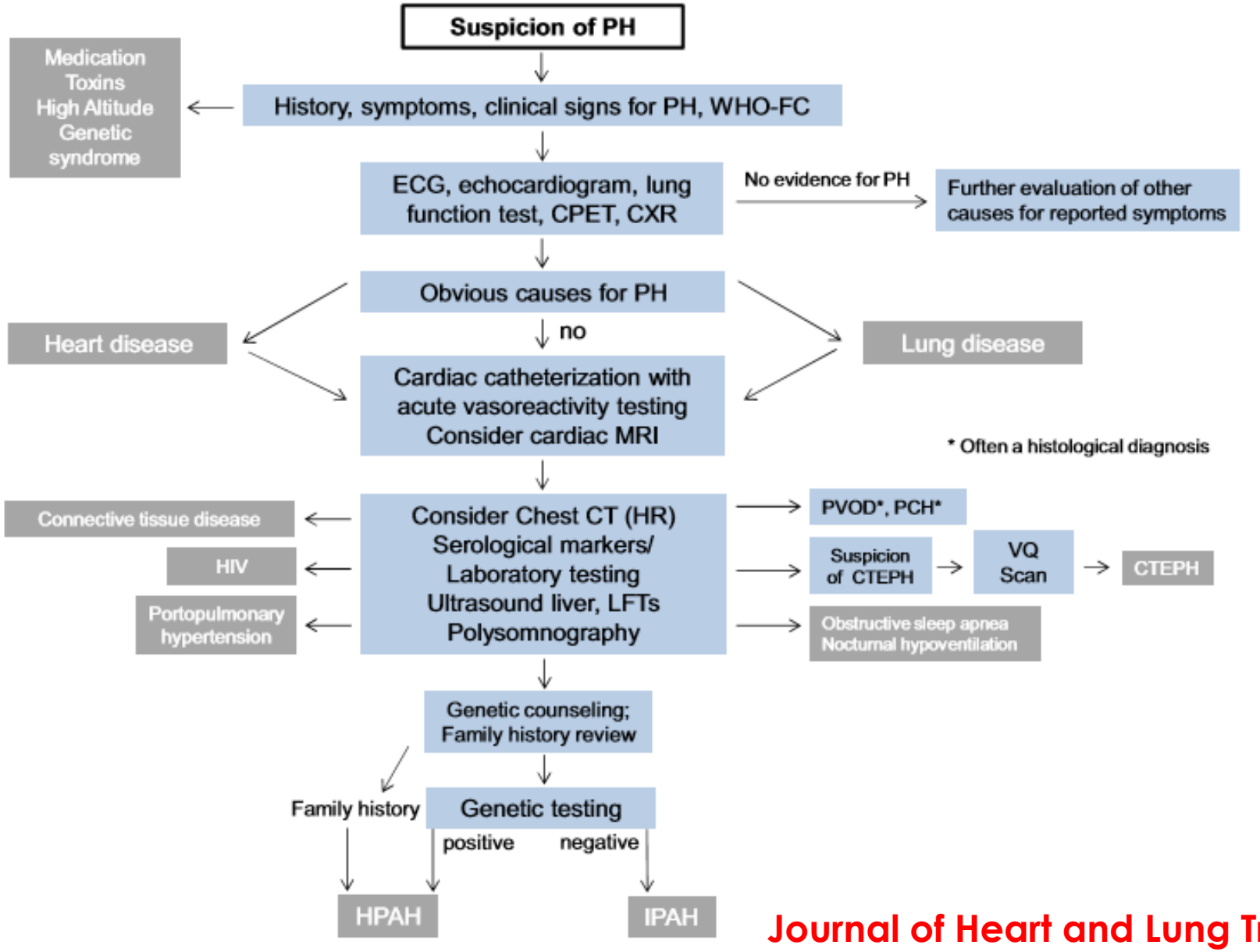
12mm Vascular plug was used to successfully close the

Venovenous collateral

Abernathy malformation is one of the causes of

Diagnostic Algorithm in PH

Indian Setup:
How Much Is Possible ?



Journal of Heart and Lung Transplantation, Sep 2

When To Go For Cardiac Catheterization?

- Ideally in all
- Diagnostic and prognostic implications
  - Before start of therapy
  - Before change of therapy
  - Clinical Worsening
  - Before intervention, before transplant
  - Assessment of operability
  - Repeat cath after 6-12 months on vasodilator

Should We Stop Pulmonary Vasodilator Drug Before Cath?

- Ideally not . May precipitate symptom
- Local/GA
  - GA is high risk for PH patients but smaller /sicker /syndromic baby/ventricular dysfunction/airway issues one need to do under GA

Cardiac Cath In PH With CHD

- Very important and decision should be taken only after detailed clinical evaluation
- Basal cath data is very crucial
- Diastolic pressure gradient should also be noted
  - Studies showing higher DPG with poor long-term outcome
- Ideally
  - Inhaled NO
  - IV sildenafil
  - Illoprost(not available in India)
- O2 commonly used
  - Fallacy :
    - Vo2 changes 22-30% with high FiO2 and affecting all calculations
    - Dec in CI,stroke volume and Incr in SVR with O2

Clinically borderline operable patients

Cath data should be interpreted very carefully

In doubt: better not to intervene

Cardiac Cath In PH, No CHD

- Cath ideally in all
- Dx and prognostic
- NO choice
- Criteria (modified Barst)
  - Decrease in mean PAP >20%
  - Increase or no change in Cardiac output
  - Dec or No change in Rp/Rs
- Stibon criteria
  - Decrease in mean PAP >10 ,absolute <40mmHg
  - Increase or no change in Cardiac output

- UK registery with use of Barst Crt
  - Not associated with
    - better survival
    - Response to CA Blocker
  - They found PVRI <4.5 better indicator

Gold standard of operability

- Age
- Clinical findings
  - CXR/ECG/Echo
- Never ignore basal data
- Why doing vasodilator testing
  - Need to reassess our technique
  - Role of Calcium Channel Blocker in Vasoreactivity Test??

Medical Management of PAH
PART1: General Measures

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- Oxygen : If Sats <92%, PAo2<60mm Hg, PH + Lung Ds(BPD/CLD etc), in high altitude, during air travel
- Diuretics & Digoxin: If documented CCF &/or RV Failure. Caution: ↓ Preload & ↑ PVR may ↓ C.O
- OSAS & GERD management if present
- Urgent Rx of RTI
- Immunizations

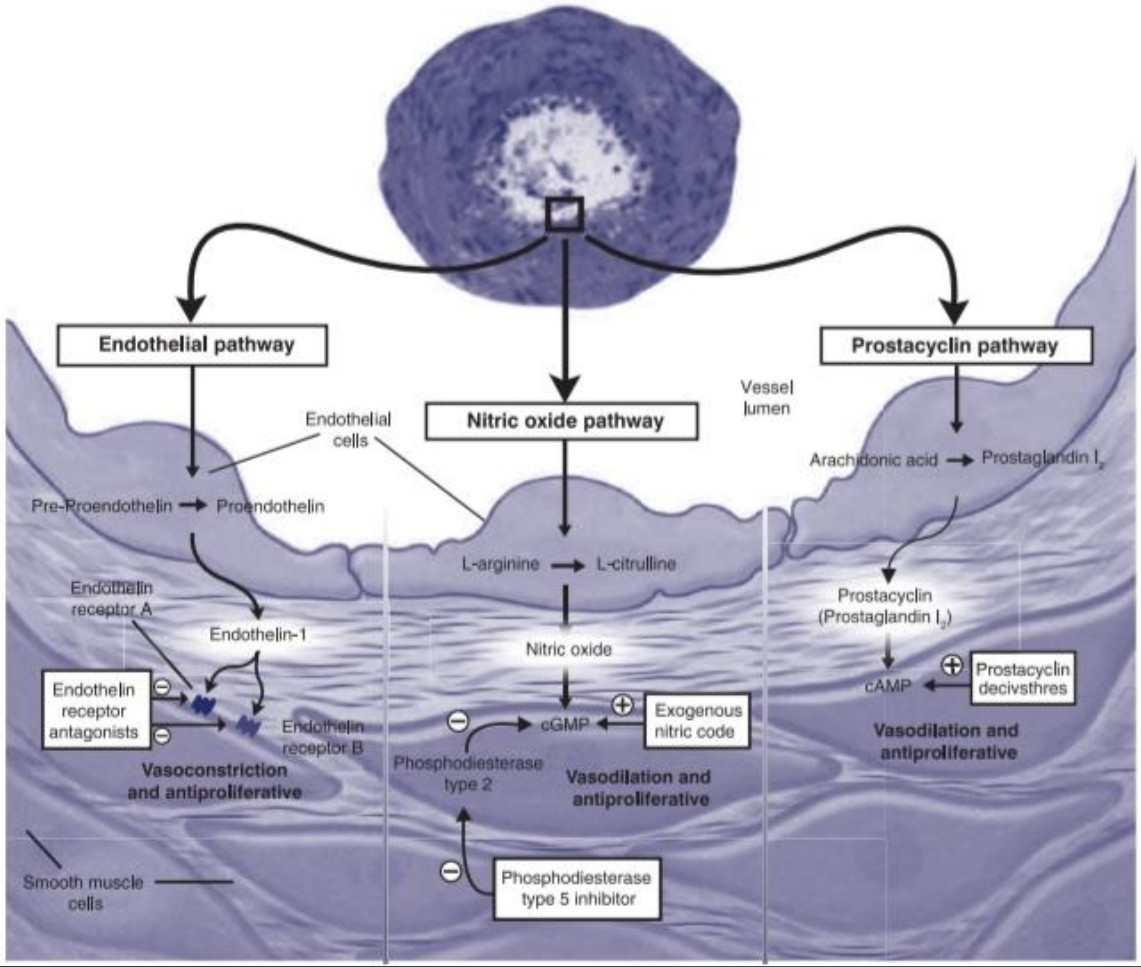
- Anti-coagulation in IPAH/HPAH/CTEPH, Hypercoagulable states/indwelling IV Port : beware of the risks
- IE Prophyaxis: esp. in Cyanotic CHD
- Exercise : FC I/II –light to moderate aerobics, FC III/IV/syncope : avoid physical exercises, competitive sports. Keep child Happy!
- Reproductive counselling , Remember Teratogenicity Too, Pregnancy Issues
- Non cardiac surgery

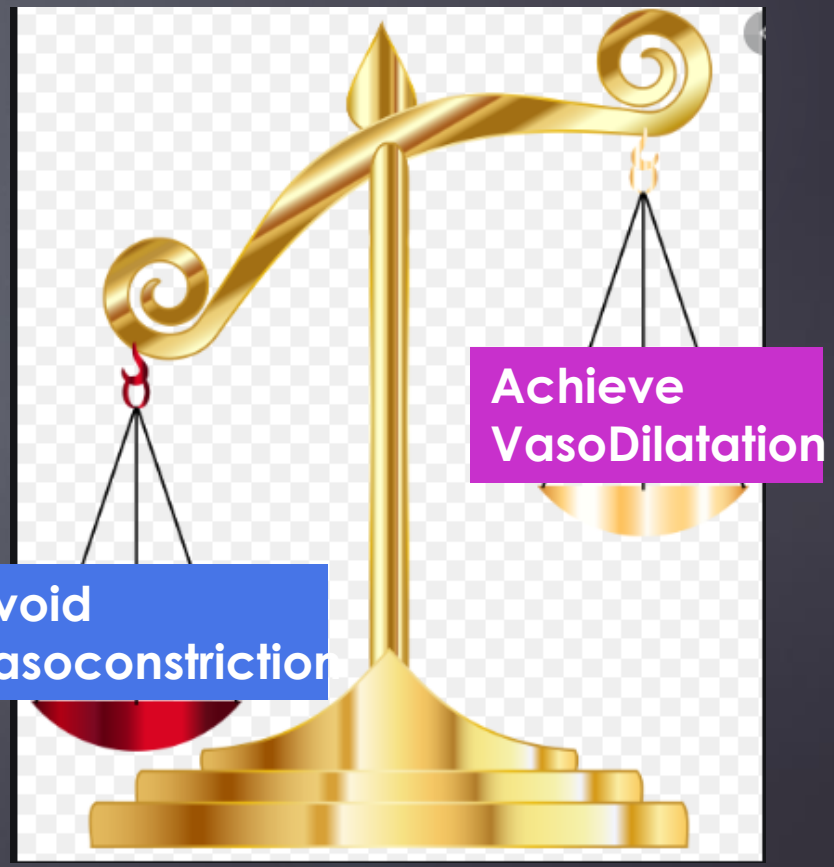
Unanticipated PH crisis

- Provide PALS
- • Administer supplemental oxygen
- • Avoid hypercarbia
- • Correct metabolic acidosis
- • Avoid hypovolemia/provide careful fluid resuscitation
- • Administer inhaled nitric oxide
- • Provide analgesia/sedation/avoid painful stimuli/strong light/noise
- • Support cardiac output with inotropes. Call For Bedside Echo.
- • Mechanical support (eg, extracorporeal membrane oxygenation) may be used in some cases

TARGETED PH THERAPY

Endothelial dysfunction is typical in PAH and involves an increased production of vasoconstrictive compounds such as endothelin and thromboxane and decreased production of vasodilatory compounds such as prostacyclin and nitric oxide. Each substance may mediate multiple effects (Fig 2).[3]





For Practising Clinicians

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GROUP A

- Sildenafil
- Bosentan
- Combo of 2

GROUP B

- Occasionally Ambrisentan
- Occasionally Tadalafil
- Combo of Above

- Inhaled Iloprost
- Intravenous Epoprostenol
- Subcutaneous & Oral Treprostinil

GROUP C
Approved in pediatrics, Not Available in India

GROUP D
Not Approved in pediatrics, Available in India

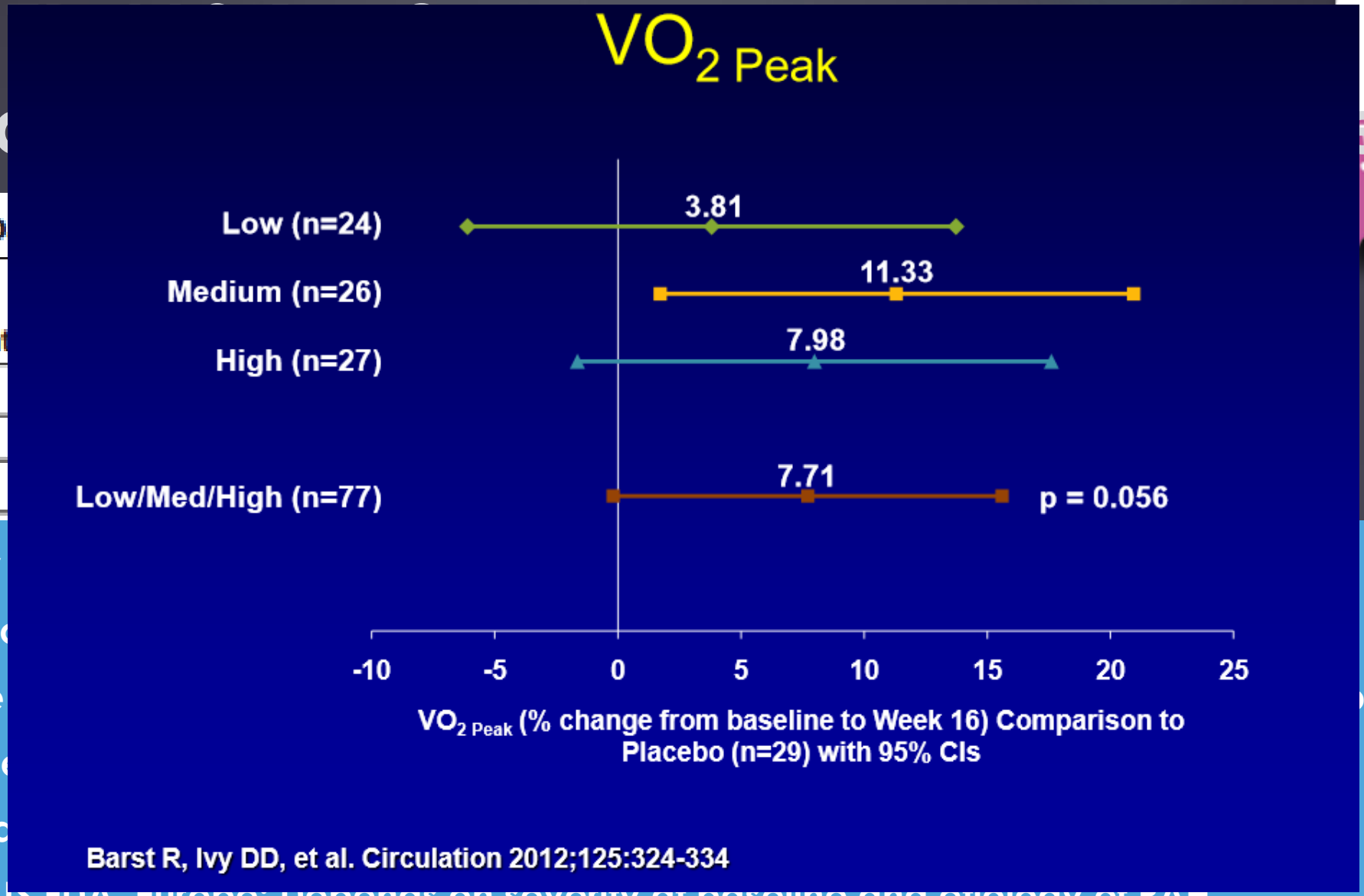
Macitentan
Riociguat
Selexipag

HOW SAFE IS SILDENAFIL IN PEDIATRICS?

STARTS (Sildena

Sildenafil Thrice-D

Body Weight
≥8 to 20
>20 to 45
>45



N=234, Primary

Low Dose As G

10.2% increase

roved.

STARTS 2 : Furth

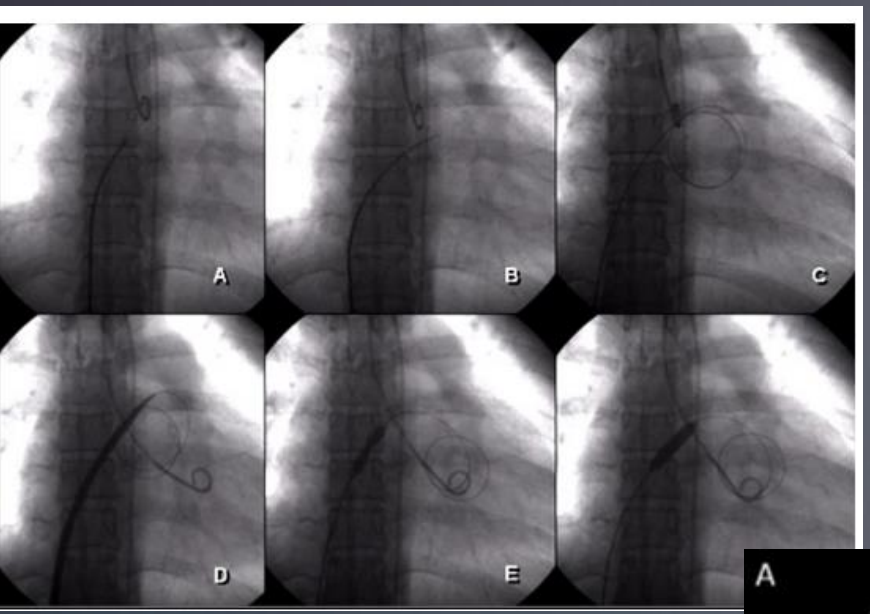
More Complic

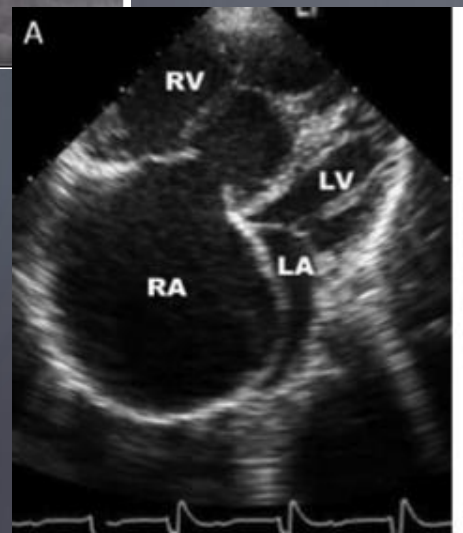
Cautioned by US FDA, Europe: Depends on severity at baseline and etiology of PAH

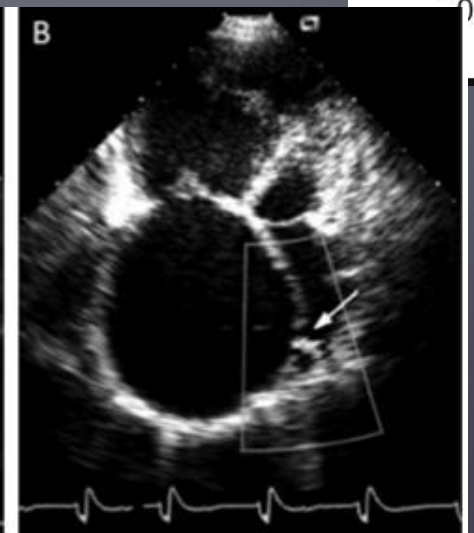
Message: Use Judiciously, Monitor and Know when to Stop!

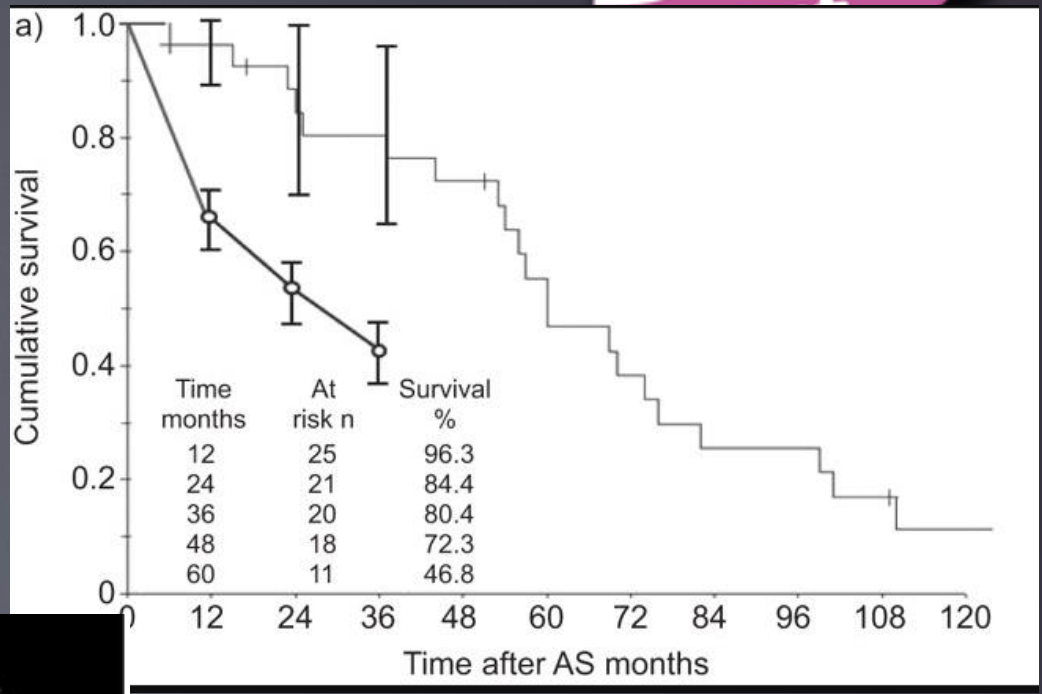
- Balloon Atrial Septostomy

IF PAH IS REFRACTORY TO MEDICINES: IS THERE A WAY AHEAD?

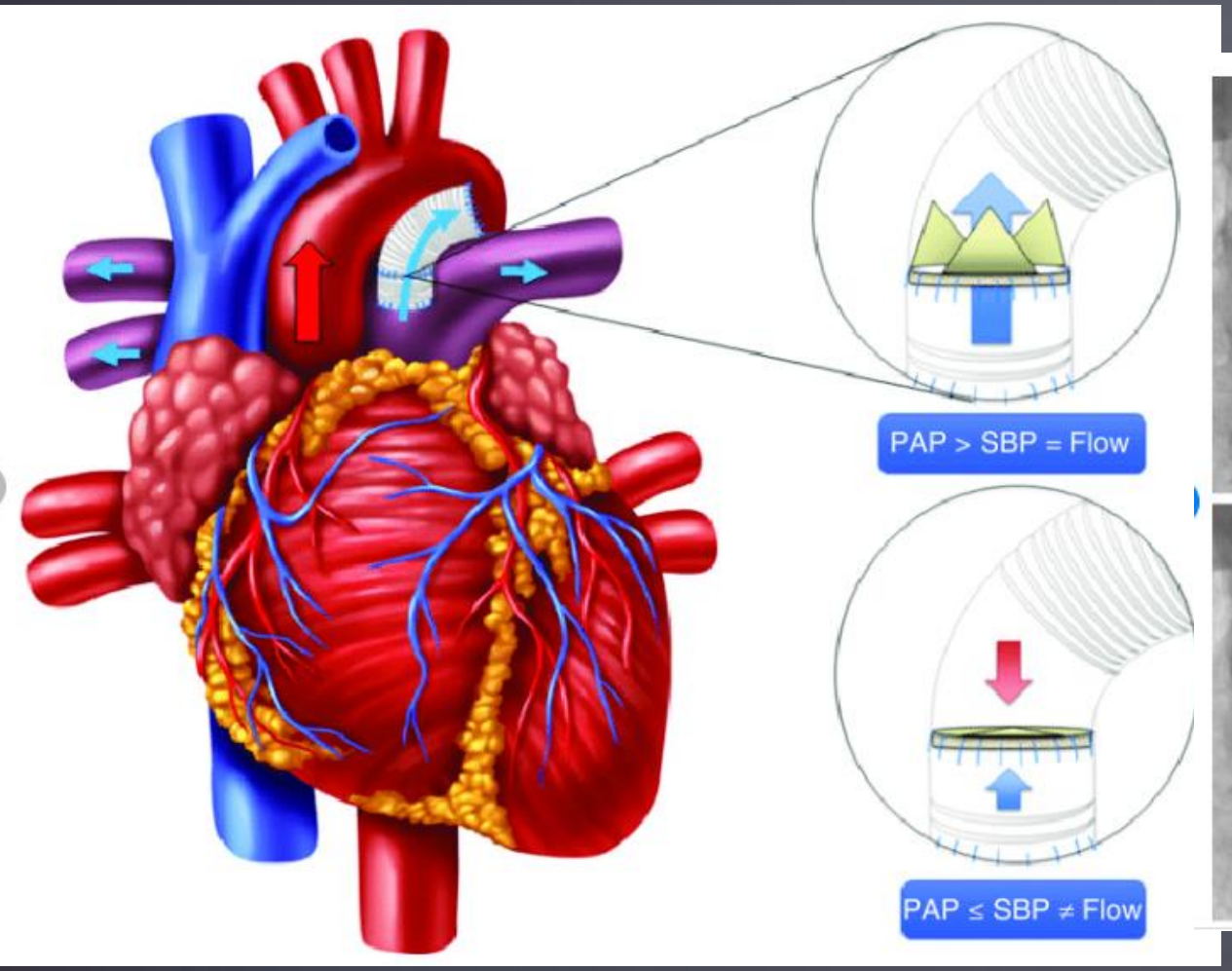


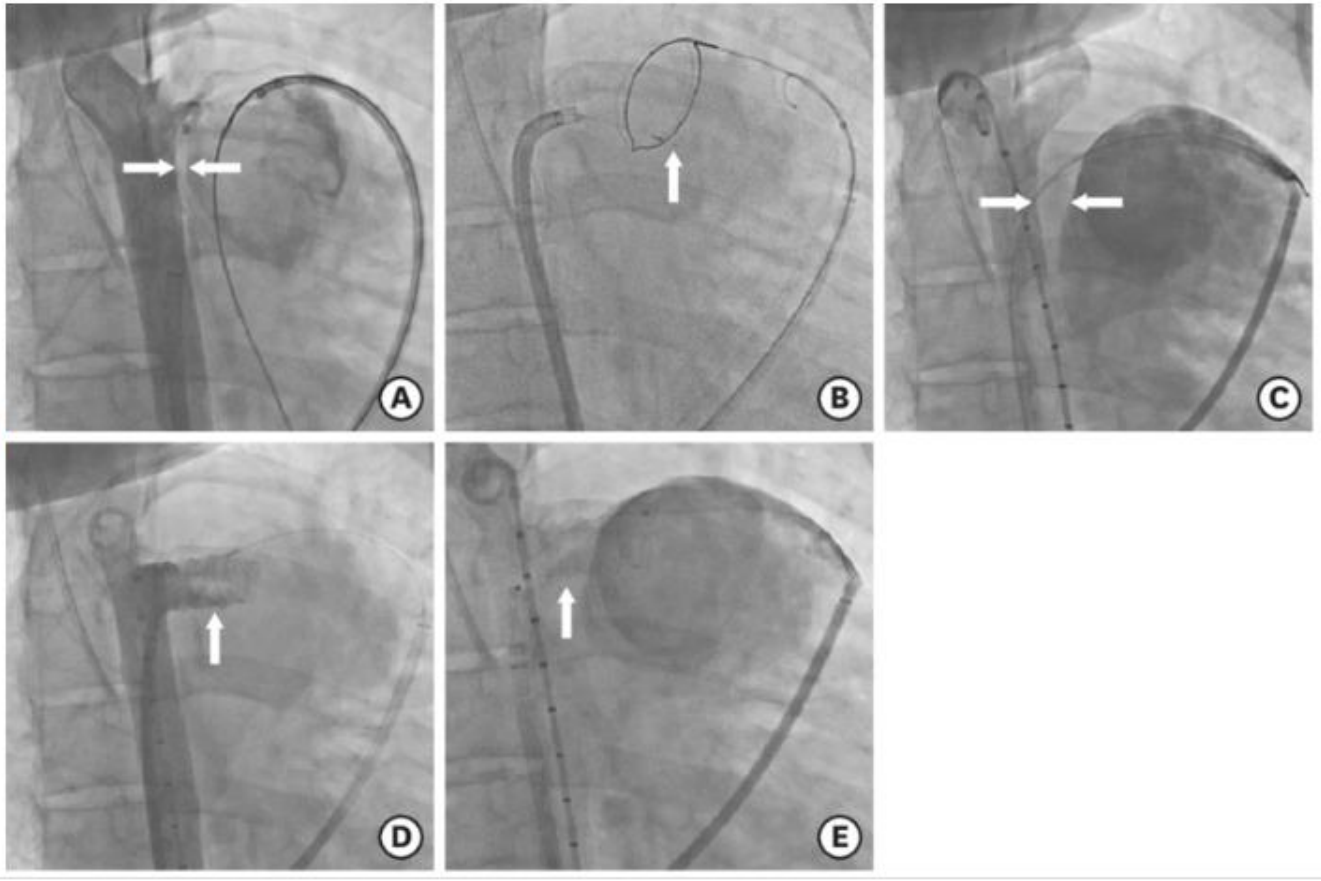






Reverse Pott's Shunt Only if Suprasystemic PAH





General Follow Up

- Most patients every three to six months
- More frequent visits for patients with severe disease and after therapeutic changes
- Follow-up visits:
  - assess symptoms & signs of right heart failure
  - exercise tolerance(6 minutes walk test)
  - BNP level at each visit(corelate well with NYHA class)
  - medication side effects &dose adjustments
  - echocardiogram.
  - Repeat cardiac catheterization is generally recommended within 3 to 12 months after starting therapy or with clinical deterioration .

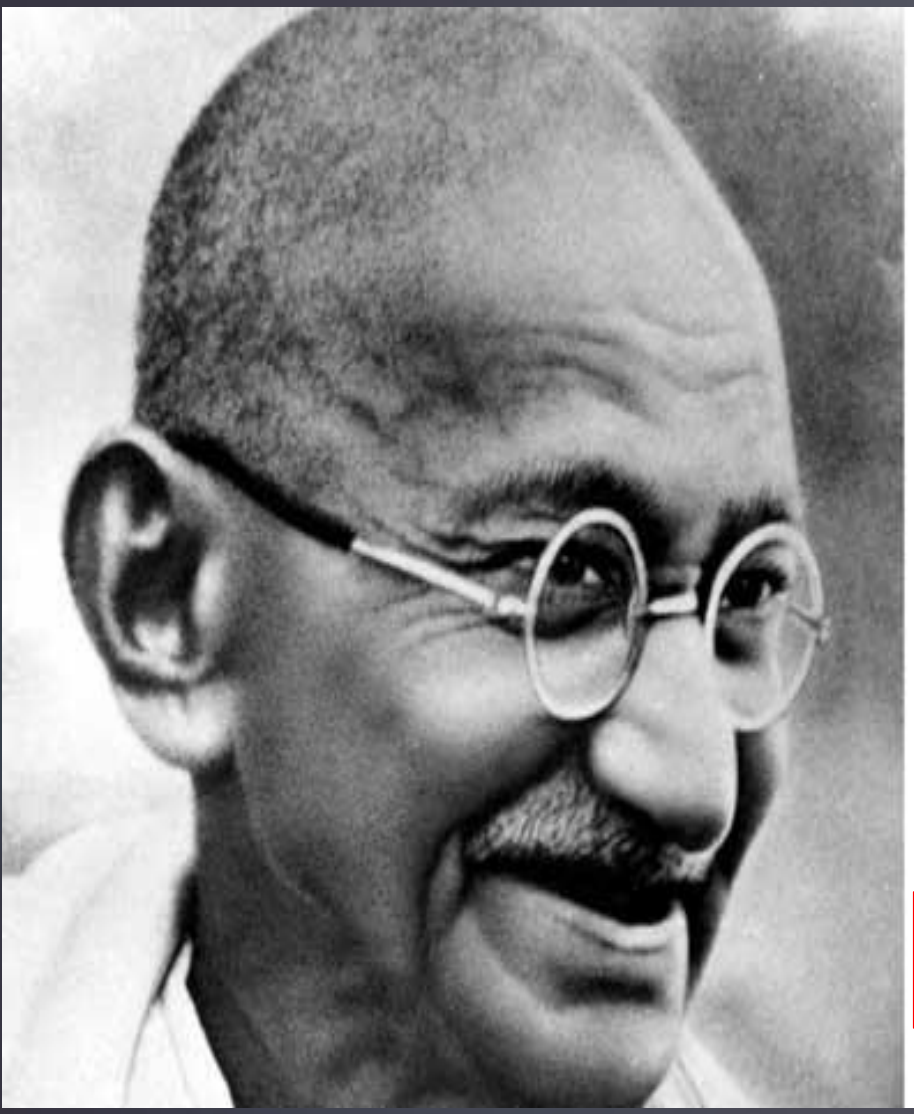
Take Home Clinical Message :

- From Syncope/Cyanosis/ Growth failure,

  Children manifest very differently in each PAH case
- Thorough Head to Toe Examination Must, Think and Think.
- ECG, CXR and ECHO are first investigations
- Echo provides a rapid non invasive estimation of PAH, Excludes CHD, Assesses Severity & Prognosticates
- Other investigations to be Tailor Made for the Child
- Right Heart Cardiac Cath is The Gold Standard,but in samll babies sometimes you need to start medication without cardiac cath

KINDLY REMEMBER

- In all PH:you don't need vasodilators
- Always try to rule out treatable causes because IPAH has guarded prognosis in pediatric age group
- Don't start pulmonary vasodilator empirically
  - Detailed work up is must
- Few Medications Available, Know Which to Use or Not Use.
- It's a Teamwork, Phone a Friend ! YES WE CAN!



"Live as if you were to die tomorrow. Learn as if you were to live forever."

- Mohandas Karamchand Gandhi

Stay Safe, Happy & Communicate Empathy in this Communicable World!

BABY heart

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