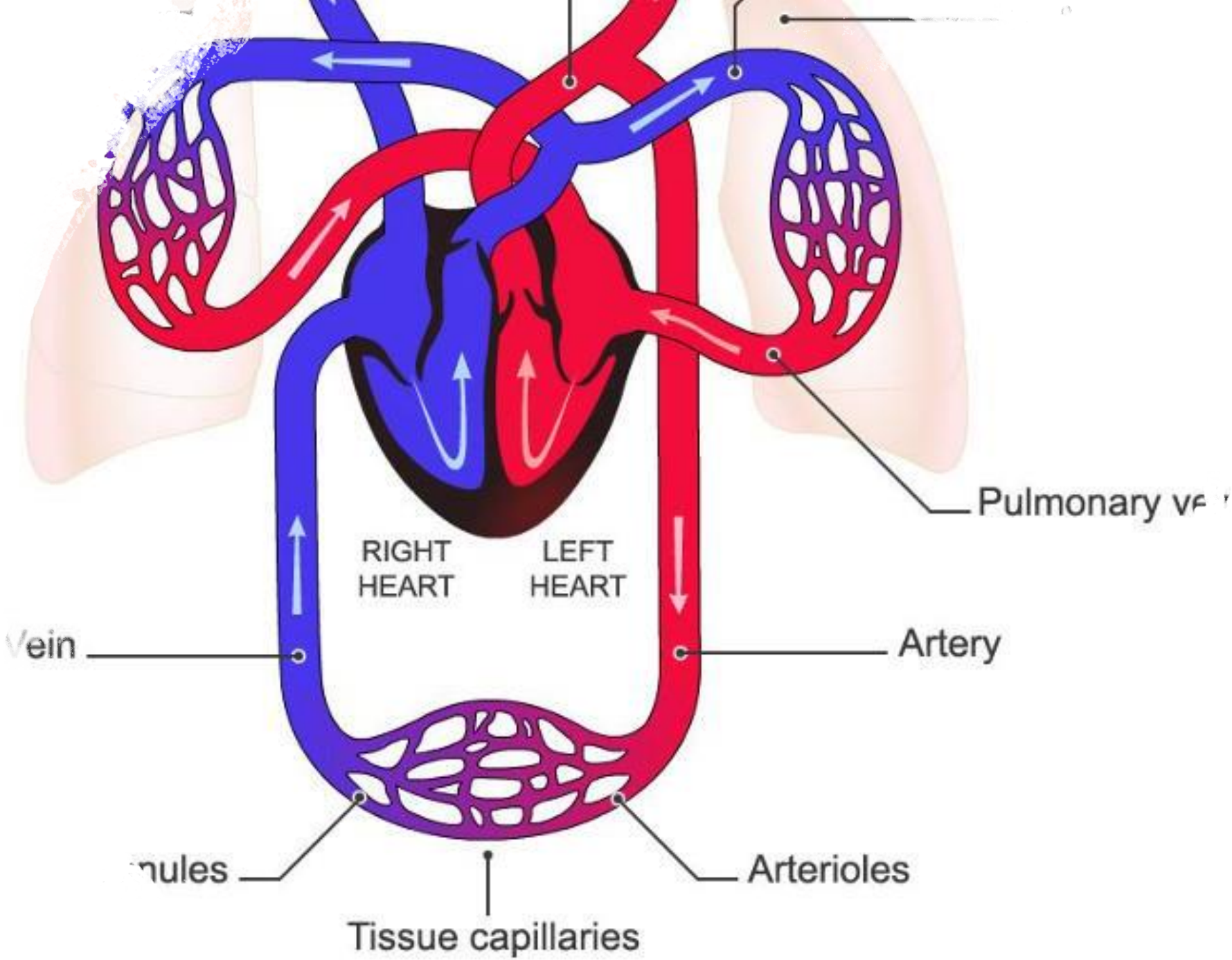

RIGHT HEART
LEFT HEART
Pulmonary ve
Artery
Arterioles
Tissue capillaries

PAH in children – Evaluation and Management

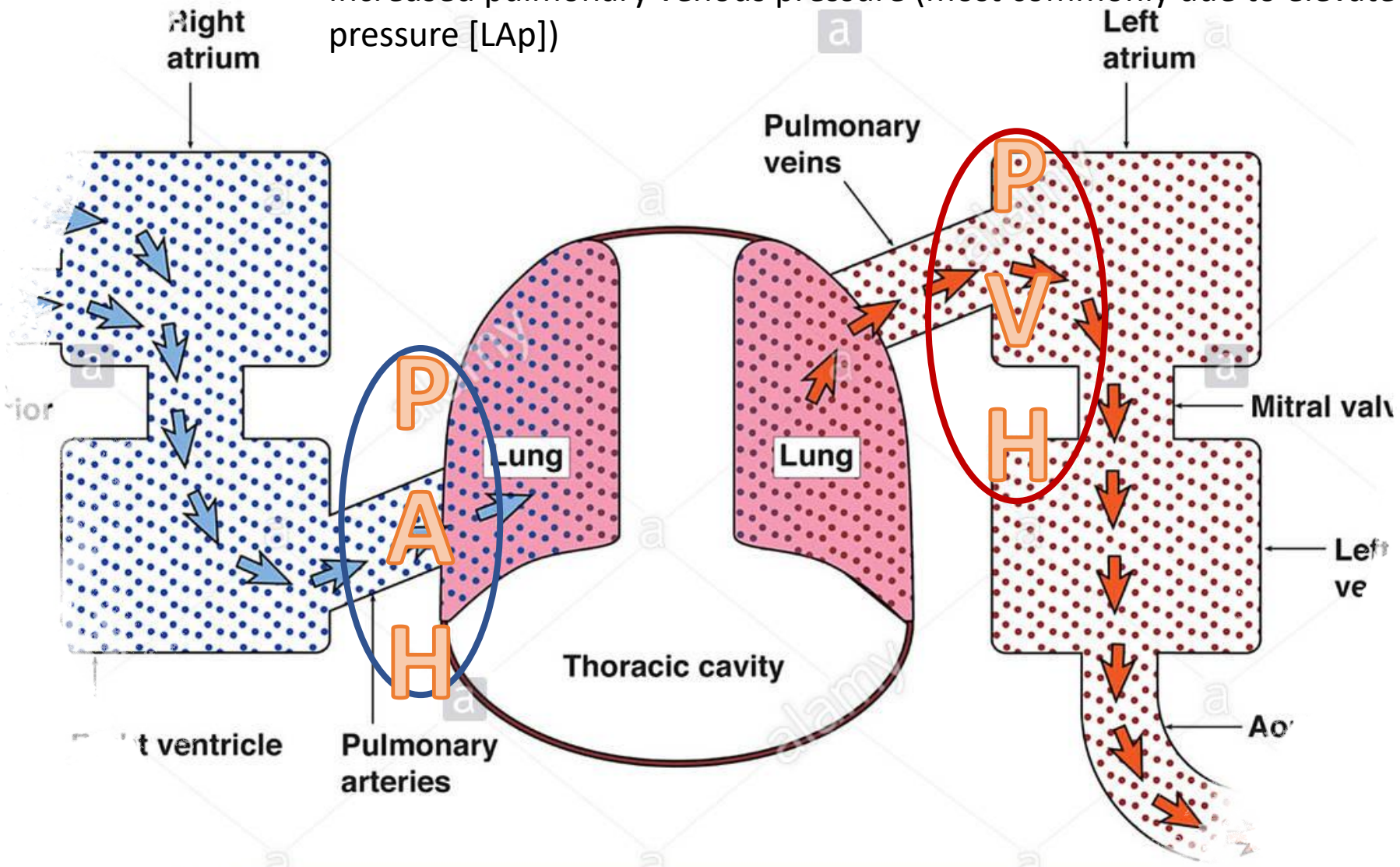
Sreekanthan Sundararaghavan

KK Women and Children's Hospital, Singhealth

Terminology in PH

- **Pulmonary hypertension (PH)** – Mean PAP ≥25 mmHg
- **Pulmonary arterial hypertension (PAH)** – PAP ≥25 mmHg and elevated PVR with normal pulmonary venous pressure (pulmonary artery wedge pressure [PAWP] <15 mmHg)
- **Pulmonary venous hypertension (PVH)** – PVH refers to elevations of pressure in the pulmonary venous and pulmonary capillary systems (PAWP ≥15 mmHg)
- **Transpulmonary gradient (TPG)** – Mean PAP - left atrial pressure (LAp)
- **Pulmonary vascular resistance (PVR)** – PVR = TPG / Qp
  - PVR is a measurement of the resistance in the pulmonary circulation. Elevated PVR indicates reduced cross-section area.
- **Pulmonary hypertensive vascular disease (PHVD)** – PHVD (previously called PVOD) PHVD is characterized by elevated PVR and/orTPG

Decreased cross-sectional area of the pulmonary vascular bed
Increased pulmonary blood flow (Qp)
Increased pulmonary venous pressure (most commonly due to elevated left atrial pressure [LAp])



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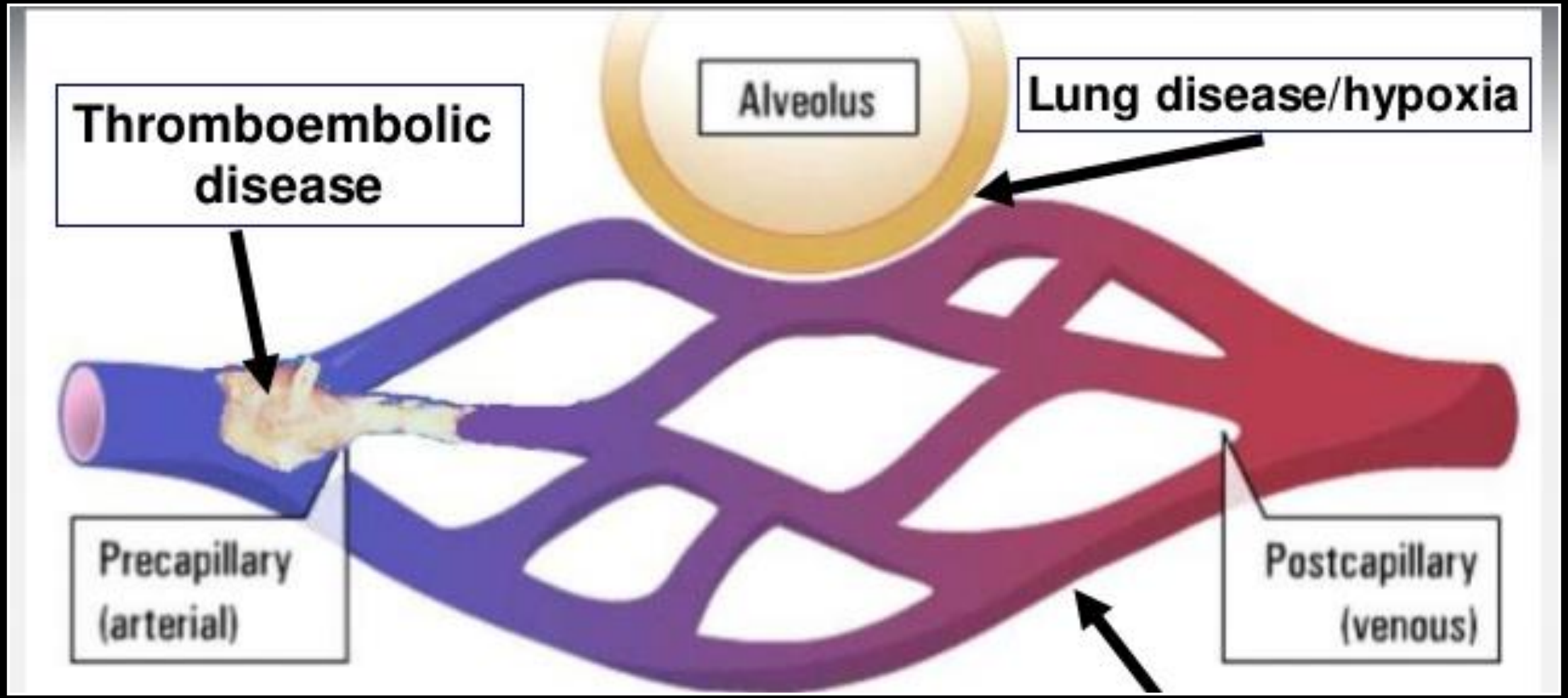

Thromboembolic disease
Alveolus
Lung disease/hypoxia
Precapillary (arterial)
Postcapillary (venous)

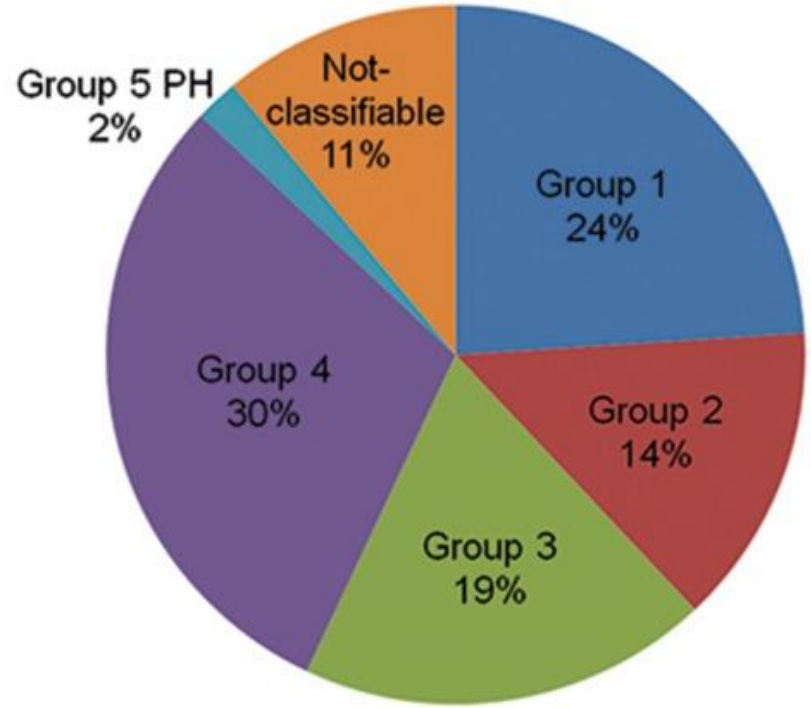
Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension (WSPH)

NICE 2018

Pediatric PAH-CHD

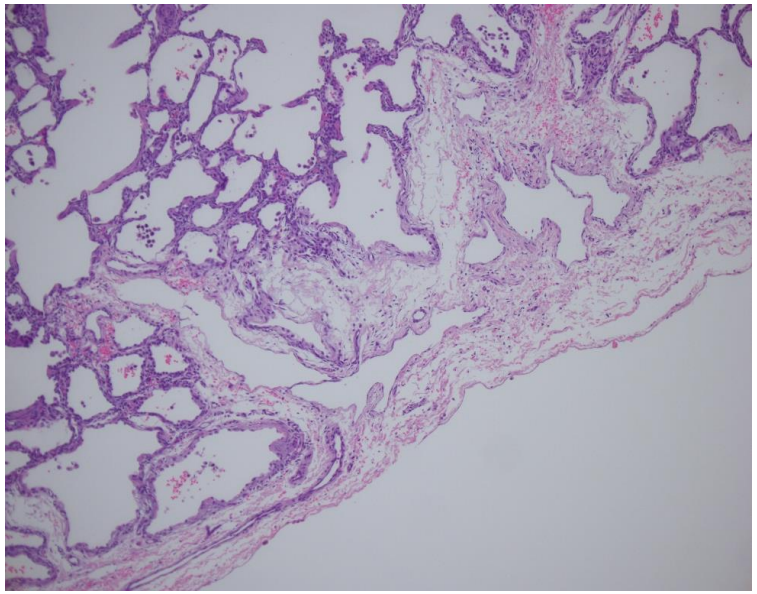
Clinical classification for Pulmonary Arterial Hypertension associated with Congenital Heart Disease

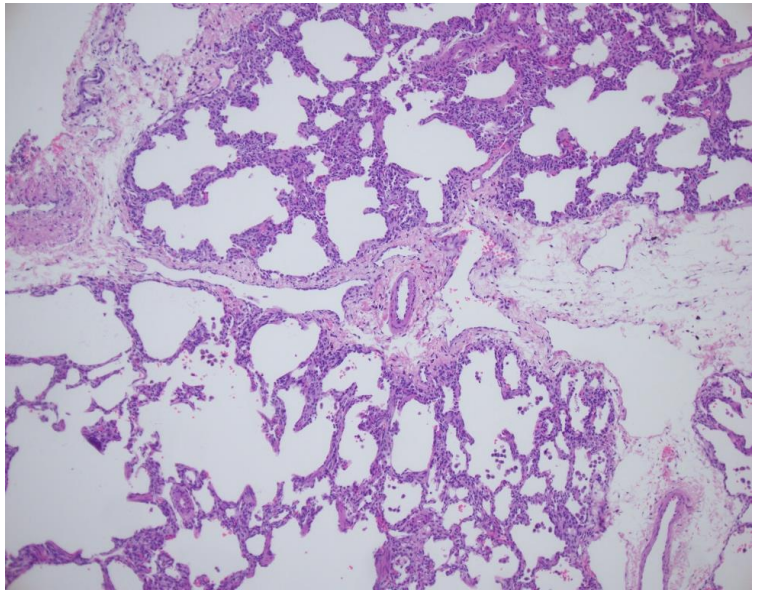
5th WSPH, Nice, 2013



Group 1 (Eisenmenger syndrome)
Group 2 (PAH due to left-to-right shunt)
Group 3 (PAH with coincidental CHD)
Group 4 (Post-operative PAH)
Not-classifiable PAH-CHD

1. Prenatal or developmental pulmonary hypertensive vascular disease
   - 1.1. Associated with maternal or placental abnormalities
     - 1.1.1 Pre-eclampsia
     - 1.1.2 Chorioamnionitis
     - 1.1.3 Maternal drug ingestion (Nonsteroidal anti inflammatory drugs)[158-165]
   - 1.2. Associated with fetal pulmonary vascular maldevelopment
     - 1.2.1. Associated with Fetal Pulmonary Hypoplasia
       - 1.2.1 a. Idiopathic pulmonary hypoplasia
       - 1.2.1 b. Familial pulmonary hypoplasia
       - 1.2.1.c. Congenital diaphragmatic hernia
       - 1.2.1.d. Hepatopulmonary fusion
       - 1.2.1.e. Scimitar syndrome
       - 1.2.1.f. Associated with fetal pulmonary compression
         - oligohydramnios
         - omphalocele/gastroschisis
         - cystic adenomatosis
         - fetal tumours or masses
       - 1.2.1.g. Associated with fetal skeletal malformations
     - 1.2.2. Associated with Fetal Lung Growth Arrest/Maldevelopment
       - 1.2.2.a. Acinar dysplasia
       - 1.2.2.b. Congenital alveolar dysplasia
       - 1.2.2.c. Alveolar capillary dysplasia with/out misalignment of pulmonary ve
       - 1.2.2.d. Lymphangiectasia
       - 1.2.2.e. Pulmonary artery abnormalities
       - 1.2.2.f. Pulmonary venous abnormalities
   - 1.3. Associated with fetal cardiac maldevelopment
     - 1.3.1. Premature closure of foramen ovale or ductus arteriosus
       - 1.3.1.a. Idiopathic
       - 1.3.1.b. Drug induced
     - 1.3.2. Congenital heart defects associated/causing pulmonary vascular disease in
       - 1.3.2.a. Transposition of the great arteries (TGA) with intact ventricular sep
       - 1.3.2.b. Hypoplastic left heart syndrome with intact atrial septum
       - 1.3.2.c. Obstructed total anomalous pulmonary venous connection
       - 1.3.2.d. Common pulmonary vein atresia





Pulmonary Lymphangiectasia

- KKH over last 20 years 4 patients
- Primary or secondary
- Survival 25%
- 3 with TAPVD
- 1 without TAPVD

4. Bronchopulmonary dysplasia
    4.1 with pulmonary vascular hypoplasia
    4.2 with pulmonary vein stenosis
    4.3 with left ventricular diastolic dysfunction
    4.4 with systemic to pulmonary shunts
        aortopulmonary collaterals
        atrial septal defect
        patent ductus arteriosus
        ventricular septal defect
    4.5. with significant hypercarbia and /or hypoxia
5. Isolated pediatric pulmonary hypertensive vascular disease (PPHVD) or isolated pulmonary arteri
    5.1. Idiopathic PPHVD/Idiopathic PAH
    5.2. Inherited PPHVD/PAH
        5.2.1. BMPR2
        5.2.2. Alk 1, endoglin
        5.2.3. Unidentified genetic cause
    5.3. Drugs and Toxins
        5.3.1. Definite association: Toxic oil
        5.3.2. Likely association
            Amphetamine
        5.3.4. Possible association
            Cocaine
            Methylphenidate
            Diazoxide
            Cyclosporin
            Phenylpropanolamine
    5.4. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis[156]

Bronchopulmonary dysplasia (BPD)

- Maldevelopment of pulmonary blood vessels underlies PH
- The vascular bed is especially prone to vasoconstriction with viral infection or other stresses
- Most patients with PH due to BPD
  - mild to moderate
  - PAP generally falls with growth and development
- Persistent PH in formerly preterm children - pulmonary vein stenosis
- PH is severe and persistent in this patient population
  - high morbidity and mortality

7. Pediatric lung disease
   7.1. Cystic fibrosis
   7.2. Interstitial lung diseases: surfactant protein deficiency etc.
   7.3. Sleep disordered breathing
   7.4. Chest wall and spinal deformities
   7.5. Restrictive lung diseases
   7.6. Chronic obstructive lung diseases

Transient PH

- Persistent pulmonary hypertension of the newborn (PPHN)
- PH related to congenital diaphragmatic hernia
- PH associated with bronchopulmonary dysplasia, which typically improves gradually, but may persist
- PH associated with acute pulmonary disease (eg, acute respiratory distress syndrome).
- Flow-related PH associated with cardiac shunting defects that are corrected in infancy

Neonatal PH - Special Considerations

- PVR is high in utero and falls rapidly after birth.
- PAP normally reaches adult levels during the first few weeks of life.
- Neonatal lung is sensitive to vasoconstrictive stimuli (eg, alveolar hypoxia)
- Delayed neonatal transition to a low-resistance pulmonary circulation
- Even asymptomatic neonates require close follow-up

Cardiac Shunt lesions

- PH due to increased pulmonary blood flow (Qp) rather than pulmonary vascular disease.
- Left heart disease associated with elevated left atrial pressure (LAp) pulmonary venous hypertension [PVH])
- Patients in these categories may actually have healthy pulmonary vessels, or reversible pulmonary vascular abnormalities.
- PVR = [mean PAP – mean LAp]/Qp)

Persistent/progressive PH in children

- PH associated with congenital heart disease (PH-CHD),
- PH due to lung disease
- Idiopathic/heritable PH

ST VINCENT'S HOSPITAL HEART HEALTH

Pulmonary Hypertension

Signs and Symptoms

- Bluish lips or skin
- Chest pain (angina)
- Fluttering chest sensation
- Short of breath
- Fatigue or weakness
- Tired

- Lightheadedness or loss of consciousness
- Dry coughing
- Abdominal bloating
- Rapid weight gain
- Swollen ankles or legs

PH in children

- Right heart failure may be the first presentation
- Effort intolerance
- Syncope usually with exertion
- Arrhythmias
- Sudden death can be the first manifestation
- Desaturation at rest – more evident if there is a shunt
- Failure to thrive

Evaluation

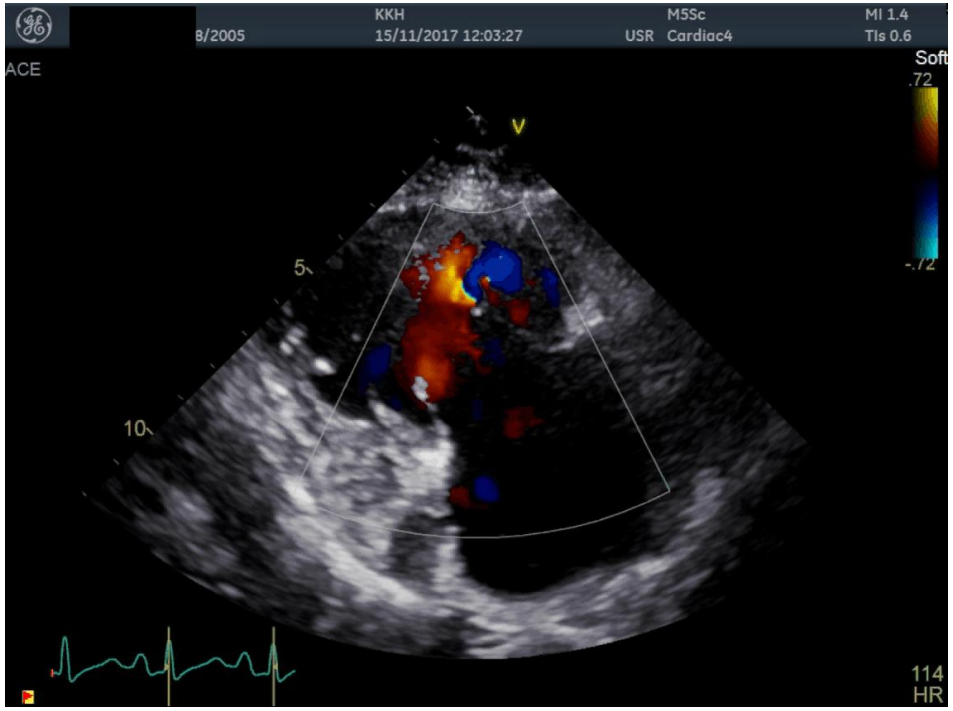
- Chest X ray
- Laboratory tests
- Chest CT with angiography
- Echocardiogram
- NT pro BNP
- Cardiac Catheterization
- Cardiopulmonary Exercise testing
- Six minute walk test

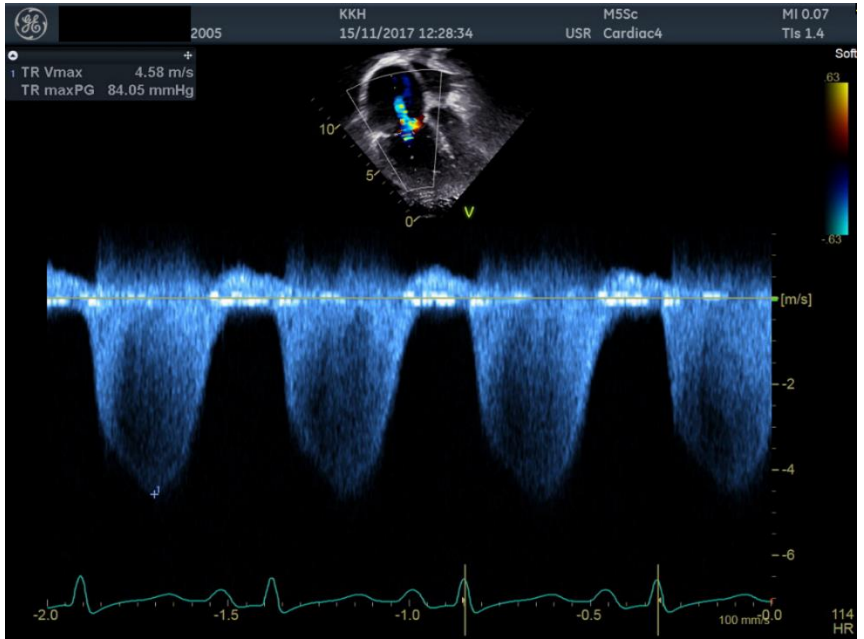
Evaluation of PH - Conditions at time of measurement

- Measurements of PAP in the echocardiography or cardiac catheterization laboratory may not reflect the PAP at other times and under different conditions.
- Bronchopulmonary dysplasia - little elevation of PAP when healthy versus a marked and clinically important increase with viral respiratory infection.
- Noncompliant pulmonary vascular beds - a modestly elevated PAP at rest (with no appreciable impact on the patient's physiology) can increase substantially with exercise.

Tricuspid Regurgitation jet

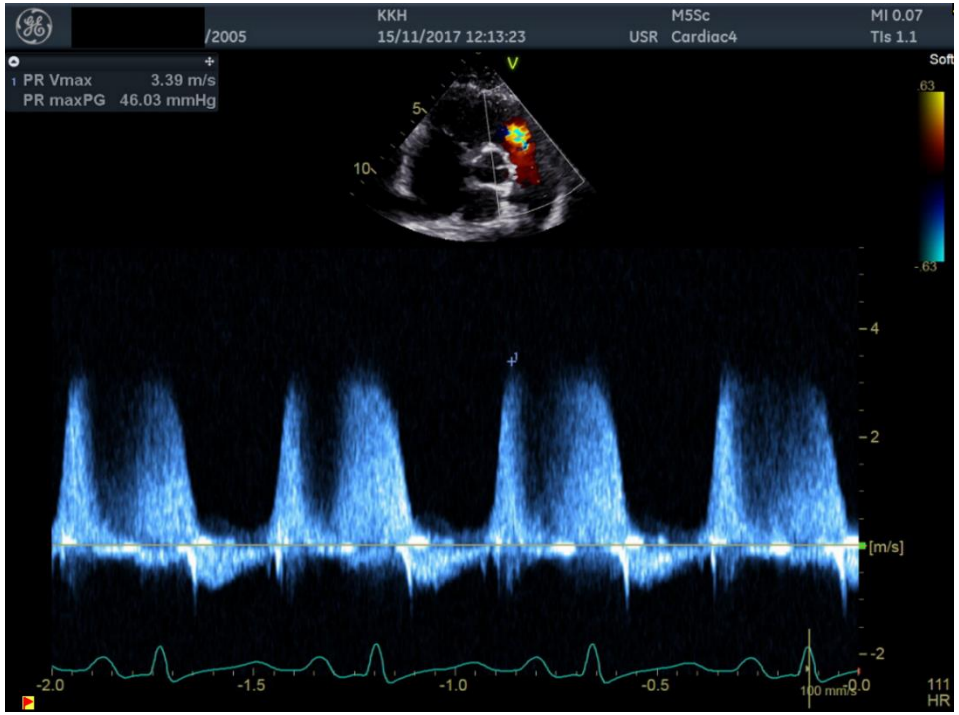
- RV pressure is measured by Doppler from velocity of TR jet
- Assumes that there is no obstruction to flow across the PA
- Assumes that the TR jet velocity is accurate
- Assumes RA mean pressure

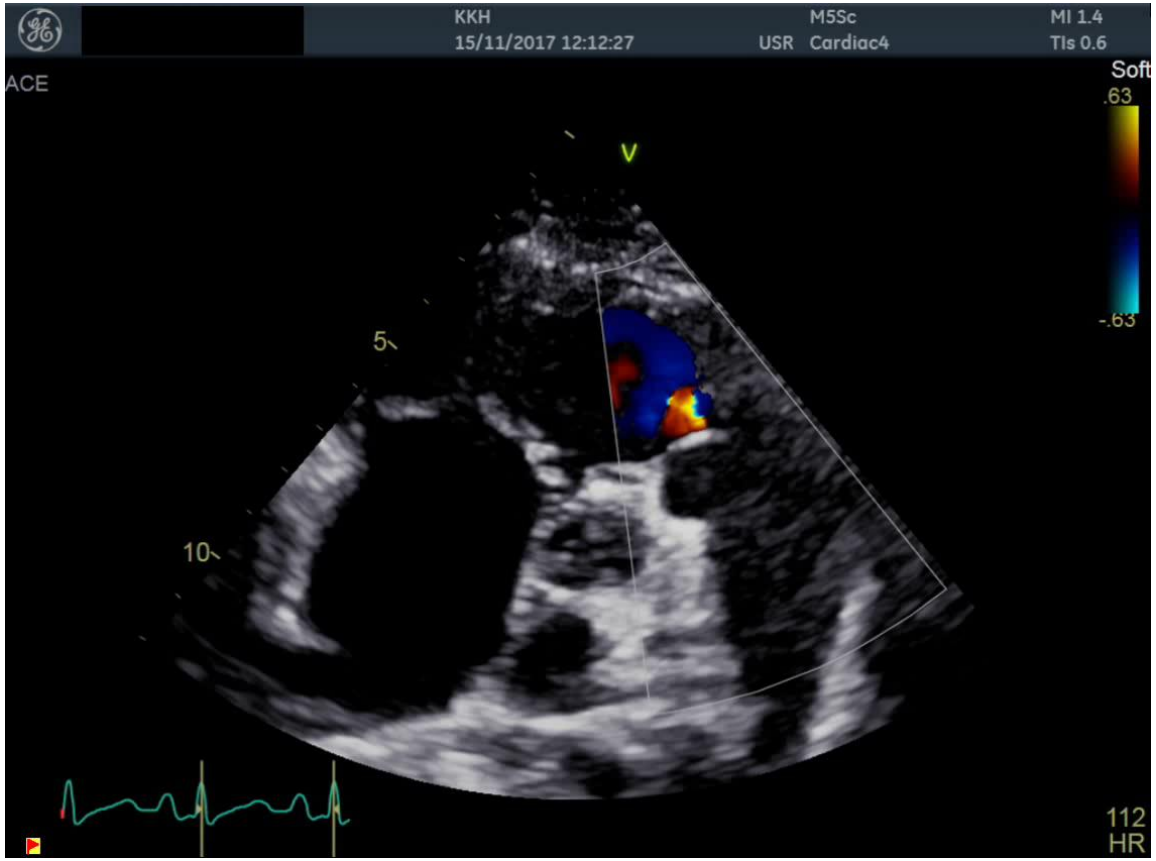




Pulmonary insufficiency jet

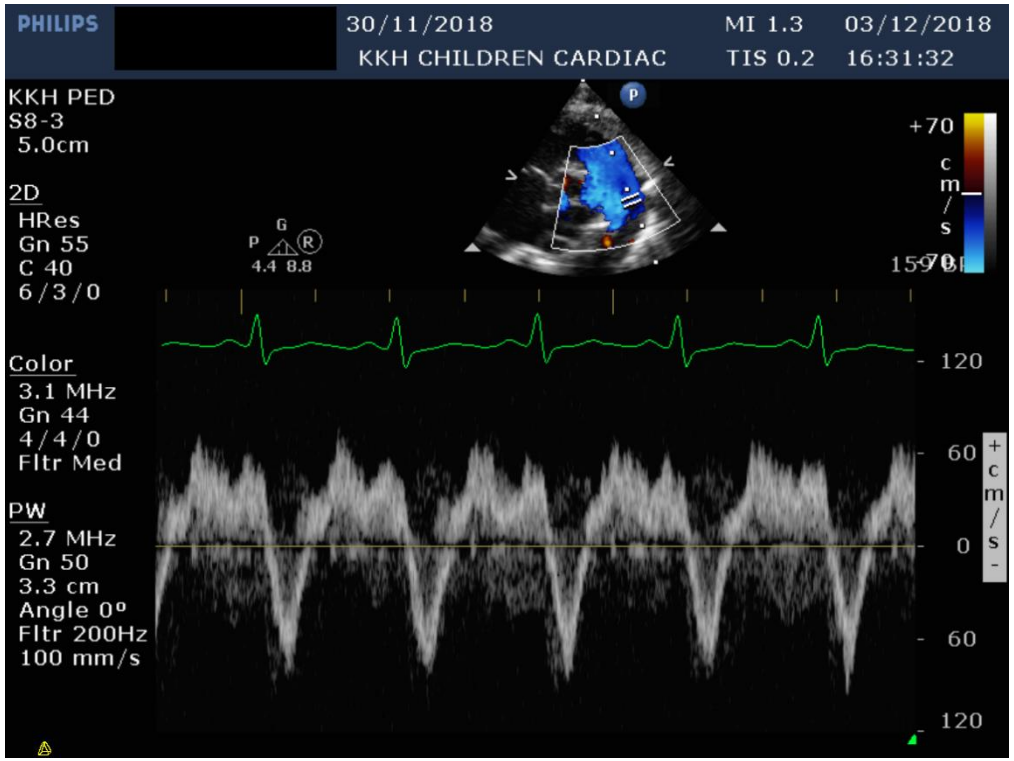
- Mean PA pressure and end diastolic pressure estimate
- Uses a constant factor from statistical model

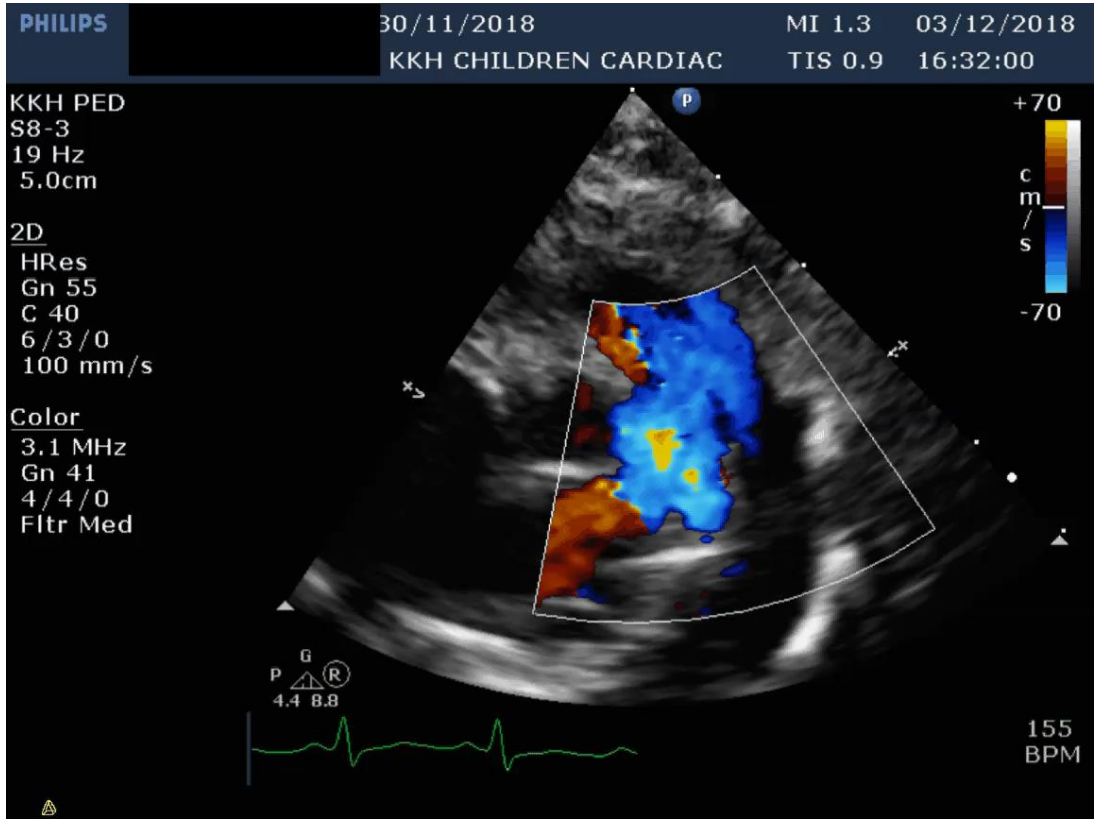




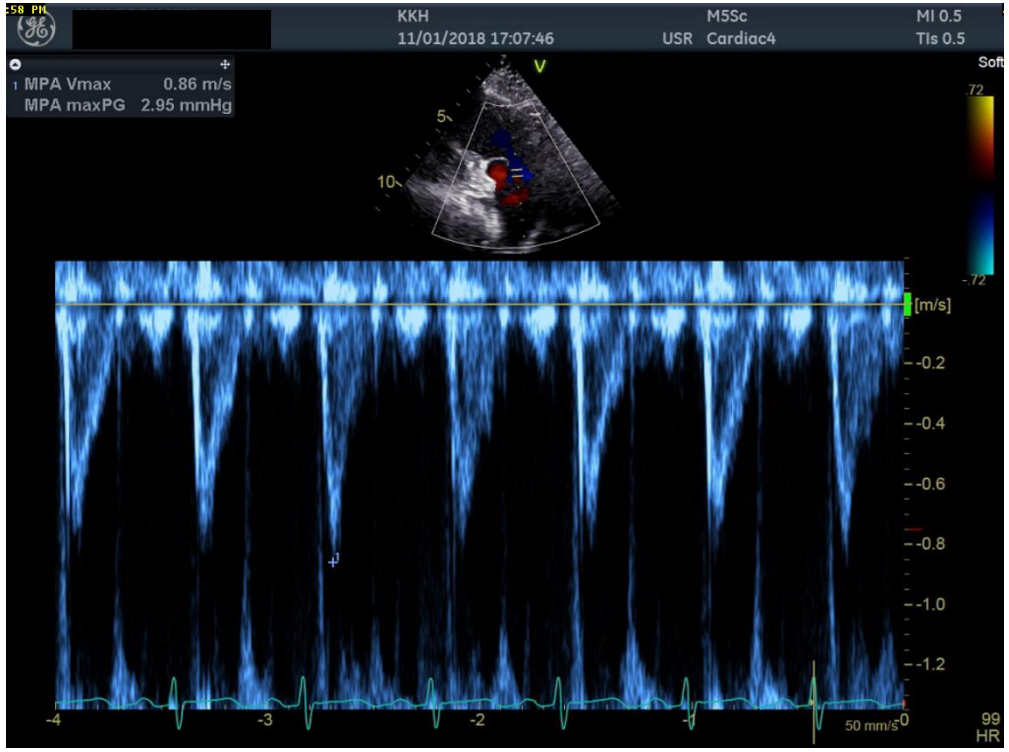
PDA or VSD jet velocity

- More accurate if available to measure





PV acceleration time

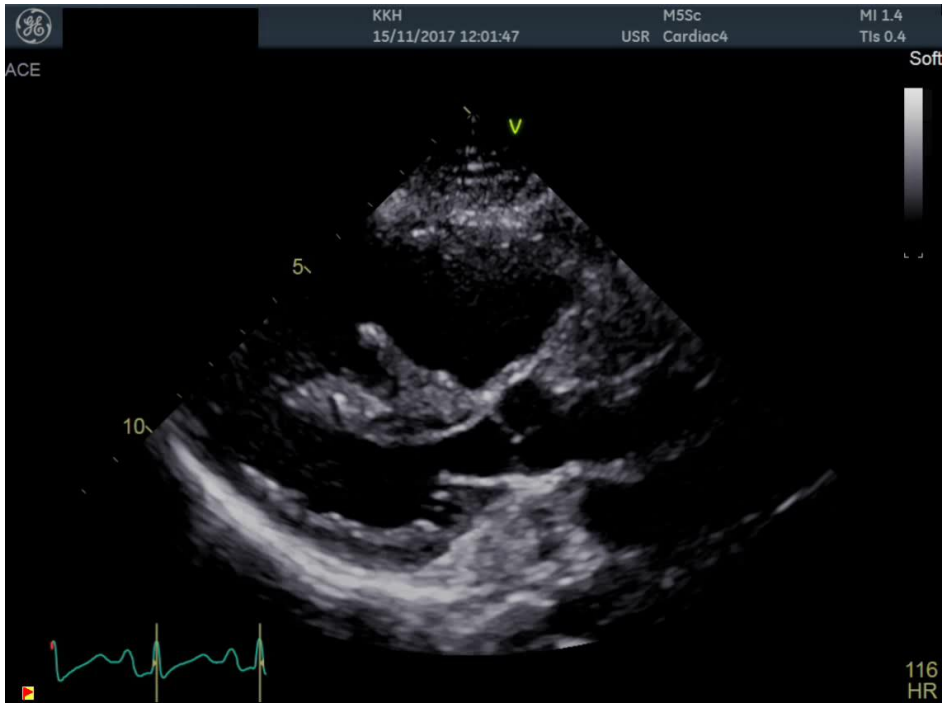


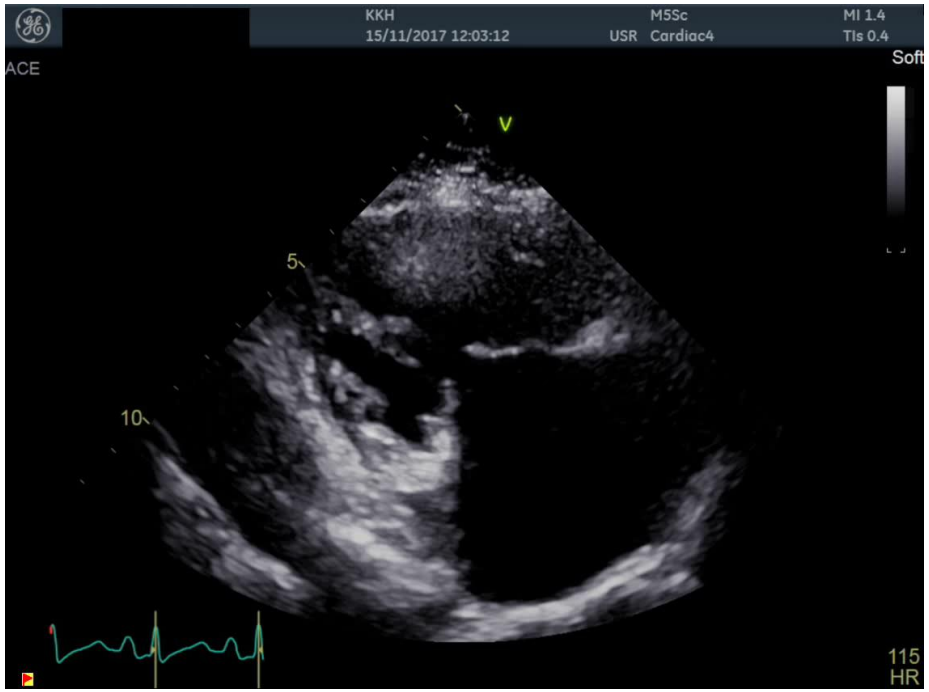
RV function estimation

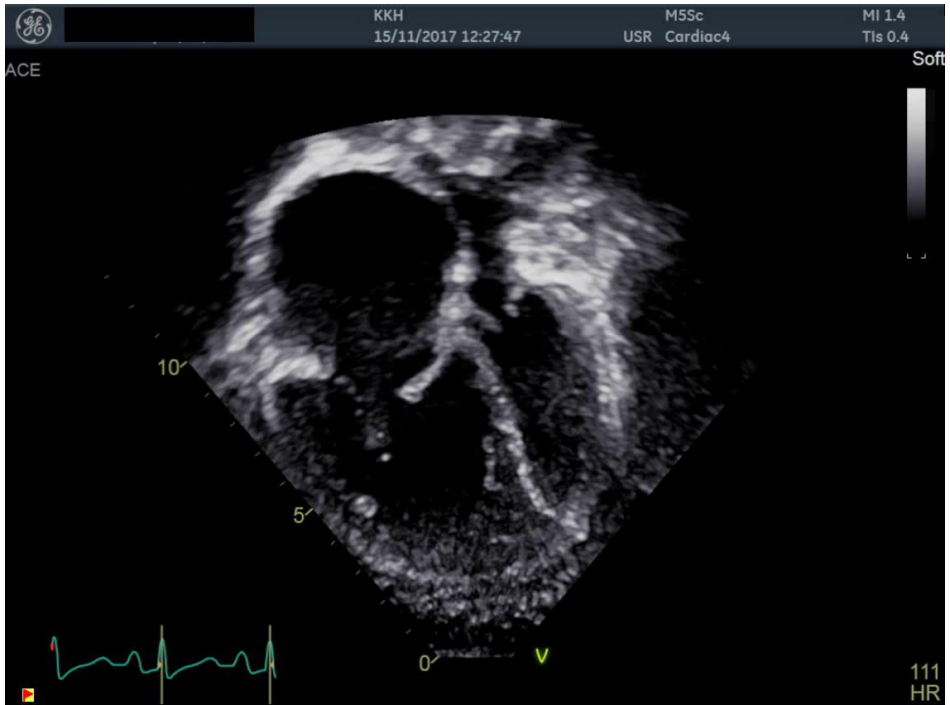
- 2D estimation (operator dependent)
  - RV hypertrophy and dilatation
  - RV function – visual estimation
  - Septal position (eccentricity index)
- Doppler evaluation
  - Flow across the PFO/ASD (RA pressure /LA pressure)
- M mode – TAPSE (age dependent)
- RV area fractional change (volume and operator dependent)
- TDI velocities
- RV strain
- 3D volume and EF estimation

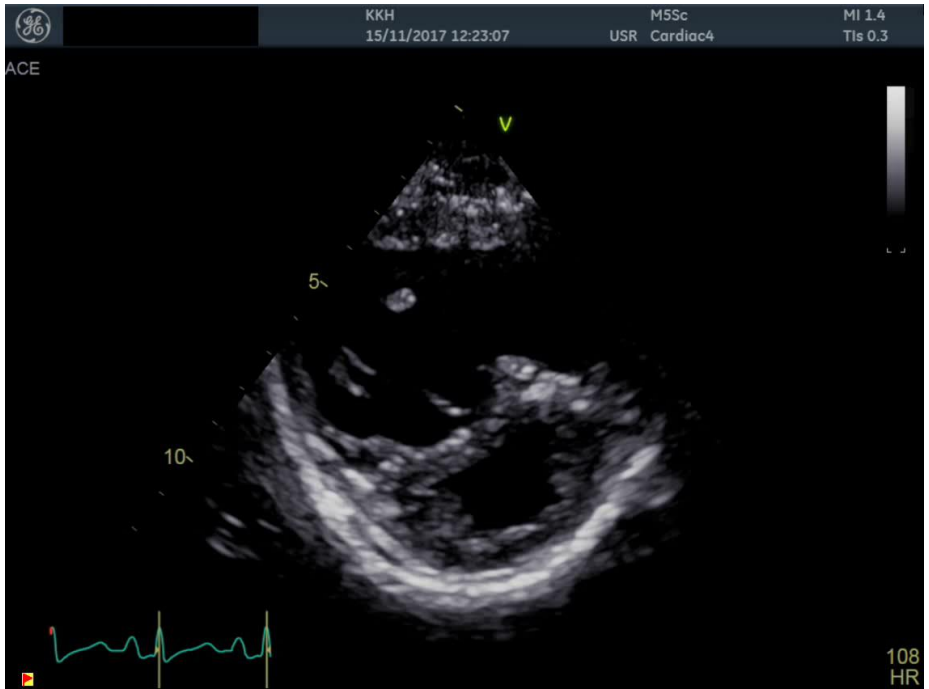
RV function

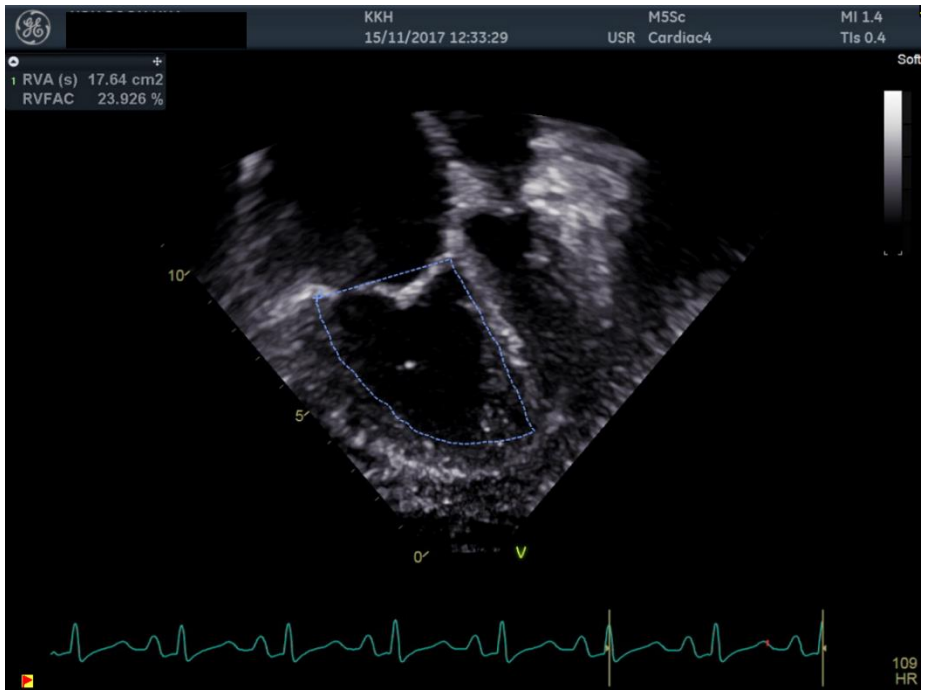
- RV hypertrophy and dilatation
- Septal position (eccentricity index)
- visual estimation
- operator dependent





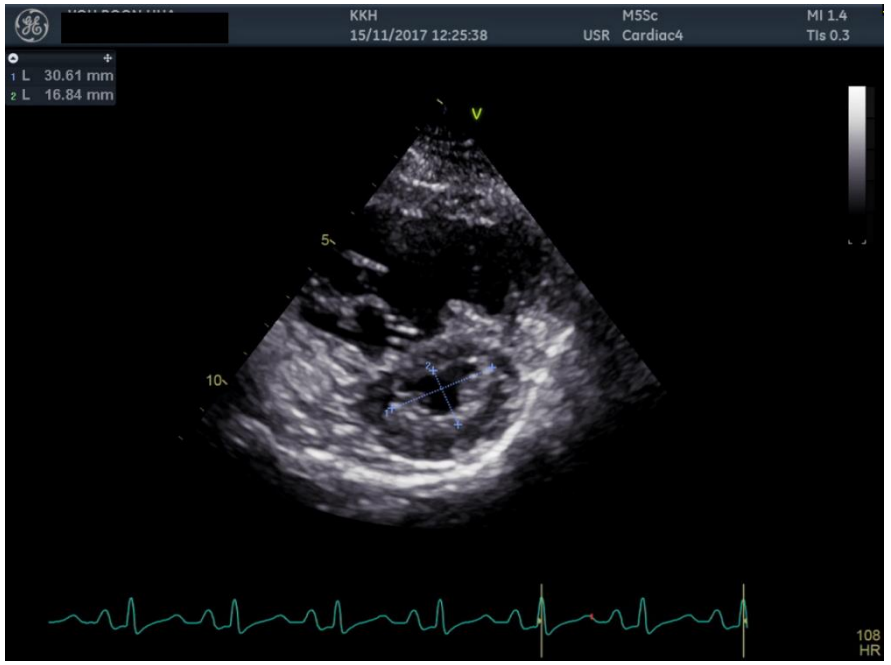


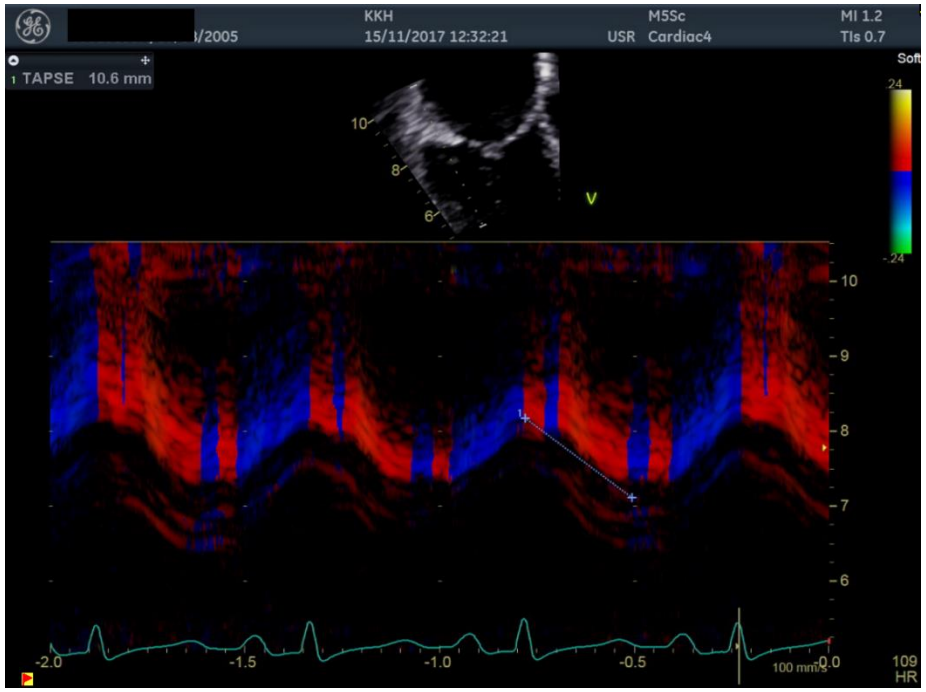




RV FAC

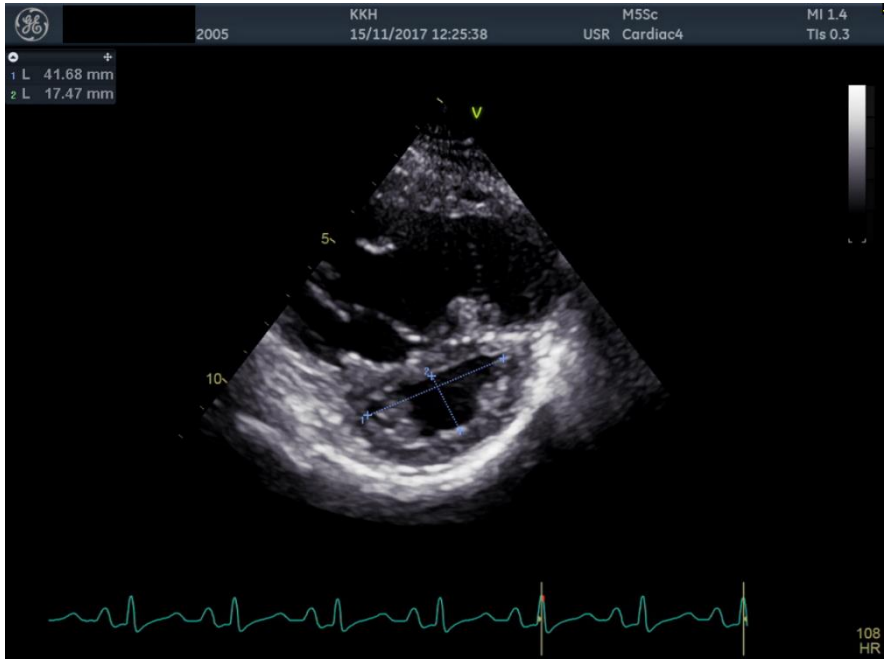
- Operator dependent
- Volume dependent





TAPSE

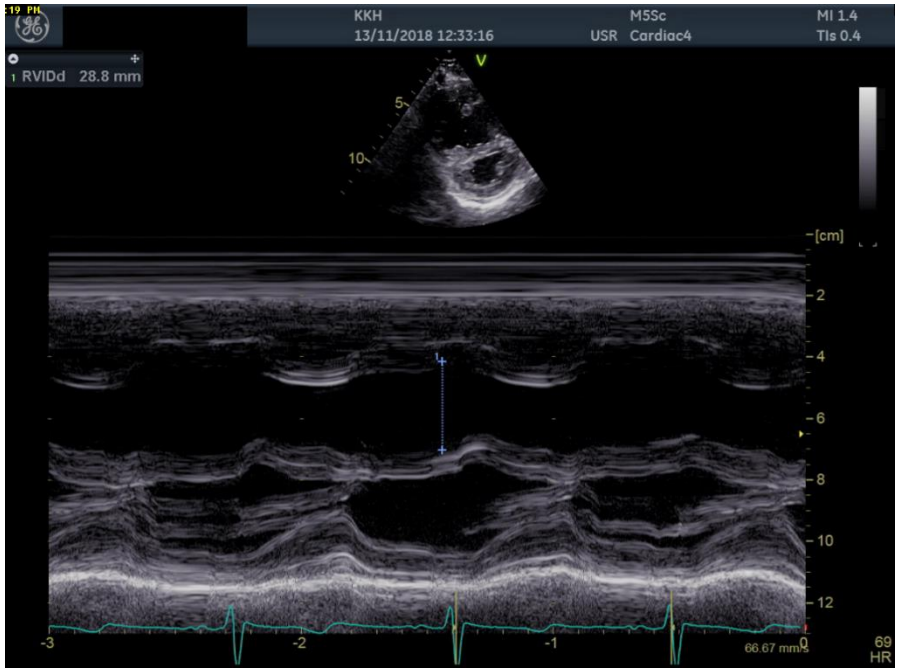
- Operator dependent
- Volume dependent

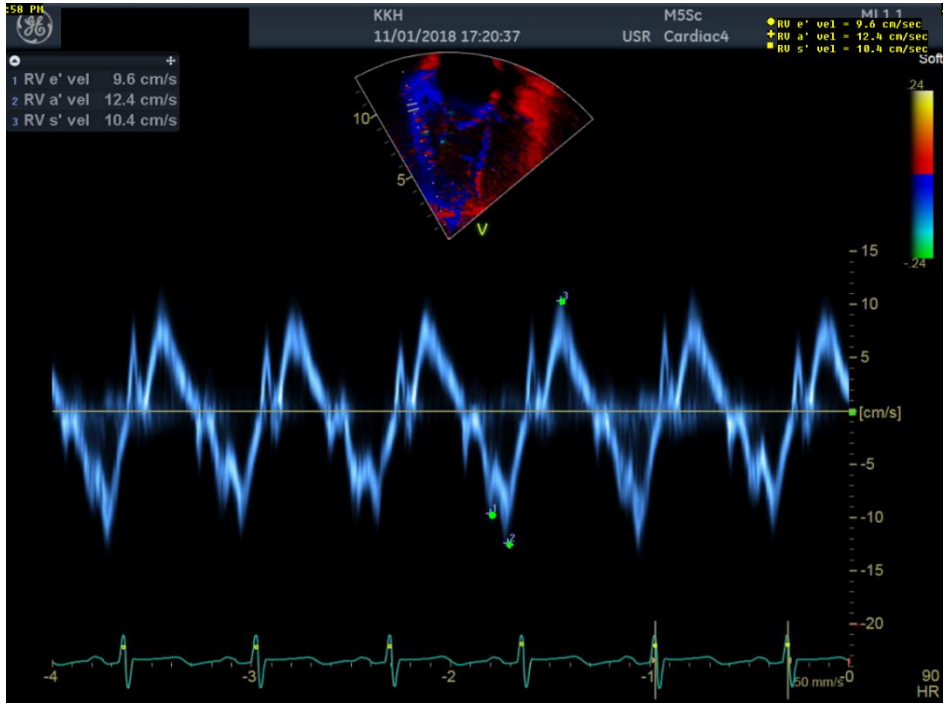


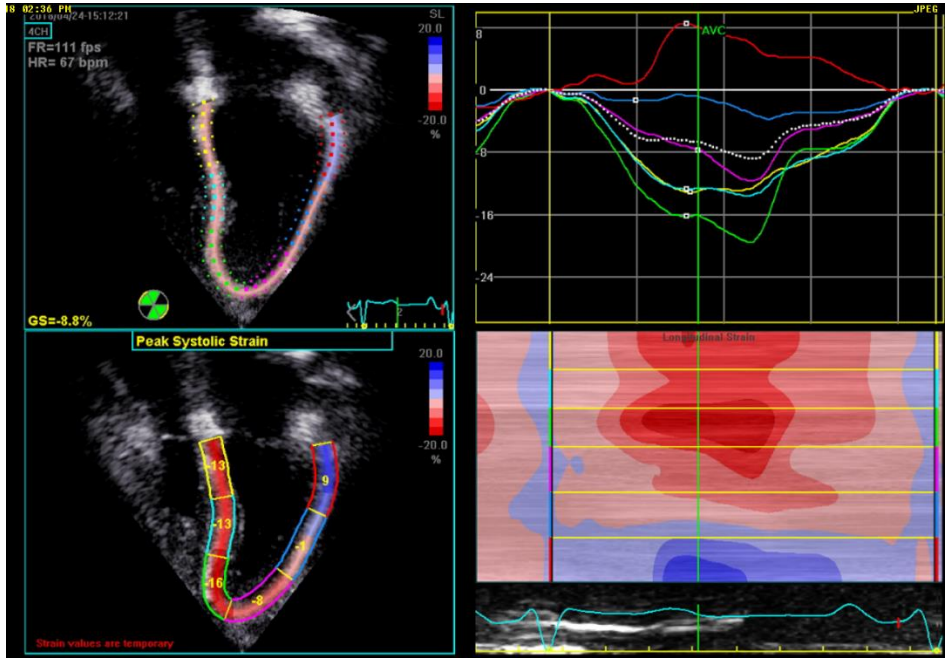
Septal position (eccentricity index)

- operator dependent

RV Strain







M-mode shows paradoxical septal motion

TDI shows abnormal RV diastolic function

Ventricular strain shows abnormal deformation forces

Right ventricular function

- Determines ventricular capacity to generate flow in different changes in PAP
- Well adapted RV
- Competency of TV
- Single ventricle physiology
- RV versus LV morphology – Corrected transposition of great arteries

Biomarkers in PH

- NT proBNP - Good for assessing treatment efficacy
- Good indicator of worsening RV function
- Serial Uric acid corelates well with disease severity and other biomarkers
- Uric acid levels > 40mmol/l differentiates survivors and non survivors
- Uric acid fluctuates reliably through out the course of the disease

Cardiac catheterization

- Most accurate
- Gold standard
- Invasive
- Assessment of vascular reversal response
  - AVT
    - mPAP to <40mmHg / drop of mPAP by 10mm Hg without drop in cardiac output
    - Can be used to assess operability in PAH-CHD
  - NO 10-80ppm
  - Epoprostenol
  - Iloprost
  - Adenosine

Pulmonary vascular resistance index WU·m^2	Pulmonary vascular resistance WU	Correctability/favourable long-term outcome
<4	<2.3	Yes
4–8	2.3–4.6	Individual patient evaluation in tertiary centres
>8	>4.6	No

Assumptions

- Oxygen consumption - VO2 (measured vs chart data)
- Pulmonary flow (Qp)
- Cardiac output (Qs) - Thermodilution vs Fick method
- Different baseline condition
- Affected by amount of oxygen given during assessment

Audience question

- RHC should always be performed in children
  - Prior to drug treatment
  - Risk stratification
  - To assess effectiveness of treatment
  - Prior to listing for lung transplantation
  - Hemodynamic changes corelate with clinical outcomes

Cardiopulmonary exercise testing

- Reasonable accurate estimation of cardiopulmonary function
- Gives information of pulmonary and cardiac function closer to real life
- Cardiopulmonary reserve
- Done when the patient is functional class 1-3
- Limited use in younger patients

Six minute walk test

- Poor functional class
- Estimates smaller functional changes in patients with effort intolerance
- Can be performed in clinic setting
- Estimates changes in heart rate, oxygen saturation and distance achieved
- Operator reliability high
- But need to accurately fix the distance and time achieved
- Useful generally in children above 6 years

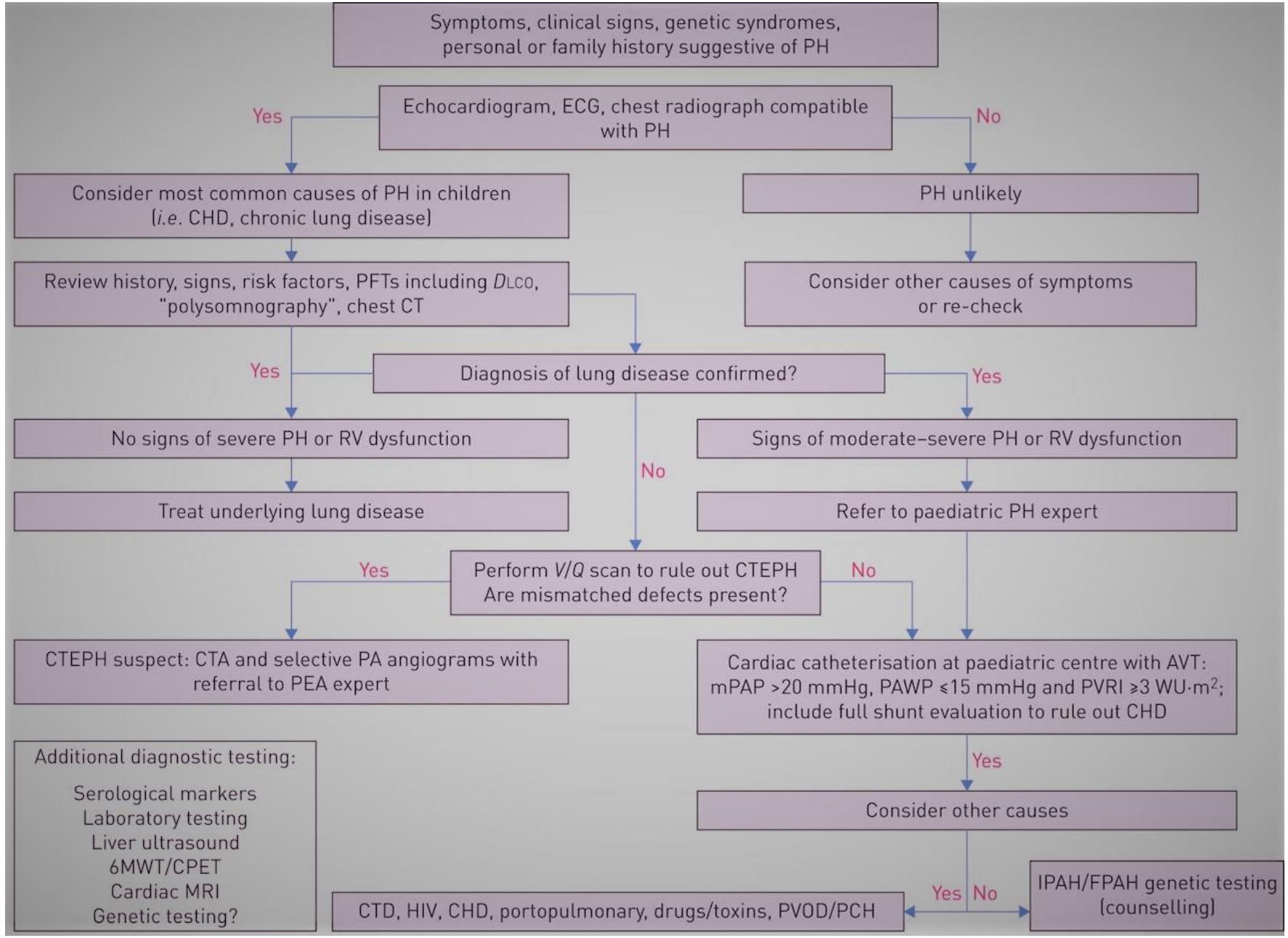
Six-Minute Walk Test in Evaluation of Children with Pulmonary Arterial Hypertension

Malgorzata Zuk[1] · Anna Migdal[1] · Dorota Jagiellowicz-Kowalska[1] · Katarzyna Mazurkiewicz[1] · Anna Sadel-Wieczorek[1] · Grazyna Brzezinska-Rajszys[1]

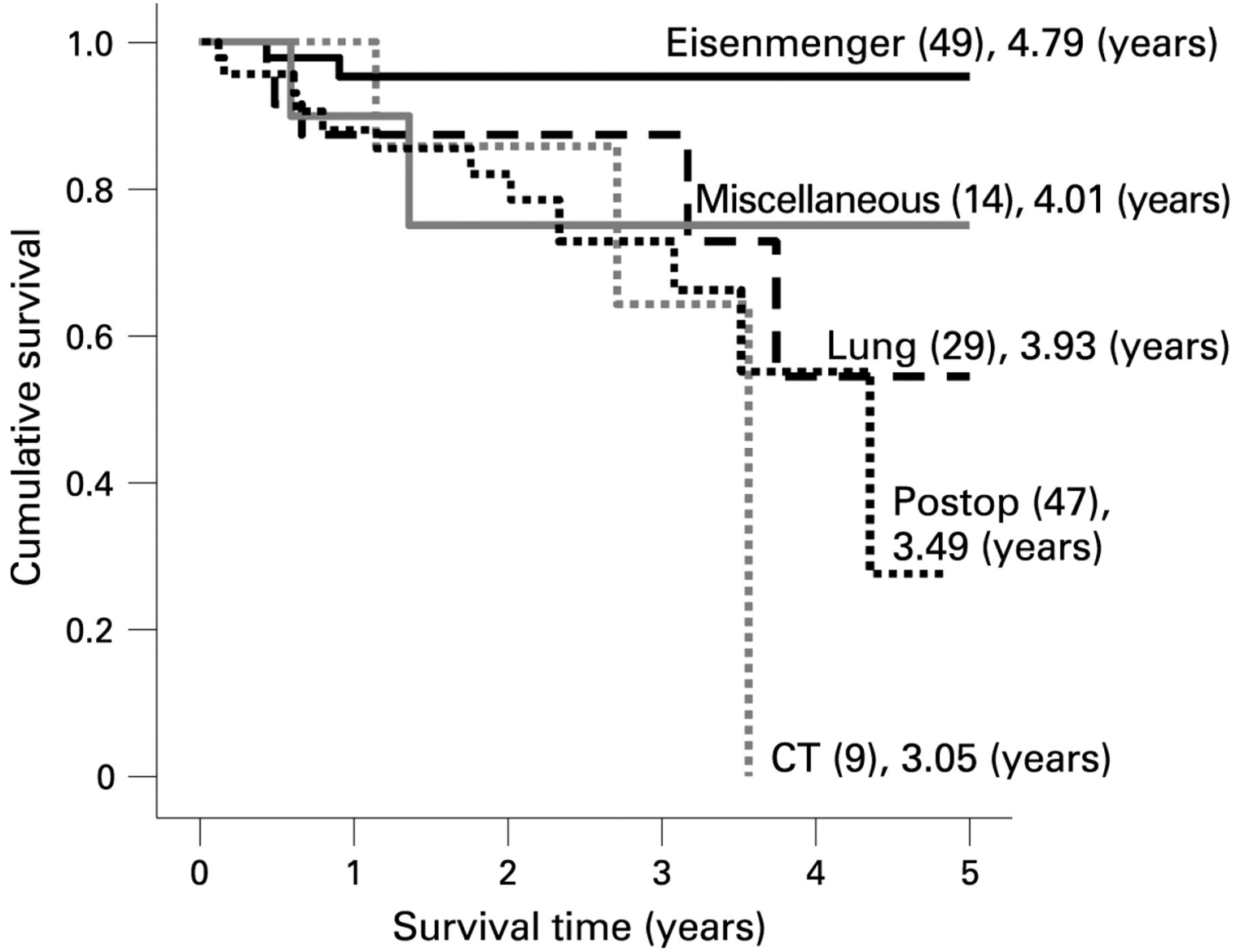
Table 3 Results of all analyzed 6MWT (data presented as mean± SD and median)

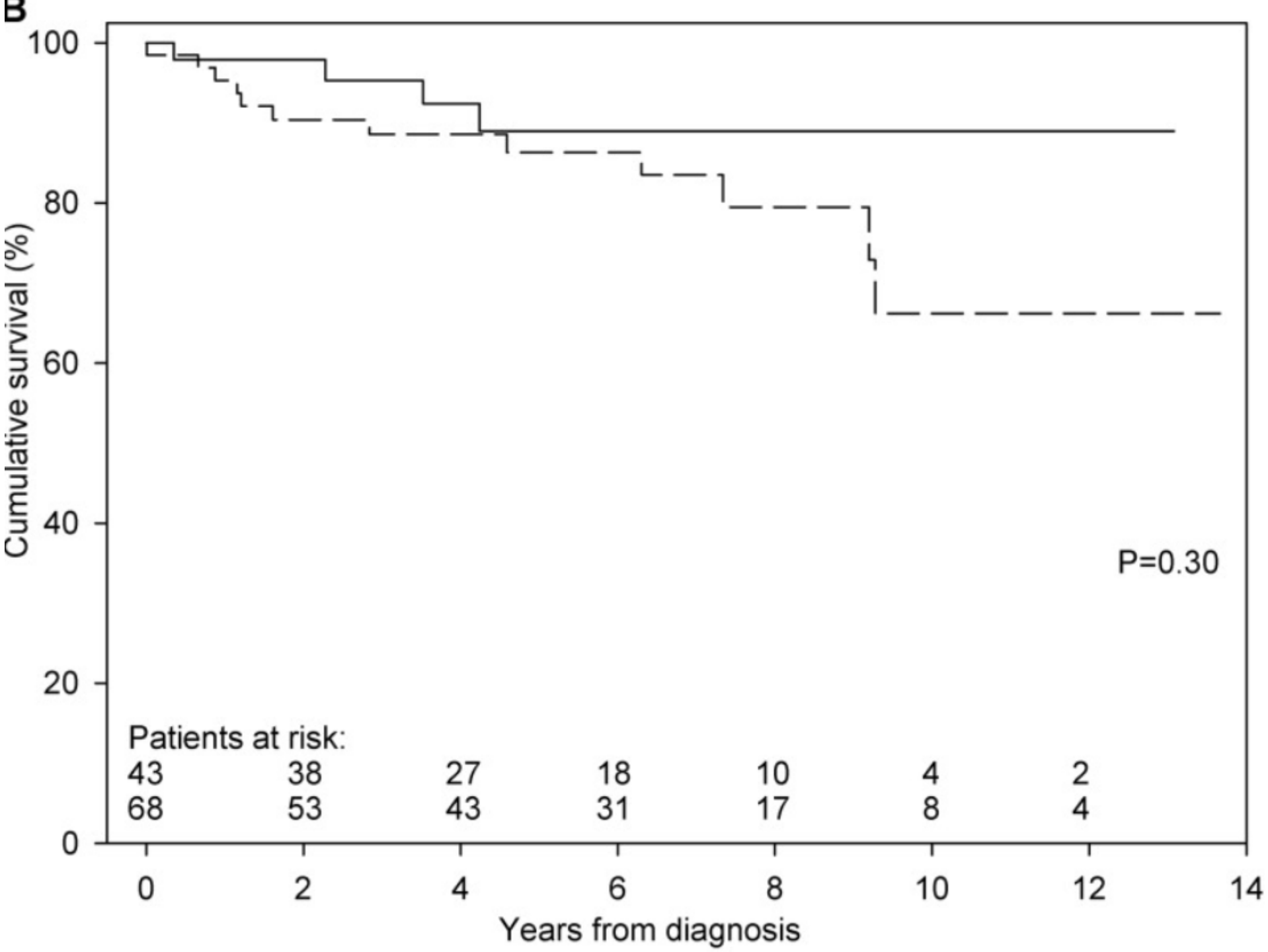
Parameters	Units	All 6MWT	Shunt	No shunt	*p*	WHO-FC I/II	WHO-FC III/IV	*p*
N		**164**	**102**	**62**		**124**	**40**	
6MWD	% of predicted	74.3 ± 12.6 76.5	**72.8 ± 12.4** **75.2**	**76.9 ± 12.5** **79.3**	**0.02**	**77.5 ± 8.9** **78.0**	**64.3 ± 16.4** **70.6**	**<0.01**
Rest SAT	%HbO2	92.6 ± 6.3 96	**89.6 ± 6.4** **91**	**97.5 ± 1.1** **98**	**<0.01**	93.1 ± 5.7 6.0	90.9 ± 7.8 95.0	NS
Desaturation	%HbO2	11.8 ± 11.2 10.0	**17.5 ± 10.4** **17.5**	**2.6 ± 4.3** **1**	**<0.01**	11.8 ± 11.4 10.0	11.7 ± 10.6 9.0	NS
Rest HR	% of median for age	101 ± 21 101	99.3 ± 2.119 9.3	102.9 ± 18.6 103.3	NS	**96.6 ± 20.9** **96.5**	**113.1 ± 18.5** **110.3**	**<0.01**
Peak HR	% of max HR for age	57.1 ± 11.9 56.9	57.3 ± 11.1 58.2	56.9 ± 13.3 54.9	NS	**55.1 ± 11.2** **54.3**	**63.1 ± 12.35** **9.4**	**<0.01**
Peak HR/6MWD		0.79 ± 0.33 0.75	0.81 ± 0.35 0.77	0.77 ± 0.29 0.7	NS	**0.71 ± 0.2** **0.7**	**1.12 ± 0.56** **1.05**	**<0.01**
NTproBNP	pg/ml	875 ± 1904 255	804 ± 1612 271	995 ± 2336 176	NS	**244 ± 244** **165**	**2766 ± 3120** **1832**	**<0.01**
ΔRV-RA	mmHg	95 ± 25 100	**101.7 ± 21.8** **103**	**83.9 ± 25** **82**	**<0.01**	94.2 ± 27.5 101.0	95.8 ± 17 90.5	NS

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
>350	6MWT (>6 years old) m	<350
Normal	Growth	Failure to thrive
III, IV	WHO FC	
		Significantly elevated
Minimally elevated	Serum BNP/NT-proBNP	Rising level
	Echocardiography	RA/RV enlargement
		Reduced LV size
		Increased RV/LV ratio
		Reduced TAPSE
		Low RV FAC
		Pericardial effusion
Systemic CI >3.0 L·min^{-1}·m^{-2}	Haemodynamics	Systemic CI <2.5 L·min^{-1}·m^{-2}
Systemic venous saturation >65%		mRAP >10 mmHg
Acute vasoreactivity		PVRI >20 WU·m^{2}
		Systemic venous saturation <60%
		PACI <0.85 mL·mmHg^{-1}·m^{-2}


Symptoms, clinical signs, genetic syndromes, personal or family history suggestive of PH
Echocardiogram, ECG, chest radiograph compatible with PH
Yes
No
Consider most common causes of PH in children (i.e. CHD, chronic lung disease)
PH unlikely
Review history, signs, risk factors, PFTs including DLCO, "polysomnography", chest CT
Consider other causes of symptoms or re-check
Yes
Diagnosis of lung disease confirmed?
Yes
No signs of severe PH or RV dysfunction
Signs of moderate–severe PH or RV dysfunction
No
Treat underlying lung disease
Refer to paediatric PH expert
Yes
Perform V/Q scan to rule out CTEPH Are mismatched defects present?
No
CTEPH suspect: CTA and selective PA angiograms with referral to PEA expert
Cardiac catheterisation at paediatric centre with AVT: mPAP >20 mmHg, PAWP ≤15 mmHg and PVRI ≥3 WU·m2; include full shunt evaluation to rule out CHD
Additional diagnostic testing:
Serological markers
Laboratory testing
Liver ultrasound
6MWT/CPET
Cardiac MRI
Genetic testing?
Yes
Consider other causes
Yes
No
CTD, HIV, CHD, portopulmonary, drugs/toxins, PVOD/PCH
IPAH/FPAH genetic testing (counselling)

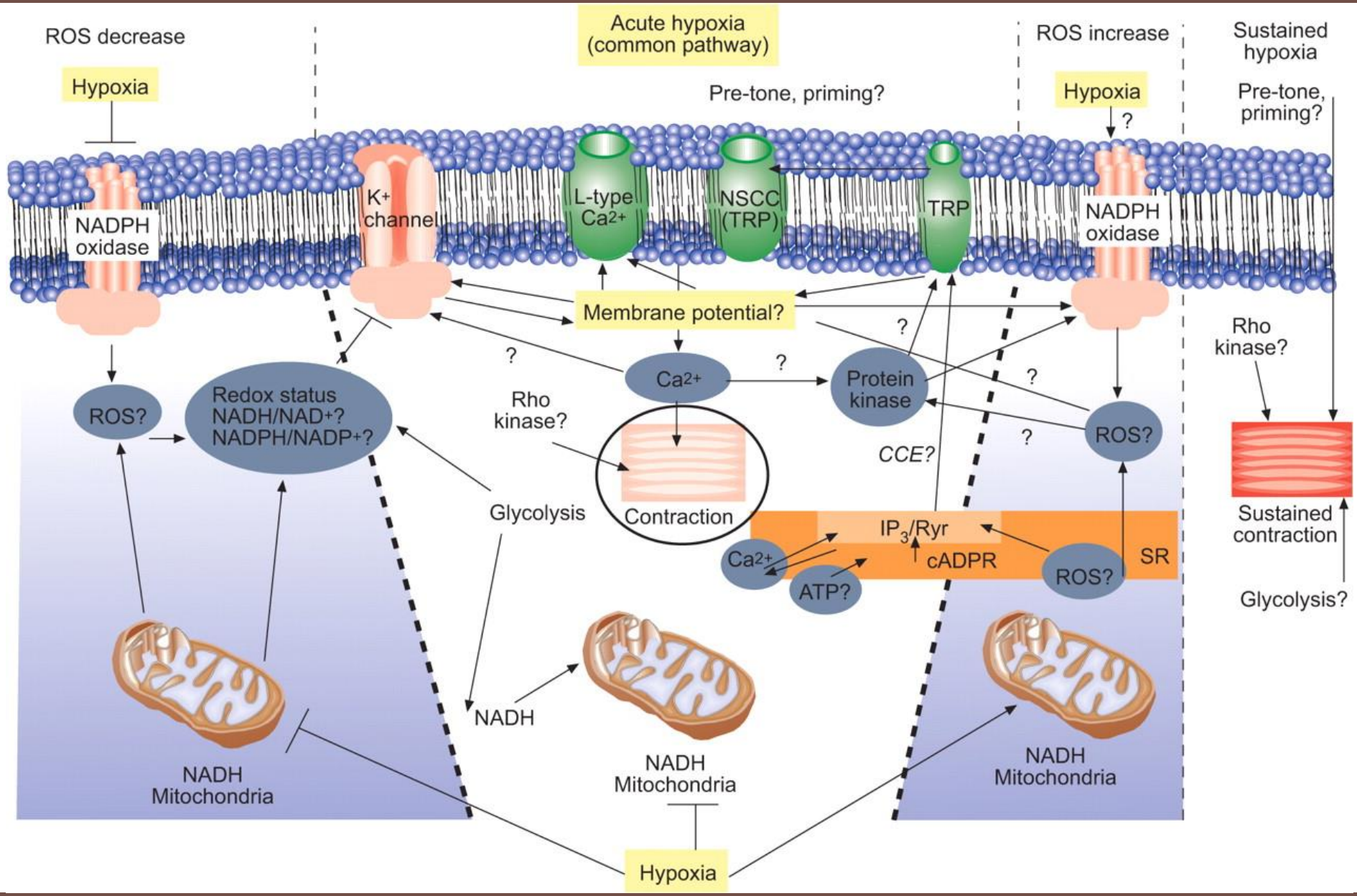

DANGER
HIGH PRESSURE
High Pressure ... IN THE LUNGS?


Eisenmenger (49), 4.79 (years)
Miscellaneous (14), 4.01 (years)
Lung (29), 3.93 (years)
Postop (47), 3.49 (years)
CT (9), 3.05 (years)
Cumulative survival
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Survival time (years)


B
100
80
60
40
20
0
Cumulative survival (%)
P=0.30
Patients at risk:
43 38 27 18 10 4 2
68 53 43 31 17 8 4
0 2 4 6 8 10 12 14
Years from diagnosis

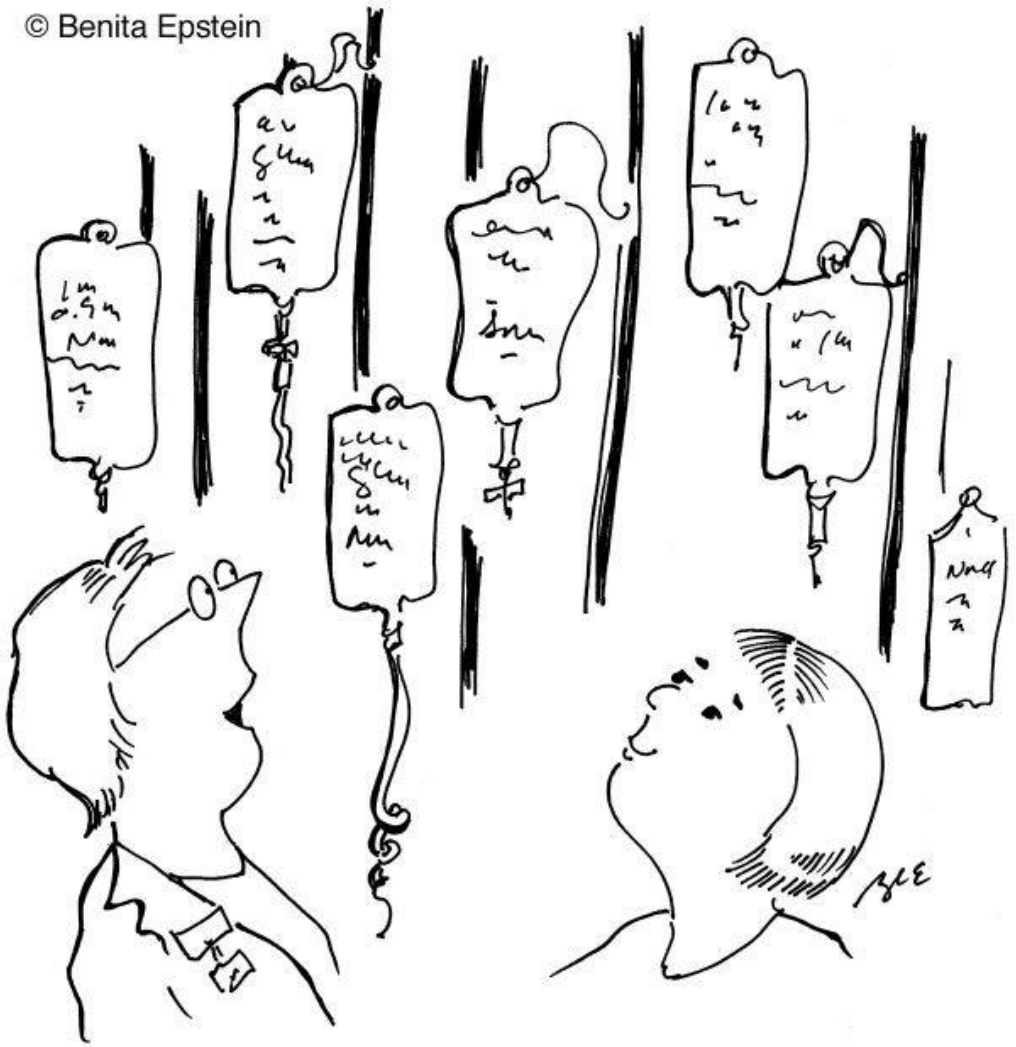
Management of PH

- Alteration of pulmonary vascular resistance and remodelling
  - Oxygen
  - NO
  - PDE5 inhibitor
  - Endothelin antagonist
  - Prostacyclin analogues
- Modify RV function
  - Diuretics
  - Milrinone/Amrinone
- Prevent Thrombosis
  - Anticoagulation
  - Aspirin
- Recognize and treat Acute PH crisis

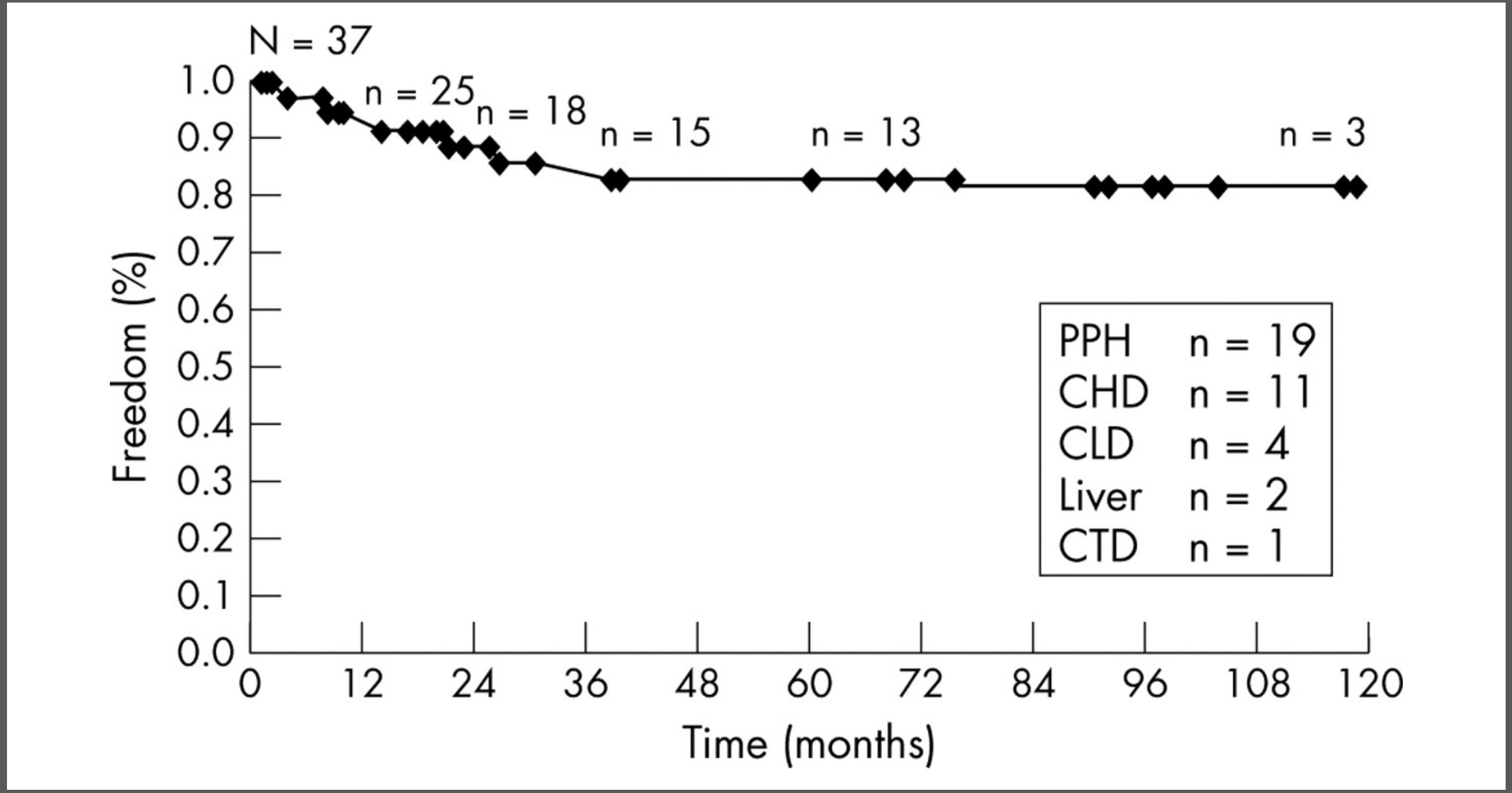

ROS decrease
Hypoxia
NADPH oxidase
Acute hypoxia (common pathway)
Pre-tone, priming?
K+ channel
L-type Ca2+
NSCC (TRP)
TRP
Membrane potential?
ROS increase
Hypoxia
?
NADPH oxidase
Sustained hypoxia
Pre-tone, priming?
Rho kinase?
Ca2+
Protein kinase
ROS?
Redox status NADH/NAD+? NADPH/NADP+?
Rho kinase?
Contraction
CCE?
Glycolysis
IP3/Ryr
cADPR
Ca2+
ATP?
ROS?
SR
Sustained contraction
Glycolysis?
NADH
NADH Mitochondria
NADH Mitochondria
NADH Mitochondria
Hypoxia

Targeted PH therapy

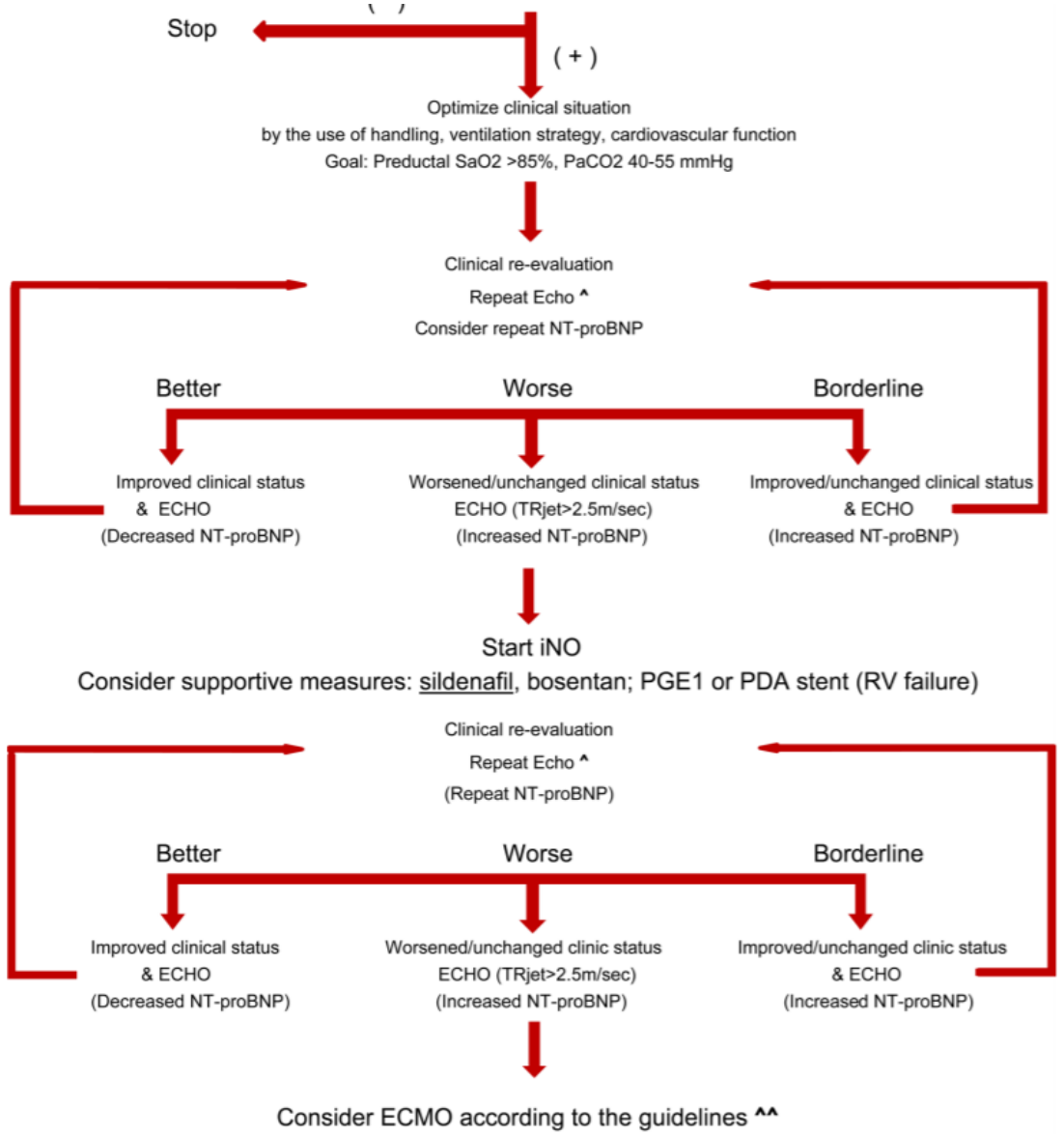
- Calcium channel blockers (nifedipine, amlodipine, diltiazem – but not verapamil)
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
- Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
- Prostacyclin analogues (epoprostenol, treprostinil, iloprost)



"Welcome to the I.V. league."

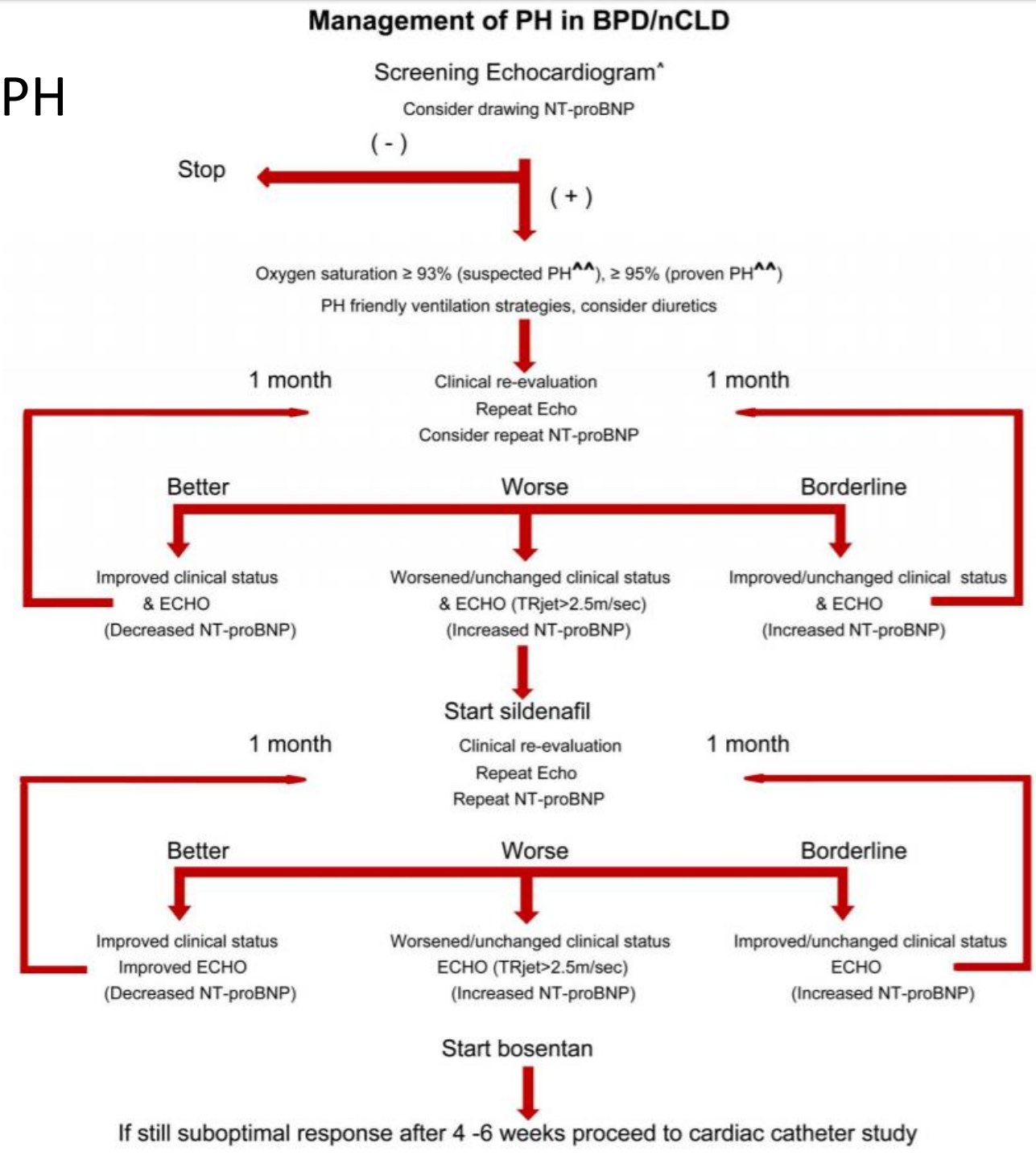

N = 37
n = 25
n = 18
n = 15
n = 13
n = 3
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Freedom (%)
0
12
24
36
48
60
72
84
96
108
120
Time (months)
PPH n = 19
CHD n = 11
CLD n = 4
Liver n = 2
CTD n = 1

PPHN Algorithm

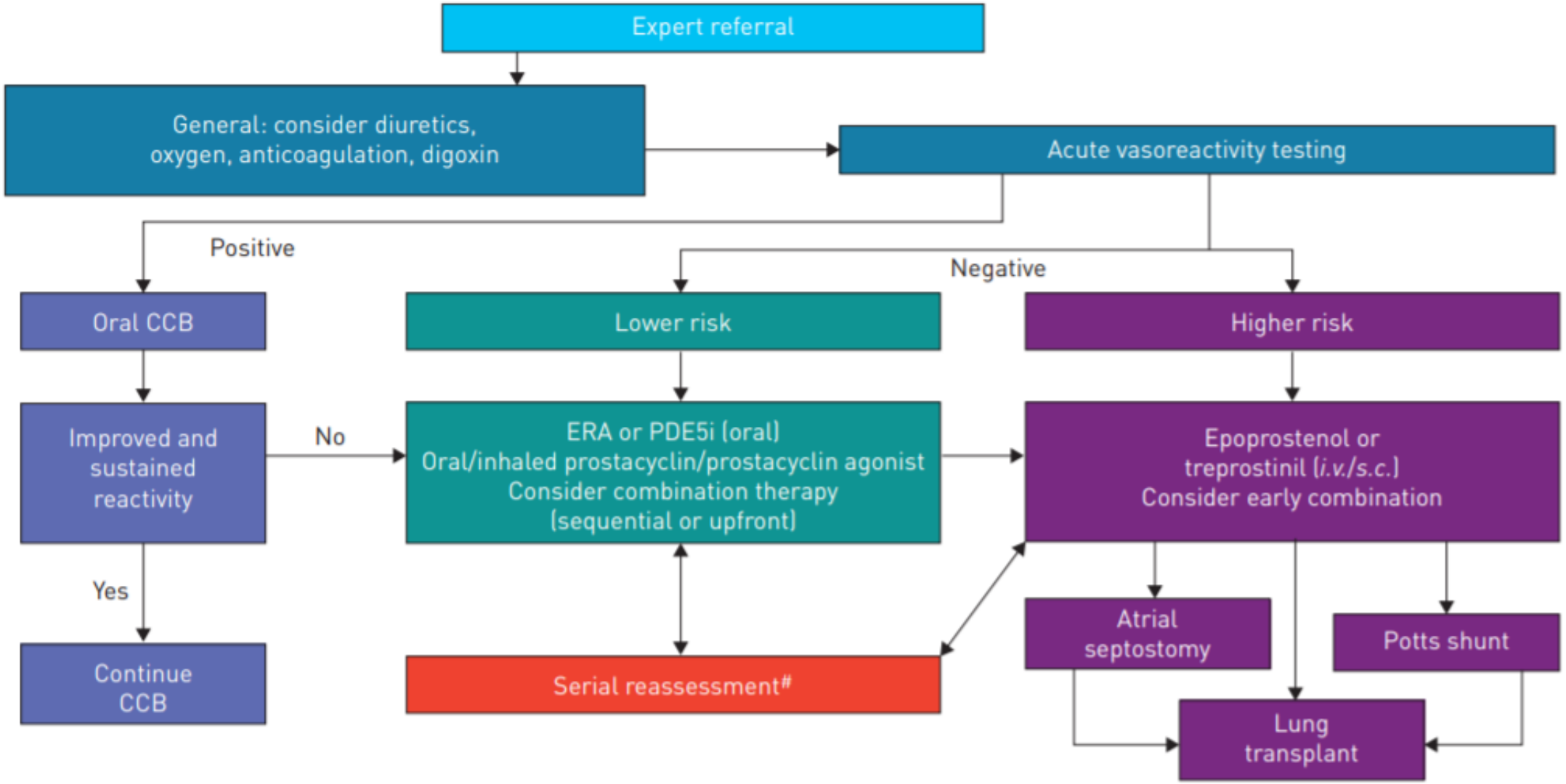


Hilgendorff A, et al. Heart 2016;102:ii49–ii56. doi:10.1136/heartjnl-2015-308591

BPD and CLD with PH



Hilgendorff A, et al. Heart 2016;102:ii49–ii56. doi:10.1136/heartjnl-2015-308591


Expert referral
General: consider diuretics, oxygen, anticoagulation, digoxin
Acute vasoreactivity testing
Positive
Negative
Oral CCB
Lower risk
Higher risk
Improved and sustained reactivity
No
ERA or PDE5i (oral)
Oral/inhaled prostacyclin/prostacyclin agonist
Consider combination therapy
(sequential or upfront)
Epoprostenol or treprostinil (i.v./s.c.)
Consider early combination
Yes
Continue CCB
Serial reassessment#
Atrial septostomy
Potts shunt
Lung transplant


PRESCRIPTIONS
"Take with meals? After I pay for these, how can I afford food?"

Palliative shunts for refractory PH

- Atrial septostomy
  - WHO FC 3-4
  - Syncope on combination therapy
  - Bridge to transplant
- Contraindicated if
  - mRAP >20mm Hg
  - Resting saturation<90%
  - Severe RV failure
  - Near death

- Reverse Potts Shunt/ PDA stent
  - WHO FC 4
  - Refractory to combination meds
  - Improves RV function
  - Immediate post operative death
  - Survivors have improvement in FC and symptoms

Audience question

- During the treatment of refractory pulmonary hypertension
  - IV Epoprostenol or SC Treprostonil should be added
  - BNP levels decrease after atrial septostomy
  - Potts shunt improves oxygen saturation
  - Potts shunt improves functional capacity

Summary

- PAH with CHD is the commonest in children
- PH in pulmonary disease has a varied pathophysiology but hypoxia plays an important role
- Evaluation of PH in children includes assessment of etiology, severity of PH and testing for pulmonary vascular reactivity
- Survival in PH is at best modest
- PH with cardiac shunt tends to have longer survival
- Newer pulmonary vasodilators have improved QOL and survival
- Improvement in functional class corelates well with outcomes
- Effective management of PH requires a multiteam approach


SOMEHOW YOU GOT PHOTOBOMBED DURING YOUR X-RAYS!
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