Malaysian Society of Paediatric Anaesthesiologists (MSPA)

Asian Society of Paediatric Anaesthesiologists

Pulmonary Hypertension Associated with Congenital Heart Disease

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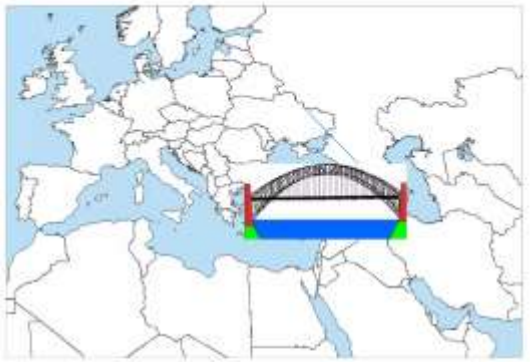

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No disclosures

Objectives

- Definition
- Description of groups and subgroups of PH-CHD
- PH crisis
- Patient evaluation, imaging modalities
- Anesthetics techniques to minimize risk of intraoperative morbidity/mortality
- Treatment strategies

Pulmonary Hypertension in Congenital Heart Disease

2018 Latest Classification, NICE

Definition of PH and PAH: Clinical, Hemodynamic

1. • **mPAP>20 mmHg - PH**
2. • **PAWP≤15 mmHg**
3. • **PVR≥3 wood units (WU)**

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

6th World Symposium of Pulmonary Hypertension (WSPH)-2018

Pulmonary Hypertension in Congenital Heart Disease

In single ventricule physiology PAH is defined as:

1. **mPAP >20 mmHg - PH**
2. **PVRI >3 WU.m^2**
3. **Transpulmonary gradient (TPG) > 6 mmHg**

Incidence and prevalence of PAH associated with CHD: 2.2-15.6/1 million

PH is significant risk factor for morbidity/mortality in patients with CHD

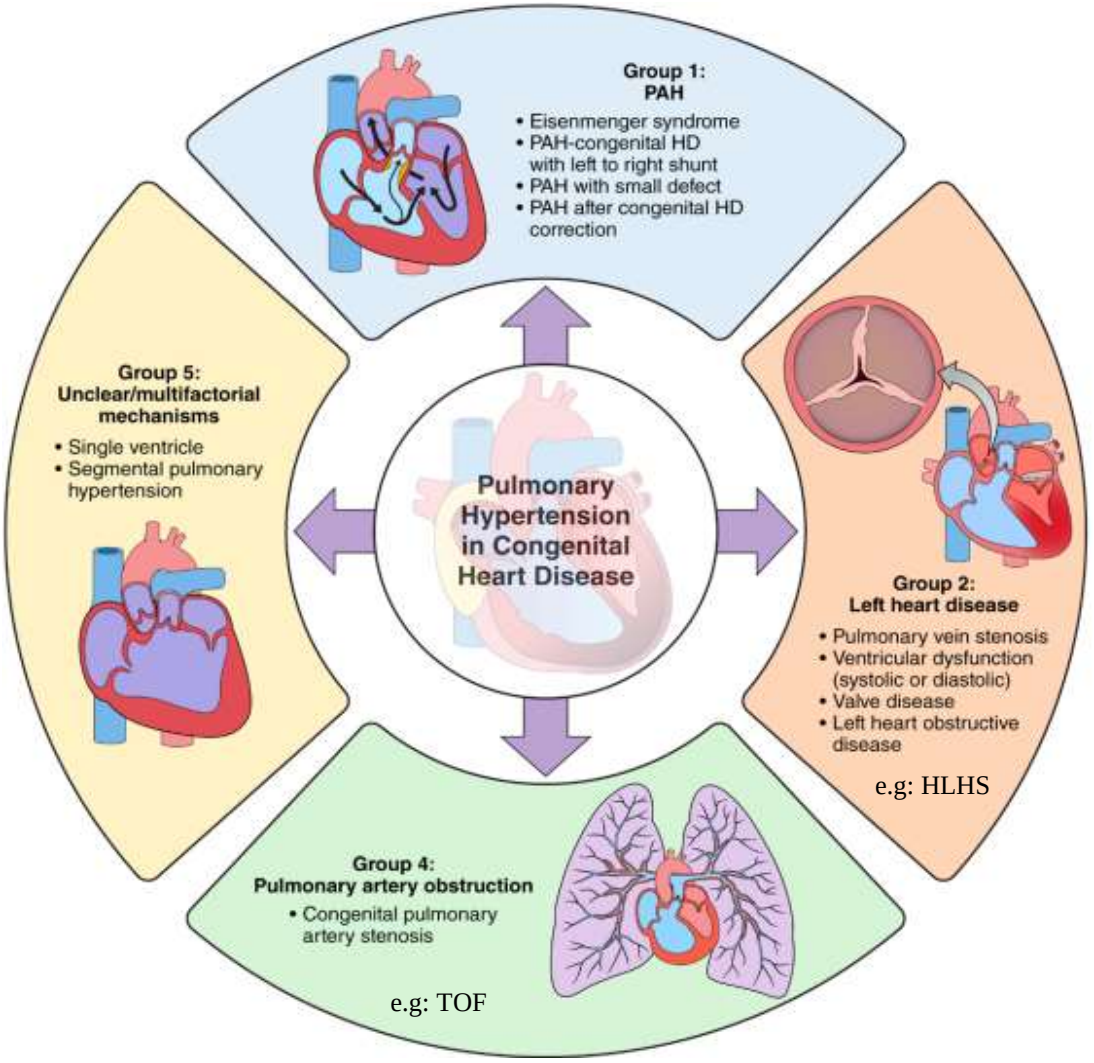
New Hemodynamic Definitions

Definition	Hemodynamic characteristics	
	6thWSPH (2018)	**ESC (2022)**
PH	**mPAP>20 mmHg**	**mPAP>20 mmHg**
Pre-capillary PH (PAH)	mPAP>20 mmHg PCWP or LAP ≤15 mmHg PVRI ≥3WU.m^2 Diastolic TPG ≥7 mmHg	mPAP>20 mmHg PCWP or LAP ≤15 mmHg **PVR ≥2WU.m^2**
Post-capiller PH	mPAP>20 mmHg PCWP>15 mmHg PVR<3WU.m^2 Diastolic TPG <7 mmHg	mPAP>20 mmHg PCWP>15 mmHg **PVR≤2WU.m^2**
Pre-capiller + post-capiller PH	mPAP>20 mmHg PCWP>15 mmHg PVR ≥3WU.m^2	
Exersize		**mPAP/CO>3 mmHg/L/min**

6th World Symposium of Pulmonary Hypertension (WSPH)-2018

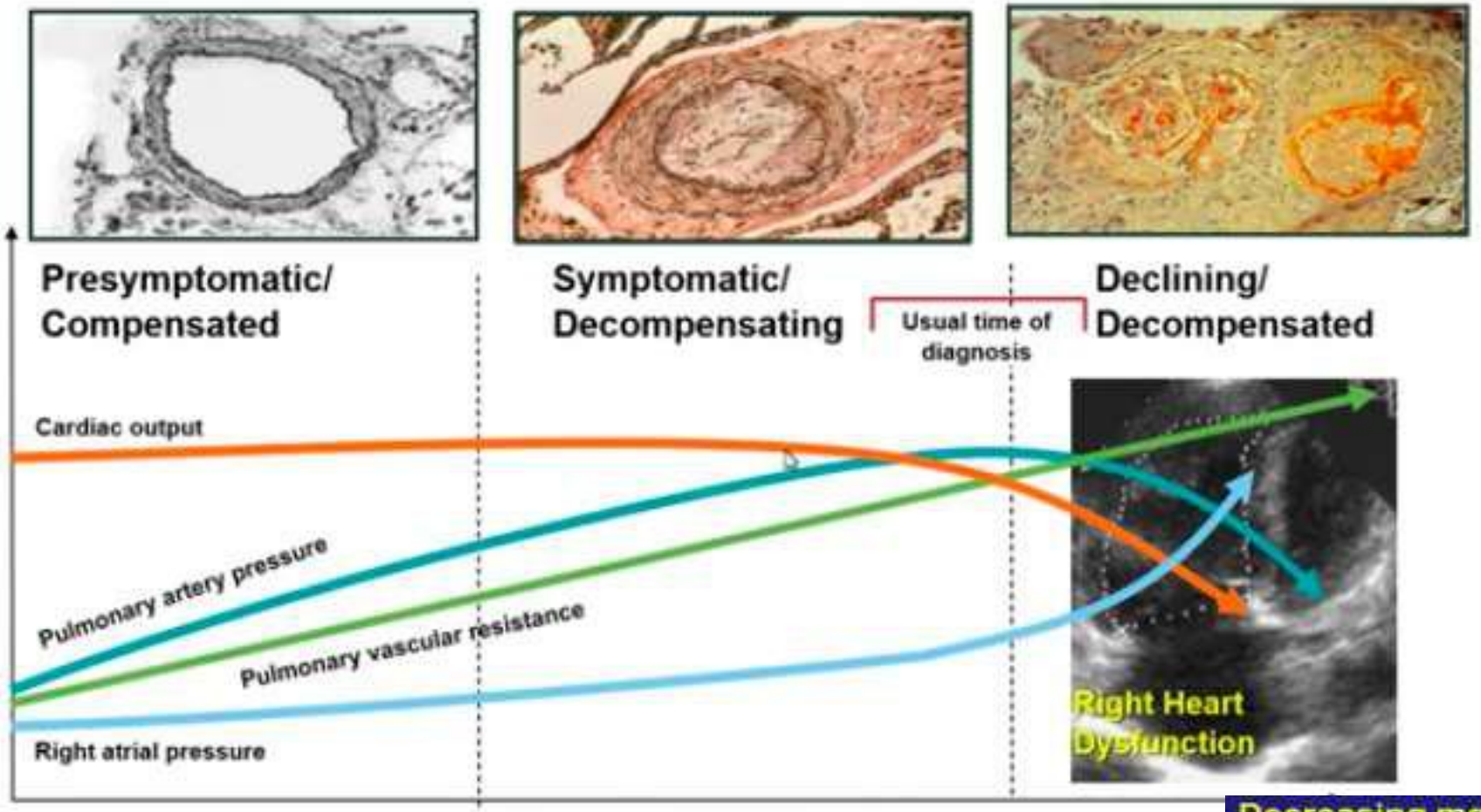
Different subgroups of PH in CHD

2018 Latest Classification, NICE



6th World Symposium of Pulmonary Hypertension (WSPH)-2018

Schematic Progression of PAH



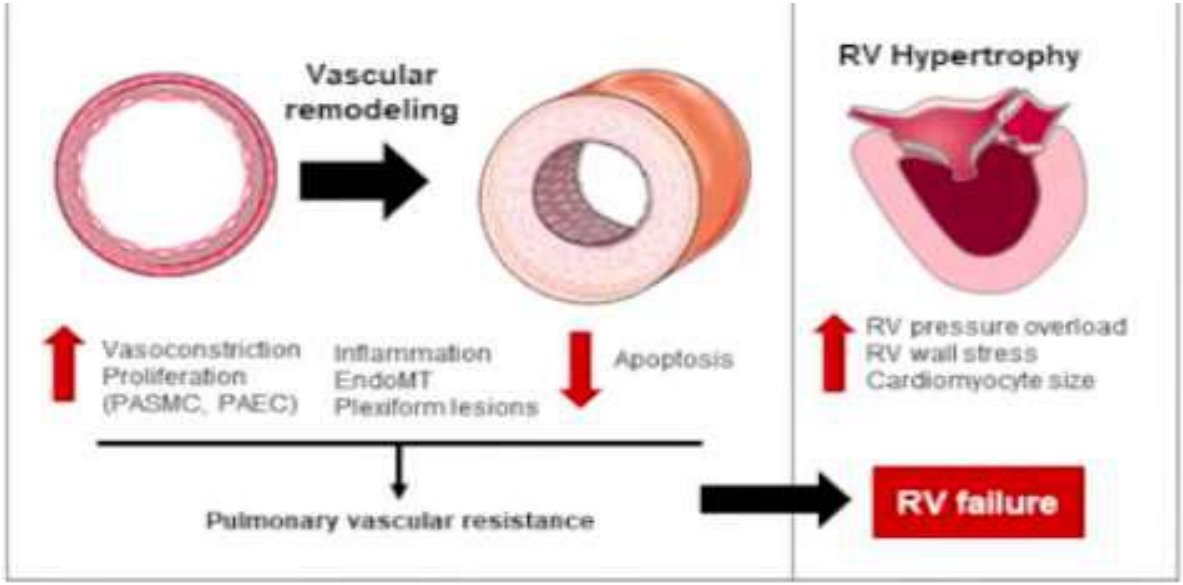
Adapted from: Hill NS. *Pulmonary Hypertension Therapy*. Summit Communications, LLC; 2006:9.

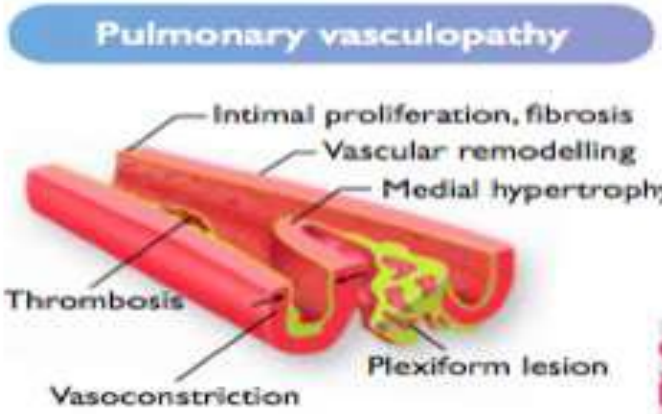
Decreasing mean PAP may not reflect improvement

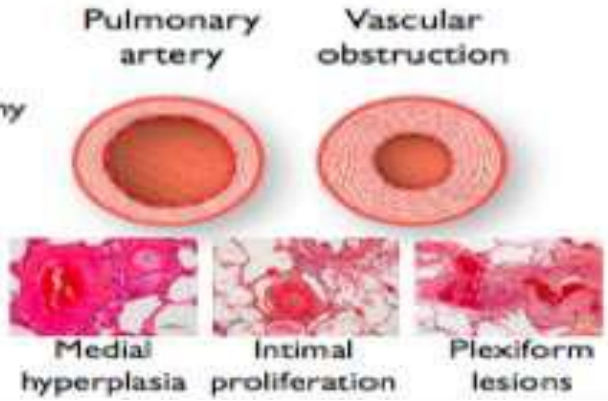
Pathophysiology of PAH

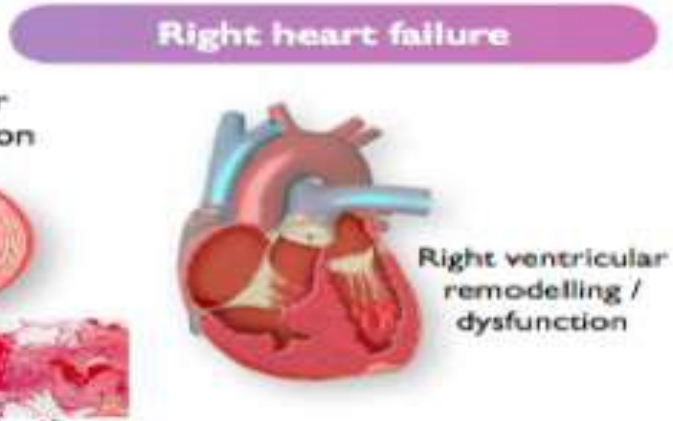
WHO group I:

Characterized by progressive growth and vasoconstriction of small pulmonary arteries









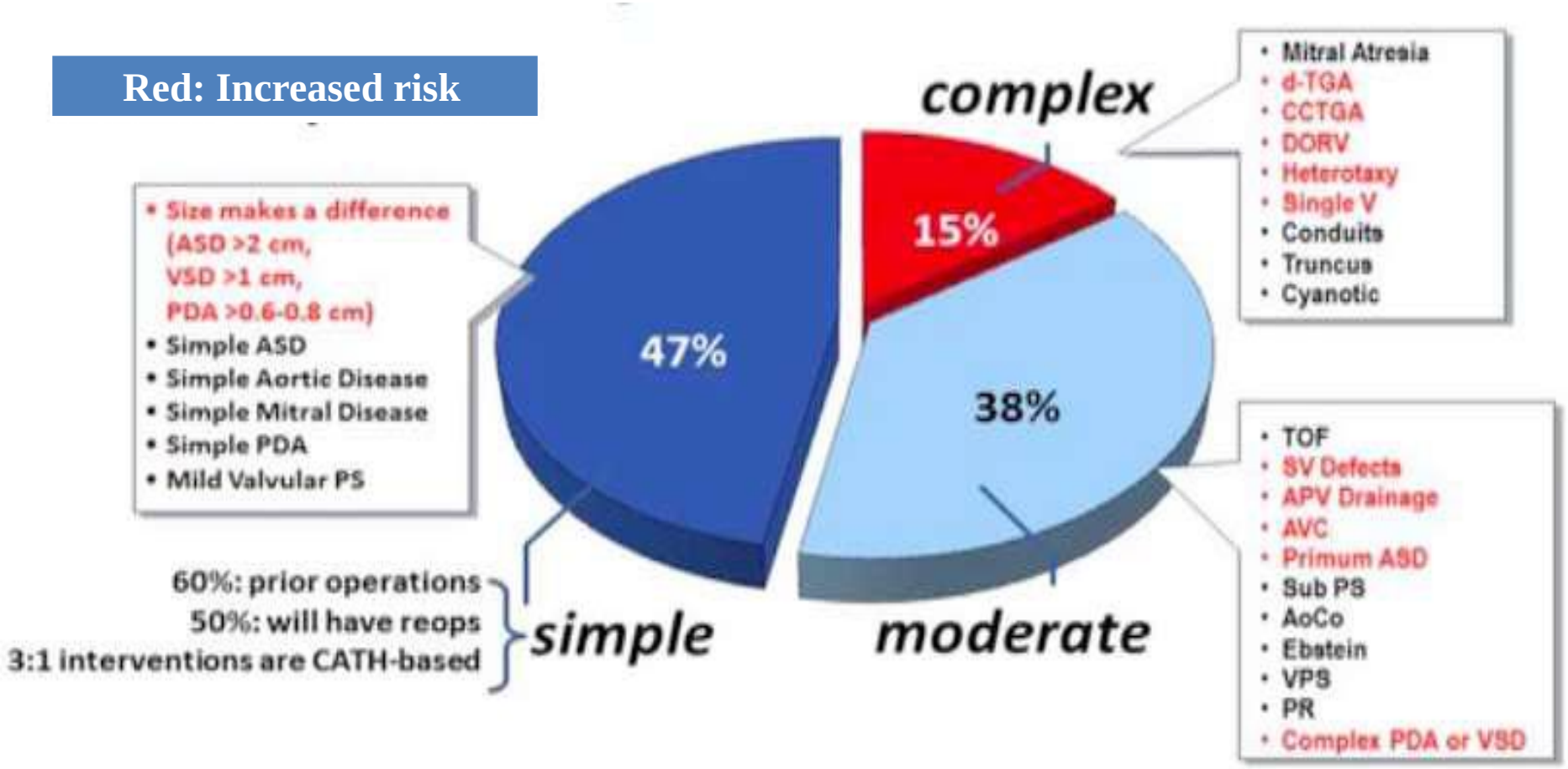
Risk factors for PAH with CHD

- **Type** and **size** of defect
- **Pressure** and **magnitude** of shunt flow of L→R shunt (Qp/Qs)
- **Age** (older age greater risk)
- **Surgical repair** (correction, palliations, repair)
- **Associated noncardiac syndromes** (e.g. Down syndrome)

Insights into pathophsiology

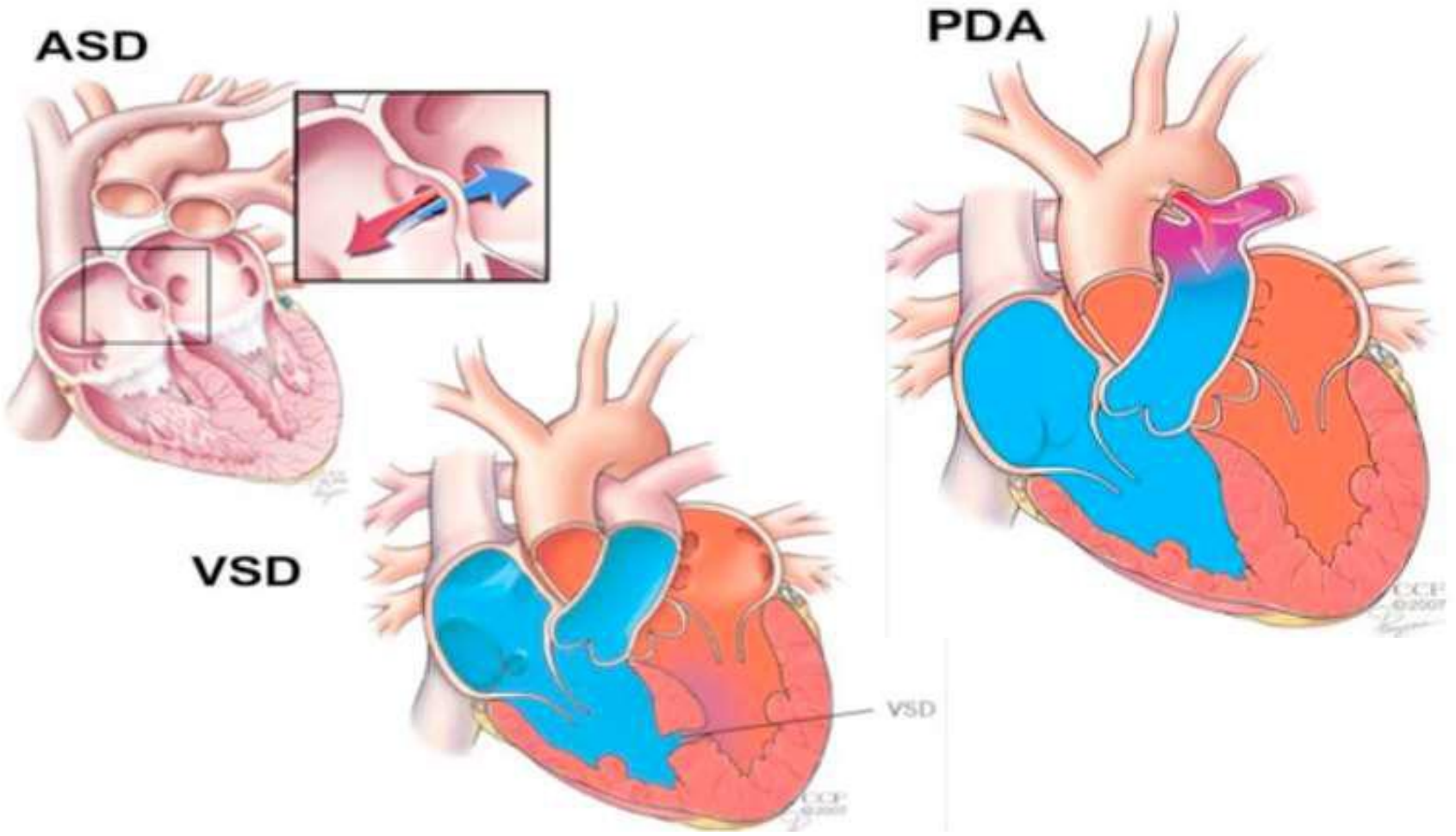
- **Cardiac biomarkers**
  - Markers of endothelial dysfunction/damage
    - ADMA
    - VEGF
  - Markers of inflammation
    - CRP
    - IL-6
  - Markers of RV strain
    - BNP
    - NT-proBNP
- **Potential genetic mediators**
    - BMPR2, TBX4, ACVRLI, SOX17

PAH complicates congenital systemic to pulmonary shunts

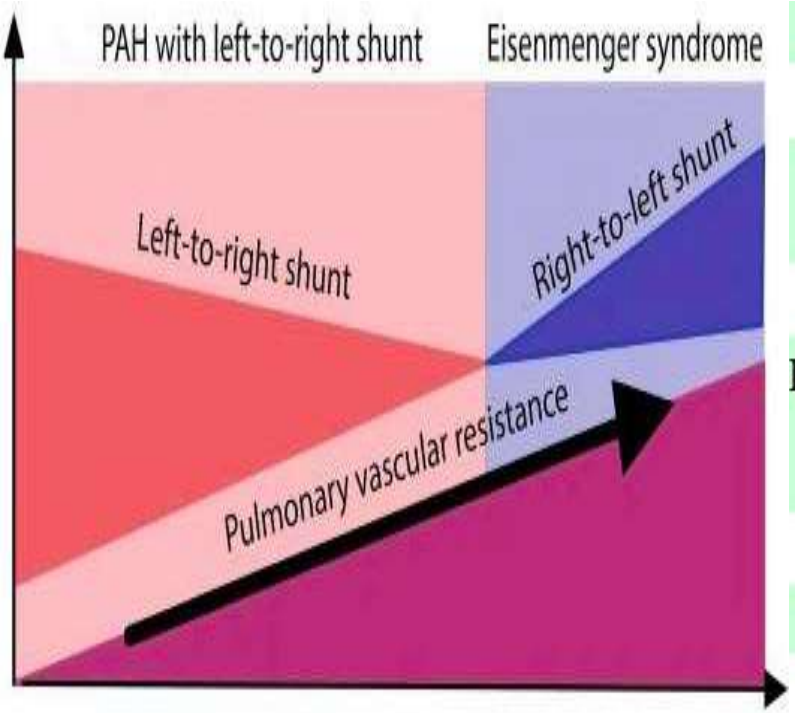


Patients with repaired and unrepaired defects can develop PAH (2-10%)

Major Culprit: Simple shunt lesions



Progression of PAH-CHD to Eisenmenger Syndrome



The most severe form of CHD-PAH

Systemic-Pulmonary Shunt (L-R shunt)

↓

Increased pulmonary blood flow and pressure
(shear stress/circumferential strecth)

↓

Endothelial dysfunction and pulmonary vascular remodeling
(Smooth muscle cell proliferation, increase in extracellular matrix, intravascular thrombosis)

↓

Increase in PVR

↓

Reversed shunt (R-L): pulmonary to systemic

↓

Cyanosis (Eisenmenger Syndrome)

Clinical Presentation

Symptoms frequently subtle and may delay diagnosis of PAH-CHD

Symptoms:

- Poor feeding
- Shortness of breath–dyspnea
- Tachypnea
- Tachycardia
- Poor growth
- Chest pain or discomfort
- Senkop or near-senkop

Signs:

- Juguler venous distension
- Increased central venous pressure
- Loud split 2nd heart sound
- Gallop
- Holosystolic murmur
- Edema
- Hepatomegaly

} Late signs of RH failure

Screening and Diagnostic Evaluation

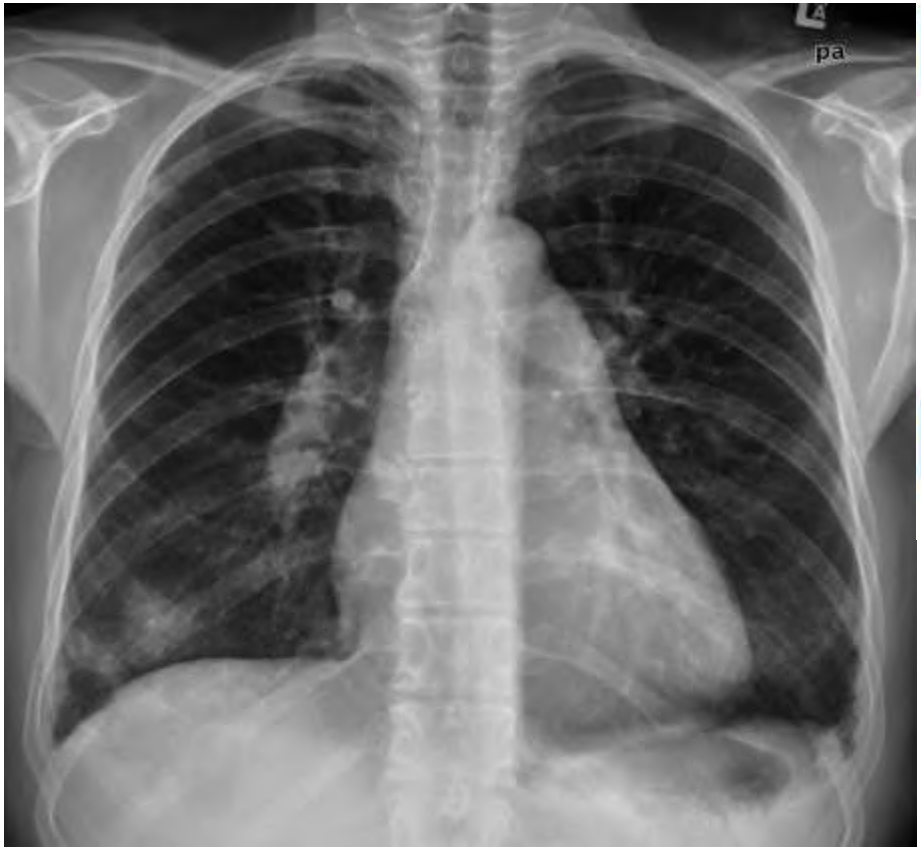
- ✓ Chest X-ray
- ✓ ECG: Right axis deviation, RV hypertrophy
- ✓ Echocardiography: RV hypertrophy, RV dysfunction
- ✓ Cardiac MR
- ✓ Imaging of pulmonary vascular structures
- ✓ V/P scintigraphy
- ✓ CT, HRCT
- ✓ Pulmoner angiography, cardiac cathaterization

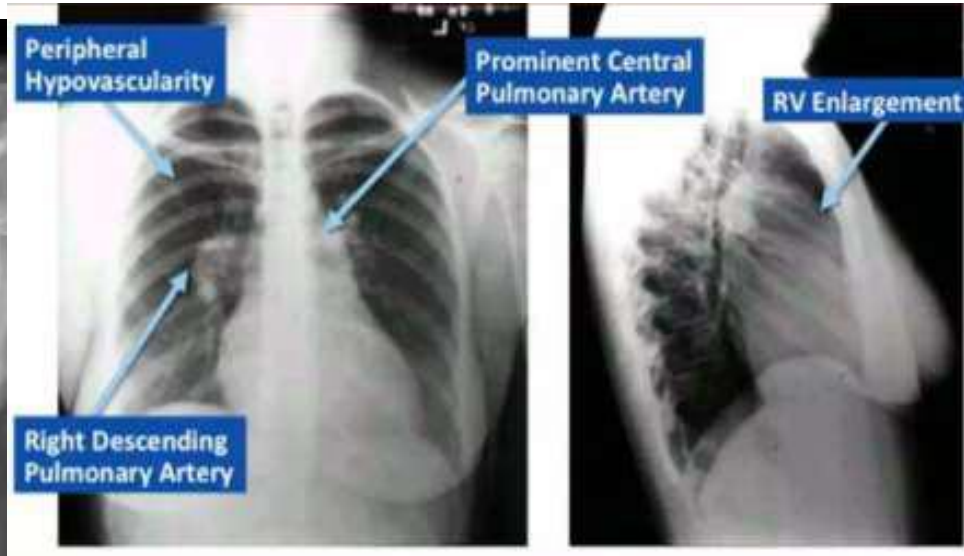
Perioperative directly measurement of PAP

- ✓ Swan-ganz cathaterization
- ✓ Perioperative TEE
- ✓ TTECHO

Chest Radiography

Gives clues about the degree of shunting

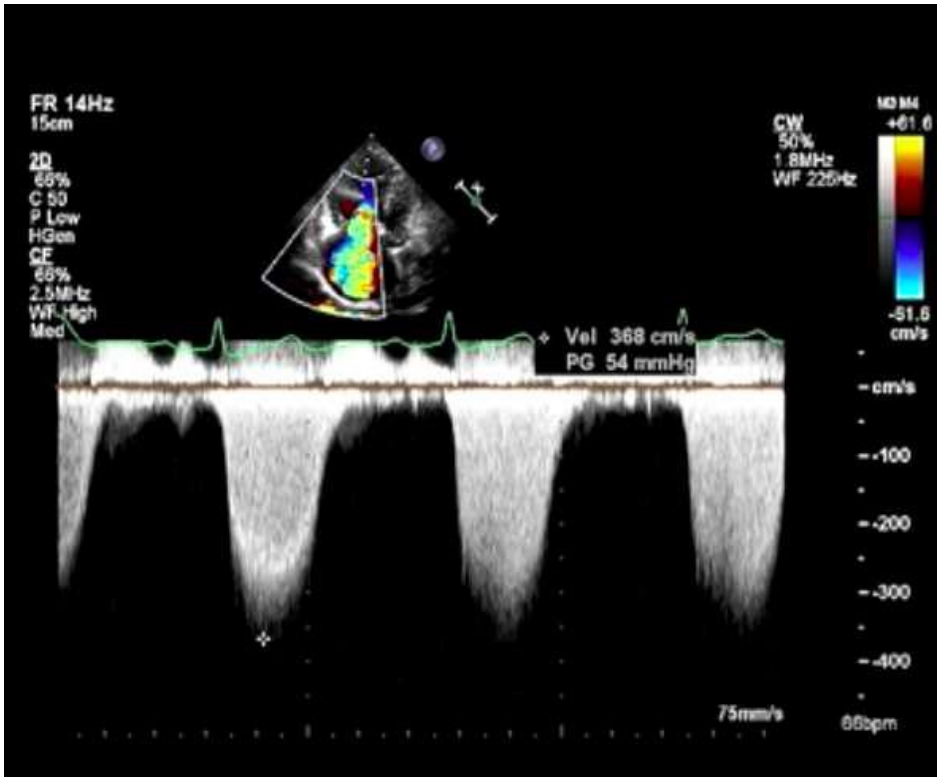




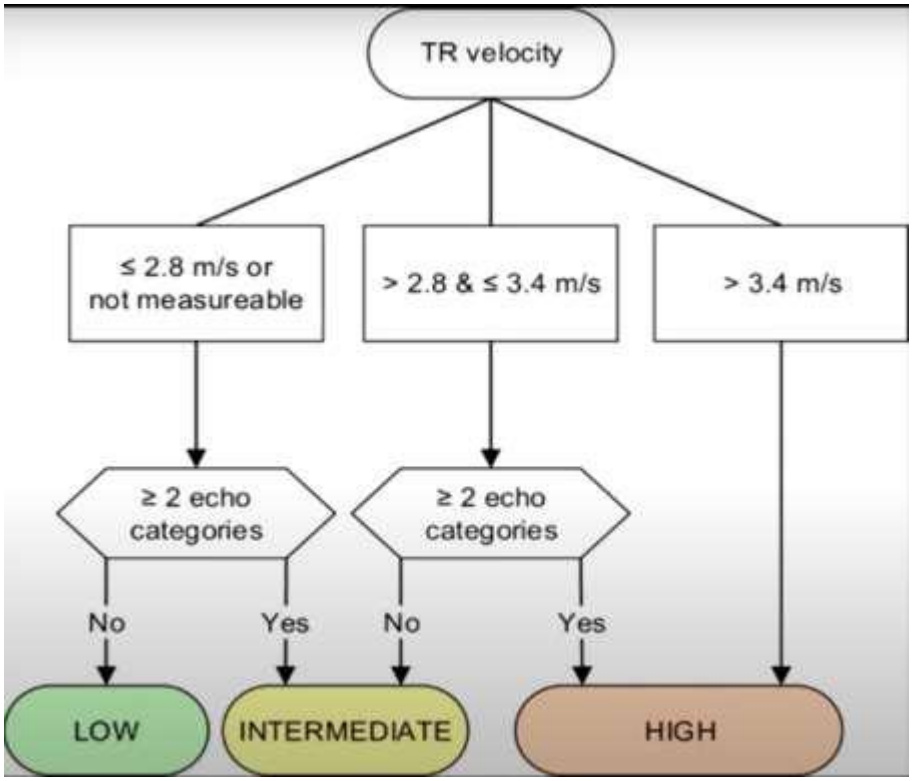
Enlarged cardiac silhouette with prominent pulmonary trunk pulmonary arteries proximally

Transthoracic Echocardiography

First-line cardiovascular imaging modality for diagnosis of PH

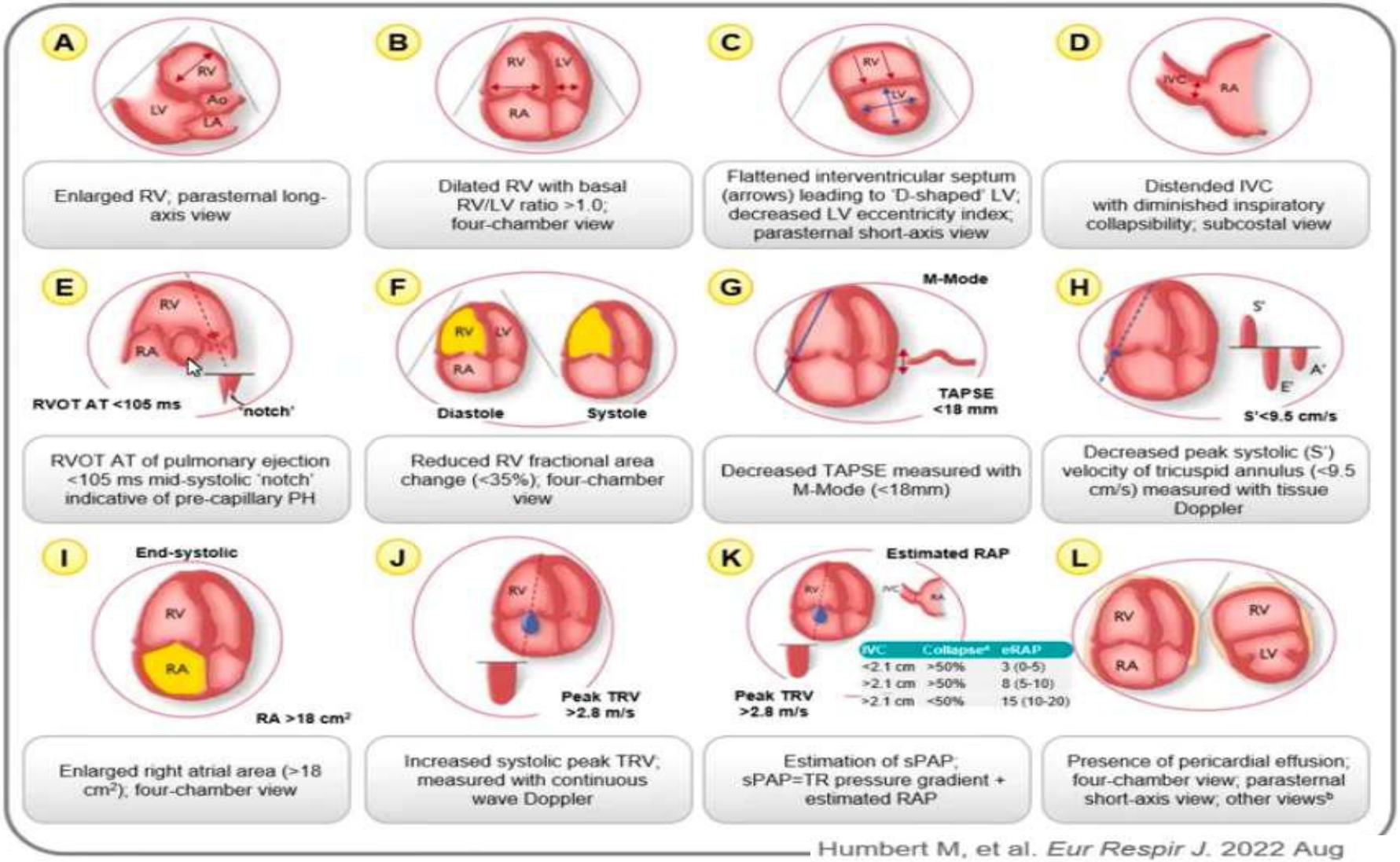


1st step in assessing PH by ECHO is to measure the peak TR Vmax



>3.4m/s➔high probaility of PH
<3.4 m/s➔assess the probability with other markers

TTE parameters in assessment



Humbert M, et al. *Eur Respir J.* 2022 Aug 30:2200879; Humbert M, et al. *Eur Heart J.* 2022 Aug 26:ehac237.

CT and MRI in pediatric PH

Cross-sectional imaging plays key role

- **CT** and **MRI** offer simultaneous view of structures in all 3D to helps describe complex CHD
- MRI angiography can identify extracardiac lesions
- MRI phase-contrast imaging can be used to calculate hemodynamic data, direction of intracardiac shunting, degree of shunting and identify physiological sequelae

Advantages and disadvantages

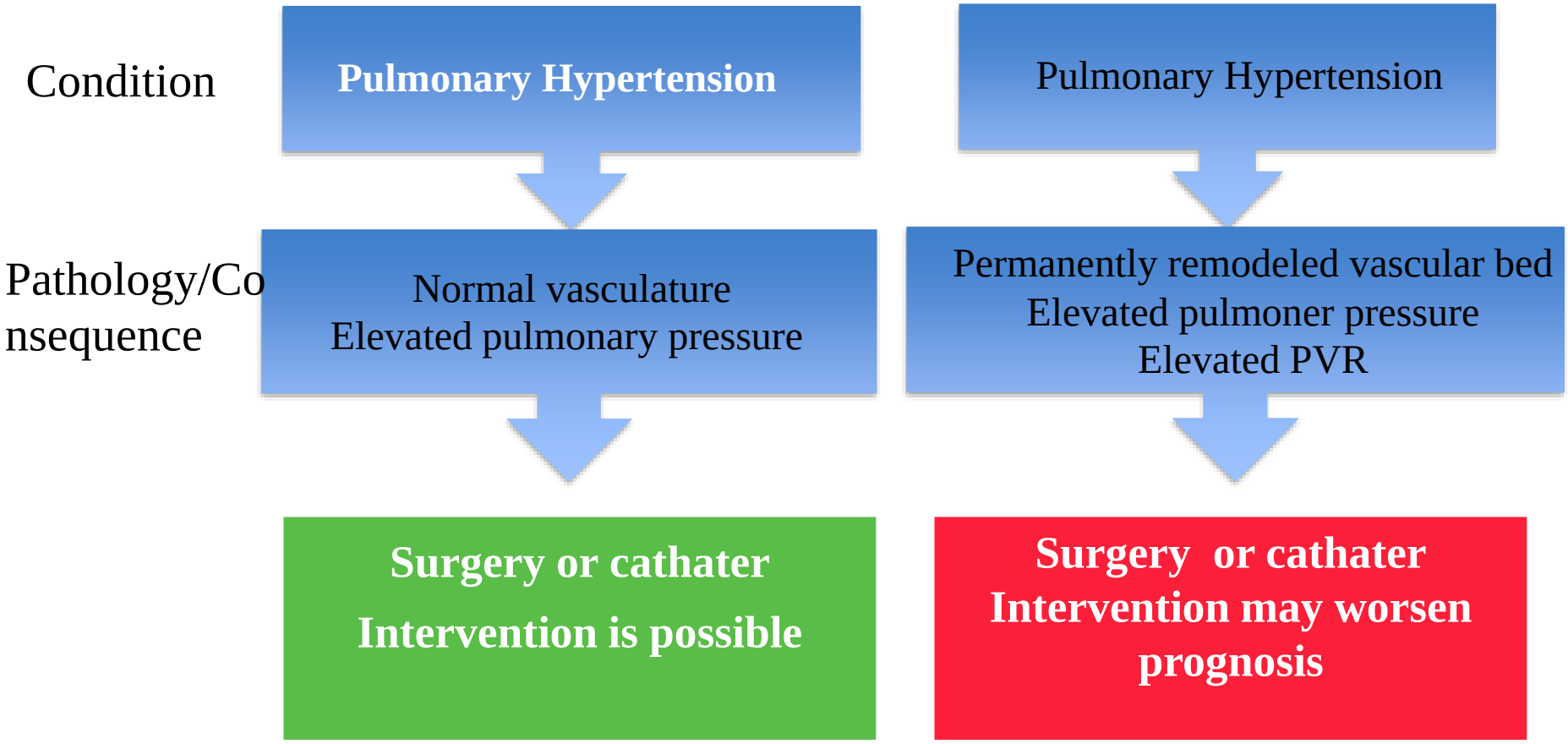
Characteristics of Imaging Techniques

Diagnostic Application	Right Heart Catheterization	Echocardiography	Multidetector CT	V/Q Scintigraphy	Cardiac MRI
RV assessment	+++	++	+	No	+++
PA vessel wall	No	+	++	No	+++
PA hemodynamics	+++	+	+	+	++
mPAP estimation	+++	++	No	No	+
Reproducibility	++	+	+++	++	+++
Ionizing radiation	Yes	No	Yes	Yes	No
Invasiveness	Yes	No	No	No	No
Role in PH diagnosis	Standard of reference Confirm diagnosis Pressure measurements	First-line imaging test Detection Rule out cardiac cause Rule out intracardiac shunt	Rule out specific cause Interstitial lung disease CTEPH Rule out intra- or extracardiac shunt PVOD/PCH	Rule out CTEPH	Functional assessment of RV and PA
Role in PH follow-up	Complicated owing to invasiveness Assessment of response to vasodilators	Adequate for first assessment and follow-up	Interstitial lung disease CTEPH	CTEPH	Well suited Role in treatment selection

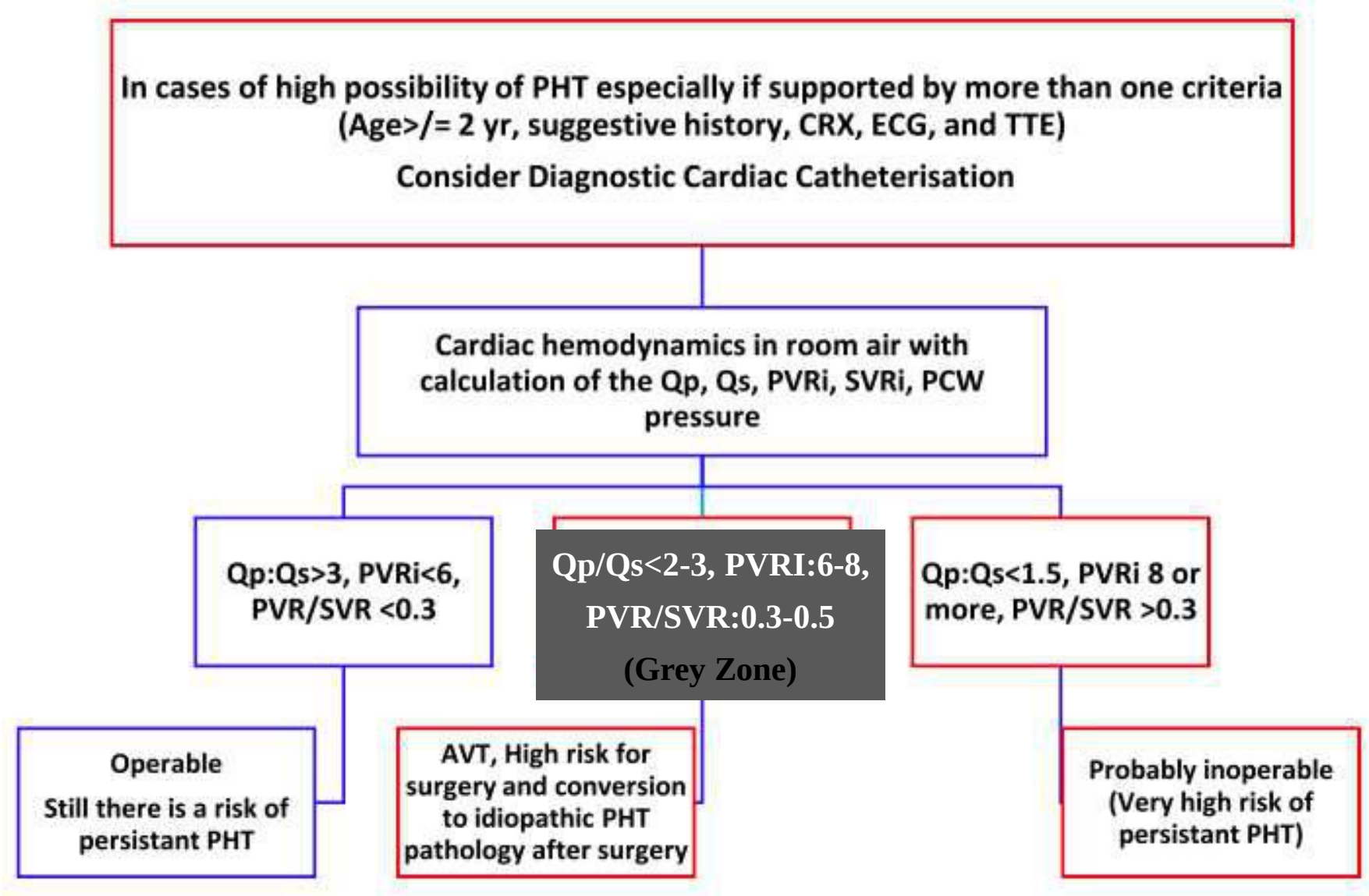
Cardiac Cathaterization

- **Gold standard**
- Should be done for all borderline cases
- Basal values should be taken under 21% O_2
- PVR, SVR, PVR/SVR and Qp/Qs
- **Acute vasoreactivity test** (AVT) for operability risk assessment with *iNO*, *epprostenol*, *adenosine*, *iloprost*, *treprostinil*, *milrinon*, *nitroglycerine*

Lesion Repair in CHD
Severities of Disease State to Consider



Operability risk assessment



Operability risk assessment

Qp/Qs<2-3, PVRI:6-8
PVR/SVR:0.3-0.5
(Grey Zone)

AVT recommended before surgery

After AVT:

Qp/Qs>1.5

- **20% decrease in PVRI**
- **20% decrease in PVR/SVR**
- **Final PVRI < 6 WU.m^2**
- **Final PVR/SVR < 0.3**

Positive response of AVT

Acute PVR Increase

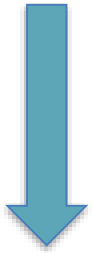
- Alveolar hypoxia (most potent)
- Hypoxemia
- Hypercarbia
- Sympathetic nervous system activation

- SIRS to CPBP
- Hypotermia
- Protamine
- PEEP
- Ventilatory dsynchrony

Pulmonary vasoconstriction

Acute PVR Increase

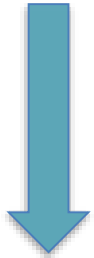
Rapidly developing RV failure



Pulmonary hypertensive crisis

ACUTE PVR INCREASE

Slowly developing RV failure (over years)



Eisenmenger Syndrome

Pulmonary Hypertensive Crisis

- Potentially fatal complication
- Pulmonary vasospasm ➔ **rapid increase in PVR** and **mPAP**
- PAP exceeds SBP
- RA and RV filling pressures increases
- Decrease in pulmonar blood flow ➔ cyanosis
- Decrease in SBP ➔ cardiac arrest

Inflammatory pathways activated after CPB cause endothelial dysfunction in the lung

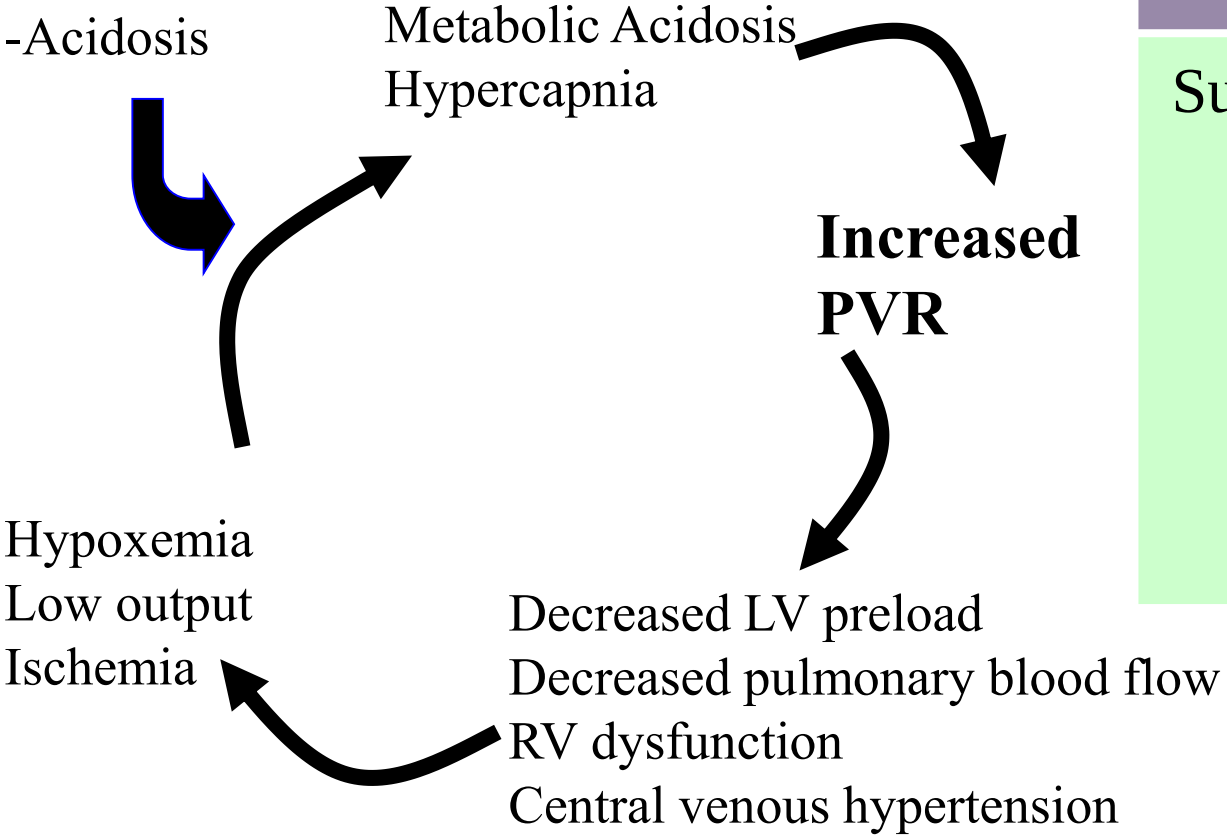
PH Crises/Acute RV Failure

Precipitating Event

-Cold stress

-Suctioning

-Acidosis



The viscious cycle of PH
Suden decrease in SpO_2
Arrhythmia
Hypoxia
Hypotension
Metabolic acidosis
Increased lactate

Treatment of PAH Crisis

TREATMENT	JUSTIFICATION
Administer 100% O_2	Increased P_aO_2 may reduce PVR
Achieve respiratory alkalosis	PAP is directly related to $PaCO_2$
Correct metabolic acidosis	PVR is directly related to H+ concentration
Avoid hypovolemia	Provide careful fluid resuscitation
Support CO/ bedside ECHO	Adequate preload and inotropic support
Reduce pain stimulation (providing analgesia), deepen anaesthesia	PAP may increase, fentanyl reduces its severity
Treat hypothermia	
Administer pulmonary vasodilator	iNO first choice (20 ppm, reduce to 5 ppm) Monitoring MetHb
Atrial septostomy in RV failure, mechanical support (ECMO)	Can benefit in some cases

Anesthetic Management of Children with PAH

Goals of anesthesia:

✓ Maintain pulmonary blood flow

✓ Prevent additional workload for RV

✓ Prevent increase in PVR

✓Avoide reduction in SVR

✓ Maintain coronary artery perfusion…

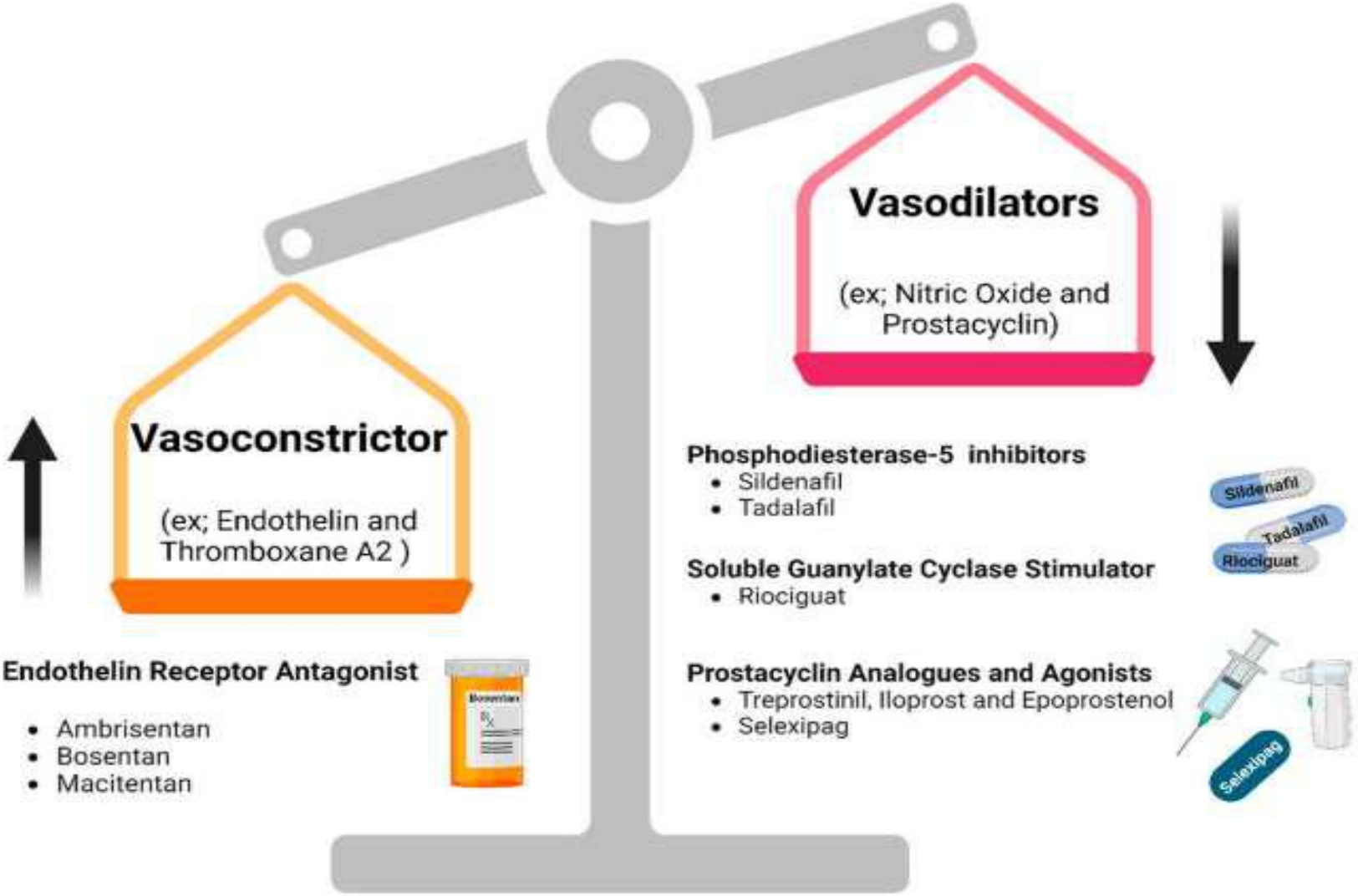
Increase in PVR and decrease in myocardial functions should be minimized

…which technique accomplishes this, is the **“right”** technique!

Ventilation strategies

- Over-aggressive ventilation can reduce RV filling, increase PVR
- Inadequate ventilation (spontaneous or mechanical) will reduce MV, increase atelectasis, hypoxia, hypercarbia, and thus PVR
- Minimal airway manipulations/aspiration
- Alcalosis

Treatment strategies



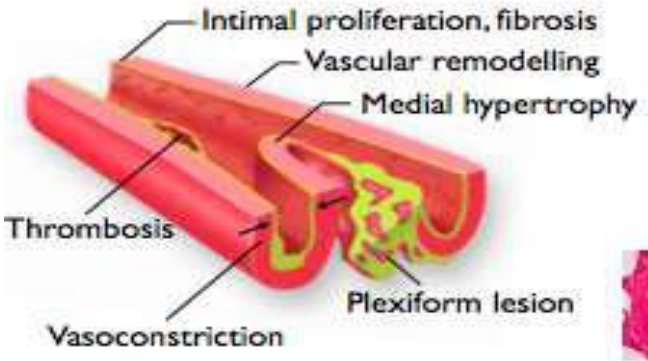
Treatment strategies

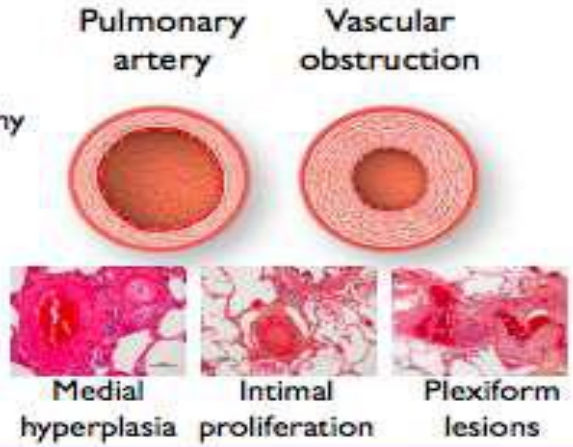
Spesific treatment strategies include;

Decrease PAP, PVR

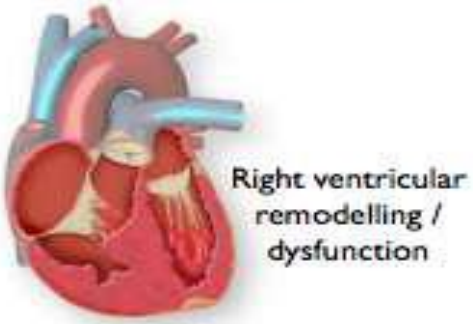
Optimise RV functions

Pulmonary vasculopathy

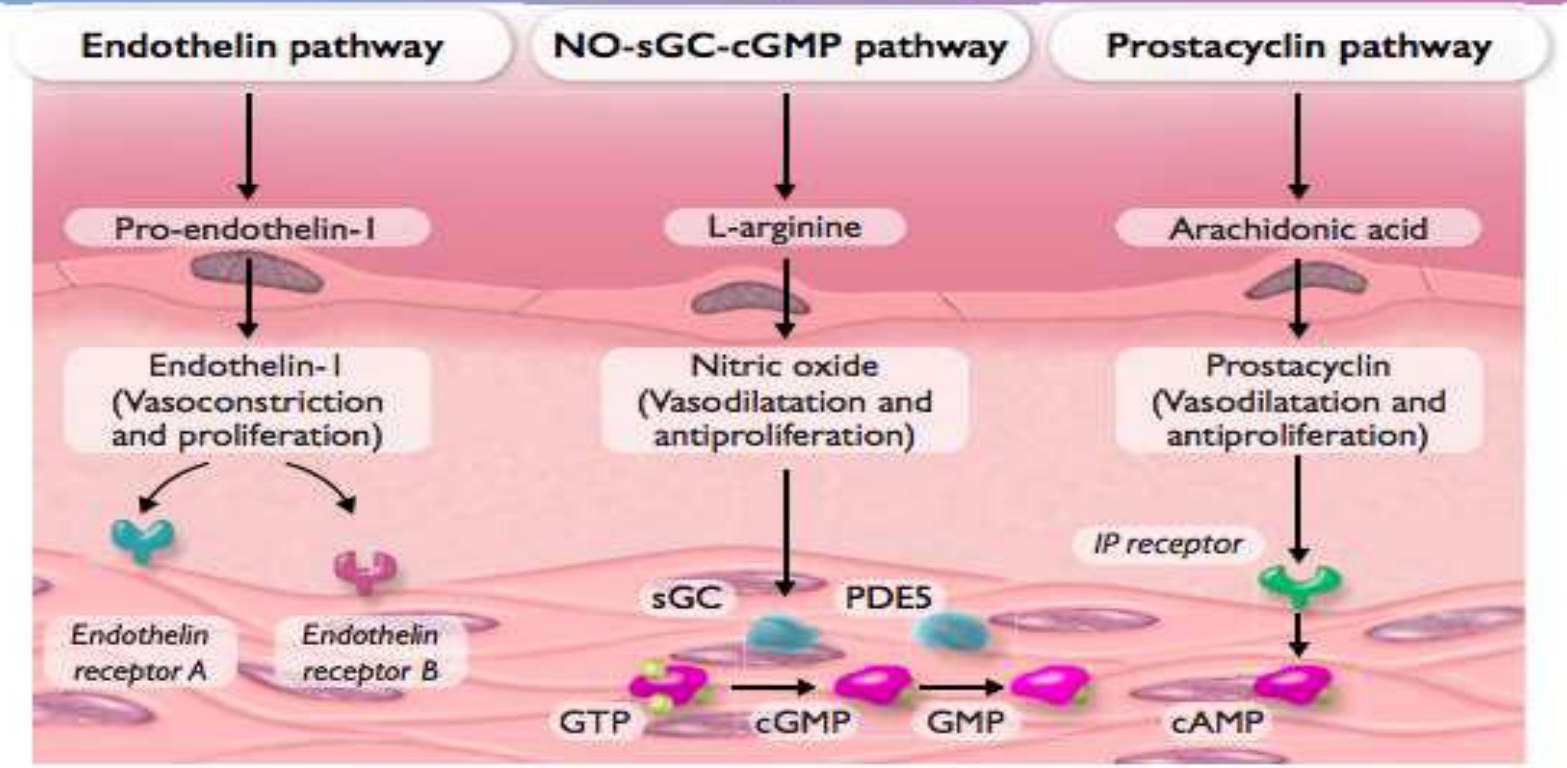




Right heart failure



Current therapeutic targets



Treatment strategies

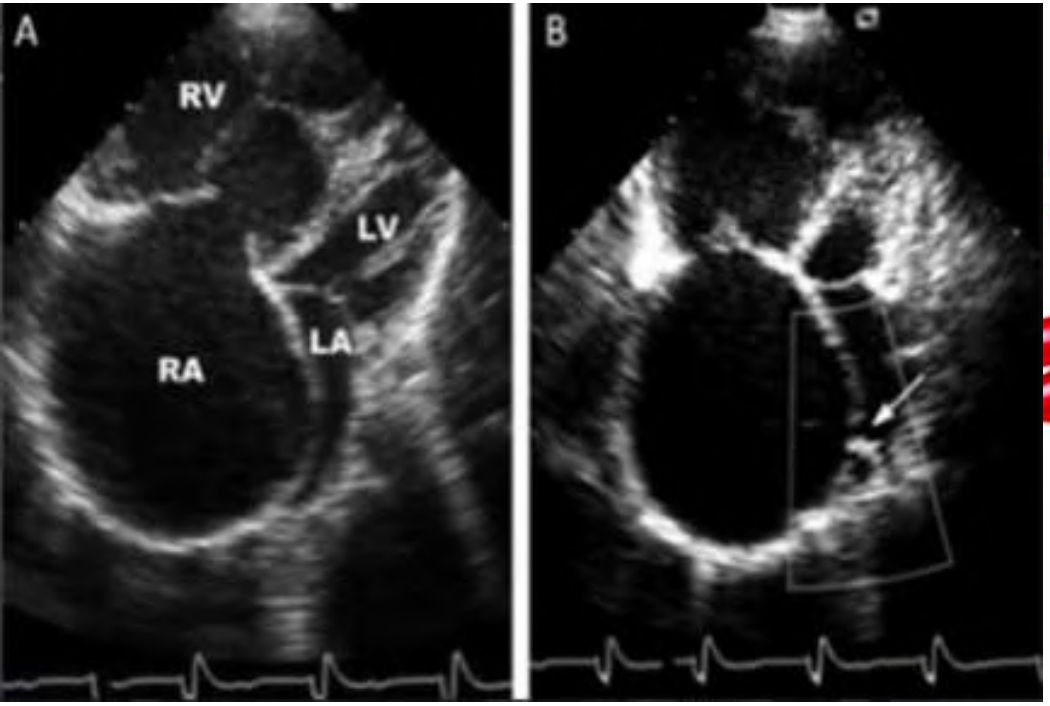
Drug Pathway	Drug Name	Dosage	Adverse Effects	Comments
CCB*	Nifedipine (oral)	Starting dose: 0.1–0.2 mg/kg x3/d	Bradycardia, Decreased cardiac output, Edema, Rash, Gum hyperplasia, Constipation	Duration of benefit may be limited even with initial favorable response, repeat assessment for response. Contraindicated in age < 1 year
	Diltiazem (Oral)	Starting dose: 0.5 mg/kg x3/d Dose range 3–5 mg/kg/d	Same above	Same above
	Amlodipine (oral)	Starting dose: 0.1–0.3 mg/kg/d dose range 2.5–7.5 mg/d	Same above	Same above
NO pathway PDE5 inhibitors	Sildenafil (oral) (IV)	Age< 1 y: 0.5–1 mg/kg x3/d weight ‘ 20 kg: 10 mg x3/d weight>20 kg: 20 mgx3/d (IV) 0.4 mg bolus/3 h	Headache, Nasal congestion, Flushing, Agitation, Hypotension, Vision and hearing loss, Priapism.	iv sildenafil may be used in PPHN (COR II b, LOE C) postop CHD** Avoid higher dosing. Approved in Europe and Canada, FDA: warning for use in children. Avoid nitrates.
	Tadalafil**(oral)	Starting dose: 0.5–1 mg/kg/d max. dose 40 mg/d. Evaluated only in children >3 years	Same above	Safety and efficacy data in children are limited
Endothelin pathway ERAs	Bosentan* dual ETA, ETB antagonist (oral)	Weight, < 10 kg: 2 mg/kg x 2/d, 10–20 kg: 31.25 mg x2/d, 20–40 kg: 62.5 mg x2/d, >40 kg: 125 mg x2/d	Hepatotoxicity, anemia, edema, teratogenicity, male infertility, may decrease sildenafil level	Also effective in Eisenmenger
	Ambrisentan**Selective ETA antagonist (oral)	Dose range: 5–10 mg/d use in pediatric patients< 5 y unstudied	Same above	Safety and efficacy data in children are limited, avoid use in neonates or infants
	Macitentan dual ETA, ETB antagonist (oral)	Dose range: 3 mg/d or 10 mg/d in adults (SERAPHİN trial)	Hepatotoxicity, peripheral edema	Approved for adult PAH
Prostacyclin pathway	Epoprostenol*(iv)	Starting dose: 1–2 ng/kg/min. infusion in pediatric pt. 50–80 ng/kg/min. Max.dose 150 ng/kg/min.	Flushing, jaw, foot, bone, pain, headaches, diarrhea, hypotension, catheter complication	Standard therapy for severe PH
	Treprostinil*(Remodulin) (iv and sc) (inh.)	Starting dose: 2 ng/kg/min in pediatric patients stable dose 50–80 ng/kg/min. (inh)18mcg x4/day	Flushing, muscle pain, headaches, diarrhea, site pain in sc use	For iv and sc use
	Iloprost** (intermittent inhalation)	6–9 inhalation per day each lasting 10–15 min. Start with 2.5 µg, up to 5 µg	Flushing, jaw pain, headaches, reactive airway symptoms	For inhalation** nebulizer required, patient activation and controlled inhalation, limited by age
	Selexipag IPreceptor agonist) (oral)	Initial dose 200 mcg x2/d increase by 200 mcg/d at weekly intervals max. dose 1600 mcg x2/d	Flushing, headache, diarrhea, vomiting, myalgia, arthralgia	Approved for adult PAH
Soluble guanylate cyclase (sGC) stimulator	Riociguat (oral)	Initial dose 0.5 mg x3/d if blood pressure >95 mm Hg increase the dose with two weeks intervals to max dose (2.5 mg x3/d)	Headache, palpitations, peripheral edema, dizziness, dyspepsia, nausea, diarrhea, vomiting, gastritis, constipation.	Approved for adult PAH

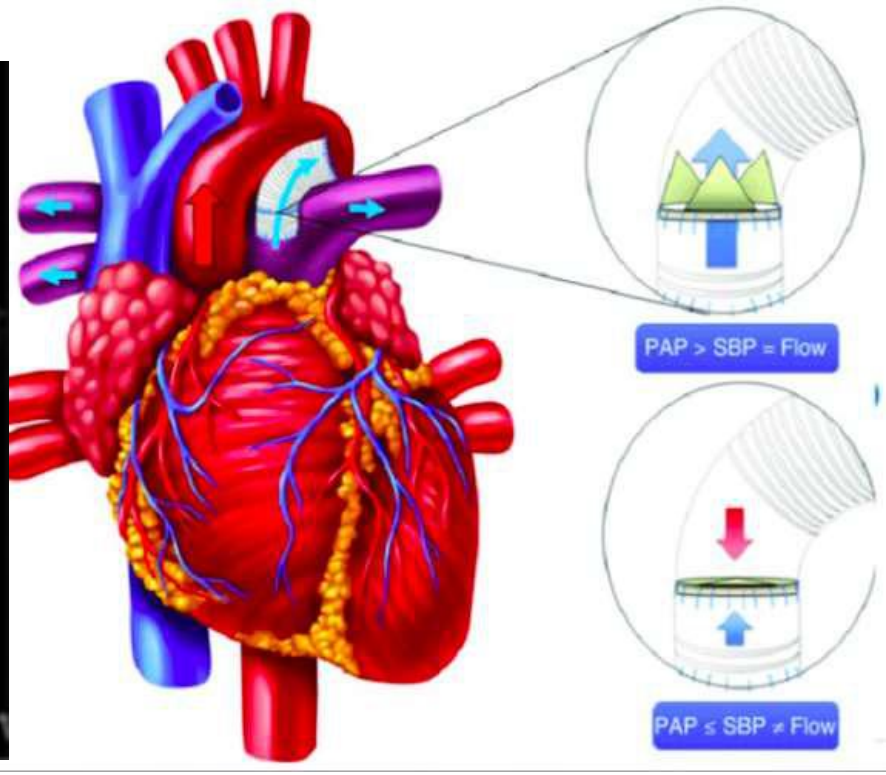
COR: class of recommendation LOE: level of evidence, In Europe all drugs except Bosentan and Sildenafil are considered off-label drugs for pediatric PAH patients.
*COR I, LOE B, **COR IIa, LOE B

Drugs used in ICU for treatment of PH

Drug	Dose	Caution
Epoprosetenol iv	1-3 ng/kg/min iv (start) 60 ng/kg/min (max dose)	Arterial hypotension Change iv pathway in 12-24 hr Need to pause at 10-20 ng/kg/min Change drug delivery system every 12-24 hr
Iloprost inhalation/iv	0.25 mcg/kg max 10 mcg; Inhalation 6-9 inhalations/24 hrs/continuous inh. 1-5 ng/kg/min iv	Systemic hypotension.
iNO	Inhalation 2-40 ppm continuous	Monitor MetHgb
Sildenafil iv, po	2-4 mg/kg/d iv (no bolus) 8-20 kg BW: 3x10 mg p.o >20 kg BW: 3x20 mg p.o	Max dose 7.2 mg/kg/day iv <8 kg: 1mg/kg/dose q 6 hrs (drug not approved no RCT data)
Epinephrine	0.01-1 mcg/kg/min iv infusion	(+) inotropy, ↑ myocardial O_2 consumption, tachycardia Moderate effect on PVR and SVR
Norepinephrine	0.01-1 mg/kg/min iv infusion	↑SVR, ↑ PVR
Vasopresin	0.0003-0.002 IU/kg/min iv infusion	No increase in PVR (advantages vs. norepinephrine)
Terlipresin iv	5-10 ng/kg/min iv infusion	No increase in PVR (advantages vs. norepinephrine)
Dobutamine	5-20 mcg/kg/min	↑Myocardial O_2 consumption, tachycardia
Milrinone	0.3-1.0 mcg/kg/min iv infusion	PVR↓, Arterial hypotension
Levosimendan	0.1-0.2 mcg/kg/min iv infusion	PVR↓, Arterial hypotension Long half-life
Treprostinil iv	1-3 ng/kg/min (start), increase gradually, efective-midterm dose:2-3 fold higher for treprositinil than epoprostenol	No increase in PVR (advantages vs. norepinephrine)

Invasive Therapies

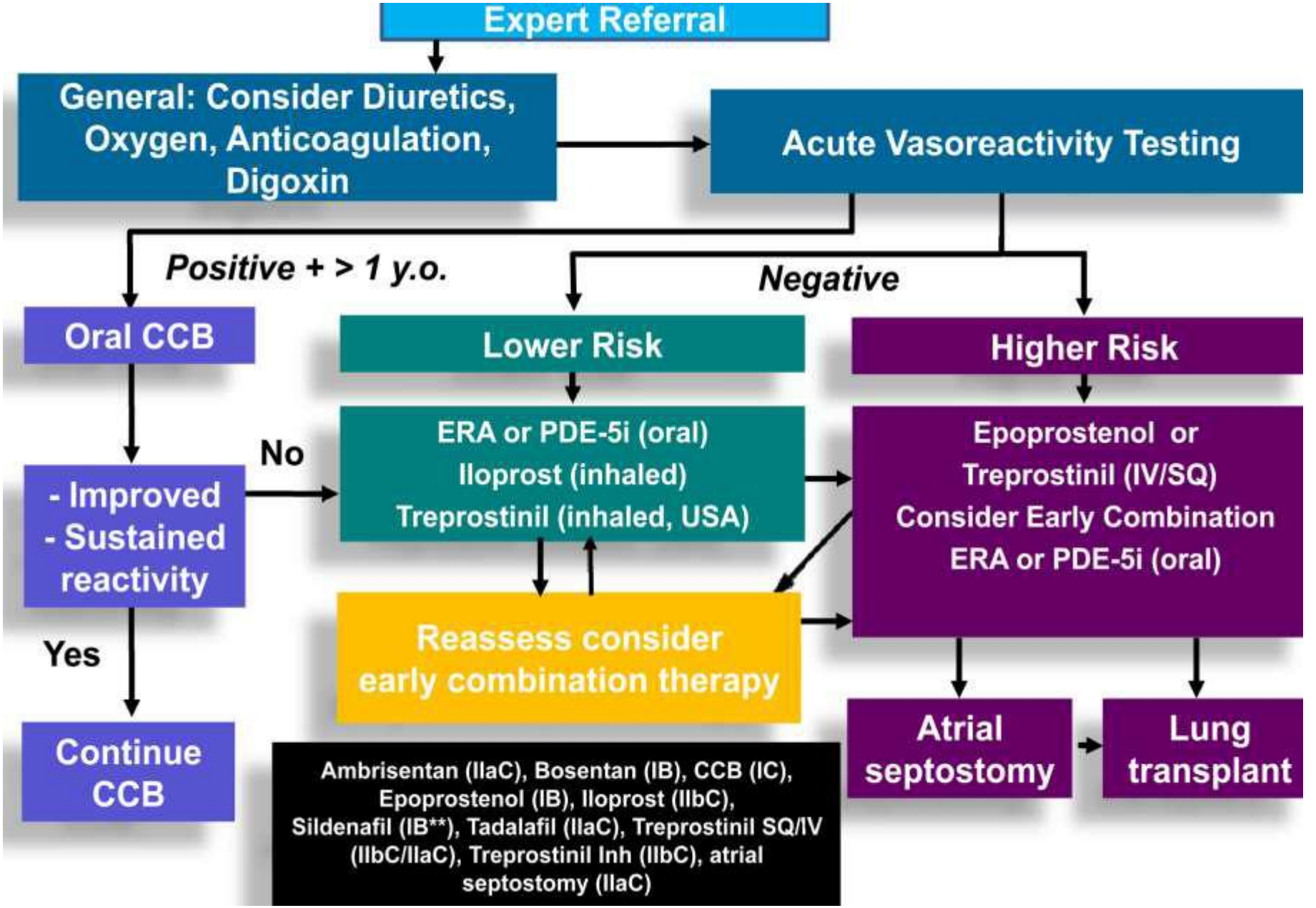




Balloon atrial septostomy

In patients with severe PAH, right heart failure, markedly elevated PVR not recommended because of massive R-L shunt and severe hypoxemia.

Reverse Poot's Shunt only for suprasistemic PAH



World Symposium on PH 2018 Consensus Pediatric IPAH/FPAH Treatment Algorithm*

Conclusion

✓ CHD is frequent and important cause of PAH in children

✓ Early repair of cardiac lesion with intensive postoperative care is best strategy to prevent development of progressive PAH

✓ Once PAH develops, aggressive medical treatment ensues in the hopes of reversibility.

✓ **ECG, CXR, ECHO are first investigations**

✓ ECHO provides rapid noninvasive estimation of PAH; excludes CHD; assesses severity&prognicates

Conclusion

✓ Look for PH in CHD patients, even if repaired

✓ Right heart cathaterization is the GOLD standard PRIOR to initiating selective drug therapy, but in small babies sometimes start medication before cath.

✓ Adapt your approach – simply following a PAH algorithm can lead to complications

✓ Chronic PAH increase morbidity and mortality, anesthetic management must be carefully considered!

Surname, First Name ..... Date of Birth ..... Patient´s ID .....

Parameter	Measured Variable	Lower Risk Criteria	Higher Risk Criteria
Clinical Presentation	Clinical evidence of RV failure (e.g. exertional dyspnoea, fatigue, dizziness, ankle swelling, epigastric fullness and right upper abdominal discomfort or pain)	no ☐	yes ☐
	Progression of symptoms	no ☐	yes ☐
	Syncope	no ☐	yes ☐
	Growth	Normal (height, BMI) ☐	Failure to thrive ☐
	WHO functional class	*I, II ☐	*III, IV ☐
Laboratory Results	Serum NT-proBNP	*Minimally elevated for age or not elevated ☐	*Greatly elevated for age, i.e. >1200 pg/mL (>1yr old) Rising NT-proBNP level ☐
Medical Imaging	Echocardiography, CMR	Minimal RA/RV enlargement ☐ No RV systolic dysfunction ☐ RV/LV endsystolic ratio < 1 (PSAX) ☐ TAPSE normal (z > -2) ☐ S/D ratio <1.0 (TR jet) ☐ PAAT > 100 ms (>1yr old) ☐	Severe RA/RV enlargement ☐ RV systolic dysfunction ☐ RV/LV endsystolic ratio >1.5 (PSAX) ☐ TAPSE (z < -3) ☐ S/D ratio >1.4 (TR jet) ☐ PAAT <70 ms (>1yr old) ☐ Pericardial effusion ☐
Cardiac Catheterization Last CATH study (date): ..... (preceding 12 months)	Invasive Hemodynamics	*Cardiac index >3.0 l/min/m² ☐ *mRAP <10 mm Hg ☐ mPAP/mSAP <0.5 ☐ Acute vasoreactivity + ☐	*Cardiac index <2.5 l/min/m² ☐ *mRAP >15 mm Hg ☐ mPAP/mSAP >0.75 ☐ PVRi >15 WU x m² ☐

Lower Risk	Intermediate Risk	Higher Risk
= at least 3 starred (*) lower-risk and no higher-risk criteria (CATH available). or = at least 5 non-starred lower-risk and no higher-risk criteria (CATH not available). Date:..... ☐	= definitions of lower or higher risk not fulfilled. Date:..... ☐	= at least 2 starred (*) higher-risk criteria including cardiac index (CATH available). or = greatly elevated NT-proBNP* and at least 5 non-starred higher-risk criteria (CATH not available). Date:..... ☐

Pediatric PH – Individual Risk Stratification

Teşekkür ederim

Terima Kasih