Pediatric Pulmonary Hypertensions

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Malformations Cardiaques Congénitales Complexes-M3C

Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN

NICE

February 27-28
March 1, 2018

TASK FORCE 12
Pediatrics

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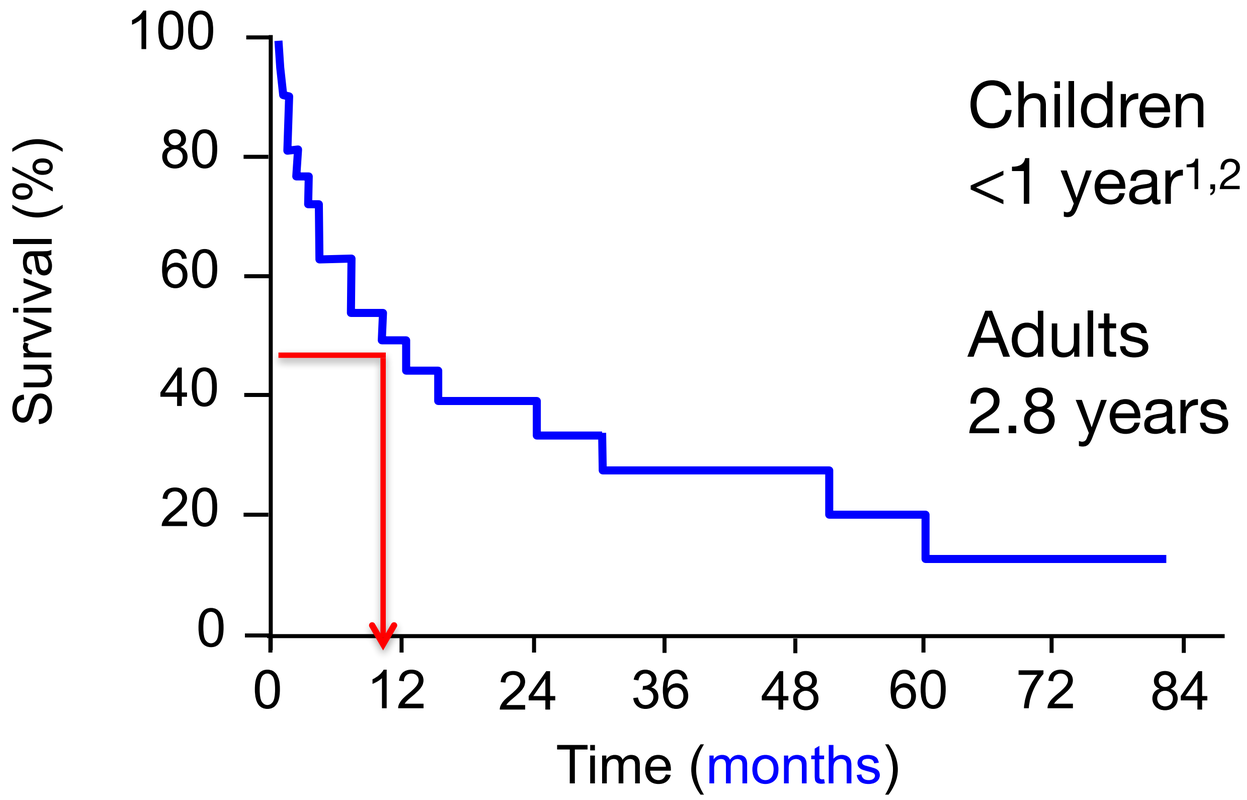
WORLD SYMPOSIUM
ON PULMONARY HYPERTENSION

Key messages
in pediatric pulmonary hypertensions

Natural History of IPAH: NIH Registry

Median survival: 2.8 years (n=194)

Pediatric median survival: 0.8 years (n=16)



1. Houde C, *et al. Br Heart J* 1993;70:461-8.
2. Barst, RJ, *et al. Circulation* 1999; 99:1197-208.

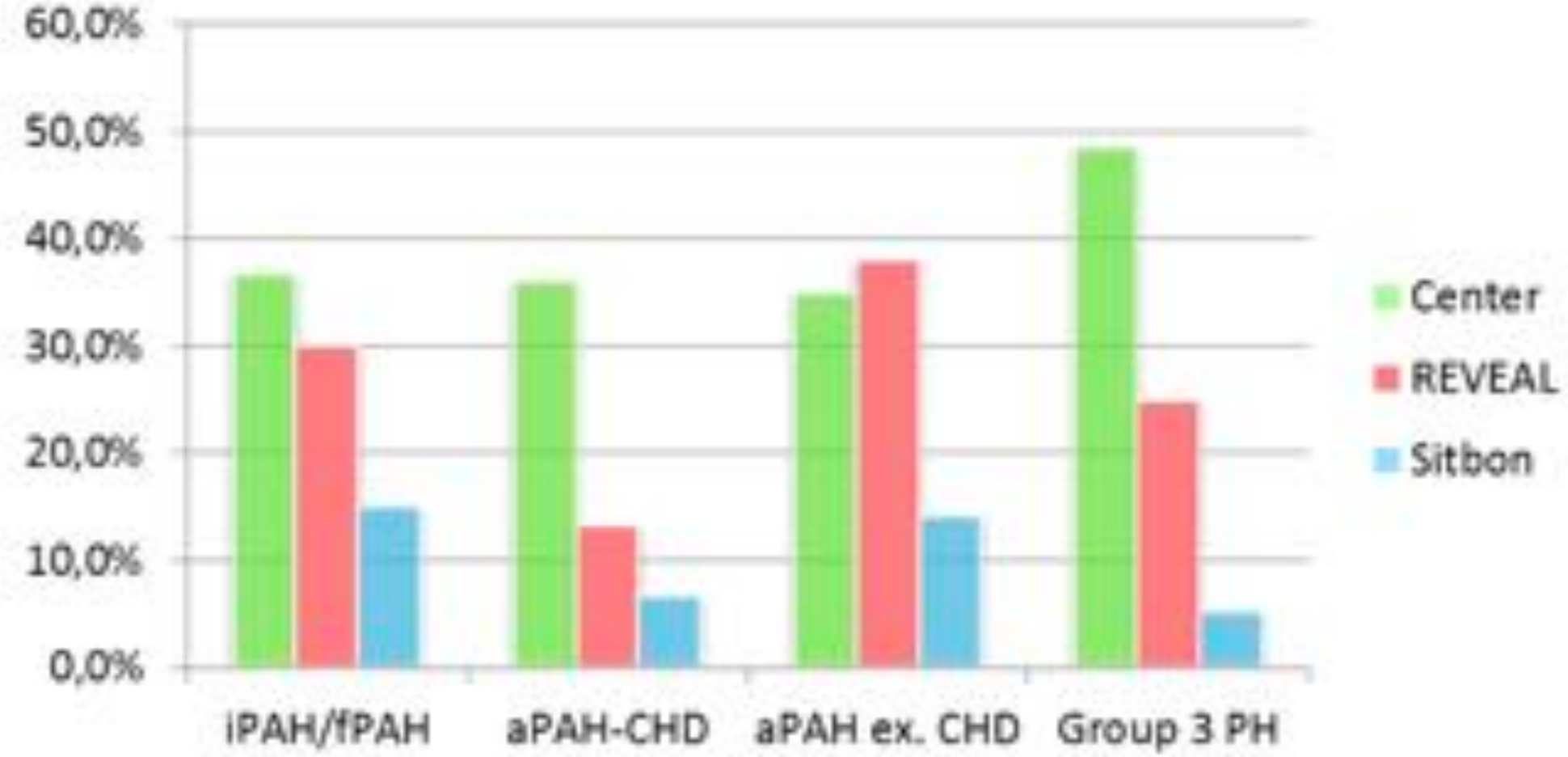
Definition of pediatric PH/PAH

- A mean pulmonary arterial pressure of >25 mmHg with a capillary wedge pressure of <15mmHg and a PVRi >3WU*m2 in children > 3 months of age with two ventricle anatomy.

- Limited data to extend the definition to children with mean PAP 21-24 mmHg.

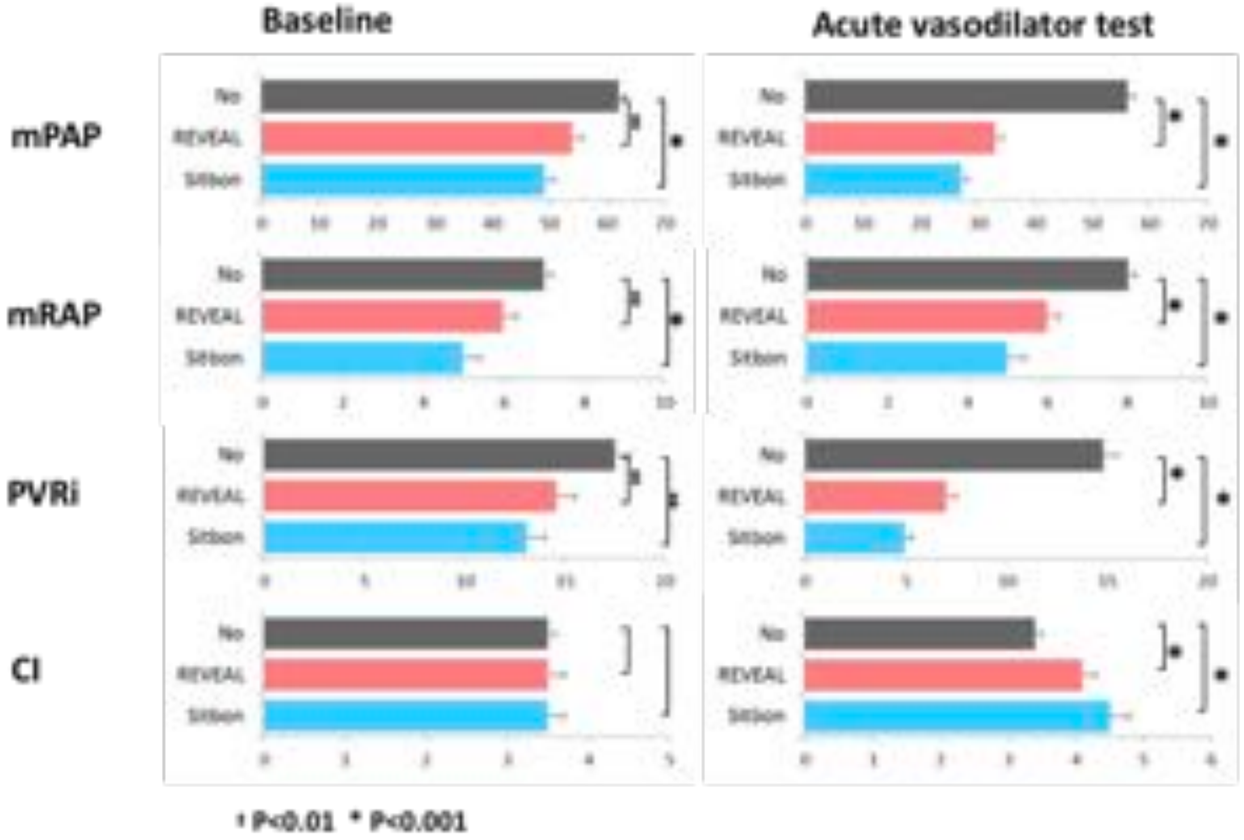
- Age is a pending problem:
  - Definition of PH in children less than 3 months of age
  - No RHC measure of pulmonary pressure in neonates with PPHN or PH associated with developmental lung disease

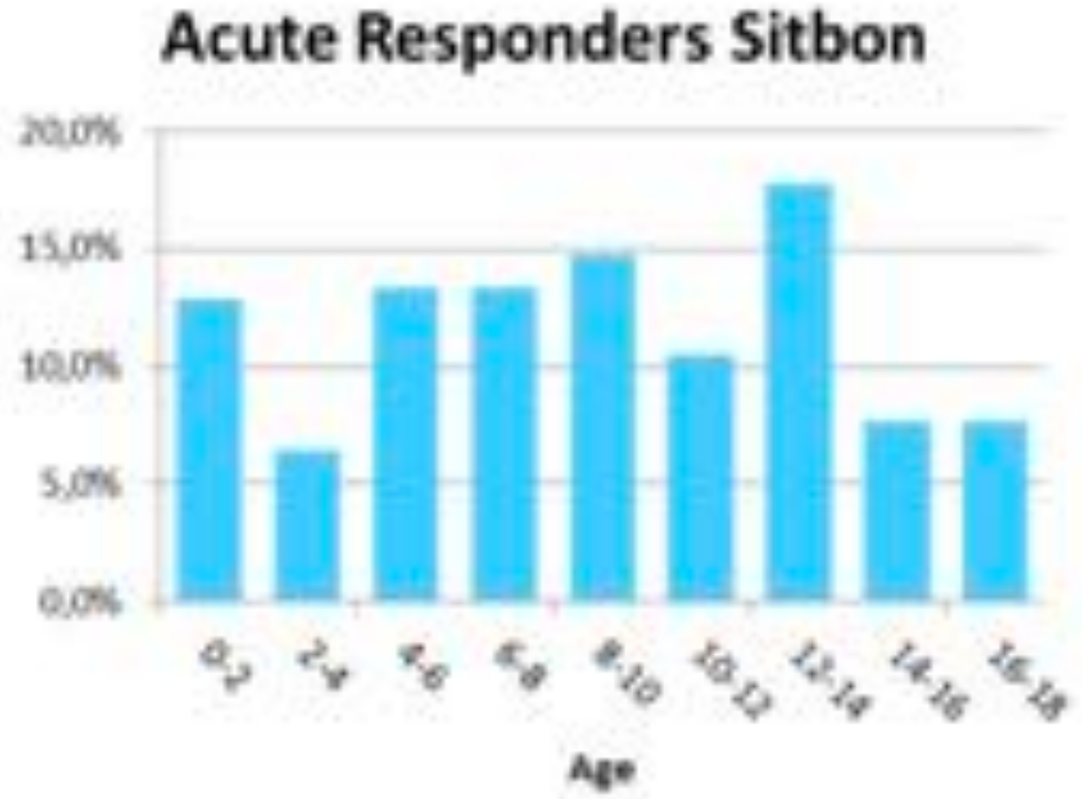
Definition of vasoreactivity in children



Douwes M et al. JACC 2016

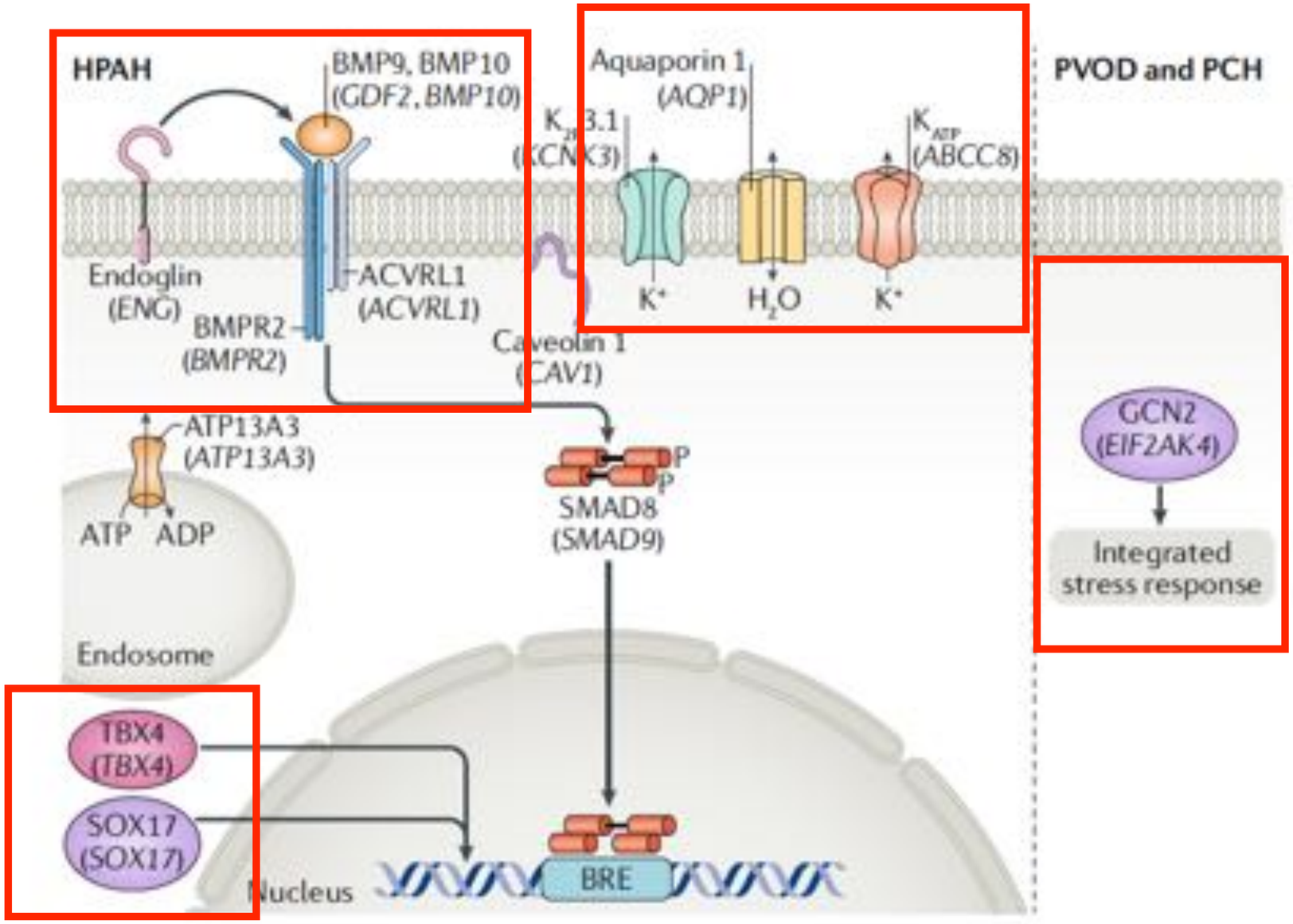
Definition of vasoreactivity in children





Douwes M et al. JACC 2016

Genetic architecture of hPAH



Southgate L et al. Nat Rev Cardiol 2019

PAH

PVOD

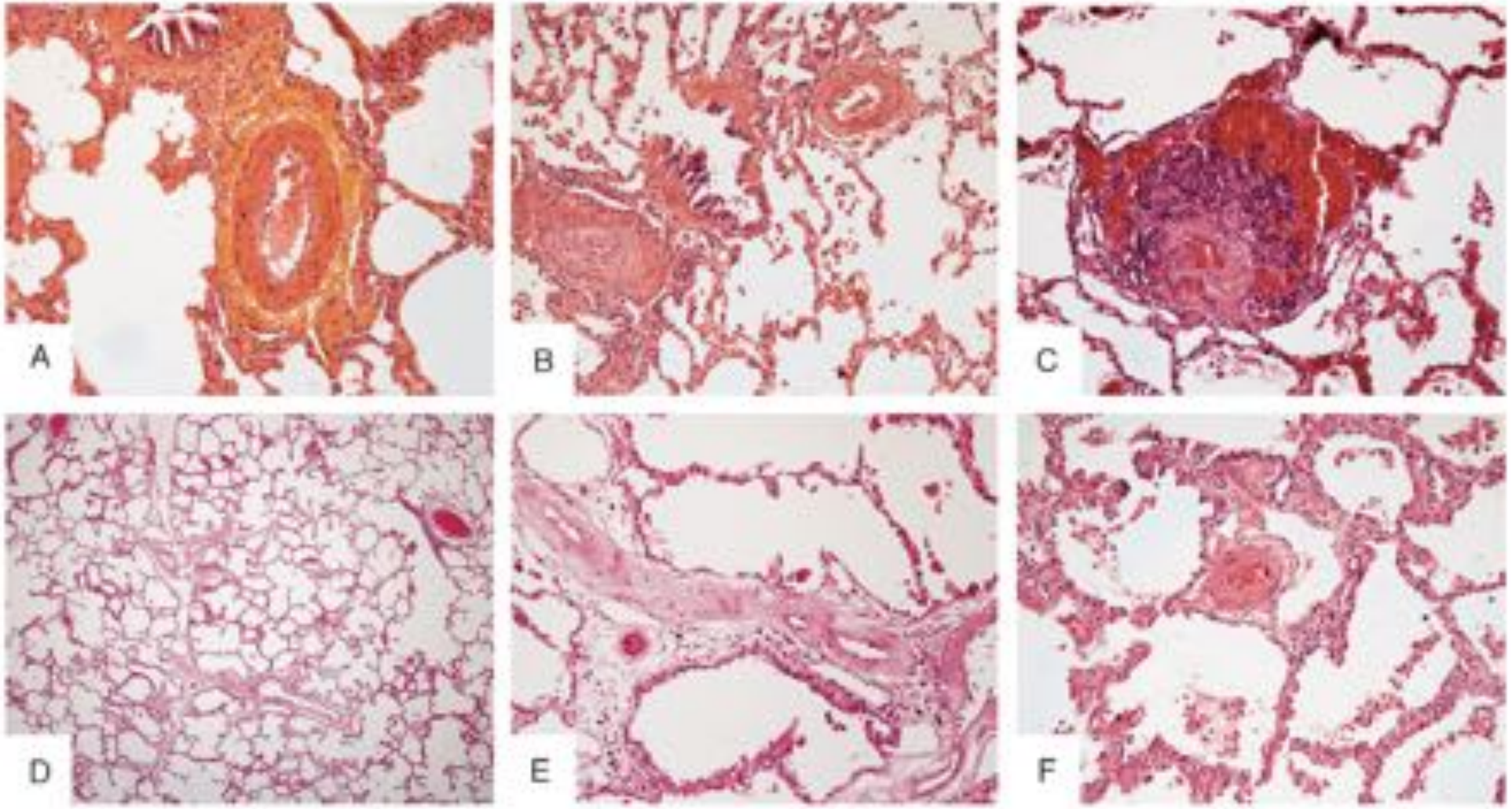
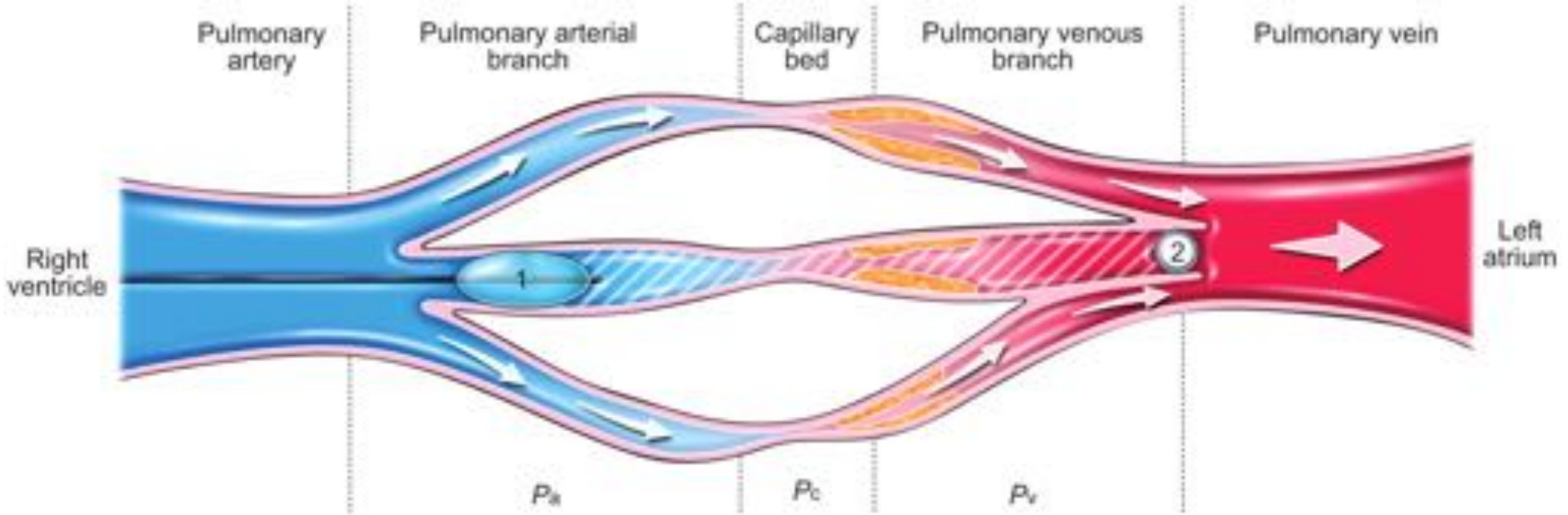


FIGURE 1. Pulmonary vascular lesions in lungs of patients displaying severe PAH (A–C) and PVOD (D–F). **A.** Muscular pulmonary artery with isolated medial hypertrophy. **B.** Two pulmonary arteries with intimal fibrosis; note the onion skin-like concentric fibrous pattern (left) and the association of fibrosis and medial hypertrophy (right). **C.** Pulmonary artery with characteristic complex lesion; note the plexiform or glomeruloid proliferation of endothelial cells, surrounded by thin-walled ectatic and congestive blood channels, known as dilation lesions. **D.** Septal veins and preseptal venules obstructed by loose, cushion-like fibrosis; note congestive pulmonary artery (top right) bearing any vascular lesion. **E.** Occluded preseptal venule with loose intimal fibrosis. **F.** Small pulmonary artery with medial hypertrophy in a patient suffering from PVOD; note multiplication of septal capillaries and numerous intraalveolar siderophages.

Montani D et al. Medicine 2013

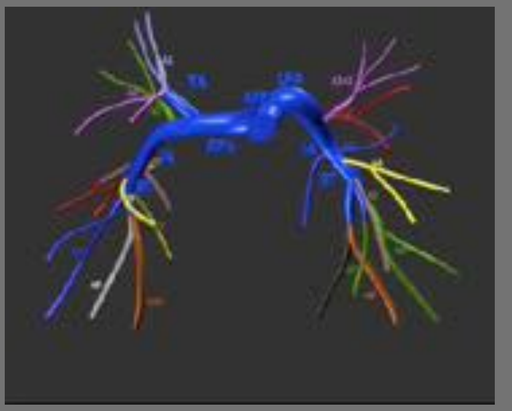
PVOD

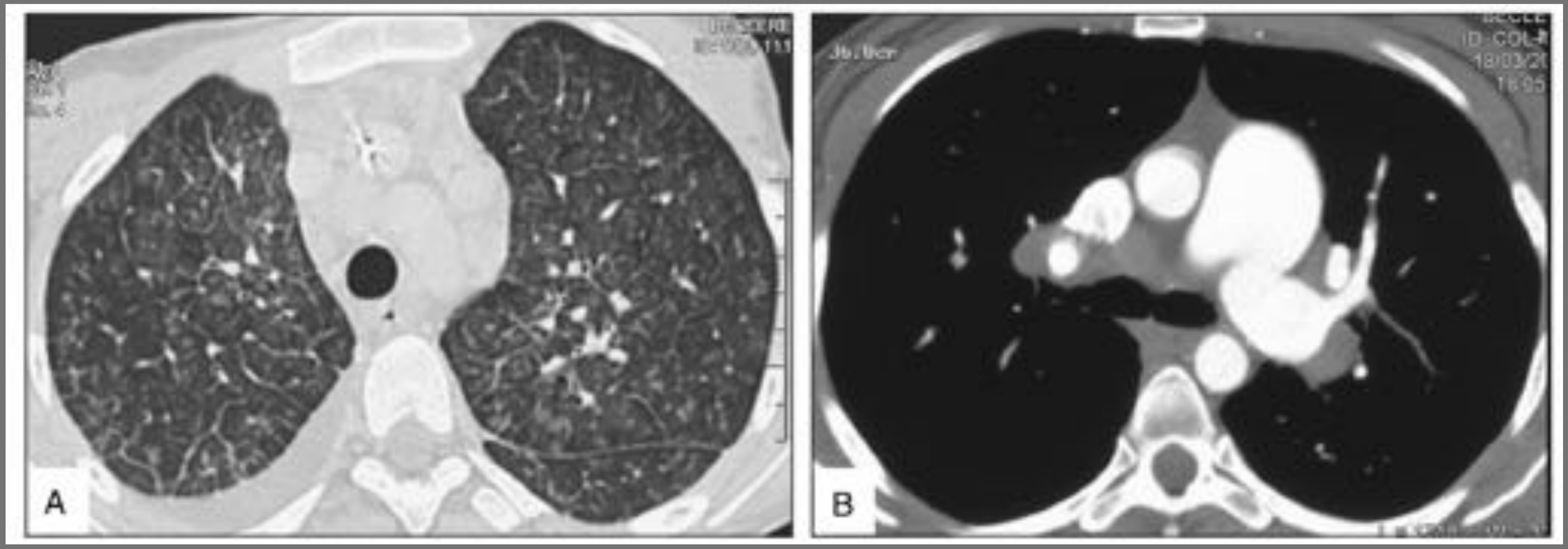


True capillary pressure is increased but PCWP is normal because it is a reflection of the pressure in the large veins that are not affected by obstruction

Montani D *et al.* Eur Respir J 2016

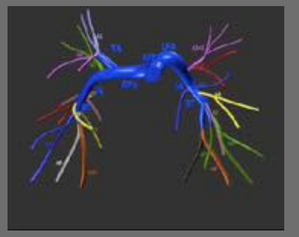
PVOD

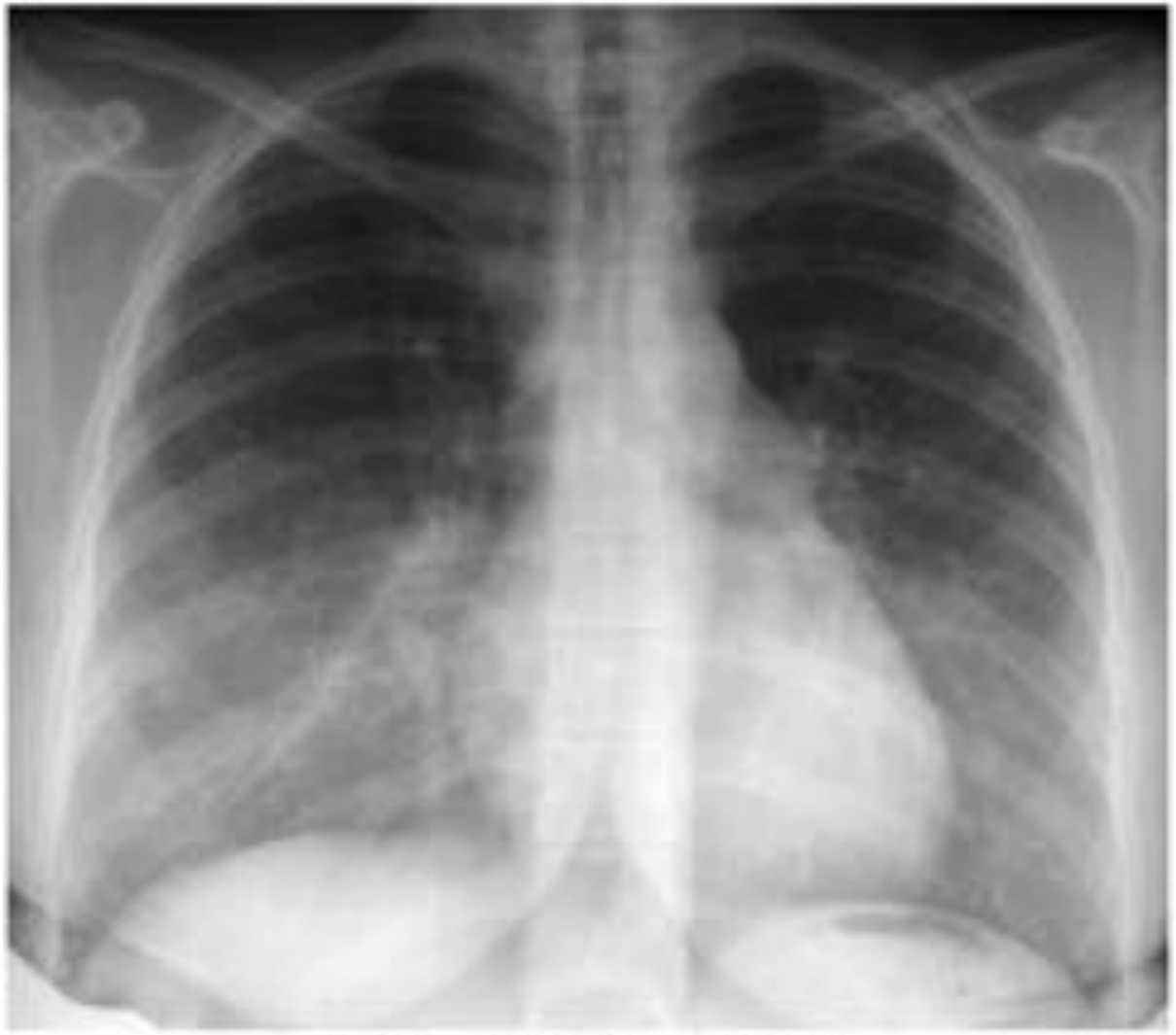




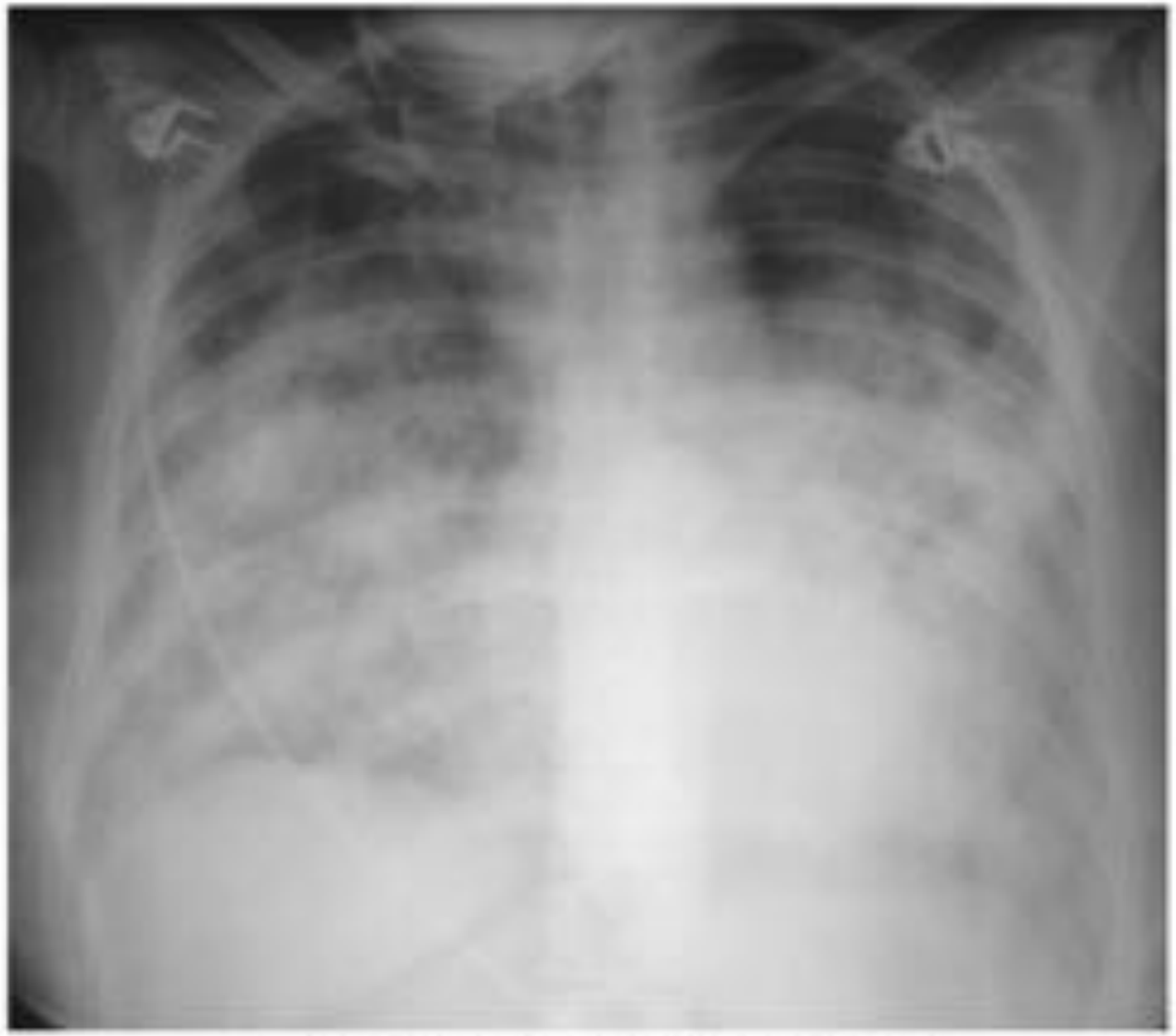
PVOD

Eyries M et al. Nat Genet 2014
Lévy M et al. Eur Resp J 2016
Montani D et al. Lancet Resp Med 2017
Berteloot L et al. Pediatr Radiol 2019





Prior to diltiazem therapy



After 2 days of diltiazem therapy

Heritable PAH in pediatrics

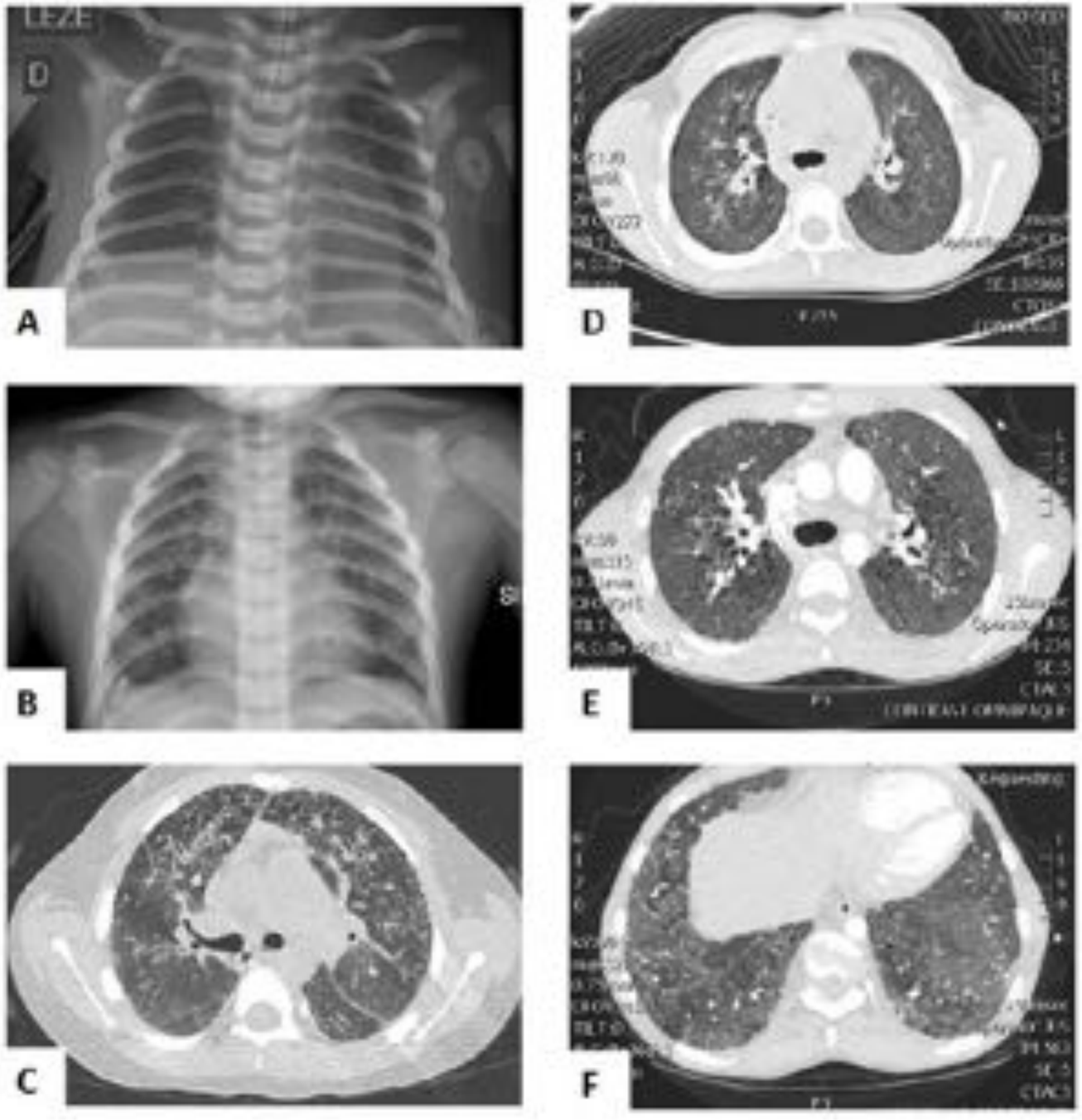
- Known mutations: BMPR2, ALK1, ENG, CAV1, KCNK3, EIF2AK4

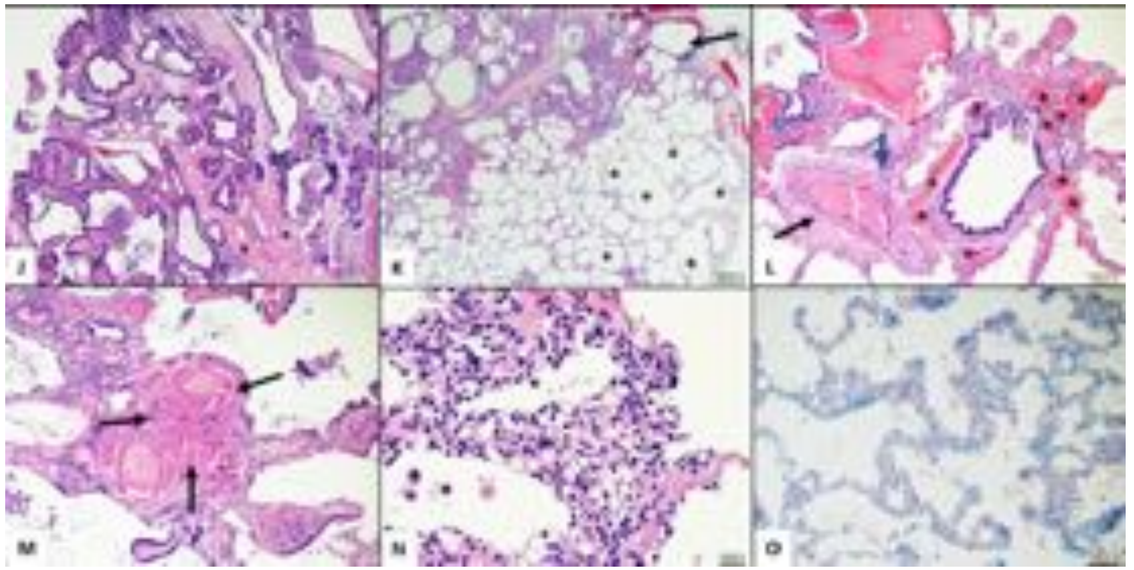
- TBX4 – described potential role in pediatric PAH and small patella syndrome and lung development [1]

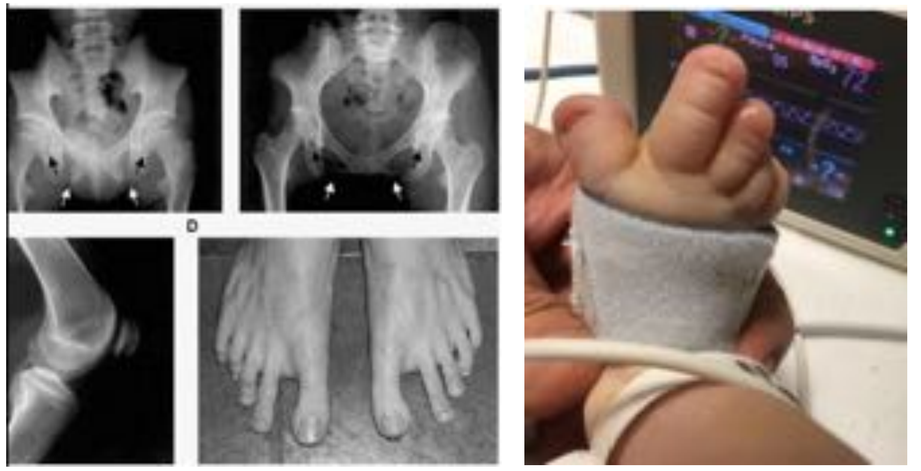
- SOX17 - role in PAH and cardiac development

1-Kerstjens-Frederikse WS, J Clin Genet 2013
2-Levy M, ERJ, 2016

TBX4 mutation
Neonatal lung disease
PAH (bimodal)







Galambos et al. ERJ 2019

Pathogenesis of PPHN

PRENATAL FACTORS

- Maternal NSAID, SSRI use;
- Premature closure of the DA
- C-section delivery
- Post-term (> 41 weeks)
- Large for gestational age
- Abnormal placenta
- Altered lung development
- Cardiovascular abnormaliities

POSTNATAL FACTORS

- Hyperoxia/oxidative stress
- Ventilator Induced Injury
- Asphyxia
- Inflammation/Infection

Injury to the Developing Lung Circulation

Impaired Vasoreactivity

Decreased Angiogenesis

Altered Vascular Structure

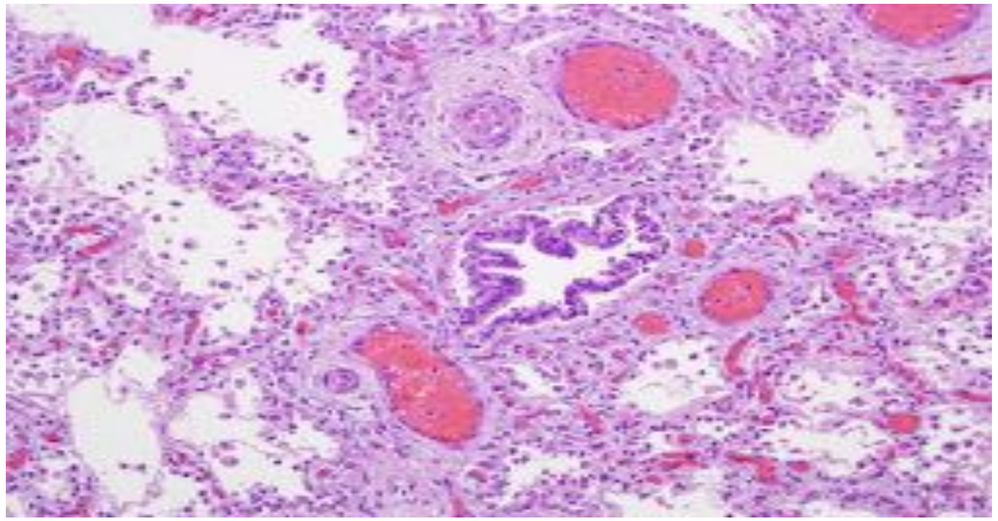
↓

<u>Persistent Pulmonary Hypertension of the Newborn</u>

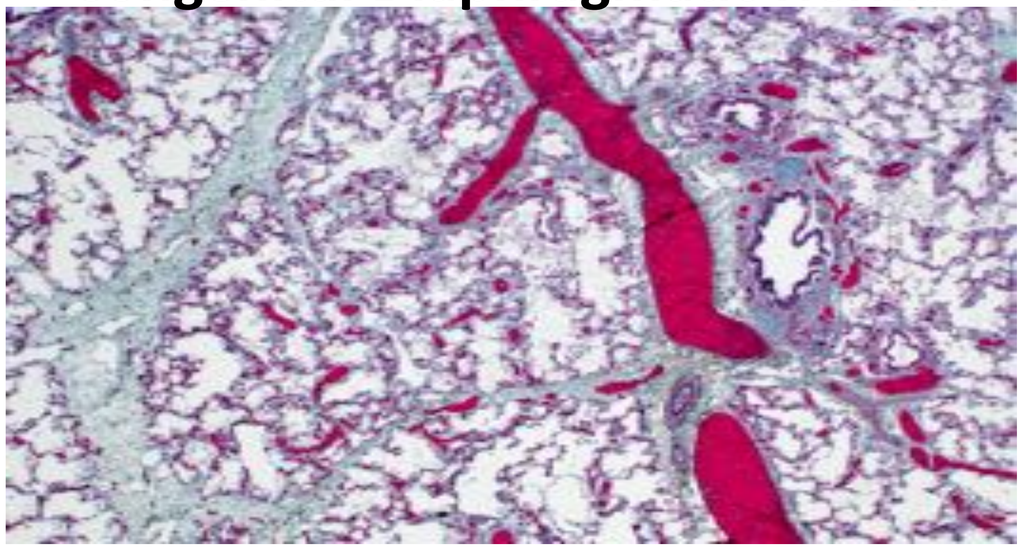
- Failure to decrease PVR at birth
- Extra-pulmonary shunting across DA, PFO
- Severe hypoxemia, Respiratory Failure

Pulmonary Vascular Disease in Developmental Lung Disorders

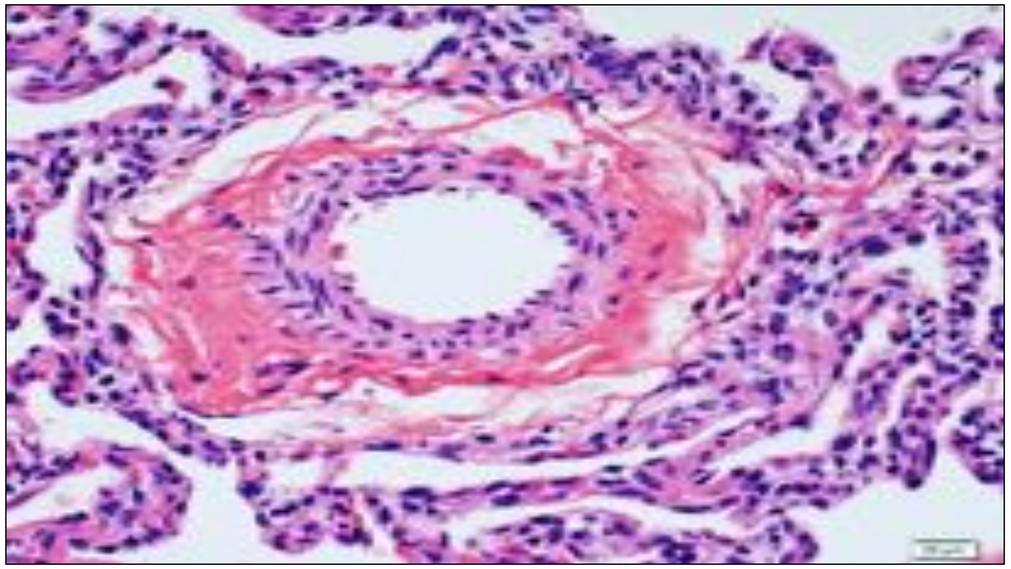
Alveolar Capillary Dysplasia



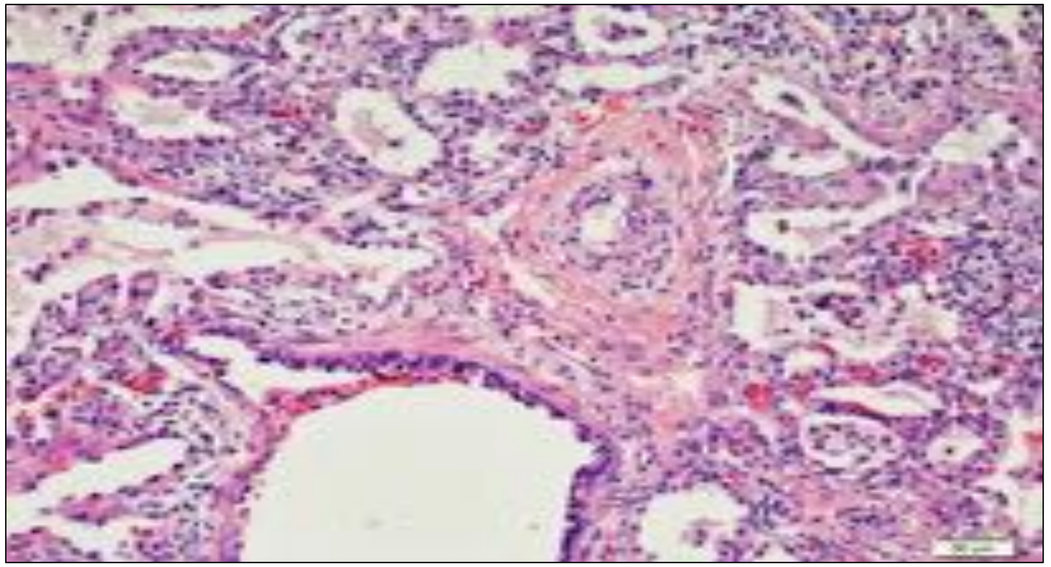
Congenital Diaphragmatic Hernia



Pulmonary Interstitial Glycogenosis

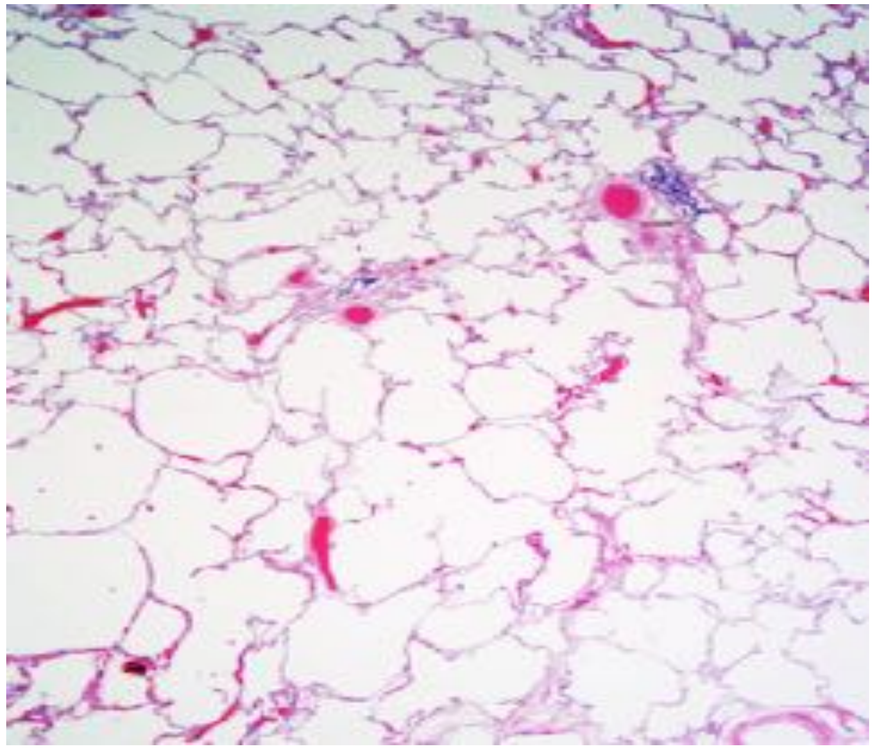


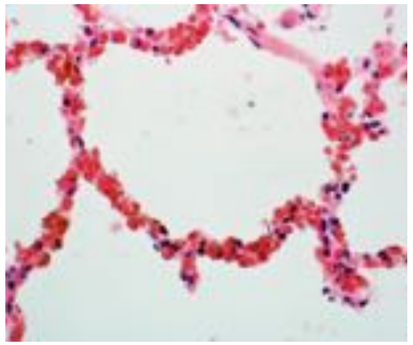
Surfactant Protein B Deficiency

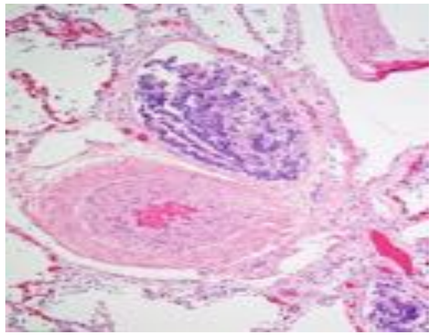


(Courtesy Csaba Galambos)

PH in Down syndrome/trisomy 21 is a developmental lung disorder







- PPHN more frequent in Down syndrome
- APAH-CHD has an earlier onset in DS

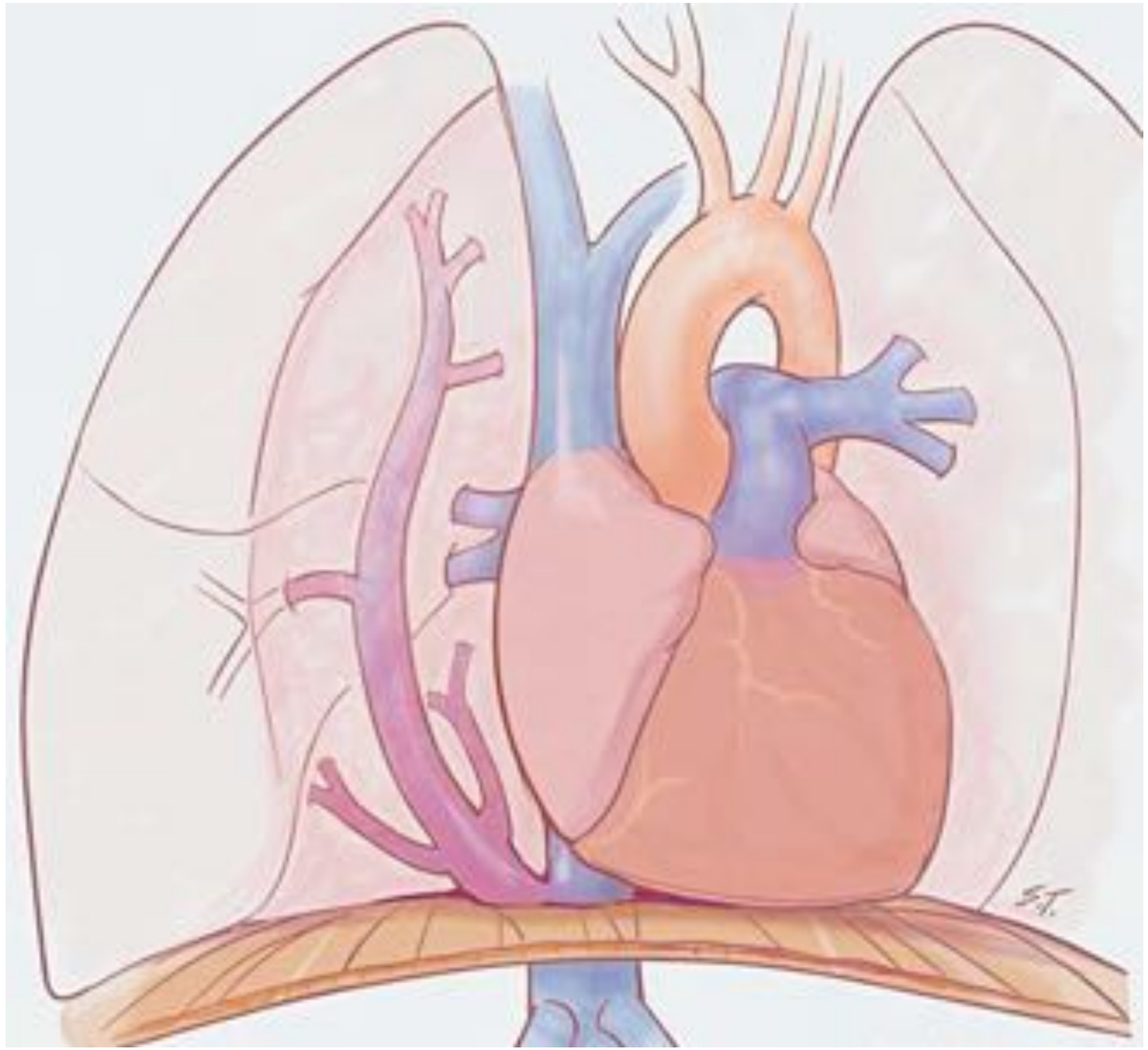
Bush D et al. J Pediatr 2017

Multifactorial pulmonary hypertension in children

Lung disease

Post-capillary PH

Systemic supply to the lung

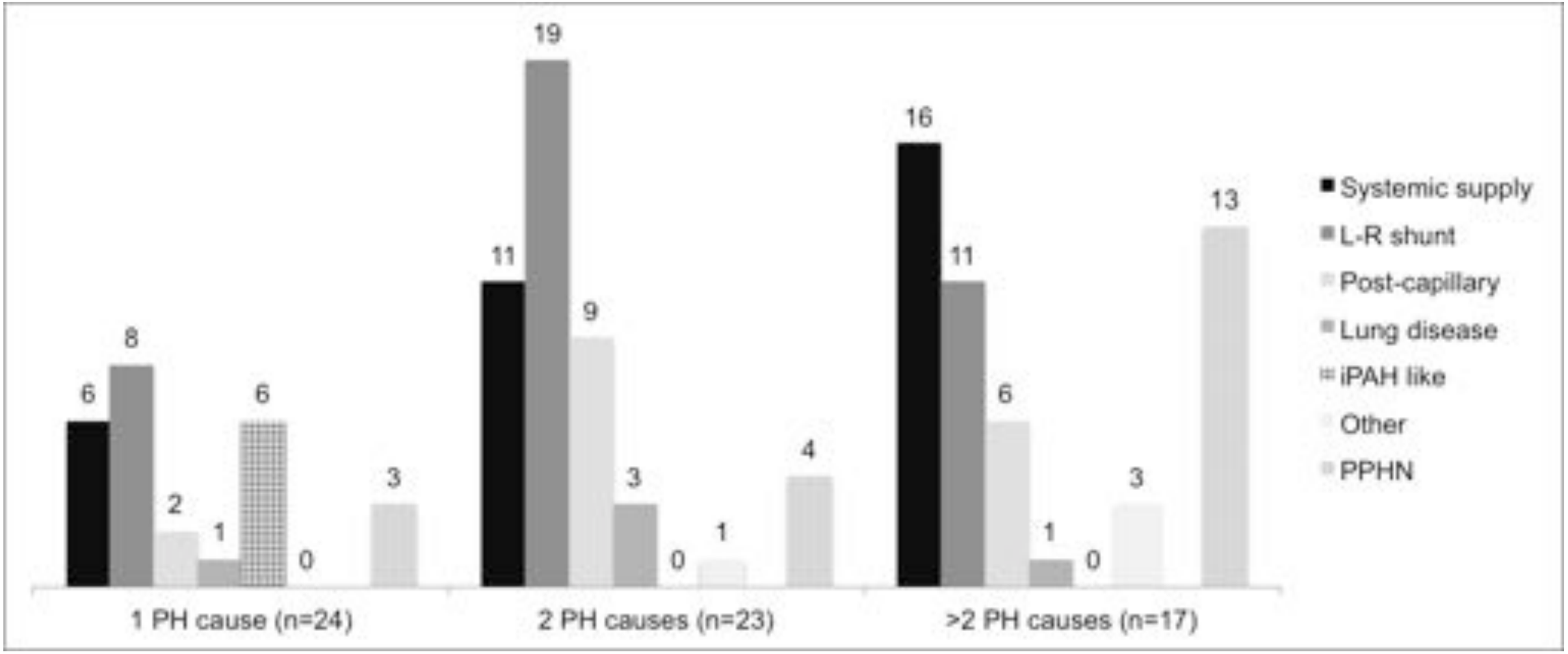


Pulmonary vascular disease /maladaptation

Left-to right shunt /CHD

Scimitar syndrome

Multifactorial pulmonary hypertension in scimitar syndrome



Bonnet D et al. 2019

Modified Classification of PH

1.Pulmonary Arterial Hypertension
- **1.1 Idiopathic PAH**
- **1.2 Heritable PAH**
- **1.2.1. BMPR2**
- **1.2.2.ALK-1,endoglin,SMAD9, CAV1, KCNK3**
- **1.2.3 Unknown**
- **1.3 Drugs and toxins induced**
- **1.4 Associated with:**
- **1.4.1 Connective tissue disease**
- **1.4.2 HIV infection**
- **1.4.3 Portal hypertension**
- **1.4.4 Congenital Heart diseases**
- **1.4.5 Schistosomiasis**

1’ Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis

1.'' PPHN

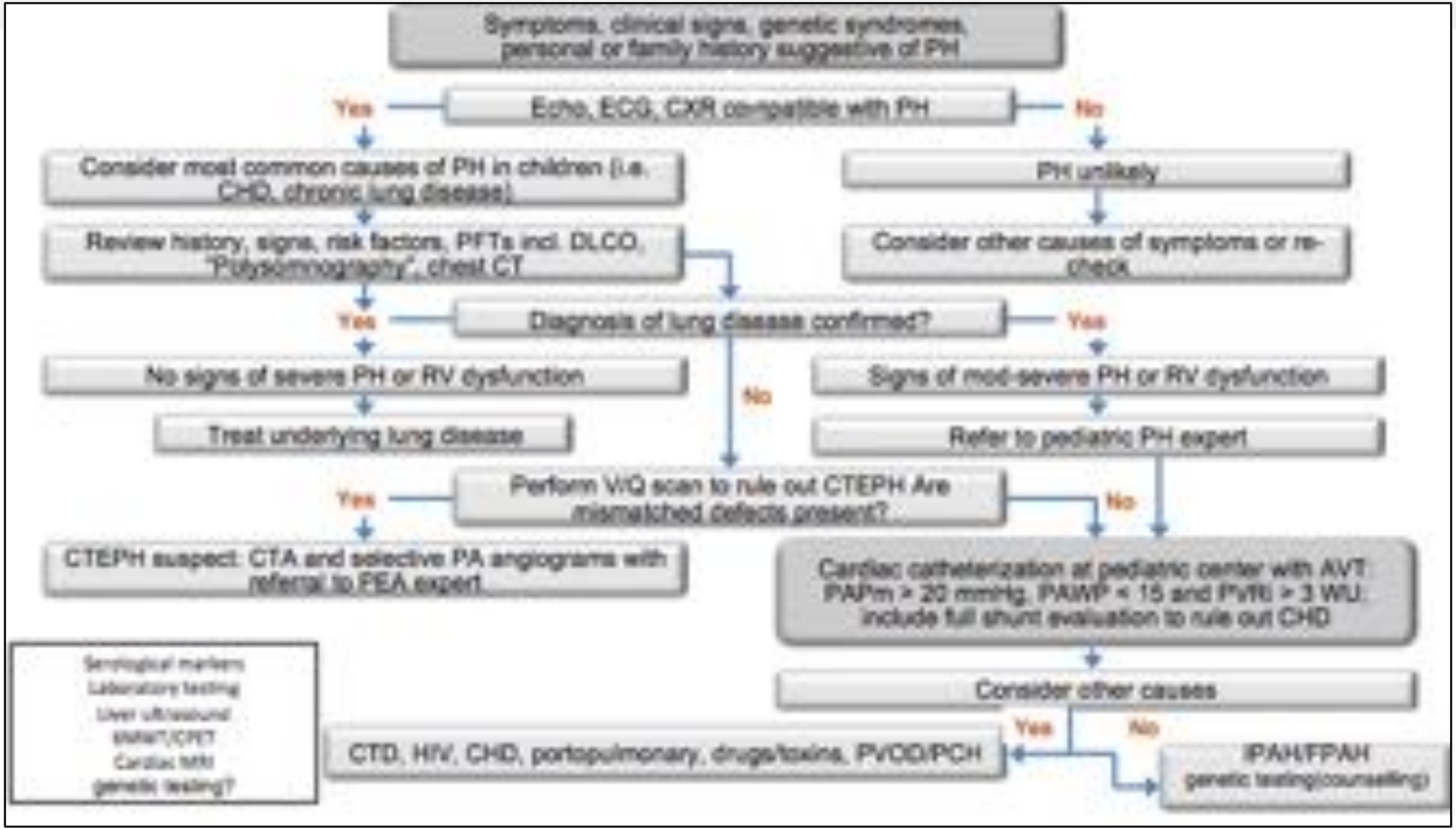
2. Pulmonary Hypertension Due to Left Heart Disease
- **2.1 Left Ventricular Systolic Dysfunction**
- **2.2 Left Ventricular Diastolic Dysfunction**
- **2.3 Valvular disease**
- **2.4 Congenital / acquired left heart inflow/outflow tract obstruction**

3.Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
- **3.1 Chronic obstructive pulmonary disease**
- **3.2 Interstitial lung disease**
- **3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern**
- **3.4 Sleep-disordered breathing**
- **3.5 Alveolar hypoventilation disorders**
- **3.6 Chronic exposure to high altitude**
- **3.7 Developmental lung diseases**
- **3.7.1 Congenital diaphragmatic hernia**
- **3.7.2 Bronchopulmonary dysplasia**

4.Chronic Thromboembolic Pulmonary Hypertension

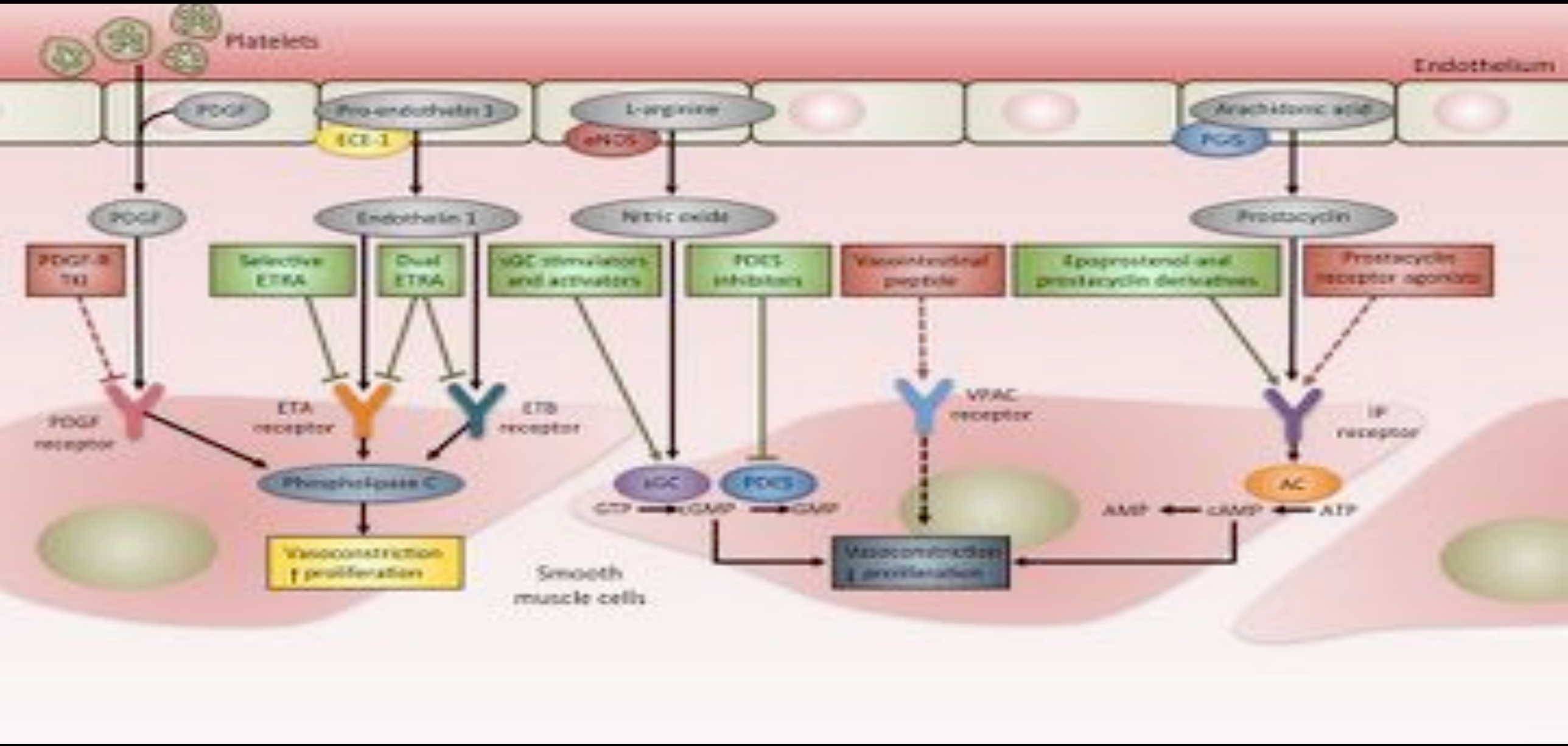
5.Pulmonary Hypertension with Unclear Multifactorial Mechanisms
- **5.1 .Hematologic disorders:chronic hemolytic anemias myeloproliferative disorders splenectomy,**
- **5.2 Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculatis**
- **5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders**
- **5.4 Others: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure**

Diagnostic algorithm pediatric Task force WSPH Nice 2018



Rosenzweig et al. ERJ 2019

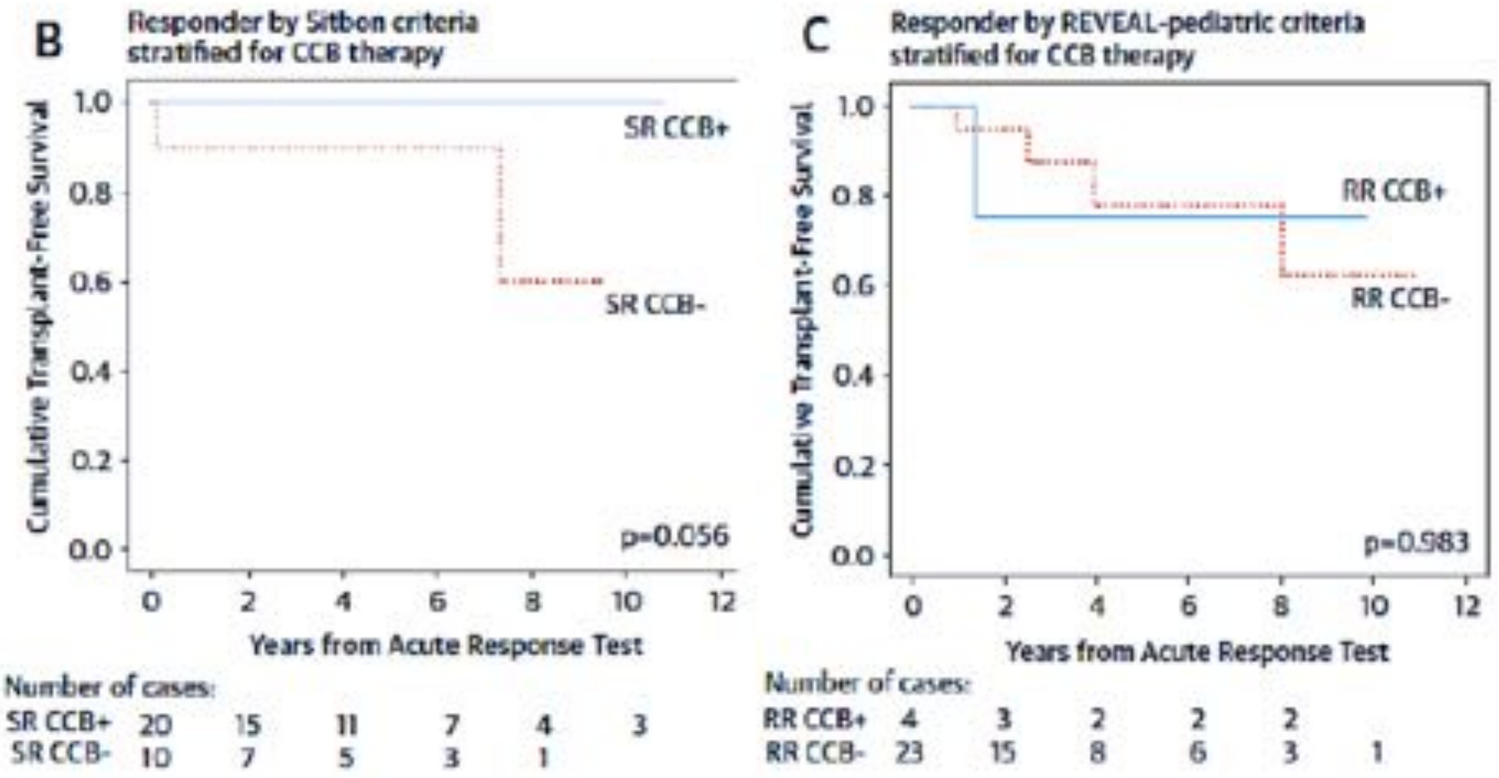
Treatment of pediatric pulmonary hypertensions



Lador F. et al, Expert Opin Pharmaco 2015

Treatment of pediatric PAH/PH and current challenges

1. AVT responders should receive Calcium channel blockers

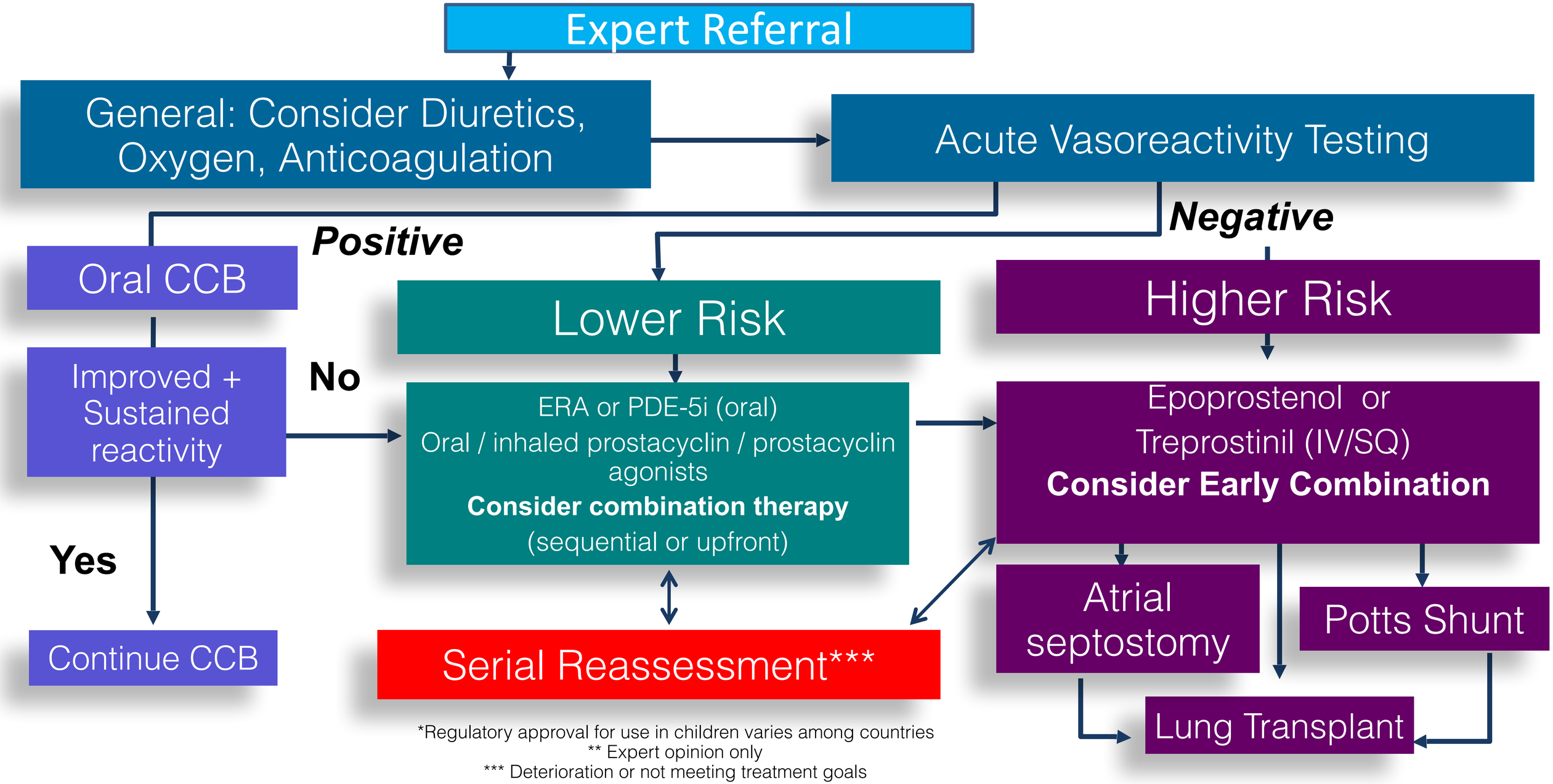


Douwes M et al. JACC 2016

Low and high risk pediatric patients with PAH

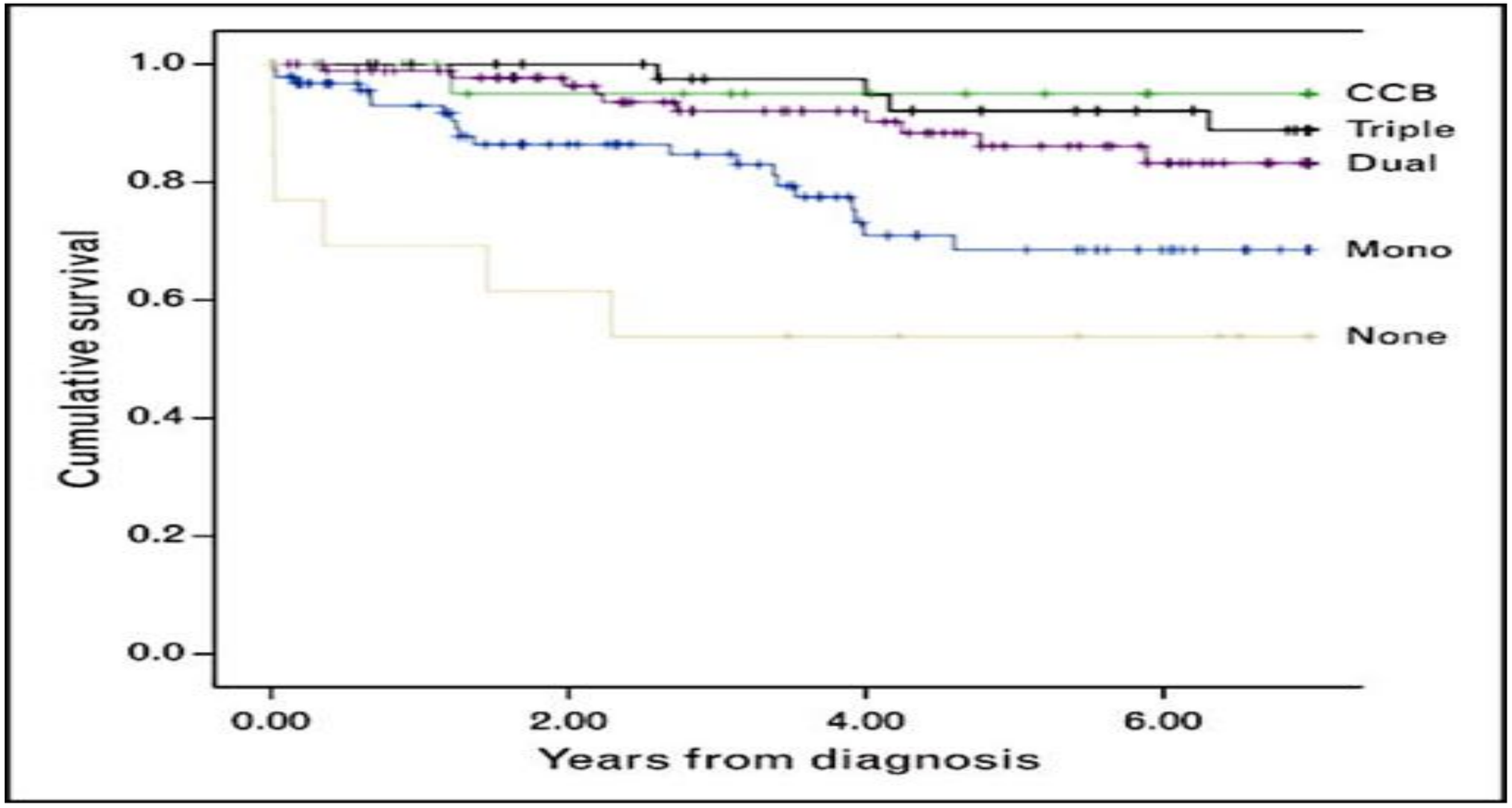
LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
No	Progression of Symptoms	Yes
> 350 meters	6MWT (>7 yrs old)	< 350 meters
	Growth	Failure to thrive
I,II	WHO Functional Class	III,IV
Minimally elevated	BNP / NTproBNP	Significantly elevated Rising level
	Echocardiography	RA / RV Enlargement Reduced LV size Increased RV/LV Ratio Reduced TAPSE Low RV FAC Pericardial Effusion
Systemic CI > 3.0 L/min/m^2 Systemic venous saturation >65% + Acute Vasoreactivity	Hemodynamics	Systemic CI < 2.5 L/min/m^2 RAP > 10mmHg PVRI > 20 WU*m^2 Systemic venous saturation < 60% PACi <0.85

Pediatric IPAH/HPAH Treatment algorithm WSPH 2018



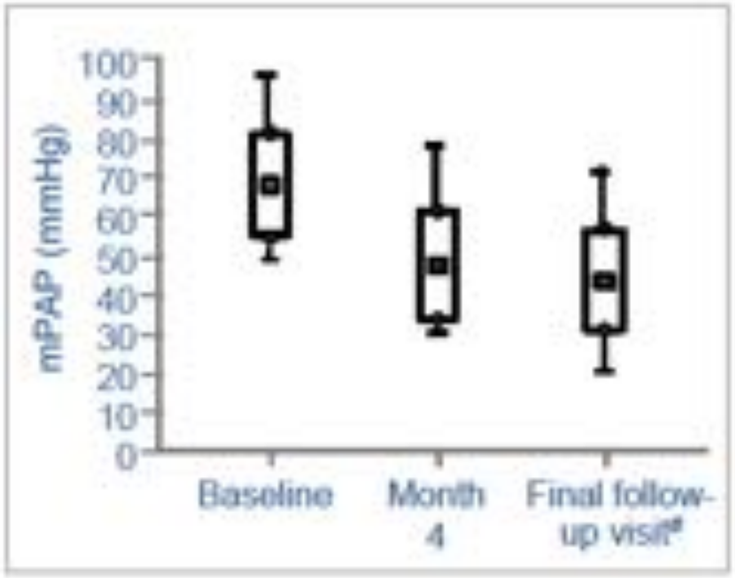
*Regulatory approval for use in children varies among countries
** Expert opinion only
*** Deterioration or not meeting treatment goals

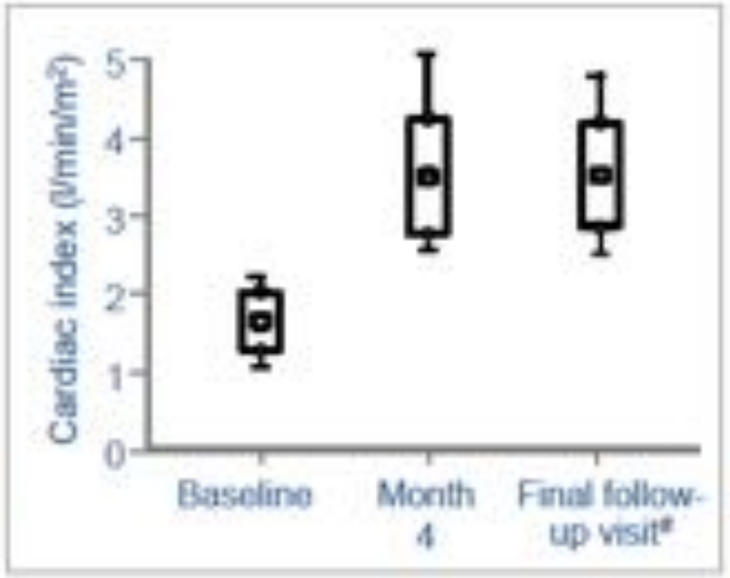
Limited evidence in RCT for this algorithm but convincing registries data

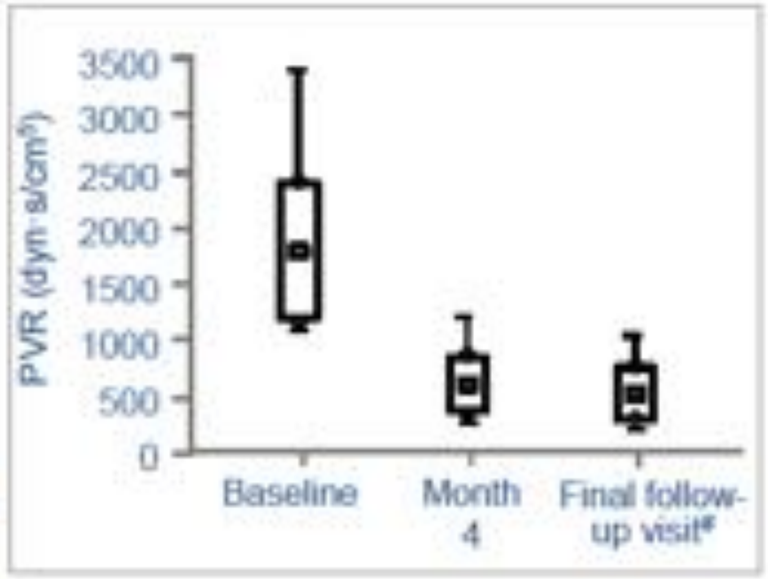


Zijlstra WMH, et al. JACC 2014

Up-front combination therapy with epoprostenol, bosentan and sildenafil





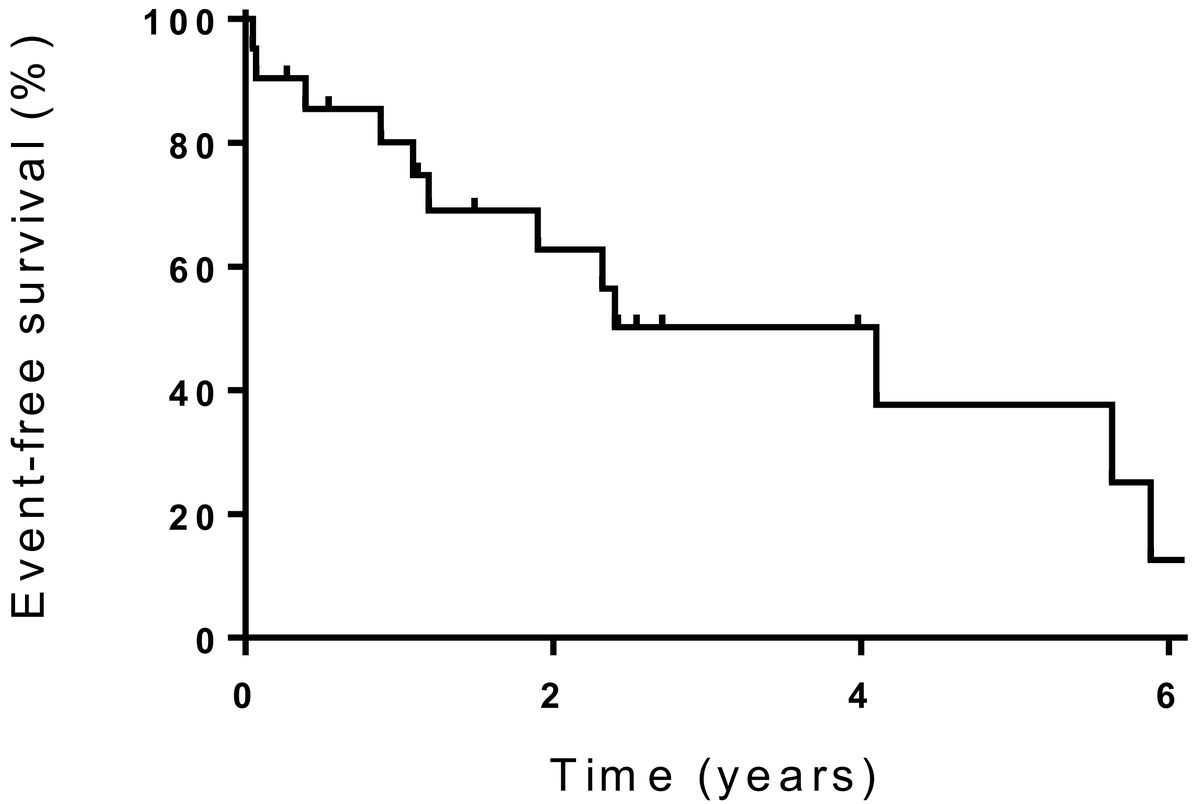


	Baseline	Month 4	Final follow-up#
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l / min / m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*

#32 ± 19 months
**p < 0.01 versus* baseline

Sitbon O *et al.* Eur Respir J 2014.

Up-front triple therapy in children with severe PAH



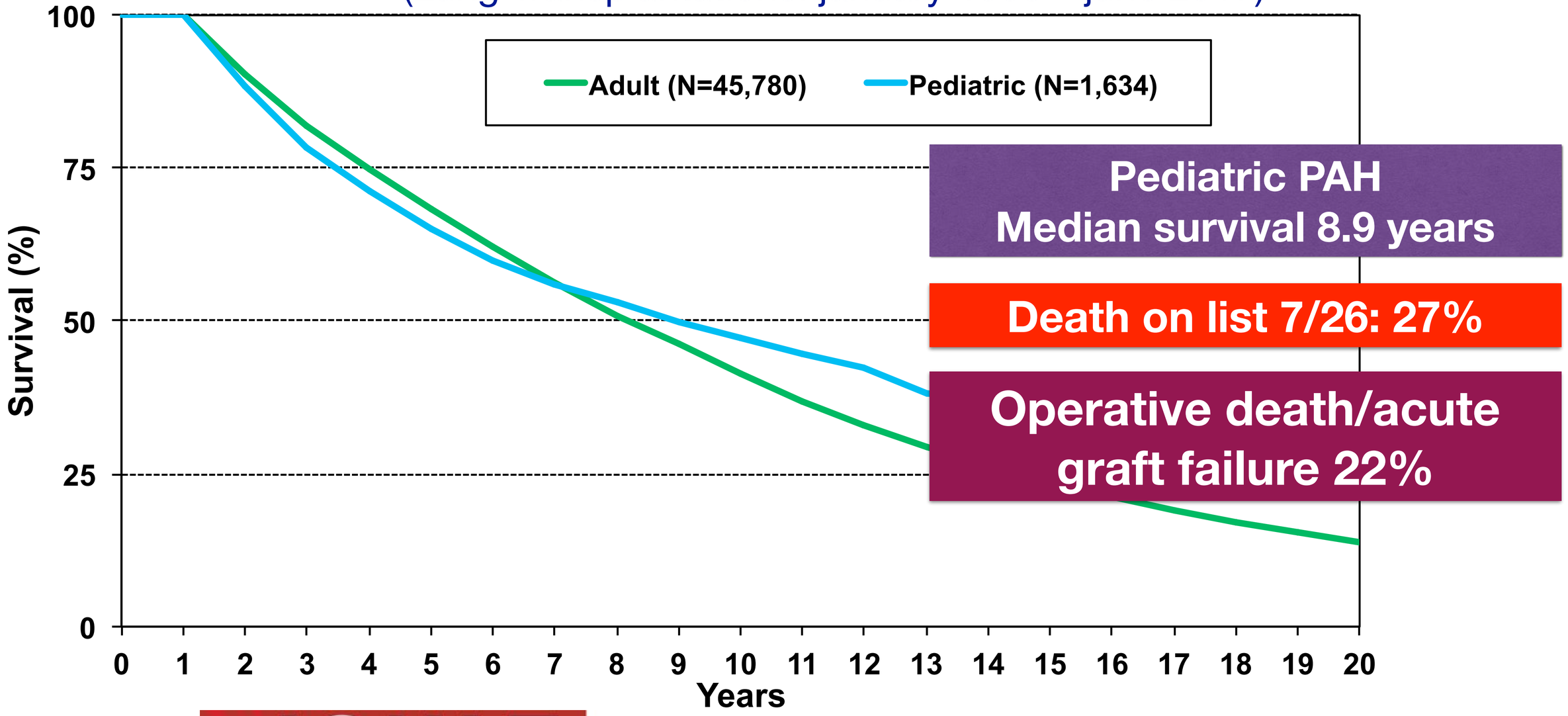
Patients at risk, n

21	10	4	1

Haarman M, Berger RMF, Bonnet D. 2019

Lung transplantation in children

(Lung Transplantations: january 1995 – june 2017)



Pediatric PAH
Median survival 8.9 years

Death on list 7/26: 27%

Operative death/acute graft failure 22%

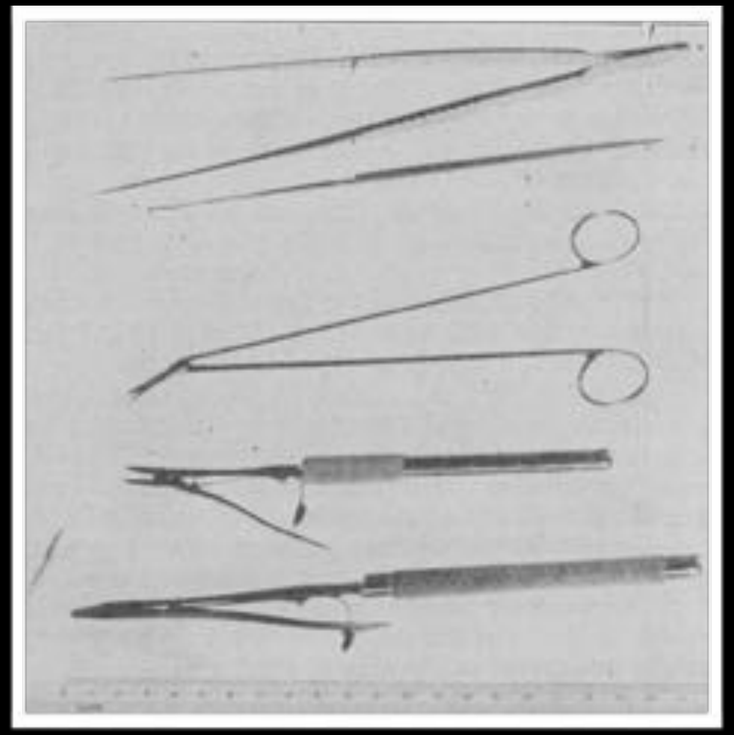
ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2018

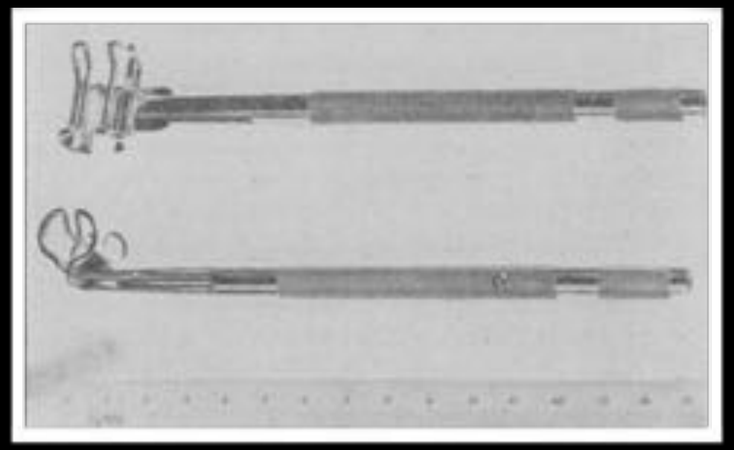
ANASTOMOSIS OF THE AORTA TO A PULMONARY ARTERY

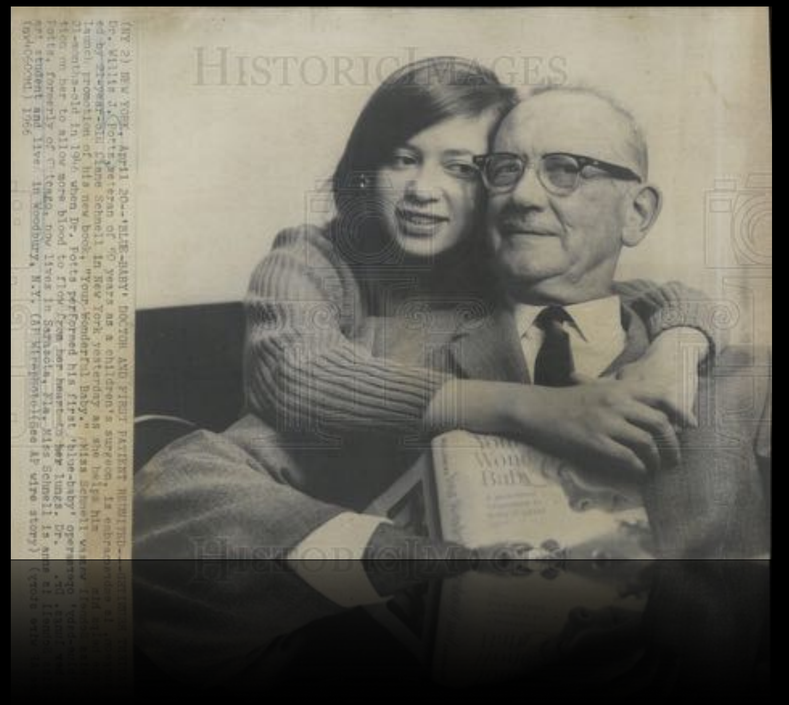
Certain Types in Congenital Heart Disease

WILLIS J. POTTS, M.D.
SIDNEY SMITH, M.D.
and
STANLEY GIBSON, M.D.
Chicago

In 1945 Blalock and Taussig[1] introduced a new surgical procedure for the relief of anoxemia due to pulmonary stenosis or pulmonary atresia. By anastomosing the subclavian or innominate artery to either the right or the left



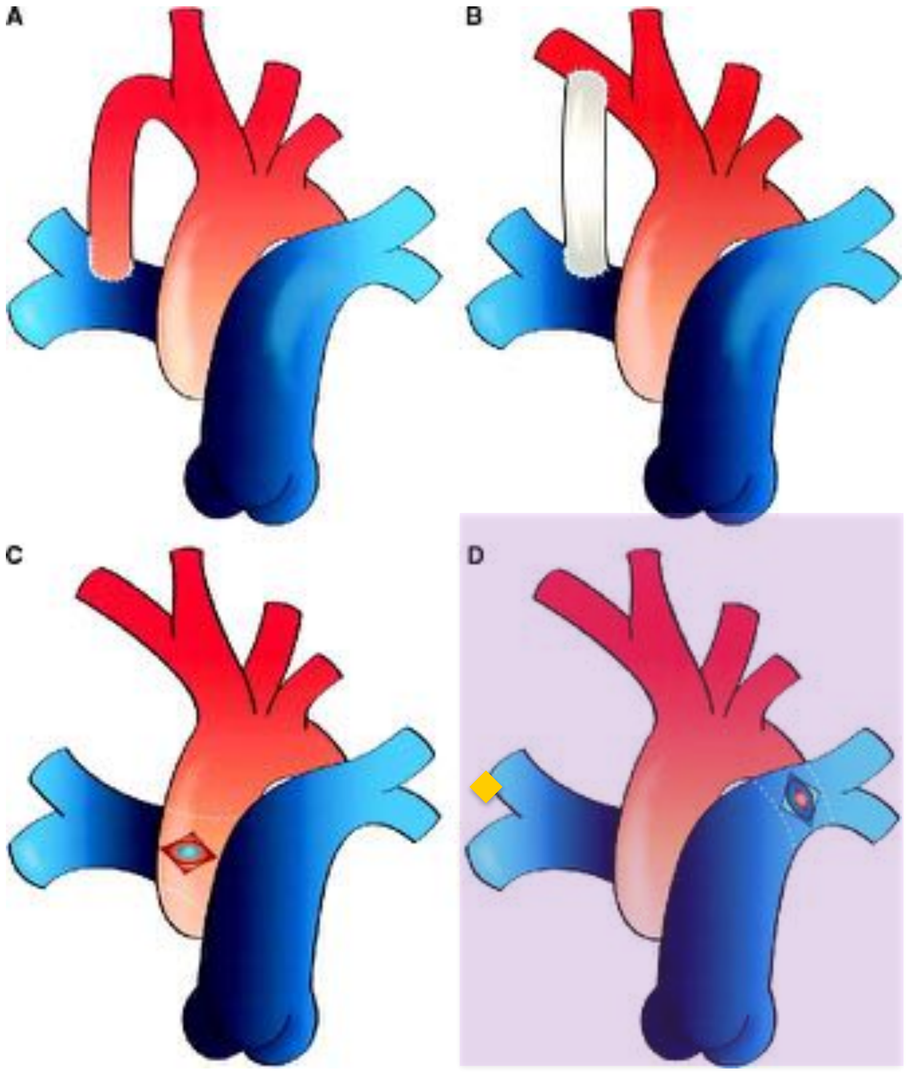




JAMA 1946

Different types of systemic-to-pulmonary shunts to palliate cyanotic CHDs with pulmonary stenosis/atresia

Blalock
Taussig
Thomas

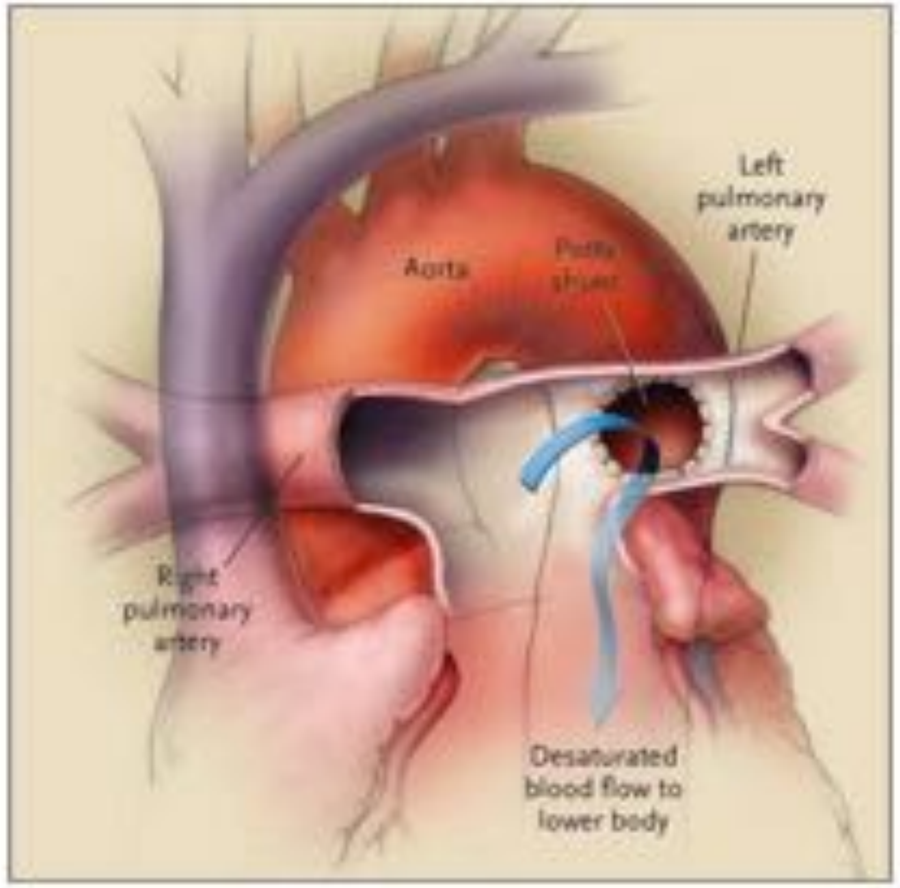


Modified
Blalock
Deleval

Waterston

Potts

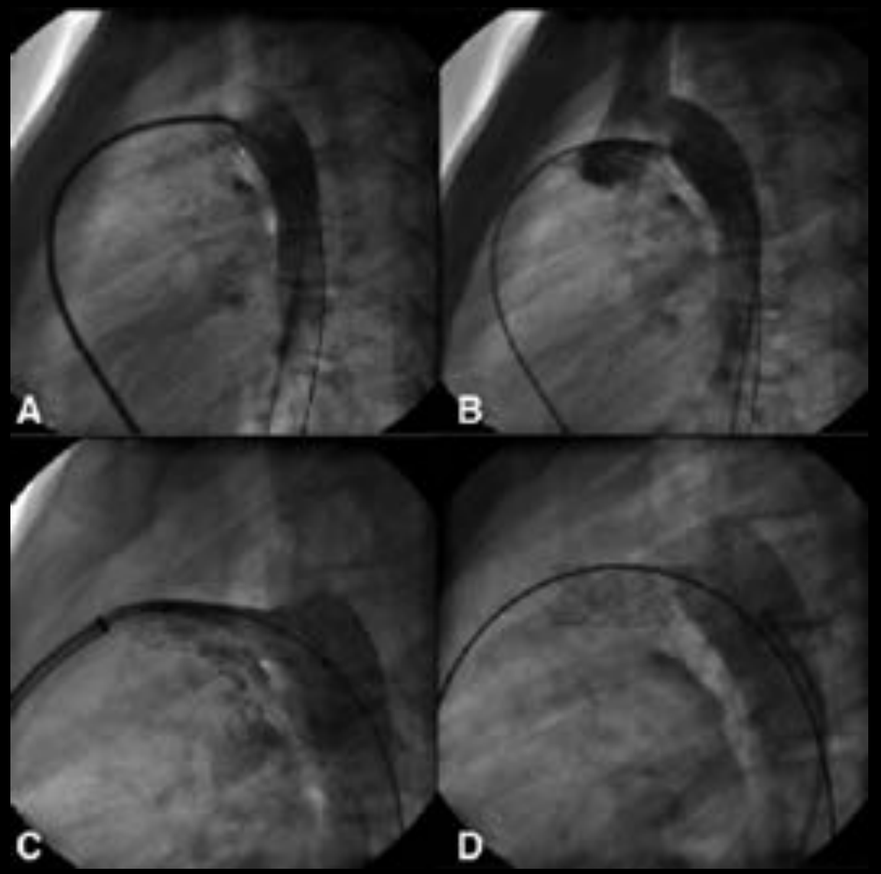
Potts shunt in pediatric PAH

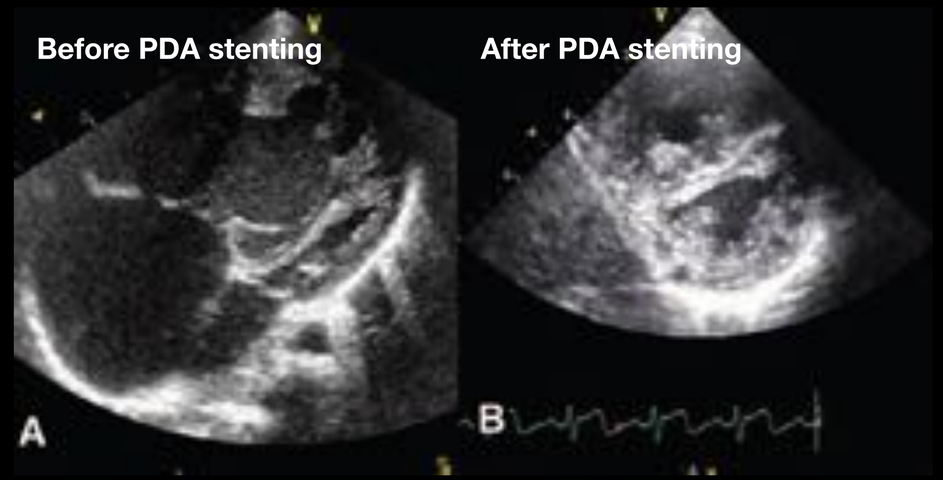


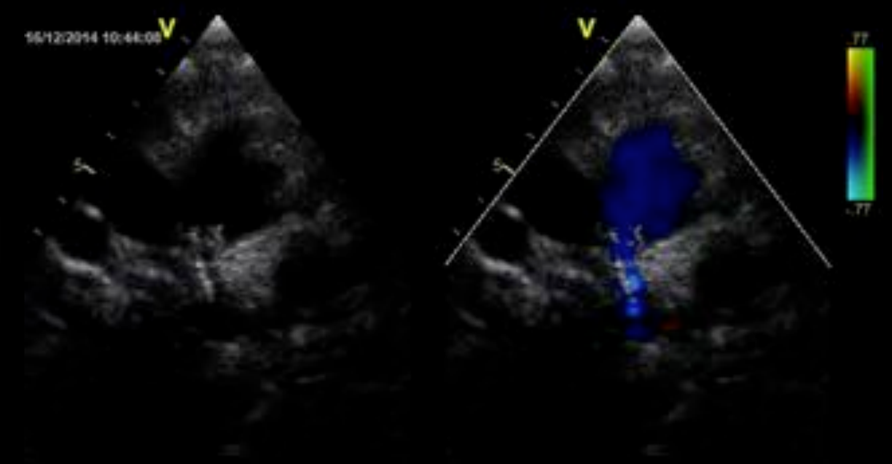
- Good long term responders
- Still high risk procedure
- Need to further define indications/ contraindications
- Registry data from PePH association

Blanc J, Vouhe P, Bonnet D. N Engl J Med. 2004 Feb 5;350(6):623

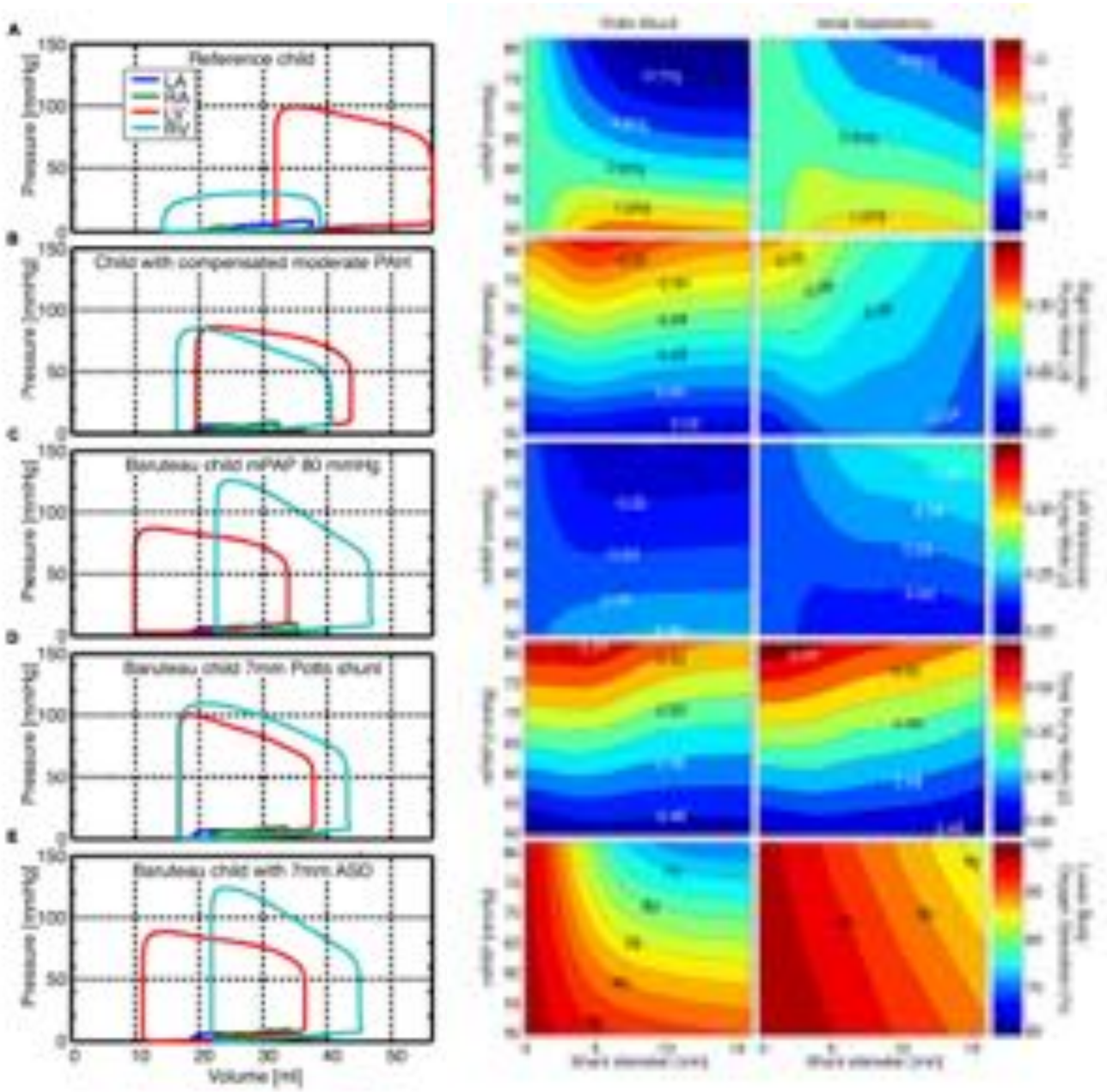
Stenting of tiny arterial duct in PAH



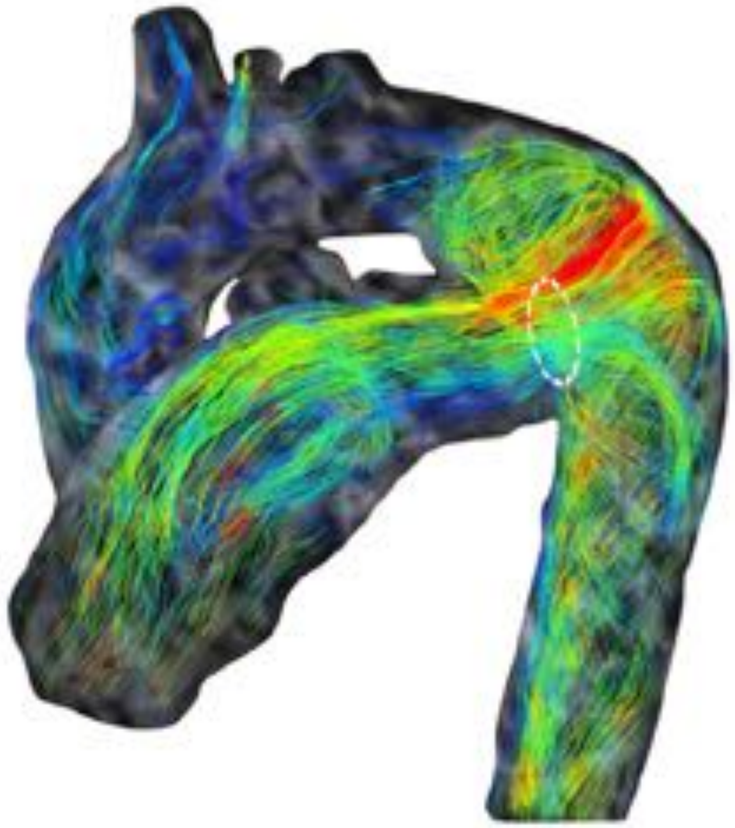




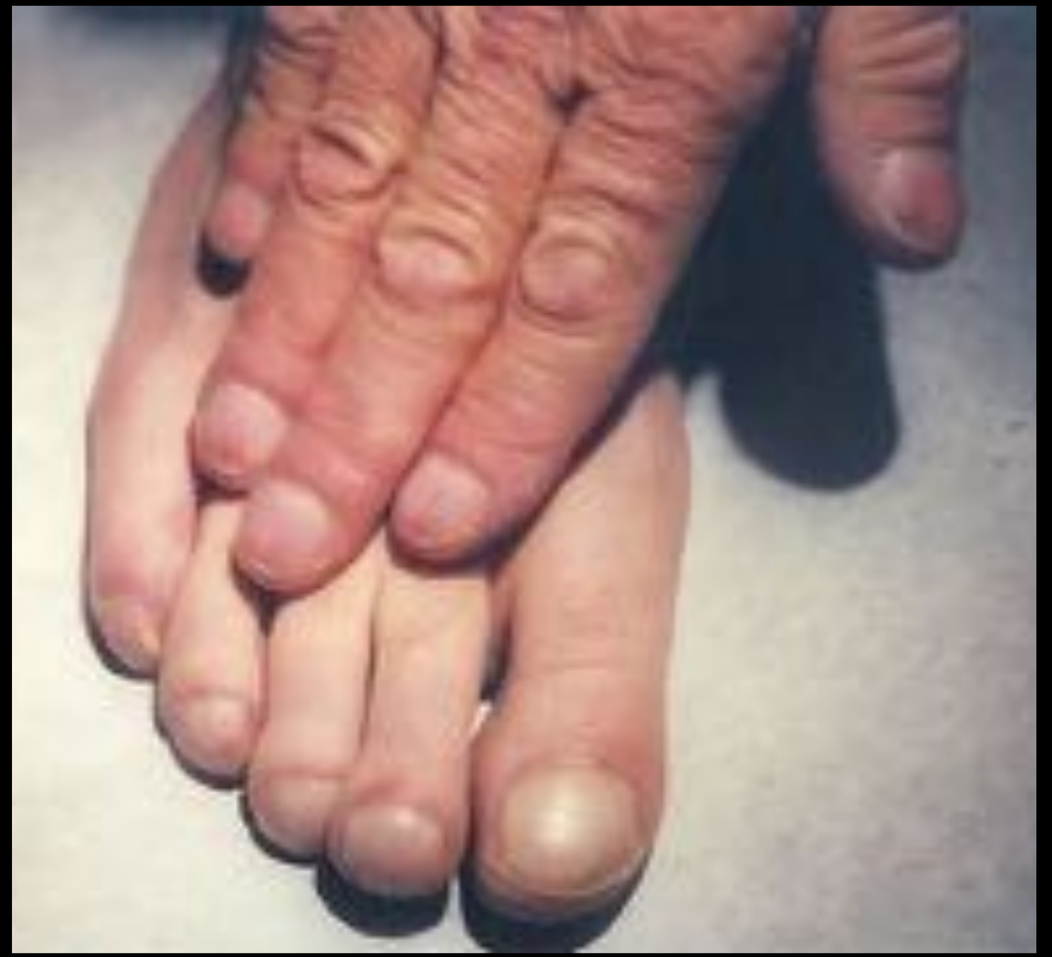
Boudjemline Y et al. Circ Cardiovasc Interv 2013
Baruteau A et al. Ann Thorac Surg 2012
Baruteau A et al. Eur J Cardiovasc Surg 2015

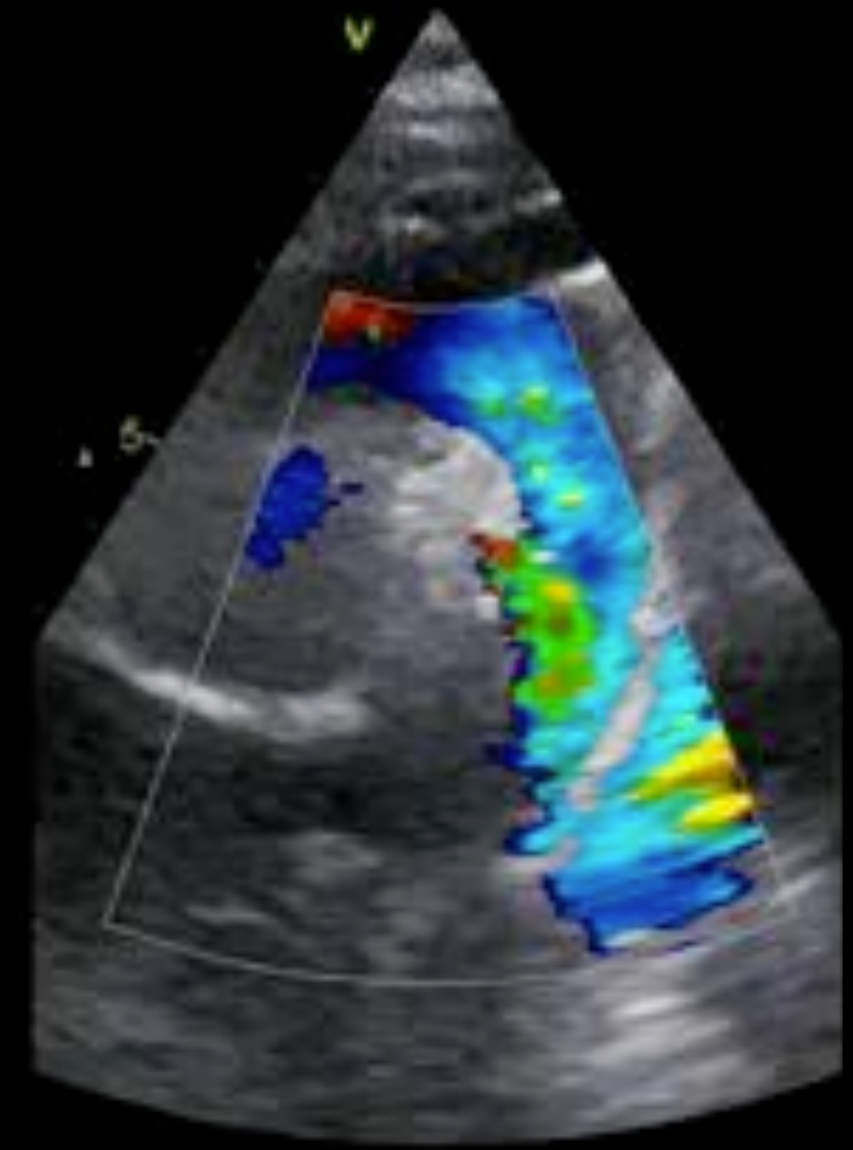


Potts shunt should be preferred to atrial septotomy



Delhaas T et al. Frontiers in Physiology 2018
Schäfer M et al. J Magn Res Imaging 2018





PePH Potts Registry

Preliminary data

Marc Grady (Saint-Louis) & Damien Bonnet (Paris)

121 patients

Early mortality 15%

Overt right heart failure is a contra-indication

Improvement is spectacular in 90% of survivors

Pros and cons

Pros

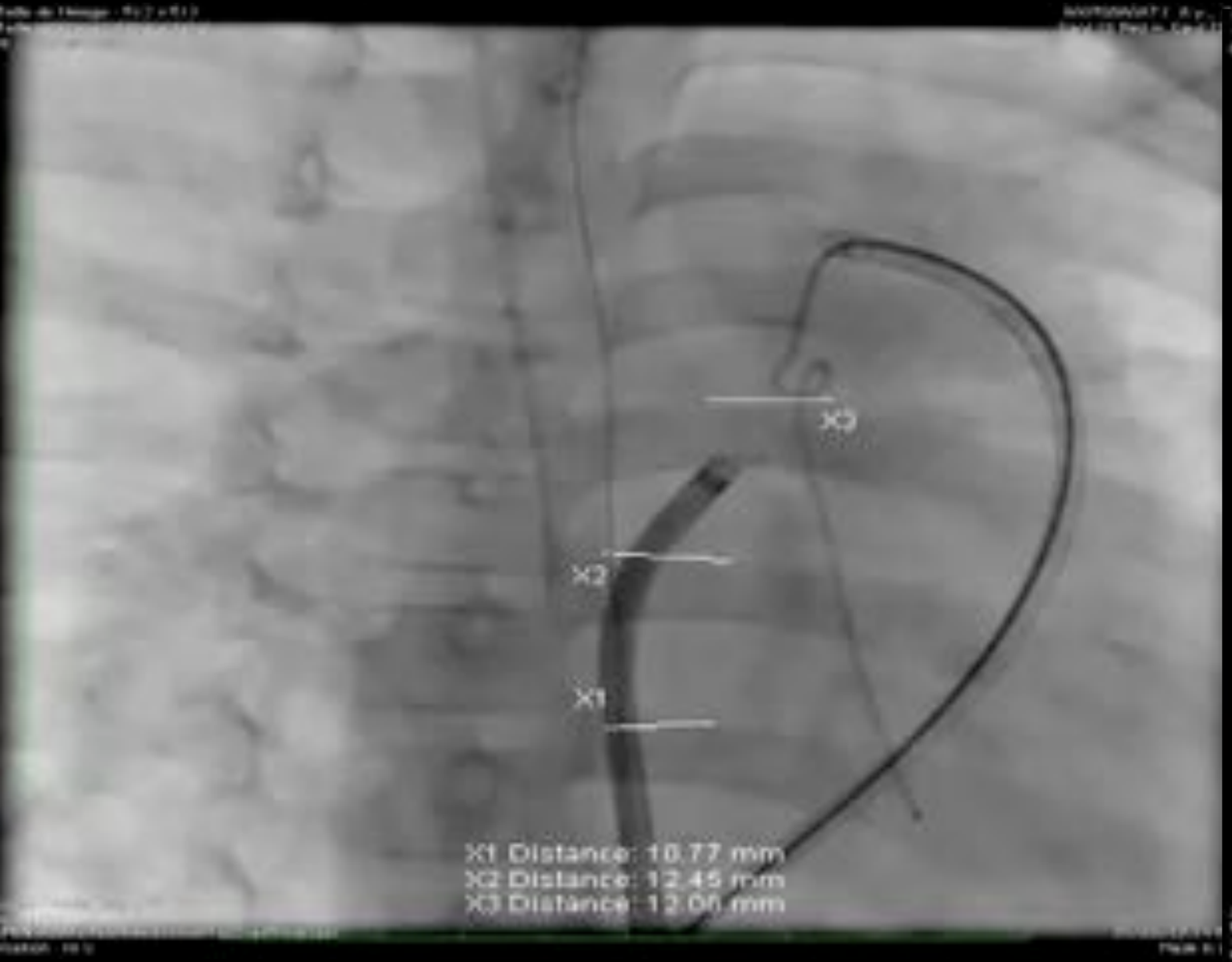
- Improvement of WHO-FC
- Convert iPAH in Eisenmenger syndrome supposed to have a better outcome
- Wean patient from IV/SC prostanoids
- Improvement of RV function
- No death on the waiting list
- 15 % mortality compared to 27 % on the waiting list + 22% in post-transplantation
- Normal oxygenation of brain and coronary arteries (vs. Atrioseptotomy)

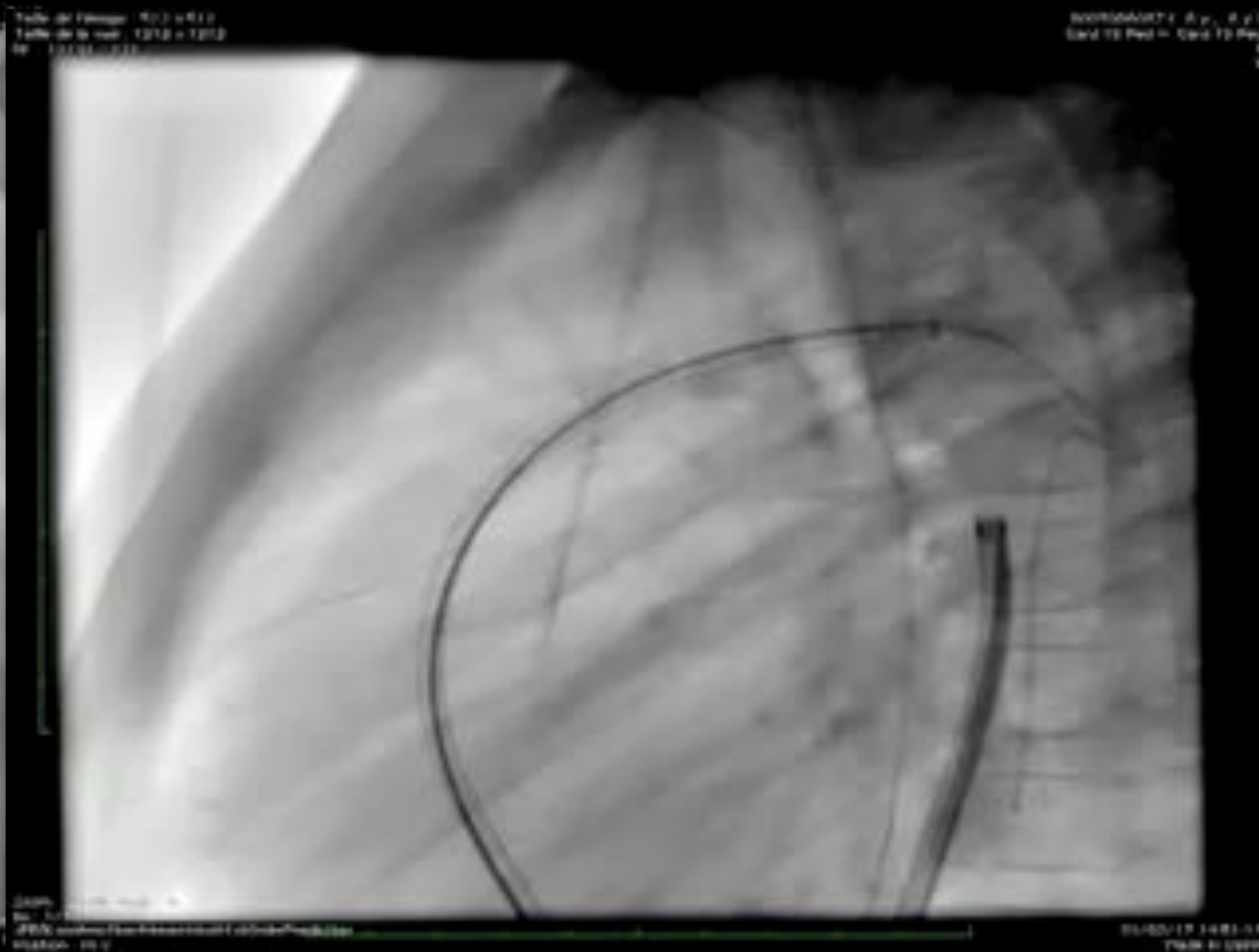
Cons

- High mortality of the procedure
- Prognosis of Eisenmenger syndrome might not be so good
- **Simple palliation not a cure of PAH**
- Risk of polycythemia
- Might increase the risk of bleeding during a subsequent transplantation

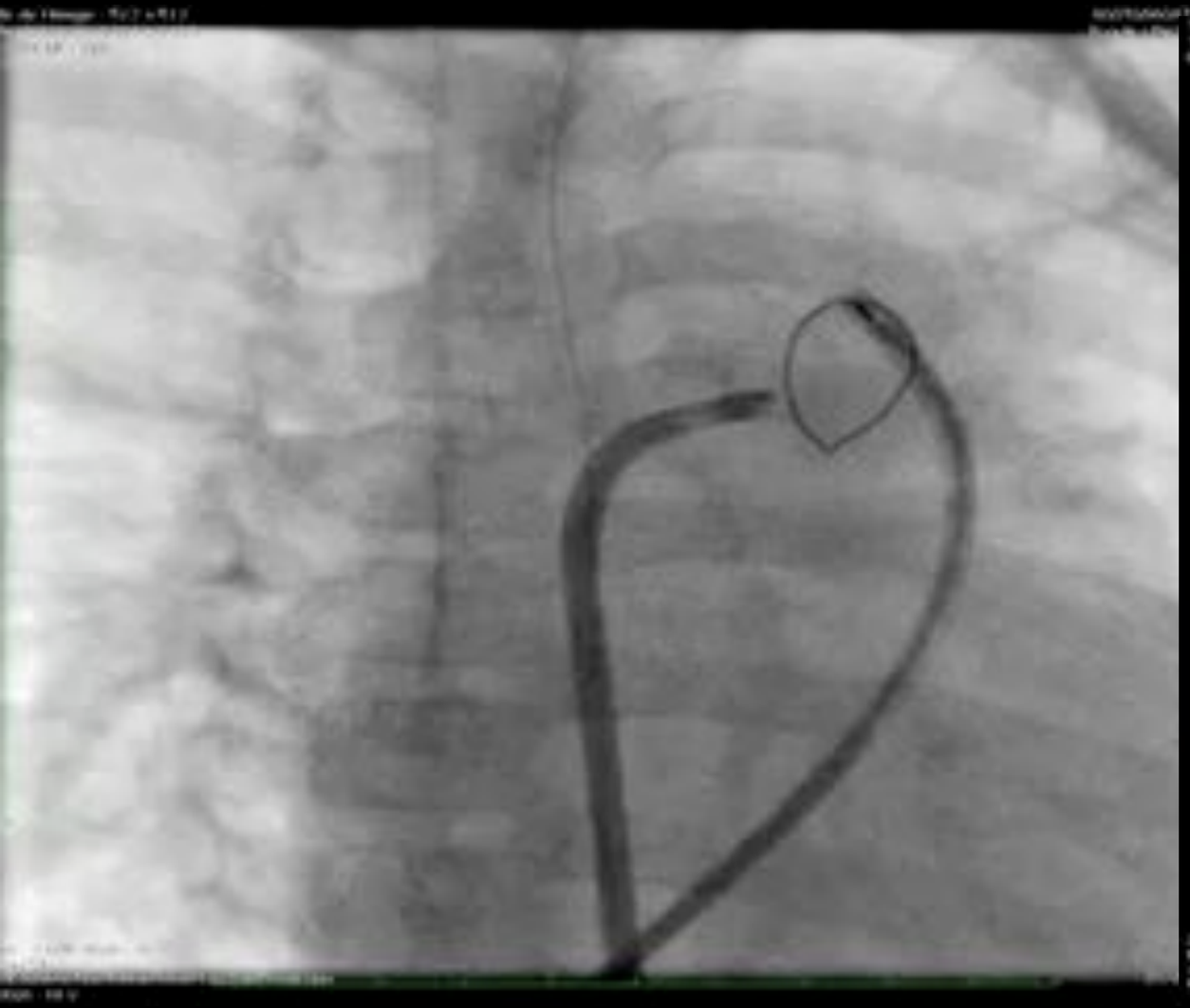
Boudjemline Y et al. Circ Cardiovasc Interv 2013
Baruteau A et al. Ann Thorac Surg 2012

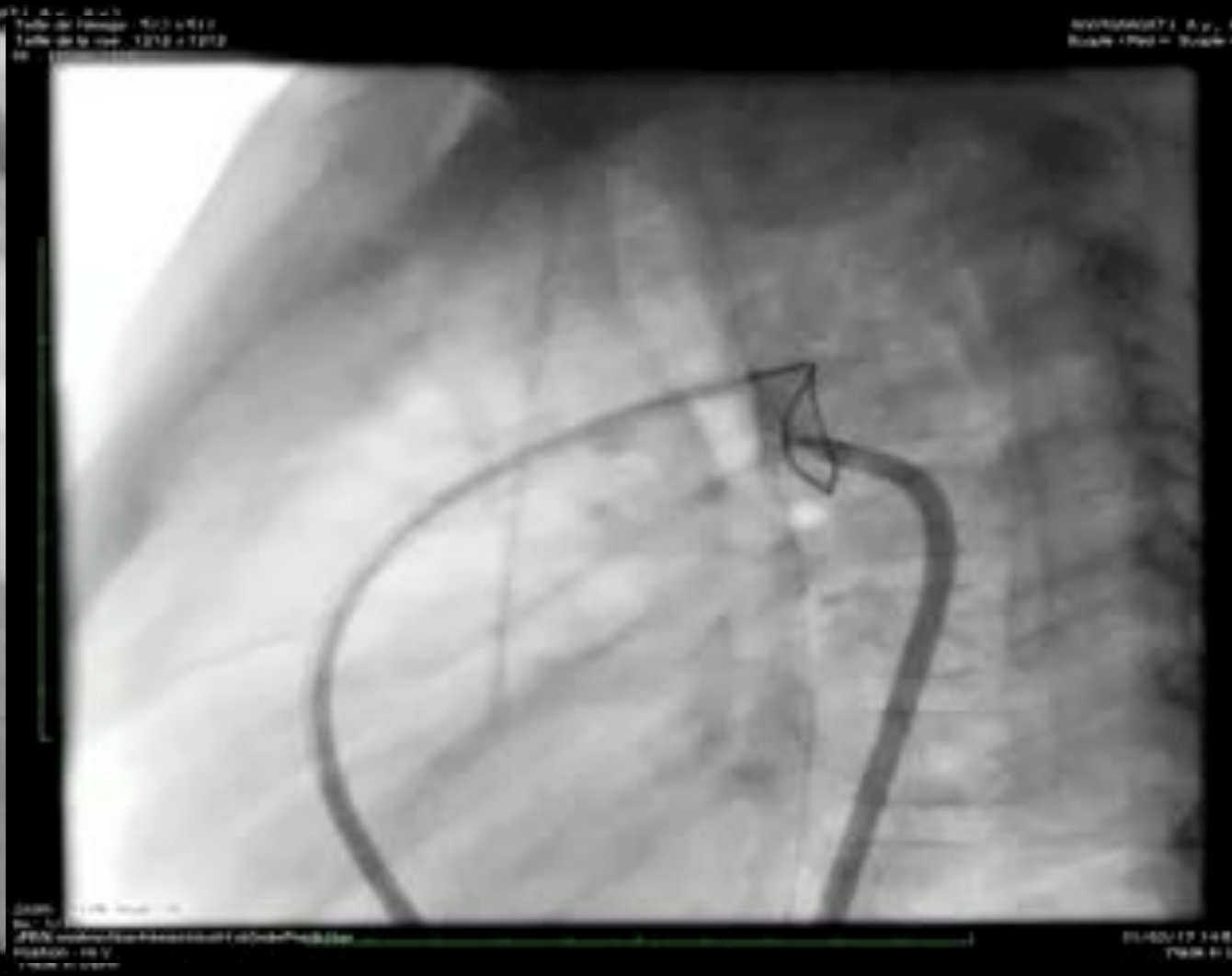
Percutaneous Potts’shunt



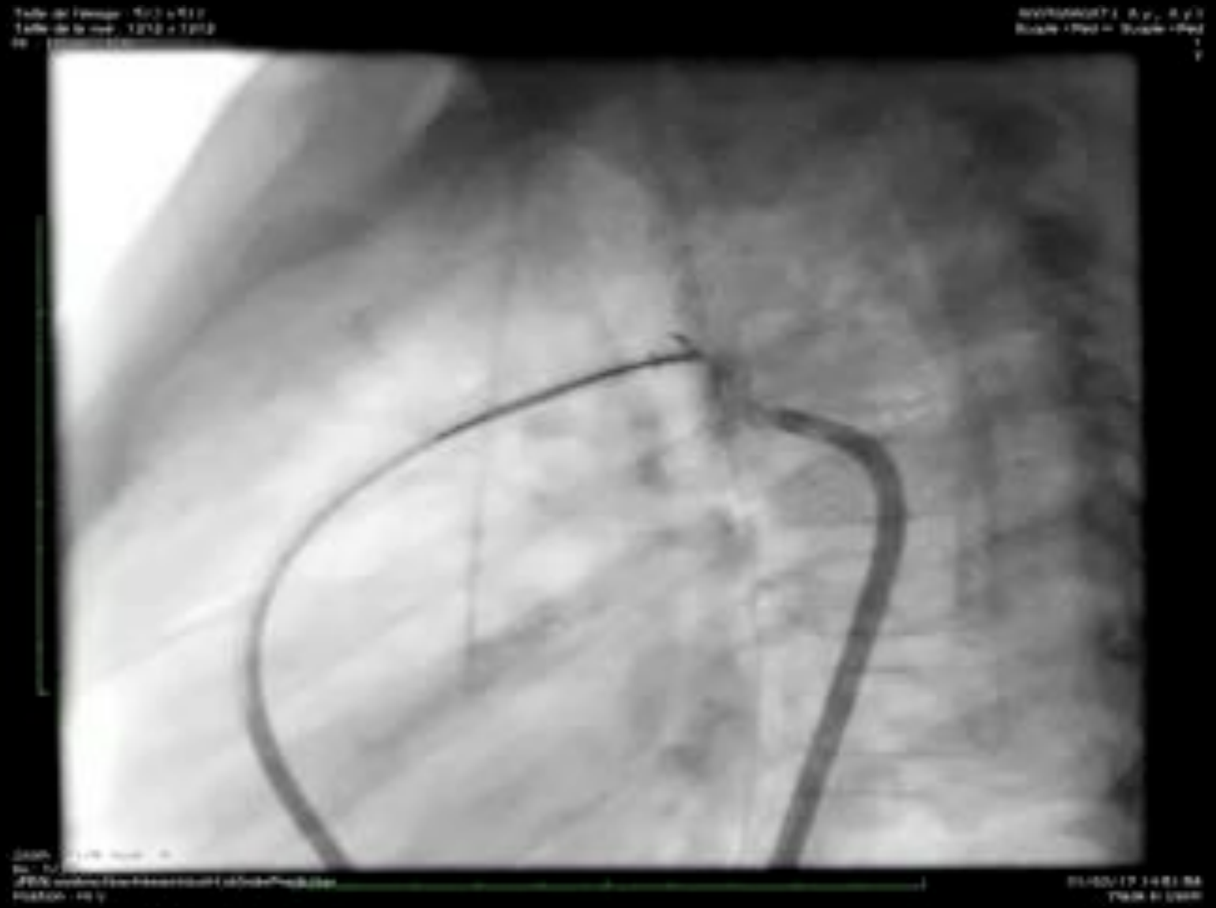


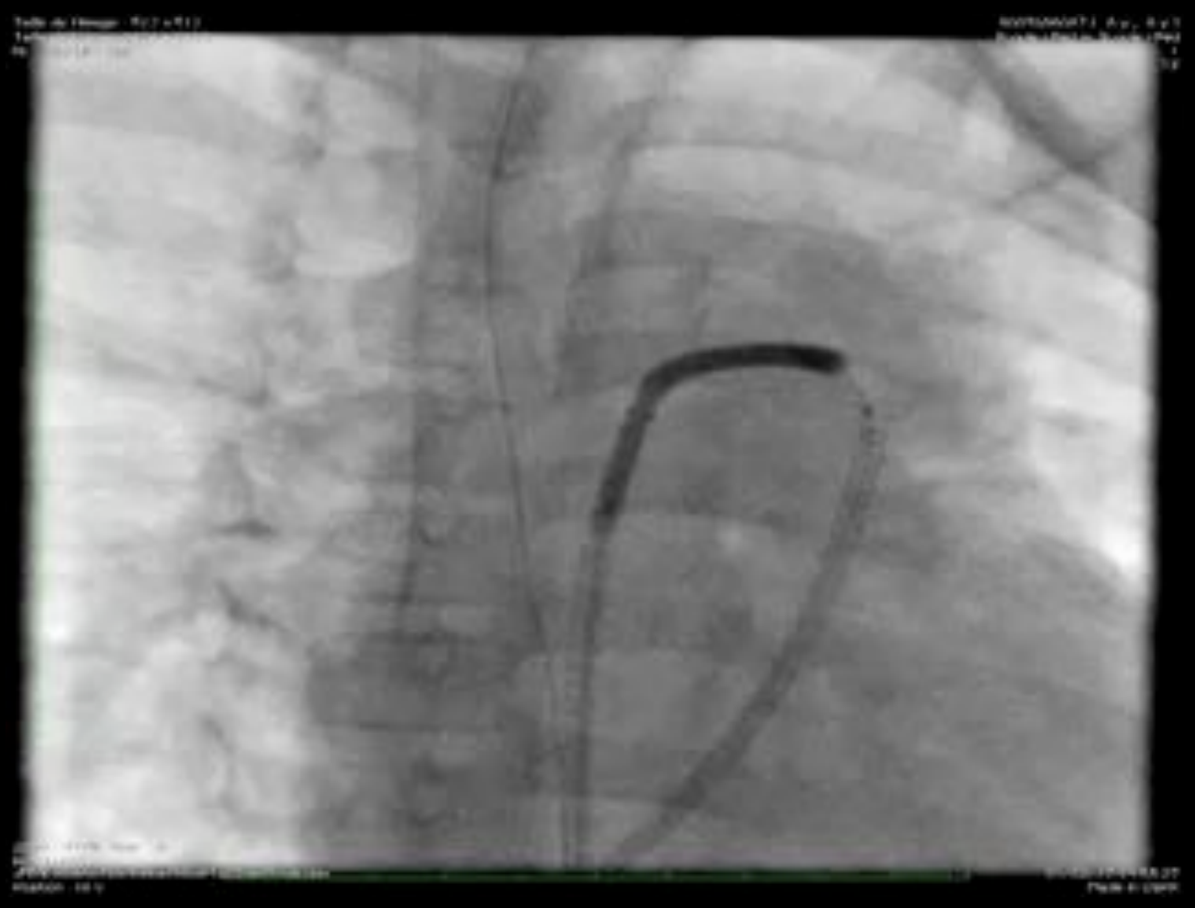
Percutaneous Potts’shunt



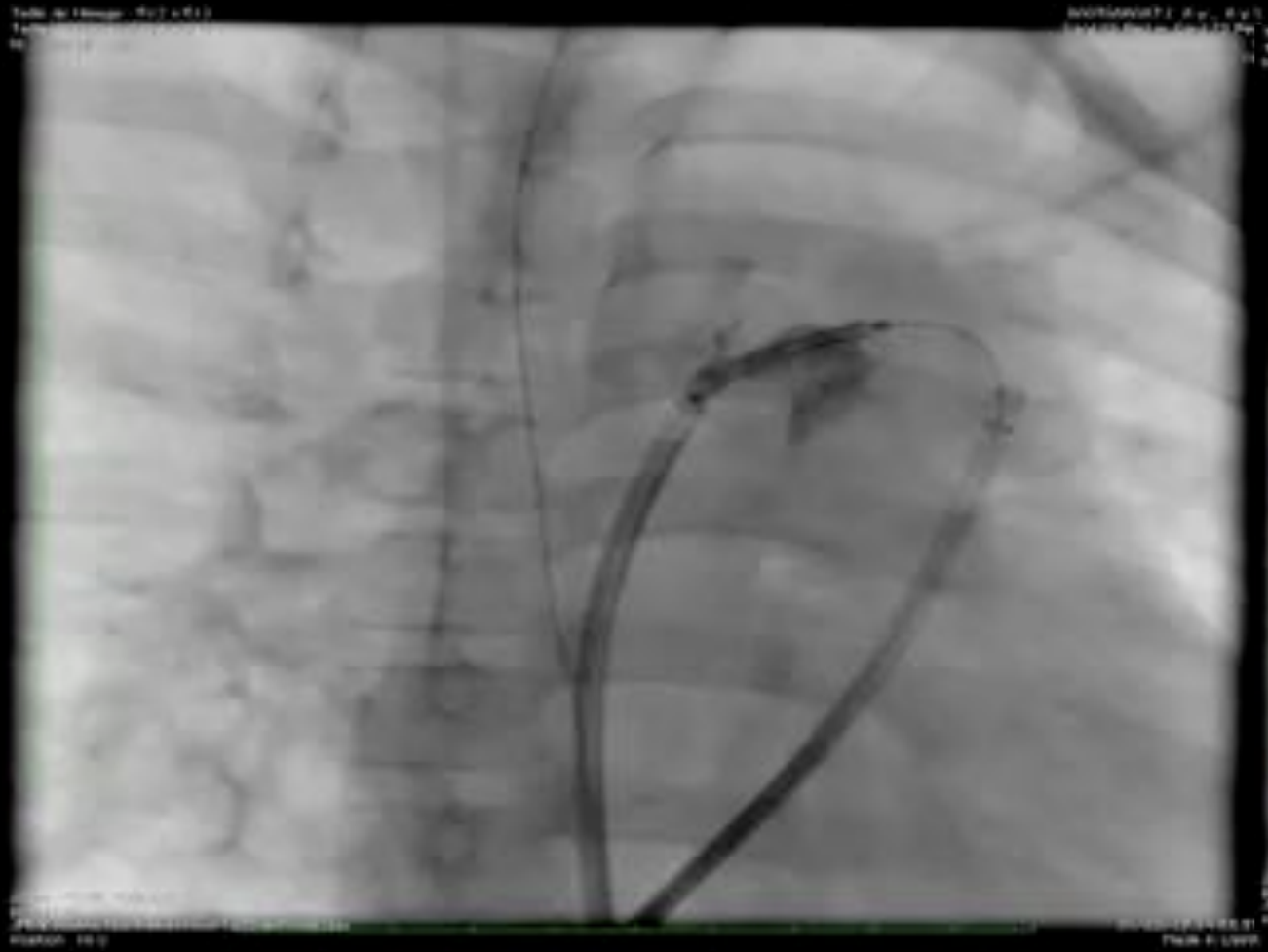


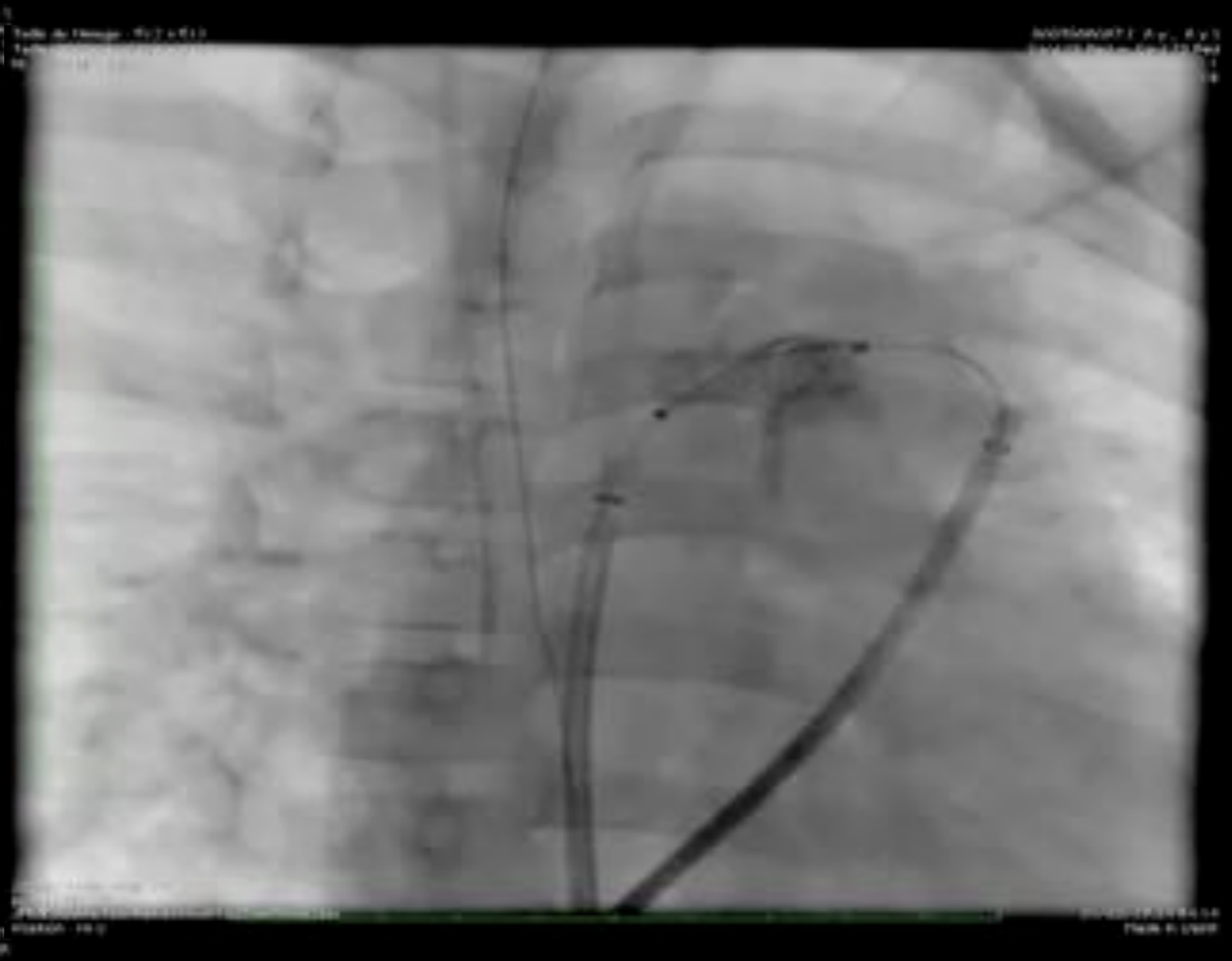
Percutaneous Potts’shunt



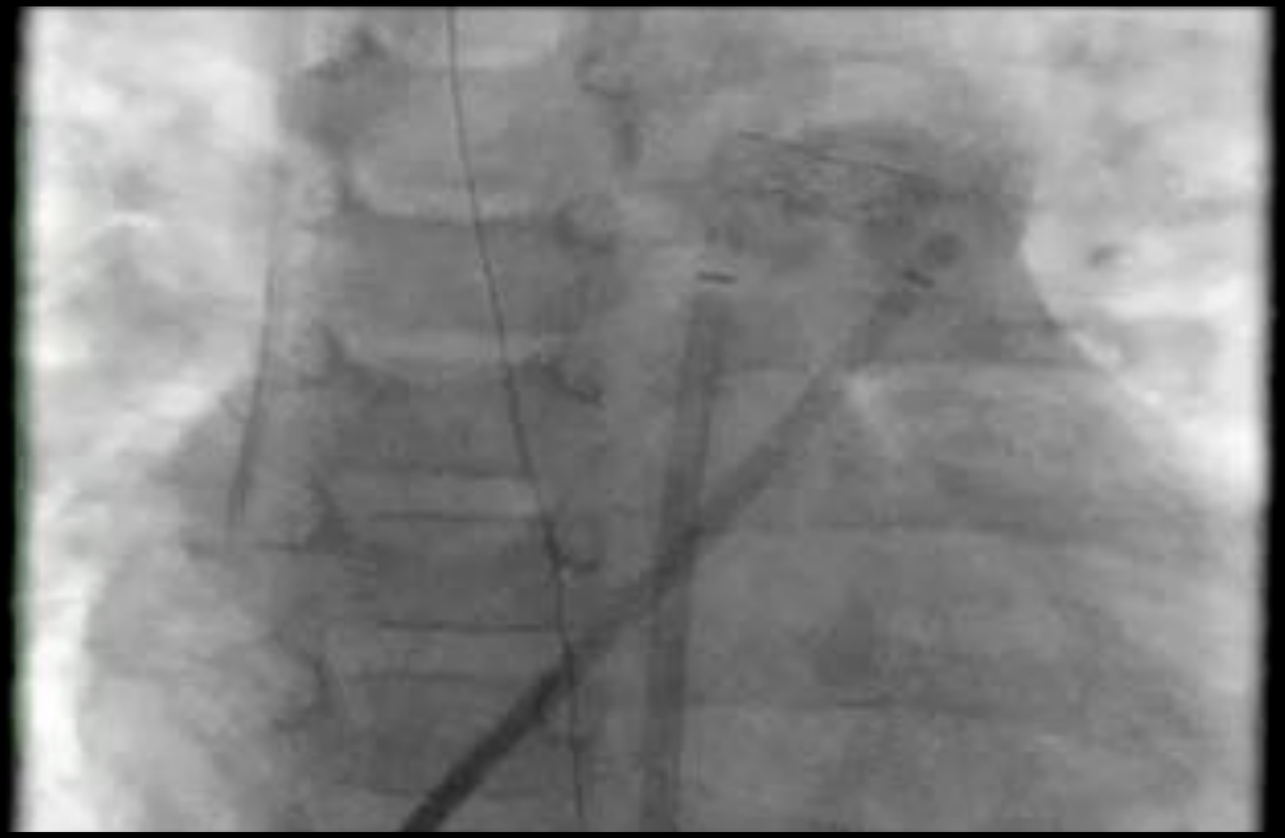


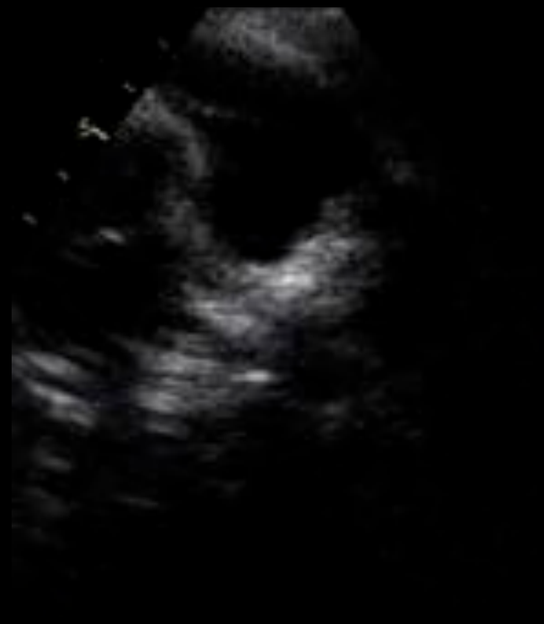
Percutaneous Potts’shunt

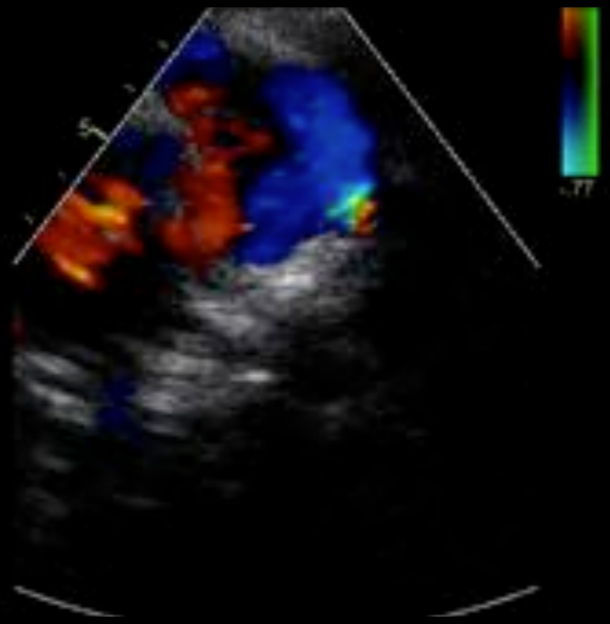




Percutaneous Potts’shunt







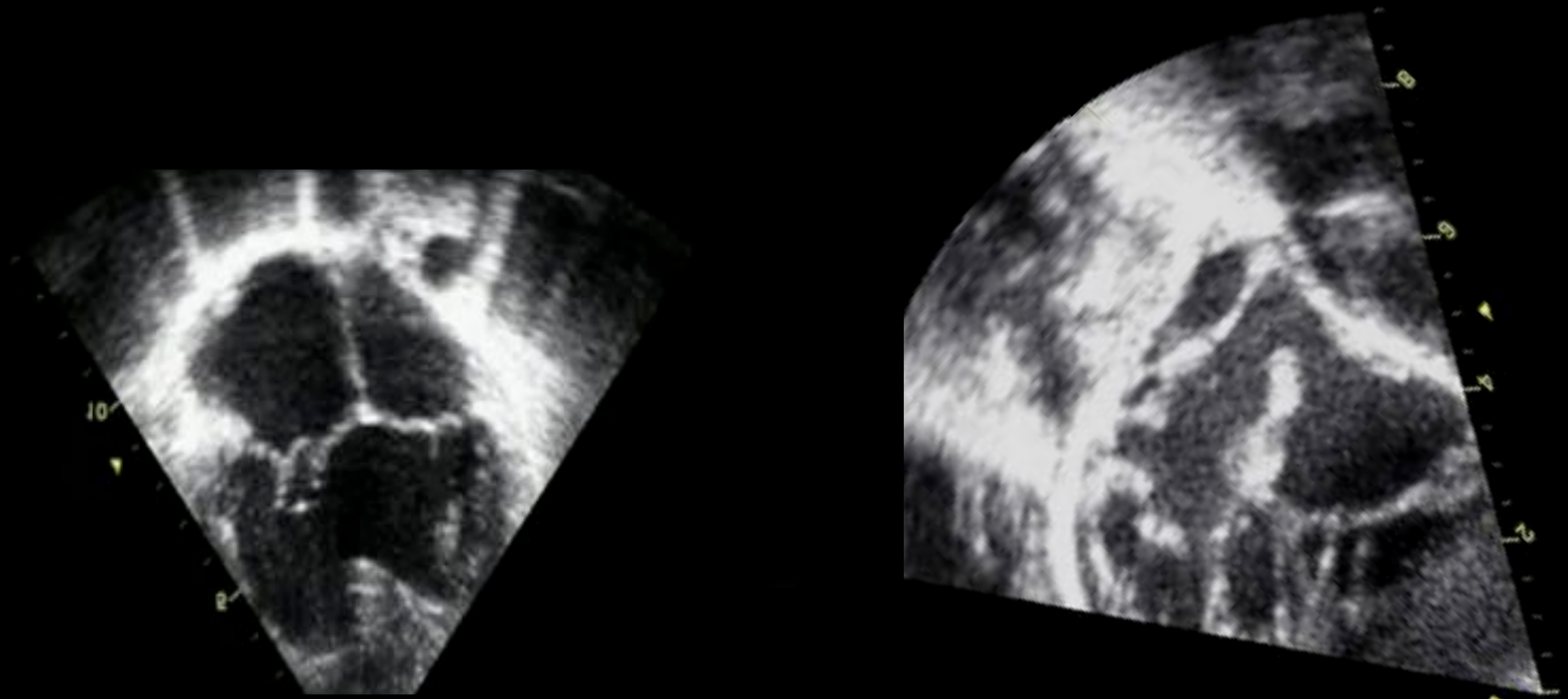
Pulmonary hypertensions and congenital heart diseases

Pulmonary HypertensionS in CHDs

$$R = P / Qp$$

P = Flow x Resistance + PCW

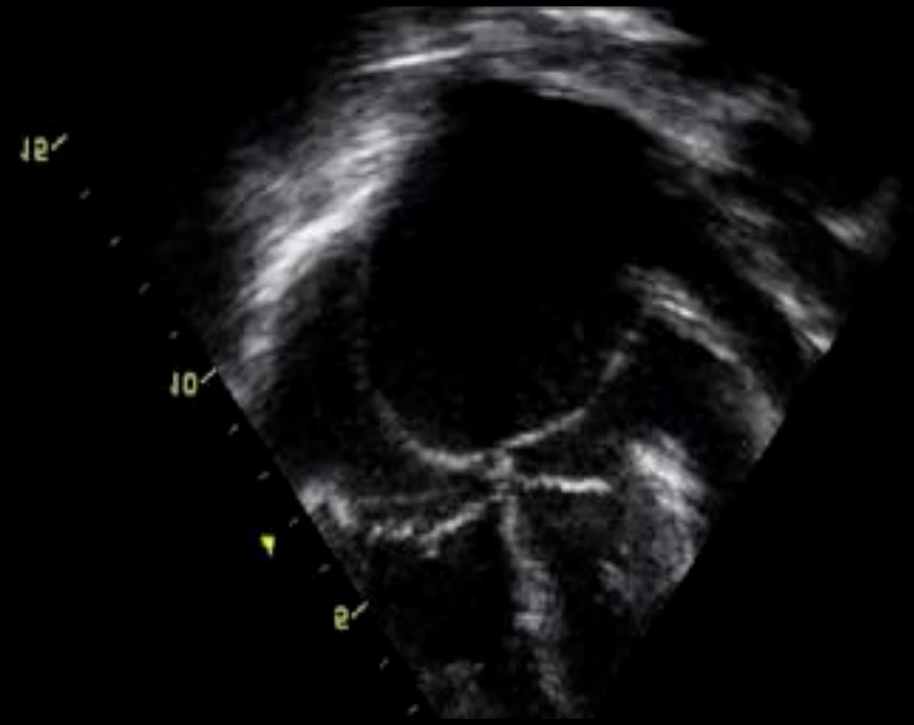
- **Flow-associated pulmonary hypertension (hyperkinetic)**
  - **congenital systemic pulmonary shunt**
- **Increased pulmonary vascular resistance**
  - **pulmonary arteriopathy (“Eisenmenger”)**
- **Pulmonary venous congestion**



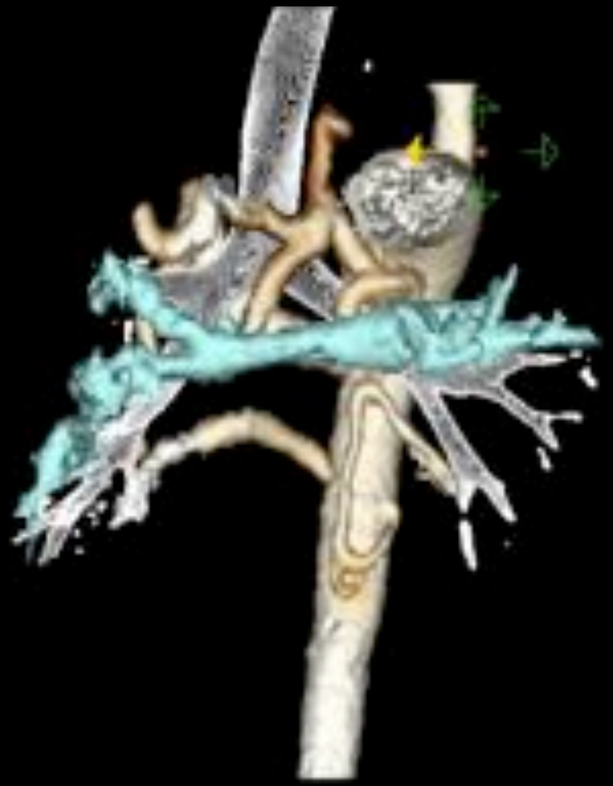
Flow-associated pulmonary hypertension (hyperkinetic)

Congenital systemic pulmonary shunt: *same physiology ?*

Cor triatriatum



Pulmonary atresia VSD

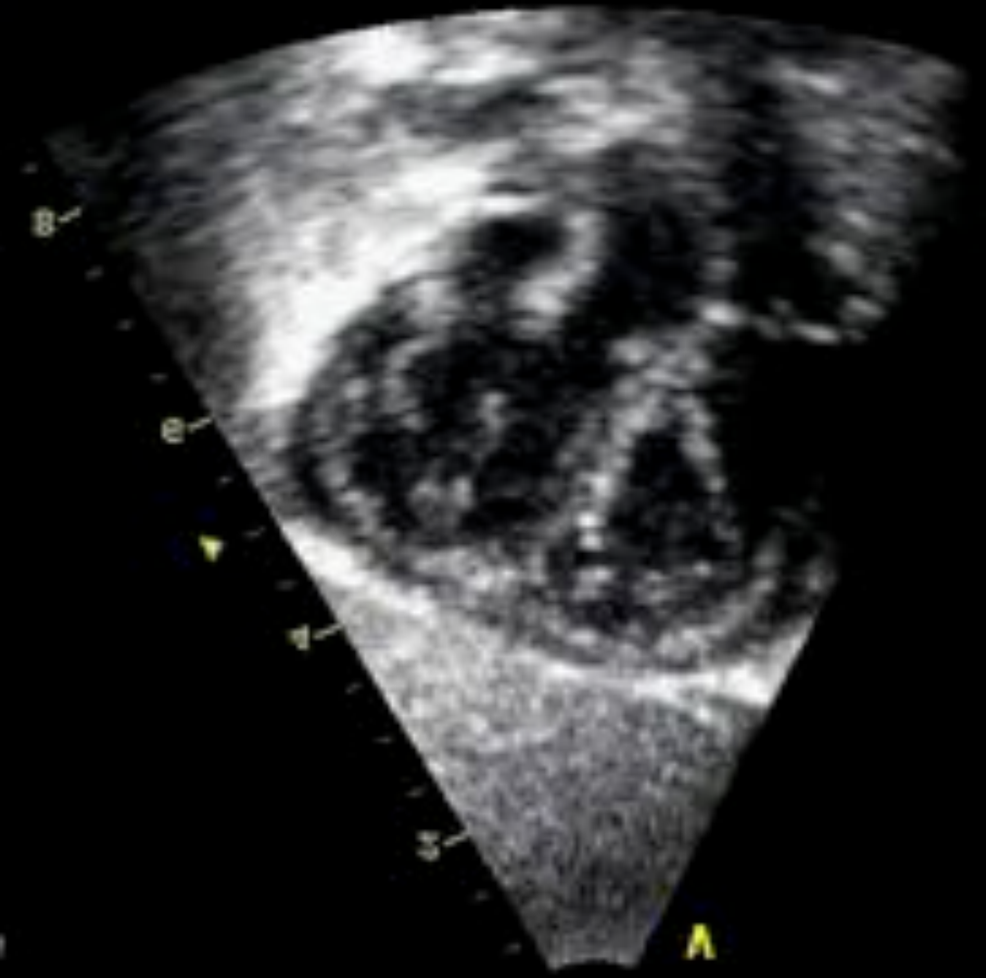


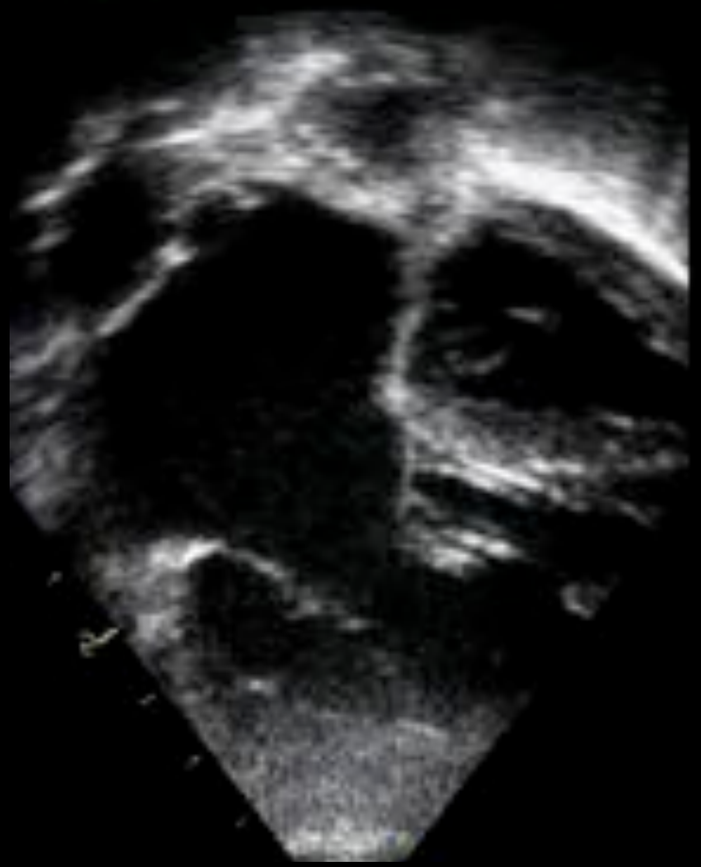
Pulmonary venous congestion

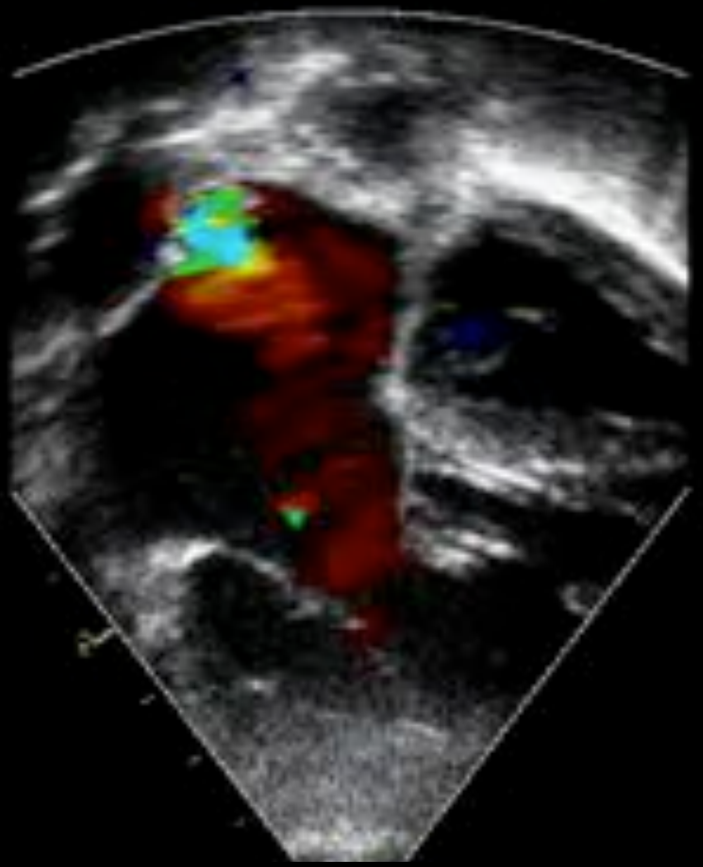
Segmental PH

Never shunt in TGA

TCPC







« Bizarre » physiopathologies with atypical/unknown vascular remodelling

2013/18 Nice
Clinical Classification of PAH Associated with CHD

A. Eisenmenger Syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

B. Left to Right Shunts
- *Operable*
- *Inoperable*

C. PAH with co-incidental CHD

D. Post-operative PAH

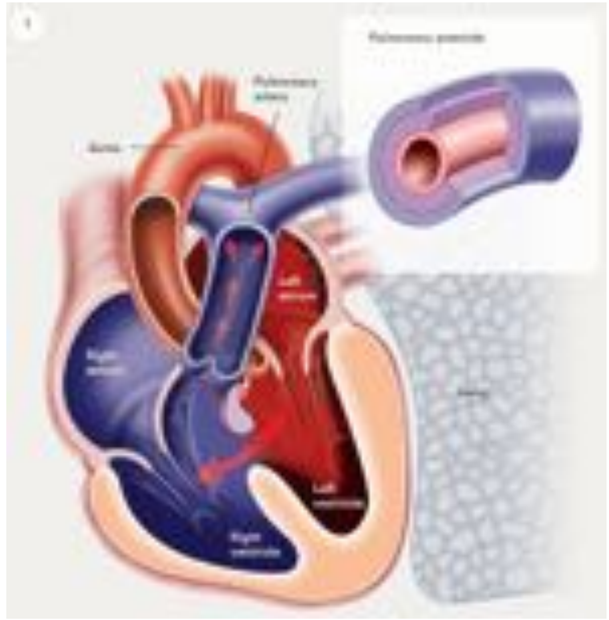
E. Never shunt/non classifiable

Definition of PAH based on mean PAP ≥ 25mmHg;
PVR provides essential information for CHD patients

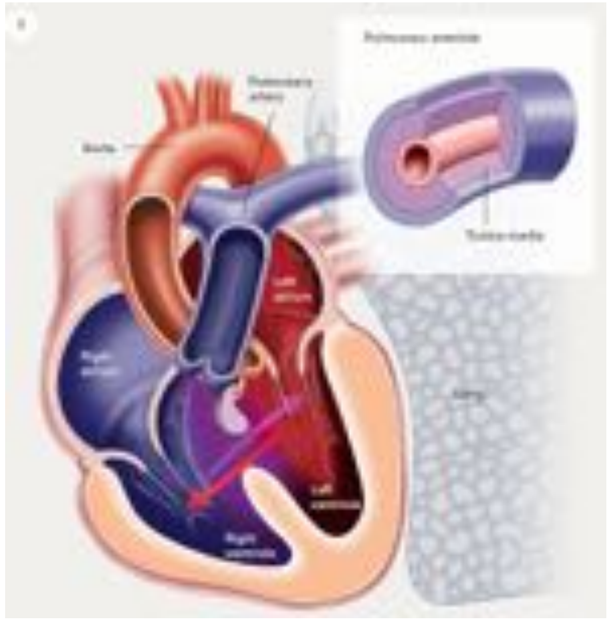
Ivy D et al. J Am Coll Cardiol 2013;62:D117–26

Left-to-right shunt: natural history/*physiology*

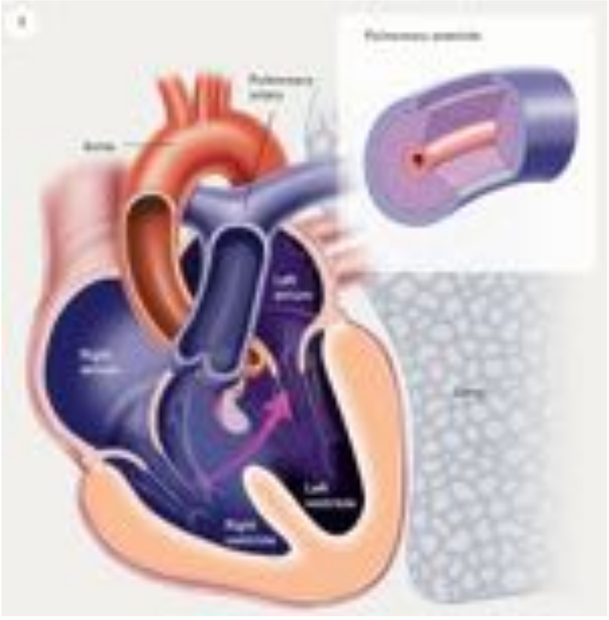
Systemic-to-pulmonary shunting can ultimately remodel the pulmonary vasculature to a characteristic irreversible phenotype similar to other forms of PAH.



ASD, VSD or complex defect, ↑ Qp and/or PAP, with left-to-right shunting

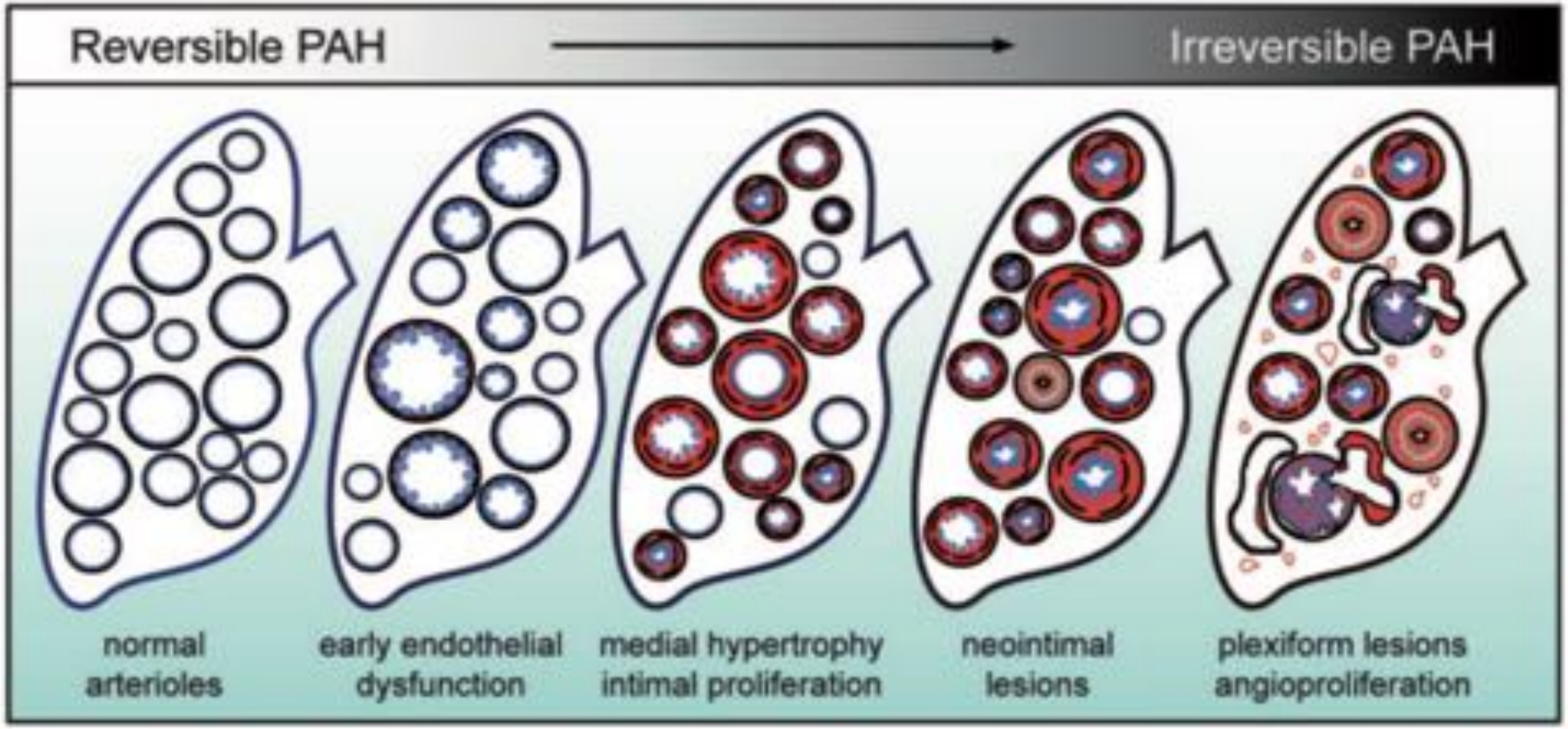


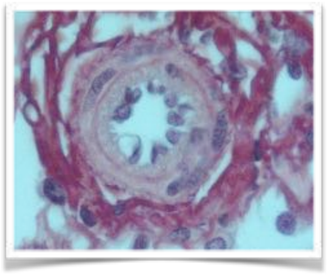
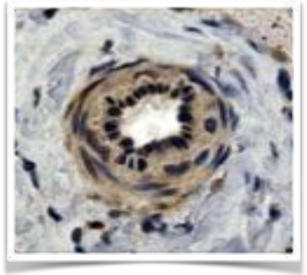
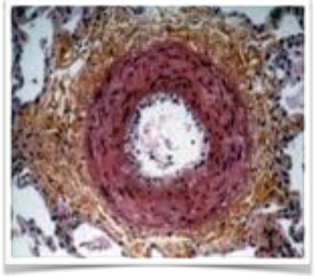
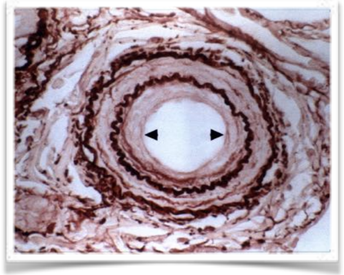
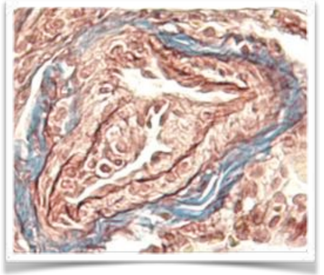
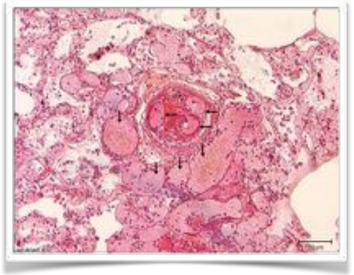
Over time, PVR ↑ resulting in bi-directional flow



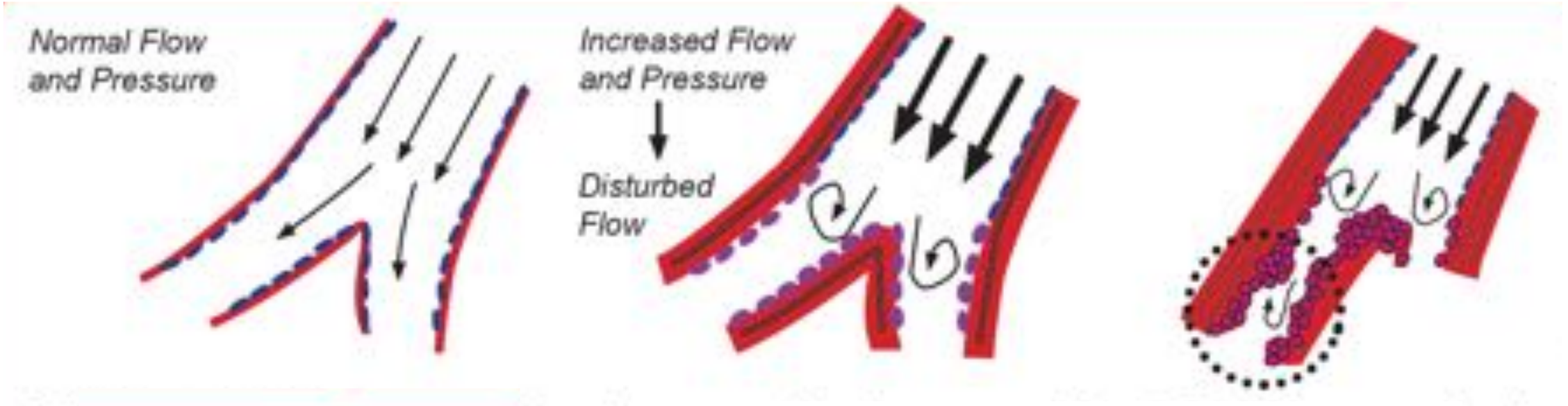
Resistance ↑ further with reversal of shunt: right-to-left → Eisenmenger syndrome – patient becomes ↑ cyanotic

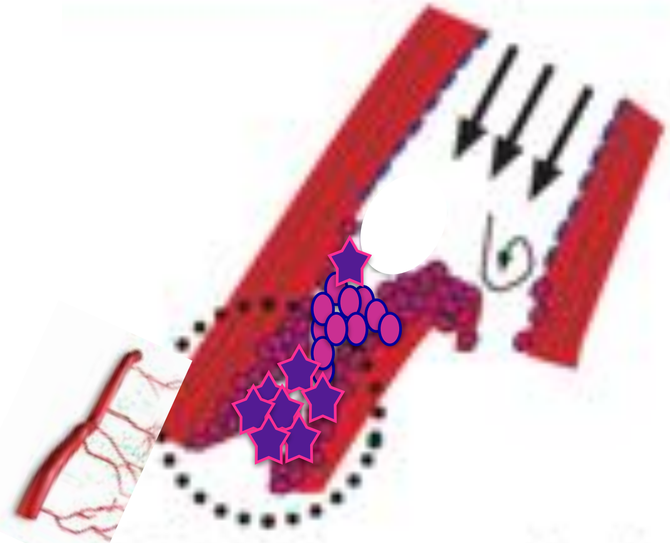
Left-to-right shunt: natural history/*pathology*

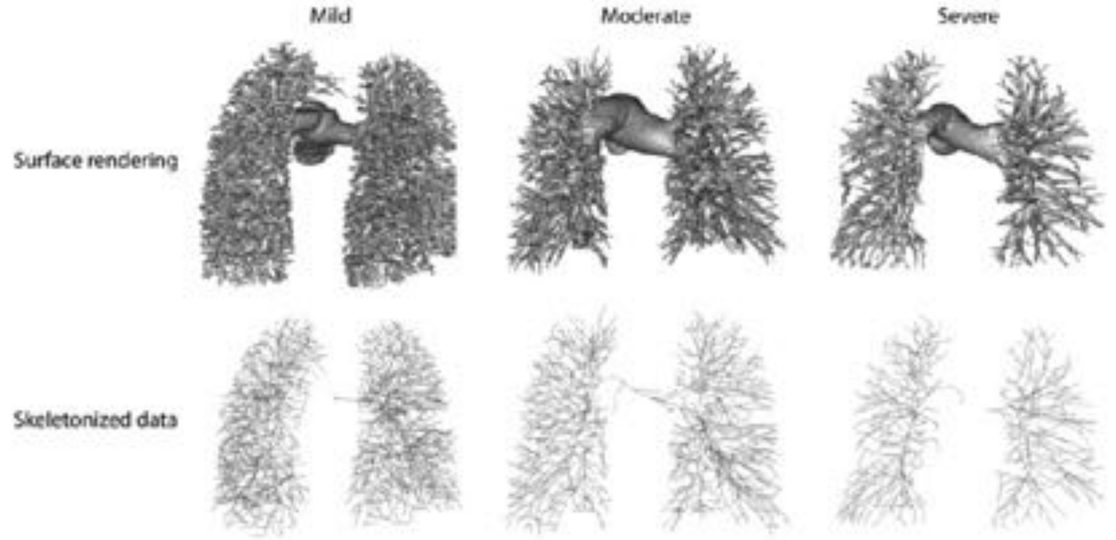


Increased flow & pressure are the essential triggers for the development of PH in CHD

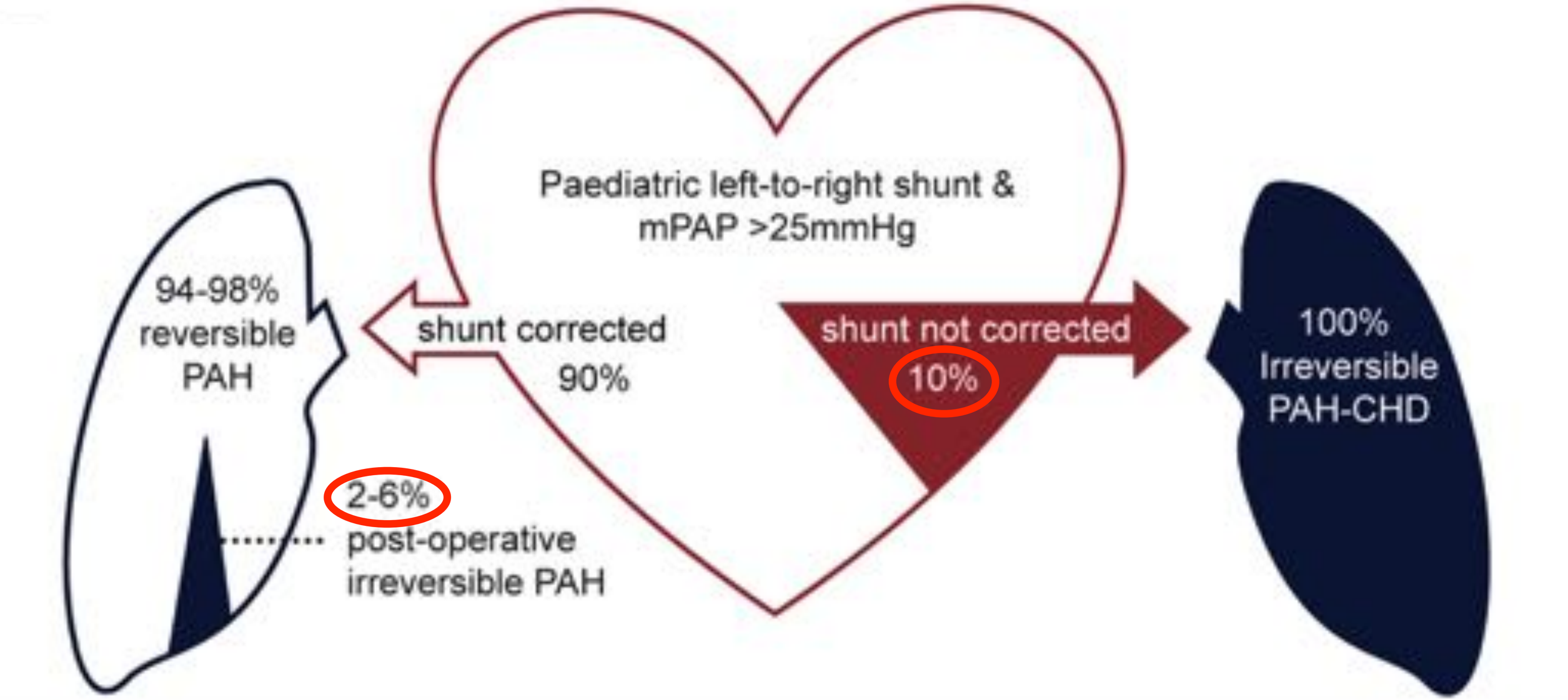




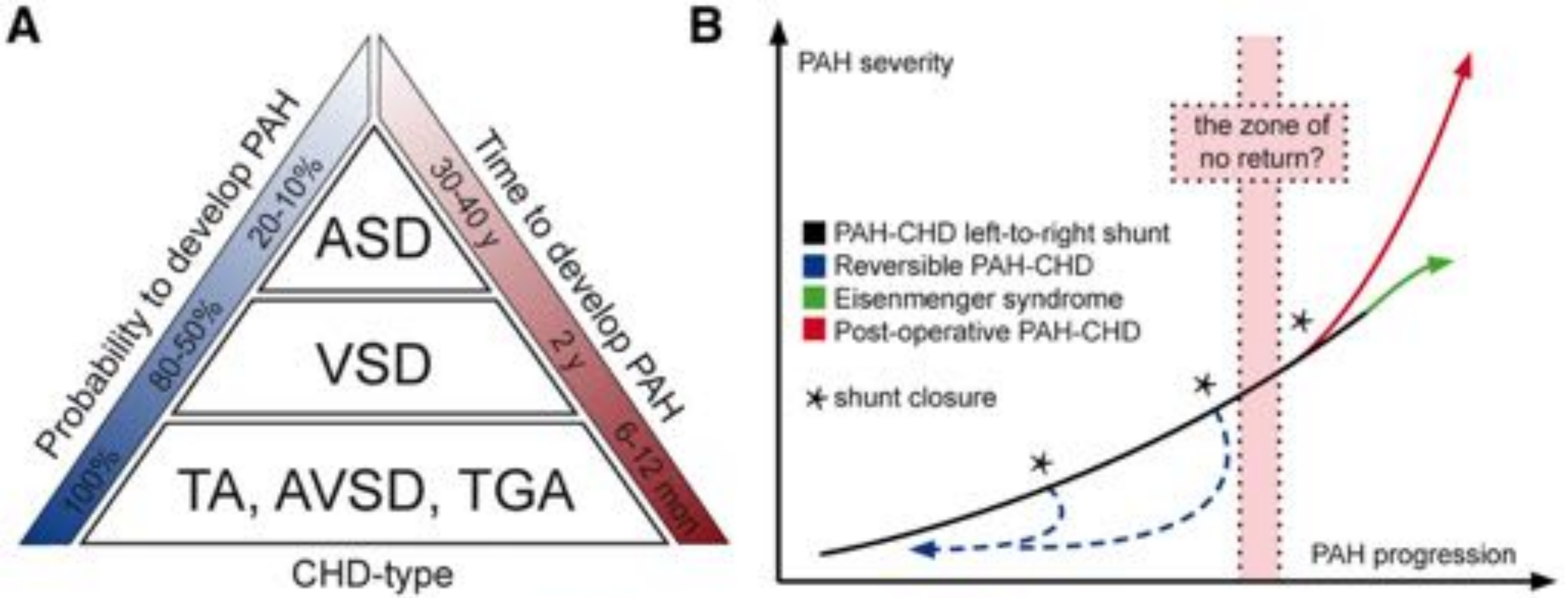


Fractal dimensions in PH

Dickinson, AJP 2013;
van der Feen, Eur Heart J 2017
Moledina S et al. Heart 2011



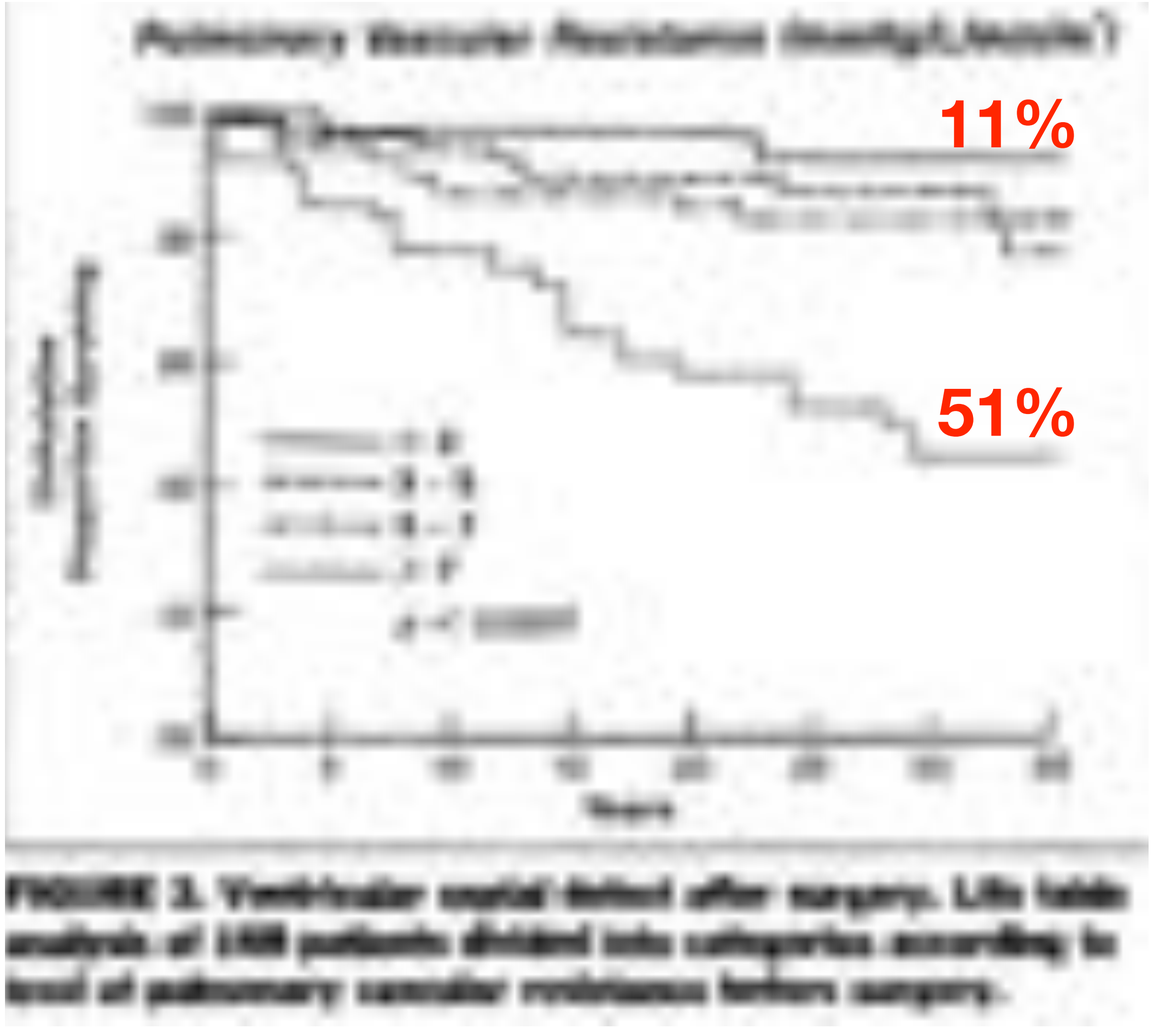
From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Eur Heart J. 2017;38(26):2034-2041.



From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Eur Heart J. 2017;38(26):2034-2041.

Recommendations for correction of CHD with prevalent systemic-to-pulmonary shunts

Recommendations			Class[a]	Level[b]	Ref.[c]
PVRi (WU • m²)	PVR (WU)	Correctable[d]			
<4	<2.3	Yes	IIa	C	317
>8	>4.6	No	IIa	C	317
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa	C	317



Moller JH, Patton C, Varco RL, Lillehei CW. Late results (30to35years) after operative closure of isolated ventricular septal defect from 1954 to 1960. Am J Cardiol 1991;68:1491–1497.

Attempt to define group 2 (ex group B): Operable vs. Inoperable

Table 3. Recommended preoperative evaluation of pediatric patients with congenital systemic-to-pulmonary shunts, with the findings that may indicate a favorable or unfavorable response to correction of cardiac lesions

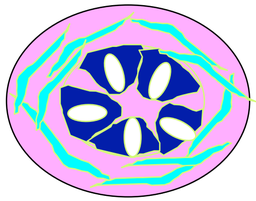
	Findings	
Source, features/parameters	Favorable	Unfavorable
Clinical history		
Age, years	<1	>2
Congestive heart failure/pulmonary congestion	Present	Absent
Tendency to respiratory disorders (inflammatory/infectious)	Yes	No
Failure to thrive	Yes	No
Use of anticongestive medication	Yes	No
Associated syndromes	No	Yes (Down syndrome)
Associated airway/lung disease	No	Yes
Physical examination		
Dyspnea	Present/overt	Mild/absent
Dynamic precordium	Present	Absent
Precordial murmur	Present	Absent
Second heart sound (pulmonic area)	Mildly increased split present	Loud split absent
Peripheral oxygen saturation, %	>93	<90
Associated airway obstruction/lung disease	No	Yes
Chest X-ray		
Size of the heart	Enlarged	"Hypertrophic"
Pulmonary vascular markings	Proeminent	Decreased distal markings
Congestion	Present	Absent
Parenchymal lung disease	Absent	Present
Transthoracic echocardiography		
Direction of flow across the communication	Left-to-right or bidirectional, but predominantly left-to-right	Bidirectional, predominantly right-to-left
Size of left cardiac chambers (posttricuspid shunts)	Enlarged	Not enlarged
Pulmonary-to-systemic blood flow ratio (Qp : Qs)	>3.0 : 1	>2.0 : 1
Right ventricular dysfunction	Absent	Present
Type of defects[a]	Simple lesions[b]	Complex anomalies[c]
Cardiac catheterization		
Pulmonary vascular resistance index, Wood units m^2	<6.0 (preferably, <4.0)	>8.0
Pulmonary-to-systemic vascular resistance ratio (PVR : SVR)	<0.3	>0.5

Pulm Circ 2014;4(2):330-341

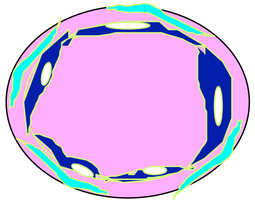
Normalisation of Flow (Haemodynamic Unloading) reverses PAH-CHD,

but not after a certain point of no return.

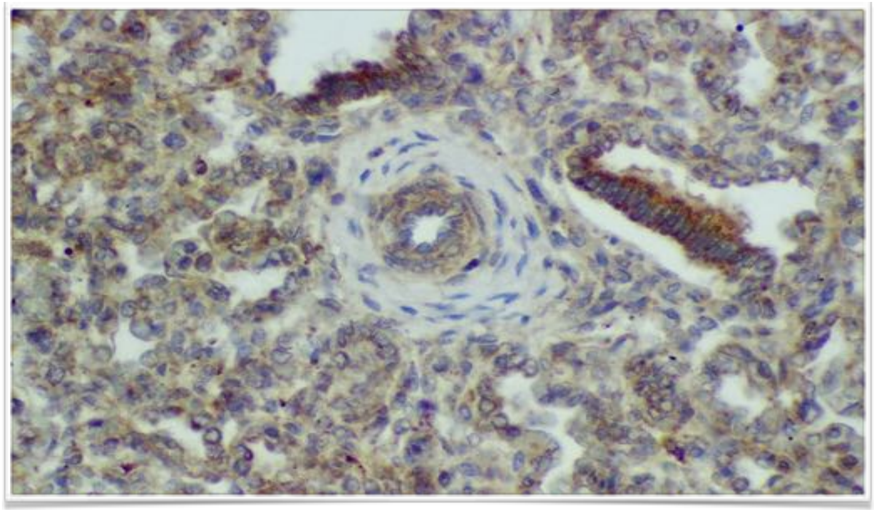
Which lesions are reversible in PAH-CHD ?



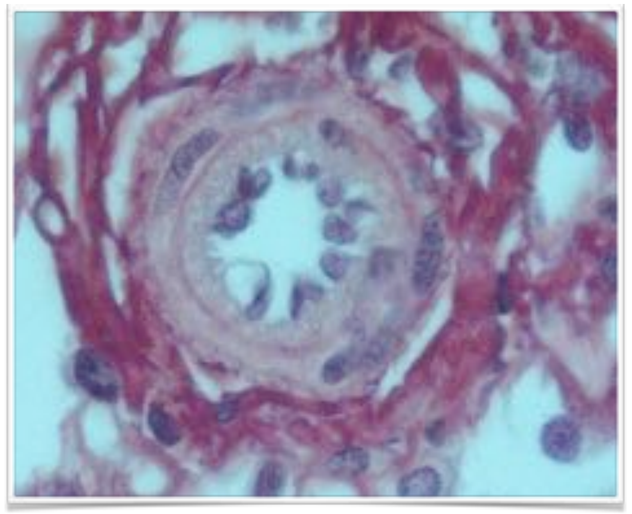
Foetus



Birth



Foetal arteriole



Mature arteriole

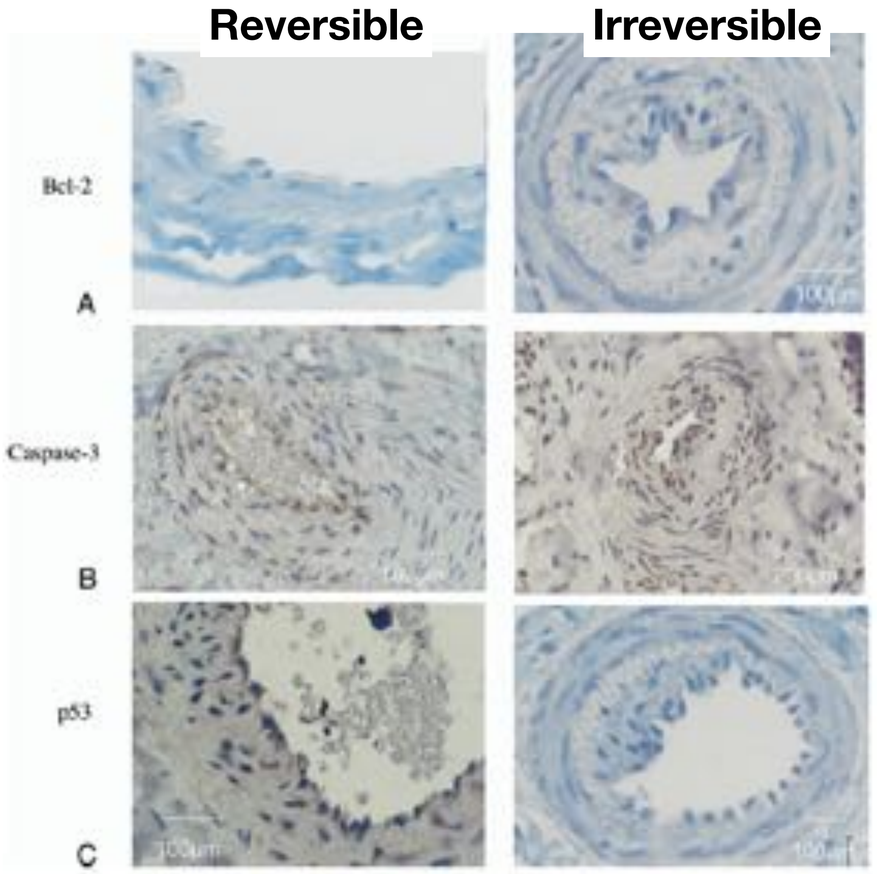
8 weeks

Wagenvoort, and Heath & Edwards

What could make PAH irreversible ?

1-Apoptosis and apoptosis resistance

Vascular immunostaining for markers of apoptosis in reversible and irreversible APAH-CHD

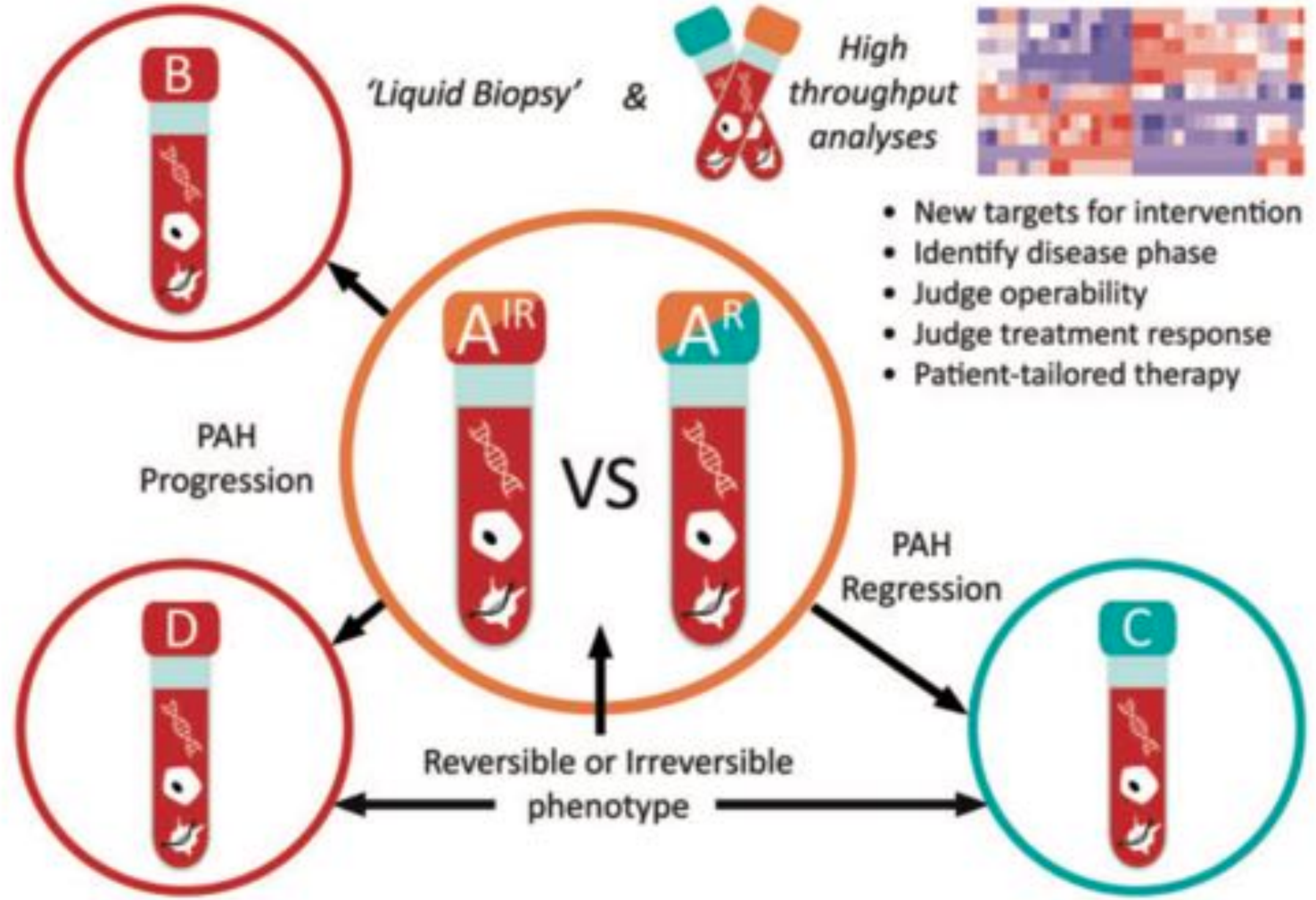


The antiapoptotic protein Bcl-2 is not expressed in reversible pulmonary hypertension (PHT), but by endothelial cells of severely damaged pulmonary arteries in irreversible PHT in all cases (A).
Endothelial cells of both groups expressed markers of apoptosis caspase-3 (B) and p53 (C).
The arrow indicates immunostaining in the endothelial layer.

Lévy M et al. JACC 2007;49:803-10

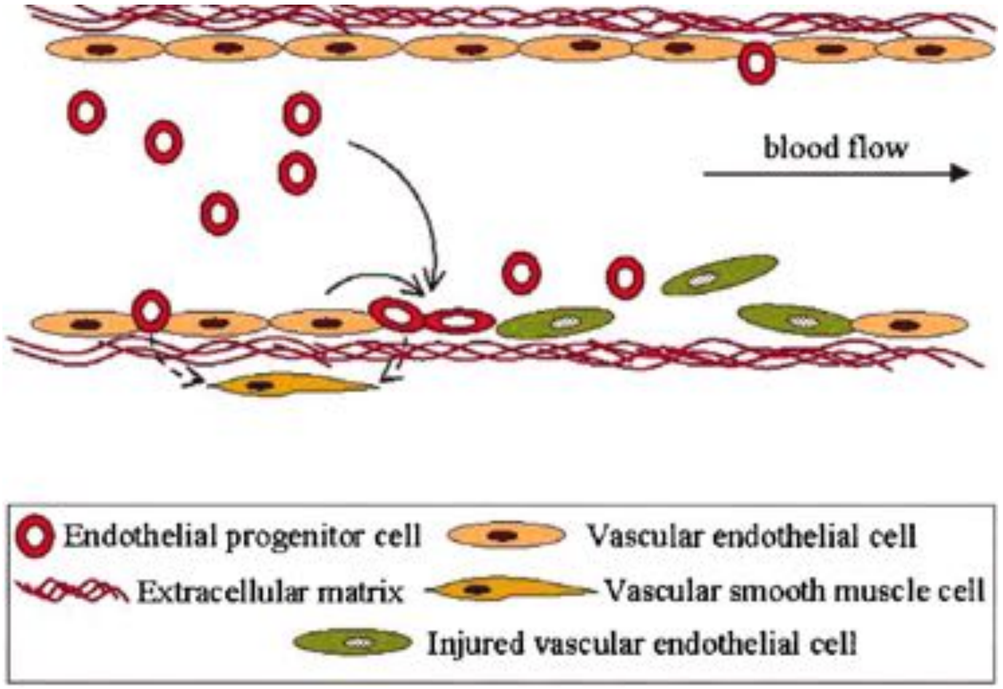
Comparison of human reversible to irreversible PAH-CHD

The liquid biopsy concept

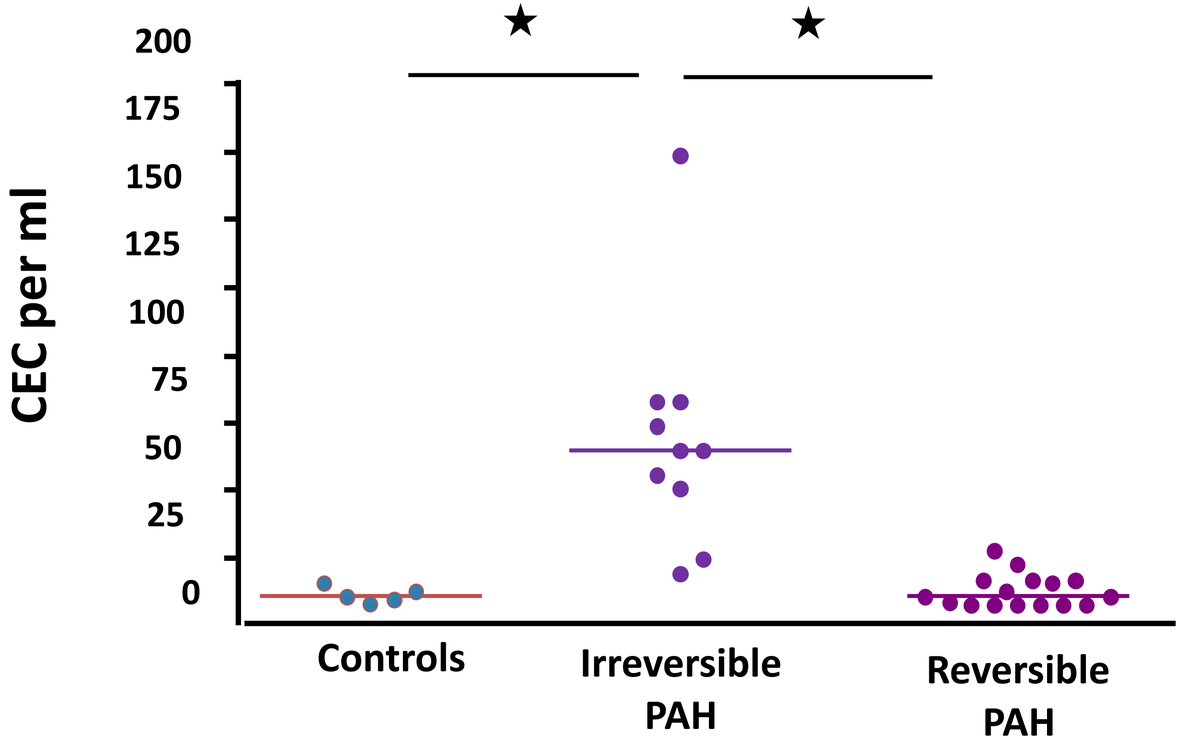


From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Eur Heart J. 2017;38(26):2034-2041.

Circulating endothelial cells: A biomarker of irreversible PH secondary to CHD

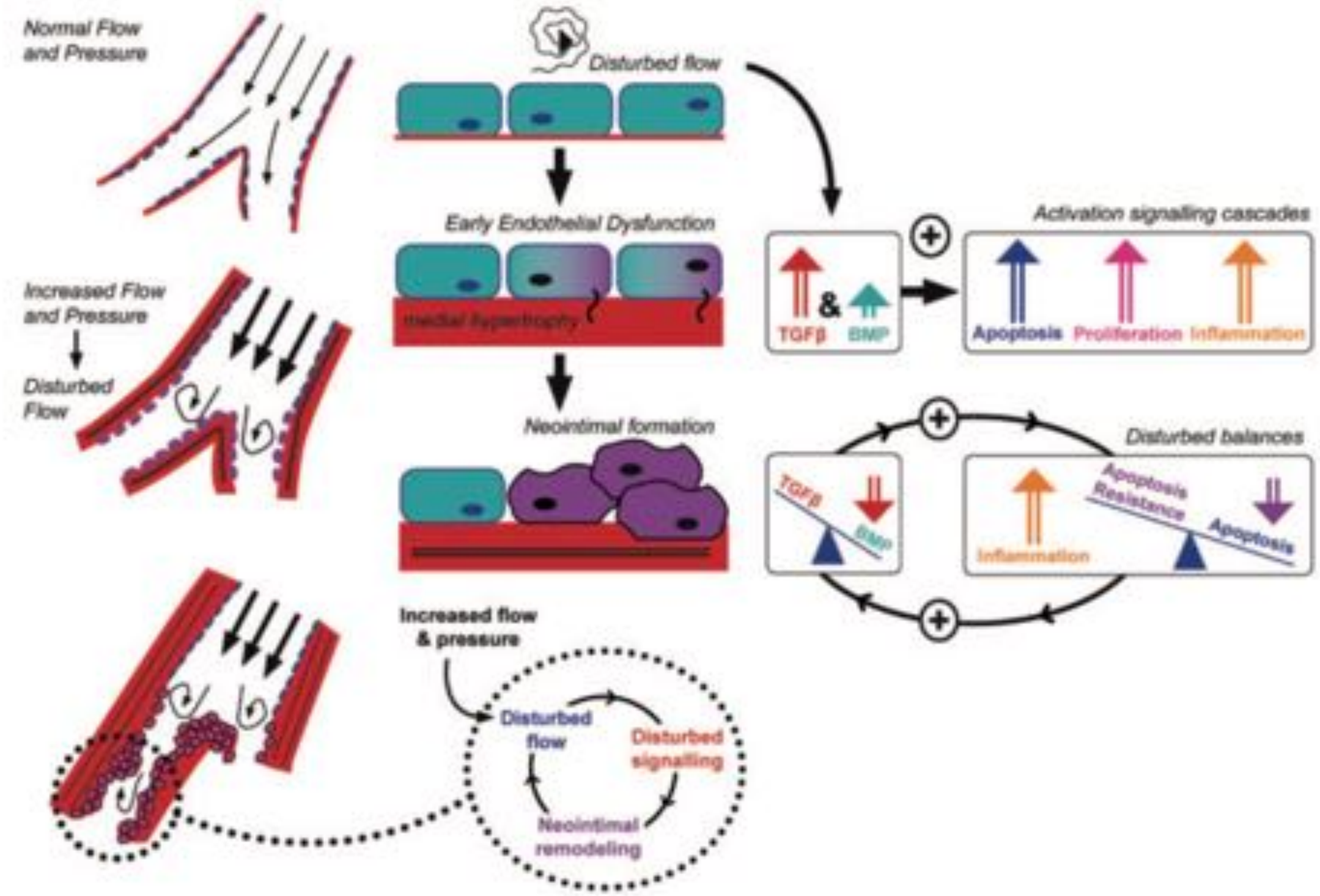


CEC counts in peripheral venous blood of CHD patients with PH



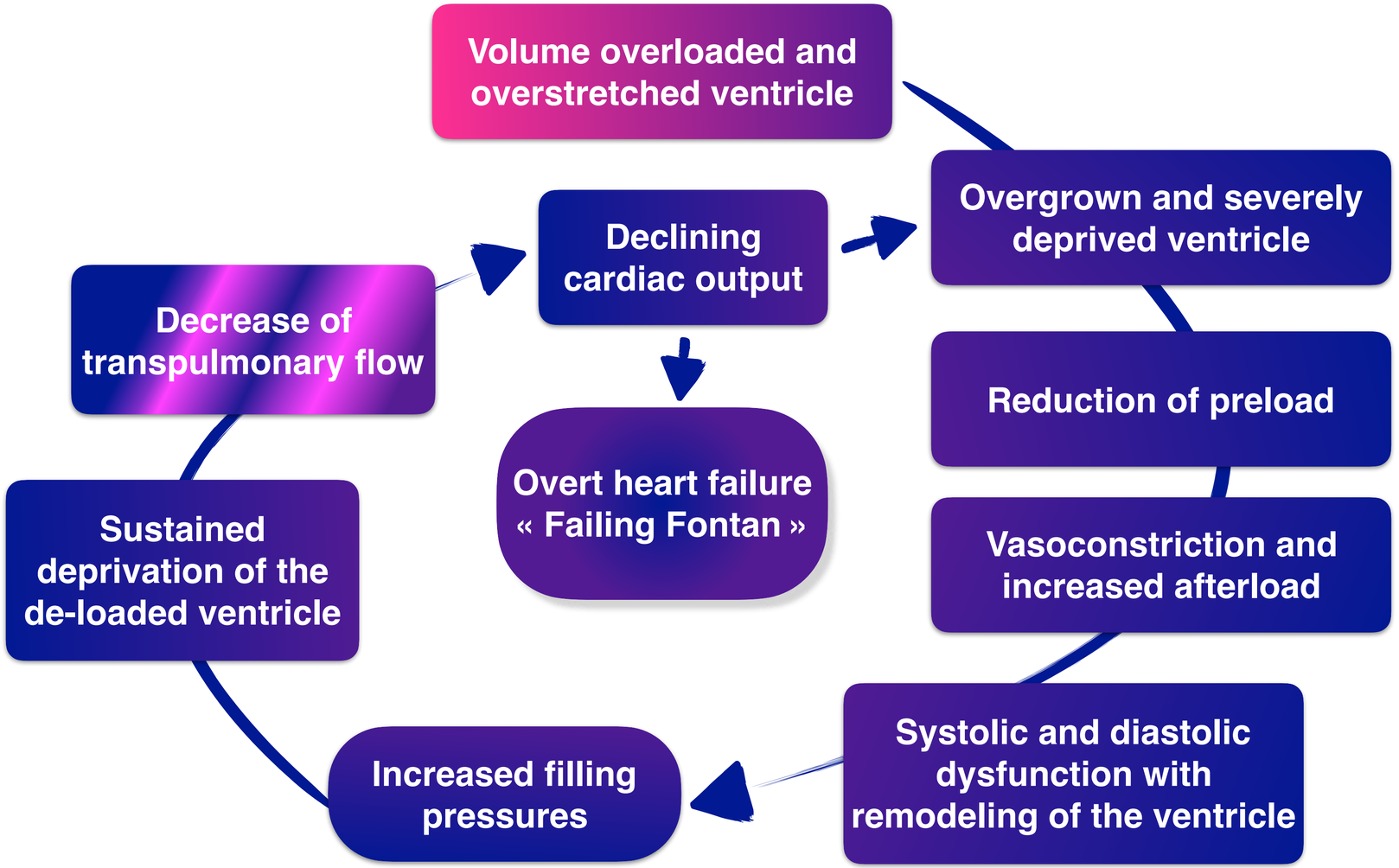
Smadja DM, et al. Circulation 2009; 119:374-81.

Summary **Flow PH in CHD**



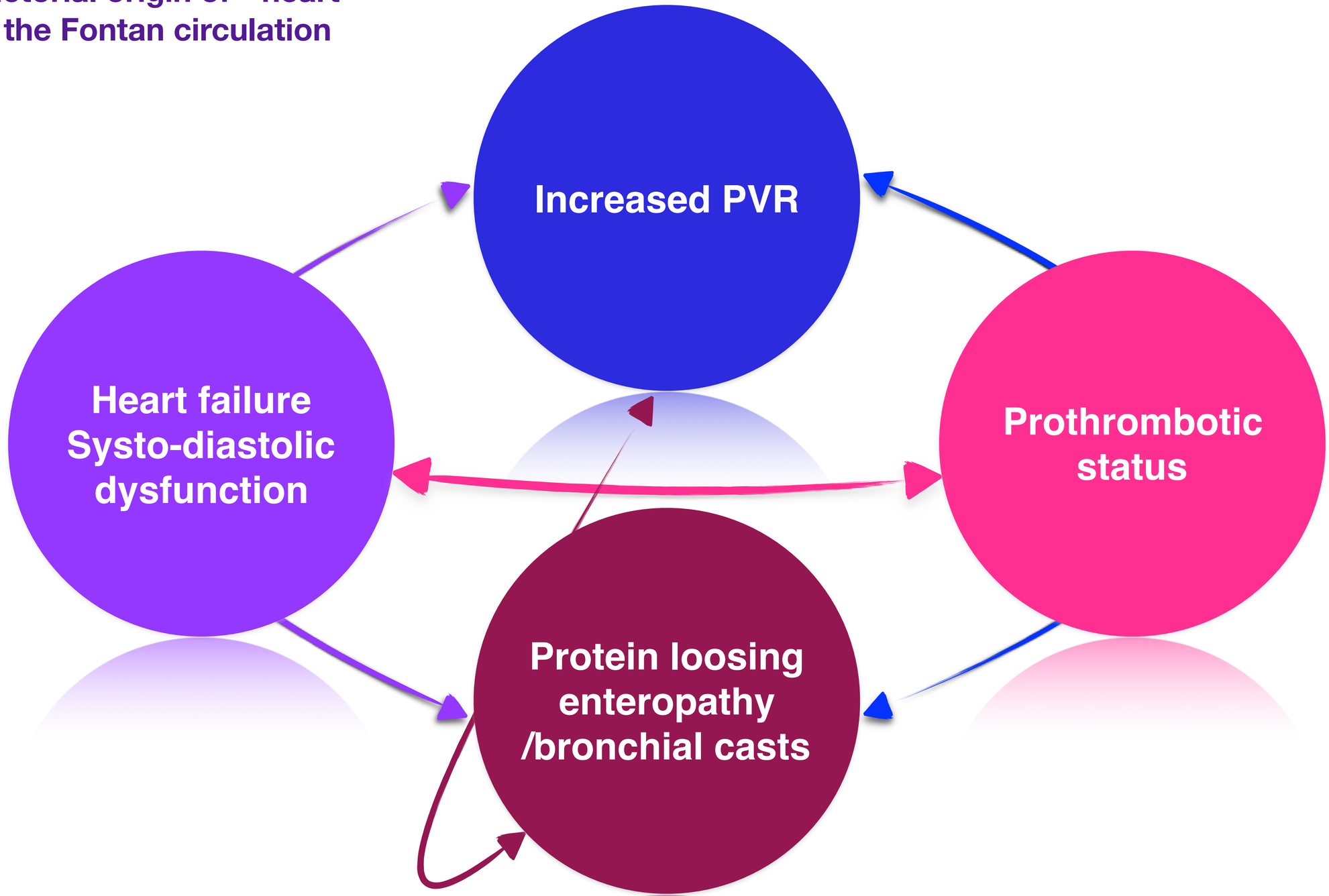
The Fontan circulation - a new portal system

The vicious circle to failing Fontan



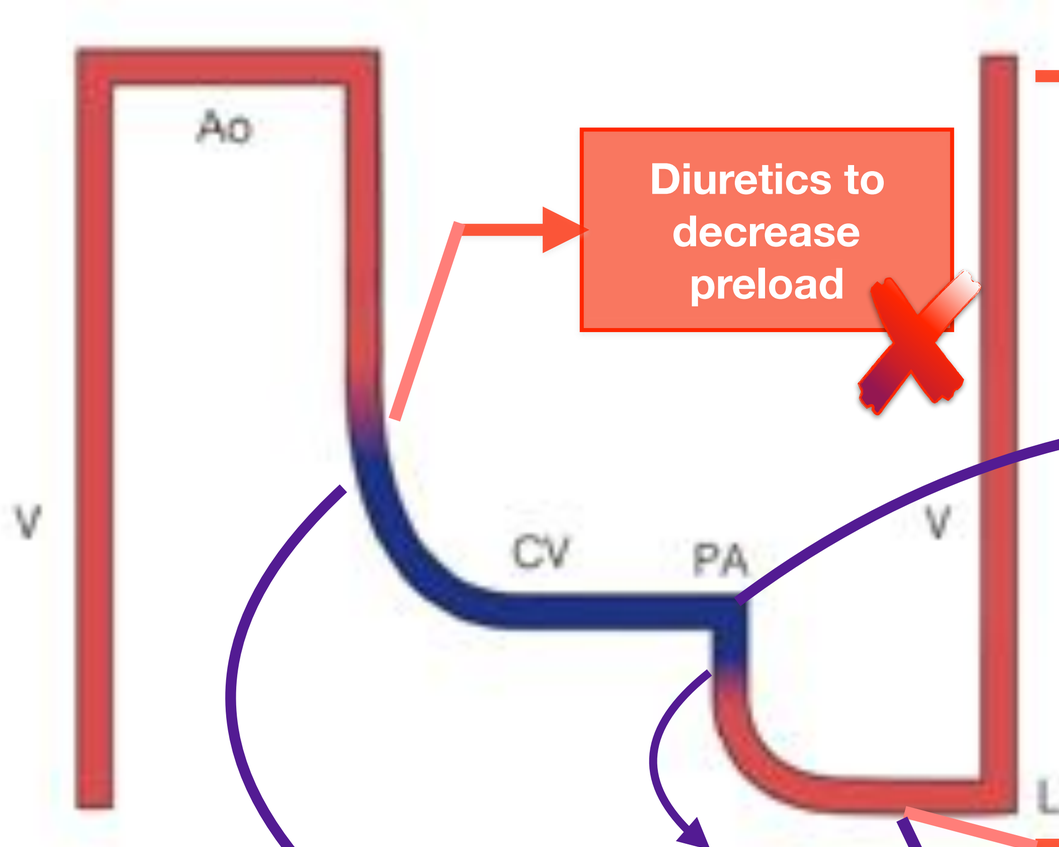
Adapted from Marc Gewillig-Heart 2016

The multifactorial origin of « heart failure » in the Fontan circulation



PAH/Heart failure drugs in Fontan circulation

Potentially a wrong reasoning and a predictable minimal effect



ACE Inhibitors to decrease after load

Diuretics to decrease preload

Pulmonary vasodilatation to increase preload

Beta-blockers to lengthen diastole and ventricular filling

Exercise to increase preload and decrease PVR

Lusitropic drugs sGC stimulators

Conclusion

- **Altered pulmonary blood flow is the trigger for pulmonary vascular remodelling in shunt lesions**

- **PAH-CHD is one of the most interesting model to examine the mechanisms or reversibility in PH**

- **The mechanisms leading to irreversibility are multiple (anti-apoptotic, inflammation, altered signalling, DNA damage) and are key to identify future therapeutic pathways in PH**

- **Lack of pulsatility is also a trigger for pulmonary vascular remodeling but with reduced involvement of SMC and higher role of intimal remodeling suggesting that alternative pathways should be explored to manipulate PVR in the Fontan circulation**

Isabelle Szezepanski

Marilyne Lévy

Collective ignorance is the motivation
Curiosity is the strength
Research is the path

Individual experience is the brake
Indifference is the weakness
Argument from authority is the threat

Thank you

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