Pulmonary hypertension in congenital heart diseases

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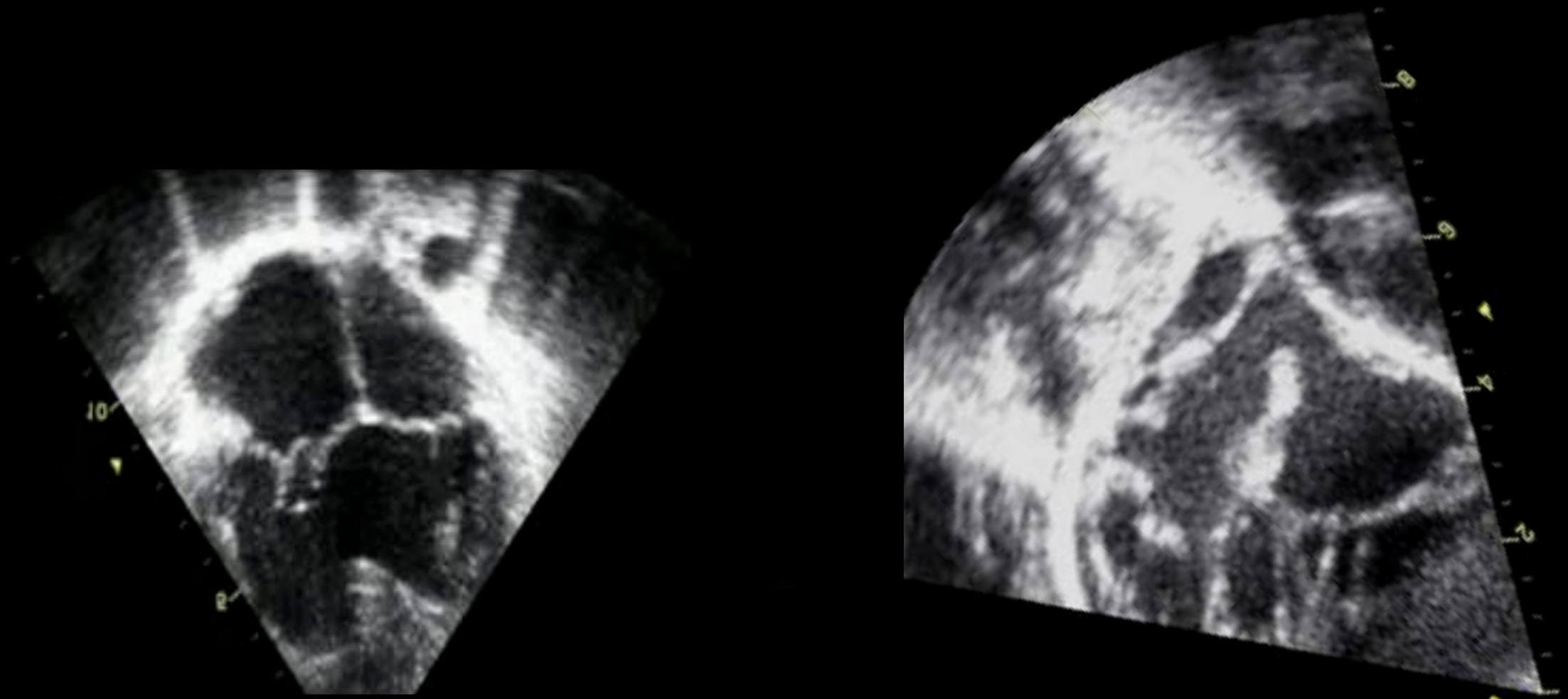
Pulmonary Hypertensions in CHD

$$R = P / Qp$$

$$P = Flow \times Resistance + PCW$$

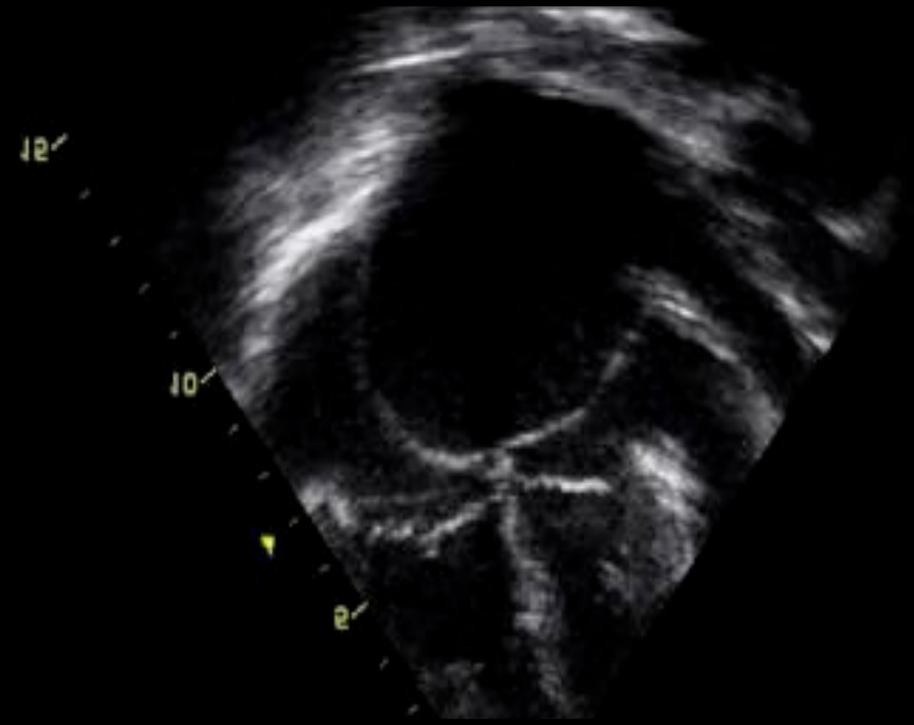
- Flow-associated pulmonary hypertension (hyperkinetic)
  - congenital systemic pulmonary shunt
- Increased pulmonary vascular resistance
  - pulmonary arteriopathy (“Eisenmenger”)
- Pulmonary venous congestion



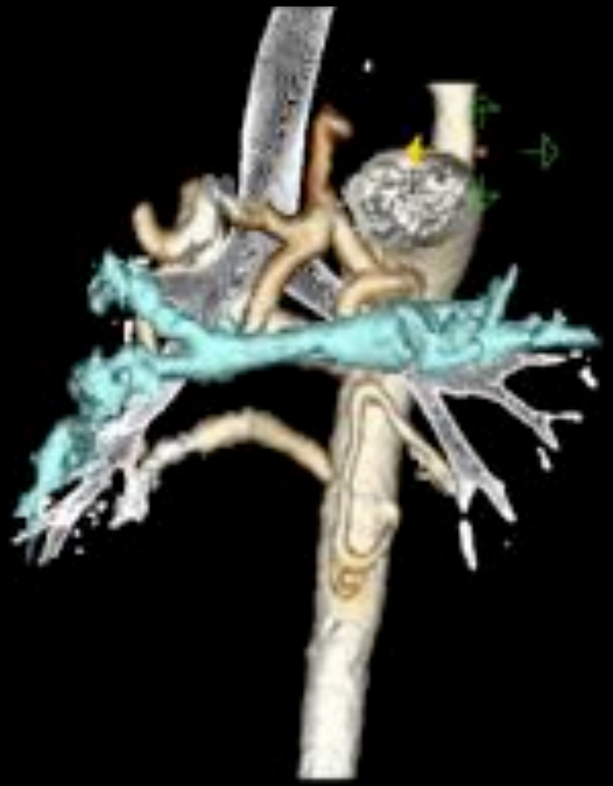
Flow-associated pulmonary hypertension (hyperkinetic)

Congenital systemic pulmonary shunt: *same physiology ?*

Cor triatriatum



Pulmonary atresia VSD

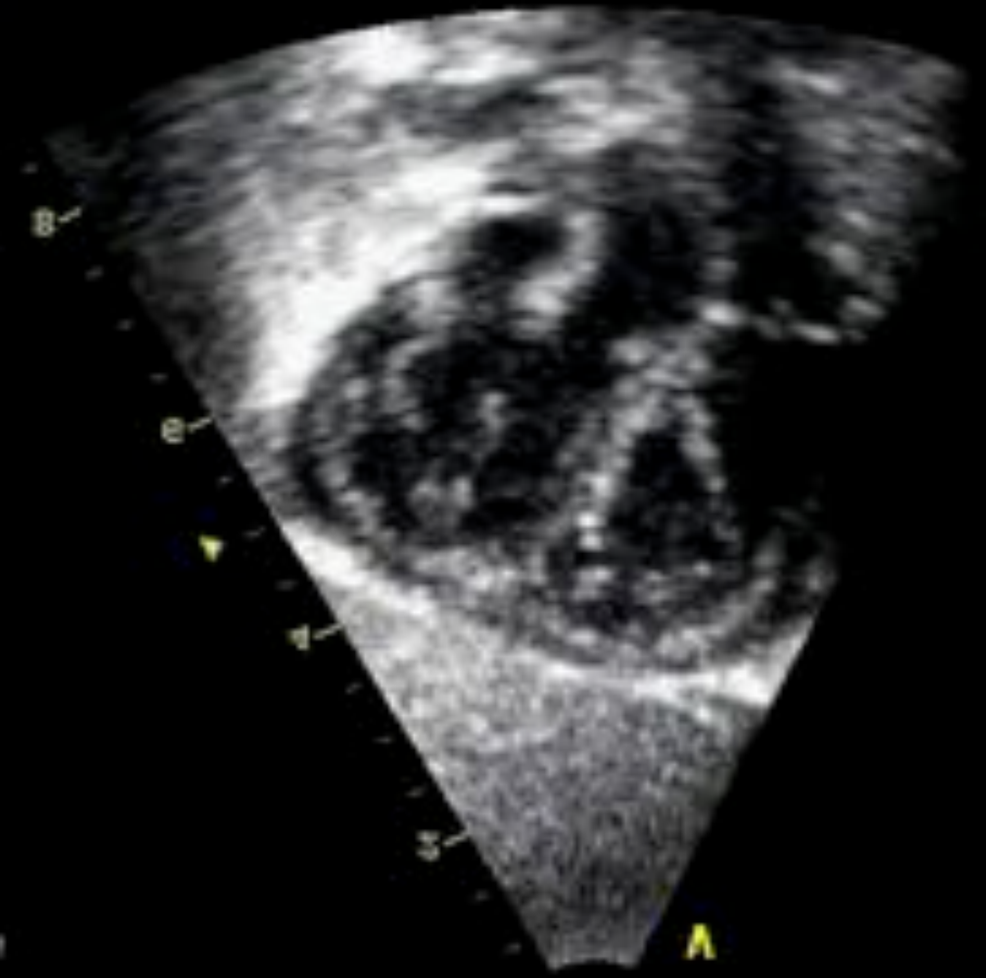


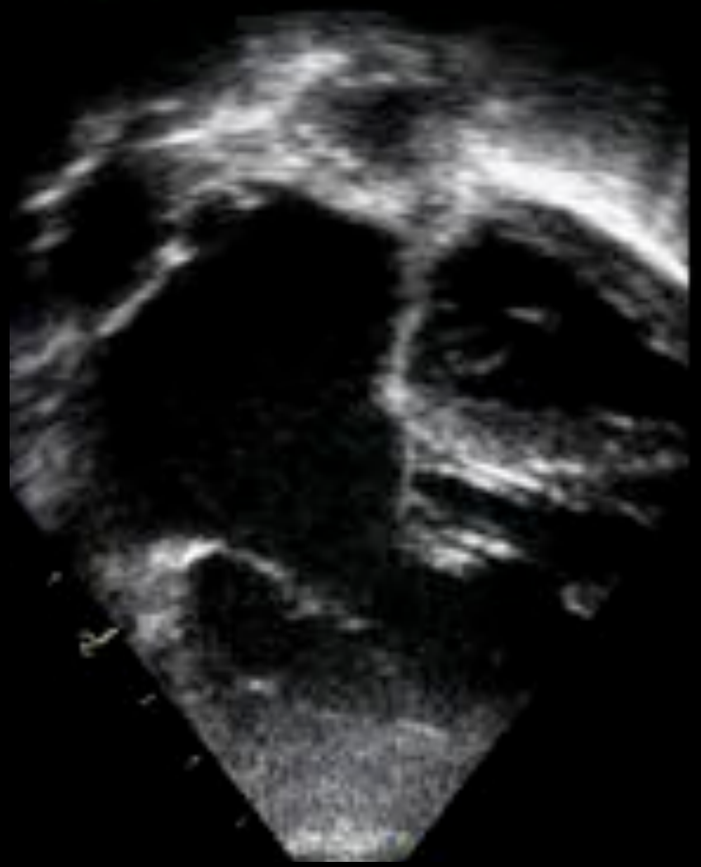
Pulmonary venous congestion

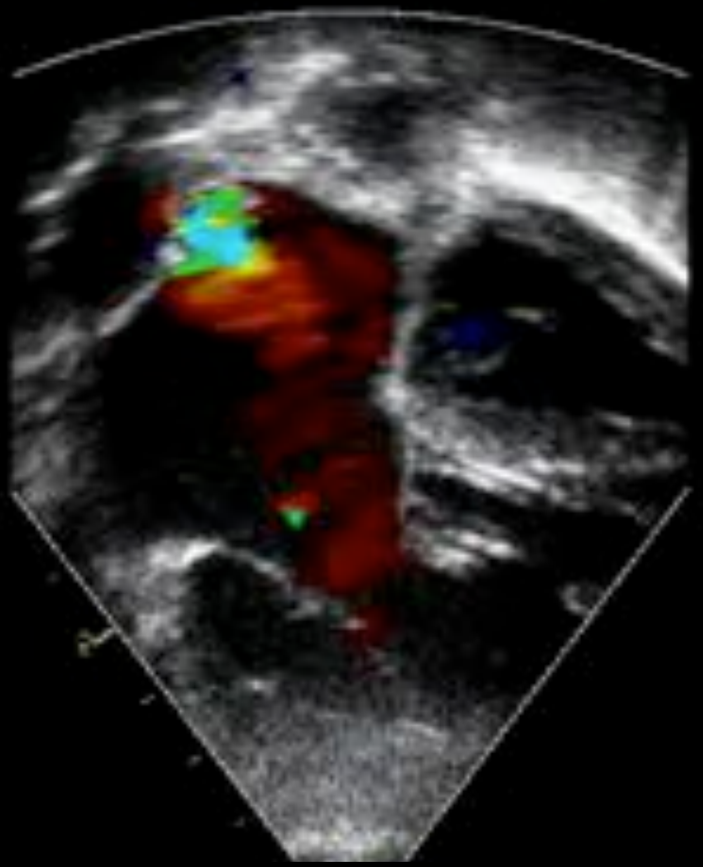
Segmental PH

Never shunt in TGA

TCPC







« Bizarre » physiopathologies with atypical/unknown vascular remodelling

Modified Classification of PH:Nice 2013

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**

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

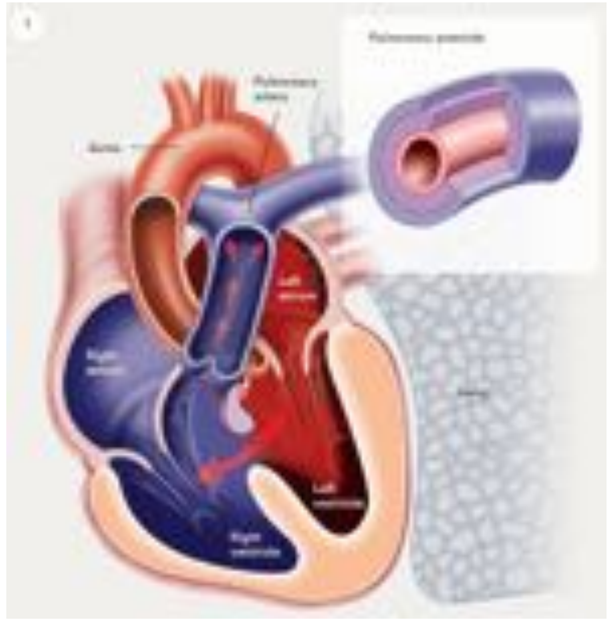
E. Never shunt/non classifiable

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

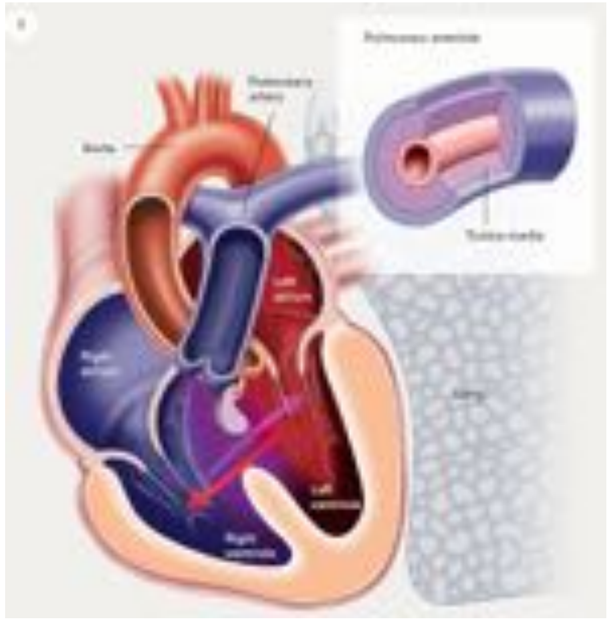
Ivy D et al. J Am Coll Cardiol 2013;62:D117–26

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

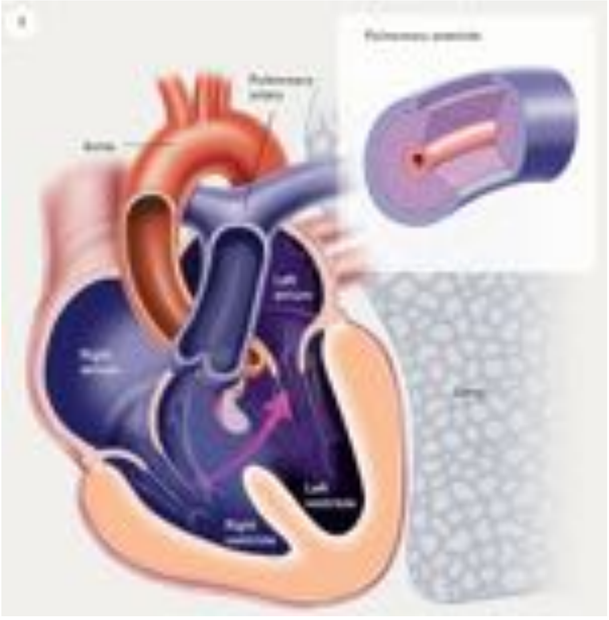
Systemic-to-pulmonary shunting can ultimately remodel the pulmonary vasculature to a characteristic irreversible phenotype similar to other forms of PAH.



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

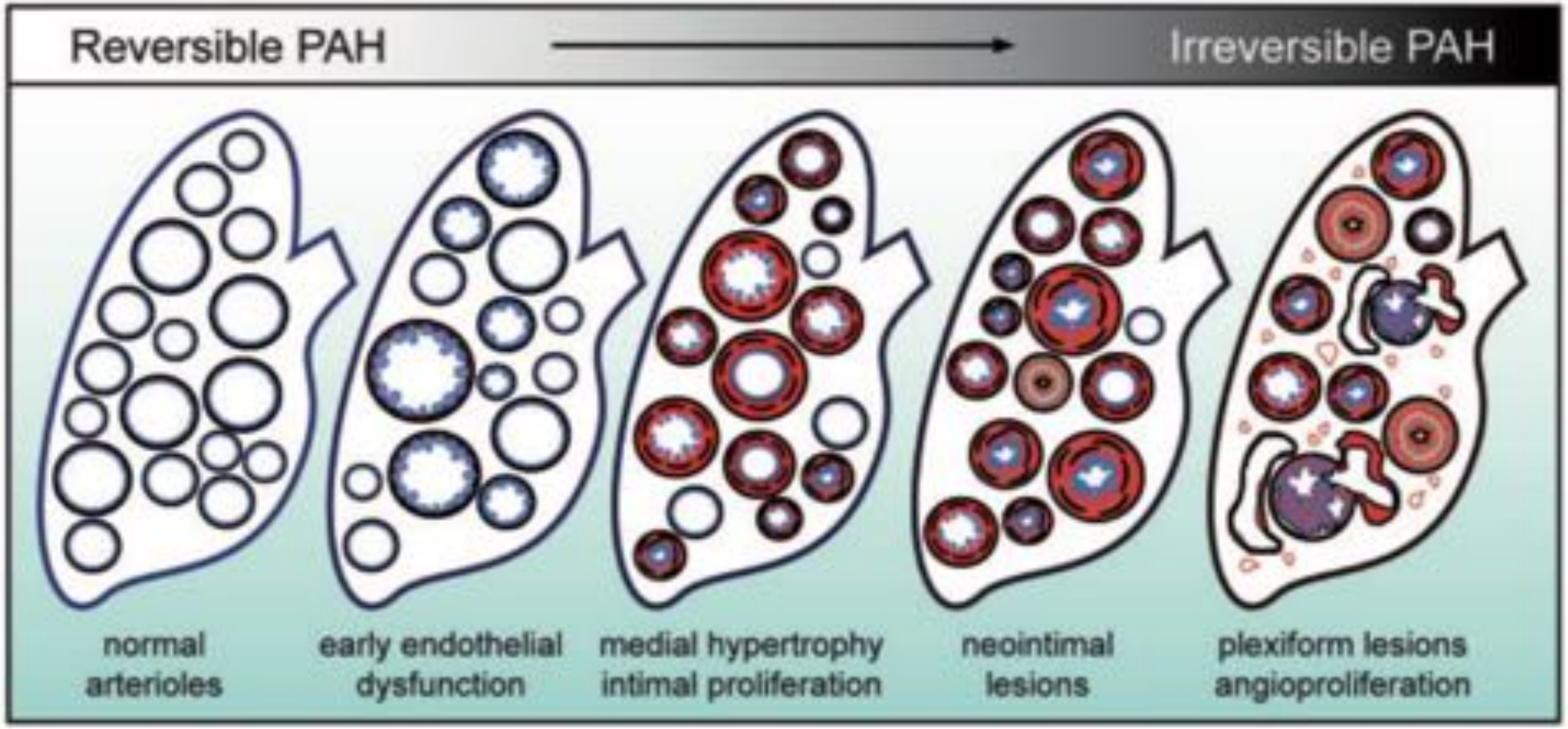


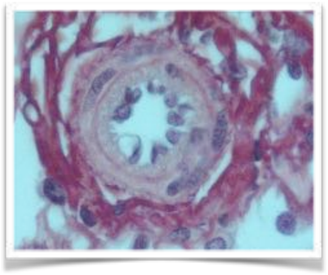
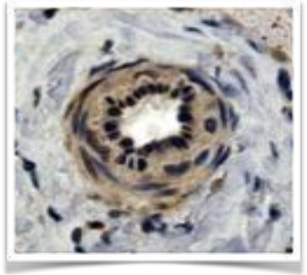
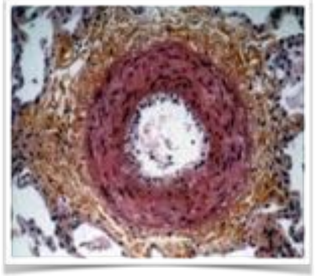
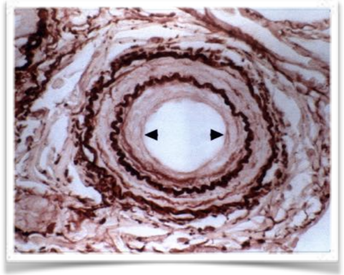
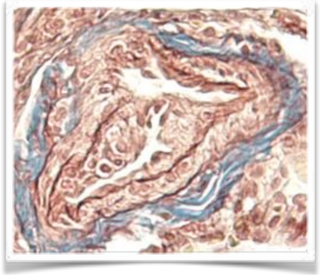
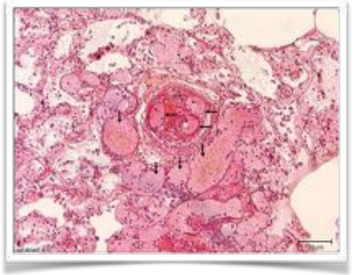
Over time, PVR ↑ resulting in bi-directional flow



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

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

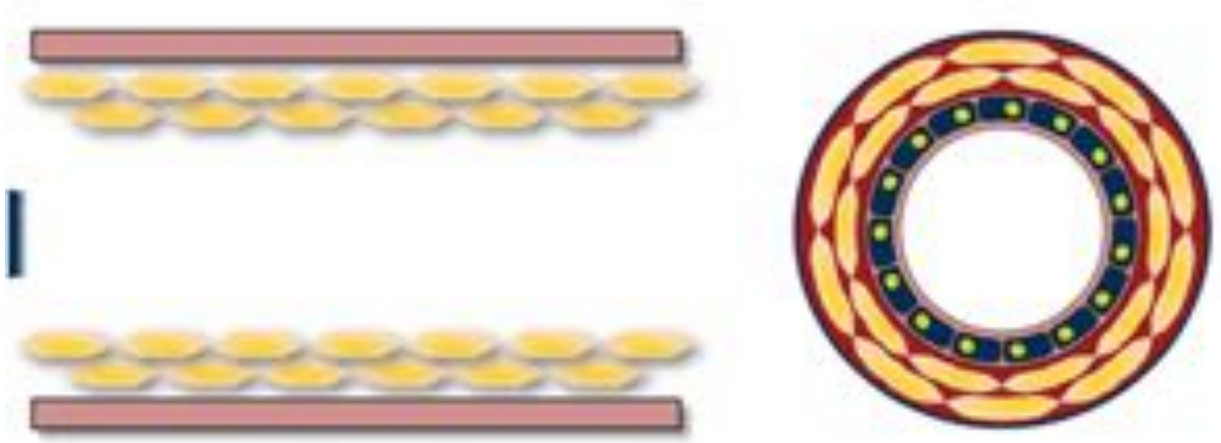


Shear stress and circumferential stretch

Shear stress

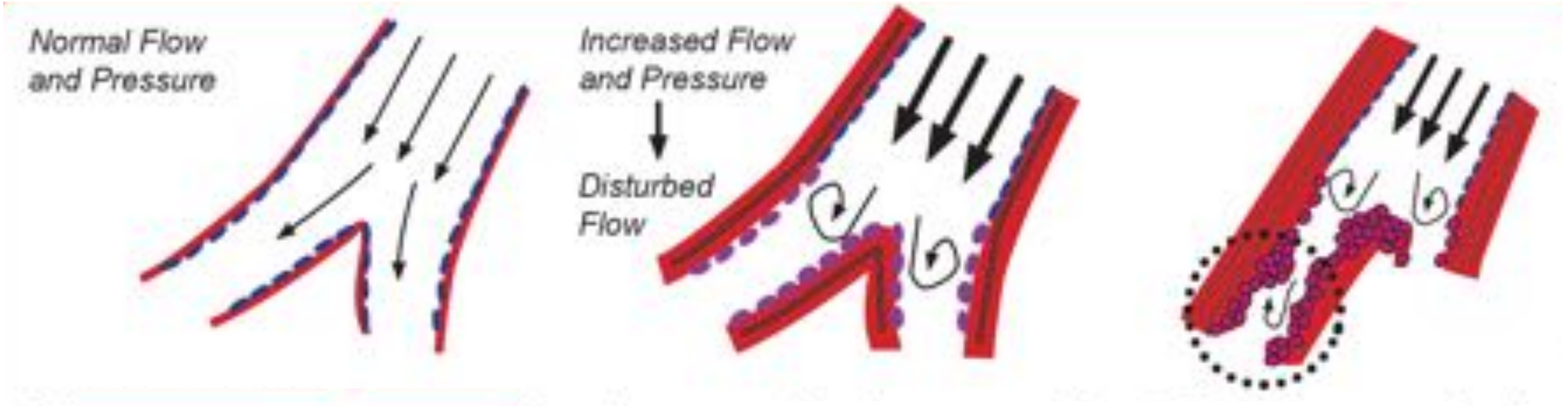
Circumferential stretch

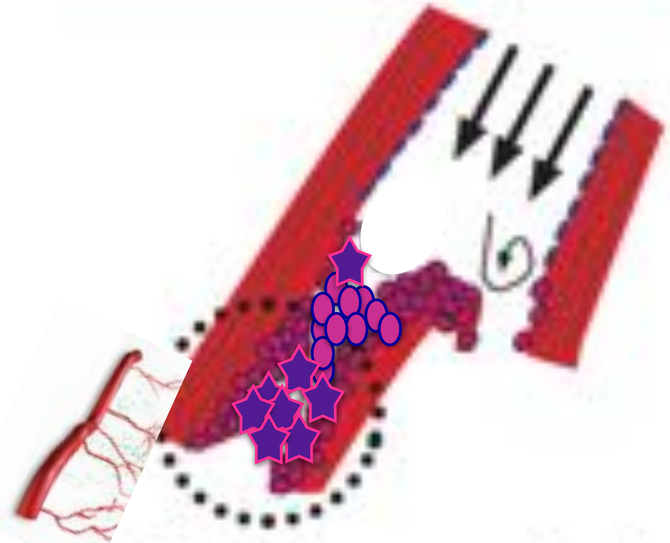


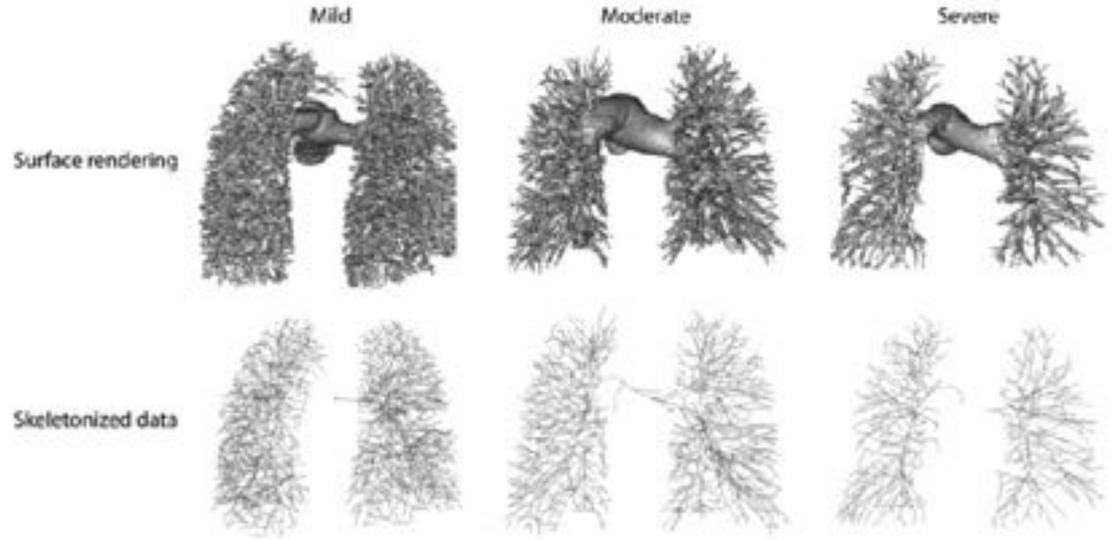
These hemodynamic forces are translated into biochemical signals

Hemodynamic forces → reaction in vessels → messengers → cellular response

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



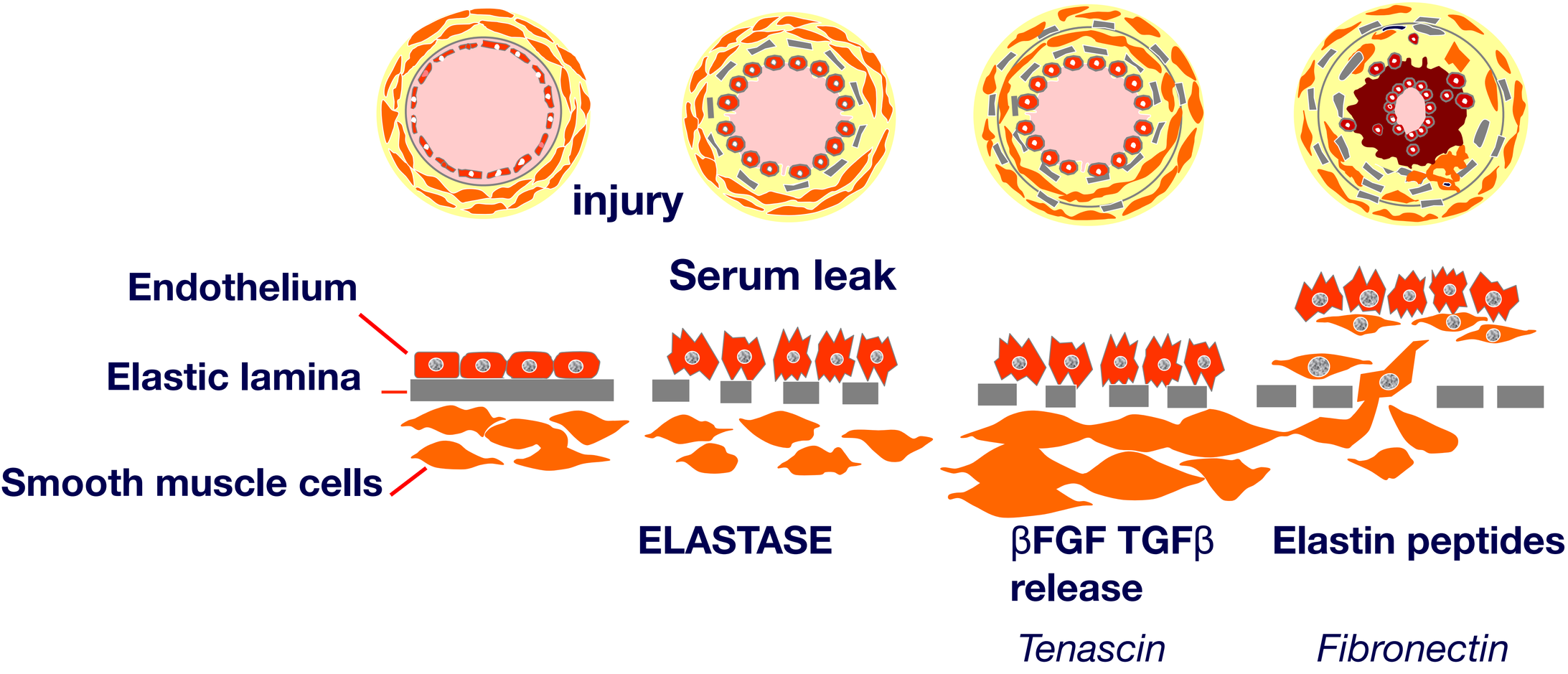




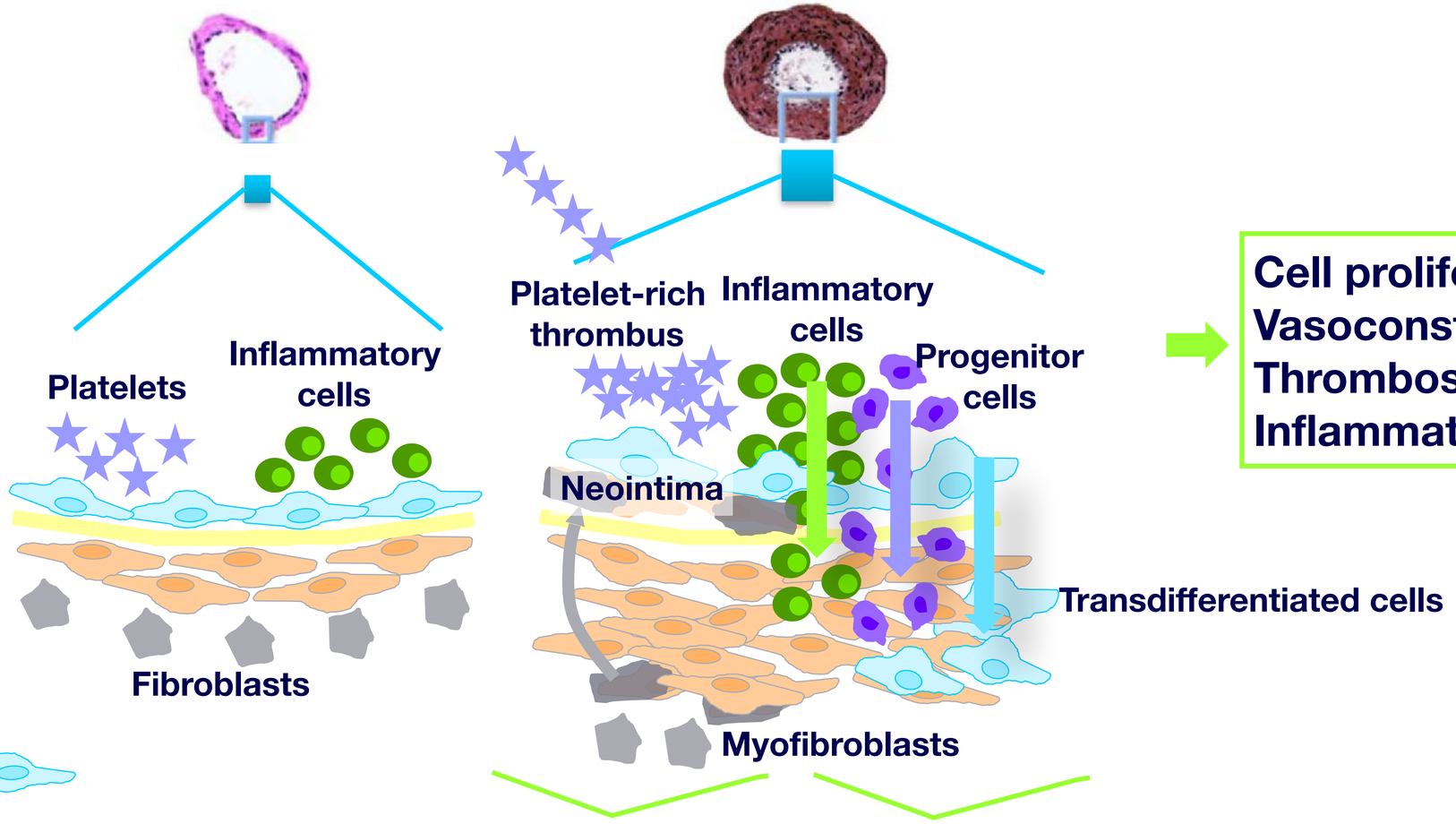
Fractal dimensions in PH

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

Progression of lesions

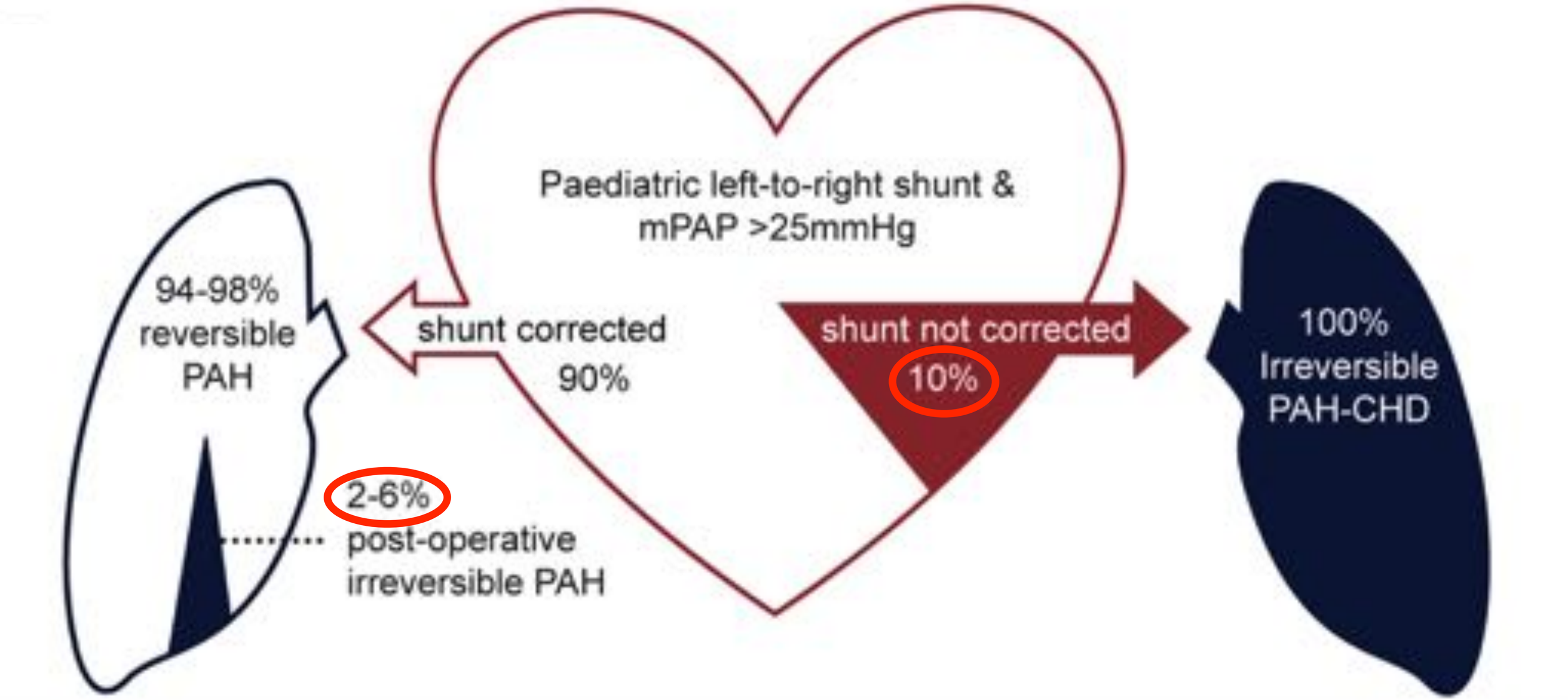


Reaction in vessels

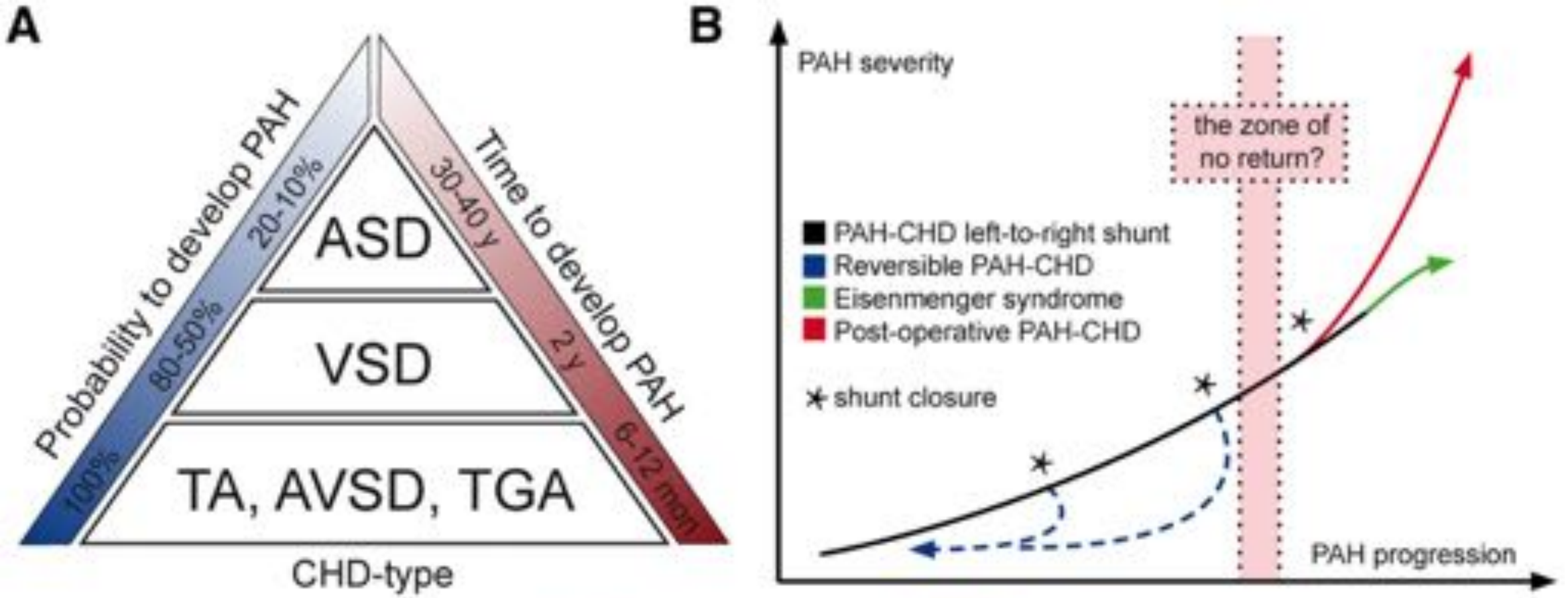


Cell proliferation
Vasoconstriction
Thrombosis
Inflammation

Chan SY and Loscalzo J. J Mol Cell Cardiol 2008; 44:14-30.

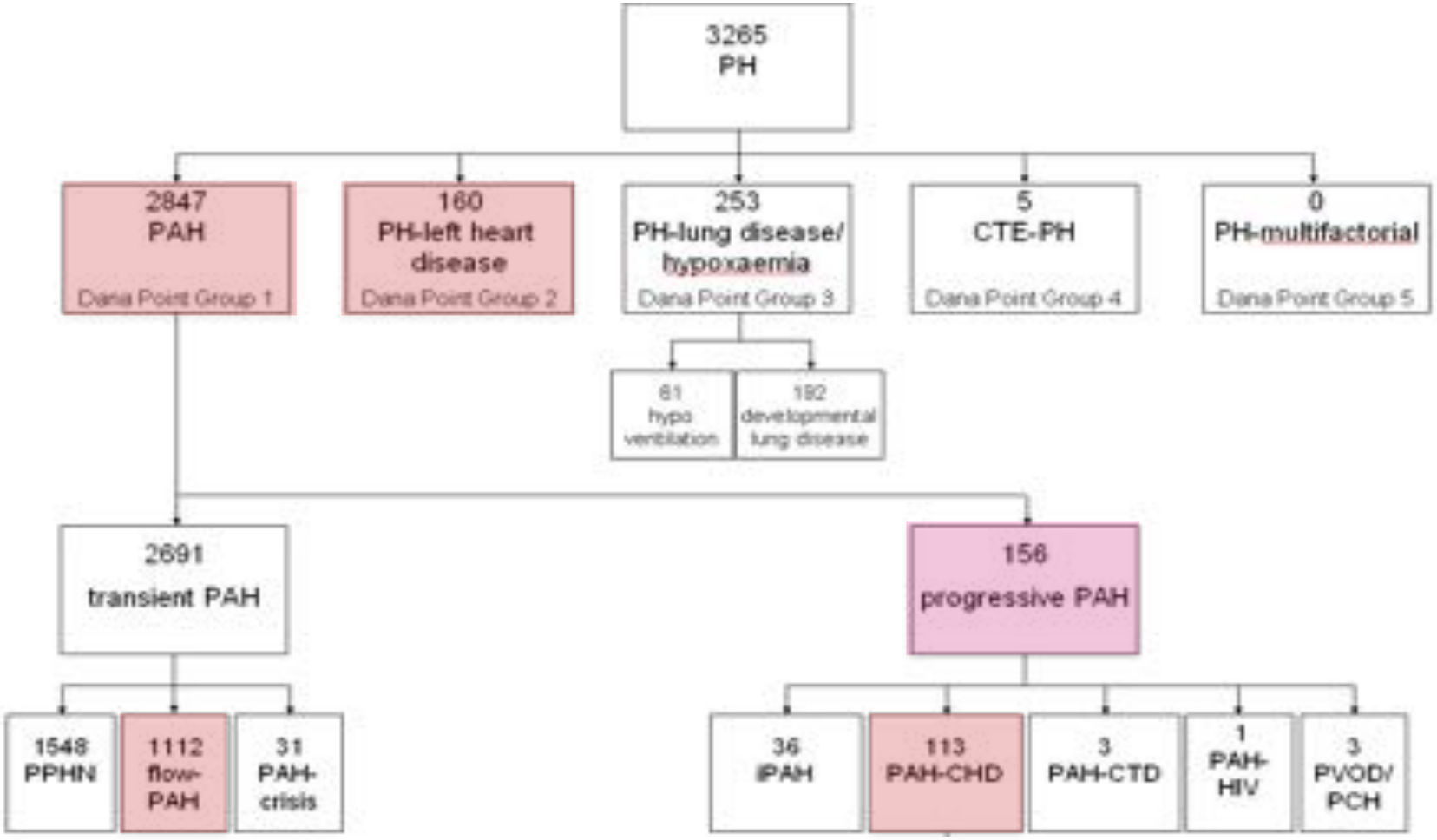


From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Eur Heart J. 2017;38(26):2034-2041.



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.

Paediatric pulmonary hypertension in the Netherlands



Van Loon, *et al*. *J Pediatr* 2009; Van Loon, *et al*. *Circ* 2010.

Epidemiology Pediatric PAH

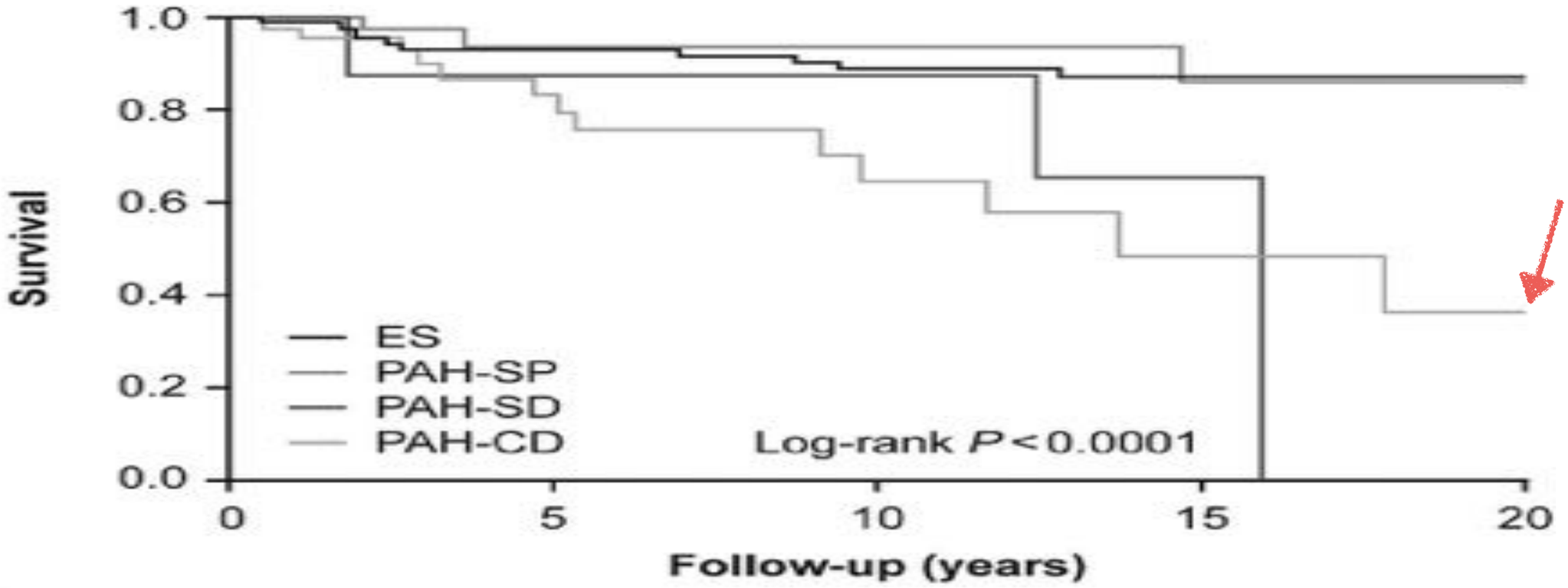
Recent data from large registries

	TOPP [1]	*Reveal-children* [2]
Patients, *n*	**362**	**216**
Age at Dx (yrs), median	**7.5**	**7**
Female, %	**59**	**64**
Group 1: PAH	**317 (88)**	**216 (100)**
IPAH/HPAH	**212 (53)**	**122 (56)**
CHD	**160 (40)**	**23 (36)**
CTD	**9 (3)**	**10 (5)**
Portopulmonary	**2 (1)**	**3 (1)**
Other	**14 (4)**	**4 (2)**
Group 3: Lung disease	**42 (12)**	**NE**
Other	**3 (1)**	**NE**

Values given are *n* (%) unless otherwise indicated

1. **Berger et al. *Lancet* 2012.**
2. **Barst et al. *Circulation* 2012.**

Kaplan–Meier survival curve of 192 patients with pulmonary arterial hypertension associated with congenital heart disease categorized according to the four clinical subgroups



Patients at risk

ES	90	71	59	52	48
PAH-SP	48	22	18	11	10
PAH-SD	10	4	4	2	0
PAH-CD	44	22	12	4	3

Manes A et al. Eur Heart J 2014;35:716-724

2013 Nice
Proposed Clinical Classification of
PAH Associated with CHD in the Adult

1. **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.

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

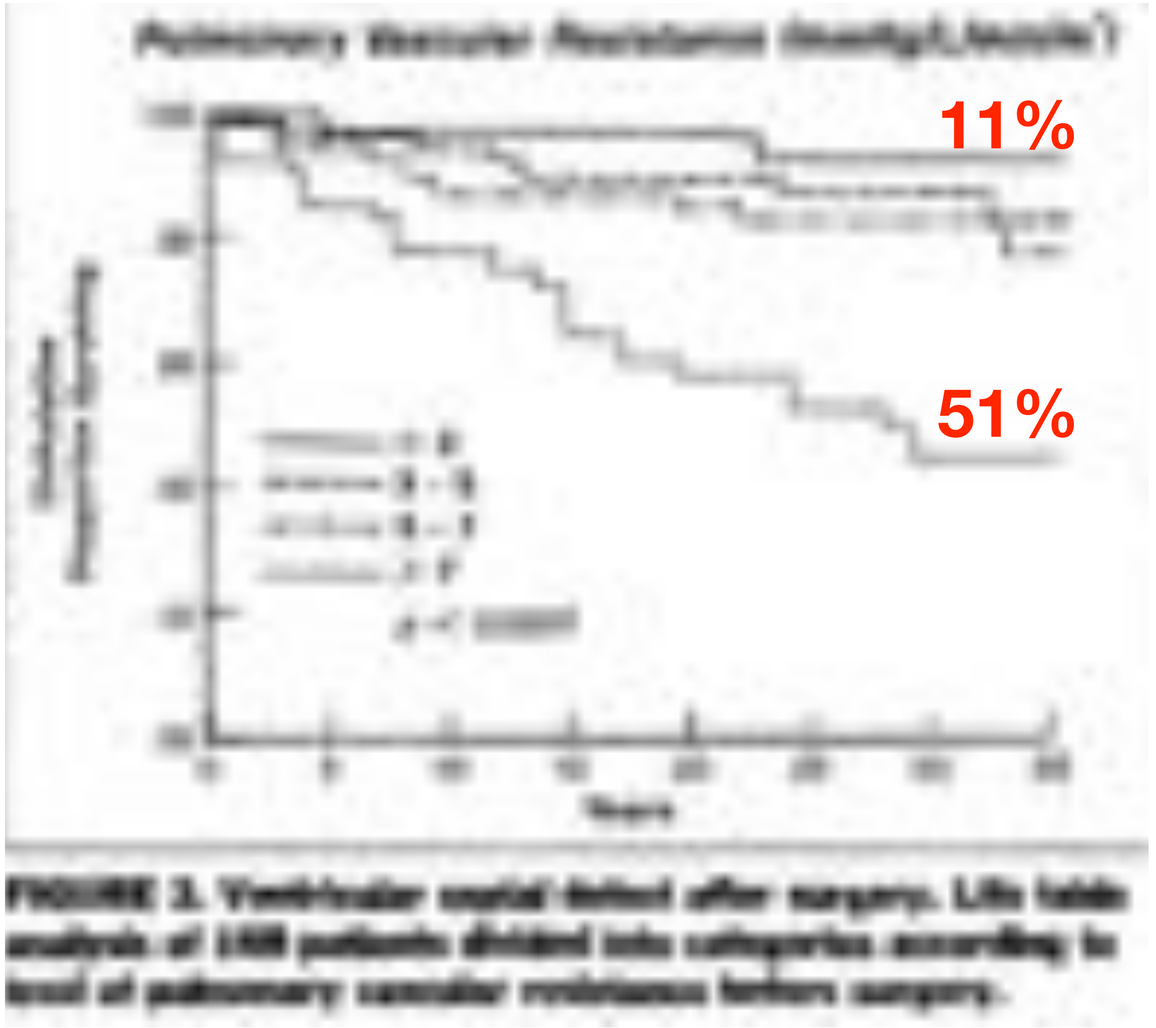
3. PAH with co-incidental CHD

4. Post-operative PAH

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

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.

Guidelines for operability of left-to-right shunts

Type	Correctable?	AHA/ACC-CHD Guidelines, 2008 [12]	ESC GUCH Guidelines, 2010 [11]	ESC/ERS PH Guidelines, 2015 [13]*
ASD	Yes	• All with RA and RV enlargement with or without symptoms	• RV volume overload and PVR < 5 WU regardless of symptoms	• PVRi < 4 WU·m^2 or PVR < 2.3 WU
	No	• Severe irreversible PAH and no L-R shunt	• ES	• PVRi > 8 WU·m^2 or PVR > 4.6 WU
	Individual patient evaluation	• Paradoxical embolism or orthodeoxia-platypnea • Net L-R shunt, PVR < 1/3 of SVR, PAP < 1/3 of systemic levels or when responsive to pulmonary vasodilators or test occlusion of defect	• Paradoxical embolism • PVR ≥5 WU but <1/3 of SVR or PAP < 2/3 of systemic levels and net L-R shunt (Qp:Qs > 1.5)	• PVRi 4–8 WU·m^2 or PVR 2.3–4.6 WU
VSD	Yes	• Qp:Qs ≥ 2 and LV volume overload • History of IE	• Symptoms of L-R shunting and no severe PVD • History of IE • Asymptomatic with LV volume overload due to VSD	• PVRi < 4 WU·m^2 or PVR < 2.3 WU
	No	• Severe irreversible PAH	• ES or exercise induced desaturation • VSD is small, not subarterial and no LV volume overload/PH	• PVRi > 8 WU·m^2 or PVR > 4.6 WU
	Individual patient evaluation	• Net L-R shunt (Qp:Qs > 1.5) and PAP < 1/3 of SVR and PVR < 1/3 of systemic levels • Net L-R shunt (Qp:Qs > 1.5) and LV systolic/diastolic failure	• Net L-R shunt (Qp:Qs > 1.5) and PAP or PVR < 2/3 of systemic levels	• PVRi 4–8 WU·m^2 or PVR 2.3–4.6 WU

* In the ESC/ERS guidelines for the diagnosis and treatment of PH, there is no distinction between ASD and VSD closure. *AHA/ACC* = American Heart Association/American College of Cardiology; *ESC* = European Society of Cardiology; *ERS* = European Respiratory Society; *GUCH* = grown-ups with congenital heart disease; *IE* = infective endocarditis; *L-R* = left-to-right (systemic-to-pulmonary); *PAP* = pulmonary arterial pressure; *PVD* = pulmonary vascular disease; *PVRi* = pulmonary vascular resistance index; *Qp:Qs* = the ratio of pulmonary blood flow to systemic blood flow; *SVR* = systemic vascular resistance; *WU* = Woods Units.

AHA/ATS Guidelines

1. Repair should be considered if PVRI < 6 WU or PVR/SVR <0.3 at baseline
2. PVRI > 6 WU or PVR/SVR >0.3 with R to L shunting can be considered for repair if AVT results in PVRI < 6 WU or PVR/SVR <0.3
3. If AVT is minimal, it is reasonable to implement PH therapy followed by repeat cath 4-6 months later and consider repair if PVRI < 6 WU

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

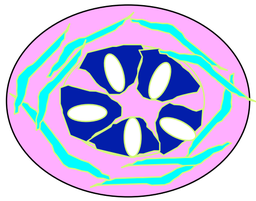
	Findings	
Source, features/parameters	Favorable	Unfavorable
Clinical history		
Age, years	<1	>2
Congestive heart failure/pulmonary congestion	Present	Absent
Tendency to respiratory disorders (inflammatory/infectious)	Yes	No
Failure to thrive	Yes	No
Use of anticongestive medication	Yes	No
Associated syndromes	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

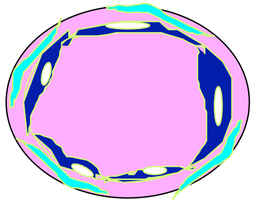
Normalisation of Flow (Haemodynamic Unloading) reverses PAH-CHD,

but not after a certain point of no return.

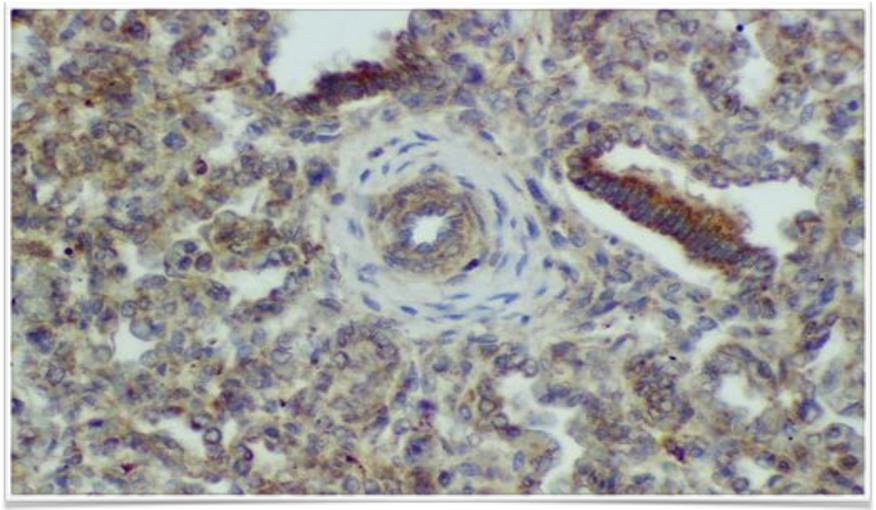
Which lesions are reversible in PAH-CHD ?



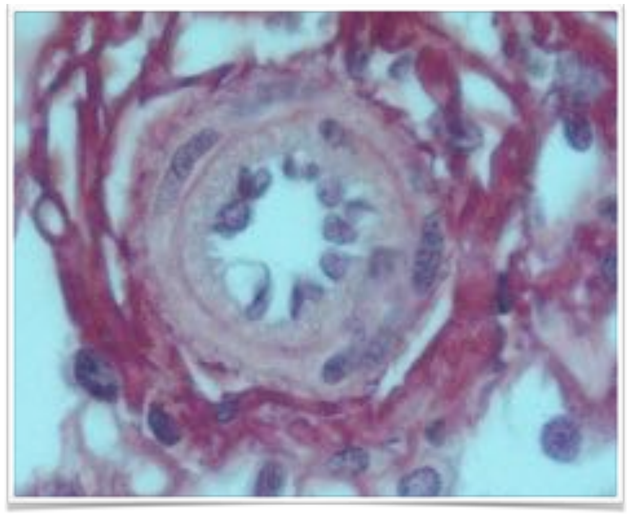
Foetus



Birth



Foetal arteriole

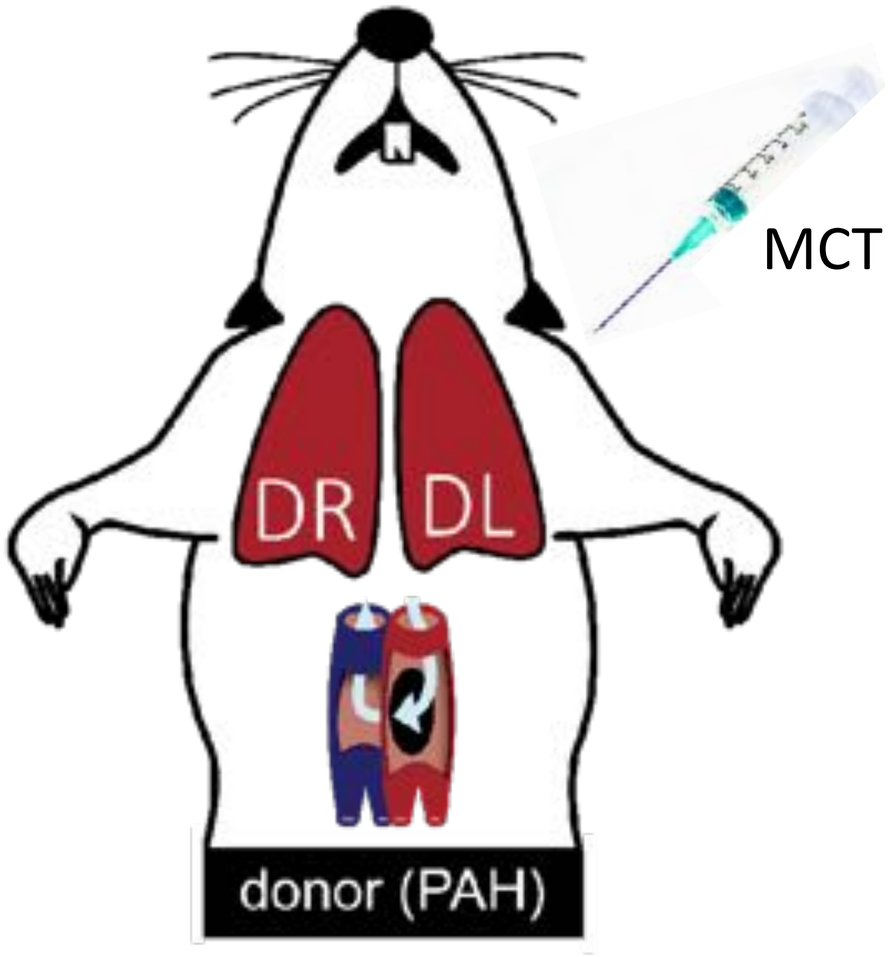


Mature arteriole

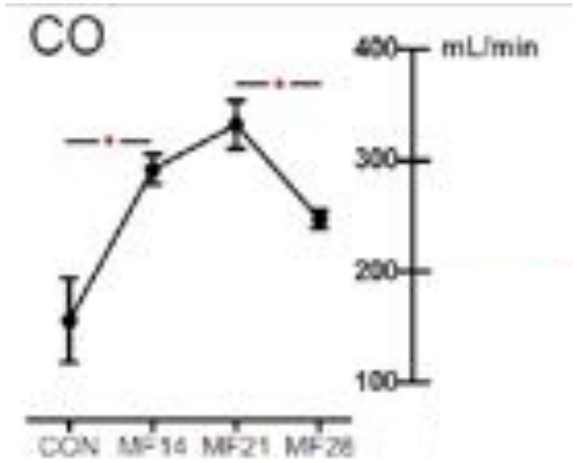
8 weeks

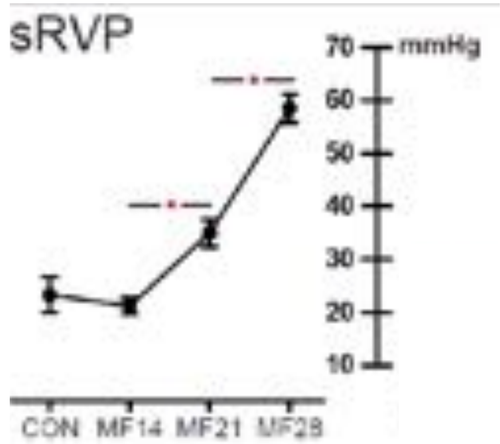
Wagenvoort, and Heath & Edwards

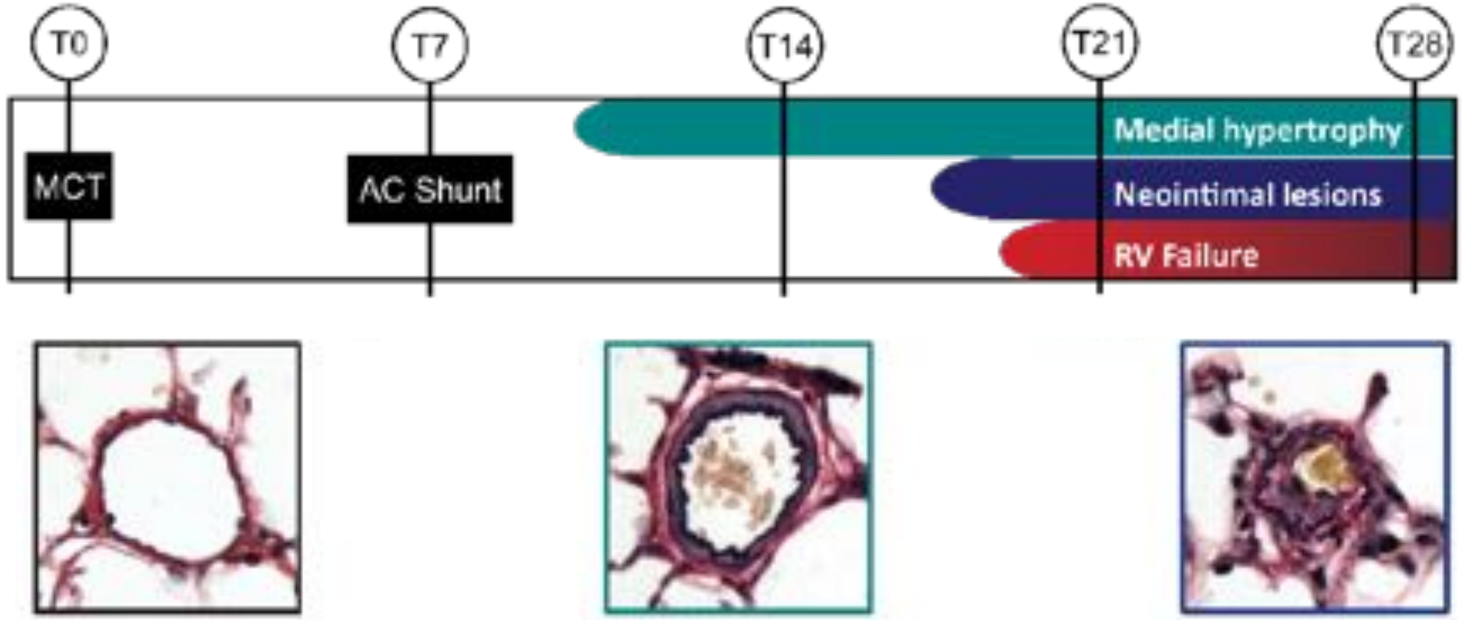
Progressive PAH



MCT



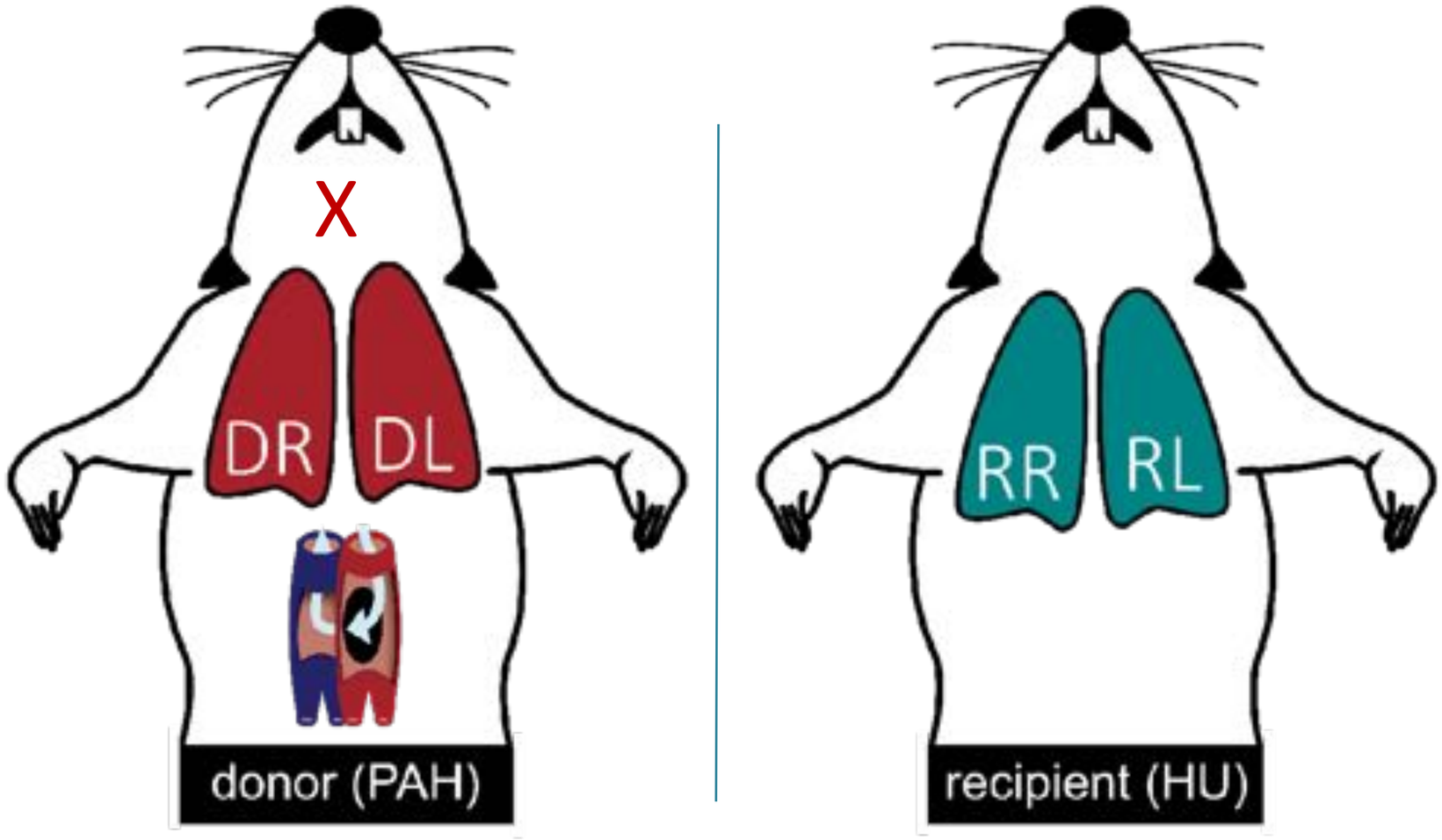




Diederik van der Feen

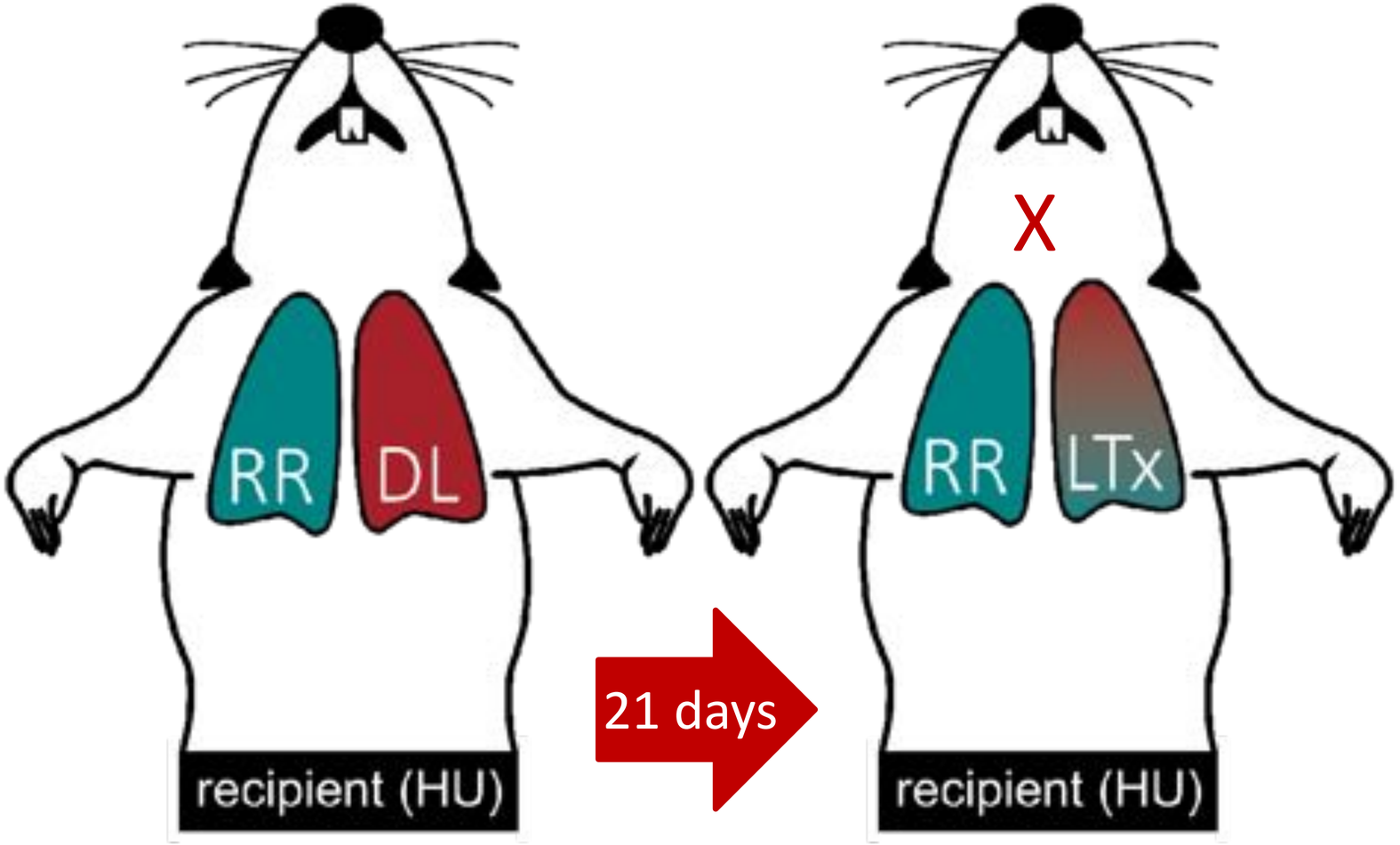
Haemodynamic Unloading by Lung Transplantation

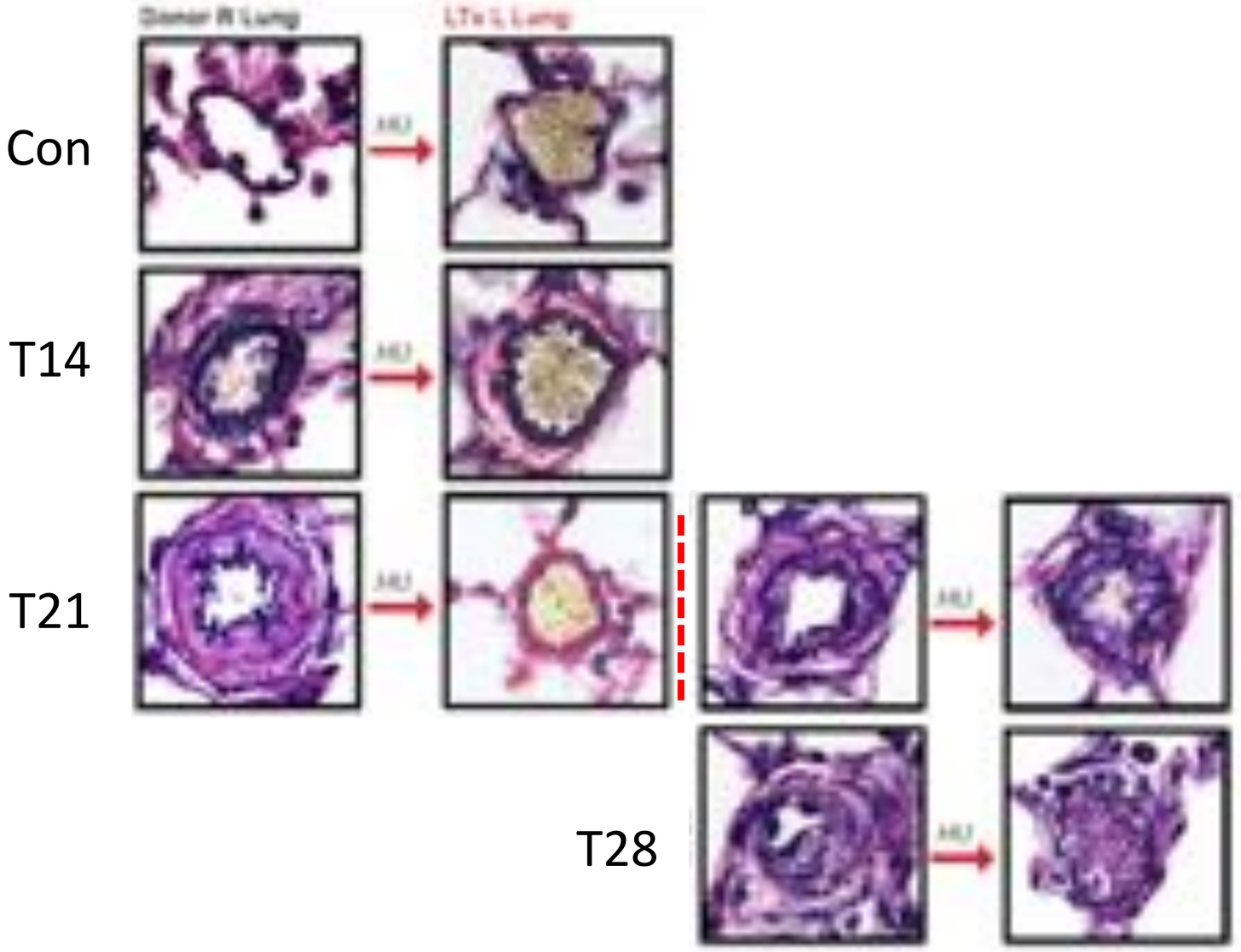
Sham
14 days
21 days
28 days

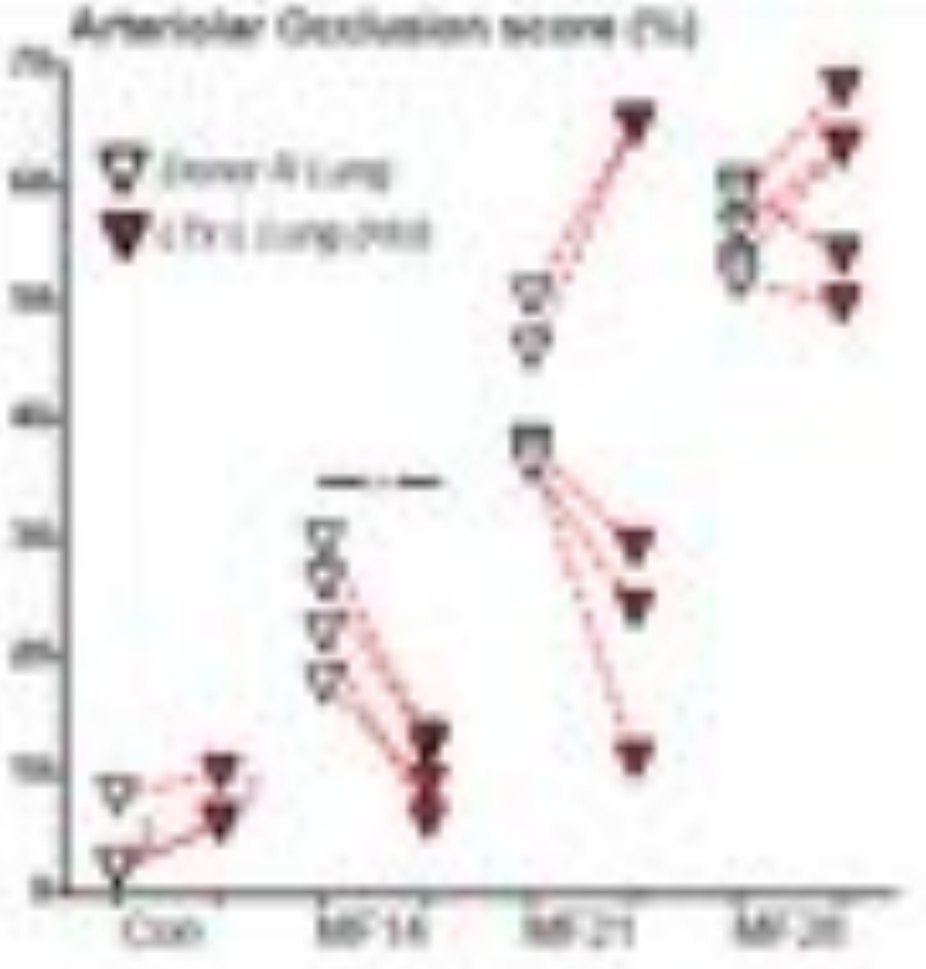


Diederik van der Feen

21 days of Haemodynamic Unloading





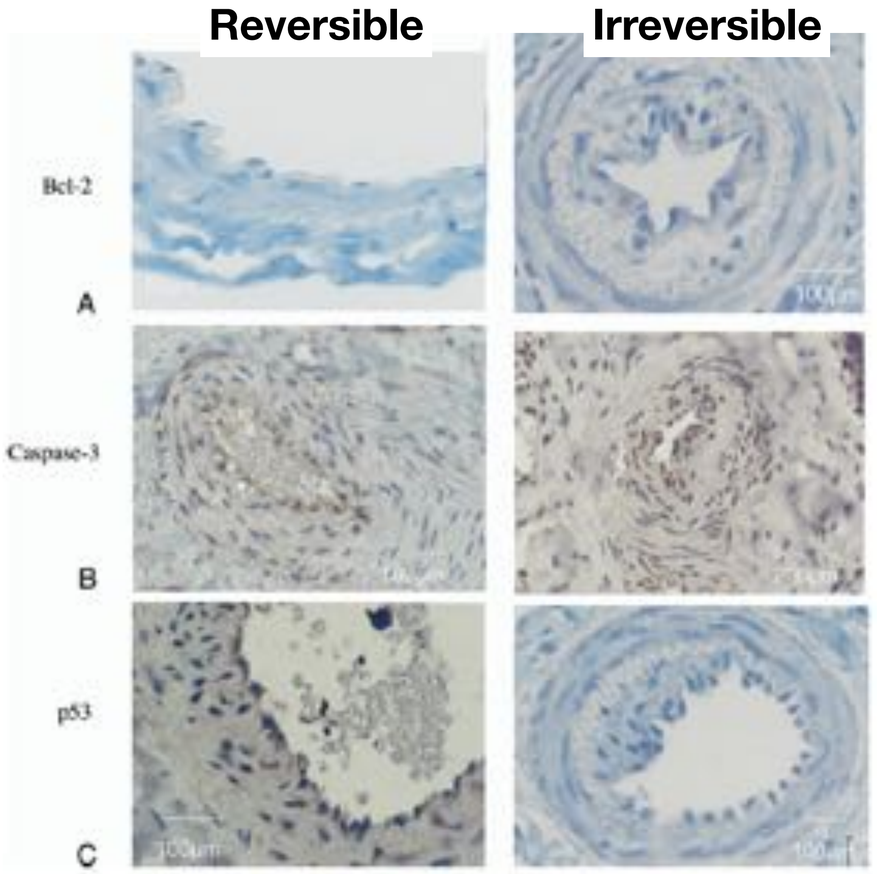


Diederik van der Feen

What could make PAH irreversible ?

1-Apoptosis and apoptosis resistance

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

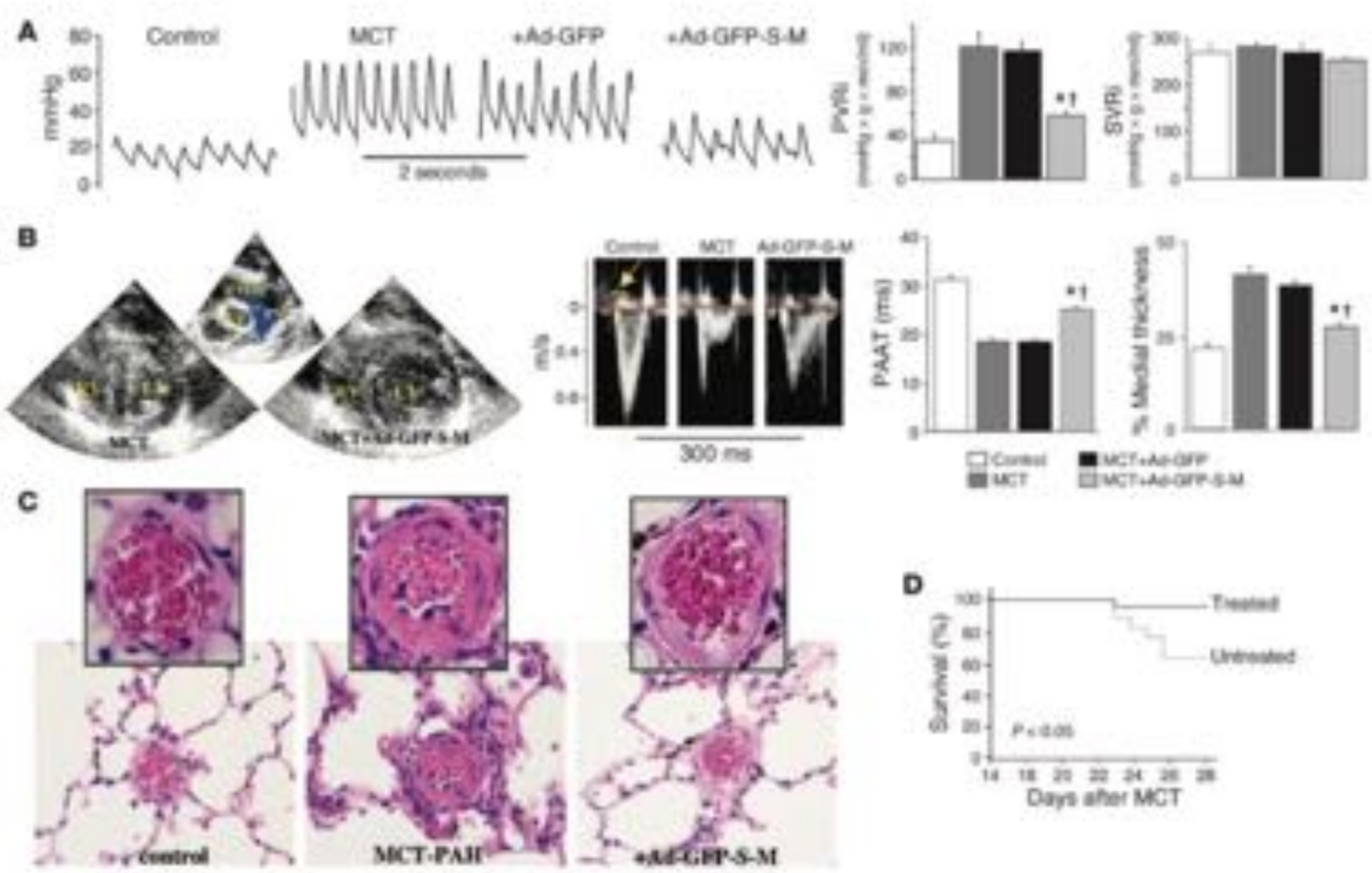


The antiapoptotic protein Bcl-2 is not expressed in reversible pulmonary hypertension (PHT), but by endothelial cells of severely damaged pulmonary arteries in irreversible PHT in all cases (A).
Endothelial cells of both groups expressed markers of apoptosis caspase-3 (B) and p53 (C).
The arrow indicates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

Lévy M et al. JACC 2007;49:803-10

What could make PAH irreversible ?

1-Apoptosis and apoptosis resistance



Survivin, a marker for apoptosis-resistance, is expressed abundantly in patients with end-stage PAH and nearly absent in CHD without PAH

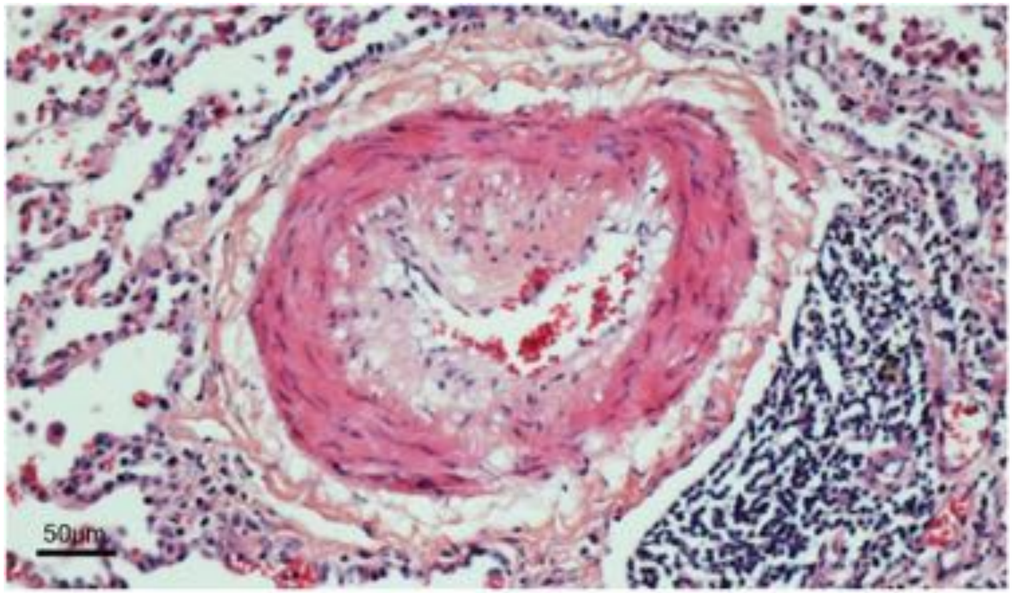
Gene therapy of rat MCT-PAH with Ad-GFP-Survivin-M improves hemodynamics, reduces remodeling of the resistance PAs, and prolongs survival

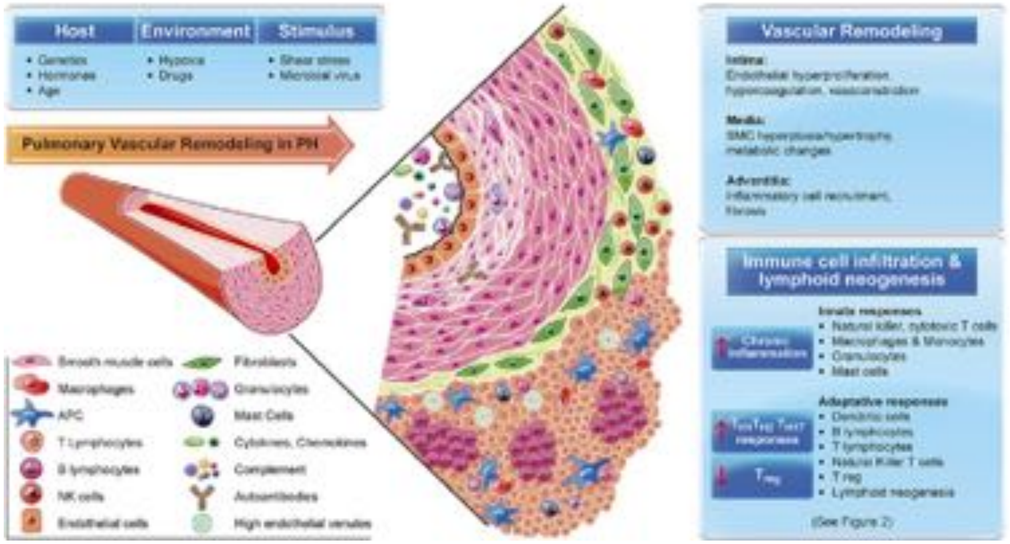
M3C

Mc Murtry MS et al. J Clin Invest 2005; 115:1479-91

What could make PAH irreversible ?

2-Inflammation





1. Inflammatory cytokines and macrophages are associated with disease progression in iPAH and PAH-CHD

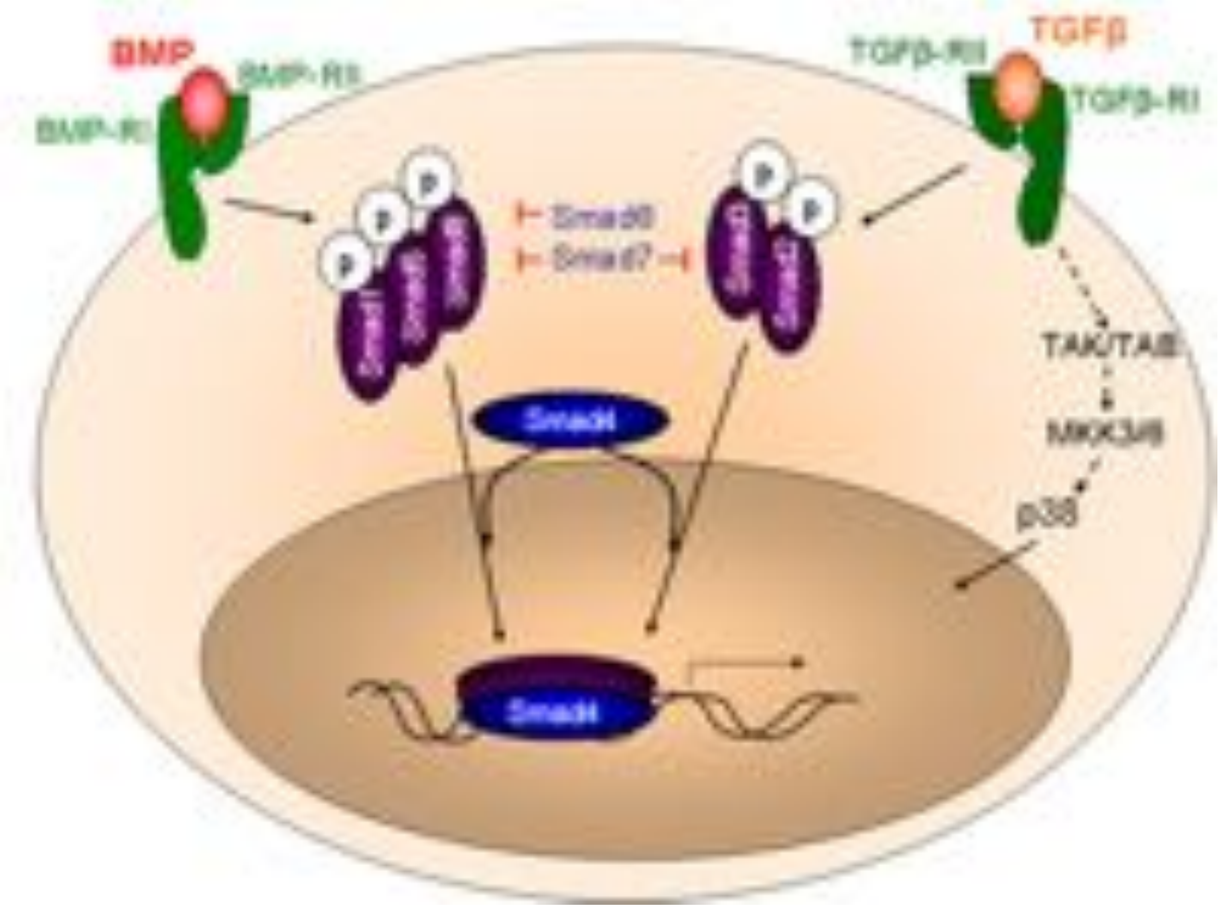
2. Plexiform lesions can be observed in HIV-PAH, schistosomiasis PAH, scleroderma and lupus, some of these conditions being associated with reversible PAH

3. Animal models of the above conditions have proven reversibility of neointimal lesions with specific therapy

4. Anti-inflammatory drugs can be a valuable adjunct in the therapy of PAH-CHD

What could make PAH irreversible ?

2-Tgf-b/BMPR signalling imbalance



Proliferation, anti-apoptotic, inflammation

1. **BMP-9**, an endogenous stimulator of BMP-signalling, has shown to reverse medial hypertrophy in BMPR2-deficient mice and MCT rats, but also neointimal lesions in SuHx rats.

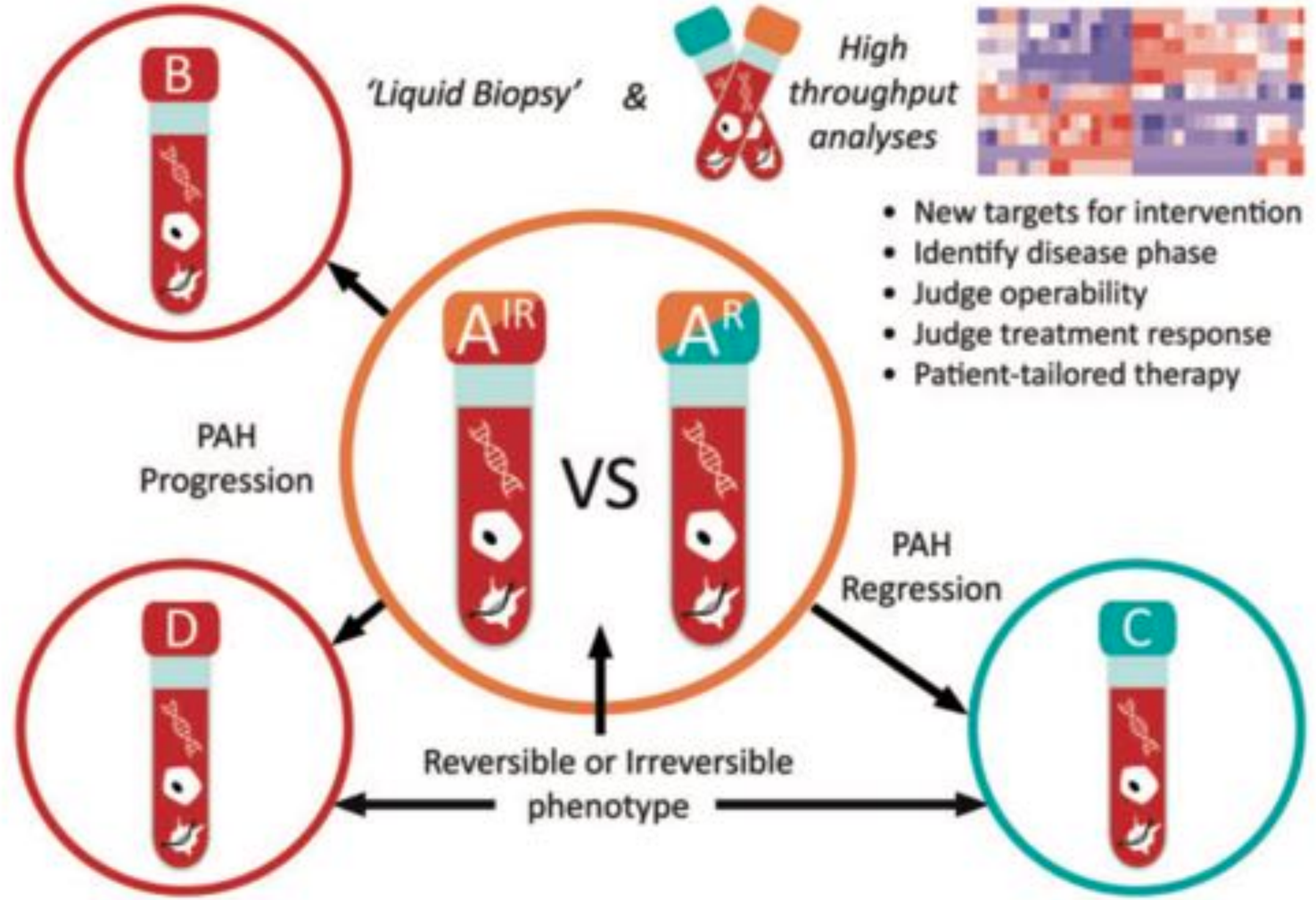
2. **FK506** (Tacrolimus) showed to (1) restore disturbed BMPR2-signalling and endothelial function in PAECs from IPAH patients, (2) prevent PAH progression in BMPR2-deficient mice, and (3) reverse established neointimal lesions in SuHx rats. Low-dose Tacrolimus was associated with relieved symptoms of right heart failure and improved WHO-FC3 IPAH patients.

3. **Elafin**, an endogenous serine protease inhibitor that enhances BMPR2 signalling, has been shown to reverse neointimal lesions in SuHx rats and reduce neointimal thickness of pulmonary arteries in cultured sections from lung explants of patients with PAH.

Spiekerkoetter EE. J Clin Invest 2013; 123:3600-13.
Long Lu L. Nat Med 2015;21:777-85.
Spiekerkoetter EE et al. Am J Respir Crit Care Med 2015;192:254-7.
Nickel NP et al. Am J Respir Crit Care Med 2015;191:1273-86.

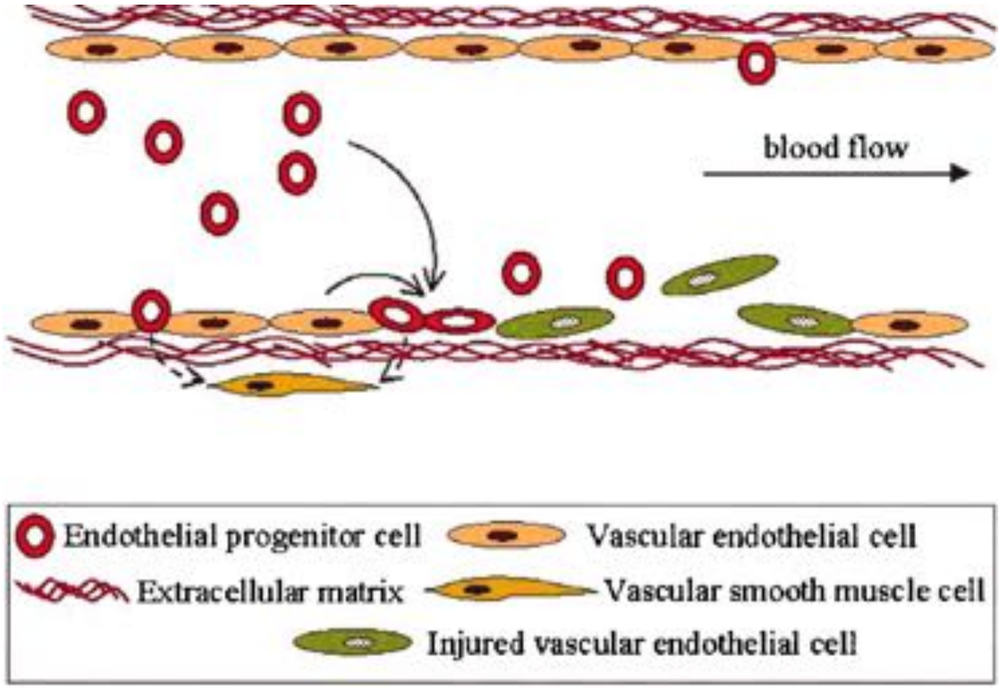
Comparison of human reversible to irreversible PAH-CHD

The liquid biopsy concept

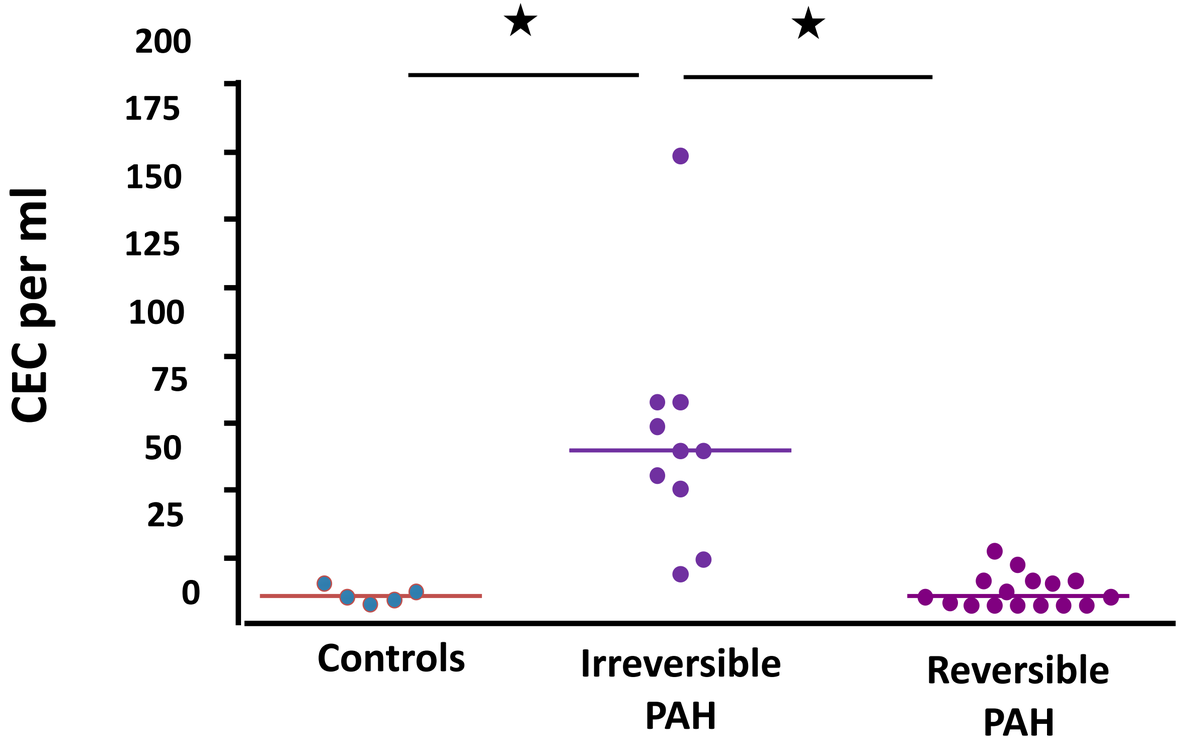


From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Eur Heart J. 2017;38(26):2034-2041.

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



CEC counts in peripheral venous blood of CHD patients with PH

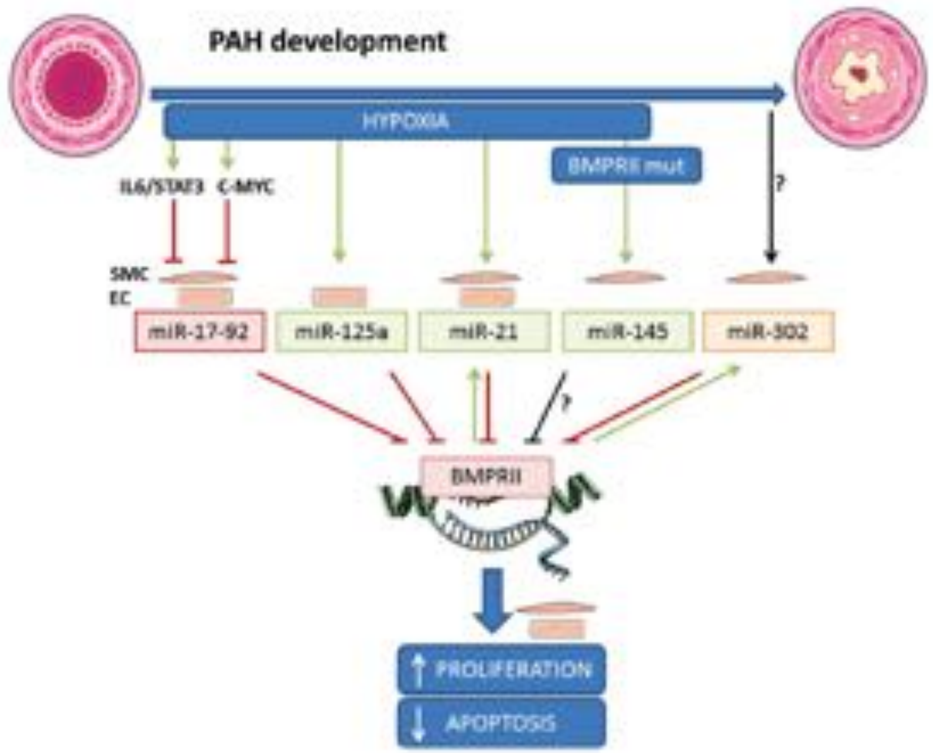


Smadja DM, et al. Circulation 2009; 119:374-81.

miRNAs : new players in the game

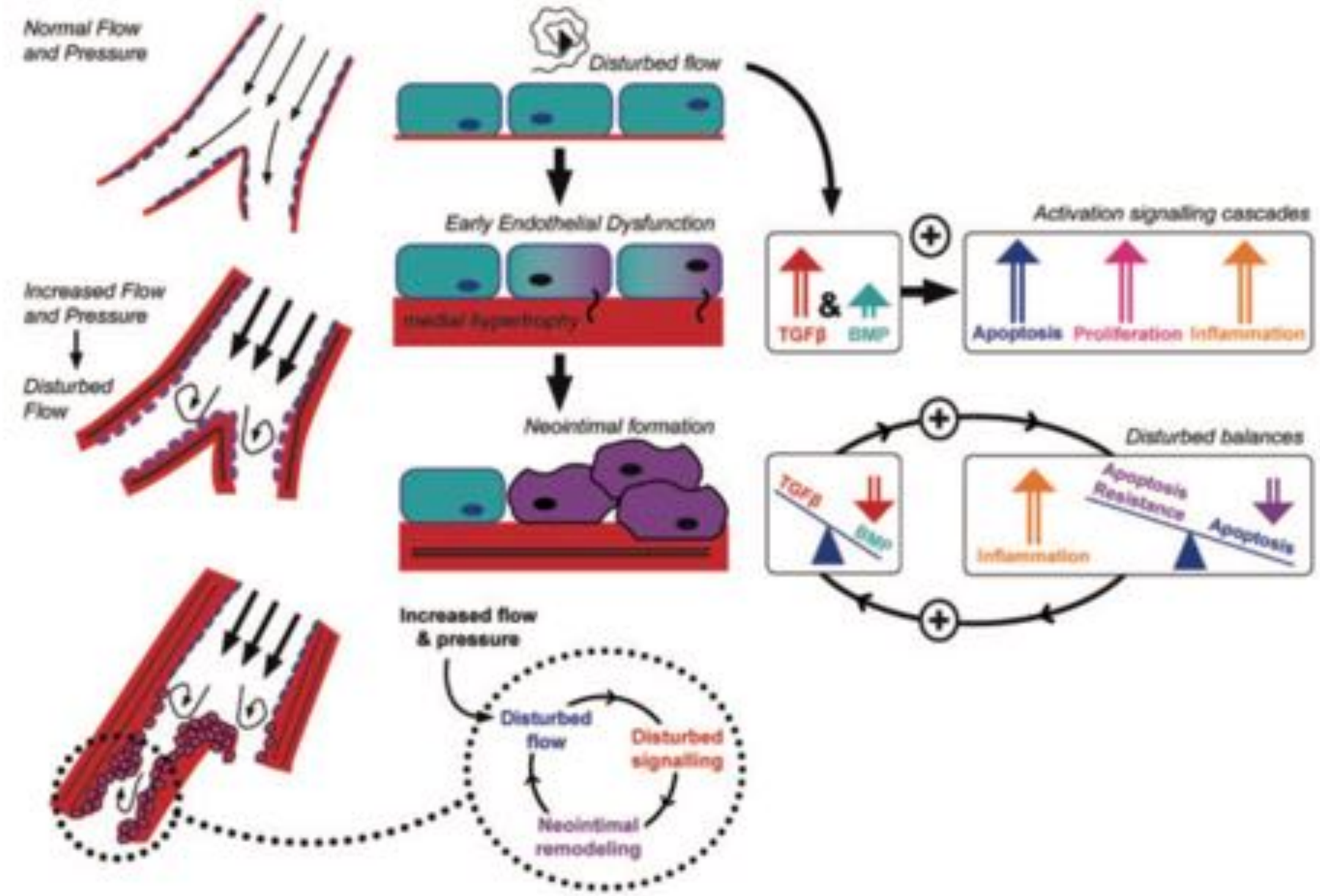
miRNAs are small non-coding RNAs that negatively, posttranscriptionally regulate the expression of target genes by interfering with both the stability of the target transcript as well as its translation

Fig. 4 miRNAs targeting BMPRII in the vascular wall. The illustration shows hypoxia and BMPRII mutations as regulators of miRNAs expression in endothelial or smooth muscle cells. These miRNAs negatively regulate BMPRII expression resulting in increased cell proliferation and impaired apoptosis. *Green arrows* indicate activation, *red arrows* represent inhibition, and black arrows correspond to unknown regulation. *EC* endothelial cells, *IL* interleukin, *miR* micro RNA, *mut* mutant, *SMC* smooth muscle cell, *STAT* signal transducer and activator of transcription



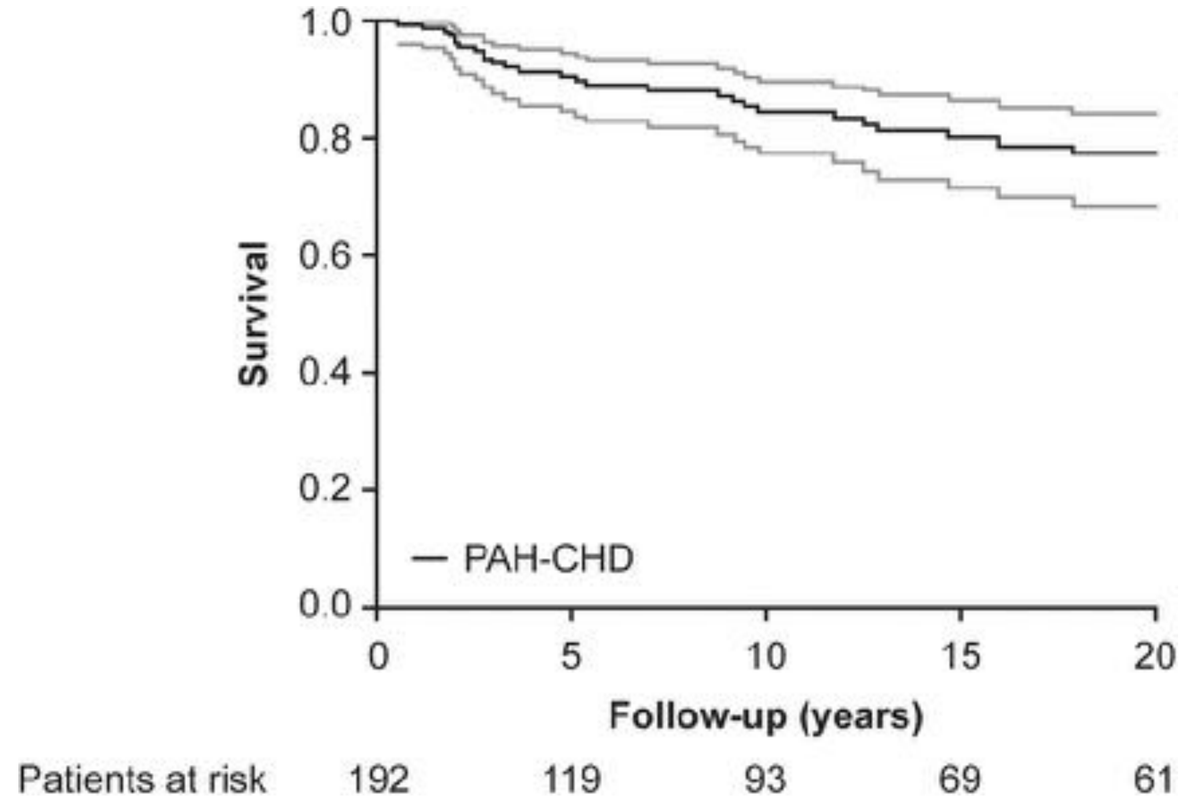
miR-145, miR-21 and the miR17/92 cluster, have been associated with the disrupted BMPRII pathway in PAH and can explain the incomplete penetrance of BMPR2 mutations

Summary **Flow PH in CHD**



Prognosis/survival in APAH-CHD

Kaplan–Meier survival curve (with 95% confidence intervals) of 192 patients with pulmonary arterial hypertension associated with congenital heart disease.



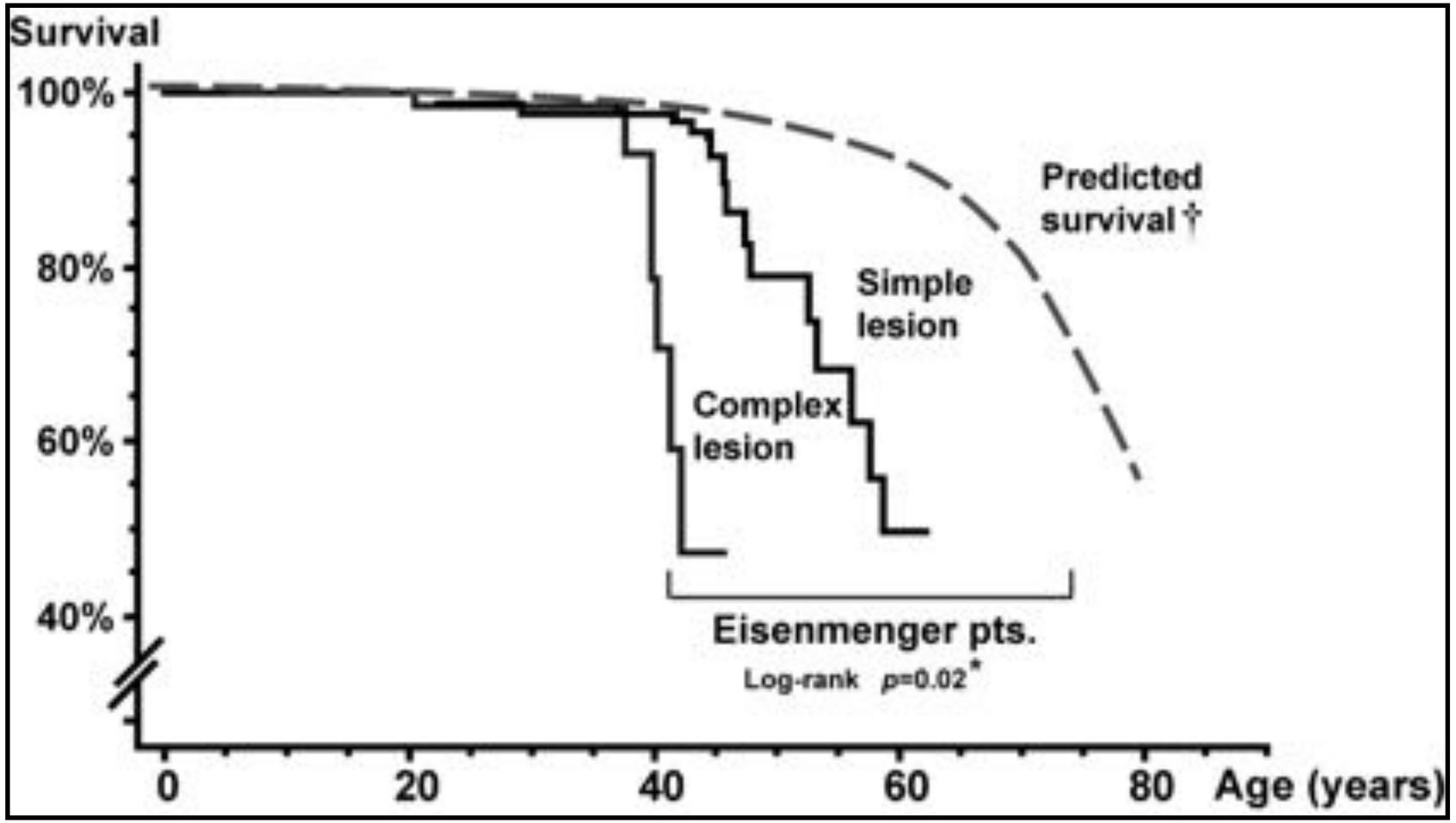
Presented from 1998-2011
Overall survival: 85% at 10 yrs; 77% at 20 yrs
IPAH: 46% at 10 yrs; 38% at 15 yrs

European Heart Journal

Manes A et al. Eur Heart J 2014;35:716-724

Adults with Eisenmenger Syndrome

Survival



Standardised mortality ratio 3.8; 95% CI 2.0 – 7.0; p<0.0001

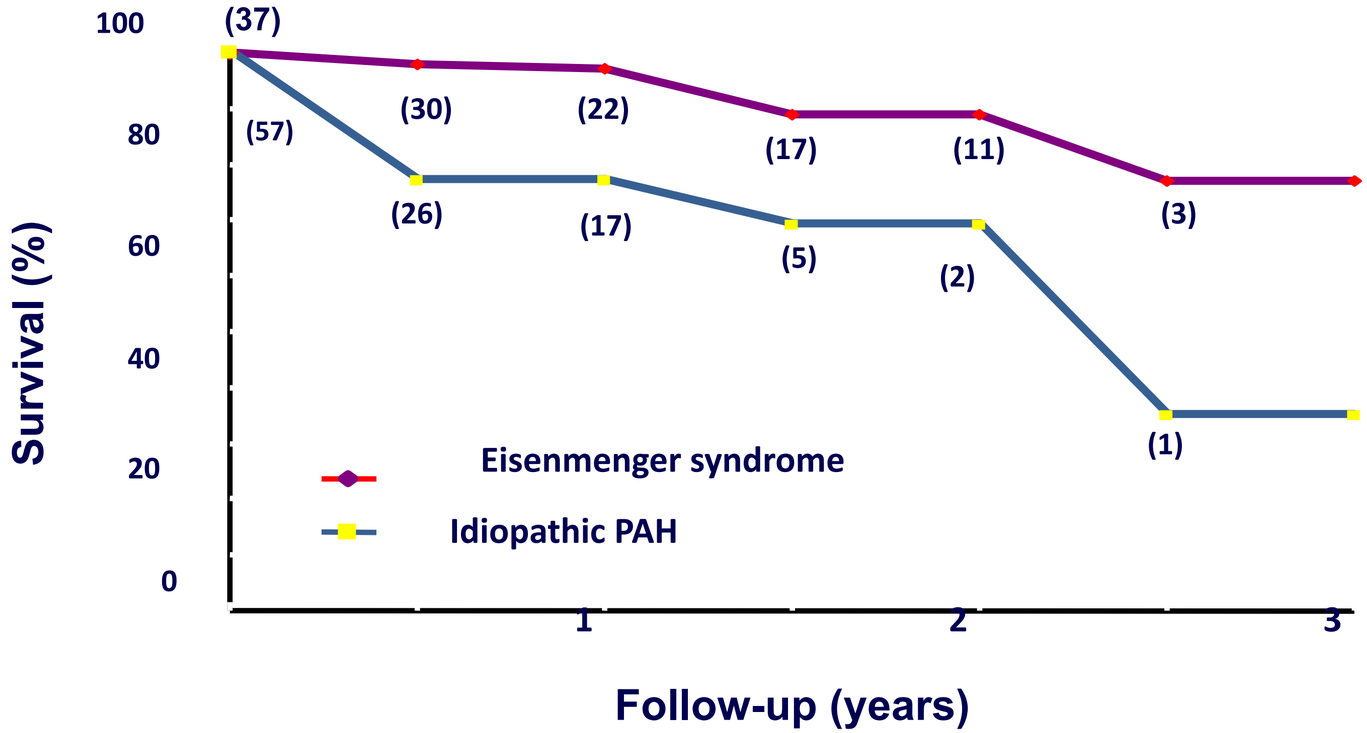
Diller *et al* *EHJ 2006*

Survival in APAH-CHD and compared to IPAH

Similar lung histology

but

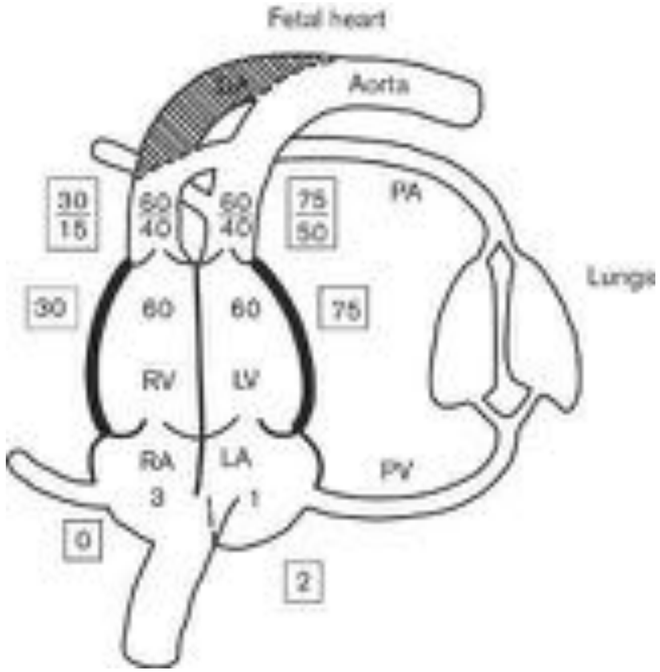
Different survival

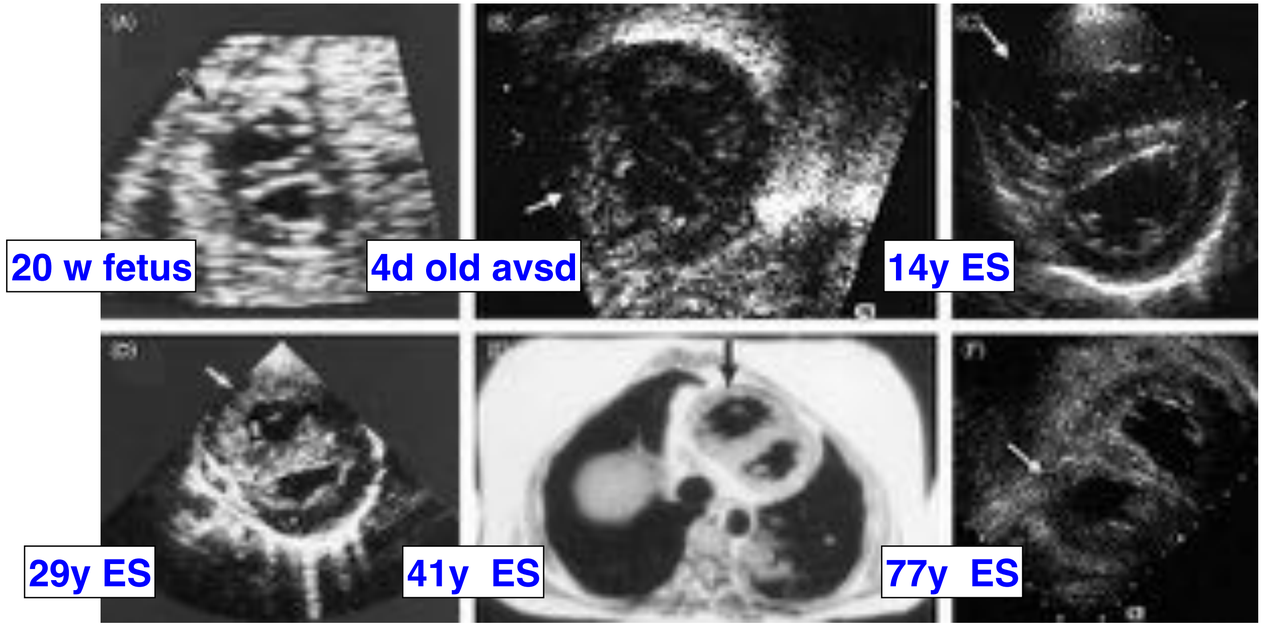


Daliento L, *et al. Eur Heart J* 1998.

Hopkins WE, *et al*. *J Heart Lung Transplant* 1996.

Eisenmenger right ventricle

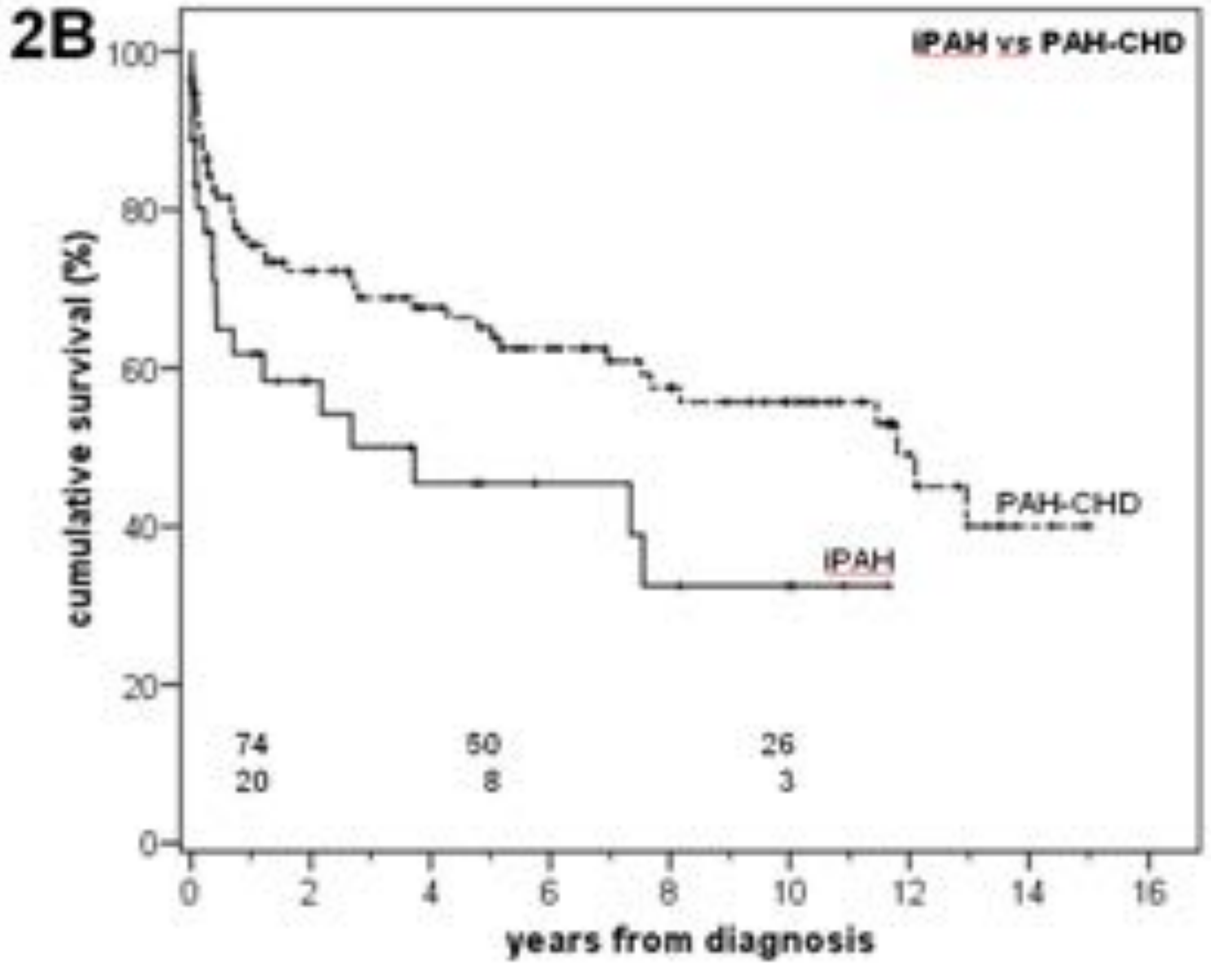




Hopkins WE. *Coron Artery Dis* 2005*;* 16:19-25.

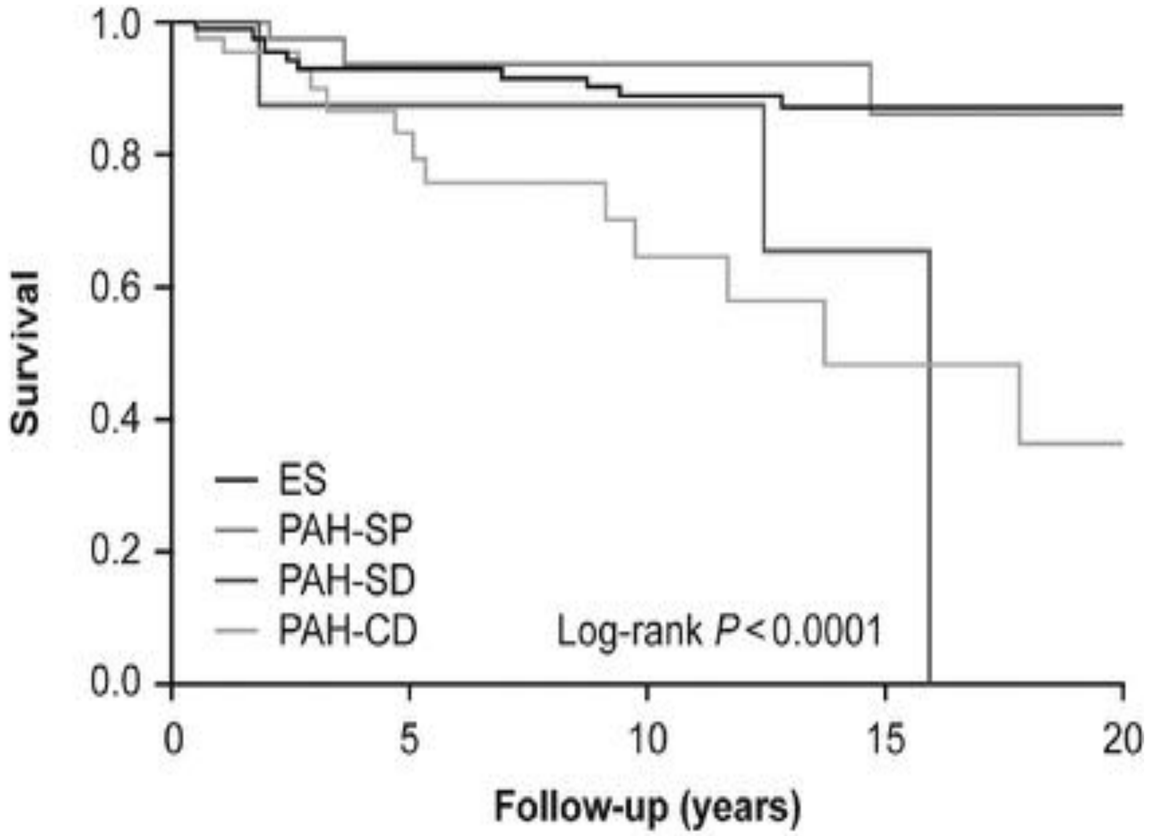
Pulmonary arterial hypertension in children in the Netherlands 1991-2005

survival



Van Loon et al; Am J Cardiol 2010

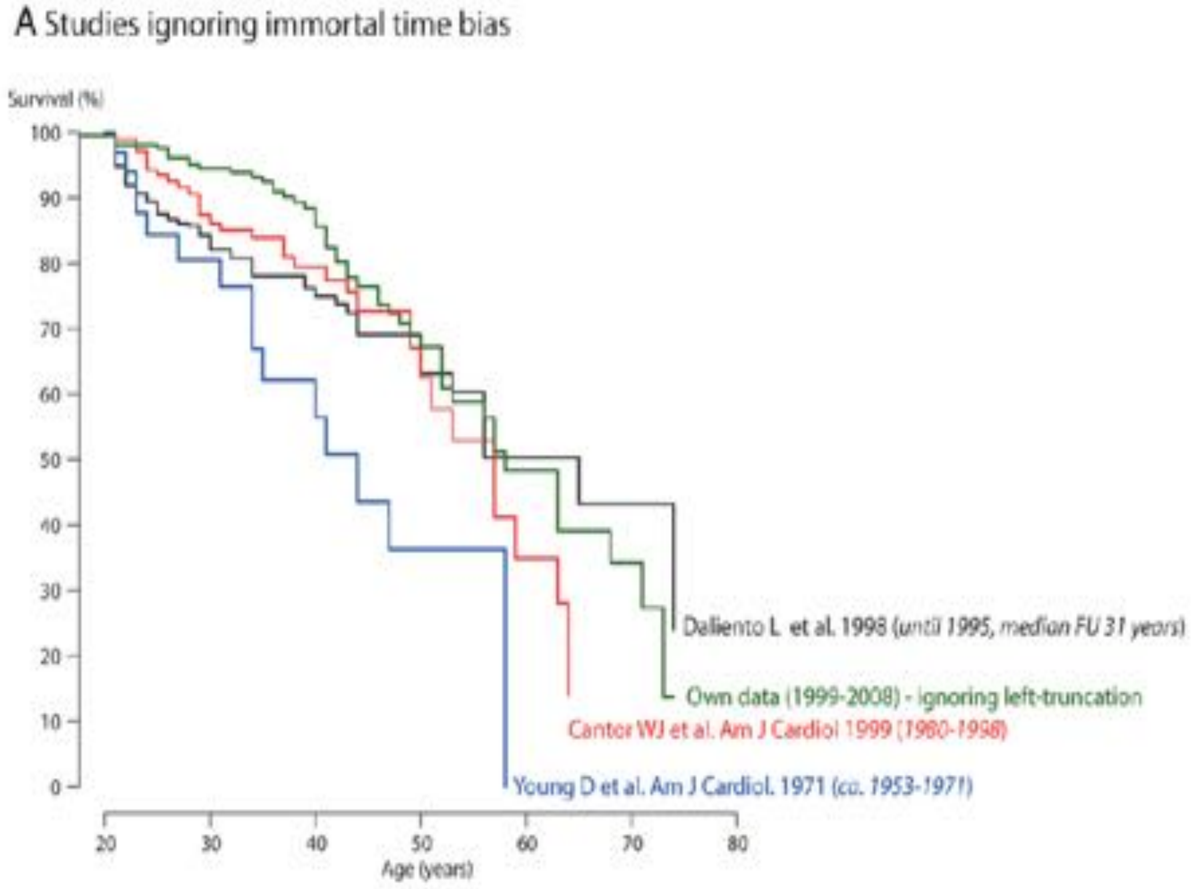
To Repair or Not To Repair?

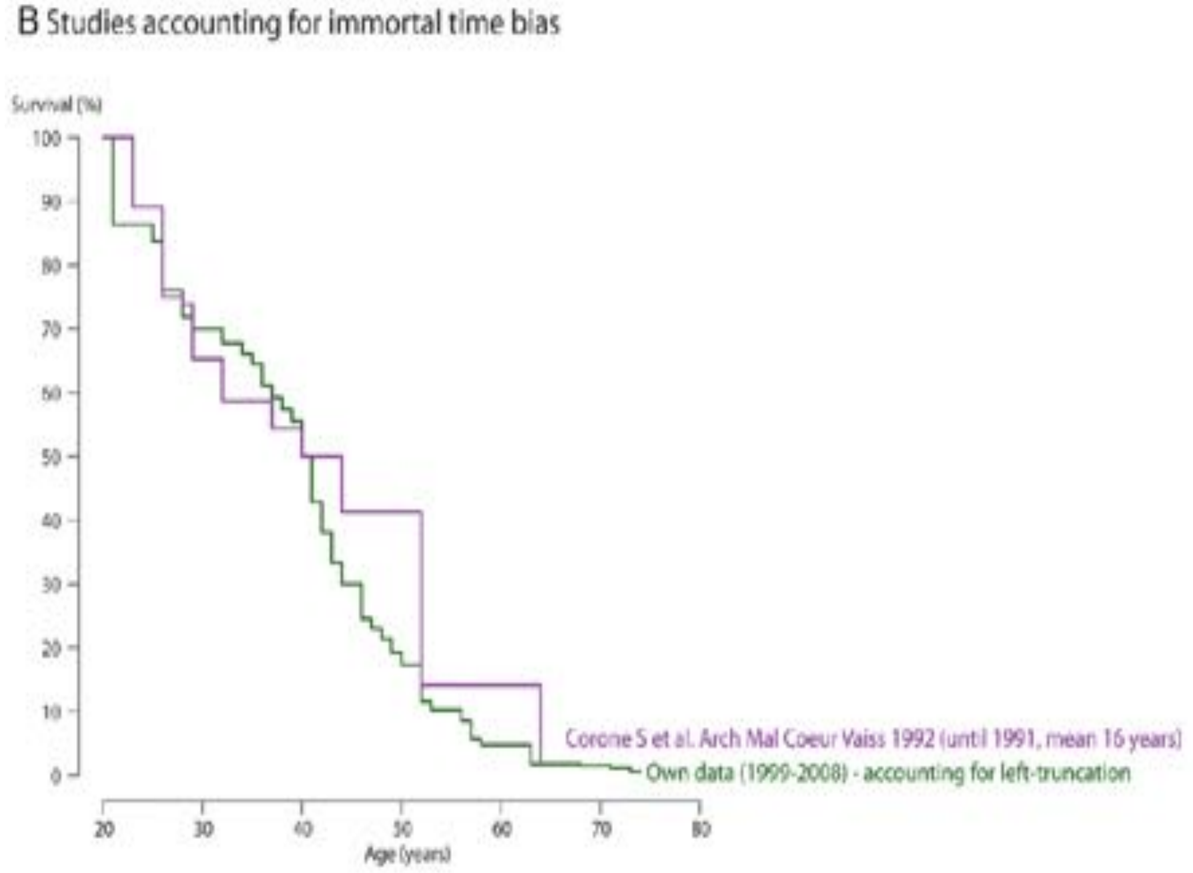


ES-eisenmengers n=90 (87% survival at 20 yrs)
PAH-SP-systemic-to-pulmonary shunt n=48 (86% survival at 20 yrs)
PAH-SD – small defect n=10 (66% at 15 yrs)
PAH-CD – after defect correction n=44 (36% survival at 20 yrs)

Manes A et al. Eur Heart J 2014;35:716-724

Immortal time bias in ES





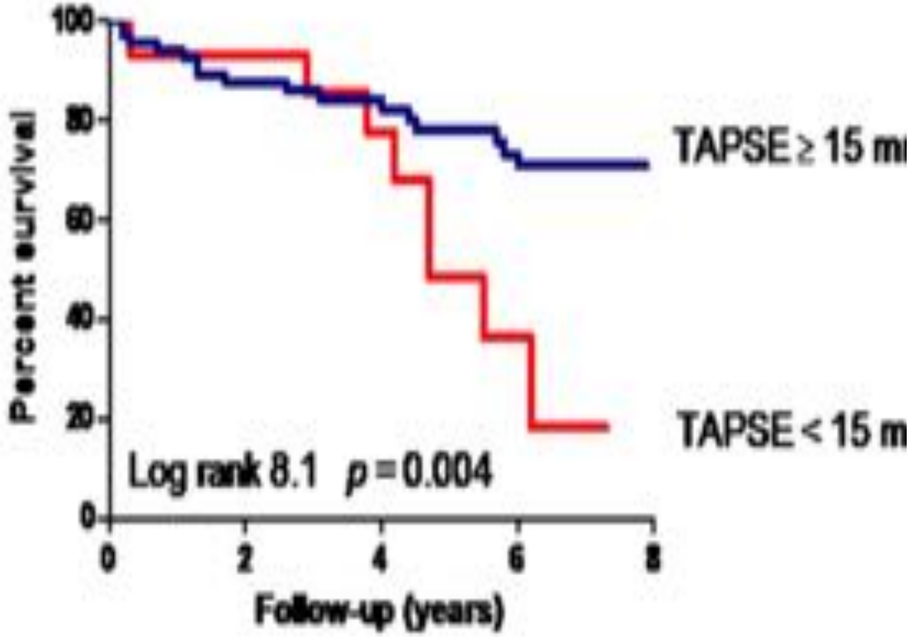
Diller G-P, et al. Heart 2014;100:1366–1372.

Monitoring and prognostication the adult Eisenmenger syndrome patient.

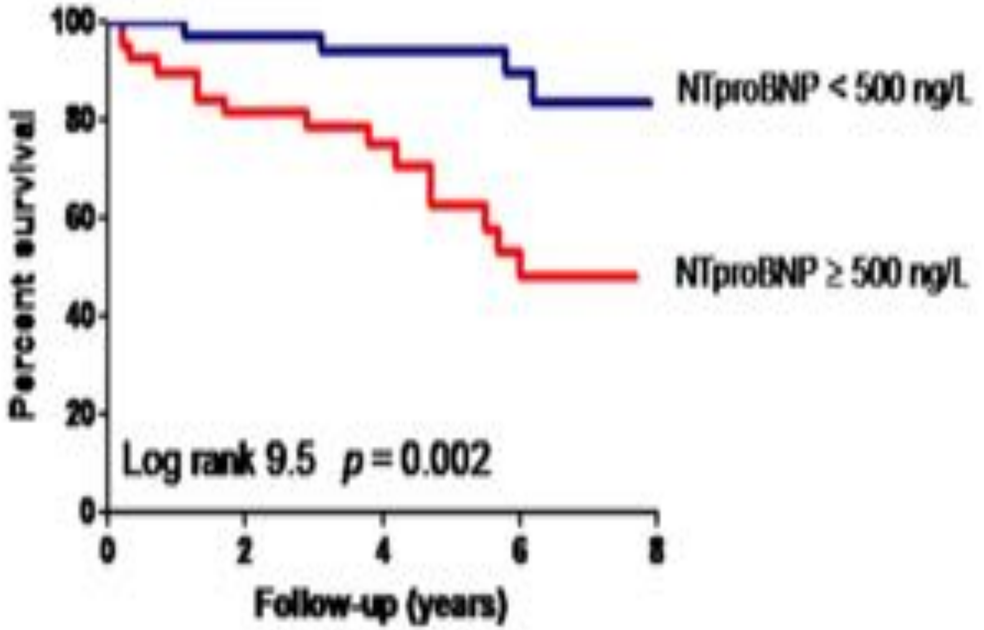
Better prognosis	Determinants of prognosis	Worse prognosis
No	Right ventricular failure[a]	Yes, guarded
No	Syncope[b]	Uncertain
I, II	WHO functional class[c] [42]	III, IV
Longer (>350 m)	6MWD [24,25]	Shorter (<300 m)
>85%	Oxygen saturation [24,25]	<85% or a drop of >2%/year
Transferrin saturation ≥ 20%	Iron deficiency [60]	Transferrin saturation < 20%
Normal or near normal	BNP plasma levels[d]	>30 pmol/L
TAPSE ≥ 1.5 cm	Echocardiographic findings[e]	TAPSE < 1.5 cm
RA area < 25 cm^2		RA area ≥ 25 cm^2
RA/LA < 1.5		RA/LA ≥ 1.5
RAP < 8 mm Hg and CI ≥ 2.5 L/min/m^2	Haemodynamics[f]	RAP > 15 mm Hg and CI ≤ 2.0 L/min/m^2

M.A. Gatzoulis et al. / International Journal of Cardiology 177 (2014) 340–347

Kaplan-Meier graphs on NT-proBNP serum level and TAPSE in relation to mortality



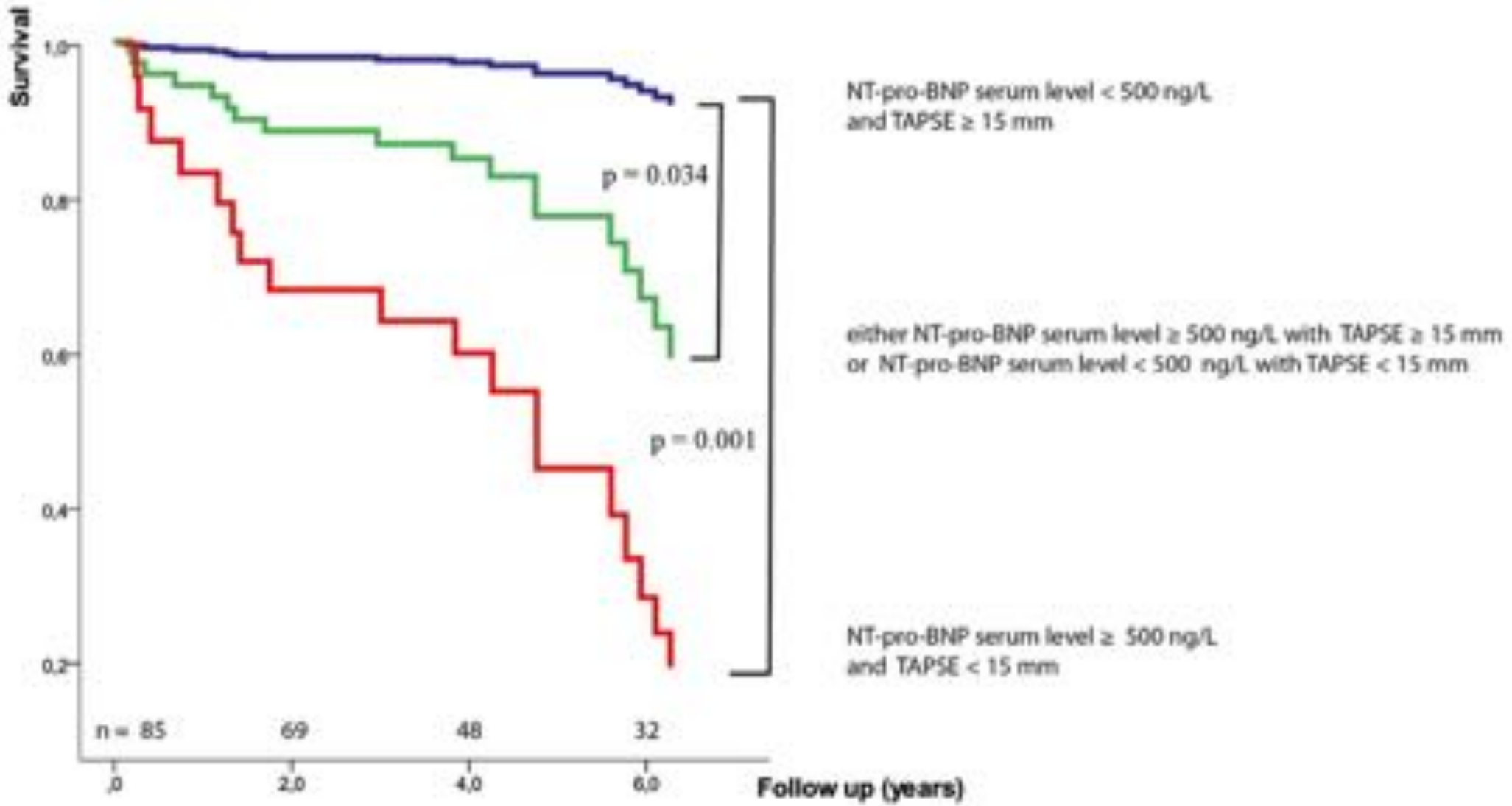
TAPSE ≥ 15 mm	60	49	38	29	1
TAPSE < 15 mm	14	13	8	2	0



NT-pro-BNP < 500 ng/L	36	33	26	18	1
NT-pro-BNP ≥ 500 ng/L	39	28	18	10	0

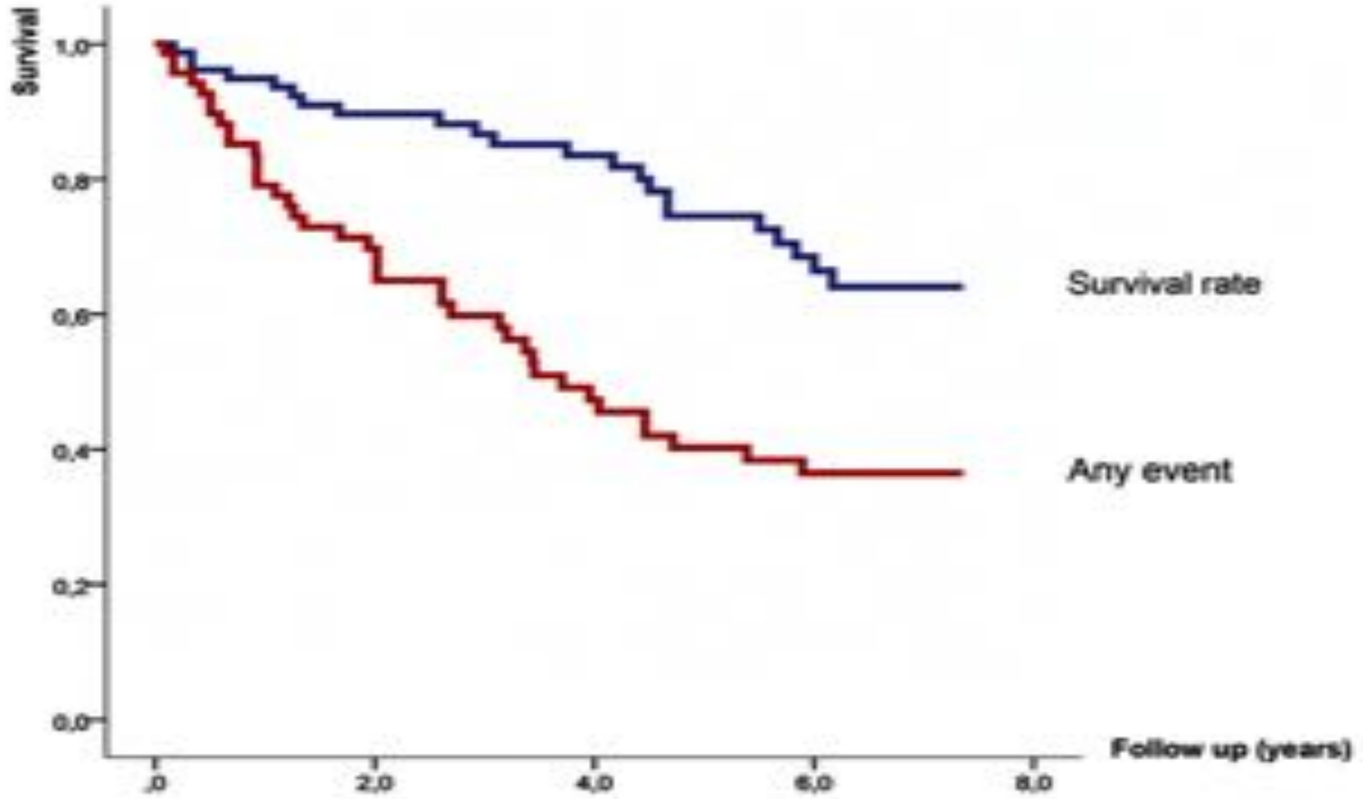
Schuuring M et al.International Journal of Cardiology 181 (2015) 270–276

Predicted survival model based on NT-proBNP serum level and TAPSE



Schuuring M et al.International Journal of Cardiology 181 (2015) 270–276

Mortality and events combined with mortality in Eisenmenger



Patients at risk	85	69	48	32
Cumulative events				
Mortality	0	9	14	23
Admission for HF	0	6	9	9
Arrhythmias	0	7	9	8
Haemoptysis	0	2	4	4
Worse NYHA	0	4	8	15
Vascular	0	1	1	1
Syncope	0	0	1	1

Schuuring M et al.International Journal of Cardiology 181 (2015) 270–276

Therapy in APAH-CHD

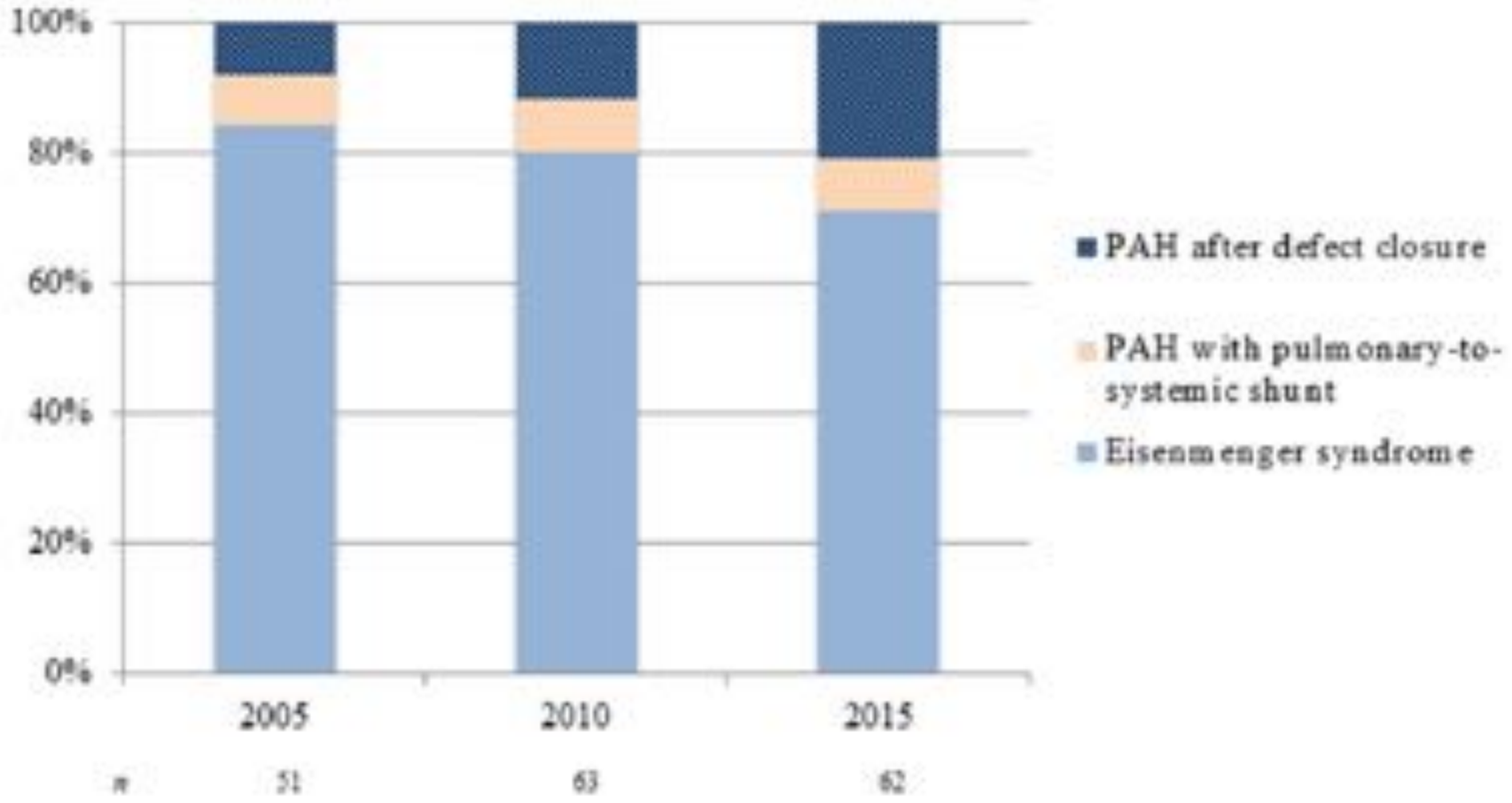


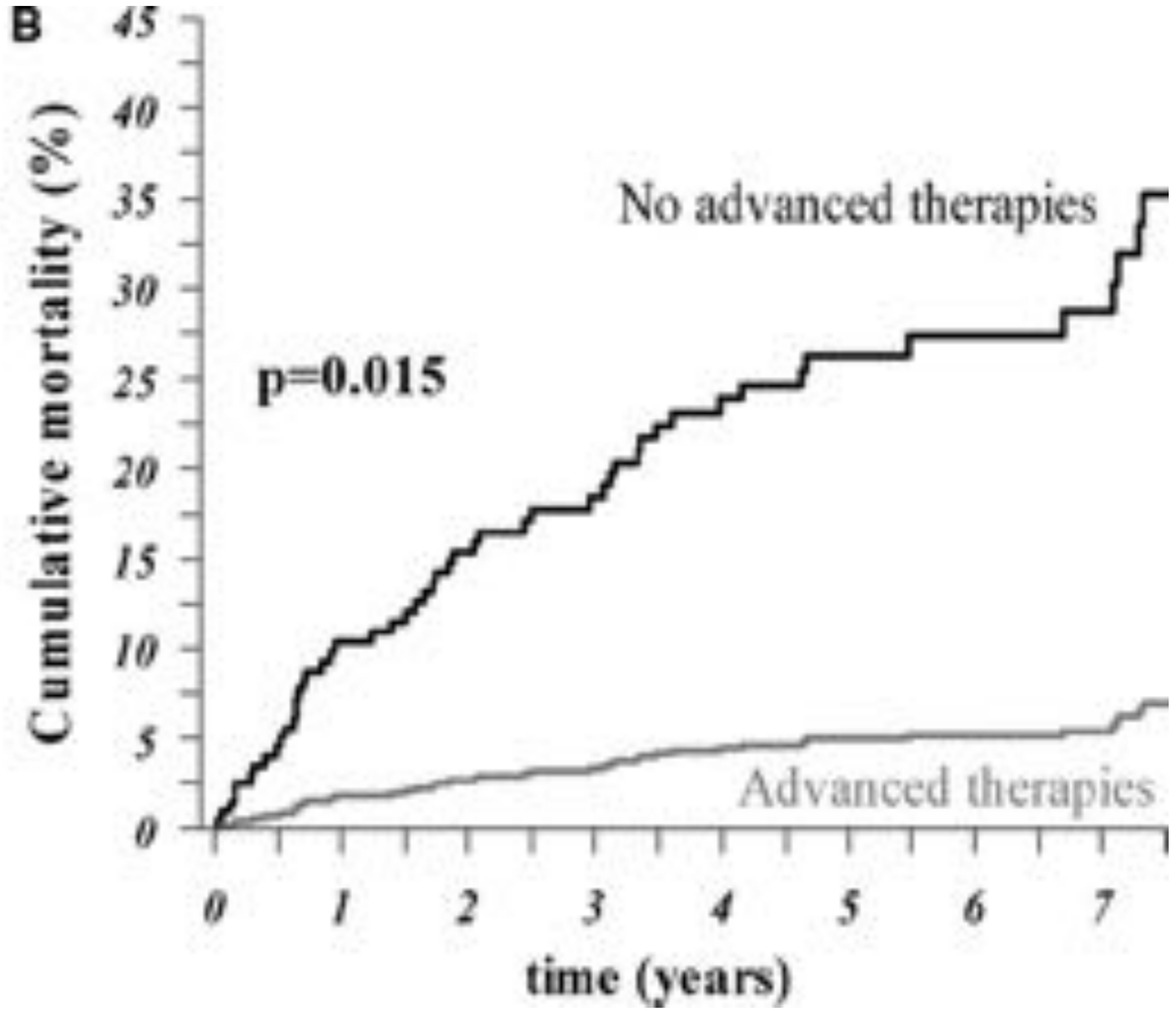
Figure 1. Changing subgroup distribution of pulmonary arterial hypertension in adult congenital heart disease: patients on treatment at two congenital heart disease (CHD) designated centers in the Netherlands from 2005 to 2015. PAH: pulmonary arterial hypertension.

Van Dissel AC et al. J Clin Med 2018

First Author (Study Acronym)	n with CHD (% of Study Population)	Background Therapy	Intervention	Follow-Up (Weeks)	Primary Outcome	Study Conclusion
			Study Population Including Mixed Group of PAH-CHD			
Simonneau et al. [illegible]	109 (23)	None	Treprostinil	12	Δ 6MWD	↑ PVR, symptoms
Galiè et al. [illegible] (EARLY)	32 (17)	None	Bosentan	24	Δ 6MWD and PVR	↑
Galiè et al. [illegible] (PHIRST)	47 (12)	None or bosentan	Tadalafil	16	Δ 6MWD	↑ TTCW
Ghofrani et al. [illegible] (PATENT-1)	35 (8)	None, ERA or prostanoids	Riociguat	12	Δ 6MWD	↑ PVR, WHO, TTCW, NT-proBNP
			Study Population Including CHD with Closed Defects			
Simonneau et al. [illegible] (PACES)	30 (8)	Epoprostenol	Sildenafil	16	Δ 6MWD	↑ PVR, TTCW, QoL
Galiè et al. [illegible] (SUPER-1)	16 (6)	None	Sildenafil	12	Δ 6MWD	↑ WHO class, and hemodynamics
Tapson et al. [illegible] (FREEDOM-C)	22 (6)	ERA, PDE-5i or both	Treprostinil	16	Δ 6MWD	=
Tapson et al. [illegible] (FREEDOM-C2)	8 (3)	ERA, PDE-5i or both	Treprostinil	16	Δ 6MWD	=
Pulido et al. [illegible] (SERAPHIN)	62 (8)	PDE-5i or prostanoids	Macitentan	85–115	TTCW	↑
Jing et al. [illegible] (FREEDOM-M)	14 (5)	None	Treprostinil	12	Δ 6MWD	↑
McLaughlin et al. [illegible] (COMPASS-2)	30 (9)	Sildenafil	Bosentan	+/− 179	TTCW	−
Galiè et al. [illegible] (AMBITION)	13 (3)	None	Ambrisentan + tadalafil vs. ambrisentan vs. tadalafil	74	TTCW	↑ with initial combination therapy > ambrisentan or tadalafil monotherapy
Sitbon et al. [illegible] (GRIPHON)	110 (10)	None, ERA, PDE-5i or both	Selexipag	67	TTCW	↑ in all baseline treatment groups
			Study Population Including Eisenmenger Syndrome			
Galiè et al. [illegible] (BREATHE-5)	54 (100)	None	Bosentan	16	Δ SpO2 and PVR	↑ w/o worsening SpO2
Singh et al. [illegible]	20 (100)	None	Sildenafil	6	Δ 6MWD	↑ NYHA class, PVR
Iversen et al. [illegible]	21 (100)	None	Bosentan, add sildenafil cross-over	24	Δ 6MWD	Bosentan alone ↑ with addition of sildenafil, but ↑ DCO
Mukhopadhyay et al. [illegible]	28 (100)	None	Tadalafil	6	Δ 6MWD	↑ 6MWD, DCO, and PVR

Treated vs. non treated Eisenmenger patients

Unadjusted survival rate curves (with 95% CIs) by treatment with AT (n=287)



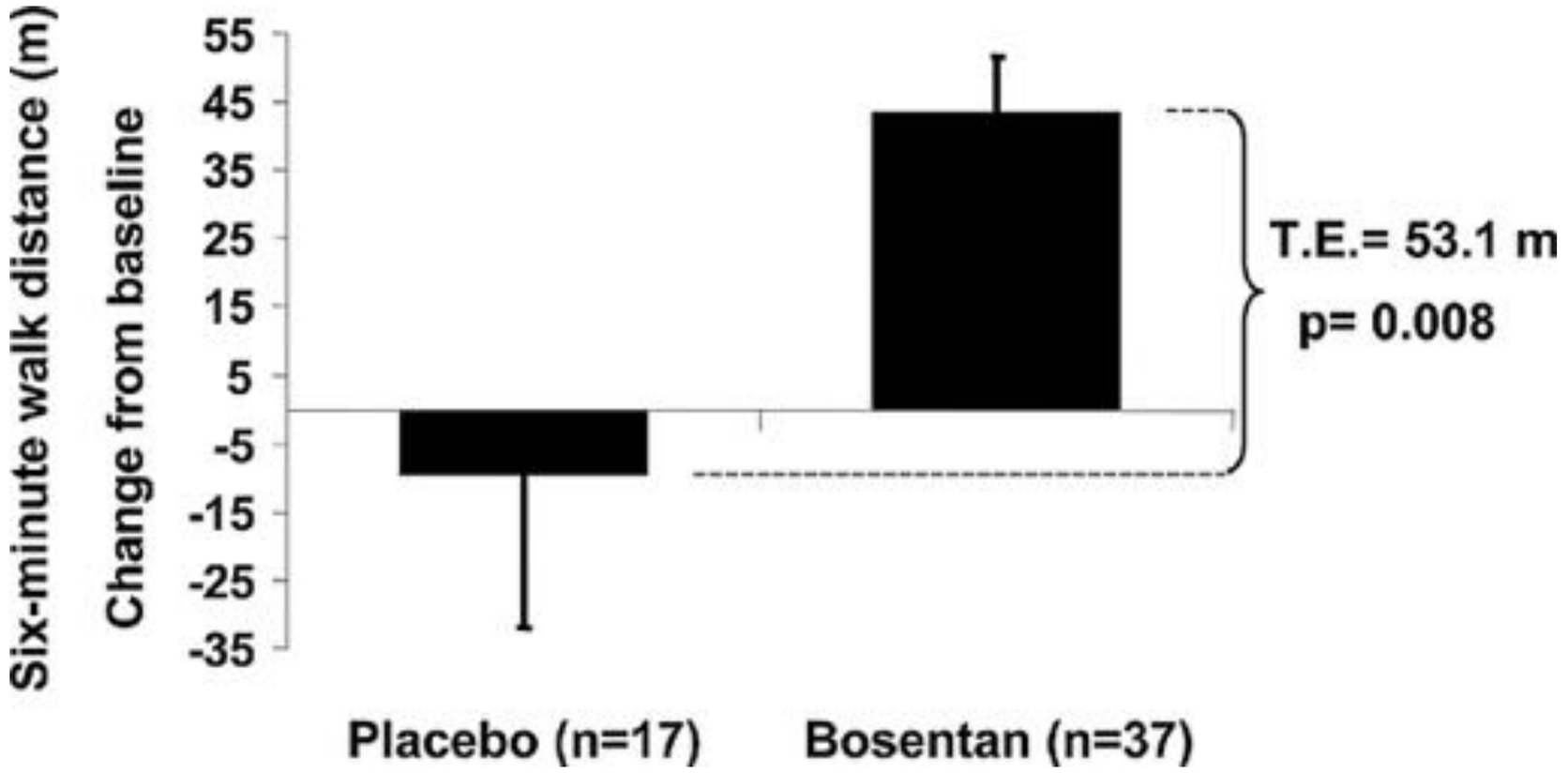
Dimopoulos, K. et al. Circulation 2010;121:20-25

Management of “border line” patients

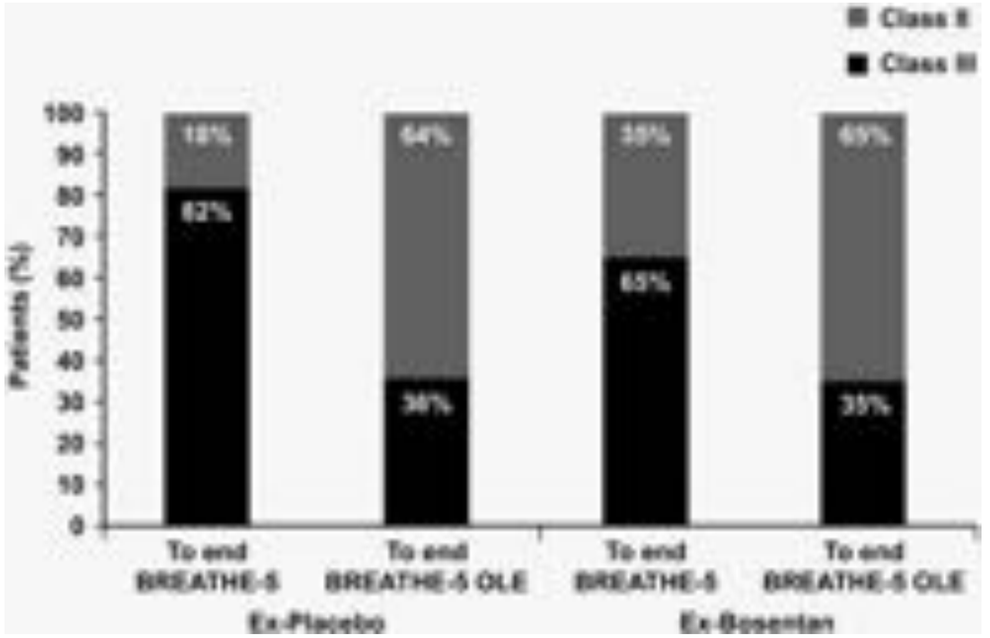
- **How should patients with CHD and elevated PVR be treated ?**

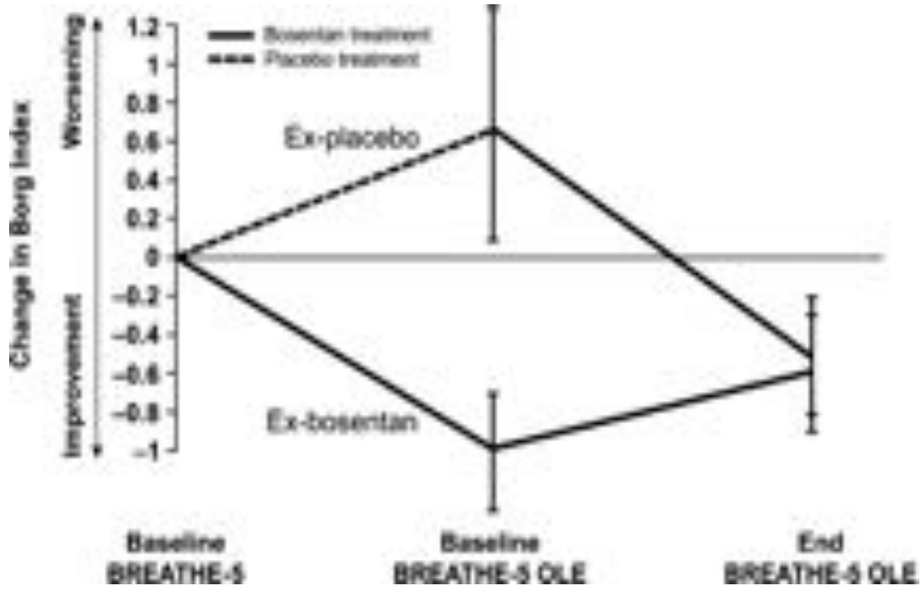
  1. Leave them to their natural history
  2. Close the shunt
  3. Challenge pulmonary vessels with a palliative procedure
  4. Treat and repair

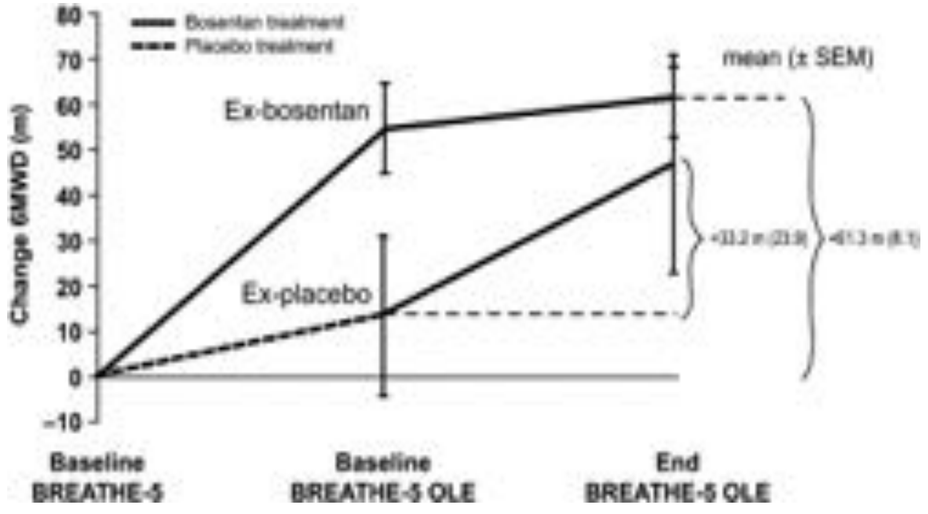
BREATHE-5



Nazzareno Galiè et al. Circulation. 2006;114:48-54

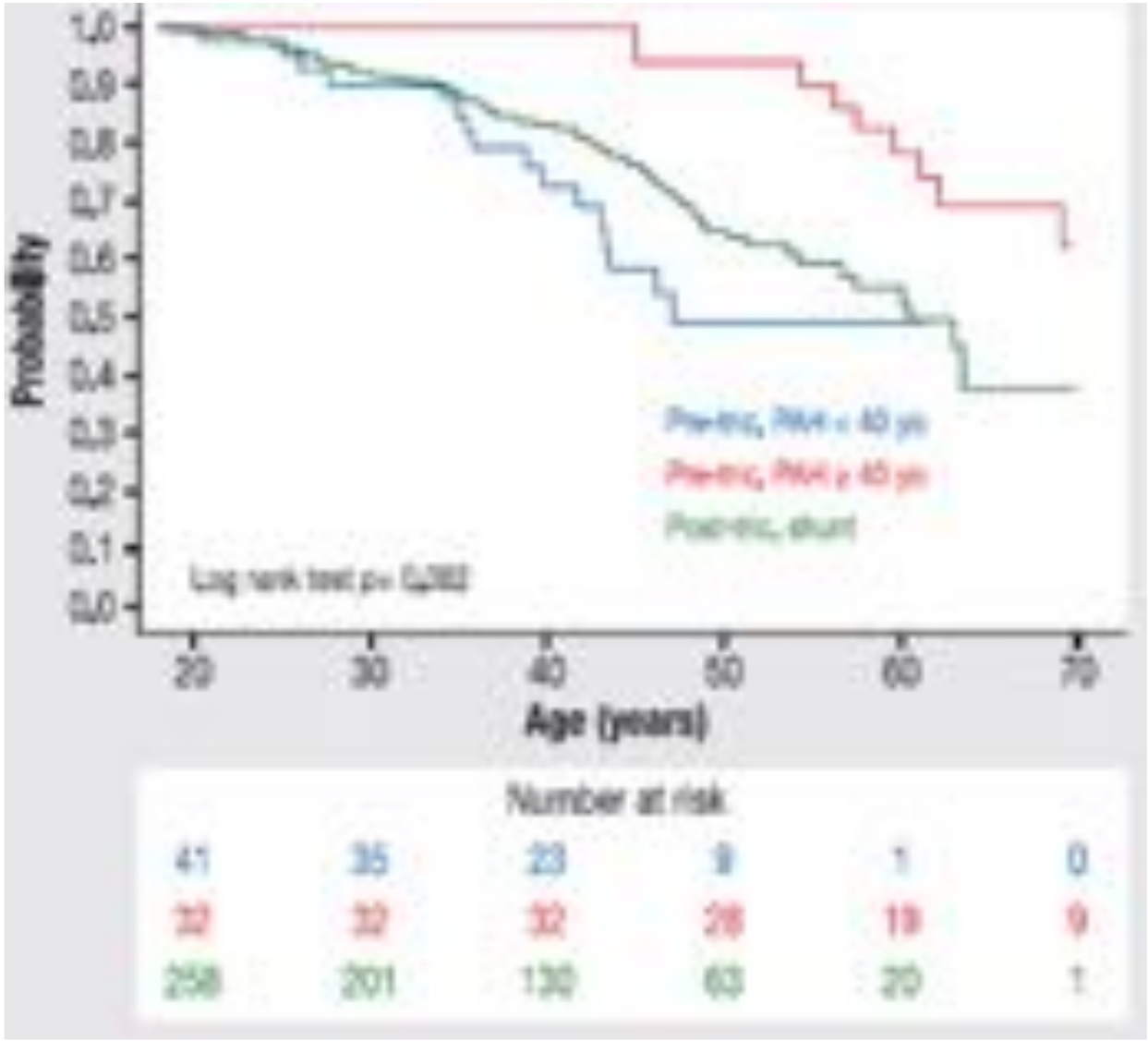






BREATHE-5 – open label extension

Outcomes of adult patients with Eisenmenger syndrome treated with PAH drugs

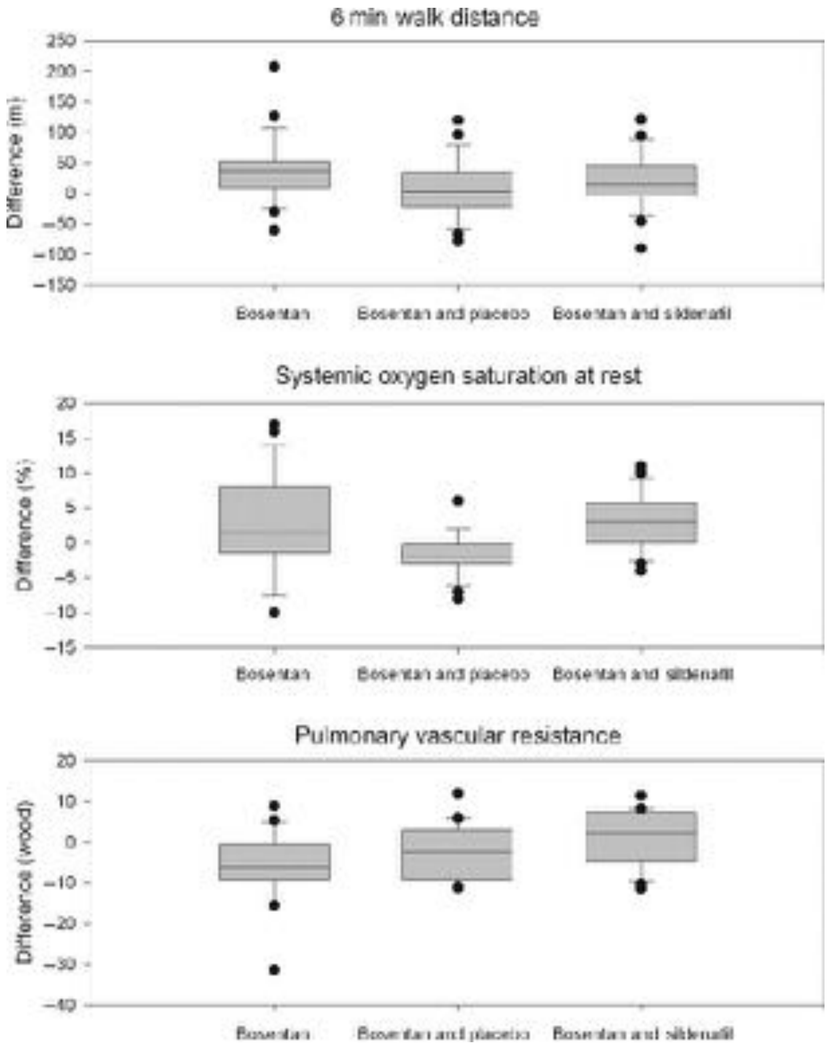


Hascoet S et al. Arch Cardiovasc Dis 2017

Recommendations for therapies in APAH-CHD

Recommendations	Class[a]	Level[a]
Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome	I	B
Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure	IIb	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%	IIa	C
The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels	IIb	C
Combination drug therapy may be considered in patients with Eisenmenger syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger syndrome	III	C

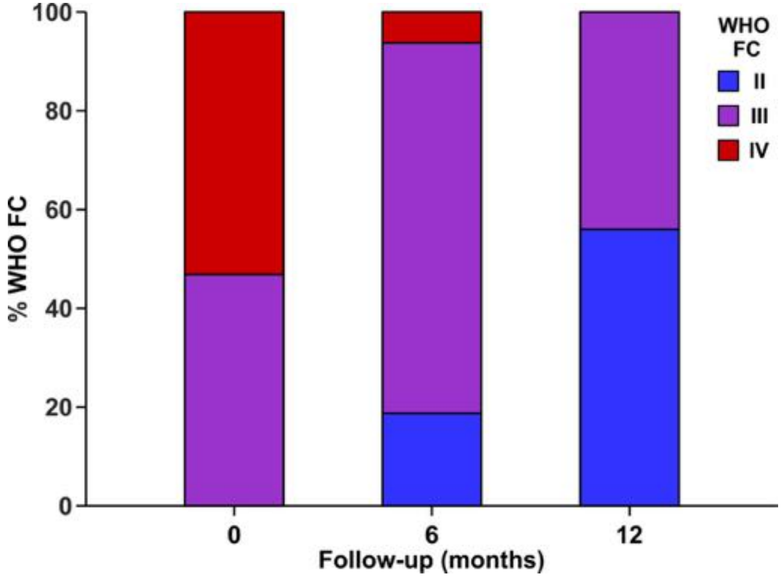
Differences between bosentan monotherapy and combination therapy with bosentan and sildenafil for selected endpoints.



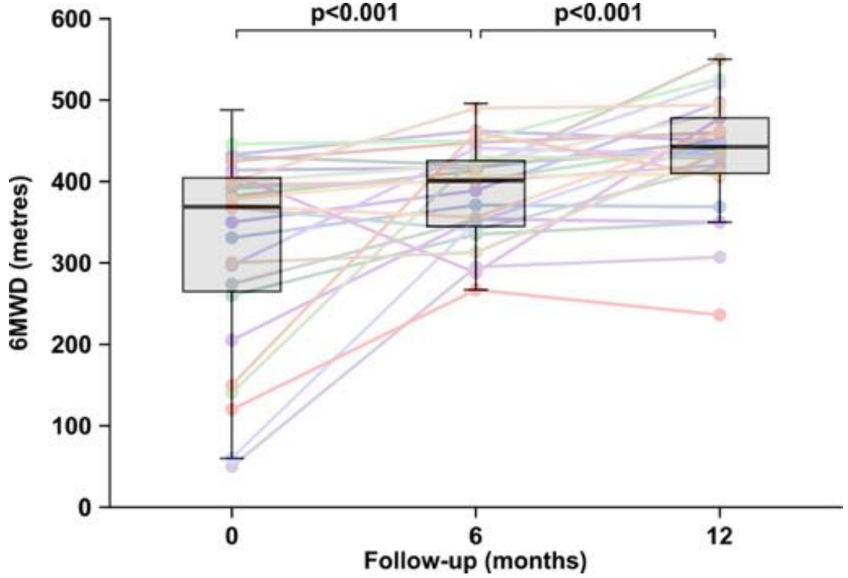
Iversen K et al. Eur Heart J 2010;31:1124-1131

European Heart Journal

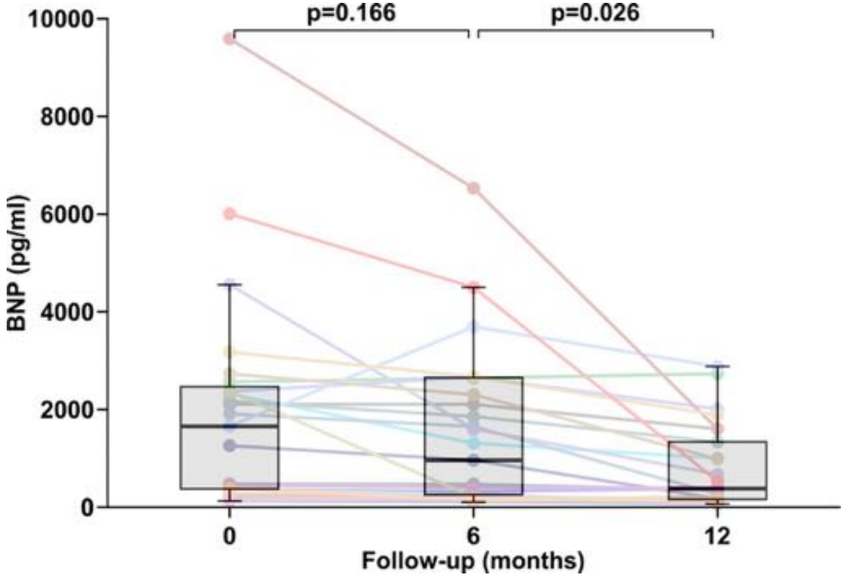
Subcutaneous treprostinil in congenital heart disease related pulmonary arterial hypertension



Effect of treprostinil treatment on WHO_FC
at 6 and 12 months of treatment

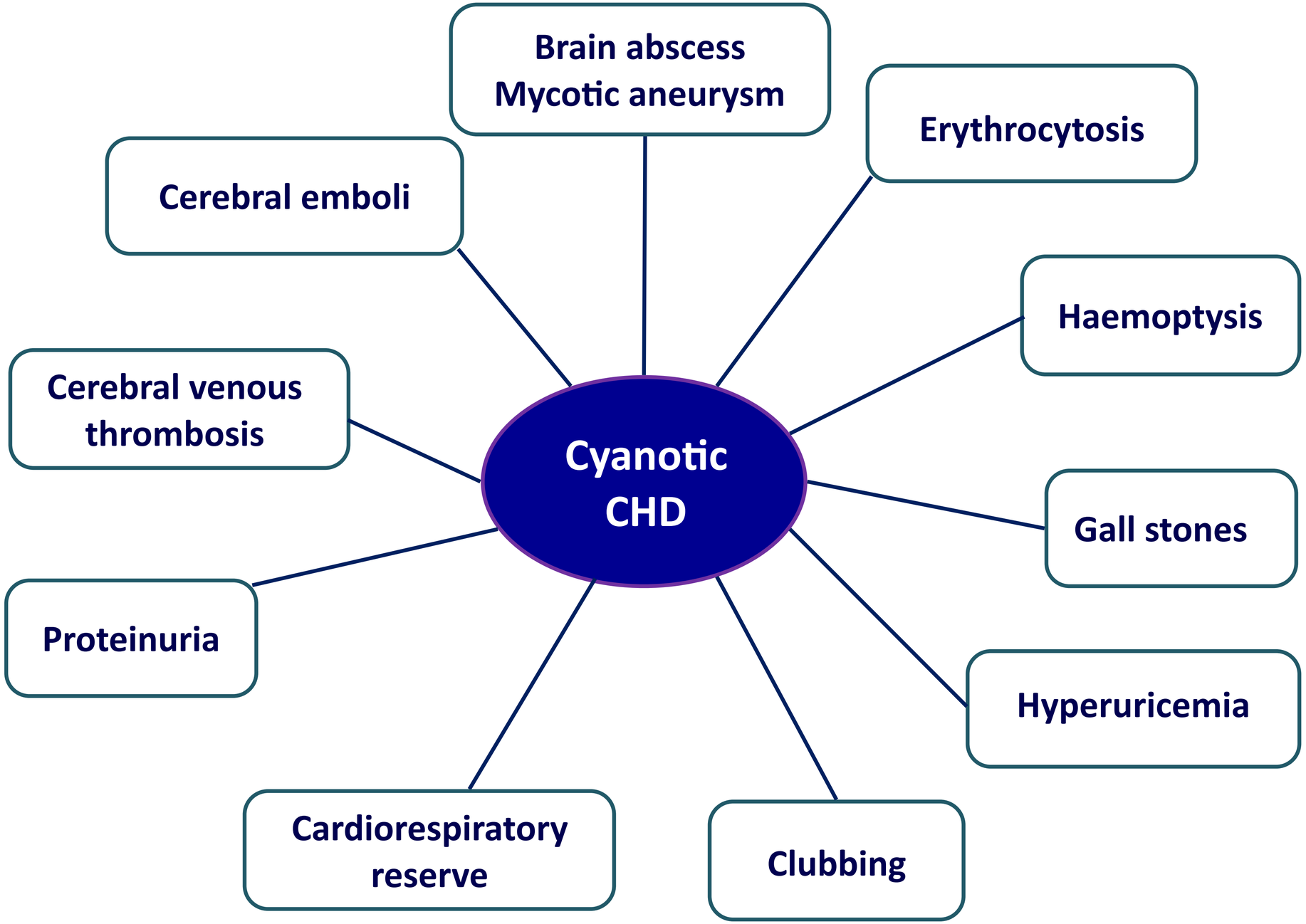


Effect of treprostinil treatment on 6-MWD
at 6 and 12 months of treatment



Effect of treprostinil treatment
on BNP serum levels
at 6 and 12 months of treatment

Nika Skoro-Sajer et al. Heart doi:10.1136/heartjnl-2017-312143


Cyanotic CHD
Brain abscess
Mycotic aneurysm
Erythrocytosis
Cerebral emboli
Haemoptysis
Cerebral venous thrombosis
Gall stones
Proteinuria
Hyperuricemia
Cardiorespiratory reserve
Clubbing

Recommendations for supportive therapies in Eisenmenger syndrome

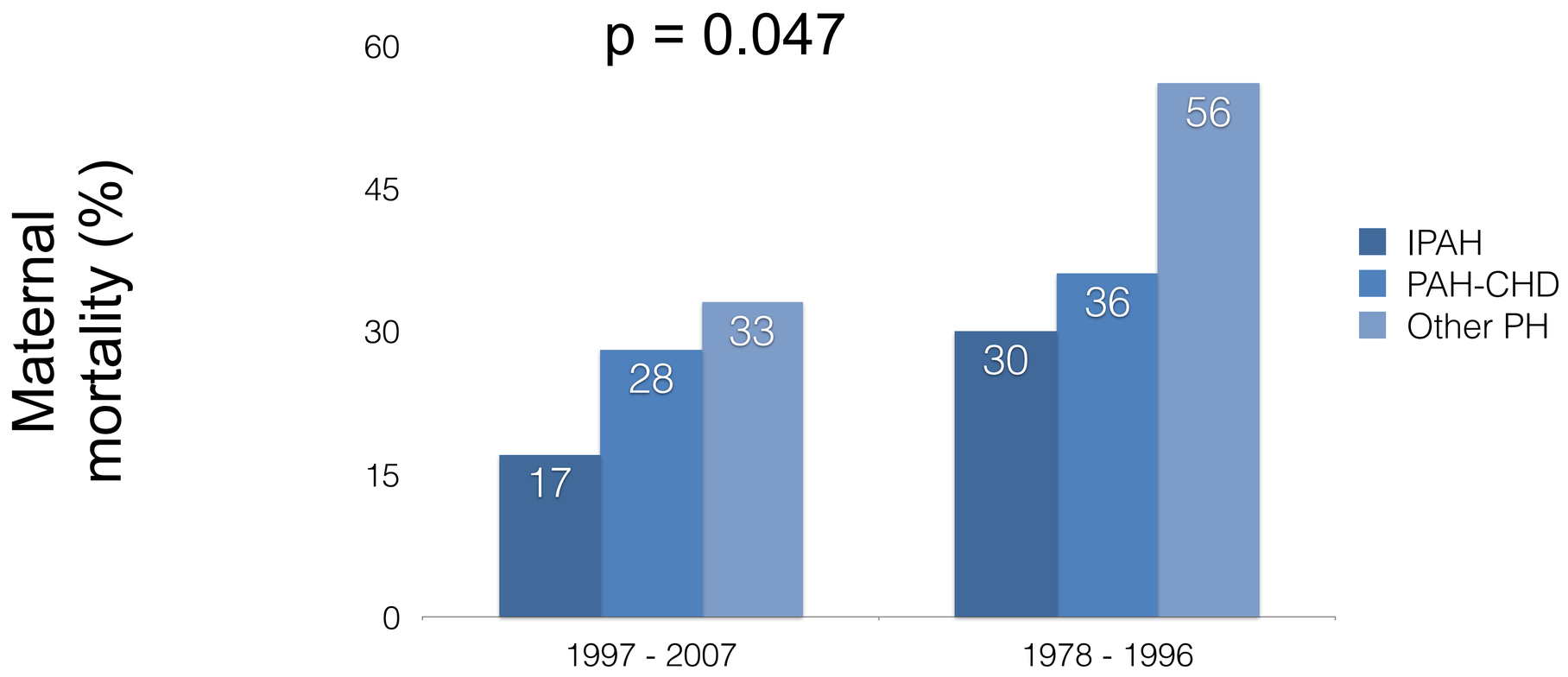
Recommendations	Class[a]	Level[b]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[c]	I	C
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C

Eisenmenger syndrome

General management principles

- Avoid dehydration, extreme isometric exercise
- Avoid high altitude
- Air travel is safe Broberg et al Heart 2006
- Special anaesthetic management
- Special care around angiography and non-cardiac surgery
- Avoid pregnancy Bedard et al Eur Heart J 2009 (≈ 30% maternal mortality)
- Contraception issues

Pregnancy and PAH in association with CHD



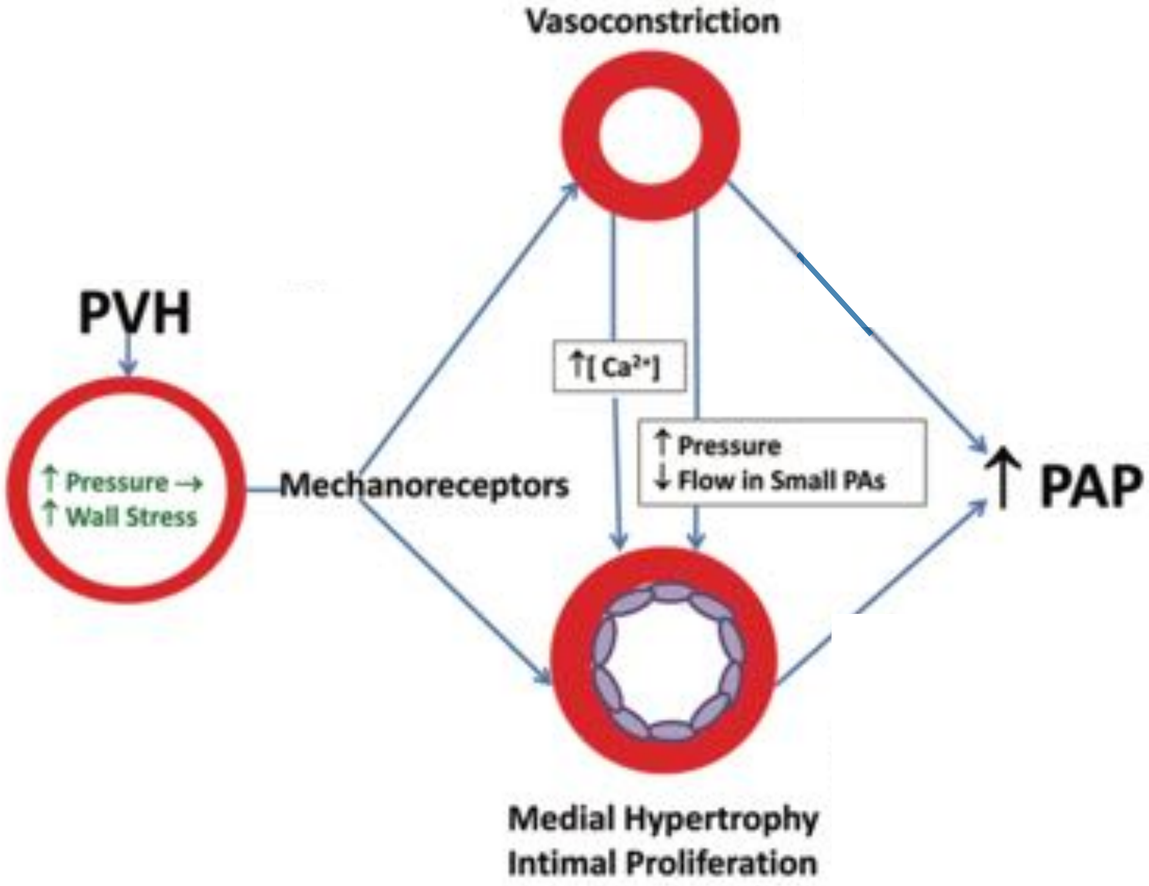
Bedard E, et al. Eur Heart J 2009; 30:256-65.
Ladouceur M et al. Circulation 2017

Pulmonary hypertension caused by pulmonary venous hypertension

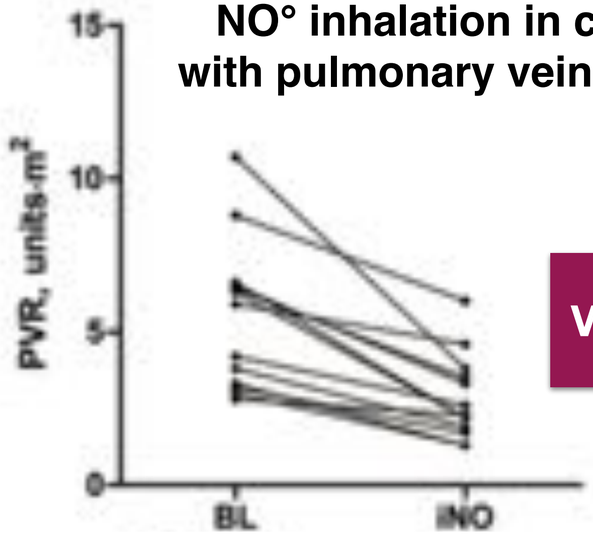
1. The effect of pulmonary venous hypertension (PVH) on the pulmonary circulation is extraordinarily variable, ranging from no impact on pulmonary vascular resistance (PVR) to a marked increase

2. PVH-PH is one of the very few “models” of increased PVR in which removal of the stimulus is often possible, which is followed by substantial reduction of PVR.

How pulmonary venous hypertension (PVH) causes increased pulmonary vascular resistance (PVR)

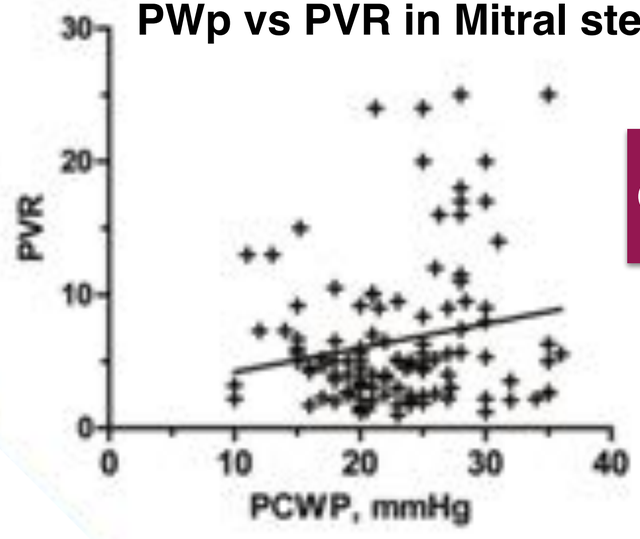


NO° inhalation in children with pulmonary vein stenosis



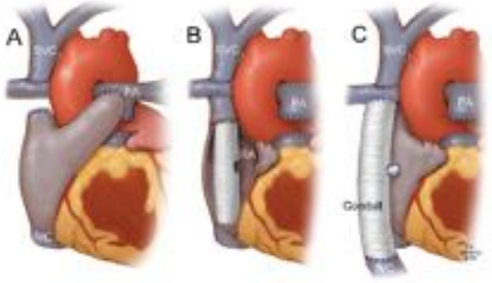
Vasoconstriction

PWp vs PVR in Mitral stenosis



Out-of-proportion

Wood P, Besterman E, Towers MK, McIlroy MB. The effect of acetylcholine on pulmonary vascular resistance and left atrial pressure in mitral stenosis. Br Heart J 1957;19: 279–286.
Atz AM, Adatia I, Jonas RA, et al. Inhaled nitric oxide in children with pulmonary hypertension and congenital mitral stenosis. Am J Cardiol 1996;77:316–319.



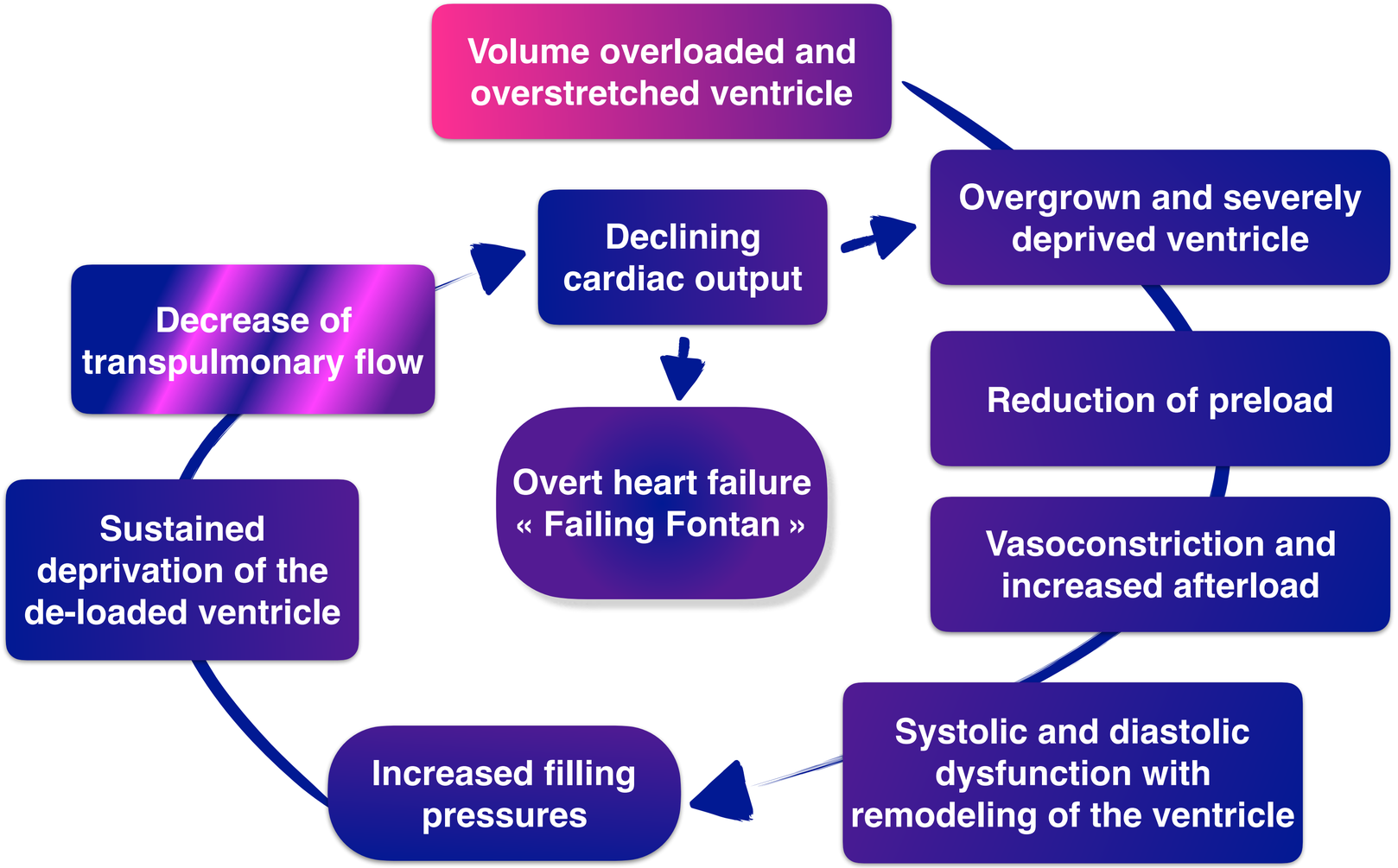
Increased PVR in the Fontan circulation

Pulsatile flow is important for shear stress-mediated release of endothelium-derived nitric oxide and for the lowering of the PVR by the passive recruitment of capillaries

Fontan patients do not fulfil the hemodynamic characteristics for PH but have increased PVR and exhibit pulmonary vascular remodelling « resembling » that of other forms of PH

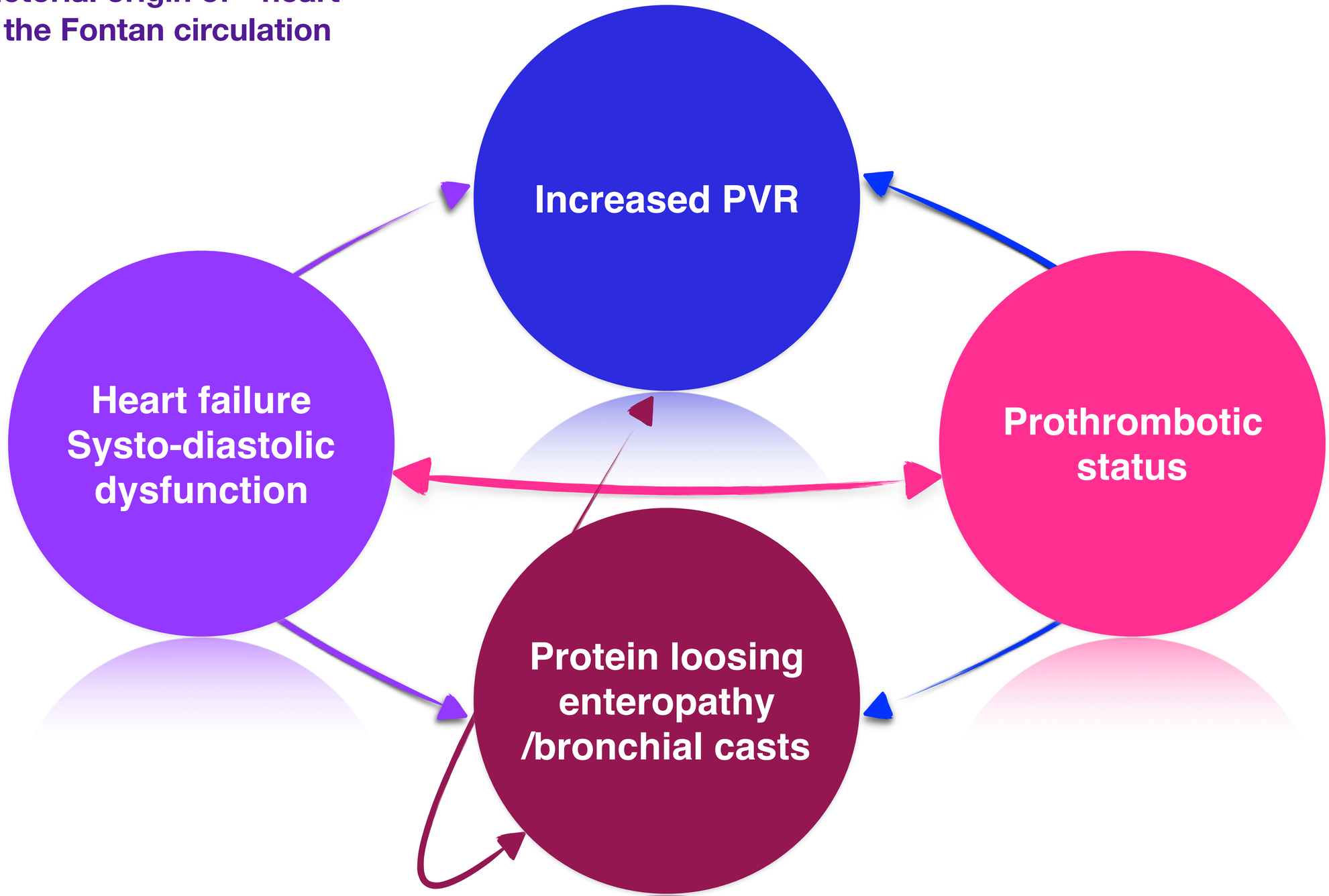
The Fontan circulation - a new portal system

The vicious circle to failing Fontan



Adapted from Marc Gewillig-Heart 2016

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



Endothelial function in TCPC

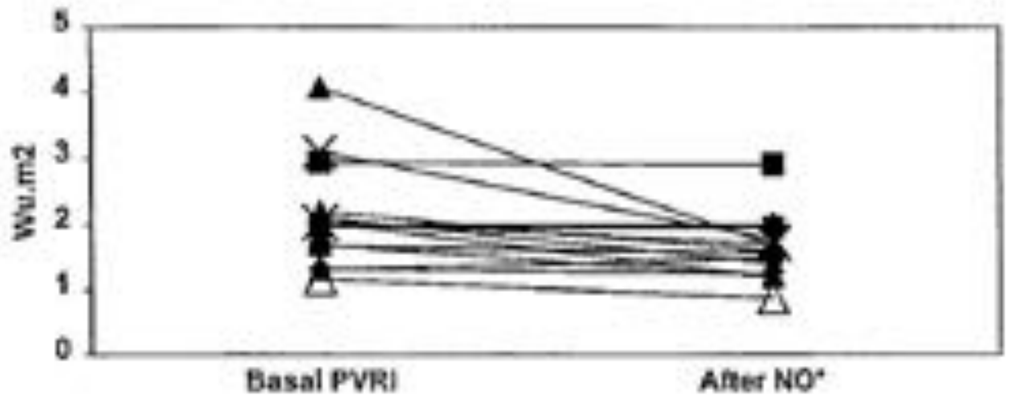


Figure 4. Effect of exogenous NO on PVRI late after Fontan operation. NO caused a significant drop of mean PVRI in the study group (*P=0.016).

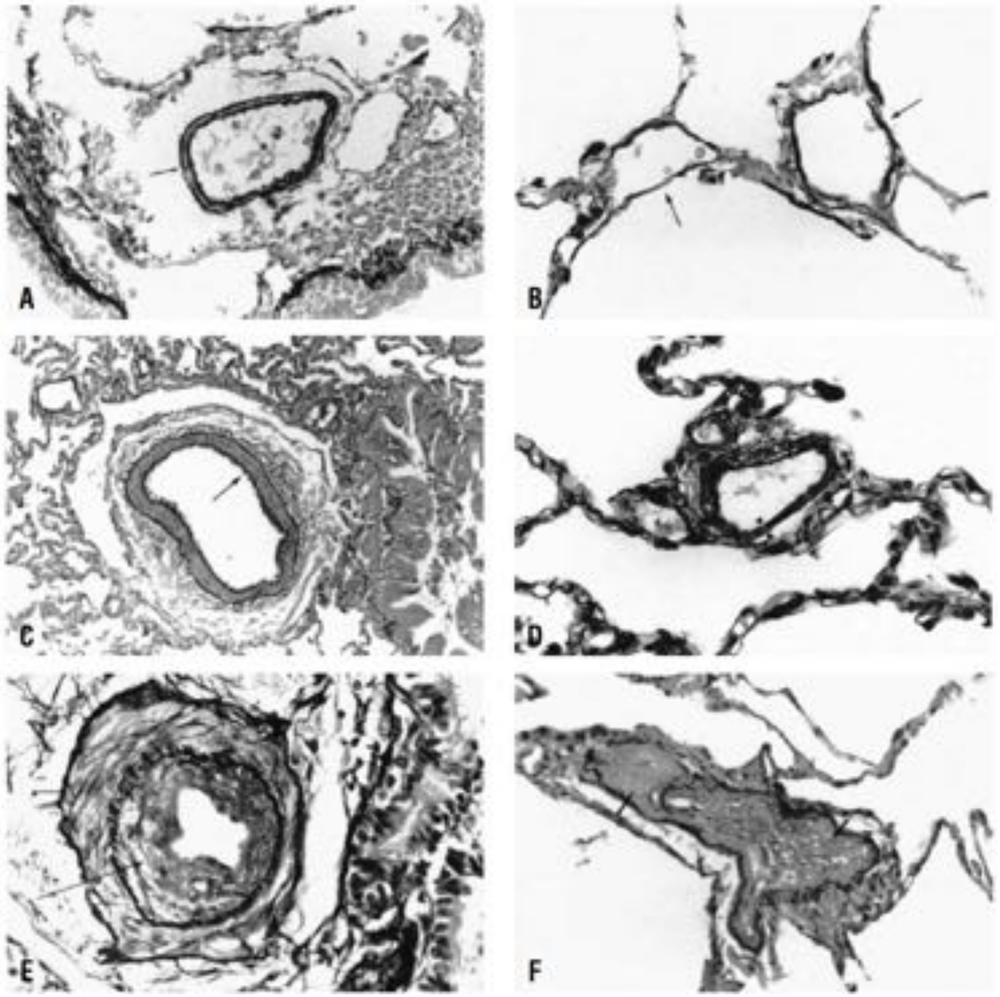
- Fontan patients have elevated PVRi
- Patients in NYHA 1 have a significantly lower mean PVRI (1.72+-0.38 WU.m2) compared with patients in NYHA 2 and 3 (2.82+/-0.88) (P=0.05)
- Significant drop in PVRi with NO°

Pulmonary endothelial dysfunction is related, at least in some part, to lack of pulsatility in the pulmonary circulation because of altered flow characteristics after Fontan operation

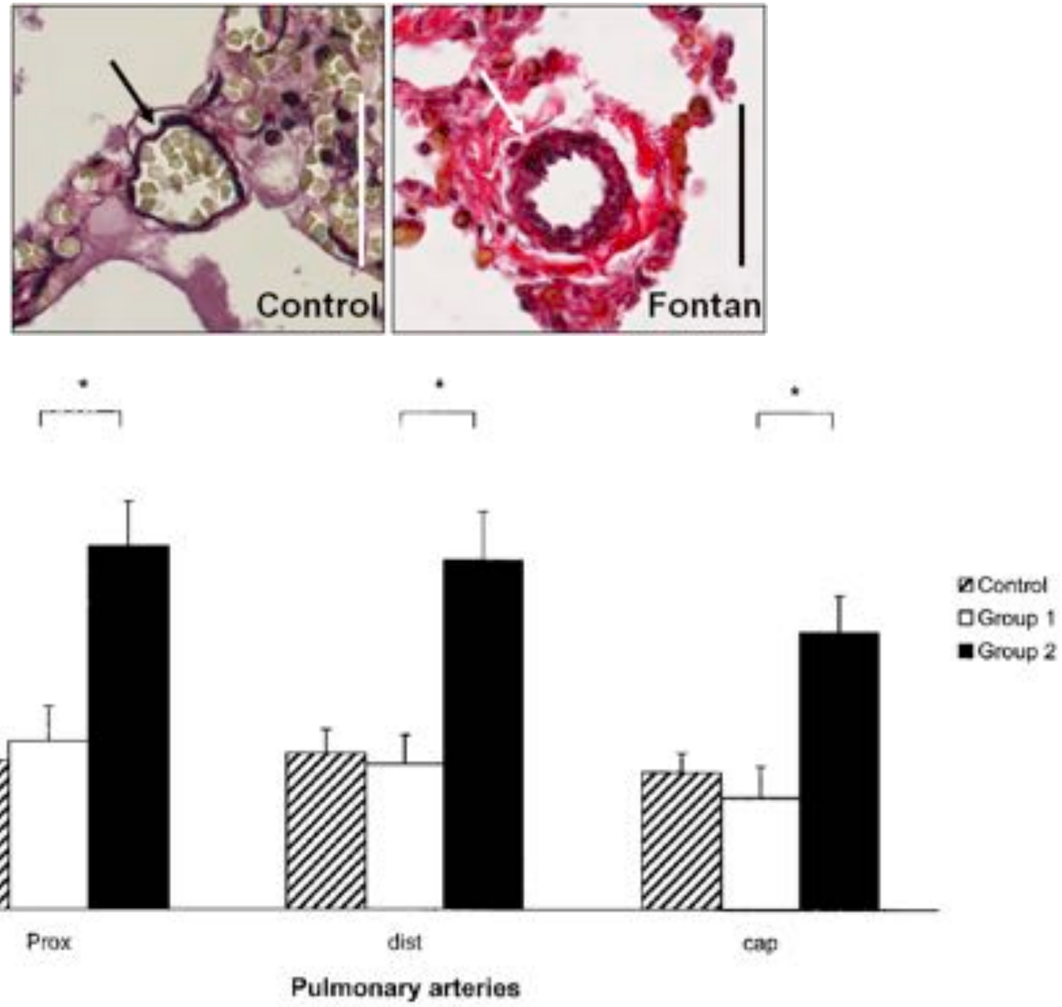
M3C

Khambadkone S et al. Circulation 2003;107:3204-8
Henaine R et al. J Thorac Cardiovasc Surg 2013;146:522-9

Vascular remodelling in TCPC



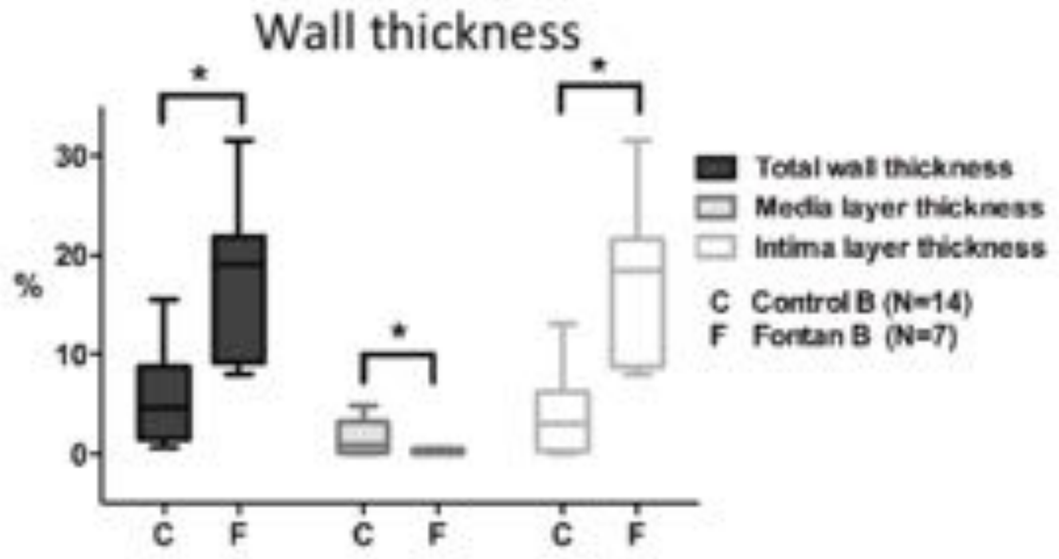
Remodeling of pulmonary arteries is present in half of patients with favorable hemodynamic at surgery and predicts outcome

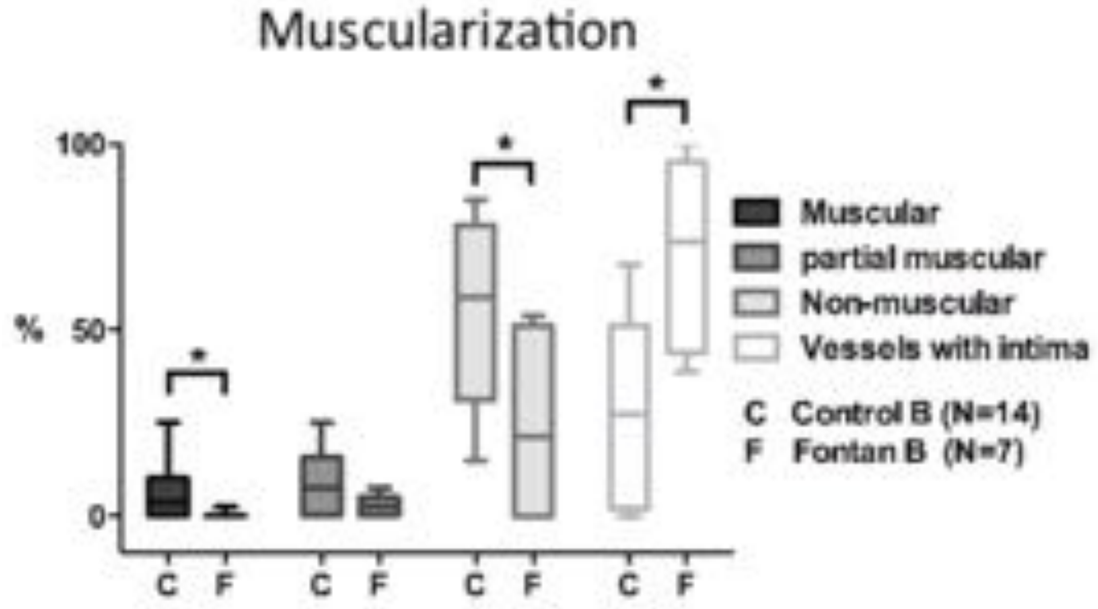


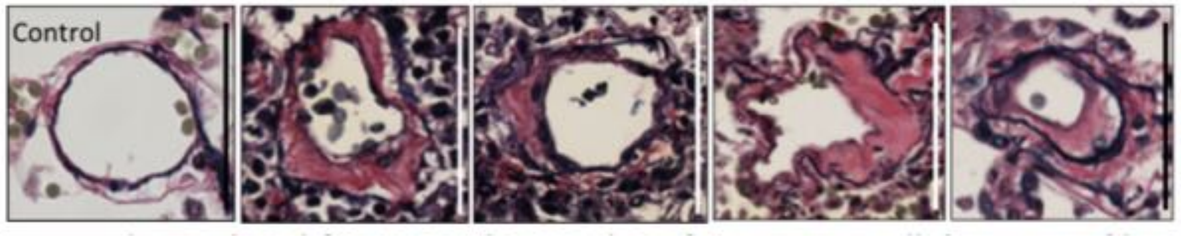
eNOS and ET1 expression is increased from baseline in « failed » Fontan procedures

Juaneda E, Hawaorth S. Br Heart J 1984
Levy M et al. J Thorac Cardiovas Surg 2002;123:263
Levy M et al. J Thorac Cardiovasc Surg 2003;125:1083

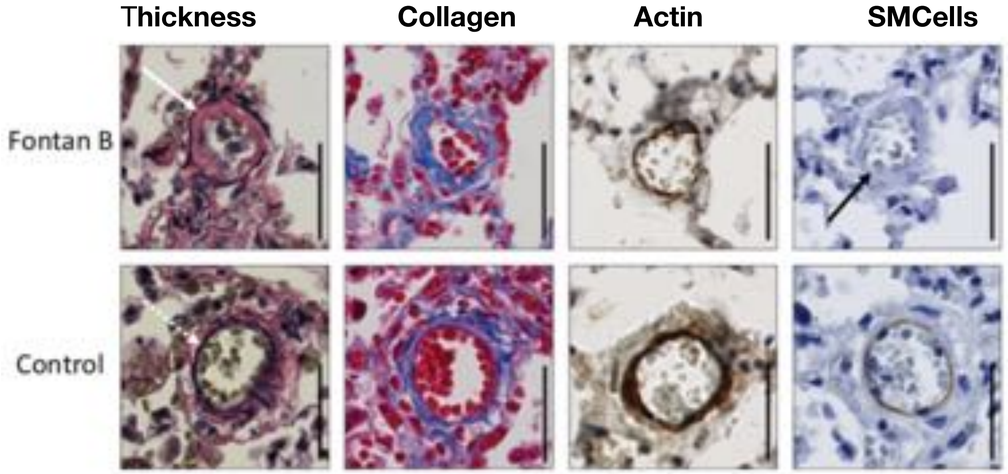
The unusual remodelling of intra-acinar pulmonary vessels in TCPC







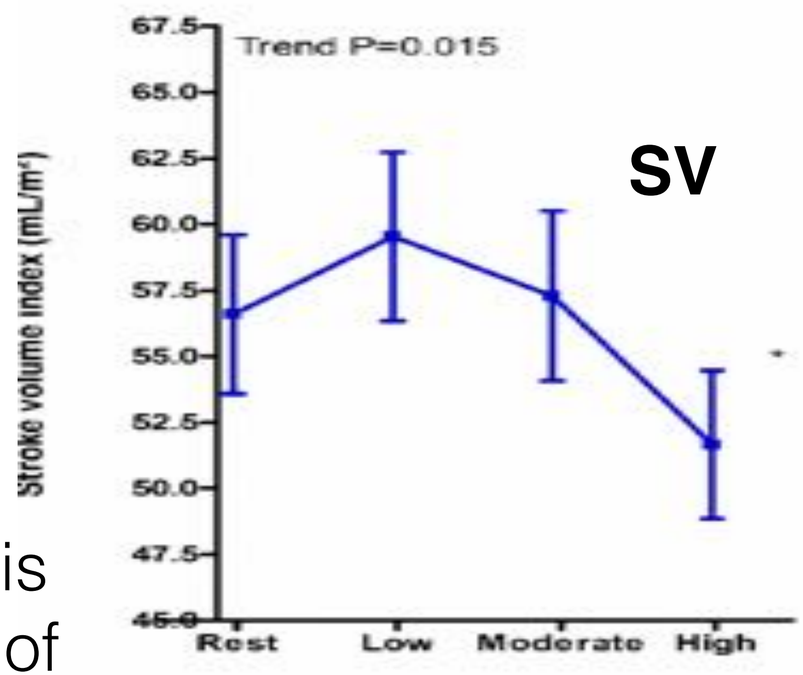
eccentric acellular intima fibrosis in the intra-acinar pulmonary vessels



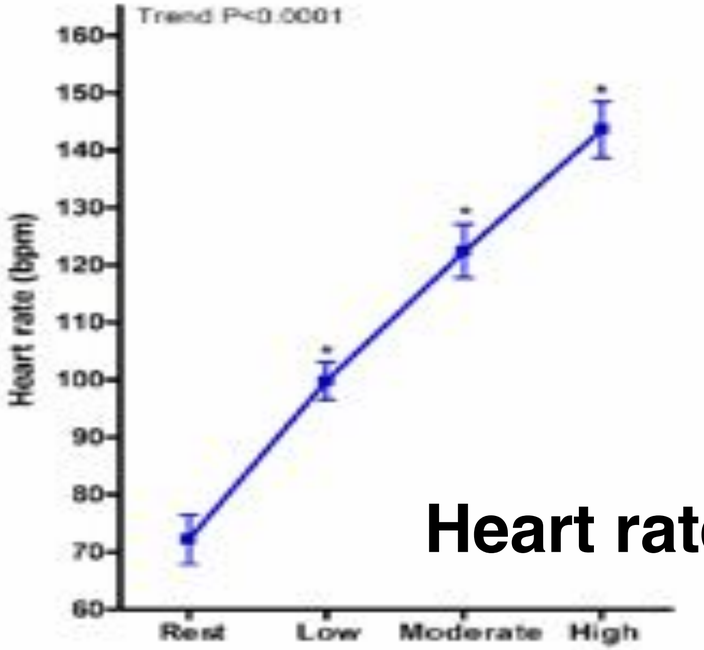
Ridderbos FJS et al.

Fontan Ergo MRI

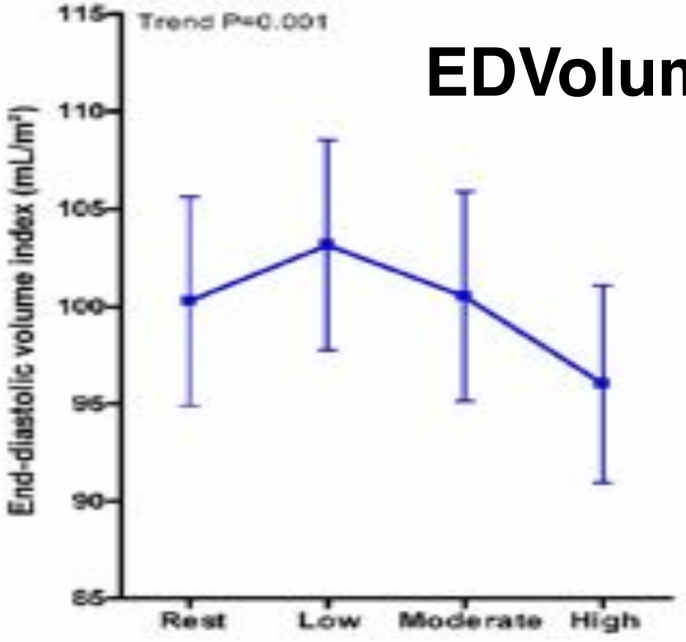
Stroke volume decrease is related to impaired filling of the single ventricle at exercise



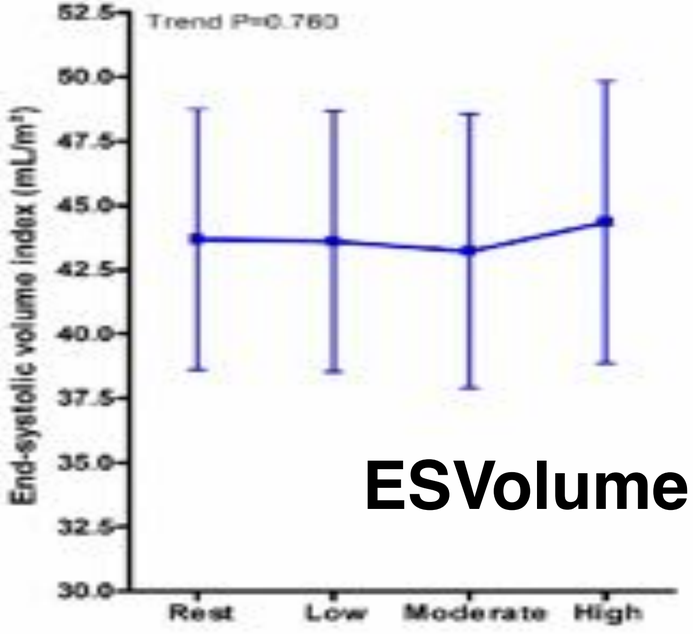
SV



Heart rate



EDVolume



ESVolume

Post-transplantation increased PVR in TCPC

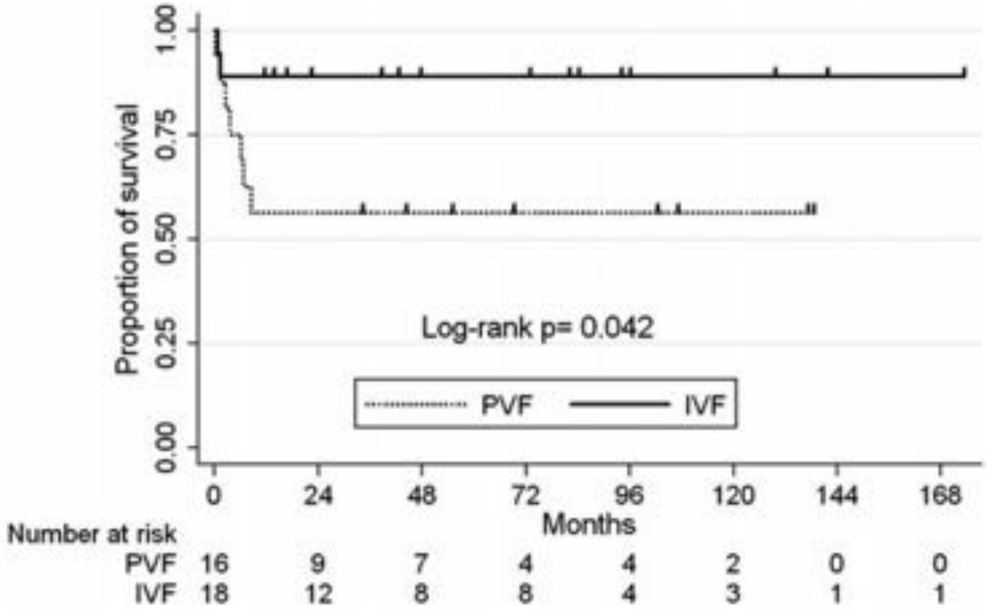
Post-transplantation PVR is elevated (2.0 Wood units · m2) in the majority of survivors past initial hospitalization (mean 3.3+/-1.7 Wood units · m2).

Only patients with early Fontan failures (<1 year) had normal post-transplantation PVR.

In paired comparisons, post-transplantation transpulmonary gradient was increased by a mean of 6.8 mm Hg (P=0.0001) relative to pretransplantation value.

Mitchell M et al. J Thorac Cardiovas Surg 2004;128:693

Fontan patients with reduced EF are different from those with preserved EF



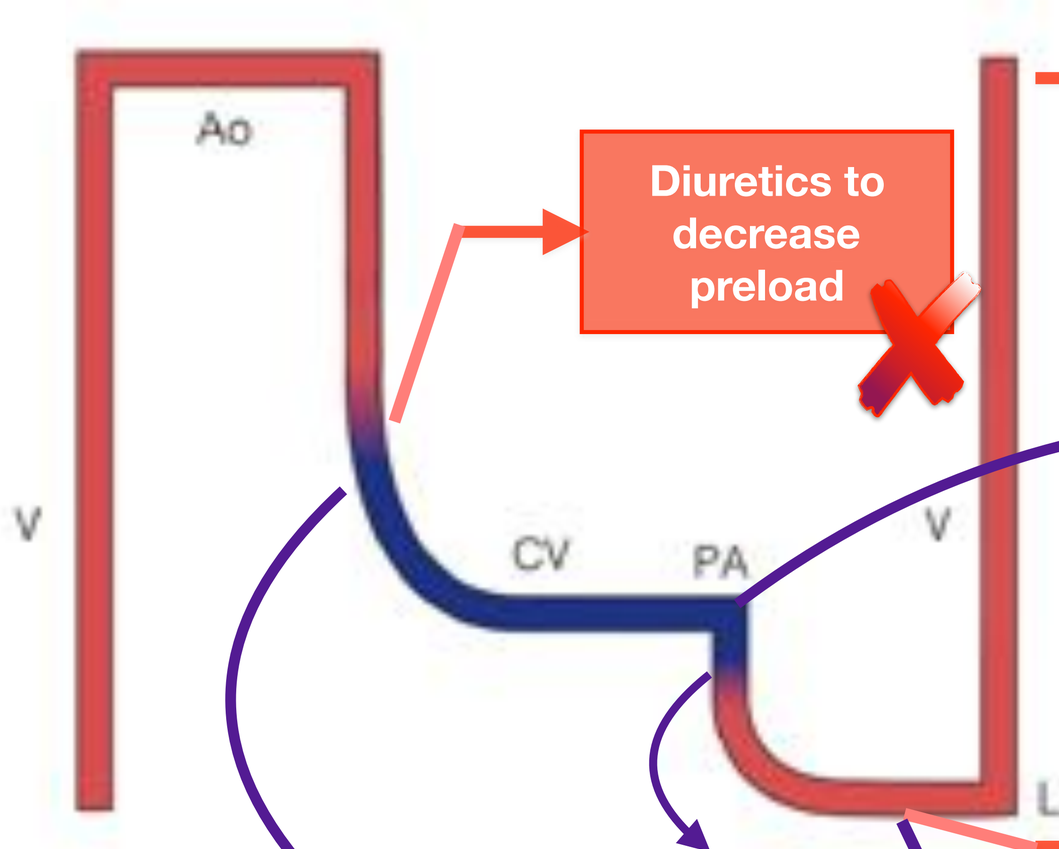
- In a group of Fontan patients undergoing transplantation, **patients with preserved EF had significantly worse outcomes than those with reduced EF** suggesting that important mechanisms other than systolic dysfunction contributed to heart failure in the former group.

- This also suggests that **preventive treatment with heart failure drugs** aiming to prevent deleterious remodeling of the SV **might not be beneficial**.

Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of death. Ann Thorac Surg. 2009;88:558–563.

Heart failure drugs in Fontan circulation

Potentially a wrong reasoning and a predictable minimal effect



Diuretics to decrease preload

ACE Inhibitors to decrease after load

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

M3C

Thank you

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

Individual experience is the brake
Indifference is the weakness
Authority argument is the threat