# Pediatric Pulmonary Vascular Disease: Pathobiology and Therapeutic Implications

## The Pediatric Pulmonary Vascular Laboratories

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The UCSF Pediatric Pulmonary Hypertension Service
DEDICATED TO EXCELLENCE IN PATIENT CARE, ADVOCACY, RESEARCH, AND EDUCATION

UCSF Benioff Children's Hospital San Francisco

# Disclosures

- None relevant to this talk
- UCSF PH service participates in industry-sponsored clinical trials

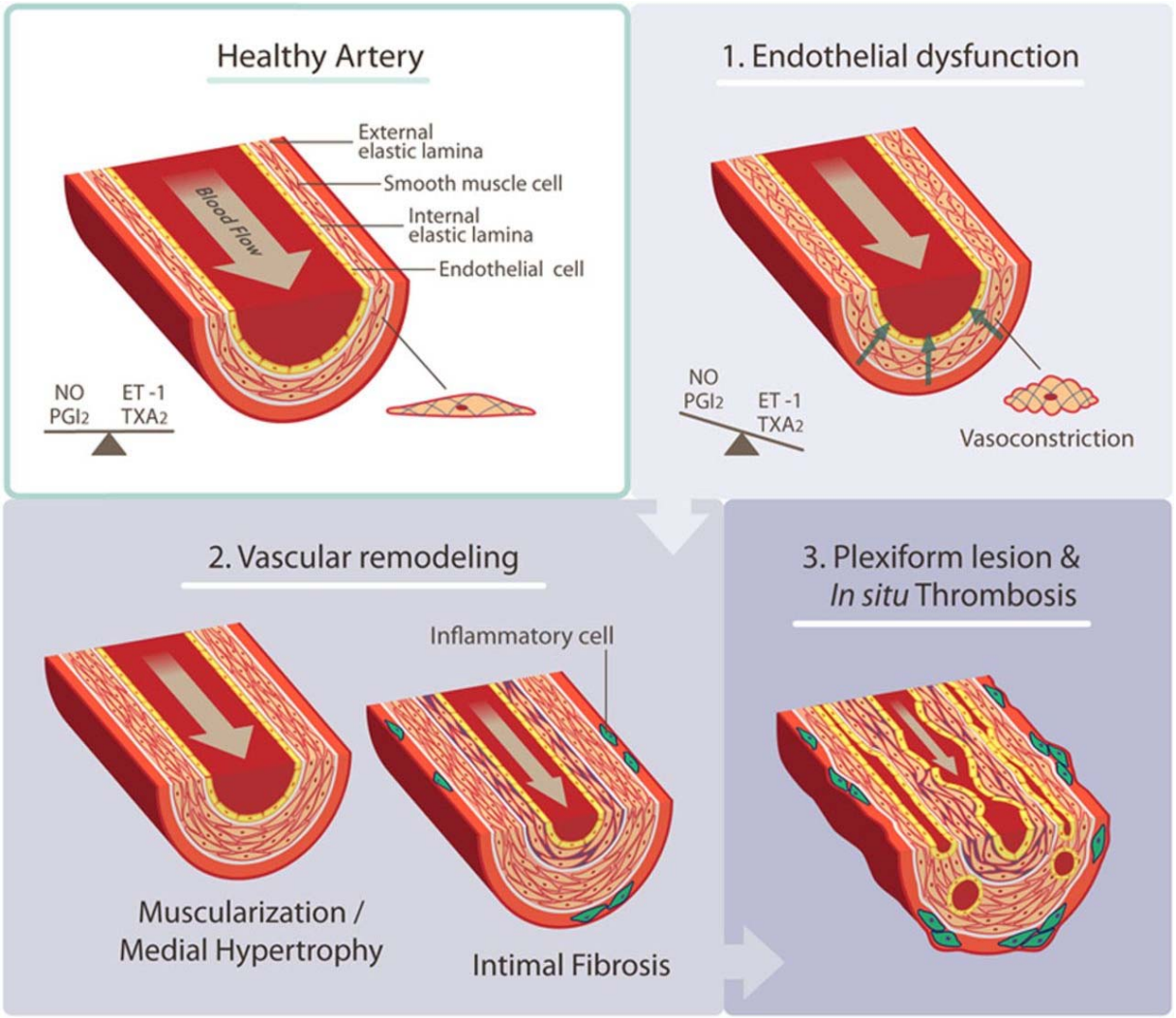
# Overview

- Pulmonary Hypertension Definition and Vascular Phenotype
- Classification
  - When PPHN Persists
  - PAH-CHD
- Therapeutic Options and Outcomes

# Pulmonary Hypertensive Vascular Disease

- Hemodynamic Disease
  - Increased pulmonary vascular pressure and resistance
    - Pulmonary Hypertension
      - PA Pressure
        - >25 mm Hg at rest; >30 mmHg at exercise
      - PVR
        - > 3 Woods units
- Structural Disease
- Functional Disease
  - Increased constriction
  - Impaired relaxation

# Pathophysiology – Progressive Structural Remodeling

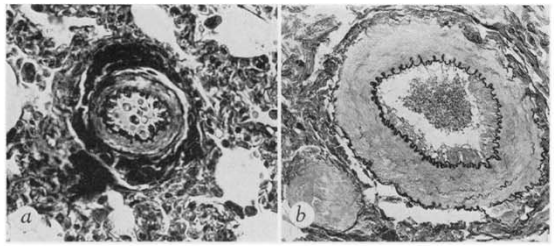


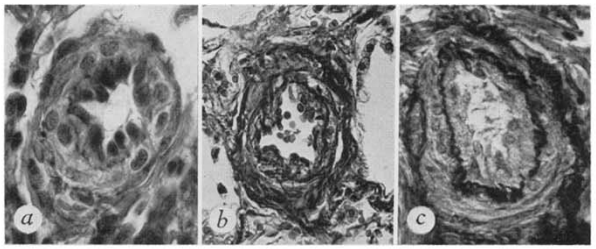
# The Pathology of Hypertensive Pulmonary Vascular Disease

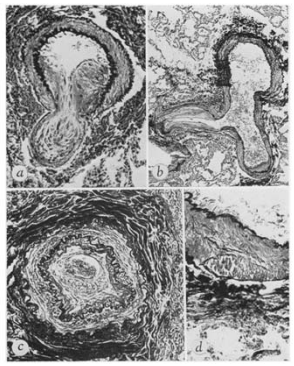
## A Description of Six Grades of Structural Changes in the Pulmonary Arteries with Special Reference to Congenital Cardiac Septal Defects

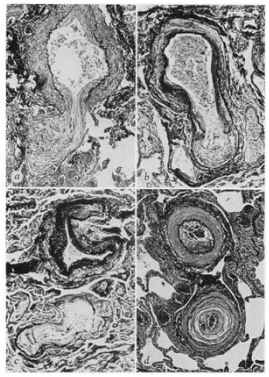
*By* DONALD HEATH, M.D., AND JESSE E. EDWARDS, M.D.

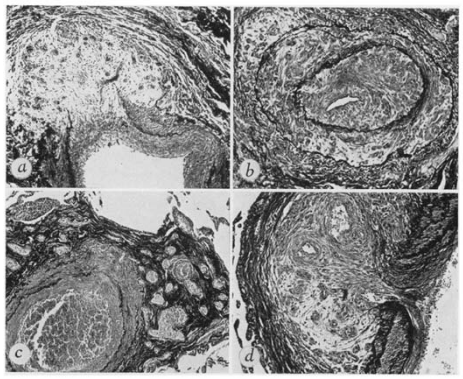
*Circulation, Volume XVIII, October 1958*

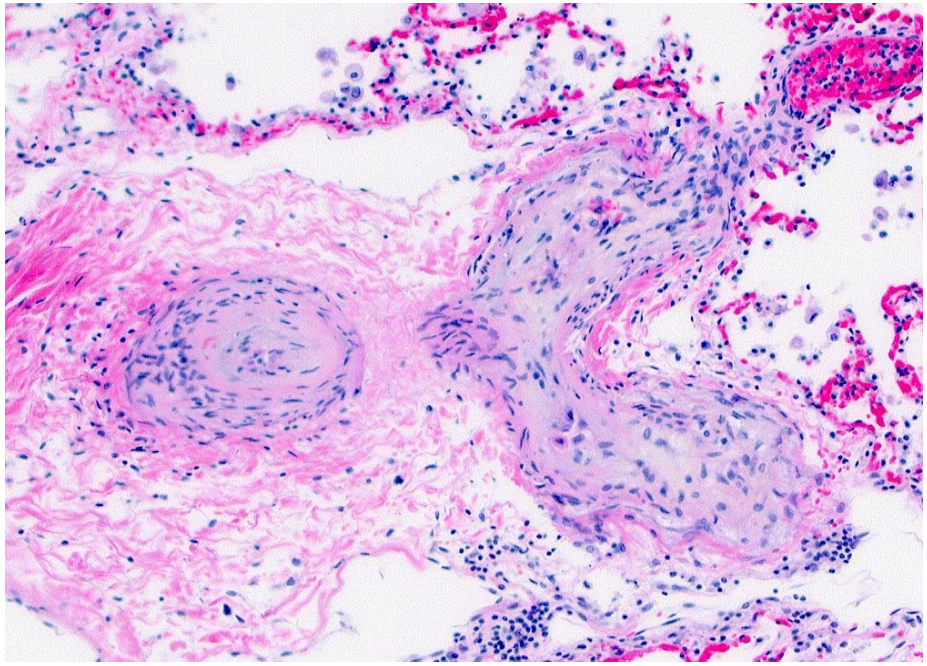


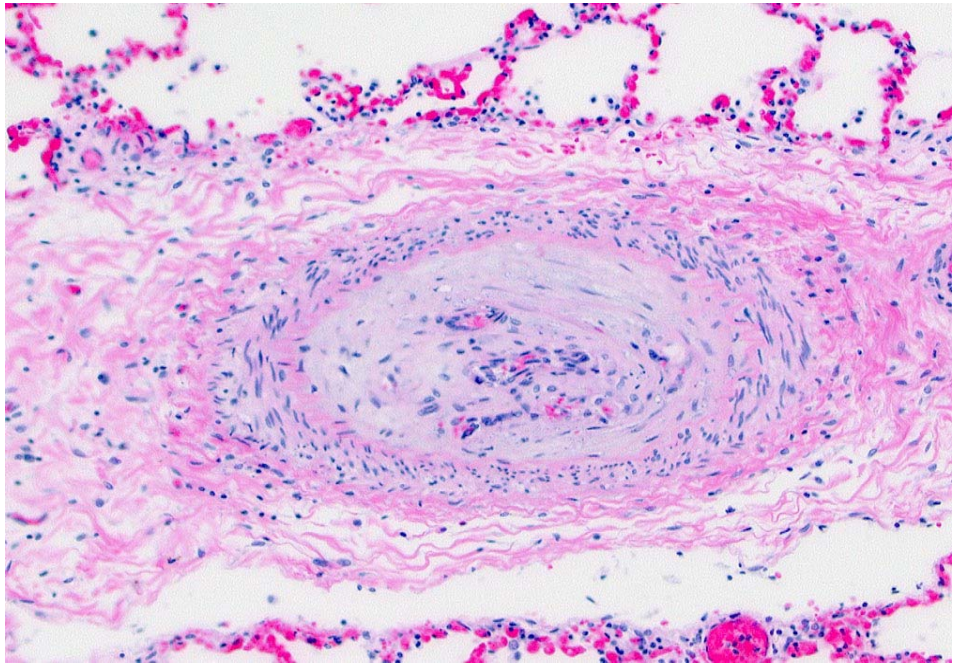


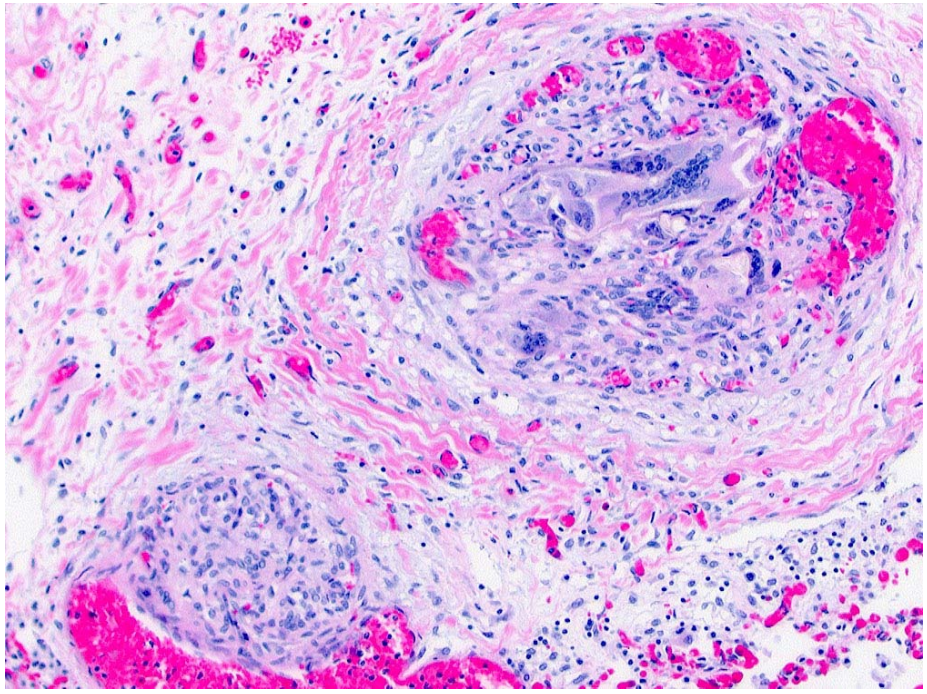


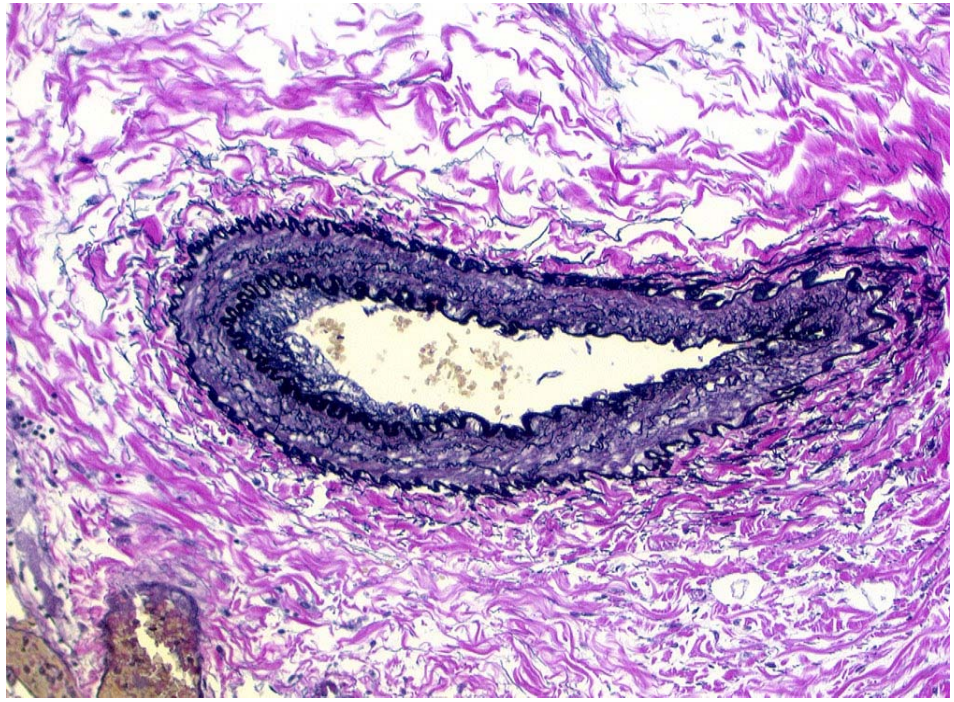




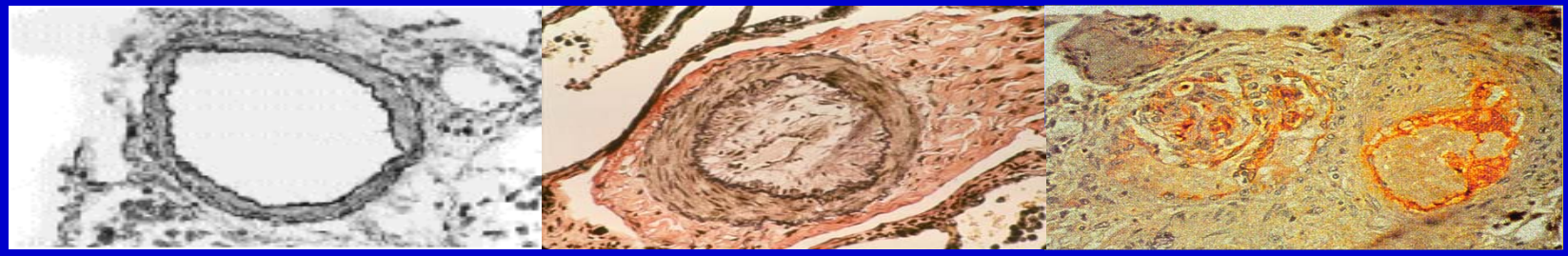








# The Role of the Right Heart: As PAH Progresses Cardiac Output Declines



Pre-symptomatic/
Compensated

Symptomatic/
Decompensating

Declining/
Decompensated

CO

PAP

PVR

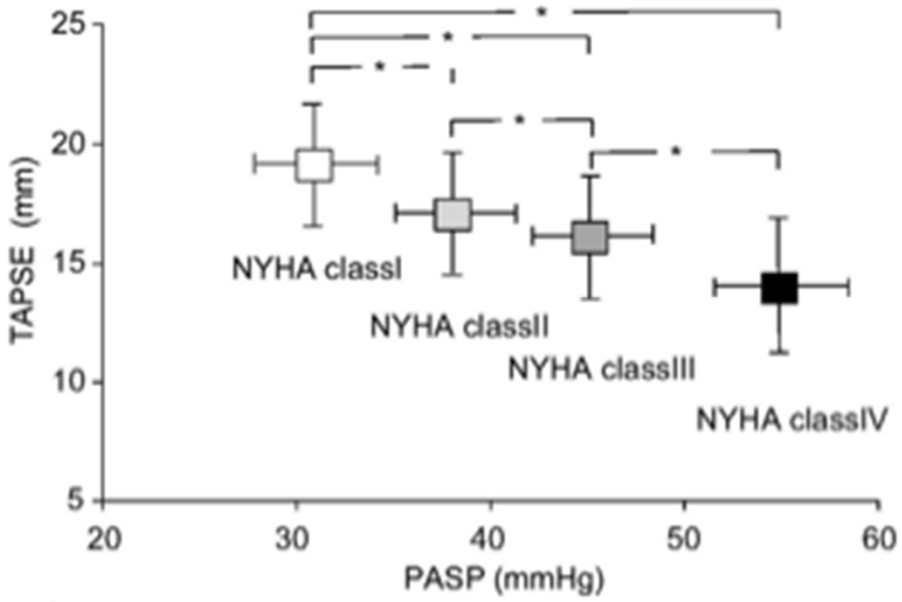
**Symptom Threshold**

**Right Heart Dysfunction**

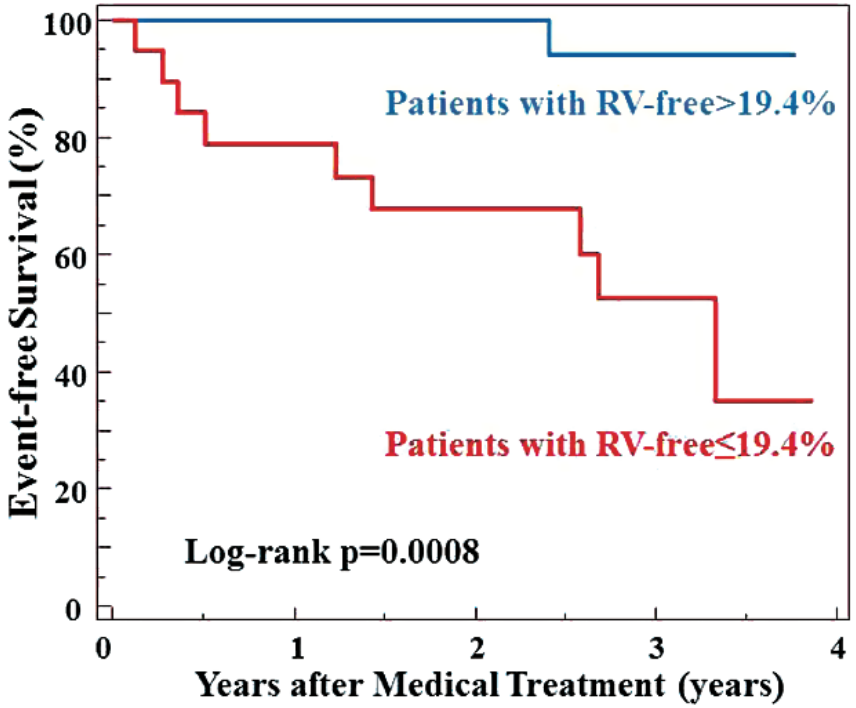
Time

# Indices of RV Function Correlate with PAH Prognosis

TAPSE




Speckle-Tracking Strain




Guazzi *AJP Heart Circ* 2013
Motoji *Circ J 2013*

# Pediatric Symptoms (Heart Failure)

**Early Symptoms**

- Dyspnea
- Fatigue
- Exercise Intolerance

**Late Symptoms**

- Cyanosis with exertion
- Chest pain
- Leg Swelling
- Abdominal fullness/pain
- Anorexia
- Seizures
- Syncope
- Dyspnea at rest

**Symptoms in Infants**

- Failure to thrive
- Decreased activity
- Diaphoresis
- Irritability

**Often have history of RAD**

# Clinical features of paediatric pulmonary hypertension: a registry study

*Rolf M F Berger, Maurice Beghetti, Tilman Humpl, Gary E Raskob, D Dunbar Ivy, Zhi-Cheng Jing, Damien Bonnet, Ingram Schulze-Neick, Robyn J Barst*

| | All PH confirmed |
|---|---|
| Patients | 362 (100%) |
| Dyspnoea with exertion | 235 (65%) |
| Fatigue | 149 (41%) |
| Syncope | 73 (20%) |
| Cyanosis with exertion | 64 (18%) |
| Cough | 48 (13%) |
| Cyanosis with rest | 44 (12%) |
| Dyspnoea with rest | 39 (11%) |
| Chest pain or discomfort | 39 (11%) |
| Near-syncope | 28 (8%) |
| Dizziness | 25 (7%) |
| Palpitations | 22 (6%) |
| Pallor with exertion | 17 (5%) |
| Irritability | 17 (5%) |

Data are number (%). Patients from pulmonary separately in this table. Full details are provided arterial hypertension. FPAH=familial pulmonary

N=362

Mean age 7.1 years

**Time from onset of symptoms to diagnosis – 17 months**

Lancet 2012

**Table 1** Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
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   - 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″. Persistent pulmonary hypertension of the newborn (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 and congenital cardiomyopathies**

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
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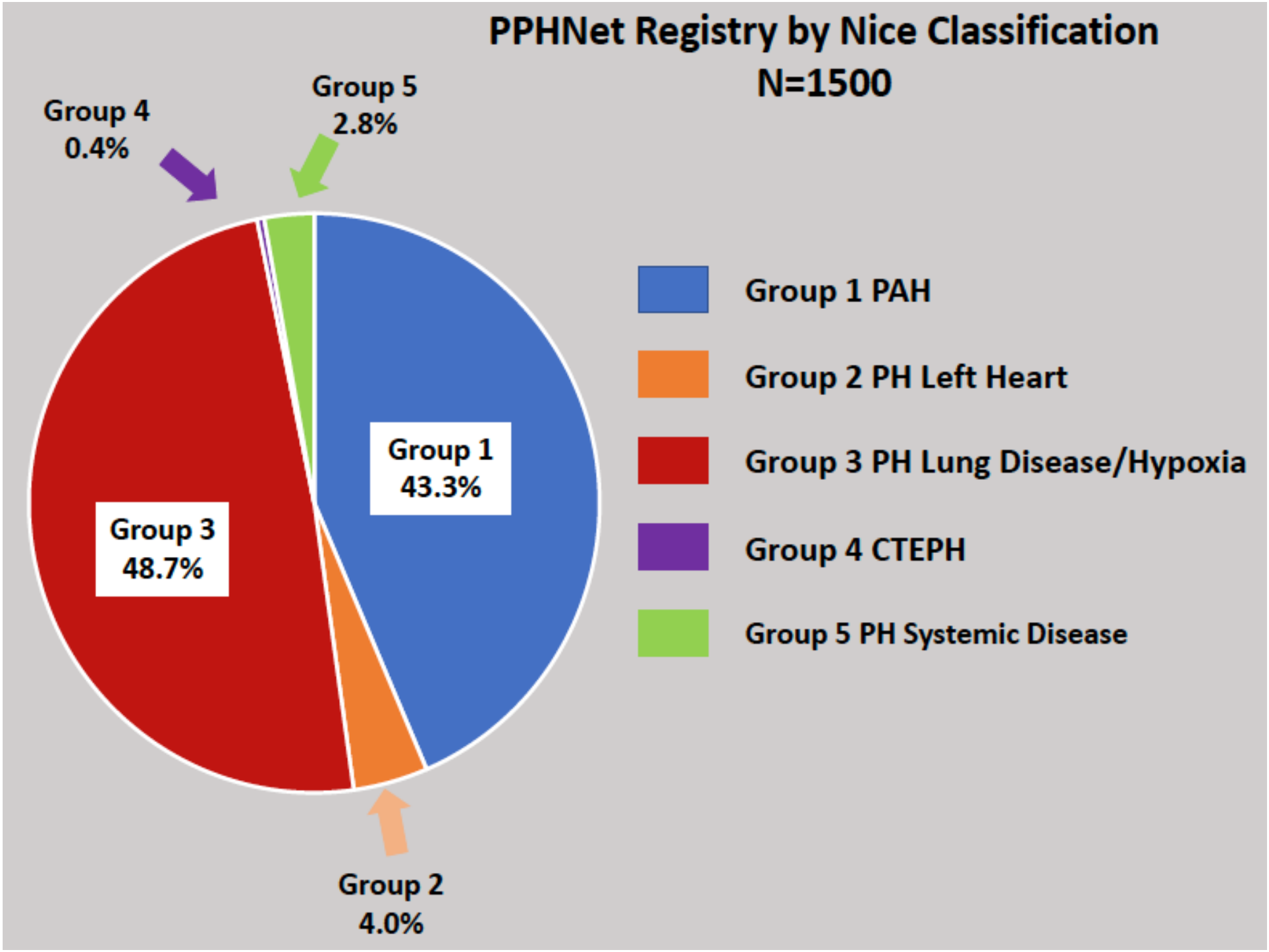
4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

# 2014 Nice Updated Classification

GROUP 1: PAH
GROUP 2: LEFT HEART DISEASE
GROUP 3: LUNG/HYPOXIA DISORDERS
GROUP 4: CTEPH
GROUP 5: OTHER


PPHNet Registry by Nice Classification
N=1500
Group 4
0.4%
Group 5
2.8%
Group 1
43.3%
Group 3
48.7%
Group 2
4.0%
Group 1 PAH
Group 2 PH Left Heart
Group 3 PH Lung Disease/Hypoxia
Group 4 CTEPH
Group 5 PH Systemic Disease

# Pathobiology of Pulmonary Vascular Disease

1. Endothelial Injury: Toxin/Mechanical Forces
2. Inflammation
3. Altered Metabolism
4. Coagulation disorders
5. Extracellular matrix and potassium channel aberrations
6. Genetic Predispositions

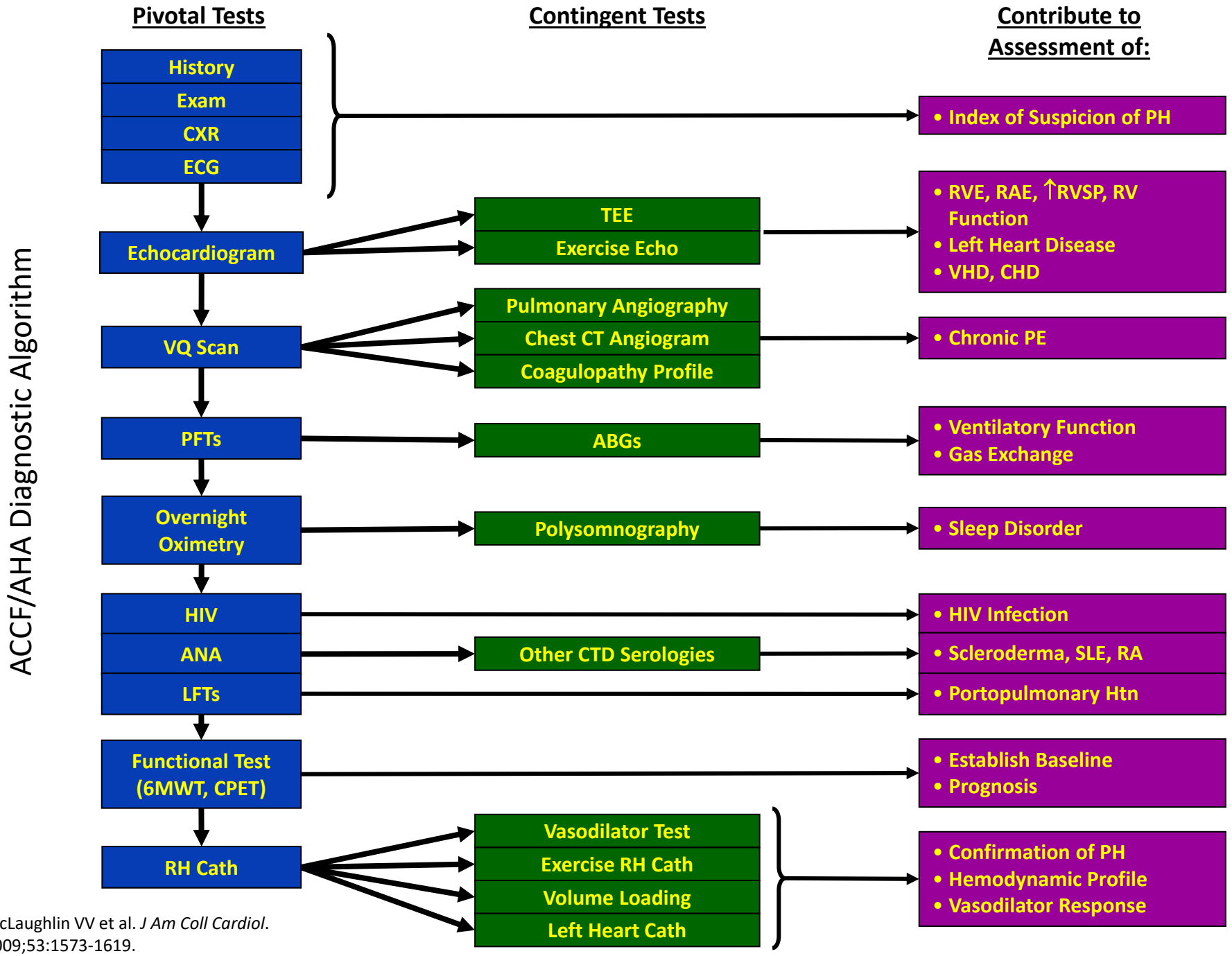
2011 Pediatric PVRI Task Force

# Diagnostic Algorithm for PH ACCF/AHA Expert Task Force 2009

- Requirements:
  - thorough evaluation
  - high quality studies and interpretation

- **Establish a suspicion of PAH**
- **Confirm the diagnosis of PH (RHC)**
- **Classify the type of PH**
- **Determine the disease severity**
- **Select the appropriate treatment for patients with PAH**

McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

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5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

## Genes Associated with an Increased Risk of Pulmonary Arterial Hypertension

- **BMPR2** (>70% of HPAH)
- ACVRL1 (HHT)
- ENG (HHT)
- SMAD 9 (TGFβ)
- **EIF2AK4** (PVOD, PCH)
- CAV1 (altered caveolar formation)
- **SOX 17** (Wnt/β catenin, Notch)
- **TBX4** (Small-Patella Syndrome)
- **FOXF1** (ACD)
- ATP13A3 (lung vascular remodeling)
- GDF2 (BMP9)
- AQP1
- KCNK3 ($K^+$ channel, TASK-1)

# Importance of Identifying Genetic/Syndromic Associations

- Aid in identifying an etiology and/or diagnosis
- Aid in identifying mechanism of disease
- Aid in guiding treatment strategy
- Aid in identifying potential novel individualized therapeutic targets

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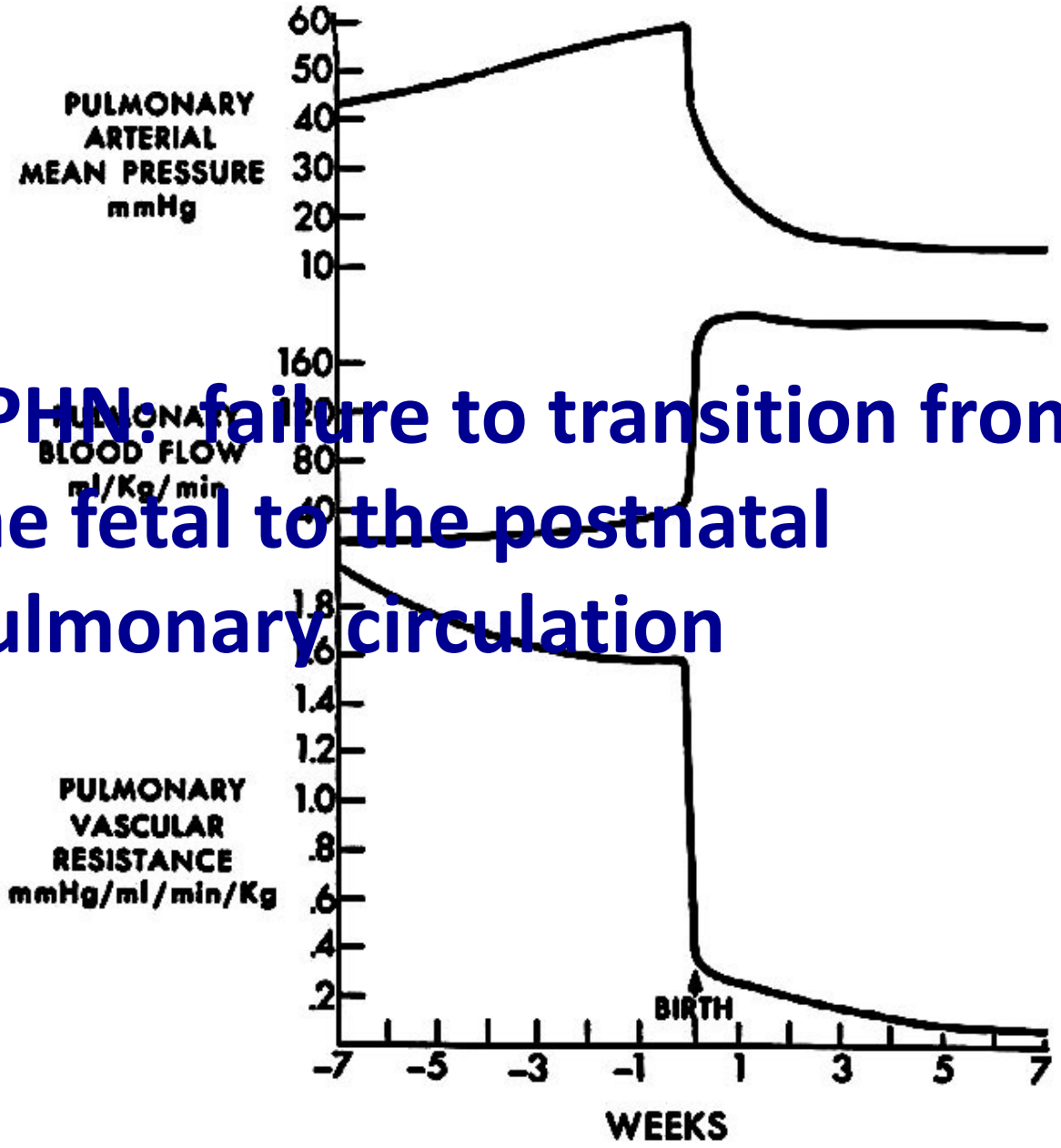



**PPHN: failure to transition from the fetal to the postnatal pulmonary circulation**

# PPHN

- **Abnormal parenchyma/increased vasoconstriction (maladaptation)**
  - **meconium aspiration syndrome**
  - **respiratory distress syndrome**
  - **pneumonia**
- **Normal parenchyma/increased vasoconstriction (maldevelopment)**
  - **remodeled pulmonary vasculature (idiopathic PPHN)**
- **Hypoplastic vasculature/ (+/-) increased vasoconstriction (hypodevelopment)**
  - **congenital diaphragmatic hernia**
- **Irreversible**
  - **alveolar capillary dysplasia**
  - **mutations of surfactant protein-B and the ATP-binding cassette family member A3**
  - **pulmonary lymphangiectasis**

# When PPHN Persists?

- Alveolar Capillary Dysplasia (FOX F1)
- Pulmonary Interstitial Glycogenosis
- TBX4 Neonatal Respiratory Failure
- Surfactant Disorders
- Pulmonary Lymphangiectasis

- Evaluation:
  - CT Angio
  - Genetic Testing
  - **Lung Biopsy**

# Alveolar Capillary Dysplasia

- Presentation:
  - Classic – refractory PPHN in neonatal period
  - Reports of atypical later presentations
- Course:
  - Refractory to therapy (transient response not uncommon)
  - Fatal; without lung transplantation
- Associated anomalies: GI, Cardiac, Urogenital
- Diagnosis: characteristic histology
- Genetics: ~10% familial; 40-80% associated with FOXF1 mutations

# FOXF1

- Member of Forkhead box transcription factors
- Regulated by Sonic hedgehog signaling
- Plays a role of embryonic lung development
- Serotonin transporter protein is a downstream target
- Mutations or deletions are associated with 40-80% of ACD cases

# T-box Factor 4

- Located on chromosome 17, region q23.2
- Expressed in a variety of tissues during organogenesis
- Loss of TBX4 disrupts
  - Hindlimb and pelvic development
  - Respiratory system development
  - Early embryonic vascularization
- Mutations of TBX4 associated with small patella syndrome (autosomal dominant)
- Mutations associated with childhood PAH
- Mutations associated with neonatal PH and respiratory failure

# Phenotypical Spectrum of TBX4 Mutations

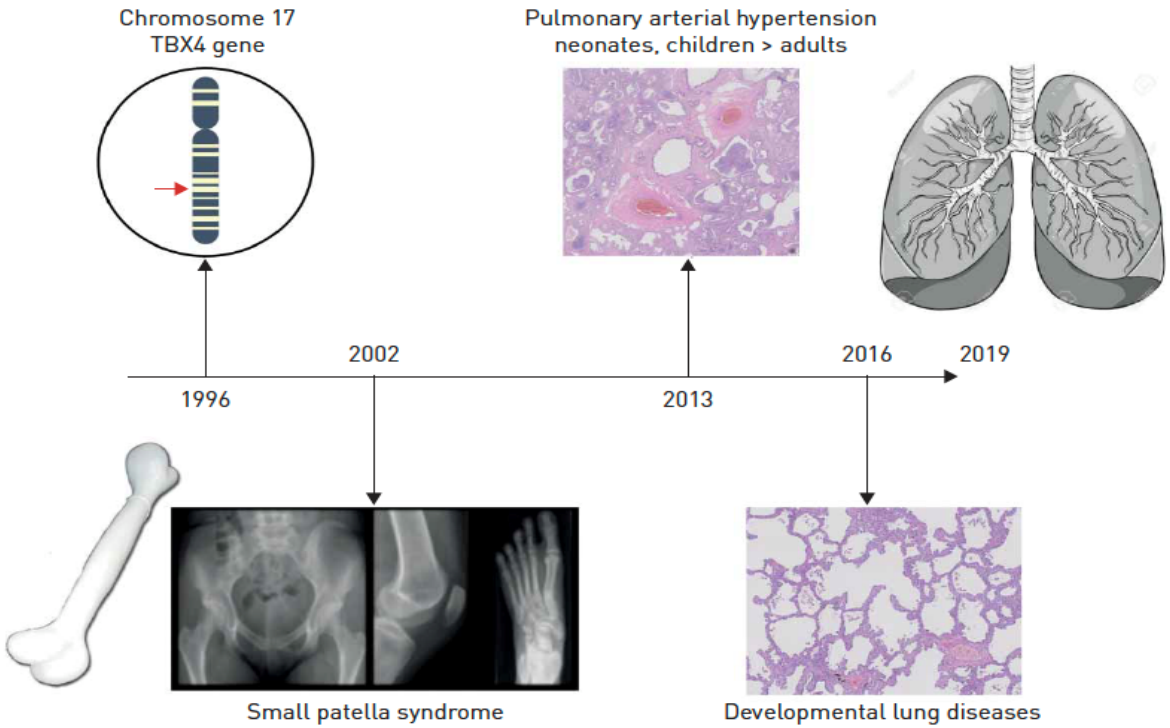
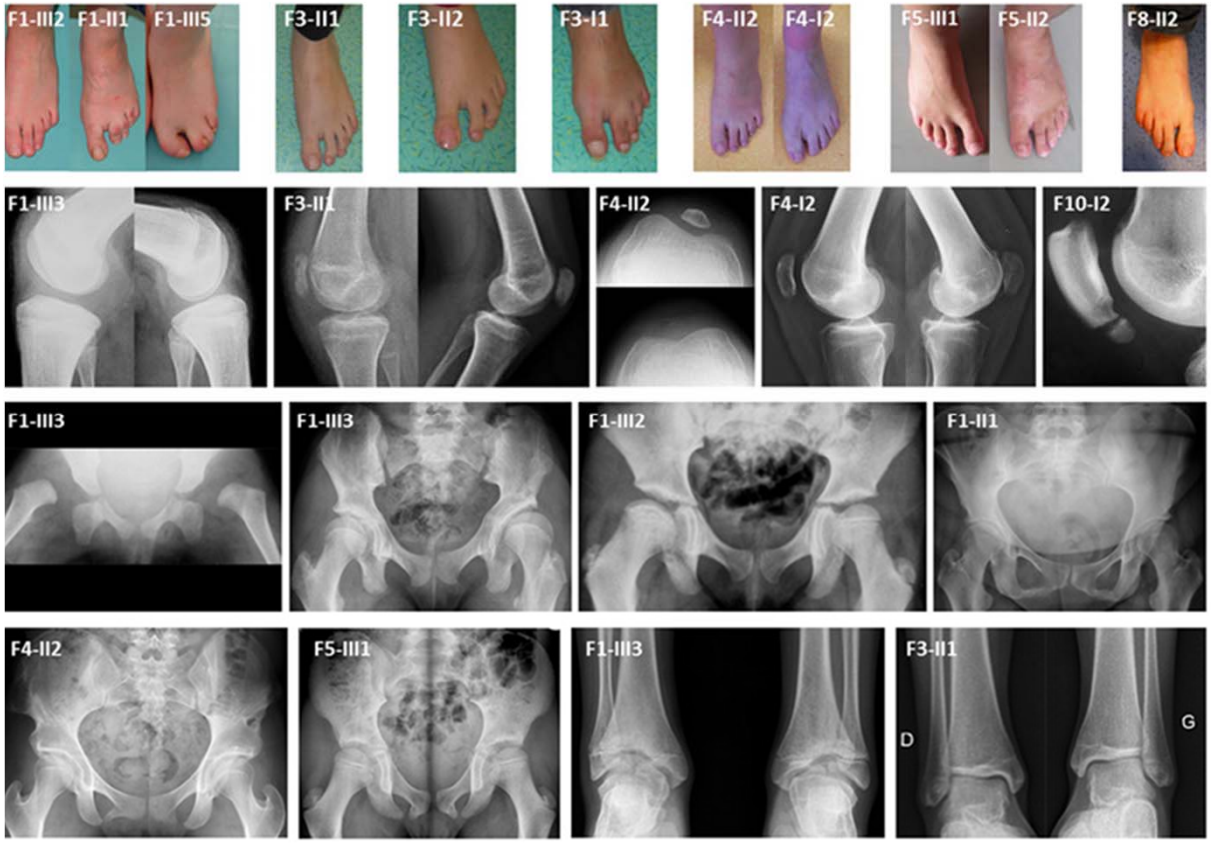



FIGURE 1 The ever-expanding phenotypical spectrum of TBX4 mutations since the discovery of the gene in 1996.

Berger et al Eur Respir J 2019

# Small Patella Syndrome



# Incidence of TBX4-induced Pediatric Onset PAH (155 Pediatric and 257 Adult-onset PAH)

**A**

| Gene | | Pediatric (n=155) | Adult (n=257) | Enrichment rate | p-value |
|---|---|---|---|---|---|
| ***BMPR2*** | IPAH, n (%) | 13 (10%) | 16 (9%) | 1.0 | 0.64 |
| | FPAH, n (%) | 14 (56%) | 42 (53.2%) | 1.1 | 0.84 |
| ***TBX4*** | IPAH, n (%) | 10 (7.7%) | 0 | N/A | <0.0001 |
| | FPAH, n (%) | 2 (8%) | 1 (1.3%) | 6.2 | 0.04 |
| **Other*** | IPAH, n (%) | 5 (3.8%) | 3 (1.7%) | 2.2 | 0.07 |
| | FPAH, n (%) | 4 (16%) | 10 (12.7%) | 1.4 | 0.52 |

*Other: *ACVRL1, BMPR1A, BMPR1B, CAV1, EIF2AK4, ENG, KCNK3, SMAD4* and *SMAD9*

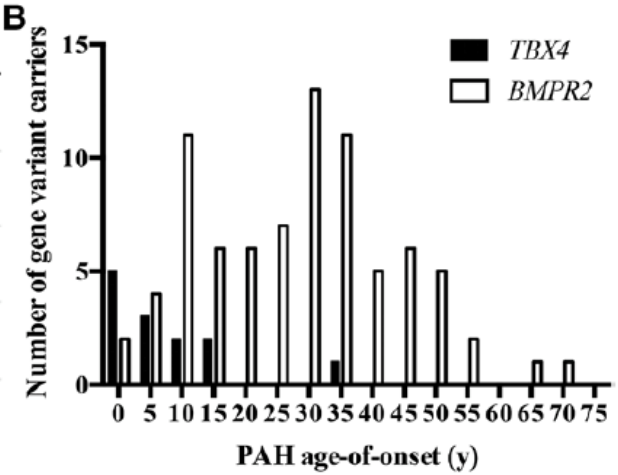



**Figure 2. Role of *TBX4* in pediatric-onset pulmonary arterial hypertension (PAH).**
**A**, Enrichment of rare, predicted deleterious variants in *TBX4*, but not other known risk genes, in pediatric-onset cases. *P* values were calculated by binomial tests. **B**, Younger age of disease onset for *TBX4* variant carriers compared with *BMPR2* variant carriers ($P<0.0001$, Mann–Whitney *U* test).

Zhu et al. Circ Genomics Precis Med 2018

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Brief Report

# Fatal Pulmonary Hypertension Associated with Short-Term Use of Fenfluramine and Phentermine

Eugene J. Mark, M.D., Eva D. Patalas, M.D.,
Howard T. Chang, M.D., Ph.D.,
Richard J. Evans, M.D., and Stanton C. Kessler, M.D.

August 28, 1997

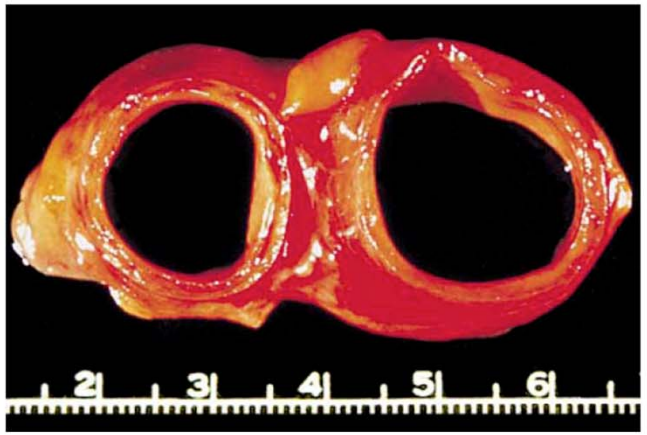


**Figure 1.** Cross Section of the Ascending Aorta (on the Left) and the Pulmonary Trunk (on the Right).
The pulmonary trunk is larger than the aorta, which is an abnormal finding indicative of pulmonary hypertension.

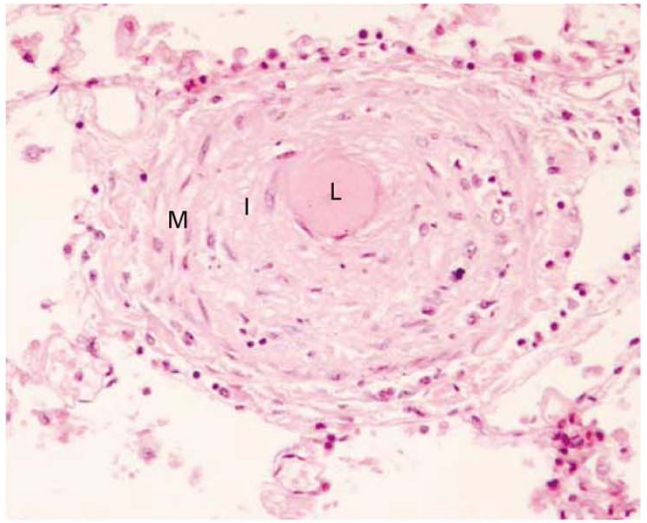


**Figure 2.** Pulmonary Hypertension with Marked Intimal (I) and Medial (M) Hyperplasia in a Muscular Pulmonary Artery (Hematoxylin and Eosin, ×20).
The lumen (L) is one fourth the normal diameter.

Likely
Amphetamines
L-tryptophan
Methamphetamines
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s, vascul
disease,
ic renal
on dialysis

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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 abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary hypertension with unclear multifactorial mechanisms**
5.1. **Hematologic disorders: myeloproliferative disorders, splenectomy**
5.2. **Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis:** lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

# PVOD – DO NO HARM
# Pulmonary Edema with Initiation of Therapy in Post-Capillary PH

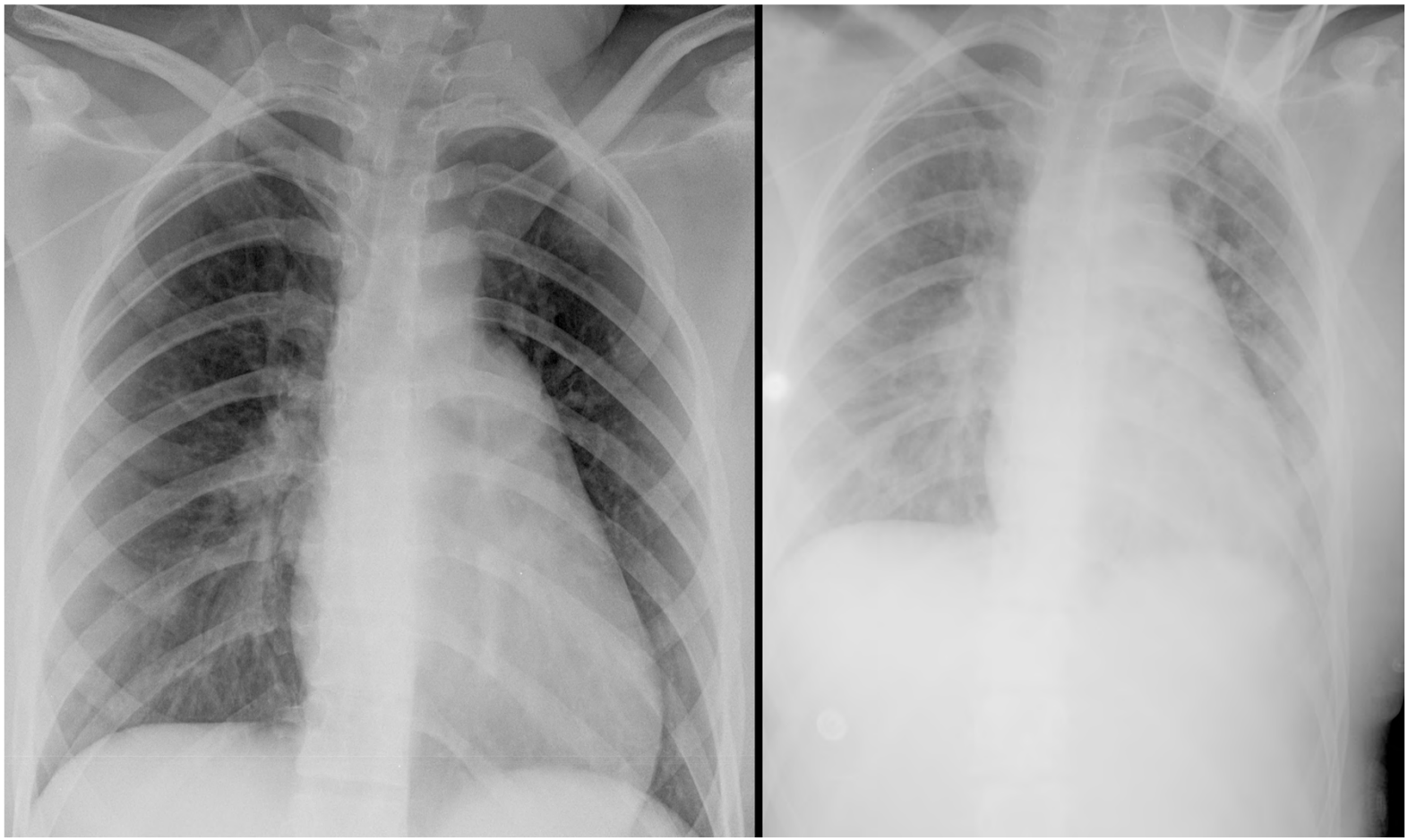

**Table 2** Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. **Heritable**
1.2.1. **BMPR2**
1.2.2. **ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3. **Unknown**
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. **Schistosomiasis**
1.4.6. **Chronic hemolytic anemia**
1.5 Persistent pulmonary hypertension of the newborn

1′. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

2. Pulmonary hypertension owing to left heart disease
2.1. **Systolic dysfunction**
2.2. **Diastolic dysfunction**
2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia
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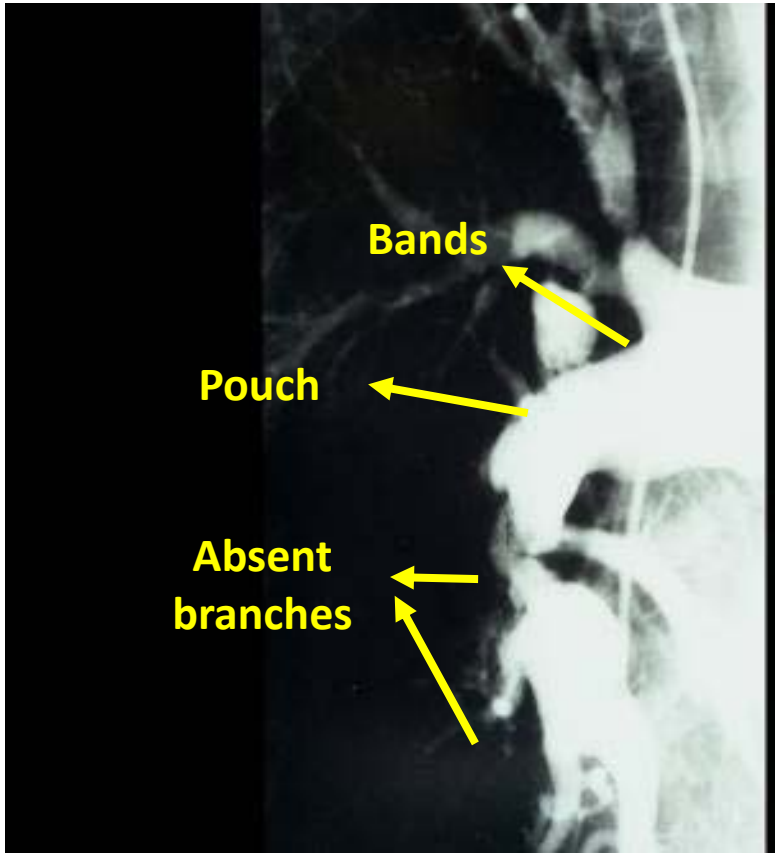
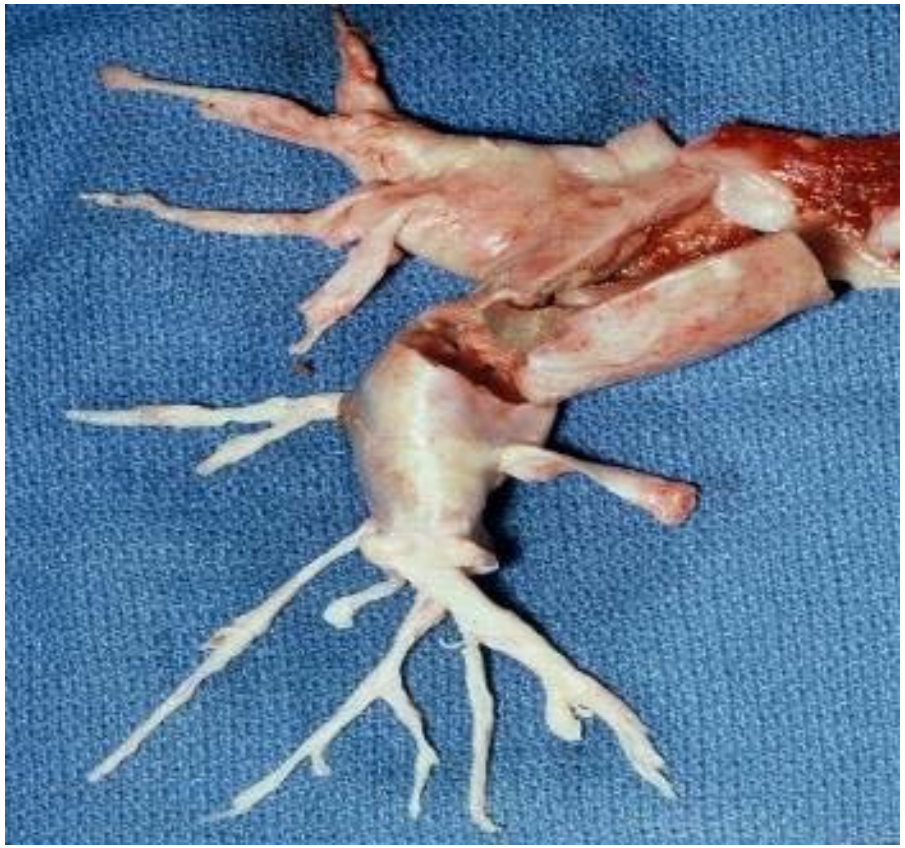
# CTEPH: A "Curable" Form of PH Not to Be Missed



- **CT appropriate when VQ in equivocal range**
- **Pulmonary angiogram required for moderate or high probability VQ and pulmonary endarterectomy considered**

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# Natural History of Pulmonary Vascular Disease Associated with CHD

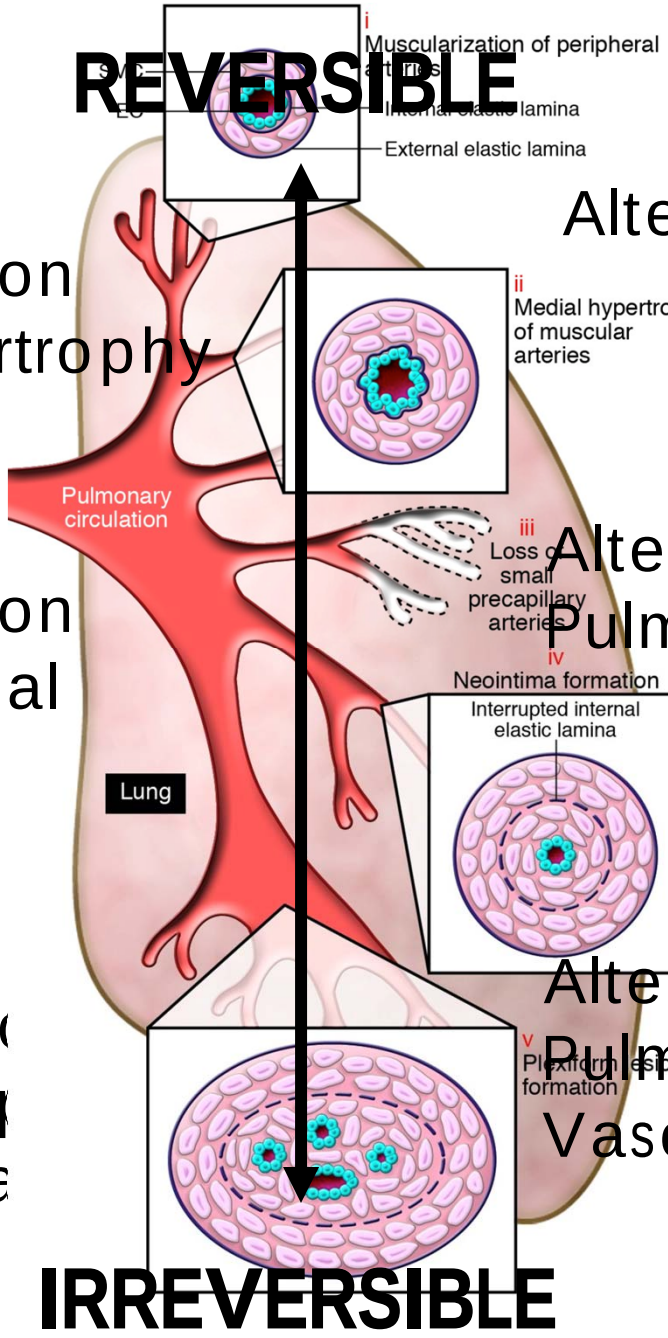
| Increased Pulmonary Blood flow | | |
|---|---|---|
| **Defect** | **Risk of PVD** | **Age** |
| **Truncus Arteriosus** | ≈ 100% | < 2 years |
| **A-V Canal** | ≈ 100% | ≈ 2 years |
| **VSD** | ≈ 15-20% | > 2 years |
| **PDA** | ≈ 15-20% | > 2 years |
| **TGA with VSD** | ≈ 70-100% | 1-2 years |
| **ASD** | ≈ 20% | > 20 years |
| **Single Ventricular Anatomy** | Variable | Variable |

| Increased Pulmonary Venous Pressure | | |
|---|---|---|
| **Defect** | **Risk of PVD** | **Age** |
| **Obstructed TAPVR** | Variable | Variable |
| **Cor Triatriatum** | Variable | Variable |
| **Mitral Stenosis** | Variable | Variable |
| **Single Ventricular Anatomy** | Variable | Variable |

**Grade A:**
Abnormal extension
Mild medial hypertrophy

**Grade B:**
Abnormal extension
Mod-severe medial hypertrophy

**Grade C:**
Abnormal extensi
Severe medial hyp
Decreased arteria
and number



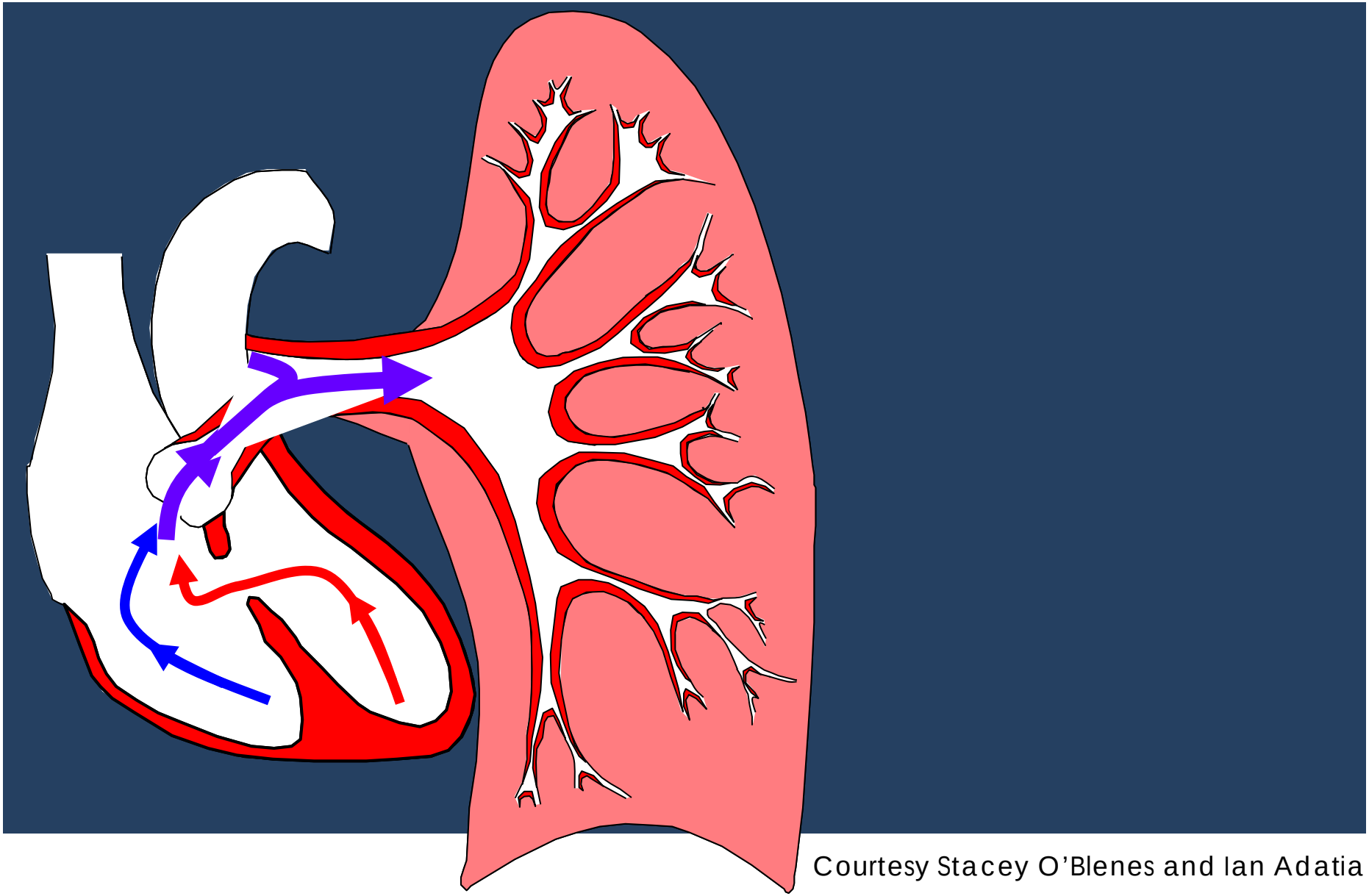

Altered Reactivity

Altered Reactivity
Pulmonary Hypertension

Altered Reactivity
Pulmonary Hypertension
Vascular Disease

Rabinovitch, *Clin. Invest.* **118**(7): 2372-2379 (2008)

# Pulmonary Vascular Changes Secondary to Increased Pulmonary Blood Flow



Courtesy Stacey O'Blenes and Ian Adatia

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 27 1958

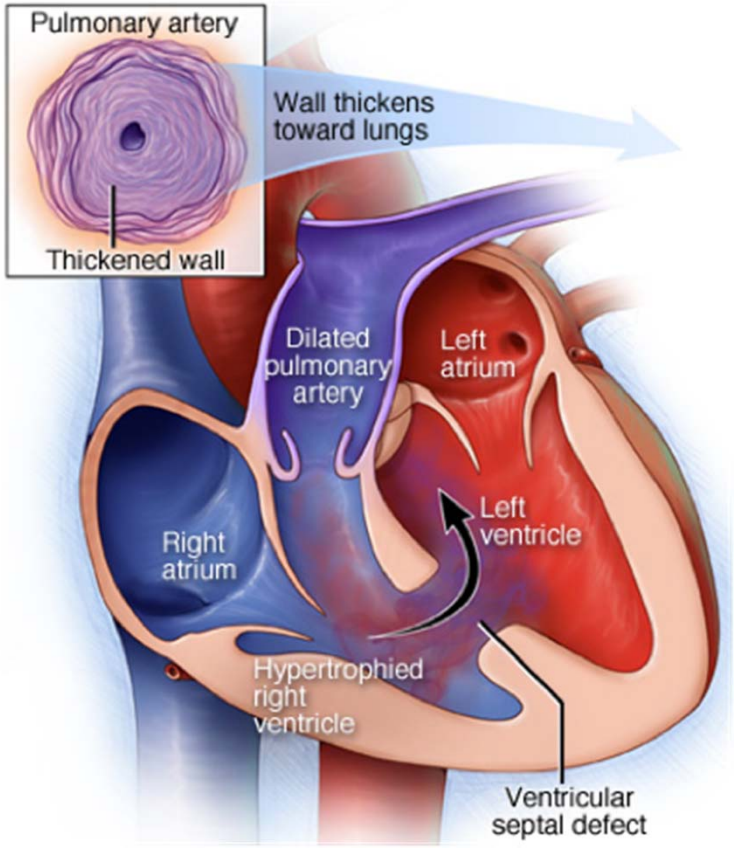
# THE EISENMENGER SYNDROME

## OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

PAUL WOOD, O.B.E., M.D., F.R.C.P.

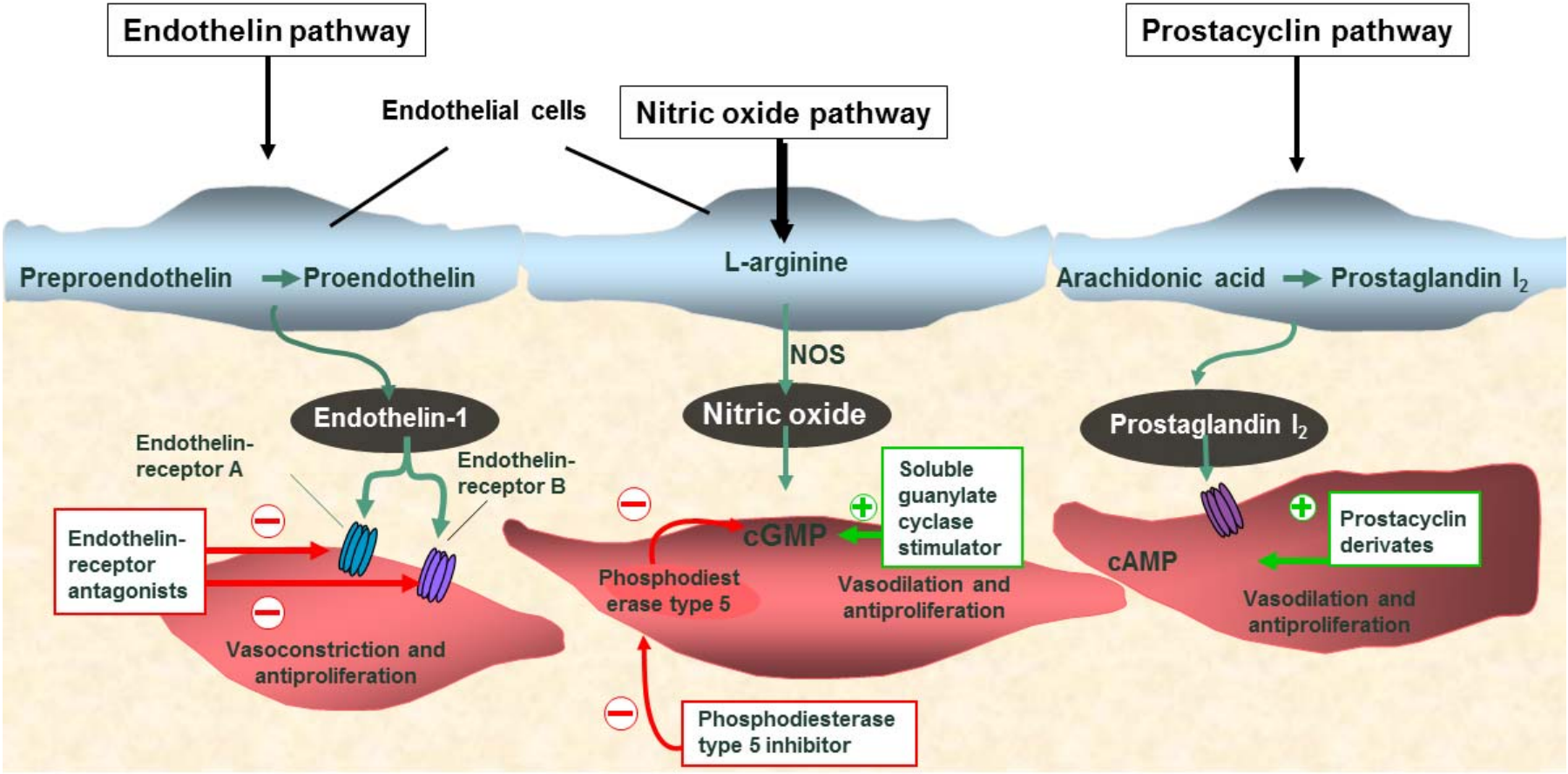
*Director, Institute of Cardiology ; Physician, National Heart Hospital ; Physician-in-Charge, Cardiac Department, Brompton Hospital, London*



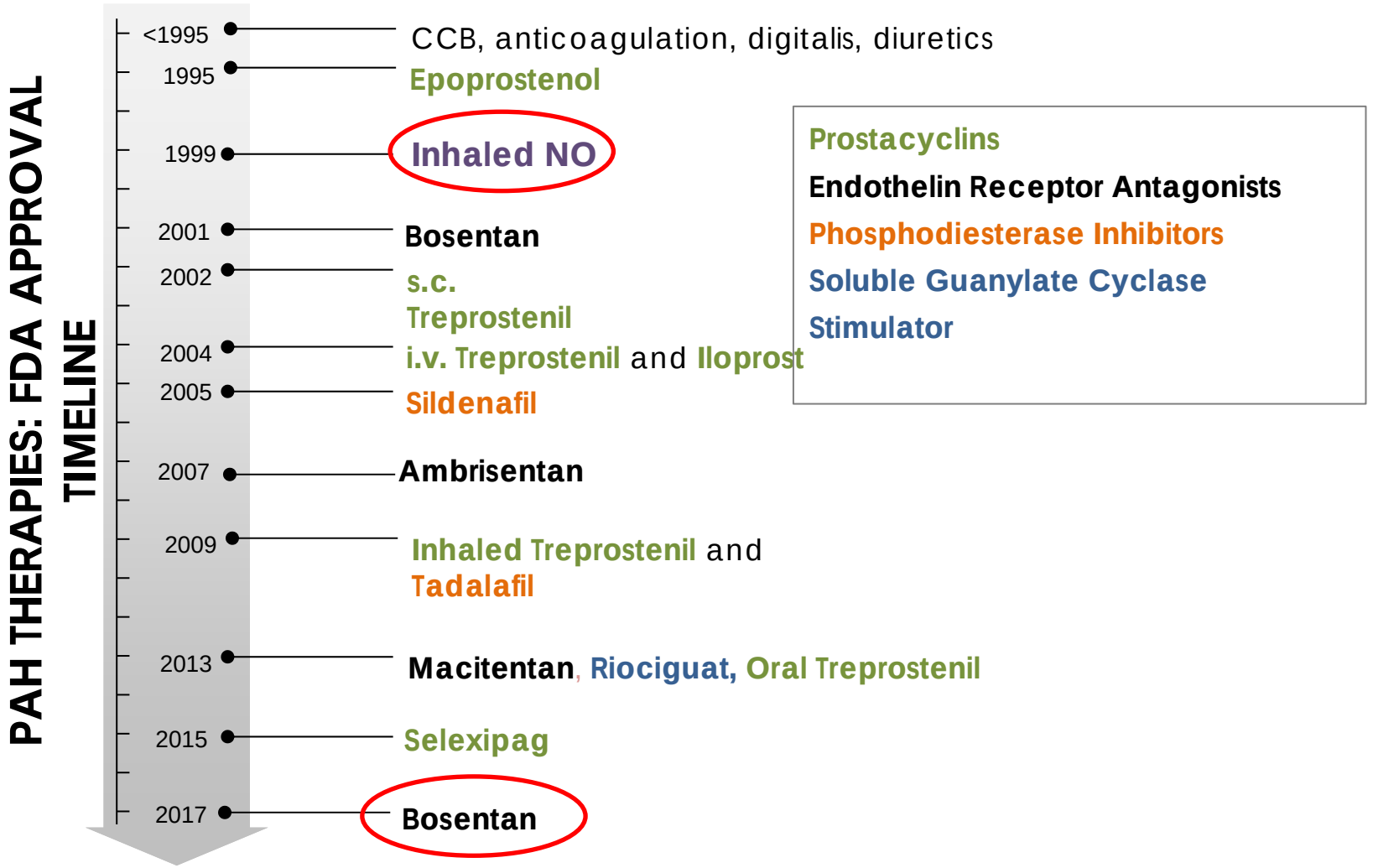

*Eisenmenger's syndrome may be defined as pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at the aorta, pulmonary, ventricular, or atrial level.*

Wood BMJ 1958

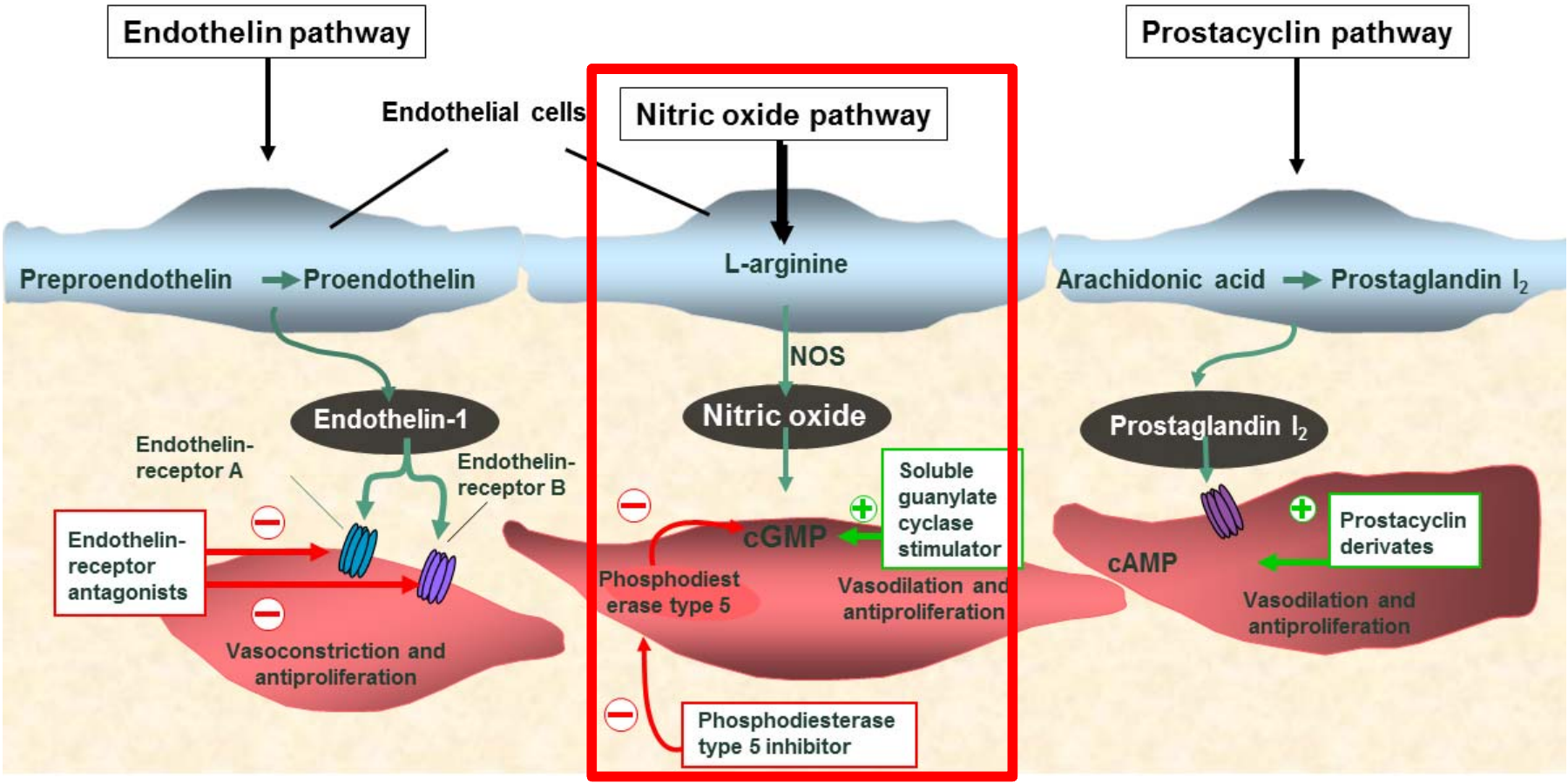
# PH Treatment Pathways




McGoon M D, Kane G C. *Mayo Clin Proc*. 2009;84:191-207


PAH THERAPIES: FDA APPROVAL TIMELINE
<1995
CCB, anticoagulation, digitalis, diuretics
1995
Epoprostenol
1999
Inhaled NO
2001
Bosentan
2002
s.c. Treprostenil
2004
i.v. Treprostenil and Iloprost
2005
Sildenafil
2007
Ambrisentan
2009
Inhaled Treprostenil and Tadalafil
2013
Macitentan, Riociguat, Oral Treprostenil
2015
Selexipag
2017
Bosentan
Prostacyclins
Endothelin Receptor Antagonists
Phosphodiesterase Inhibitors
Soluble Guanylate Cyclase Stimulator

# Nitric Oxide Pathway



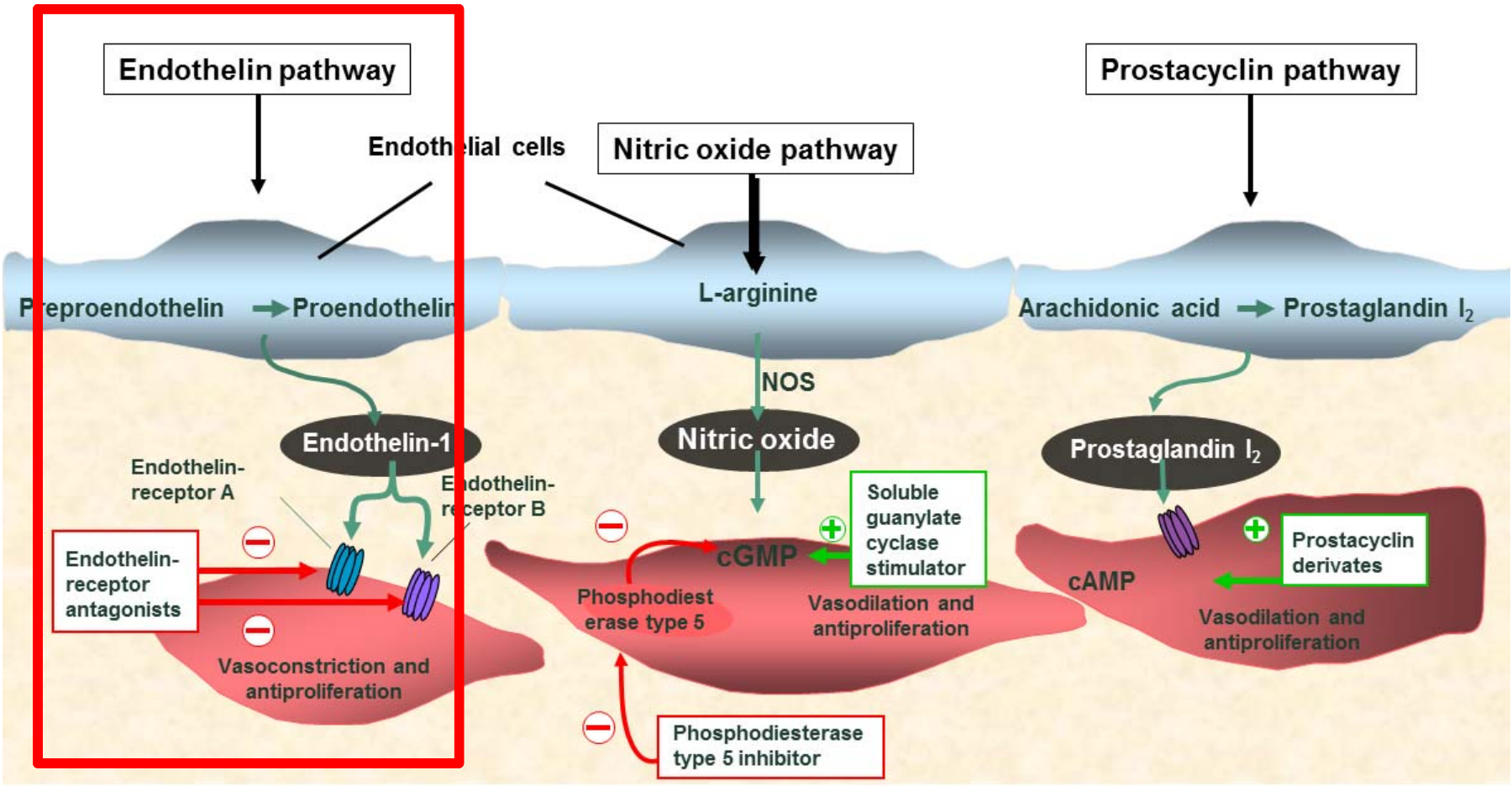

McGoon M D, Kane G C. *Mayo Clin Proc*. 2009;84:191-207

# Nitric oxide pathway


- Nitric oxide (Inhaled)
  - Inpatient settings only
  - Reactivity during cardiac catheterization
  - Dosing: 20-40 ppm
- PDE-5 Inhibitors (Oral)
  - Sildenafil (Revatio ®)
  - Tadalafil (Adcirca®, Cialas ®)


- Soluble guanylate cyclase stimulators (Oral)
  - Riociguat (Adempas ®)

# PH Treatment Pathways



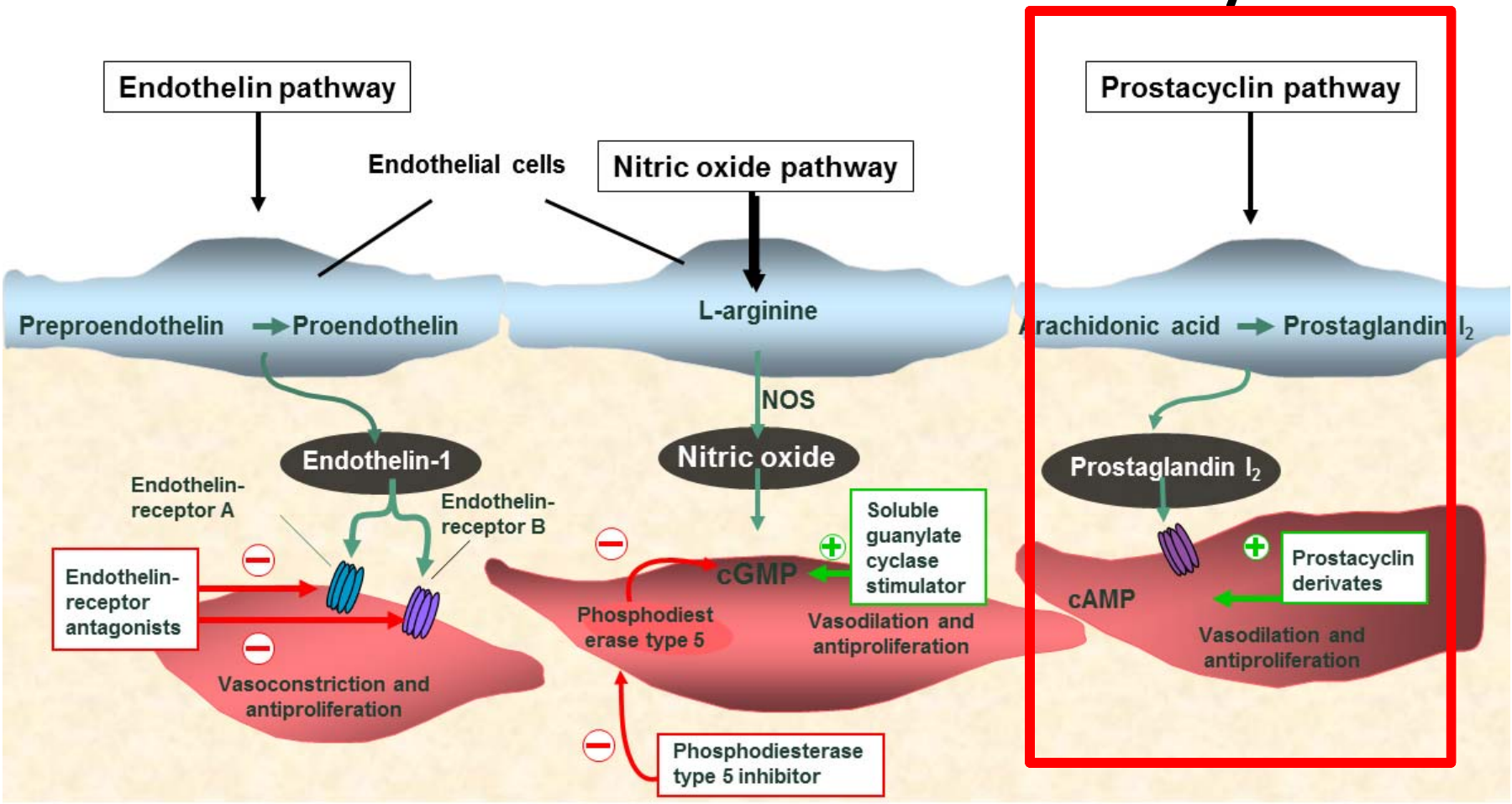

McGoon M D, Kane G C. *Mayo Clin Proc*. 2009;84:191-207

# Endothelin Receptor Antagonists (ERA)

- Bosentan (Tracleer®)
  - Pills and suspension
  - 2-4 mg/kg/dose BID
  - AST/ALT monthly, CBC every 3 months
- Ambrisentan (Letaris®)
  - Pills
  - AST/ALT monthly, CBC every 3 months
- Macitentan (Opsumit®)

Letairis™
ambrisentan
5 mg and 10 mg Tablets

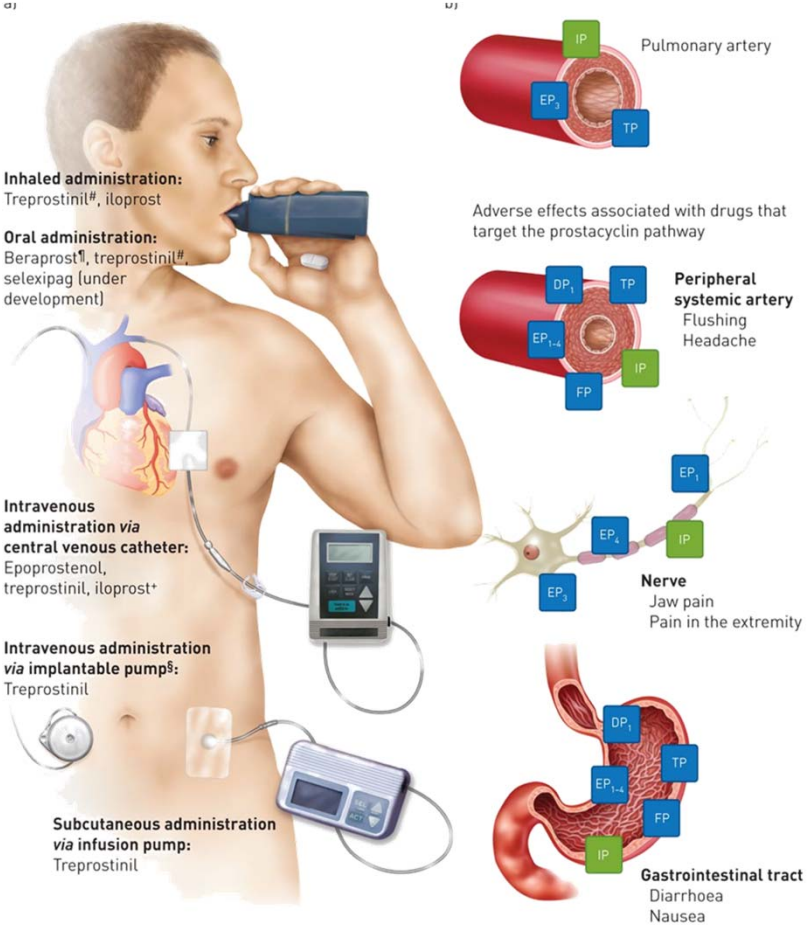
# PH Treatment Pathways




McGoon M D, Kane G C. *Mayo Clin Proc*. 2009;84:191-207

# Prostacyclins

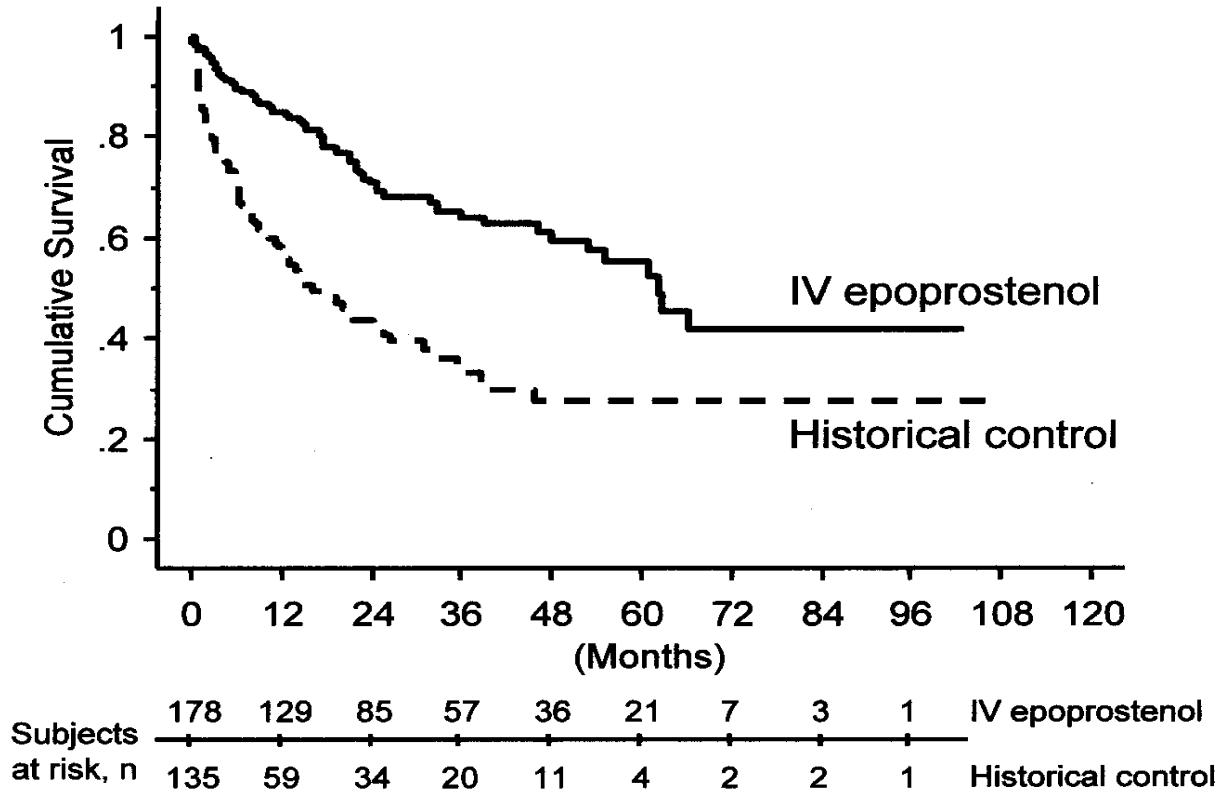
- Epoprostenol (IV or inhaled)
  - Flolan, Veletri
- Treprostinil (IV, SQ, inhaled, and oral)
  - Remodulin IV/SQ, Tyvaso, Orenitram
- Iloprost (inhaled)
  - Ventavis
- Selexipag (oral receptor analog)
  - Uptravi



# Outcomes

- VERY limited information
- Historical data for untreated pediatric PH
  - Average time to death after diagnosis ~10 months
- UK registry (single referral center)
  - Survival of pediatric IPAH reported to be 89%, 84%, and 75% at 1 year, 3 years, and 5 years
- US REVEAL registry (26 sites)
  - Five-year survival from diagnostic right heart cath was 75% for IPAH/FPAH and 71% for APAH-CHD

# Long-Term Intravenous Epoprostenol: Survival with IPAH



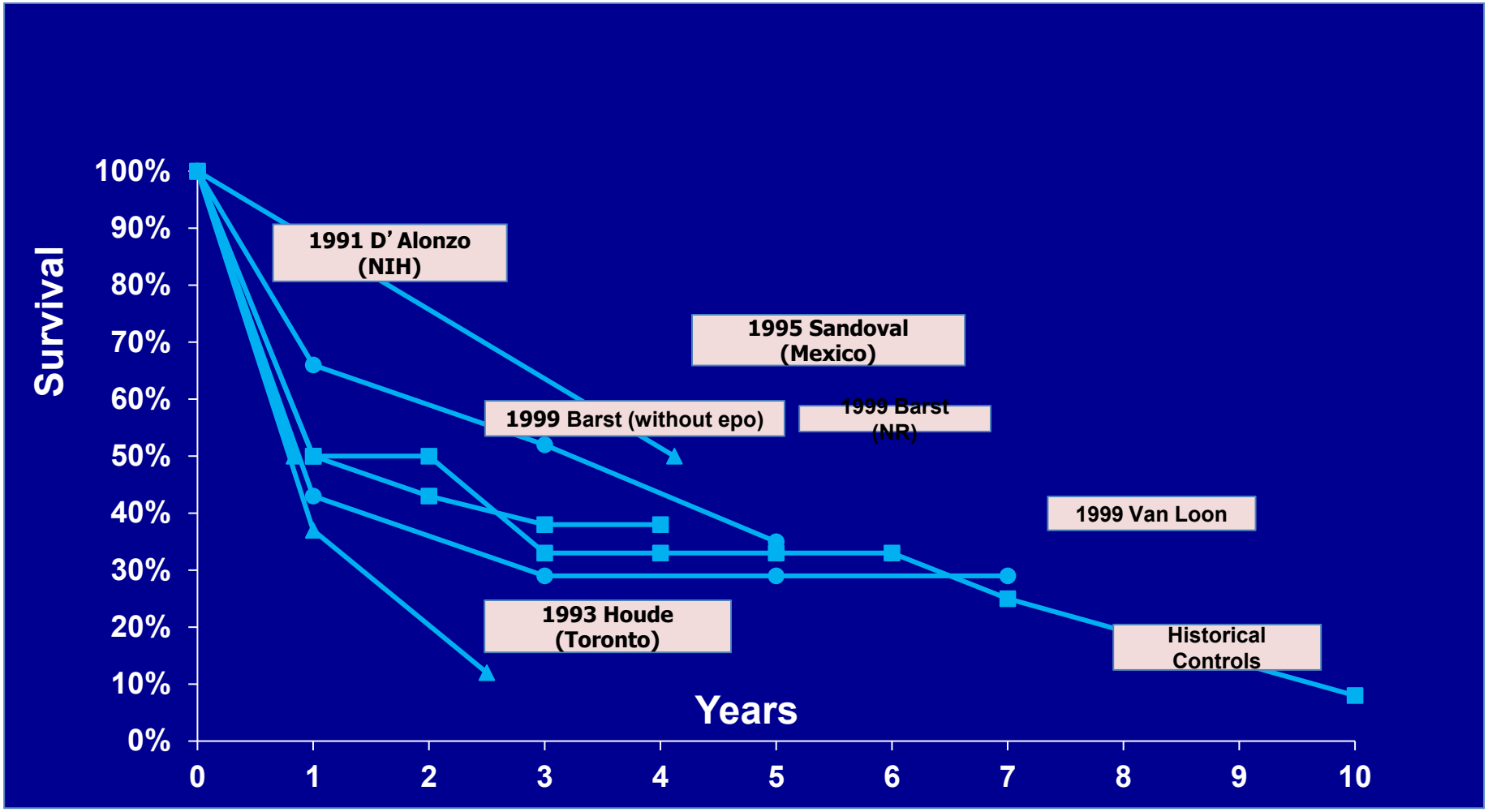

Sitbon O, et. al. *JACC* 2002; 40: 780-788

# Historical Data:
## Before Currently Available Treatments (Prior to 1995)

- Adult Data
  - Estimated median survival was 2.8 years
  - Mean 5-year survival was less than 40%
- Pediatric Data
  - Average time from diagnosis to death in pediatrics was around 10 months

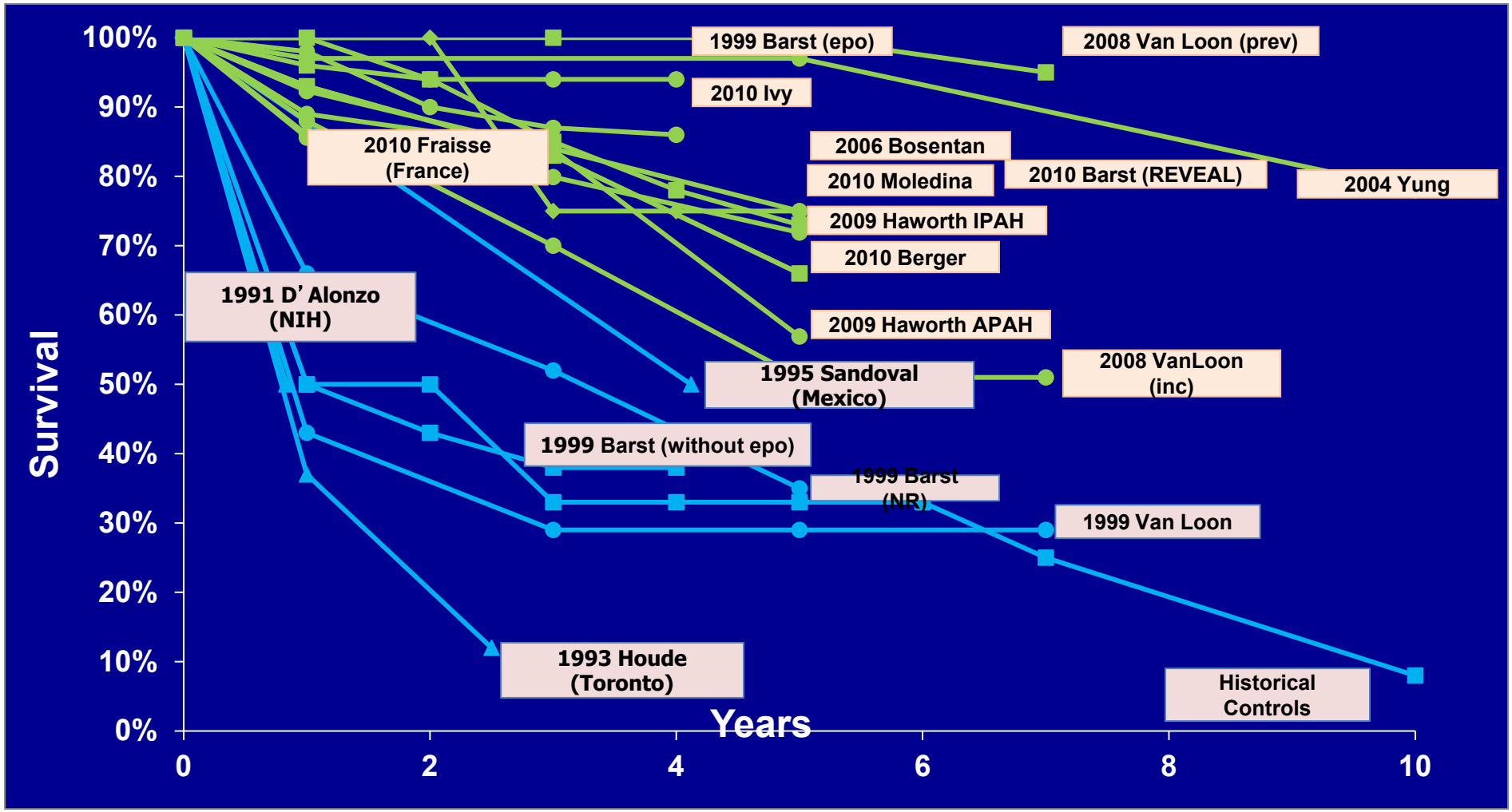
D'Alonzo, et al. Ann Intern Med. 1991;115(5):343-349

# Survival in Pediatric PAH Prior to Availability of Targeted Therapies




Courtesy Robin Barst and Dunbar Ivy

# Variability of Improved Survival in Pediatric PAH in the Current Era




Courtesy Robin Barst and Dunbar Ivy

# Conclusions and Speculations

- Neonatal and Childhood PH is a spectrum of disease with diverse pathobiology

- Understanding the role of endothelial dysfunction has led to therapeutic targets that have markedly improved outcomes

- Identification of the spectrum of mechanisms related to different forms of PH may identify new therapeutic targets and guide individual therapies