Pediatric Pulmonary Hypertension: Inside Out

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Disclosures

I have no conflicts of interest to disclose

Objectives

- Update on latest classification
- Understand the pathophysiologic basis of the disease
- Understand external factors leading to exacerbation of disease
- Understand acute management
- Learn about the therapeutic options

Case Scenario

A full term male infant is born with prenatal dx of severely underdeveloped R lung. Intubated at birth for 4 days, extubated to CPAP and required re-intubation for respiratory distress, hypoxemia and hypercarbia. An ECHO done revealed a normal heart, pulmonary hypertension and a small pulmonary artery. Over the course of the subsequent weeks he's required higher ventilatory support with HFOV due to severe hypoxemia and hypercarbia, requiring iNO and inotropic support……

He's being transferred to your unit (NICU) and you will be admitting this neonate… Any questions?

A. Wait what? Me? Admitting this patient??

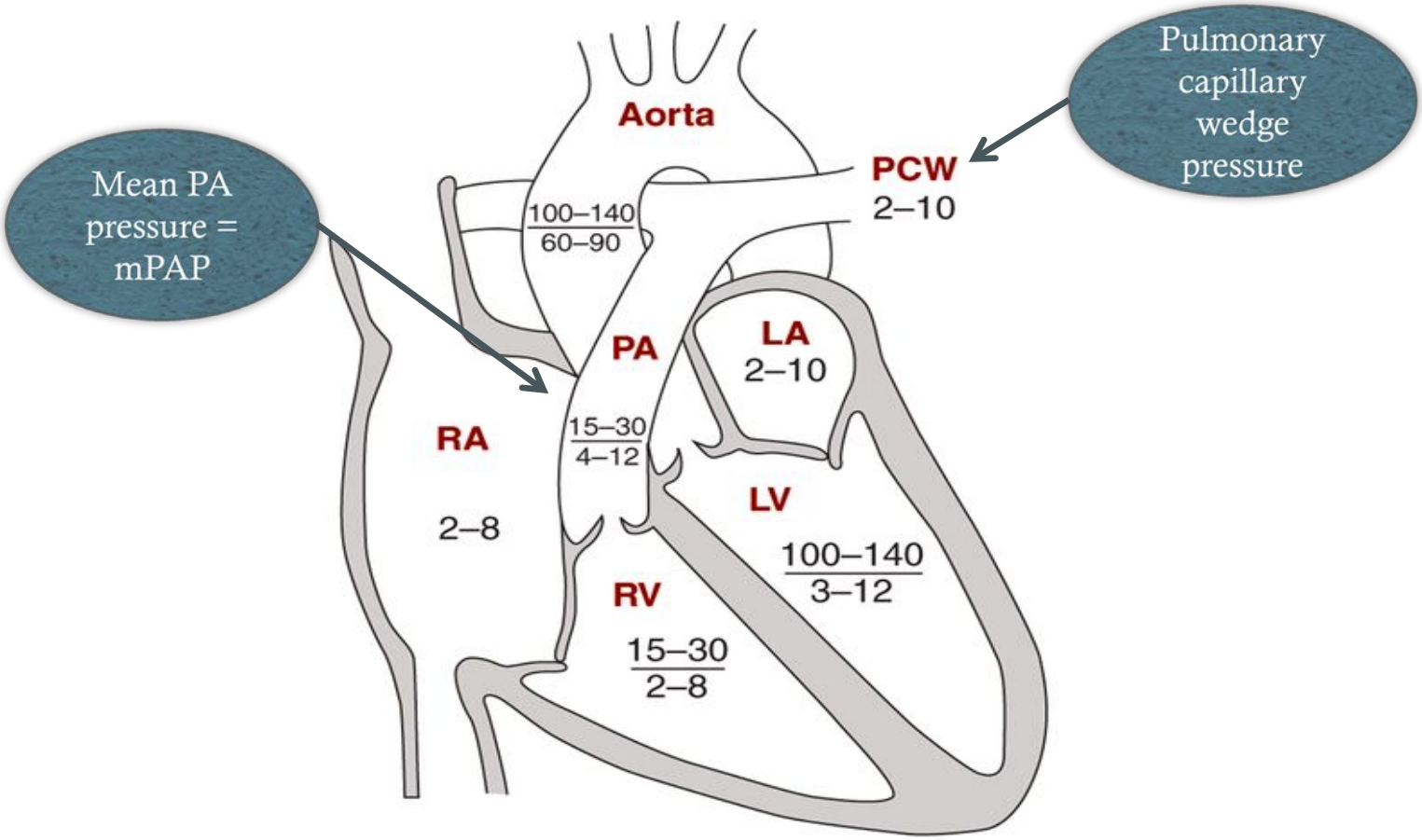
B. Uhhh my shift is over… now!

C. There must be a mistake… I only care for stable patients…

D. Piece of cake! I got this…

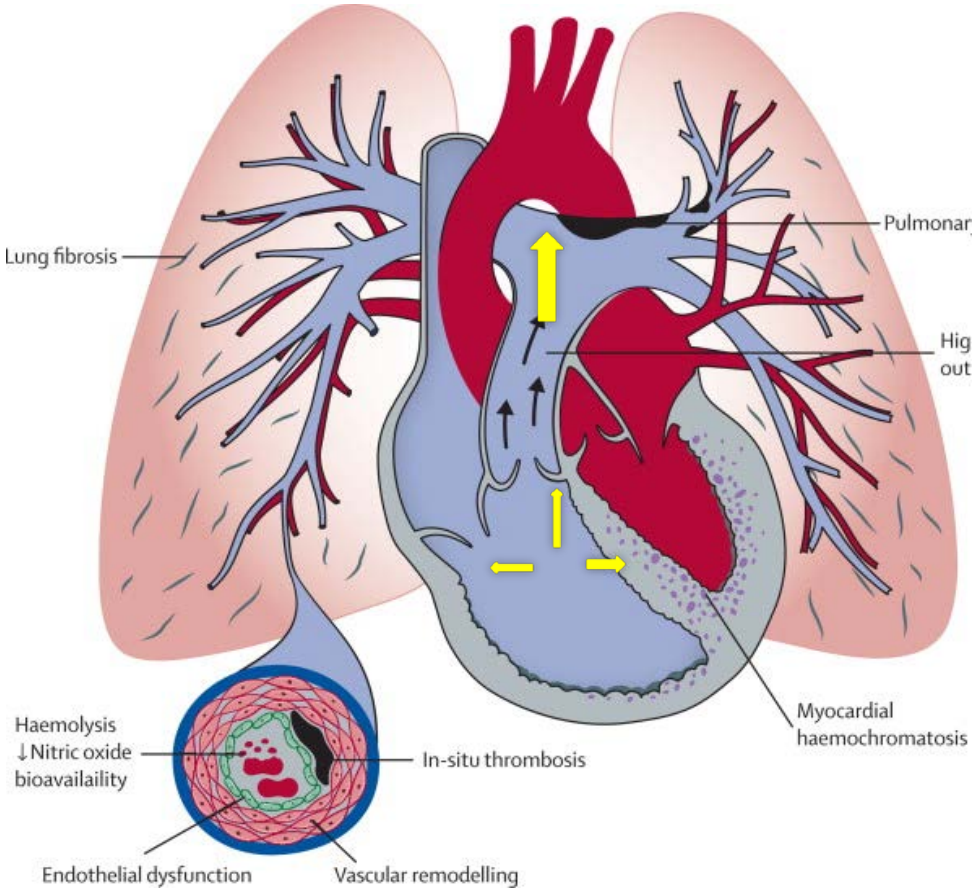
So what is pulmonary hypertension?

Intra-thoracic Pressures



Normal Cardiac Pressures

Definition



- pHTN:
  mPAP of >25mmHg at rest via cath
- Arterial pHTN:
  pHTN + pCWP < 15
- So really… the pressures in the pulmonary circulation are elevated

Are there different categories that classify pulmonary hypertension?

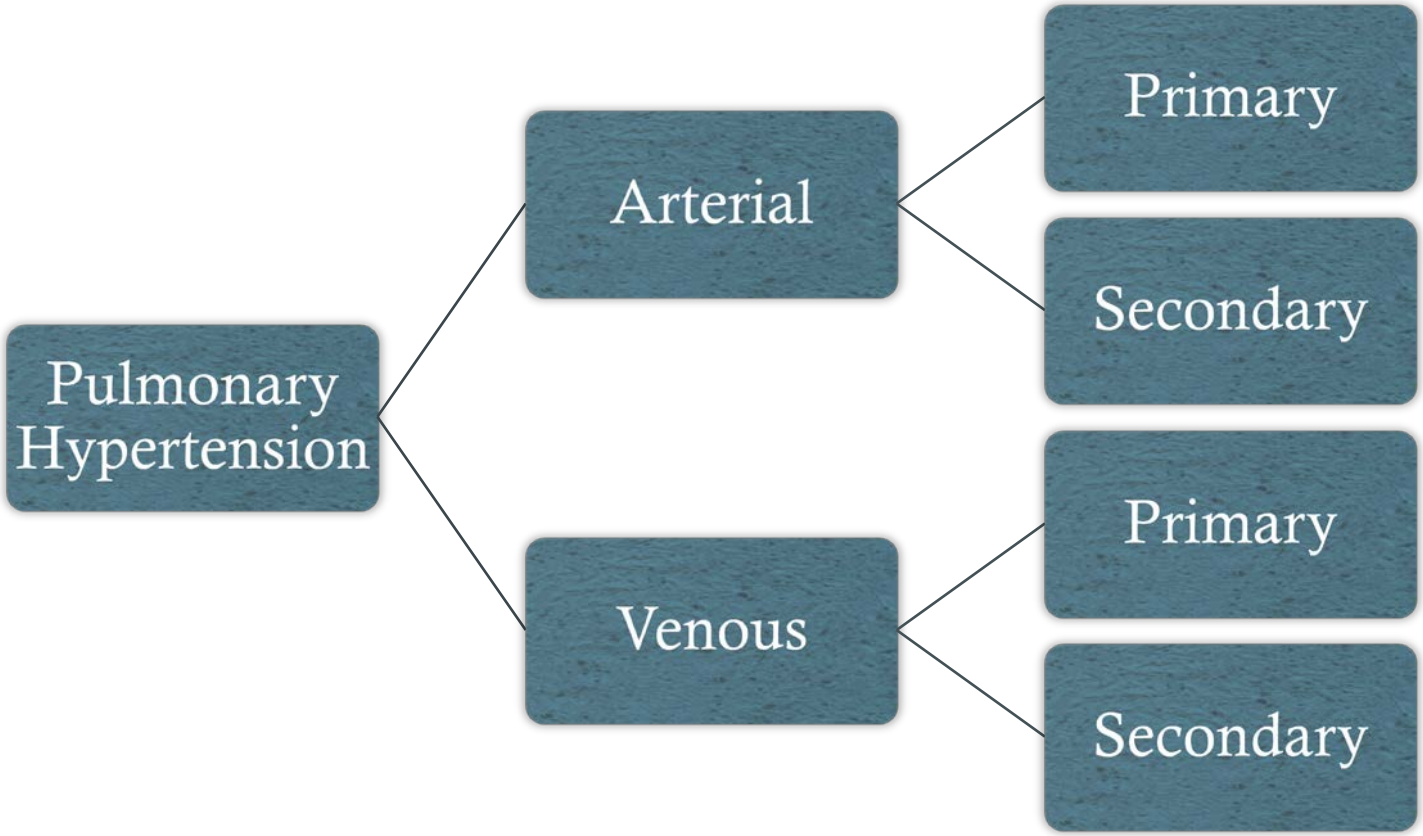
A. No, the main category is ‘pulmonary hypertension’

B. Yes, 2- arterial and venous

C. Yes, adult and pediatric

D. Yes, there are many and they have further subcategories depending on different etiologies

Background


Pulmonary Hypertension
Arterial
Venous
Primary
Secondary
Primary
Secondary

WHO Classification

- More precise terminology and precise definition

Updated Classification of Pulmonary Hypertension[1]
1. Pulmonary arterial hypertension
2. Pulmonary hypertension due to left heart disease
3. Pulmonary hypertension due to lung disease or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5.Pulmonary hypertension due to unclear multifactorial mechanism
6. Pulmonary hypertension due to toxins or drugs

WHO Classification

Updated Classification of Pulmonary Hypertension[1]
1. Pulmonary arterial hypertension
a. Idiopathic
b. Heritable
c. Drug and toxin induced
d. Multifactorial associations (connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis)
2. Pulmonary hypertension due to left heart disease
3. Pulmonary hypertension due to lung disease or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5.Pulmonary hypertension due to unclear multifactorial mechanism
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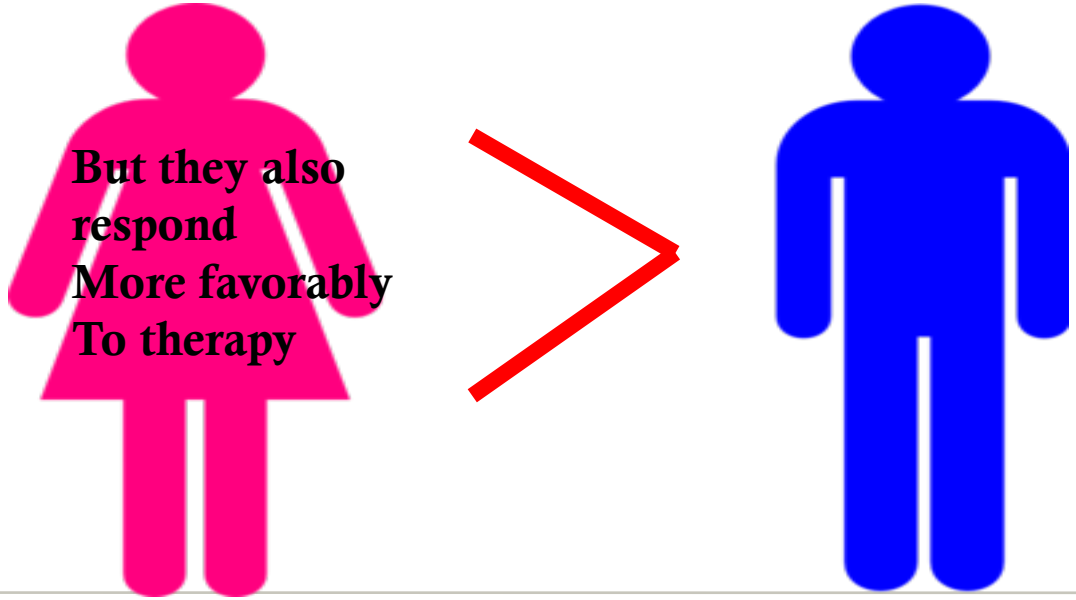
Pathogenesis

- Mediated by
  - Genetic variants
  - Inflammatory activity or infectious trigger
- Gender:

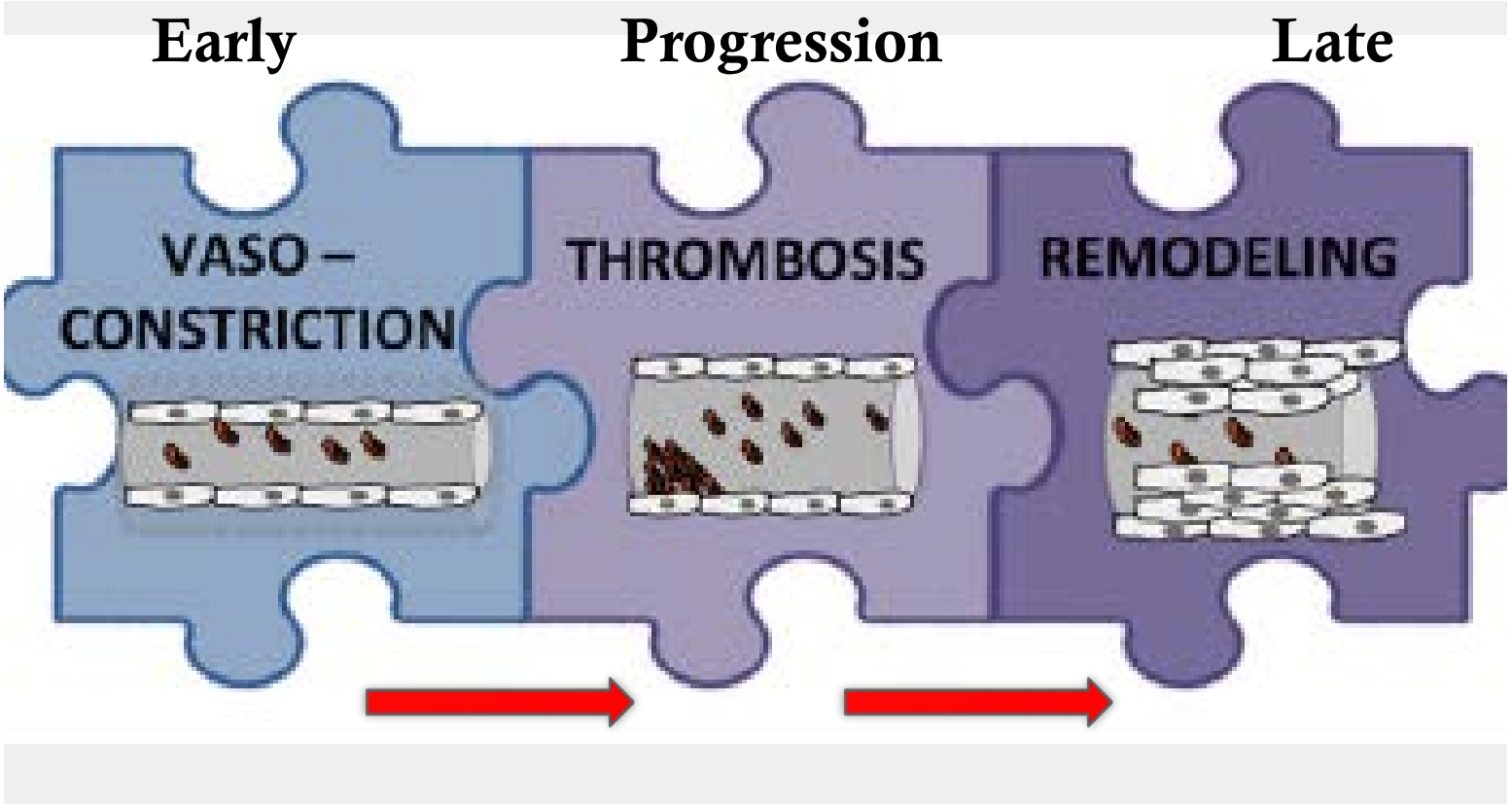


Pathophysiology

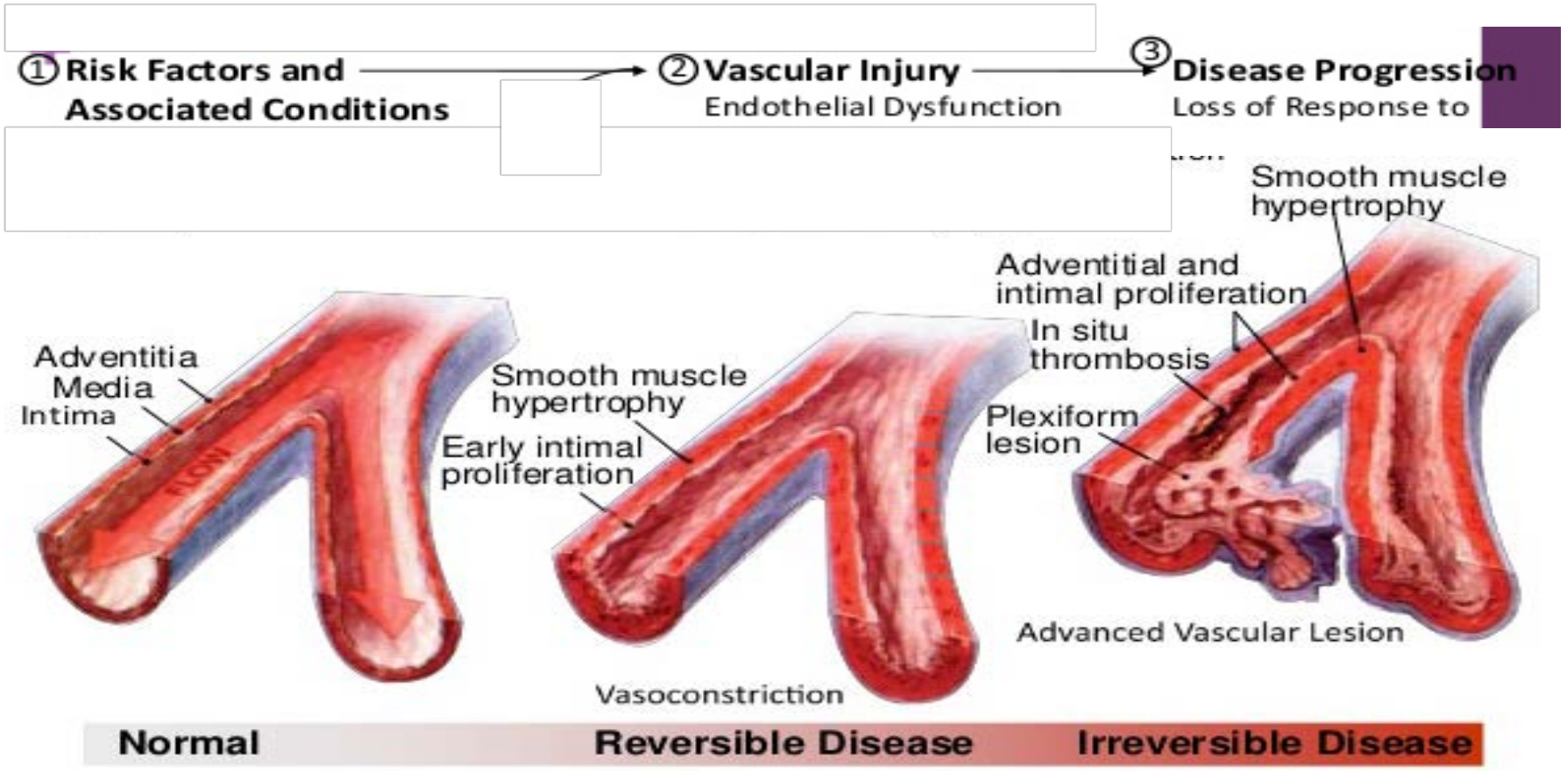
Mechanisms:

1. Increased pulmonary blood flow
2. Hypoxia induced vasoconstriction (ILD, COPD)
3. Alveolar hypoxia
4. Increased resistance in pre-capillary vasculature
5. Abnormal resistance in post-capillary vaculature

Pathophysiology: Triad

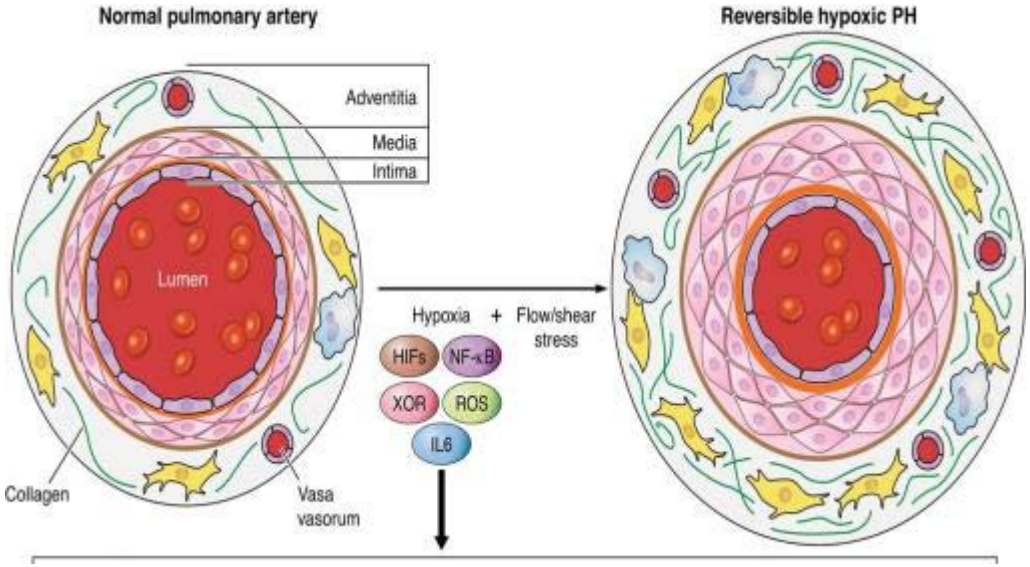


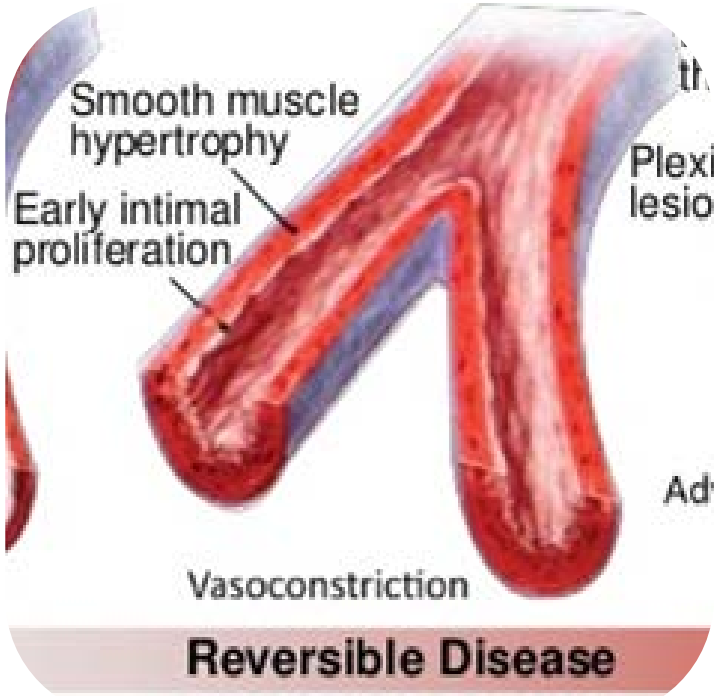
Pathophysiology: Vasculature



Gaine S. *JAMA*. 2000;284:3160-3168.

Pathophysiology: vasoconstriction

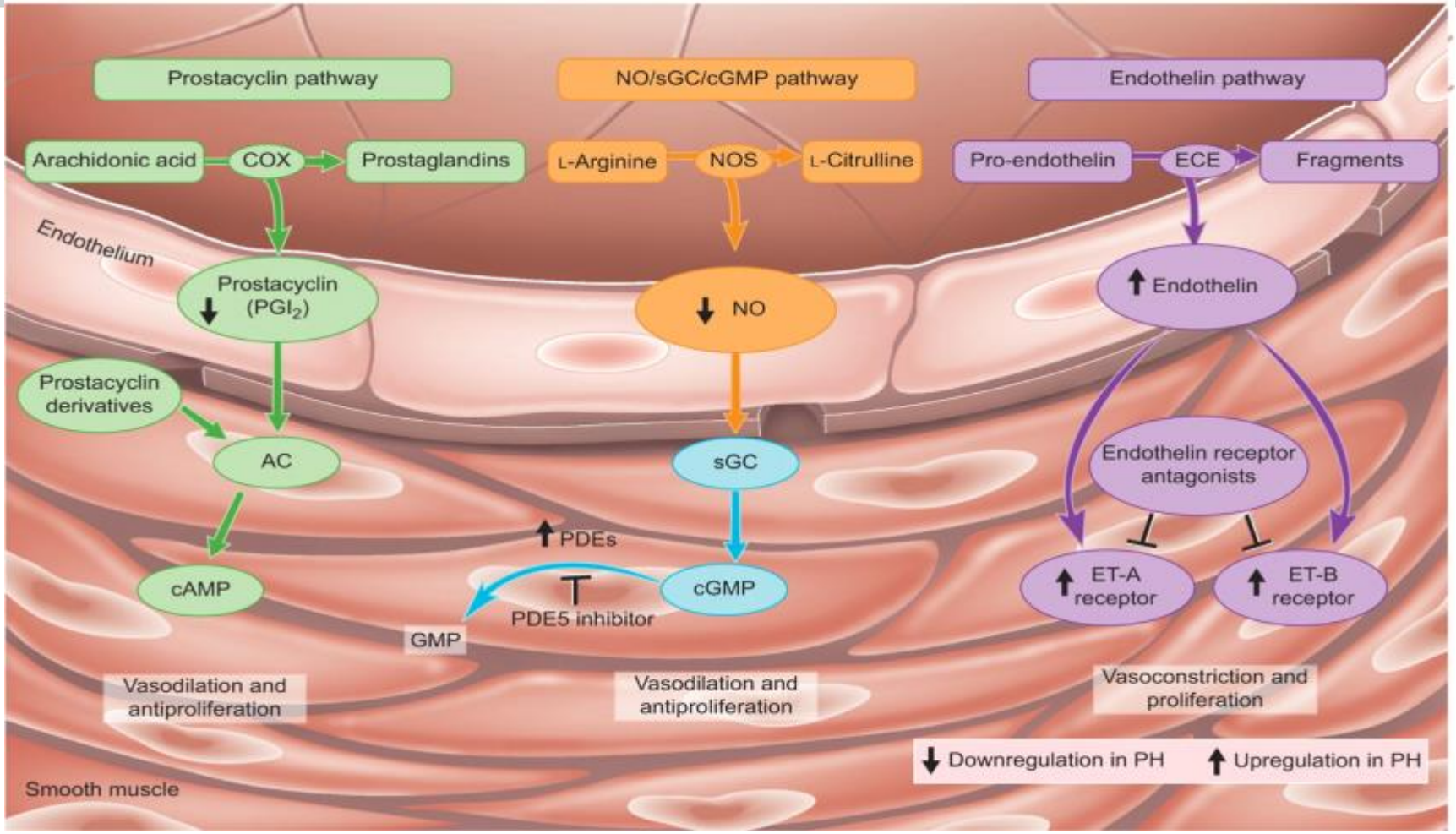




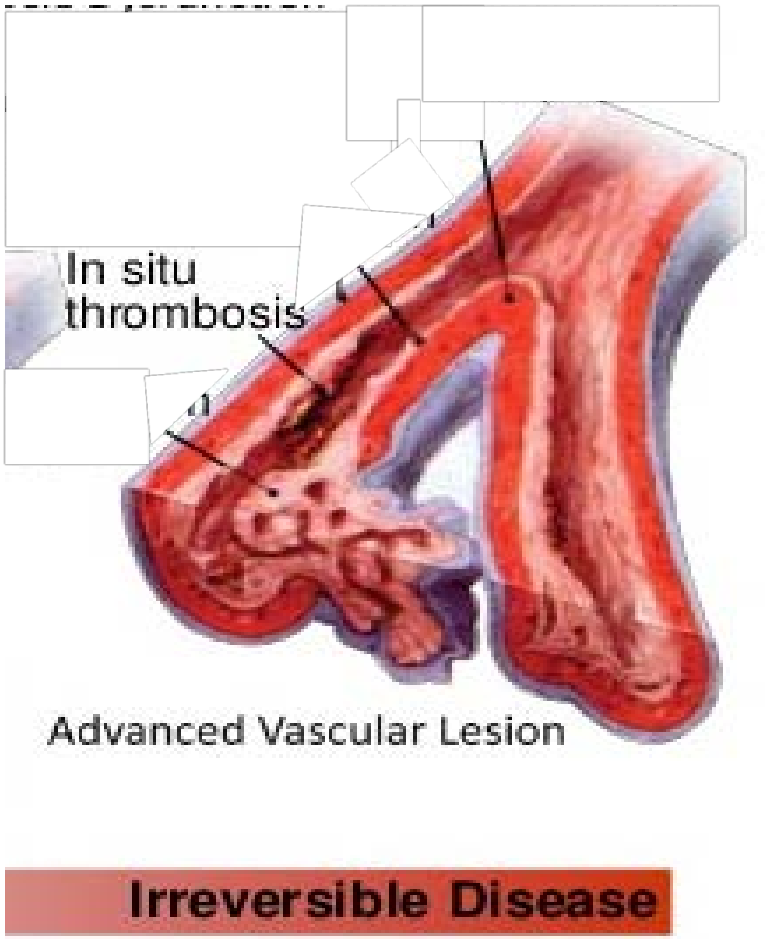
Smooth muscle proliferation in small arteries

Vasoconstriction factors > Vasodilatory factors

Pathophysiology: Vasoconstriction



Pathophysiology: Microthrombi



Etiologies:

Reduced Protein C and S

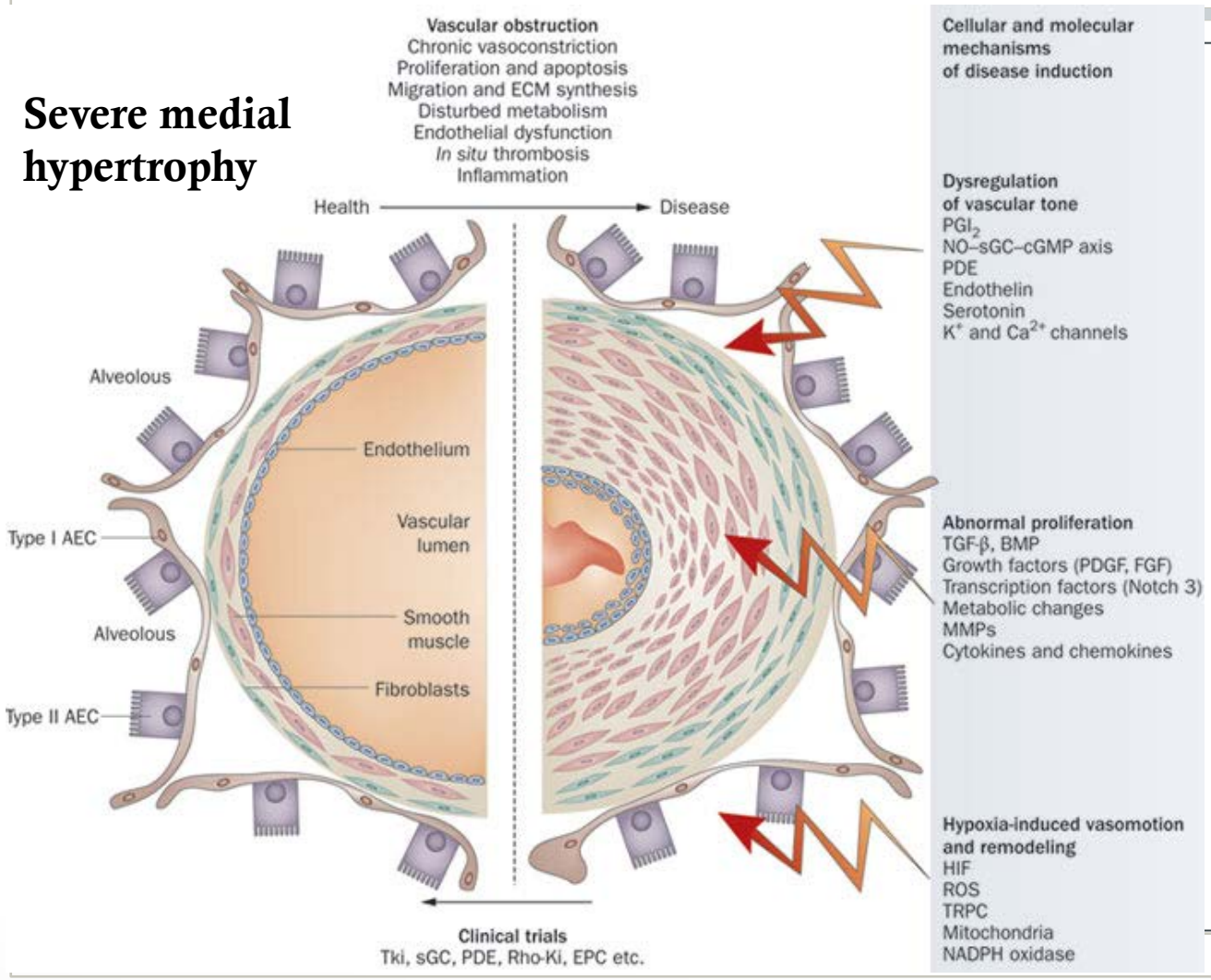
Increased vW factor

Unspecified coagulation abnormalities

Unknown

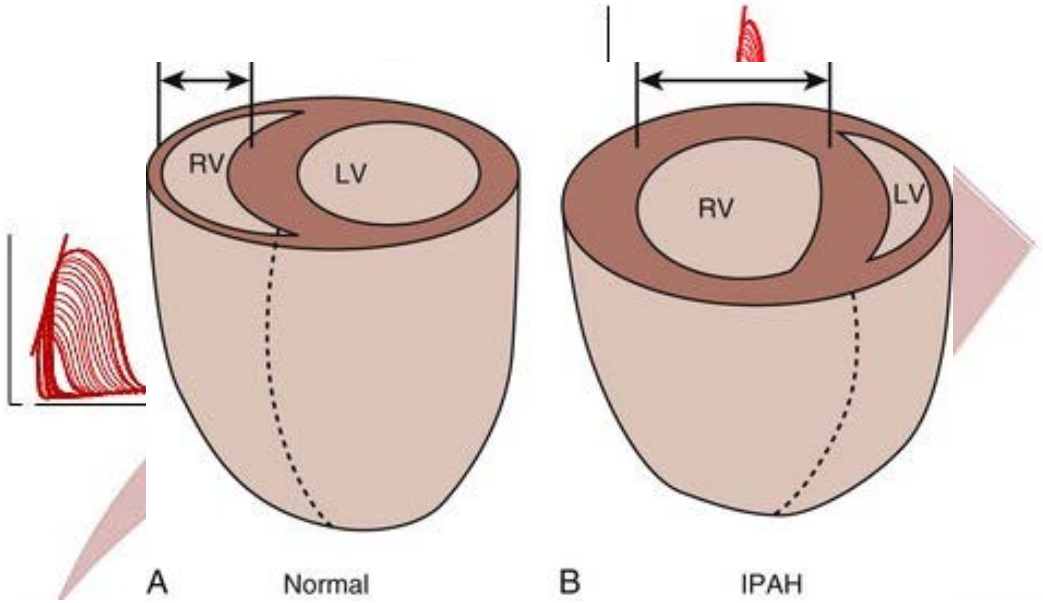
Pathophysiology: Remodeling

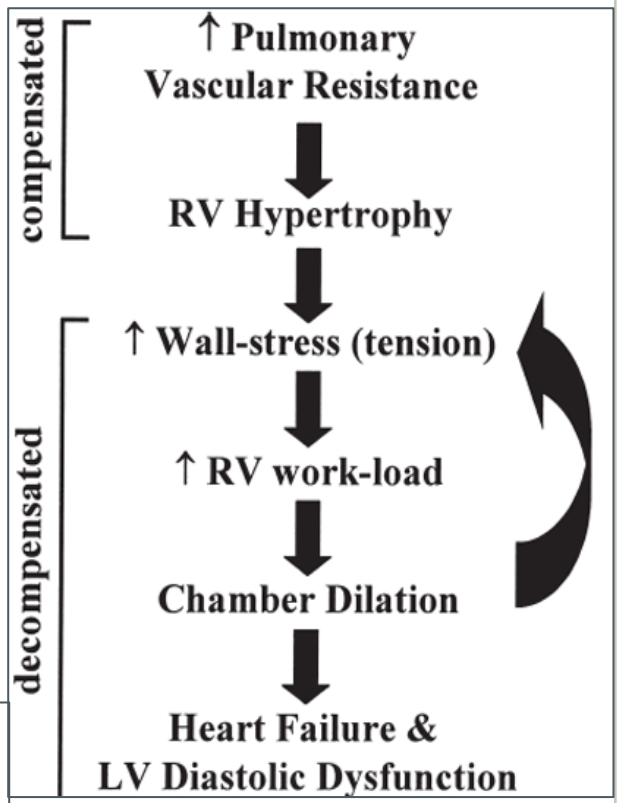
Severe medial hypertrophy



- Key aspect of PAH
- Arterial or venous
- Etiology:
  - Inflammation: toxic, infectious, autoimmune events
  - Gene defects
- Chronic & irreversible
- No therapy

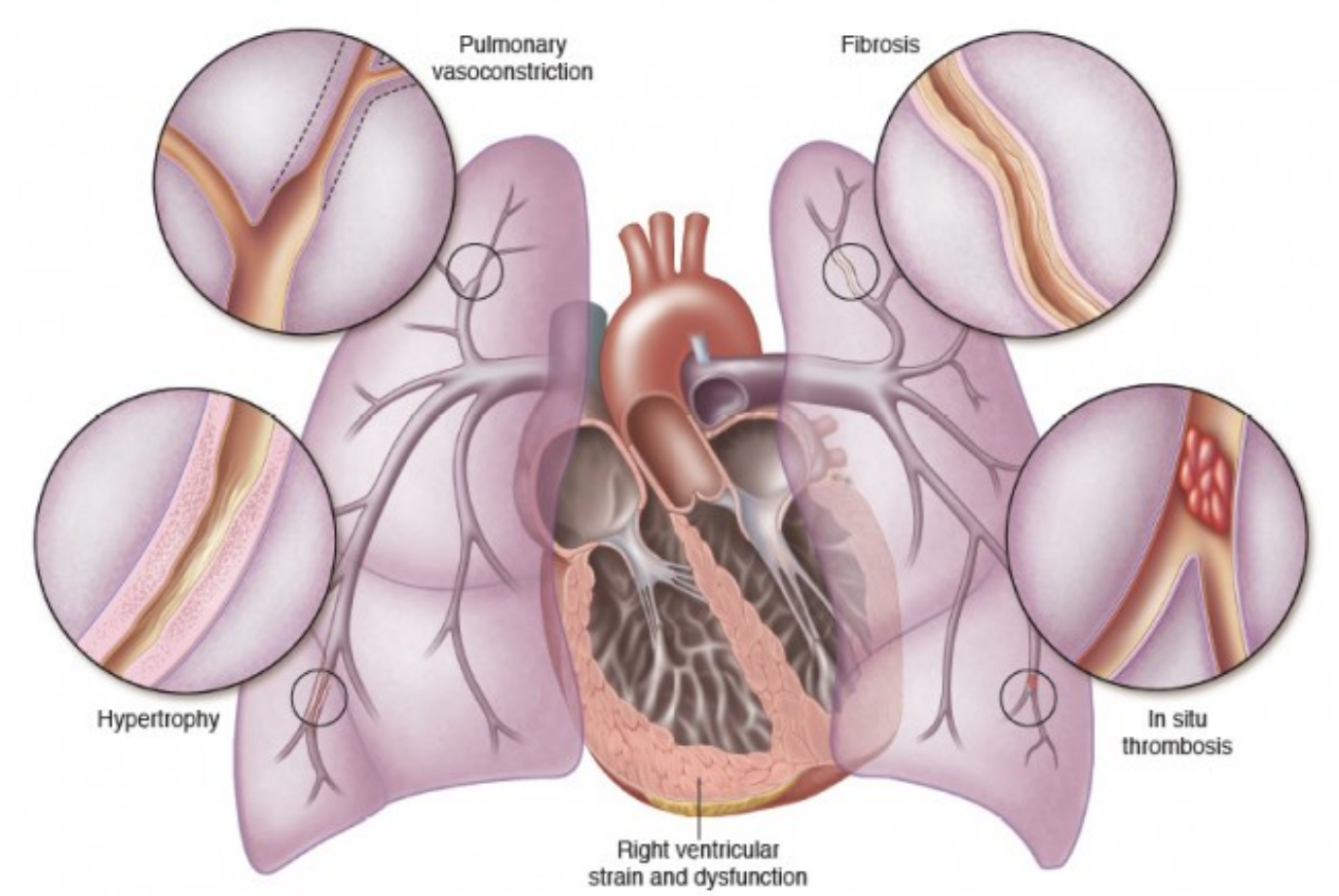
Pathophysiology: Right Heart





RV hypertrophy RV dilation intraventricular septum → LV	Increased RV P/V Impaired relaxation Myocardial ischemia Decreased CO	Oxygen demand > supply RV failure Further decreased CO

Pathophysiology: Overall



What symptoms do children with pulmonary hypertension present with?

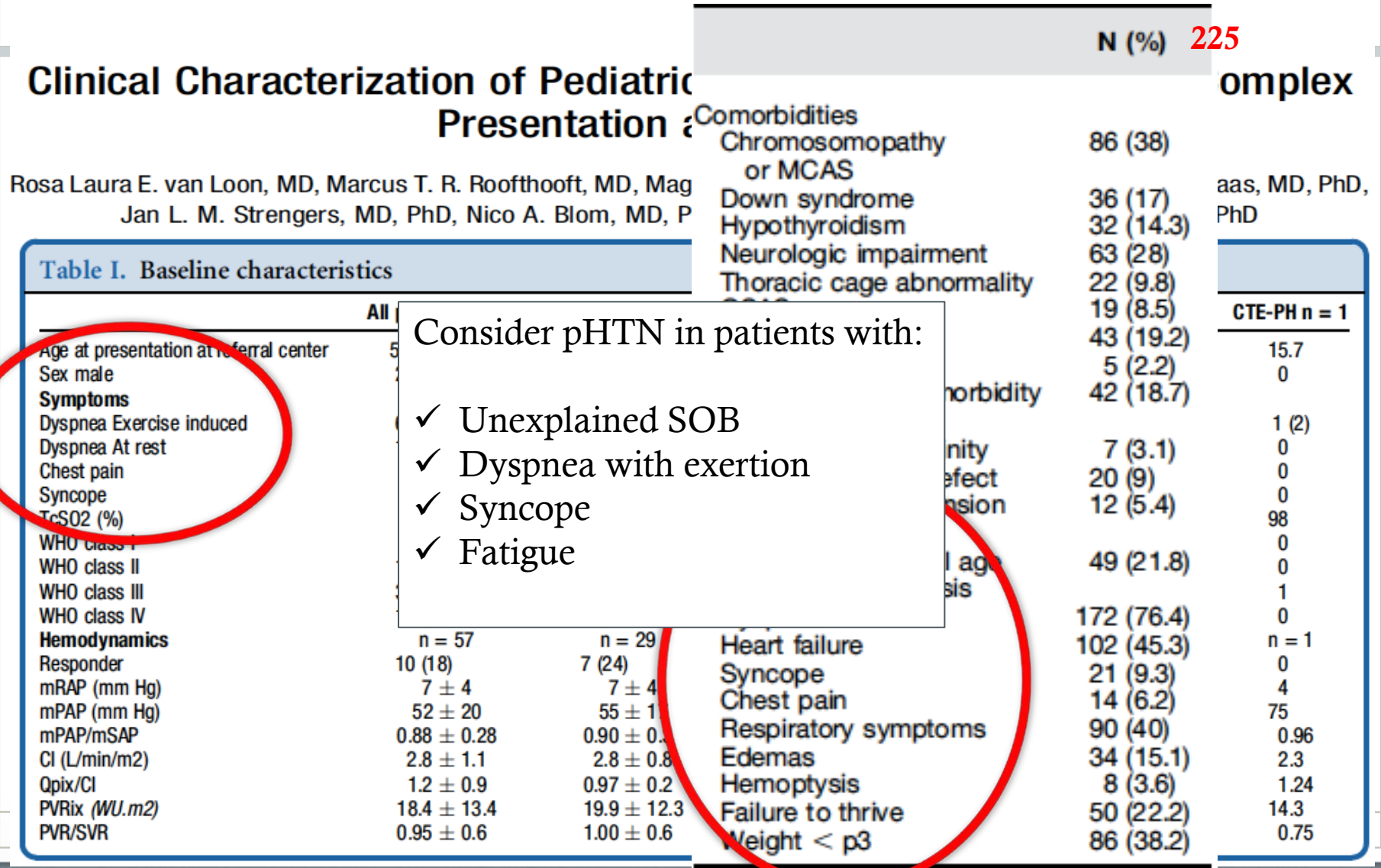
A. Non-specific with fatigue, dyspnea, FTT and SOB

B. Chest pain, cyanosis, clubbing

C. Wheezing, respiratory distress, cyanosis

D. Seizures, cyanosis, inability to be active

Clinical Presentation



Clinical Characterization of Pediatric … omplex Presentation a…

Rosa Laura E. van Loon, MD, Marcus T. R. Roofthooft, MD, Mag… …aas, MD, PhD, Jan L. M. Strengers, MD, PhD, Nico A. Blom, MD, P… PhD

Table I. Baseline characteristics

	All		CTE-PH n = 1
Age at presentation at referral center	5		15.7
Sex male			0
Symptoms			
Dyspnea Exercise induced			1 (2)
Dyspnea At rest			0
Chest pain			0
Syncope			0
TcSO2 (%)			98
WHO class I			0
WHO class II			0
WHO class III			1
WHO class IV			0
Hemodynamics	n = 57	n = 29	n = 1
Responder	10 (18)	7 (24)	0
mRAP (mm Hg)	7 ± 4	7 ± 4	4
mPAP (mm Hg)	52 ± 20	55 ± 1	75
mPAP/mSAP	0.88 ± 0.28	0.90 ± 0.	0.96
CI (L/min/m2)	2.8 ± 1.1	2.8 ± 0.8	2.3
Qpix/CI	1.2 ± 0.9	0.97 ± 0.2	1.24
PVRix *(WU.m2)*	18.4 ± 13.4	19.9 ± 12.3	14.3
PVR/SVR	0.95 ± 0.6	1.00 ± 0.6	0.75

Consider pHTN in patients with:

- ✓ Unexplained SOB
- ✓ Dyspnea with exertion
- ✓ Syncope
- ✓ Fatigue

	N (%) 225
Comorbidities	
Chromosomopathy or MCAS	86 (38)
Down syndrome	36 (17)
Hypothyroidism	32 (14.3)
Neurologic impairment	63 (28)
Thoracic cage abnormality	22 (9.8)
	19 (8.5)
	43 (19.2)
	5 (2.2)
…orbidity	42 (18.7)
…nity	7 (3.1)
…efect	20 (9)
…nsion	12 (5.4)
…l age	49 (21.8)
…sis	
	172 (76.4)
Heart failure	102 (45.3)
Syncope	21 (9.3)
Chest pain	14 (6.2)
Respiratory symptoms	90 (40)
Edemas	34 (15.1)
Hemoptysis	8 (3.6)
Failure to thrive	50 (22.2)
Weight < p3	86 (38.2)


RECOVERY
CRISIS

How do we describe the mechanism of a pulmonary hypertensive crisis?

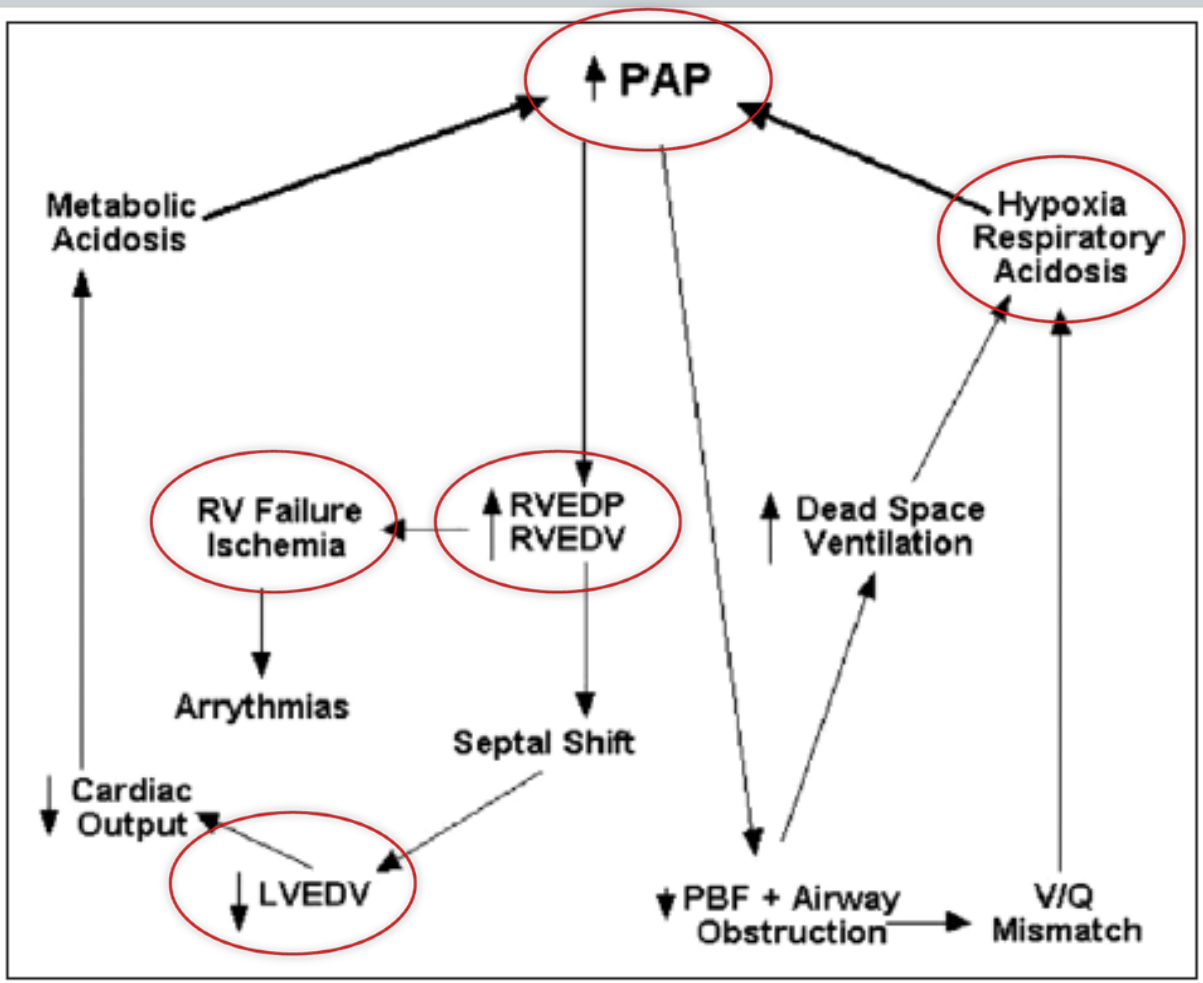
A. Pulmonary hypertension with loss of consciousness

B. Severe pulmonary hypertension → decreased pulmonary CO → RV strain → abnormal O2/CO2 exchange→ decreased systemic CO + hypoxemia +hypercarbia

C. Pulmonary hypertension with no blood pressure and arrhythmias

D. Pulmonary hypertension with RV failure and hypotension

Clinical Presentation: PH Crisis



How do we manage patients with suspected pulmonary hypertension?

A. Start treatment with Bosentan,sildenafil, iNO, O2, CCB and inhaled prostacycline and….

B. Catheterize them all

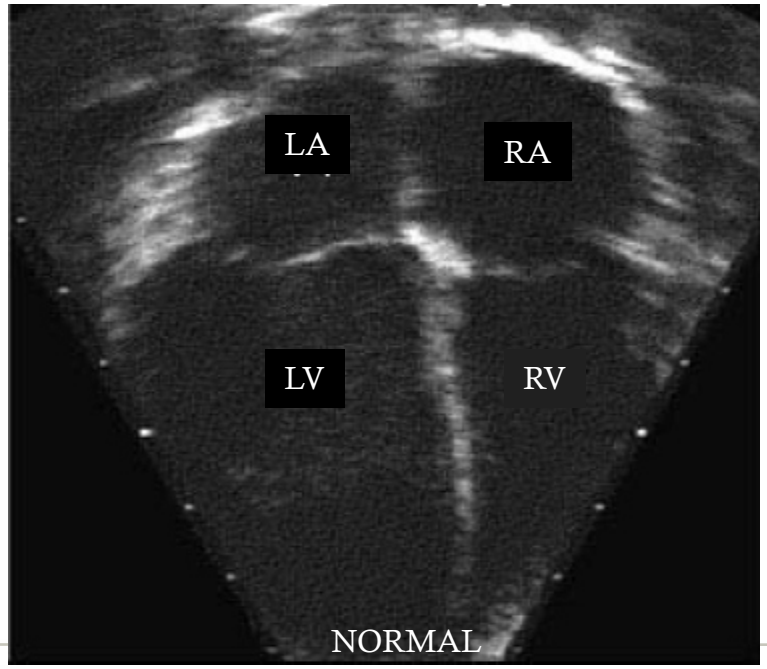
C. Echocardiography

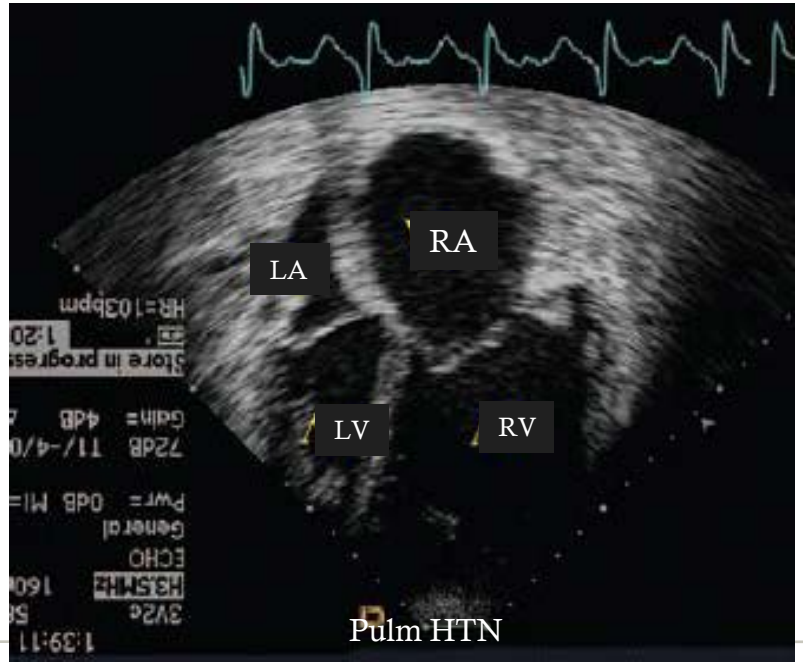
D. Always intubate them

Diagnostic Tree

Diagnostics: ECHO

- Echocardiogram
  - Important non-invasive screening tool to assess pHTN
  - Anatomy, RV-LV relationship, function



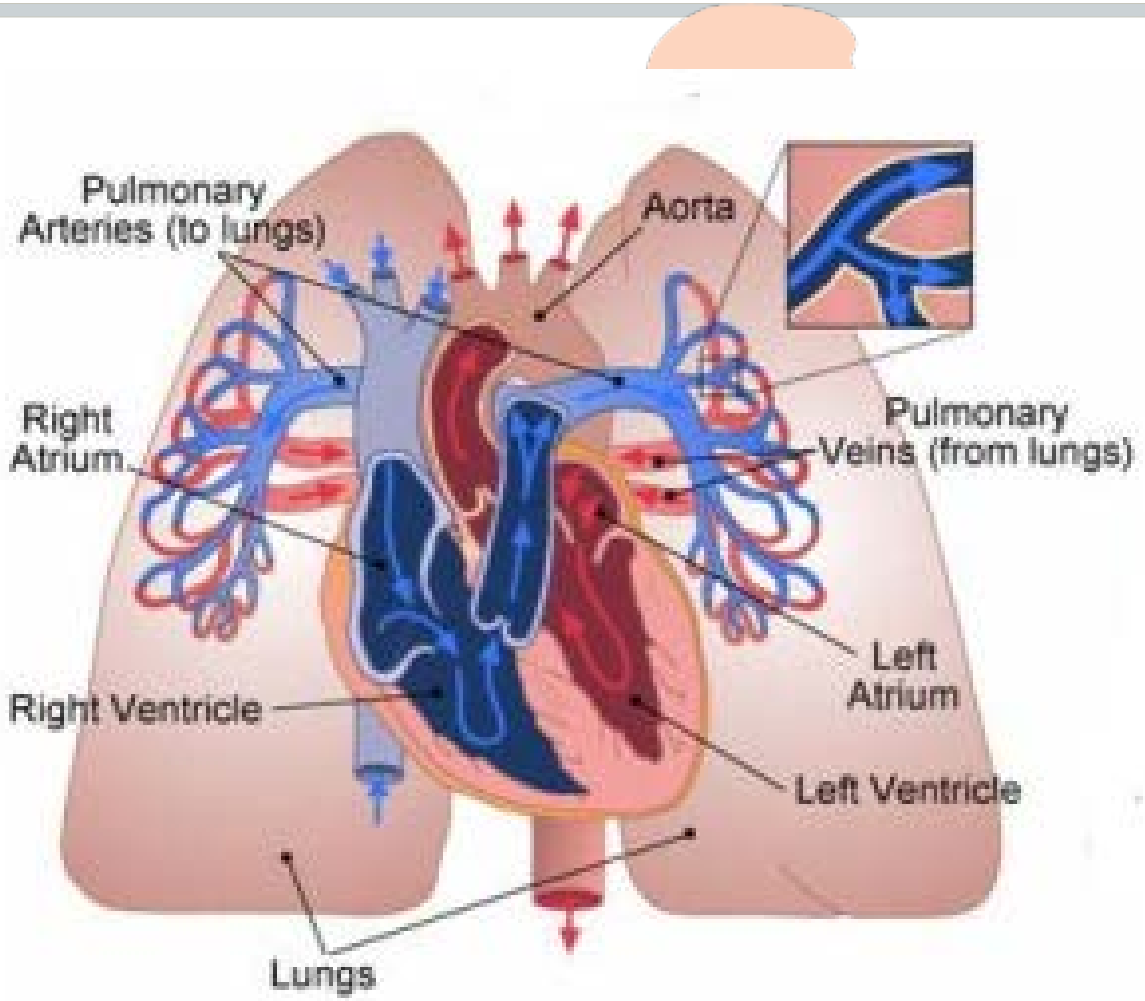


Diagnostics: Cath

- Gold standard for diagnosis
- Goals for cardiac catheterization in children:
  - (1) Confirm diagnosis and assess severity of disease;
    - a. Pressures, saturations, obstruction, resistance
  - (2) Assess the response to pulmonary vasodilators;
  - (3) Evaluate the response to therapy;
  - (4) Exclude other, potentially treatable, diagnoses;
  - (5) Assess operability of patients;
  - (6) Assist in suitability for transplantation.

*Catheterization should performed before initiating therapy

Diagnostics: Cath



Measure:

- Pressures
- Shunts
- Function
- Saturations
- CO
- Vascular:
  - Anatomy
  - Reactivity


Crisis
Recovery

Therapy: Goals

- Avoid increases in Pulmonary artery pressures
- Maintain coronary artery perfusion pressure

Management: Do No Harm!

Viscosity

CPB

acidosis

Hypotension

Hypercarbia

Fluid overload

Hypoxemia

Vaso-constrictors

Platelet transfusion

Anesthetics

PPV

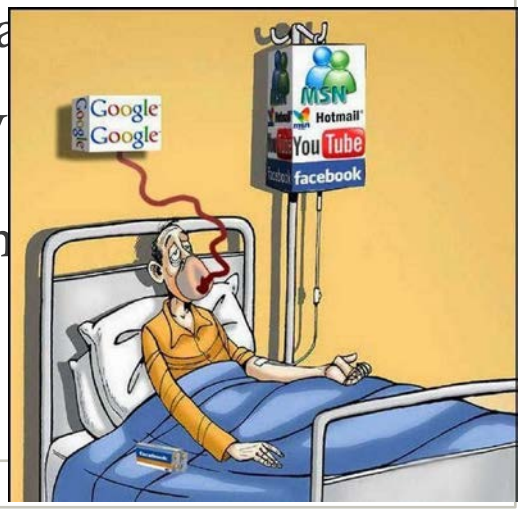
Dehydration

CPB

Contrast

Therapy: Treatment

- First line: oxygenation and alkalinzation
  - Maintain saturations >95%
  - Avoid any hypoxemia (elevation, flight, illness)
  - Correct acidosis
- Respiratory treatment
- iNO (best studied and widely used)
- Minimizing catecholamine stimulation (pain/agita
- Ventilator: Avoid over/under expansion with PPV
- Pharmaceutical: alter one of three endothelial sign cascades: NO-cGMP, PGI2 , and ET-1
- Sedation: Avoid ketamine

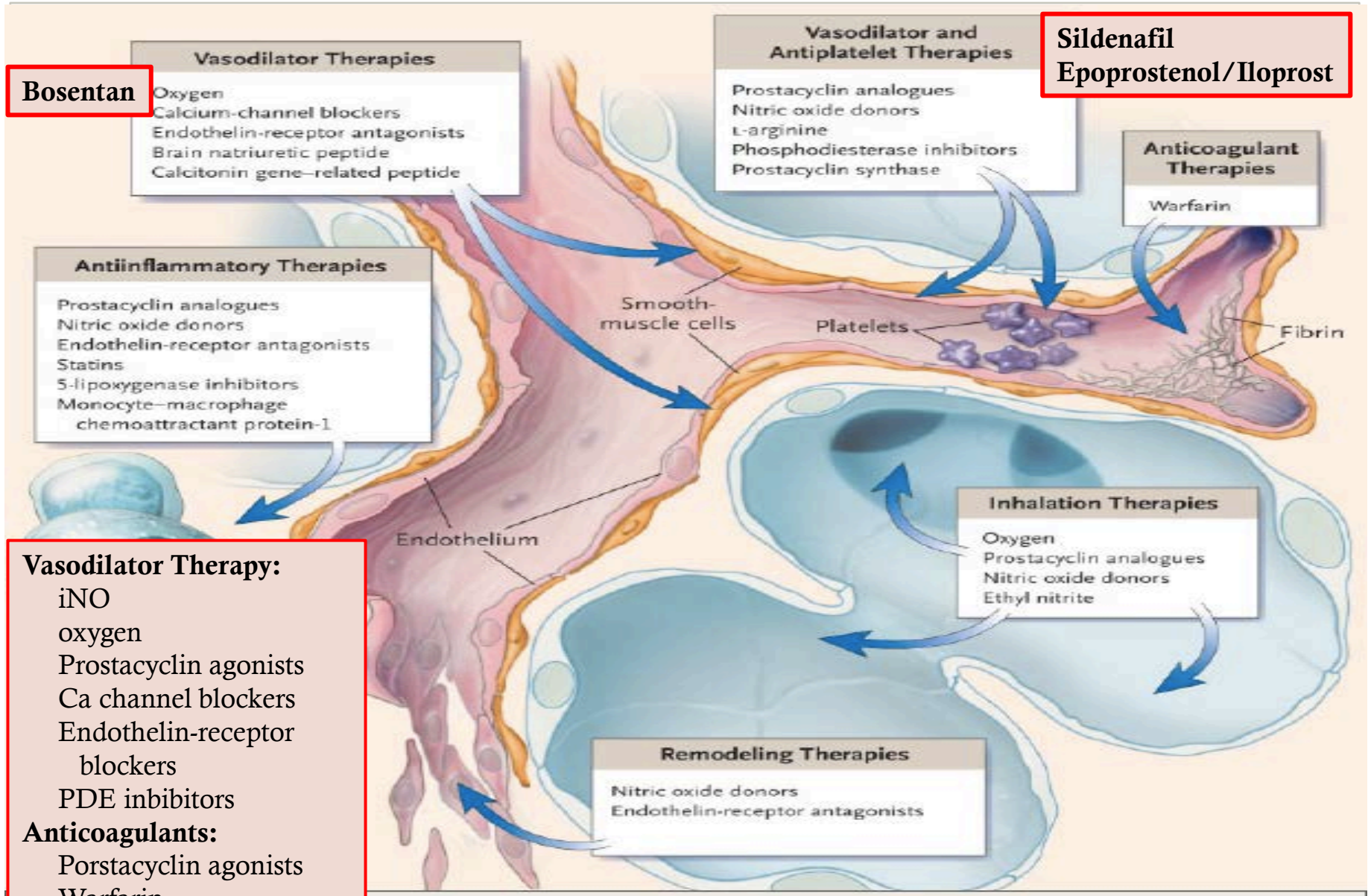


Therapy: Acute

- Pulmonary vasodilation
  - Oxygen
  - BVM
  - Sedation/Paralysis
  - Pain medication
  - Correct acid/base disorder
  - Evaluate lung fields
  - Optimize respiratory status
  - Treat cause: drugs, toxins, infection
  - Pharmaceuticals: iNO, milrinone. Epinephrine
- Correct any respiratory disease
  - Bronchodilators, abx, recruitment
- Assess and support RV
- Surgical: atrial septostomy

Bosentan

Sildenafil
Epoprostenol/Iloprost



Vasodilator Therapy:
- iNO
- oxygen
- Prostacyclin agonists
- Ca channel blockers
- Endothelin-receptor blockers
- PDE inbibitors

Anticoagulants:
- Porstacyclin agonists
- Warfarin

…es to Pulmonary Hypertension.

A model pulmonary arteriolar system and alveolus are illustrated, with the sites of action of each of six major classes of agents. Pulmonary vascular smooth-muscle cells are indicated in orange, platelets in purple, leukocytes in blue with pale nuclei, and fibrin as tan strands.

What therapies have been studied and approved for the use in children?

A. Bosentan, inhaled Epoprostenol only

B. Sildenafil only

C. Oxygen and iNO only

D. Oxygen, iNO, sildenafil only

Therapy: FDA

- **August 2012, adding a warning stating that "use of Revatio (sildenafil), particularly chronic use, is not recommended in children."**

5 WARNINGS AND PRECAUTIONS

5.1 Mortality with Pediatric Use

In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations (8.4)]*.

FDA Drug Safety Communication: FDA clarifies Warning about Pediatric Use of Revatio (sildenafil) for Pulmonary Arterial Hypertension

The purpose of the recommendation was to raise awareness of clinical trial results showing a higher risk of mortality in pediatric patients taking a high dose of Revatio when compared to pediatric patients taking a low dose. This recommendation was **not** intended to suggest that Revatio should *never* be used in children; however, some health care professionals have interpreted this information as a

Therapy: Challenges

- Except for the use of iNO in PPHN and severe respiratory failure, no approved therapies for pulmonary hypertension exist for children.
- None of the adult therapies have been formally approved for children
- Lung transplant: last resort and low 5- year survival

Prognosis

- Mortality:
  - Prior to vasodilator therapy, survival after diagnosis: 1-2 years
  - 2009 U.K. report in children: survival of 85.6%, 79.7%, 71.9% at 1, 3, and 5 years.
  - Short-term vasodilator testing responsiveness: 5-yr survival of 90%.
  - Short-term vasodilator testing unresponsive: 5-yr survival of 33%
  - Directly related to RV function
- Morbidity:
  - Related to arrhythmias, CO, line infections

What we know..

- How to define pulmonary hypertension
- Classification
- Non-specific clinical symptoms
- The 2 approved therapies in children
- Mortality has improved

What else do we know?

- Not a whole lot!
  - The cellular and molecular basis is still not well understood
  - Adult and pediatric pulmonary hypertension etiology differs, so we can't really extrapolate from adults
  - Therapeutic strategies for adults haven't been sufficiently studied in children
  - We treat pHTN with unapproved therapies for pediatric patients…


LET'S
PRETEND
WE KNOW
WHAT WE'RE
TALKING
ABOUT
marc johns


FUTURE
PAST
PRESENT

Research

- Ongoing studies looking at new medications and their responses
- Focusing on the molecular and cellular basis of the disease
- Studies establishing evidence based therapies for children
- RV focused therapies
- Enhance quality of life of afflicted individuals
- CURE

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