Pediatric Pulmonary Hypertension: Inside Out

Asma Razavi, MD
Assistant Professor Pediatric Critical Care Medicine
Loma Linda University Children’s Hospital
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
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

Mean PA pressure = mPAP

PCW
2–10

Pulmonary capillary wedge pressure

Aorta

RA
2–8

PA
100–140
60–90

LA
2–10

RV
15–30
2–8

LV
100–140
3–12
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

Primary
Secondary

Venous

Primary
Secondary
WHO Classification

• More precise terminology and precise definition

<table>
<thead>
<tr>
<th>Updated Classification of Pulmonary Hypertension¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>2. Pulmonary hypertension due to left heart disease</td>
</tr>
<tr>
<td>3. Pulmonary hypertension due to lung disease or hypoxia</td>
</tr>
<tr>
<td>4. Chronic thromboembolic pulmonary hypertension</td>
</tr>
<tr>
<td>5. Pulmonary hypertension due to unclear multifactorial mechanism</td>
</tr>
<tr>
<td>6. Pulmonary hypertension due to toxins or drugs</td>
</tr>
</tbody>
</table>
Updated Classification of Pulmonary Hypertension

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
6. Pulmonary hypertension due to toxins or drugs
Pathogenesis

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

- Gender:
  - But they also respond more favorably to therapy
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 vasculature
Pathophysiology: Triad

Early  Progression  Late

VASO-CONSTRICITION  THROMBOSIS  REMODELING
Pathophysiology: Vasculature

1. Risk Factors and Associated Conditions
2. Vascular Injury
3. Disease Progression

Endothelial Dysfunction
Loss of Response to

Smooth muscle hypertrophy
Adventitial and intimal proliferation
In situ thrombosis
Plexiform lesion
Advanced Vascular Lesion

Vasoconstriction

Normal
Reversible Disease
Irreversible Disease

Pathophysiology: vasoconstriction

Smooth muscle proliferation in small arteries

Vasoconstriction factors > Vasodilatory factors
Pathophysiology: Vasoconstriction

- **Prostacyclin pathway**
  - Arachidonic acid → COX → Prostaglandins → Prostacyclin (PGI₂) → Prostacyclin derivatives → AC → cAMP → Vasodilation and antiproliferation

- **NO/sGC/cGMP pathway**
  - L-Arginine → NOS → L-Citrulline → NO → sGC → cGMP → Vasodilation and antiproliferation
  - cGMP → GMP → PDE5 inhibitor → Vasodilation and antiproliferation

- **Endothelin pathway**
  - Pro-endothelin → ECE → Endothelin → Endothelin receptor antagonists → ET-A receptor → ET-B receptor → Vasoconstriction and proliferation
  - Downregulation in PH → Upregulation in PH
## Pathophysiology: Microthrombi

<table>
<thead>
<tr>
<th>Etiologies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Protein C and S</td>
</tr>
<tr>
<td>Increased vW factor</td>
</tr>
<tr>
<td>Unspecified coagulation abnormalities</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

- **In situ thrombosis**
- **Advanced Vascular Lesion**
- **Irreversible Disease**
Pathophysiology: Remodeling

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

Severe medial hypertrophy

Vascular obstruction
Chronic vasoconstriction
Proliferation and apoptosis
Migration and ECM synthesis
Disturbed metabolism
Endothelial dysfunction
In situ thrombosis
Inflammation

Dysregulation of vascular tone
PGI₂, NO–sGC–cGMP axis
PDE
Endothelin
Serotonin
K⁺ and Ca²⁺ channels

Abnormal proliferation
TGF-β, BMP
Growth factors (PDGF, FGF)
Transcription factors (Notch 3)
Metabolic changes
MMPs
Cytokines and chemokines

Hypoxia-induced vasomotion
and remodeling
HIF
ROS
TRPC
Mitochondria
NADPH oxidase

Clinical trials
Tki, sGC, PDE, Rho-Ki, EPC etc.
Pathophysiology: Right Heart

RV hypertrophy
RV dilation
Intraventricular septum $\rightarrow$ LV

Increased RV P/V
Impaired relaxation
Myocardial ischemia
Decreased CO

Oxygen demand > supply
RV failure
Further decreased CO

$\uparrow$ Pulmonary Vascular Resistance
$\downarrow$ RV Hypertrophy

$\uparrow$ Wall-stress (tension)
$\downarrow$ RV work-load
Chamber Dilation

Heart Failure & LV Diastolic Dysfunction
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

Consider pHTN in patients with:

- Unexplained SOB
- Dyspnea with exertion
- Syncope
- Fatigue
How do we describe the mechanism of a pulmonary hypertensive crisis?

A. Pulmonary hypertension with loss of consciousness

B. Severe pulmonary hypertension $\rightarrow$ decreased pulmonary CO $\rightarrow$ RV strain $\rightarrow$ abnormal O2/CO2 exchange $\rightarrow$ 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

- Metabolic Acidosis
- Hypoxia
- Respiratory Acidosis
- RV Failure Ischemia
- RVEDP
- RVEDV
- Septal Shift
- Cardiac Output
- LVEDV
- PBF + Airway Obstruction
- V/Q Mismatch

Dead Space Ventilation
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

NORMAL Pulm HTN
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
Therapy: Goals

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

*KEEP CALM*  
and...  
*Ok, not THAT calm!*
Management: Do No Harm!
Therapy: Treatment

- First line: oxygenation and alkalinization
  - Maintain saturations >95%
  - Avoid any hypoxemia (elevation, flight, illness)
  - Correct acidosis

- Respiratory treatment

- iNO (best studied and widely used)

- Minimizing catecholamine stimulation (pain/agitation)

- Ventilator: Avoid over/under expansion with PPV

- Pharmaceutical: alter one of three endothelial signaling 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
Vasodilator Therapy:
- iNO
- oxygen
- Prostacyclin agonists
- Ca channel blockers
- Endothelin-receptor blockers
- PDE inhibitors

Anticoagulants:
- Prostacyclin agonists
- Warfarin

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
• 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
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


