Pediatric Pulmonary Hypertension

Damien Bonnet

Unité médico-chirurgicale de Cardiologie Congénitale et Pédiatrique
Hôpital Universitaire Necker Enfants malades – APHP,
Université Paris Descartes, Sorbonne Paris Cité
IcarP Cardiology, Institut Hospitalo-Universitaire IMAGINE

Centre de Référence Maladies Rares
Malformations Cardiaques Congénitales Complexes-M3C
Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN
TASK FORCE 12
Pediatrics

ERIKA ROSENZWEIG MD, Chair
ROLF M. F. BERGER MD, Chair
STEVEN ABMAN, MD
IAN ADATIA, MD
MAURICE BEGHETTI, MD
DAMIEN BONNET, MD
CHRISTINE GARNETT, Pharm.D.
SHEILA HAWORTH, MD
DUNBAR IVY, MD

New York, NY USA
Groningen, THE NETHERLANDS
Aurora, CO USA
Edmonton, CANADA
Geneve, SWITZERLAND
Paris, FRANCE
Silver Spring, MD USA
London, UK
Aurora, CO USA
Key messages
in pediatric pulmonary hypertension
Natural History of IPAH: NIH Registry

Median survival: 2.8 years (n=194)
Pediatric median survival: 0.8 years (n=16)

Definition of pediatric PH/PAH

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

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

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

Douwes M et al. JACC 2016
Definition of vasoreactivity in children

Douwes M et al. JACC 2016
Genetic architecture of hPAH
FIGURE 1. Pulmonary vascular lesions in lungs of patients displaying severe PAH (A–C) and PVOD (D–F). A. Muscular pulmonary artery with isolated medial hypertrophy. B. Two pulmonary arteries with intimal fibrosis; note the onion skin-like concentric fibrous pattern (left) and the association of fibrosis and medial hypertrophy (right). C. Pulmonary artery with characteristic complex lesion; note the plexiform or glomeruloid proliferation of endothelial cells, surrounded by thin-walled ectatic and congestive blood channels, known as dilation lesions. D. Septal veins and preseptal venules obstructed by loose, cushion-like fibrosis; note congestive pulmonary artery (top right) bearing any vascular lesion. E. Occluded preseptal venule with loose intimal fibrosis. F. Small pulmonary artery with medial hypertrophy in a patient suffering from PVOD; note multiplication of septal capillaries and numerous intraalveolar siderophages.
PVOD

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

Heritable PAH in pediatrics

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

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

- SOX17 - role in PAH and cardiac development

1-Kerstjens-Frederikse WS, J Clin Genet 2013
2-Levy M, ERJ, 2016
TBX4 mutation
Neonatal lung disease
PAH (bimodal)
Pathogenesis of PPHN

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

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

Injury to the Developing Lung Circulation

Impaired Vasoreactivity

Decreased Angiogenesis

Altered Vascular Structure

Persistent Pulmonary Hypertension of the Newborn
- Failure to decrease PVR at birth
- Extra-pulmonary shunting across DA, PFO
- Severe hypoxemia, Respiratory Failure
Pulmonary Vascular Disease in Developmental Lung Disorders

Alveolar Capillary Dysplasia

Congenital Diaphragmatic Hernia

Pulmonary Interstitial Glycogenosis

Surfactant Protein B Deficiency

(Courtesy Csaba Galambos)
PH in Down syndrome/trisomy 21 is a developmental lung disorder

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

Multifactorial pulmonary hypertension in children

Lung disease

Post-capillary PH

Systemic supply to the lung

Pulmonary vascular disease /maladaptation

Left-to right shunt /CHD

Scimitar syndrome
Multifactorial pulmonary hypertension in scimitar syndrome

Bonnet D et al. 2019
Modified Classification of PH

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

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

1’’. PPHN

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

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

4. Chronic Thromboembolic Pulmonary Hypertension

5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy,
   5.2. Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3. Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure
Diagnostic algorithm pediatric Task force WSPH Nice 2018

Symptoms, clinical signs, genetic syndromes, personal or family history suggestive of PH

Yes

Echo, ECG, CXR compatible with PH

No

PH unlikely

Consider other causes of symptoms or re-check

Consider most common causes of PH in children (i.e., CHD, chronic lung disease)

Review history, signs, risk factors, PFTs incl. DLCO, "Polysonmography", chest CT

Yes

Diagnosis of lung disease confirmed?

No

Signs of mod-severe PH or RV dysfunction

Refer to pediatric PH expert

No

No signs of severe PH or RV dysfunction

Treat underlying lung disease

Yes

Perform V/Q scan to rule out CTEPH. Are mismatched defects present?

No

CTEPH suspect. CTA and selective PA angiograms with referral to PEA expert

Yes

Cardiac catheterization at pediatric center with AVT: PAPm > 20 mmHg, PPAWP < 15 and PVRi > 3 WU. Include full shunt evaluation to rule out CHD

Consider other causes

CTD, HIV, CHD, portopulmonary, drugs/toxins, PVD/PCH

IPA/FP/PAH

genetic testing/counseling

Rosenzweig et al. ERJ 2019
Treatment of pediatric pulmonary hypertensions
Treatment of pediatric PAH/PH and current challenges

1. AVT responders should receive Calcium channel blockers
Low and high risk pediatric patients with PAH

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETERMINANTS OF RISK</th>
<th>HIGHER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Progression of Symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt; 350 meters</td>
<td>6MWT (&gt;7 yrs old)</td>
<td>&lt; 350 meters</td>
</tr>
<tr>
<td>I,II</td>
<td>Growth</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP / NTproBNP</td>
<td>Significantly elevated Rising level</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>RA / RV Enlargement Reduced LV size Increased RV/LV Ratio Reduced TAPSE Low RV FAC Pericardial Effusion</td>
</tr>
<tr>
<td>Systemic CI &gt; 3.0 L/min/m² Systemic venous saturation &gt;65% + Acute Vasoreactivity</td>
<td>Hemodynamics</td>
<td>Systemic CI &lt; 2.5 L/min/m² RAP &gt; 10mmHg PVRI &gt; 20 WU*m² Systemic venous saturation &lt; 60% PACi &lt;0.85</td>
</tr>
</tbody>
</table>
Pediatric IPAH/HPAH Treatment algorithm WSPH 2018

Expert Referral

General: Consider Diuretics, Oxygen, Anticoagulation

Acute Vasoreactivity Testing

Positive

Oral CCB

Improved + Sustained reactivity

Lower Risk

ERA or PDE-5i (oral)
Oral / inhaled prostacyclin / prostacyclin agonists
Consider combination therapy (sequential or upfront)

Serial Reassessment***

Negative

High Risk

Epoprostenol or Treprostinil (IV/SQ)
Consider Early Combination

Atrial septostomy

Potts Shunt

Lung Transplant

*Regulatory approval for use in children varies among countries
** Expert opinion only
*** Deterioration or not meeting treatment goals
Limited evidence in RCT for this algorithm but convincing registries data

Zijlstra WMH, et al. JACC 2014
Up-front combination therapy with epoprostenol, bosentan and sildenafil

|                | Baseline     | Month 4     | Final follow-up
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>11.9 ± 5.2</td>
<td>4.9 ± 4.9*</td>
<td>5.2 ± 3.5*</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>65.8 ± 13.7</td>
<td>45.7 ± 14.0*</td>
<td>44.4 ± 13.4*</td>
</tr>
<tr>
<td>CI (l / min / m²)</td>
<td>1.66 ± 0.35</td>
<td>3.49 ± 0.69*</td>
<td>3.64 ± 0.65*</td>
</tr>
<tr>
<td>PVR (d.s.cm⁻⁵)</td>
<td>1718 ± 627</td>
<td>564 ± 260*</td>
<td>492 ± 209*</td>
</tr>
</tbody>
</table>

*32 ± 19 months
*p < 0.01 versus baseline

Up-front triple therapy in children with severe PAH

![Graph showing event-free survival over time for patients at risk in children with severe PAH. The graph indicates a substantial decline in event-free survival from 100% at time 0 to approximately 10% at 6 years. The number of patients at risk decreases from 21 at time 0 to 1 at 6 years.]

Haarman M, Berger RMF, Bonnet D. 2019
Lung transplantation in children
(Lung Transplantations: January 1995 – June 2017)

Median survival (years): Adult = 5.6; Pediatric = 5.1

Survival (%)
Years
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Adult (N=45,780)  Pediatric (N=1,634)

Pediatric PAH
Median survival 8.9 years

Death on list 7/26: 27%

Operative death/acute graft failure 22%
ANASTOMOSIS OF THE AORTA TO A PULMONARY ARTERY
Certain Types of Congenital Heart Disease

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

In 1945 Blalock and Taussig introduced a new surgical procedure for the relief of anoxemia due to pulmonary stenosis or pulmonary atresia. By anastomosing the subclavian or innominate artery to either the right or the left
Different types of systemic-to-pulmonary shunts to palliate cyanotic CHDs with pulmonary stenosis/atresia

Blalock Taussig Thomas

Modified Blalock Deleval

Waterston

Potts
Potts shunt in pediatric PAH

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

Stenting of tiny arterial duct in PAH

Before PDA stenting

After PDA stenting

Boudjemline Y et al. Circ Cardiovasc Interv 2013
Potts shunt should be preferred to atrial septotomy.
Preliminary data
Marc Grady (Saint-Louis) & Damien Bonnet (Paris)

121 patients
Early mortality 15%
Overt right heart failure is a contra-indication
Improvement is spectacular in 90% of survivors
Pros and cons

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

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

Boudjemline Y et al. Circ Cardiovasc Interv 2013
Percutaneous Potts’s shunt
Percutaneous Potts’s shunt
Percutaneous Potts’ shunt
Percutaneous Potts’s shunt
Percutaneous Potts’s shunt
Pulmonary hypertensions and congenital heart diseases
Pulmonary Hypertension in CHDs

\[ R = \frac{P}{Qp} \]

\[ P = \text{Flow} \times \text{Resistance} + \text{PCW} \]

- 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
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*
ASD, VSD or complex defect, $\uparrow$ Qp and/or PAP, with left-to-right shunting.

Over time, PVR $\uparrow$ resulting in bi-directional flow.

Resistance $\uparrow$ further with reversal of shunt: right-to-left $\rightarrow$ Eisenmenger syndrome – patient becomes $\uparrow$ cyanotic.

Systemic-to-pulmonary shunting can ultimately remodel the pulmonary vasculature to a characteristic irreversible phenotype similar to other forms of PAH.
Left-to-right shunt: natural history/pathology

Reversible PAH

- normal arterioles
- early endothelial dysfunction
- medial hypertrophy
- neointimal lesions

Irreversible PAH

- plexiform lesions
- angioproliferation
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
Paediatric left-to-right shunt & mPAP >25mmHg

94-98% reversible PAH

2-6% post-operative irreversible PAH

90% shunt corrected

10% shunt not corrected

100% Irreversible PAH-CHD

From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease
Recommendations for correction of CHD with prevalent systemic-to-pulmonary shunts

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class (a)</th>
<th>Level (b)</th>
<th>Ref. (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVRI (WU/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>&lt;2.3</td>
<td>Yes</td>
<td>IIa C</td>
</tr>
<tr>
<td>&gt;8</td>
<td>&gt;4.6</td>
<td>No</td>
<td>IIa C</td>
</tr>
<tr>
<td>4–8</td>
<td>2.3–4.6</td>
<td>Individual patient evaluation in tertiary centres</td>
<td>IIa C</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Source, features/parameters</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>Favorable: &lt;1&lt;br&gt;Unfavorable: &gt;2</td>
</tr>
<tr>
<td>Congestive heart failure/pulmonary congestion</td>
<td>Favorable: Present&lt;br&gt;Unfavorable: Absent</td>
</tr>
<tr>
<td>Tendency to respiratory disorders (inflammatory/infectious)</td>
<td>Favorable: Yes&lt;br&gt;Unfavorable: No</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Favorable: Yes&lt;br&gt;Unfavorable: No</td>
</tr>
<tr>
<td>Use of anticongestive medication</td>
<td>Favorable: No&lt;br&gt;Unfavorable: Yes (Down syndrome)</td>
</tr>
<tr>
<td>Associated syndromes</td>
<td>Favorable: No&lt;br&gt;Unfavorable: Yes</td>
</tr>
<tr>
<td>Associated airway/lung disease</td>
<td>Favorable: No&lt;br&gt;Unfavorable: Yes</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Favorable: Present/overt&lt;br&gt;Unfavorable: Mild/absent</td>
</tr>
<tr>
<td>Dynamic precordium</td>
<td>Favorable: Present&lt;br&gt;Unfavorable: Absent</td>
</tr>
<tr>
<td>Precordial murmur</td>
<td>Favorable: Present&lt;br&gt;Unfavorable: Absent</td>
</tr>
<tr>
<td>Second heart sound (pulmonic area)</td>
<td>Favorable: Mildly increased split present&lt;br&gt;Unfavorable: Loud split absent</td>
</tr>
<tr>
<td>Peripheral oxygen saturation, %</td>
<td>Favorable: &gt;93&lt;br&gt;Unfavorable: &lt;90</td>
</tr>
<tr>
<td>Associated airway obstruction/lung disease</td>
<td>Favorable: No&lt;br&gt;Unfavorable: Yes</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
</tr>
<tr>
<td>Size of the heart</td>
<td>Favorable: Enlarged&lt;br&gt;Unfavorable: “Hypertrophic”</td>
</tr>
<tr>
<td>Pulmonary vascular markings</td>
<td>Favorable: Prominent&lt;br&gt;Unfavorable: Decreased distal markings</td>
</tr>
<tr>
<td>Congestion</td>
<td>Favorable: Present&lt;br&gt;Unfavorable: Absent</td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
<td>Favorable: Absent&lt;br&gt;Unfavorable: Present</td>
</tr>
<tr>
<td><strong>Transthoracic echocardiography</strong></td>
<td></td>
</tr>
<tr>
<td>Direction of flow across the communication</td>
<td>Favorable: Left-to-right or bidirectional, but predominantly left-to-right&lt;br&gt;Unfavorable: Bidirectional, predominantly right-to-left</td>
</tr>
<tr>
<td>Size of left cardiac chambers (posttricuspid shunts)</td>
<td>Favorable: Enlarged&lt;br&gt;Unfavorable: Not enlarged</td>
</tr>
<tr>
<td>Pulmonary-to-systemic blood flow ratio (Qp:Qs)</td>
<td>Favorable: &gt;3.0:1&lt;br&gt;Unfavorable: &gt;2.0:1</td>
</tr>
<tr>
<td>Right ventricular dysfunction</td>
<td>Favorable: Absent&lt;br&gt;Unfavorable: Present</td>
</tr>
<tr>
<td><strong>Type of defects</strong></td>
<td></td>
</tr>
<tr>
<td>Simple lesions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Favorable: Present&lt;br&gt;Unfavorable: Complex anomalies&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, Wood units m&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>Favorable: &lt;6.0 (preferably, &lt;4.0)&lt;br&gt;Unfavorable: &gt;8.0</td>
</tr>
<tr>
<td>Pulmonary-to-systemic vascular resistance ratio (PVR:SVR)</td>
<td>Favorable: &lt;0.3&lt;br&gt;Unfavorable: &gt;0.5</td>
</tr>
</tbody>
</table>
Normalisation of Flow (Haemodynamic Unloading) reverses PAH-CHD, but not after a certain point of no return.
Which lesions are reversible in PAH-CHD?

- Foetus
- Birth
- Foetal arteriole
- Mature arteriole

8 weeks

Wagenvoort, and Heath & Edwards
What could make PAH irreversible?

1- Apoptosis and apoptosis resistance

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

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

Lévy M et al. JACC 2007;49:803-10
Comparison of human reversible to irreversible PAH-CHD

*The liquid biopsy concept*

From: Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease

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

CEC counts in peripheral venous blood of CHD patients with PH

Summary Flow PH in CHD
The Fontan circulation - a new portal system

The vicious circle to failing Fontan

- Volume overloaded and overstretched ventricle
- Declining cardiac output
- Overgrown and severely deprived ventricle
- Reduction of preload
- Vasoconstriction and increased afterload
- Systolic and diastolic dysfunction with remodeling of the ventricle
- Increased filling pressures
- Sustained deprivation of the de-loaded ventricle
- Decrease of transpulmonary flow
- Overt heart failure «Failing Fontan»

Adapted from Marc Gewillig-Heart 2016
The multifactorial origin of «heart failure» in the Fontan circulation

- Increased PVR
- Prothrombotic status
- Protein loosing enteropathy /bronchial casts
- Heart failure Systo-diastolic dysfunction
PAH/Heart failure drugs in Fontan circulation

Potentially a wrong reasoning and a predictable minimal effect

ACE Inhibitors to decrease after load

Diuretics to decrease preload

Pulmonary vasodilatation to increase preload

Beta-blockers to lengthen diastole and ventricular filling

Exercise to increase preload and decrease PVR

Lusitropic drugs sGC stimulators
Conclusion

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

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

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

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

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

Isabelle Szezepanski
Marilyne Lévy
Thank you

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

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