Case Presentation

FC presented at the age 6 years with history of:

- Progressive decrease in exercise tolerance
- Fatigue and dyspnea
- Getting tired easily
- Recurrent respiratory tract infections
- Was seen in a local hospital for further evaluation
Case Presentation

- **BP = 100/65 mm Hg**
- **Oxygen saturation of 98% in room air**
- **ECG**
  - sinus rhythm of 90 beats/min
  - right-axis deviation
- **Heart**
  - Pan systolic murmur G3/6 LSB
  - DM G 1-2/4 RLSB
  - No HSM
  - Splitting of S2
- **Laboratory Tests**
  - no signs of polycythemia
  - (red blood cell $5 \times 10^3$; hematocrit 41.6%; hemoglobin 14.1 g/dL).

Case Presentation

- **Echocardiography (TTE)**
  - Atrial septal defect (ostium secundum type) with left-to-right shunt and **perimembranous ventricular septal defect** with left-to-right shunt.
  - Mild enlargement of the right atrium
  - Mild enlargement of the right ventricle
  - Mild tricuspid regurgitation
  - Mild pulmonary regurgitation
  - Good systolic function
  - RVSP was estimated at 70 mm Hg based on TR jet
How Would You Proceed Next With the Patient?

A. You plan for surgery to repair both shunts
B. You start treatment with advanced PAH therapies
C. You plan for further examinations

Patient’s Diagnosis Status

CHD with congenital shunts:
- PAH
- WHO Functional Class II

Due to the Lack of Complete Hemodynamic Assessment, the Patient’s Accurate Diagnosis is Not Well Established
Assessing Hemodynamics is Key in Patients with PAH-CHD

A RHC/LHC should be performed in patients with PAH-CHD

The opportunity to perform the shunt closure should be discussed.

The decision to close left to right shunt in the presence of PAH should be based on:

- Preventing the progression of PAH
- Long term prognosis benefit and symptoms improvement

Closing the defect should not be based on:

- Procedural feasibility
- Not on reducing small left to right shunts
- Not on improving O₂ saturation once PAH is established.

Definition of PAH

Mean PA pressure > 25 mm Hg at rest with PCWP or LAP<15

Mean PAP and PVR both ↑ PA vascular disease (PVOD)

If PVR>SVR and shunt reverses: Eisenmenger Syndrome

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Simonneau G et al. JACC 2013
Dimopoulos et al, European Heart J 2014
Mechanisms Behind PAH/PVD with Shunts - Pathophysiology

- Flow ↑
- Pressure ↑

Smooth muscle cell hypertrophy, proliferation, and migration, vessel fibrosis, and in situ thrombosis, small vessel occlusion.

Disease progression:
- Normal
- Injury
- Endothelial damage
- Smooth muscle cell proliferation and migration

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PVR and Cardiac Catheterization

Normal anatomy

Blood samples for PO2 and Sat%

RAP, mean PAP, PCWP, LAP
Cardiac output (thermodilution/Fick)

PVR = Mean PAP - mean LAP (or PCWP) / Qp

Patient with a VSD, PAH and a large left to right shunt

Defect

High pulmonary blood flow
PAP > 25mmHg
PVR is low
Operable

Patient with a Fontan operation

Lung tunnel ( caval-atrial baffle)

Low pulmonary blood flow/CO
PAP < 25mmHg
PVR is high
Based on hemodynamic assessment:

- **PVR of less than 4 WU**………………Surgery
- **PVR of more than 8 WU**………………….Inoperable
- A ‘grey zone’ exists for patients with a **PVR of 4–8 WU**

A ‘grey zone’ exists for patients with a **PVR of 4–8 WU**

**Some may be suitable for surgery**

If acute **vasodilator challenge (NO/O₂)** results in ALL of the following:

- decrease in PVR of ~20%
- decrease in the ratio of PVR to SVR of ~20%
- a final PVR of < 6 WU
- a final ratio of PVR to SVR of < 0.3

**Some may be appropriate for a ‘treat and repair’ strategy**

Managed medically to reduce PVR to a level considered operable
There is a Progression of lesions in the presence of left to right shunt

This raises the opportunity to treat patients with increased PVR that contraindicates surgery in order to remodel the vascular bed and possible to allow complete correction of the underlying anatomical lesion.
In patients with high risk for surgical intervention and an elevated PVR, consider fenestration of the Patch.

When PAH develops after repair, the prognosis is worse than in patients with open shunts, even R-L i.e. ES patients.
Our patient had Corrective Surgery at the age of 6 years.

At 6 years corrective surgery was done at an outside hospital. PVR was reported to be 4.5 WU (No additional information were available).

Atrial and ventricular defects were closed.

---

At the Age of 6 Years: Examination After the Corrective Surgery

- Echocardiography 2 days after surgery
  - 2 days after the surgery, no residual shunts through atrial or ventricular septum were observed.
  - no tricuspid regurgitation
  - no elevated right ventricular systolic pressure identified

- No Right Heart Catheterization was performed

- Long Term Monitoring
  - After discharge, she was advised for routinely monitored in an outpatient clinic at least once a year.
Lost for F/U. Admission at a CHC at the age of 16 years

Patient was lost for follow up Ten years after the surgery, i.e. at 16 the patient was hospitalized due to:

- Fatigue and dyspnea
- Syncope during exercise
- Marked decrease in exercise tolerance

At the Age of 16 Years: Examination and Assessment

- Physical examination
  - arterial oxygen saturation between 96% and 100%
  - blood pressure 120/80 mmHg

- ECG
  - right-axis deviation
  - right ventricular hypertrophy
  - ST segment changes in v1-v3
  - The 24-hour ECG showed no SVT or VT
Echocardiography (TTE)
- Enlargement of the right atrium and right ventricle
- Elevated right ventricle systolic pressure (110 mmHg)
- Elevated diastolic pulmonary artery pressure (70 mmHg)

Echocardiography and PAH

Echocardiography
Signs of severe PH, including:
- Enlargement of right heart chambers
- Shortening of the acceleration time
- Systolic notch of pulmonary flow
- Severe tricuspid regurgitation,
- Elevated RV systolic pressure
- TAPSE of 16 mm.
Echocardiography and PAH

PVR (Woods) = 10 x [Peak TR velocity (m/s)/RVOT VTI (cm)] + 0.16

At the Age of 16 Years: Examination and Assessment

Right Heart Catheterization
- pulmonary arterial hypertension confirmed: mPAP 85 mmHg
- pulmonary capillary wedge pressure 14 mmHg
- cardiac output: 3.8 L/min
- cardiac index: 2.2 L/min/m²
- pulmonary vascular resistance: 17.4 Wood units
RHC and Vasodilator Trial with NO

Acute Responder

Calcium Channel Blocker

Involve a specialist with expertise

Non-Responder

NYHA II-IV

Vasodilator therapy ERA or PDE5-inh or prostacyclin analog or Combination

Not Improved

Improved

Consider LT or AS

Regulation of Pulmonary Vascular Tone

Endothelin pathway

NOS nitric oxide pathway

Prostacyclin pathway

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Potential Therapy for PAH

- Too much endothelin
- Too little prostacyclin
- Too little nitric oxide (NO)

Vasoconstriction Remodeling

Treatment Vasodilation Reverse Remodel

Block endothelin
Add prostacyclin
Enhance effect of NO
Block calcium entry

PH

At the Age of 16 Years: The Patient's Diagnosis

PAH associated to Repaired (double shunts) CHD
- WHO Functional Class III

- she was administered Sildenafil at a standard dose of 20 mg tid and vitamin K antagonist
Classification of Congenital Shunts and PAH

- Eisenmenger syndrome
- Operated shunt (VSD)
- PAH with a small shunt
- PAH with L→R shunt
- Fontan circulation

**PAH-CHD Groups and Therapy**

**TABLE 1. Clinical classification of congenital systemic-to-pulmonary shunts associated to PAH**

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenmenger syndrome</td>
<td>Includes all systemic-to-pulmonary shunts due to large defects, leading to a severe increase of PVR and resulting in a reverse pulmonary-to-systemic or bi-directional shunt. Cyanosis, erythrocytosis and multiple organs involvement are present.</td>
</tr>
<tr>
<td>PAH associated with systemic-to-pulmonary shunts</td>
<td>In patients with moderate to large septal defects the increase of PVR is mild to moderate, systemic-to-pulmonary shunt is still largely prevalent and no cyanosis is present at rest.</td>
</tr>
<tr>
<td>PAH with small septal defects</td>
<td>Small defects (usually ventricular septal defects &lt;1 cm and atrial septal defect &lt;2 cm of effective diameter assessed by echo); clinical picture similar to IPAH.</td>
</tr>
</tbody>
</table>

A. You are satisfied with current outcome and continue with treatment as is

B. You add-on another advanced PAH therapies – an ERA for example

C. You repeat cardiac catheterization in 6 months
Upon new "Guidelines" start with Upfront or Fast Sequential Combination Regimen with a advanced PAH therapies could be advised PDEi-5 + ERA

Today we have evidence that the addition of an ERA to PDE—5 dramatically improves the outcome:

- AMBITION study
- SERAPHIN study

Symptoms are improved but hemodynamic conditions are not optimal yet. An ERA should be added.

---

Treatment Algorism for PAH

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A or B</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>IIa</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>III</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>IV</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
<td>Sildenafil</td>
</tr>
</tbody>
</table>

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Treatment Decision

Upon new “Guidelines” start with Upfront or Fast Sequential Combination Regimen with a advanced PAH therapies could be advised PDEi-5 + ERA

The patient was given Bosentan 62.5 mg bid and increased to 125 mm PO bid on top of sildenafil 20mg tid

18 Years Old: Impact of the Treatment After 3 Months

<table>
<thead>
<tr>
<th></th>
<th>16 years</th>
<th>+3 months</th>
<th>18 years</th>
<th>+3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA FC</td>
<td>III</td>
<td>II</td>
<td>III</td>
<td>II</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td></td>
<td></td>
<td>17</td>
<td>330</td>
</tr>
<tr>
<td>6-MWD (m)</td>
<td>440</td>
<td>520</td>
<td>411</td>
<td>542</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>2.2</td>
<td>2.65</td>
<td>2.0</td>
<td>2.7</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>85</td>
<td>40</td>
<td>91</td>
<td>34</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>14</td>
<td>10</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>17.4</td>
<td>8.8</td>
<td>16.8</td>
<td>10</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sildenafil 20mg tid started</td>
<td>Sildenafil 20mg tid</td>
<td>Sildenafil 20mg tid + Bosentan started</td>
<td>Sildenafil 20mg tid + Bosentan started</td>
</tr>
</tbody>
</table>
A. Patient’s conditions are not satisfactory yet – I add-on a 3rd PAH specific therapy – epoprostenol for example

B. Patients improved markedly - I maintain dual regimen sildenafil + Bosentan

C. Refer patient for Lung Transplantation
NEWLY APPROVED PAH MEDICATIONS

Table 1. Newly approved PAH medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitantenn</td>
<td>EDR</td>
<td>10 mg daily</td>
<td>oral</td>
</tr>
<tr>
<td>Riociguan</td>
<td>sGC stimulator</td>
<td>1 mg three times daily titrated to</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>maximum of 2.5 mg three times daily</td>
<td></td>
</tr>
<tr>
<td>Treprostin diolamine</td>
<td>prostanoid</td>
<td>0.25 mg twice daily or 0.125 mg three</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>times daily titrated to maximum dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>based on tolerability</td>
<td></td>
</tr>
</tbody>
</table>

ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase.
Pulmonary hypertension and congenital heart disease: An insight from the REHAP National Registry

International Journal of Cardiology 184 (2015) 717-723
Conclusion I: PAH-CHD

- In the presence of cardiac shunts, a careful assessment of hemodynamic conditions prior to repair is mandatory. Generally, shunts should be repaired prior to 2 years of age and even much earlier in other conditions like AVC.

- In patients with shunts and PAH, the “Treat to Repair” approach might bring patients into better hemodynamic conditions to surgery. But we lack solid data to support this approach. Other options include “Repair and Treat”. Consider option of fenestration when closing defect(s).

- The prognosis of patients developing PAH after closure of shunts is worse than the one with open shunts, i.e. Eisenmenger Syndrome.

Conclusion II: PAH-CHD

- Patients with closed defects should be monitored once a year.
- In patients with repaired shunts and PAH, strict monitoring is a mandatory, as well as early and aggressive use of advanced therapies in combination.
- In patients with repaired defects and PAH: implement aggressive treatment up to triple combination regimen as soon as possible and as needed.
- Consider Heart-Lung transplant or Atrial septostomy in cases of maximal therapeutic regimen and failure to respond.