45th Annual International Congress of the EGYPTIAN SOCIETY OF CARDIOLOGY CardioEgypt 2018

Pulmonary Arterial Hypertension in Patients with Repaired Congenital Heart Disease- Case Presentation

Fadi Bitar, MD
Professor of Pediatrics and Adolescent Medicine and Biochemistry
Director- Children's Heart Center
Co-Director-The CHD Research Genetic Program
Executive Director for External Medical Affairs
American University of Beirut, Lebanon
Co-Founder of PACHDA
President- PACHDA

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 5×10^3; 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**:

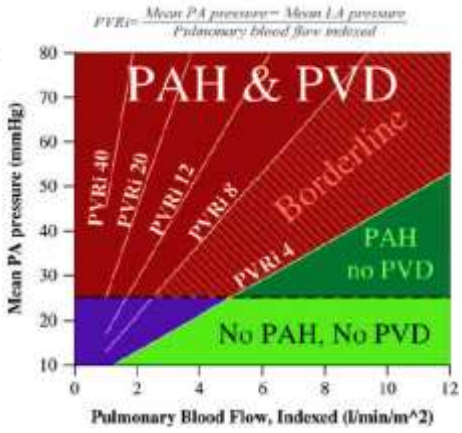
- Procedural feasibility
- Not on reducing small left to right shunts
- Not on improving O_2 saturation once PAH is established.

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



Simonneau G et al, JACC 2013
Dimopoulos et al, European Heart J 2014

Congenital Shunts and PAH

Left to right shunt lesions

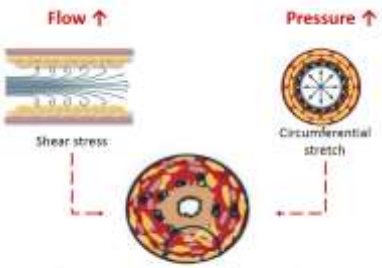
– high pulmonary blood flow
  • ASD

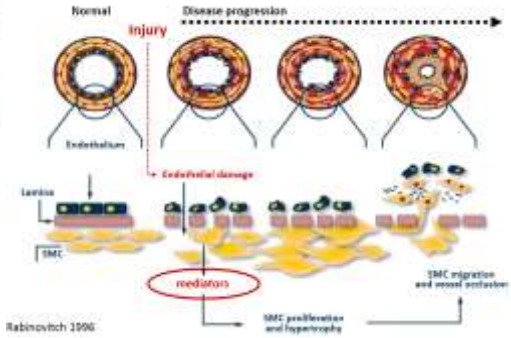
PAH late

– high pulmonary blood flow **and** pressure
  • VSD
  • PDA
  • AVSD
  • Truncus arteriosus

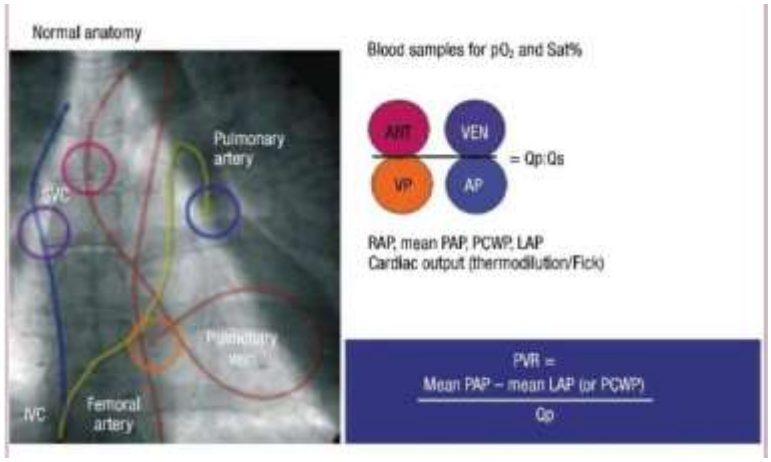
PAH early

Mechanisms Behind PAH/PVD with Shunts-Pathophysiology



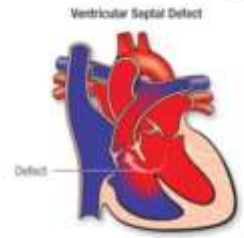


PVR and Cardiac Catheterization



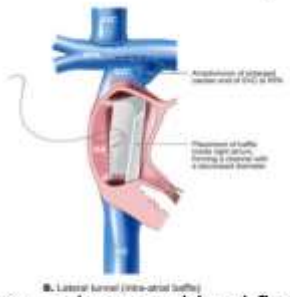
PVR and Cardiac Catheterization

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



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

Patient with A Fontan operation



Low pulmonary blood flow/CO
PAP < 25mmHg
PVR is high

Expert Consensus and PVR

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**

Expert Consensus and PVR

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

Some may be suitable for surgery

If acute **vasodilator challenge (NO/O_2)** results in ALL of the following:

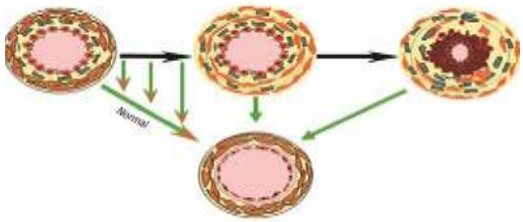
- decrease in PVR of ~20%
- decrease in the ratio of PVR to SVR of ~20%
- a final PVR of < 6 WU
- a final ratio of PVR to SVR of < 0.3

Some may be appropriate for a 'treat and repair' strategy

Managed medically to reduce PVR to a level considered operable

Left to Right Shunt and PAH and Treat and Repair Strategy

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.

Left to Right Shunt and PAH and Treat and Repair Strategy

Expert Rev Cardiovasc Ther. 2015 Jun;13(6):693-701. doi: 10.1586/14779072.2015.1047763. Epub 2015 May 17.

Approaching atrial septal defects in pulmonary hypertension.

Schwerzmann M[1], Pfammatter JP.

Targeted Therapy Is Required for Management of Pulmonary Arterial Hypertension After Defect Closure in Adult Patients With Atrial Septal Defect and Associated Pulmonary Arterial Hypertension

Takao Fujita, MD, Atsushi Yao, MD, Masaru Hatano, MD, Toshiro Inaba, MD, Hitoshi Mizuoka, MD, Shin Minatsuki, MD, Teruhiko Imamura, MD, Hisataka Maki, MD, Koichiro Kinugawa, MD, Minoru Ono, MD, Ryozo Nagai, MD, and Issei Komuro, MD

Case Report

Continuous Epoprostenol Therapy and Septal Defect Closure in a Patient With Severe Pulmonary Hypertension

Aki Hirakawa, MD, Katsumasa Miyaji, MD, and Teiji Akagi, MD

Left to Right Shunt and PAH and Repair with Fenestration

In patients with high risk for surgical intervention
and an elevated PVR, consider fenestration of the Patch

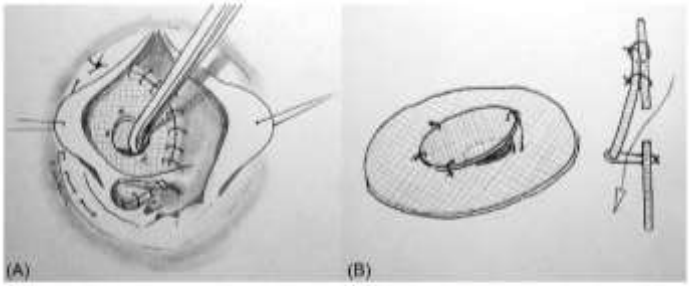
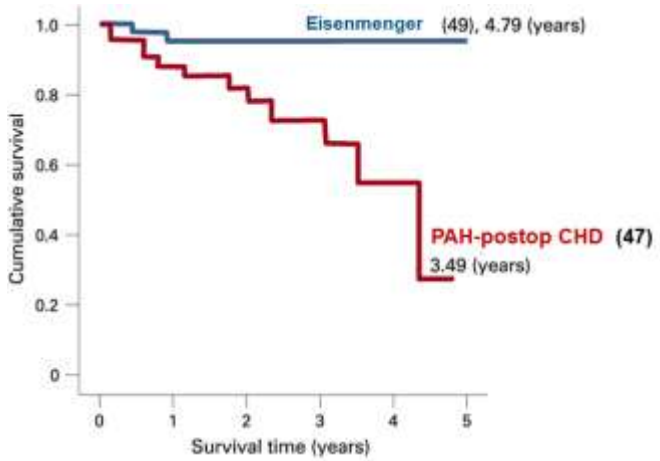


Figure 3. Double-flap valve patch for fenestrated ventricular septal defect closure. (A) View from the right atrium, through the tricuspid valve and with a probe through the flapped fenestration. (B) View of the double-flap valve patch in profile with an open valve. Reproduced with permission from Novick et al.[30]

When PAH develops after repair, the prognosis is worse than in patients with open shunts, even R-L i.e. ES patients

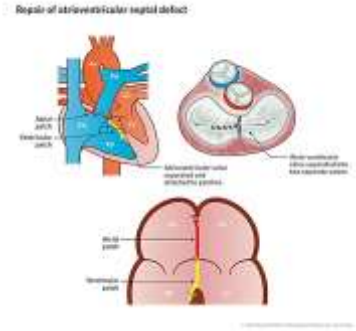


Our patient had Corrective Surgery at the age of 6 years

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

At the Age of 16 Years: Examination and Assessment

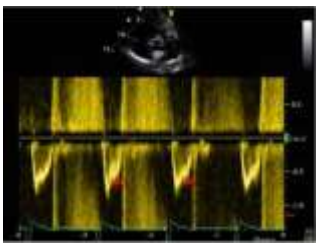
- Echocardiography (TTE)
  - enlargement of the right atrium and right ventricle
  - elevated right ventricle systolic pressure (110 mmHg)
  - elevated diastolic pulmonary artery pressure (70 mmHg)

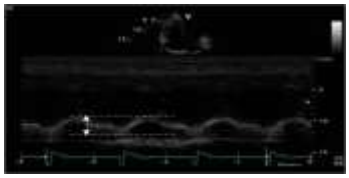
Echocardiography and PAH

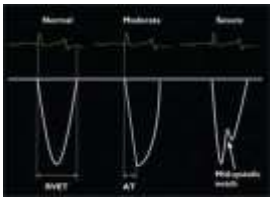
Echocardiography

Signs of severe PH, including:

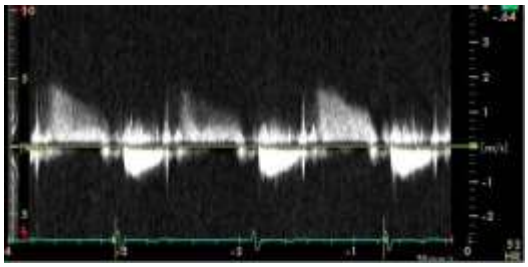
- Enlargement of right heart chambers
- Shortening of the acceleration time
- Systolic notch of pulmonary flow
- Severe tricuspid regurgitation,
- Elevated RV systolic pressure
- TAPSE of 16 mm.







Echocardiography and PAH



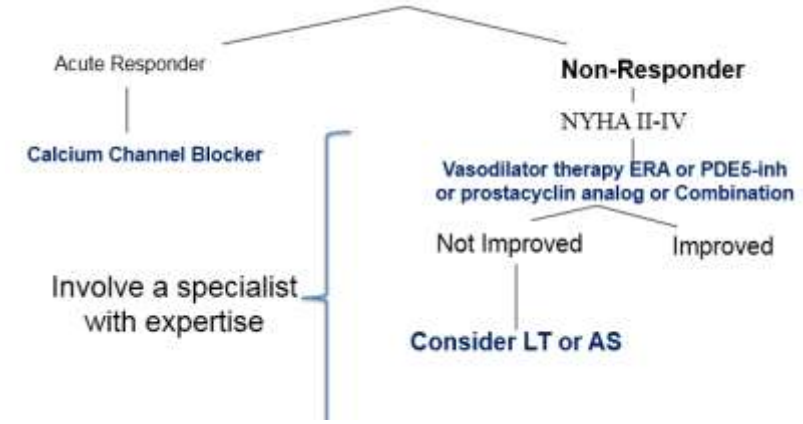
PVR (Woods) = 10 x [Peak TR velocity (m/s)/RVOT VTI (cm)] + 0.16

At the Age of 16 Years: Examination and Assessment

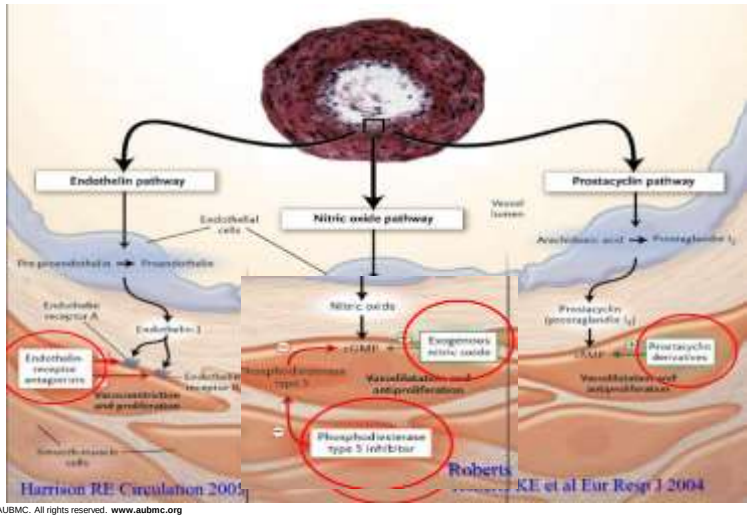
Right Heart Catheterization

- 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/m^2
- pulmonary vascular resistance: 17.4 Wood units

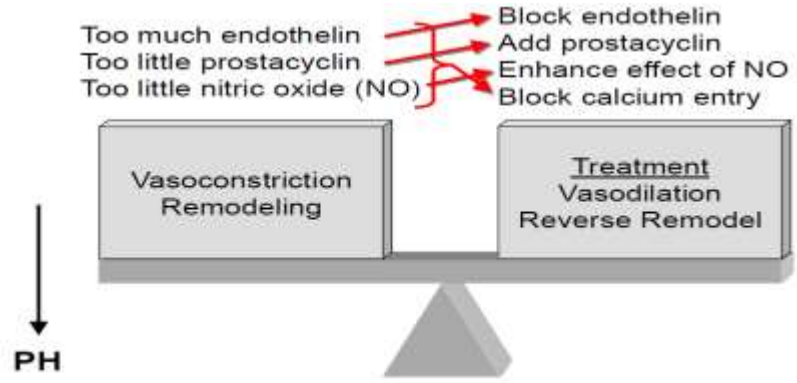
RHC and Vasodilator Trial with NO



Regulation of Pulmonary Vascular Tone



Potential Therapy for PAH



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

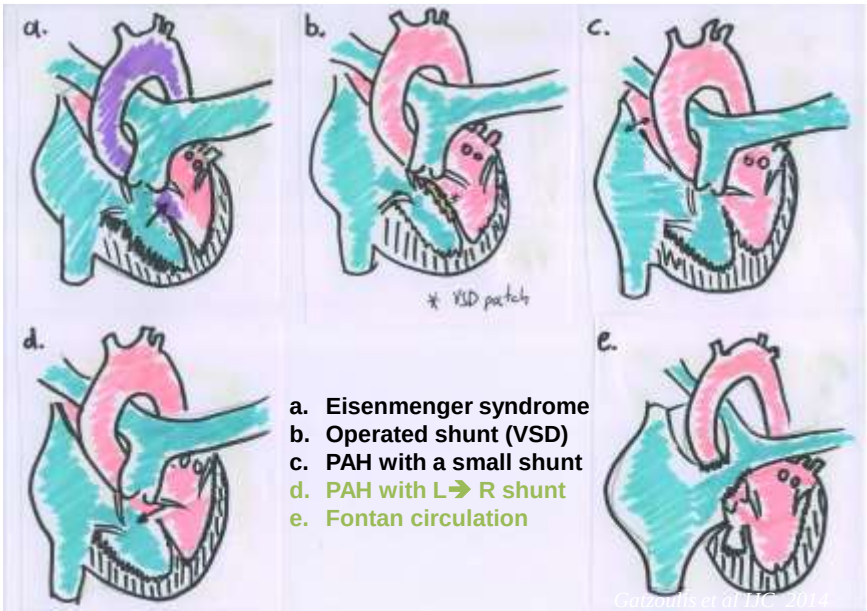
TABLE 1. **Clinical classification of congenital systemic-to-pulmonary shunts associated to PAH**

Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts due to large defects, leading to a severe increase of PVR and resulting in a reversed (pulmonary-to-systemic) or bi-directional shunt. Cyanosis, erythrocytosis and multiple organs involvement are present
PAH associated with systemic-to-pulmonary shunts	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
PAH with small septal defects	Small defects (usually ventricular septal defects <1 cm and atrial septal defect <2 cm of effective diameter assessed by echo); clinical picture similar to IPAH
PAH after corrective cardiac surgery	CHD has been corrected but PAH either is still present immediately after surgery or has recurred several months or years after surgery in the absence of significant immediate postoperative residual lesions

CHD: Congenital Heart Defect, IPAH: Idiopathic Pulmonary Arterial Hypertension, PVR: Pulmonary Vascular Resistance.
From reference No 6 with permission: Simonneau G, et al. J Am Coll Cardiol 2009; 54 (Suppl 1):S43-S54.

Rev Esp Cardiol. 2010;63:1179

PAH-CHD Groups and Therapy



a. **Eisenmenger syndrome**
b. **Operated shunt (VSD)**
c. **PAH with a small shunt**
d. **PAH with L➔ R shunt**
e. **Fontan circulation**

Gatzoulis et al IJC 2014

16 Years Old: Impact of the Treatment After 3 Months

	16 years	+3 months
NYHA FC	III	II
BNP *(pg/mL)*		
6-MWD (*m*)	440	520
Cardiac Index (*L/min/m²)*	2,2	2,65
mPAP (*mmHg*)	85	40
RAP (*mmHg*)	14	10
PVR (*wood units*)	17,4	8,8
Treatment	Sildenafil 20mg tid started	Sildenafil 20mg tid

How would you proceed next with the patient?

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

Treatments Options in Patients With Repaired Shunts PAH-CHD - Advanced PAH Therapies

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

INITIAL THERAPY WITH PAH APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)
*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.
†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea(beraprost).
‡ Positive opinion for approval of the CHMP of EMA

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Bosentan Macitentan‡ Sildenafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

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

	16 years	+3 months	18 years	+ 3 months
NYHA FC	III	II	III	II
BNP (*pg/mL*)			17	330
6-MWD (*m*)	440	520	411	542
Cardiac Index (*L/min/m²*)	2,2	2,65	2,0	2,7
mPAP (*mmHg*)	85	40	91	34
RAP (*mmHg*)	14	10	15	12
PVR (*wood units*)	17,4	8,8	16.8	10
Treatment	Sildenafil 20mg tid started	Sildenafil 20mg tid	Sildenafil 20mg tid+ Bosentan started	Sildenafil 20mg tid+ Bosentan started

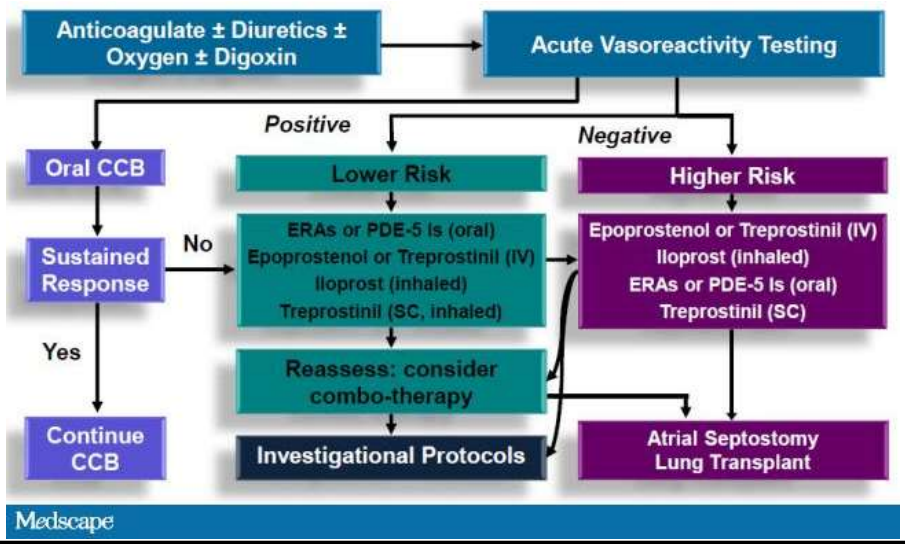
How would you proceed next with the patient?

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

Treatment Algorism for PAH



Atrial Septestomy

EXPERT REVIEWS

Atrial septostomy in patients with pulmonary hypertension: should it be recommended?

Expert Rev. Respir. Med. 5(3), 363–376 (2011)

Astrid E Lammers[†1,2], Sheila G Haworth[2] and Gerhard-Paul Diller[1,3]

[1]Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
[2]Institute of Child Health, University College, London, UK
[3]National Heart and Lung Institute, Imperial College of Science and Medicine, London, UK
[†]Author for correspondence:
Tel.: +44 207 351 8602
Fax: +44 207 351 8629

Treatment options for patients with advanced pulmonary hypertension (PH) are limited. Iatrogenic creation of an interatrial communication (i.e., atrial septostomy [AS]) has been suggested as a possible treatment option or as a bridge to transplantation in selected patients and has been incorporated into current PH guidelines. Uptake of the procedure has been slow and the worldwide experience with AS is limited to approximately 280 published cases, over a period of more than 25 years. The rationale for creating an AS has been provided by the observation that patients with congenital heart disease, shunt lesions and PH have a better survival compared with patients with idiopathic PH. We review pathophysiologic data and the published clinical experience and discuss the rationale, indication and potential pitfalls of AS in patients with severe PH.

KEYWORDS: atrial septostomy • idiopathic pulmonary hypertension • pulmonary hypertension • right heart failure • syncope

Newly Approved PAH Medications

Table 1. Newly approved PAH medications.

Medication	Class	Dose	Route
Macitentan	ERA	10 mg daily	oral
Riociguat	sGC stimulator	1 mg three times daily titrated to maximum of 2.5 mg three times daily	oral
Treprostinil diolamine	prostanoid	0.25 mg twice daily or 0.125 mg three times daily titrated to maximum dose based on tolerability	oral

ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase.

Medical treatment update on pulmonary arterial hypertension

Pulmonary hypertension and congenital heart disease: An insight from the REHAP National Registry

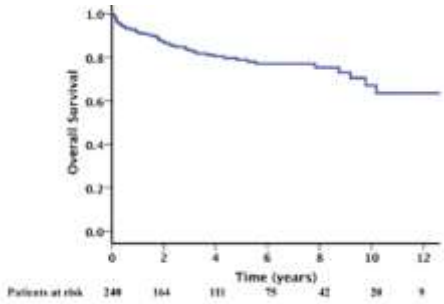
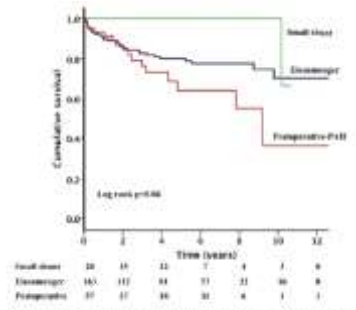
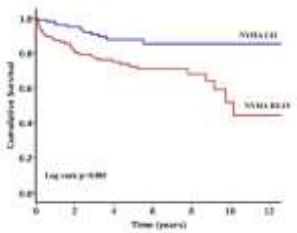
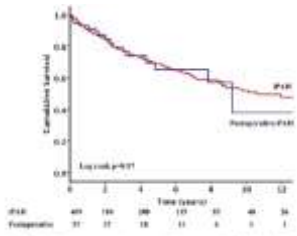


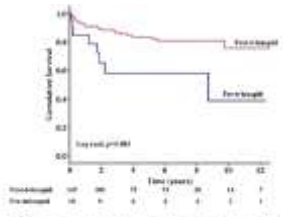
Fig. 1. Overall survival of patients with PAH–CHD.



Pulmonary hypertension and congenital heart disease: An insight from the REHAP National Registry







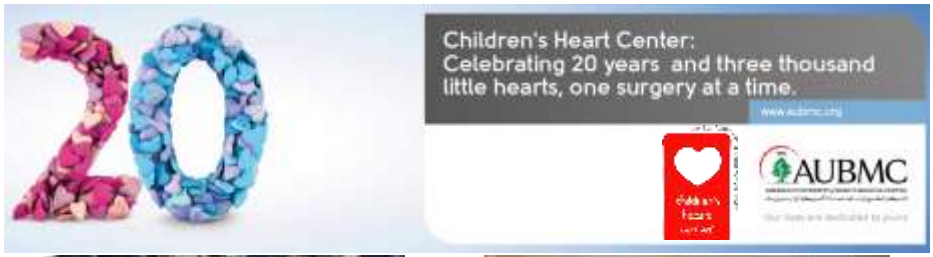
International Journal of Cardiology 184 (2015) 717–723

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.


Children's Heart Center:
Celebrating 20 years and three thousand little hearts, one surgery at a time.
www.aubmc.org
AUBMC