PULMONARY ARTERY HYPERTENSION
TOPICS

- DEFINITION
- PATHOPHYSIOLOGY
- CLASSIFICATION
- CLINICAL SYMPTOMS
- DIAGNOSIS
- TREATMENT
- PROGNOSIS
Normal pulmonary arterial pressure in a person living at sea level is 20-25/10-12 mmHg & has a mean value of 12–16 mm Hg (1600–2100 Pa) at rest.
Mean pulmonary artery pressures

- at rest exceed 25 mm Hg (3300 Pa)
- rises above 30 mm Hg (4000 Pa) with exercise
PATHOPHYSIOLOGY

- Pulmonary circulation:
  high-flow, low-pressure, highly compliant system

- Low-pressure state maintained by a variety of endothelial derived active mediators
  - relaxing factors (nitric oxide and prostacyclin)
  - constricting factors (endothelin [ET]-1, thromboxane, serotonin)

Chest 2003:124; 8-11
PATHOPHYSIOLOGY

- Exact pathogenesis and pathophysiology are unclear

- Most widely accepted: pulmonary vasoconstriction

- Imbalance of vasoactive mediators favoring vasoconstriction

- Coagulation abnormalities: supported by the finding of microthrombi in the pulmonary vascular bed (lung biopsy, autopsy, or in explanted lungs)
Imbalance of these factors
- elevate vasomotor tone,
- promote endothelial smooth-muscle–cell proliferation,
- induce vascular remodeling
- incite thrombosis

PAH regarded as a vasoproliferative rather than vasoconstrictive disorder

Chest 2003: 124; 8-11
FIGURE 2

Endothelial Injury

IL-1, IL-6, PGI2, TXA2, ET-1, ACE, NO, Thrombi, other cytokines

Pulmonary Hypertension

Vascular Remodeling
Pathogenesis of Pulmonary Arterial Hypertension

1. RISK FACTORS AND ASSOCIATED CONDITIONS
   - Collagen Vascular Disease
   - Congenital Heart Disease
   - Portal Hypertension
   - HIV Infection
   - Drugs and Toxins
   - Pregnancy

2. VASCULAR INJURY
   - Endothelial Dysfunction
   - Nitric Oxide Synthase
   - Prostacyclin Production
   - Thromboxane Production
   - Endothelin 1 Production
   - Vascular Smooth Muscle Dysfunction
   - Impaired Voltage-Gated Potassium Channel ($K_{V1.5}$)

3. DISEASE PROGRESSION
   - Loss of Response to Short-Acting Vasodilator Trial

- Adventitia
- Media
- Intima
- Early Intimal Proliferation
- Smooth Muscle Hypertrophy
- Flow

- Vasoconstriction
- In situ Thrombosis
- Adventitial and Intimal Proliferation
- Plexiform Lesion
- Advanced Vascular Lesion

NORMAL  REVERSIBLE DISEASE  IRREVERSIBLE DISEASE
Pulmonary Hypertension: Define Lesion

Post-Capillary PH
(PCWP>15 mmHg; PVR nl)

Pre-capillary PH
(PCWP≤15 mmHg)

Mixed PH

PAH
Respiratory Diseases

PE

Atrial Myxoma
Cor Triatriatum

MV Disease

Systemic HTN
AoV Disease

Myocardial Disease
Dilated CMP-ischemic/non-isc.
Hypertrophic CMP
Restrictive/infiltrative CMP
Obesity and others

↑LVEDP

PV

PV compression
PVOD

↑LVEDP
GENETIC THEORY

- In familial PAH
- Gene Coding for BMPR-2 protein
- Receptor in the TGF-B family
- Also seen in some patients with sporadic PH
- May lead to specific therapies directed at the origin of the disease
- Role of gene therapy
WHO classification of Pulmonary arterial hypertension

Group I:
- Idiopathic (IPAH)
- Familial (FPAH)

Associated with (APAH):
- Connective tissue disease
- Congenital systemic-to-pulmonary shunts
- Portal hypertension
- HIV infection
- Drugs and toxins
CLASSIFICATION

- Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)

Associated with significant venous or capillary involvement

- Pulmonary veno-occlusive disease (PVOD)
- Pulmonary capillary haemangiomatosis (PCH)

Persistent pulmonary hypertension of the newborn (PPHN)

*J Am Coll Cardiol* 2004; 43:Suppl S: 5S–12S
CLASSIFICATION

- Group II: PAH associated with left heart diseases
  - Left-sided atrial or ventricular heart disease
  - Left-sided valvular heart disease

- Group III: Pulmonary hypertension associated with respiratory diseases
  - Interstitial lung disease
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic high-altitude exposure
  - Developmental abnormalities
CLASSIFICATION

Group IV:
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease.
- Thromboembolic obstruction of proximal and/or distal pulmonary arteries

Group V: Miscellaneous group
- Sarcoidosis, histiocytosis X and lymphangiomatosis compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

J Am Coll Cardiol 2004; 43:Suppl S: 5S–12S
ETIOLOGY OF PAH

- Most common cause: COPD
- Up to 50% of patients with scleroderma
- 10% to 15% of patients with SLE
- 5% to 10% of patients with chronic liver disease
- Increased risk: History of exposure to diet pills
- HIV or a history of thromboembolic disease
FUNCTIONAL CLASSIFICATION

NYHA Classification

**Class I:** No symptoms with ordinary physical activity

**Class II:** Symptoms with ordinary activity. Slight limitation of activity. Comfortable at rest

**Class III:** Symptoms with less than ordinary activity. Marked limitation of activity

**Class IV:** Symptoms with any activity or even at rest, Manifest signs of right heart failure

J Am Coll Cardiol 2004;43 (Suppl S) :40S-47S
## Severity of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Degree of disease</th>
<th>Mean PAP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>25 - 40</td>
</tr>
<tr>
<td>Moderate</td>
<td>41 - 55</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;55</td>
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</tbody>
</table>
Clinical Evaluation of PAH

Symptoms:

- Insidious onset of shortness of breath
- Often results in delayed diagnosis
- Chest pain
- Syncope/ presyncope
- Peripheral edema or ascites
- Raynaud’s in about 10% (worse prognosis)
- Hemoptysis (rare)
Physical Findings in Pulm HTN

- Accentuated P2
- Right ventricular S4
- RV heave along left sternal border
- Large A waves from stiff RV
- Large V waves from TR
- Elevated JVP
- Graham-Steele murmur of PR
- Right ventricular S3
Physical Findings in Pulm HTN

- clear lungs
- central and peripheral cyanosis
- hoarseness of voice (Ortner syndrome)
- stigmata of secondary causes of PAH:
  - scleroderma, cirrhosis, HIV, OSA/OHS
**INVESTIGATIONS**

**FIGURE 4**

Suspect Pulmonary Hypertension

- Echocardiogram
  - Negative
    - Consider other diagnoses
  - Positive
    - History, physical, chest radiograph, PFTs, ABG, +/- CT to exclude other causes of pulmonary hypertension
    - Lung Scan
      - **POSITIVE** Evaluation for thromboembolic disease
        - **NEGATIVE** for thromboembolic disease: Consider primary pulmonary hypertension – Screen for collagen vascular diseases
  - *Positive-
    - Consider specific therapy
  - *Negative collagen vascular screen-
    - TREAT for primary pulmonary hypertension and evaluate for lung transplantation:
      - Anticoagulation
      - +/- Calcium channel blockers
      - +/- epoprostenol
Diagnostic Tools:

**NON-INVASIVE:**

- **Echocardiography**
  Can R/O cardiac disease and estimate PA pressures

- **VQ SCAN**
  Can reveal a patchy distribution of tracer “Not very conclusive”

- **6 minute walk**
  Disclose altered cardiac function, with high minute ventilation, low anaerobic threshold And increased A-a gradient.
  (good correlation with disease severity)

**INVASIVE:**

- **Swan-Ganz Catheterization**
  Directly identify Pulmonary hemodynamics and compare with left heart pressures

- **Pulmonary Arteriography**
  Can help differentiate b/w PPHT and chronic thromboembolic disease
Investigations

Hematological inv.:

- Are usually normal
- If chronic arterial desaturation is present, polycythemia may be seen
- Hypercoagulable states, abn. Platelet function, defects in fibrinolysis have been described in PPH
- LFT may be deranged if rt. ventricular failure is present.
Pulmonary function test

PFT typically shows:

- Mild restriction, reduced diffusion capacity for CO (DL_{CO})
- May show obstructive pattern with increased residual volume (COPD)
- There is a strong correlation between DL_{CO} and peak O_2 uptake, work rate, NYHA class*

E.C.G

- Right axis deviation
- Tall R waves and small S waves with R/S ratio >1in lead V1
- rSR’ pattern in lead V1
- Large S wave and small R wave with R/S ratio <1in lead V5 or V6
- Tall P wave (>2.5mm) in lead II, III and aVF
Chest x ray

- Enlarged main and hilar pulmonary arterial shadows
- Pruning of peripheral pulmonary vascular markings
- Rt. Ventricle, rt. atrial enlargement may be seen

Condition which are related to PAH:

- Hyperinflation (COPD), kyphosis (restrictive ventilatory disease), pulmonary venous congestion (veno-occlusive disease) [C]
Frontal radiograph of the chest shows an enlarged main pulmonary artery and a markedly enlarged right and left pulmonary arteries. The peripheral vasculature is normal.
CT CHEST

- Diameter of main pulmonary arteries ~ severity of pulmonary HT.

- Underlying parenchymal disease like chronic thromboembolic disease, lung fibrosis, COPD can also be diagnosed.
Echocardiography

- Echo with Color Doppler shows enlargement of Rt. atrium and ventricle with thickened septum
- Systolic prolapse of mitral valve with abnormal motion of septum
- RVSP (rt. ventricular systolic press.) can be estimated by modified Bernoulli equation
  \[ 4V + RAP \]
  (RAP - standardized value, v-velocity of tricuspid jet in meter per second)
- It may underestimate press. in severe PAH and overestimate in subjects with normal press.
Cardiac catheterization

- Is “GOLD STANDARD” for diagnosis of PAH.
- Direct measurement of RAP, PCWP, pulmonary blood flow and pulmonary vascular resistance can be done.
- It also helps in:
  - establishing severity of disease and its prognosis.
  - exclusion of other causes like intracardiac or extracardiac shunts and Lt. heart disease
  - Vasodilator testing: predicts response to CCBs
VASODILATOR RESPONSE

Done during cardiac catheterisation

Short acting agents like adenosine inhaled nitric oxide, or epoprostenol used, CCBs never used

Positive vasodilator response: fall in both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance of at least 20%

Newer recommendation: decrease in mean PAP of at least 10 mm Hg to < 40 mm Hg with an increased or unchanged cardiac output
GOALS OF THERAPY

- Alleviate symptoms, improve exercise capacity and quality of life
- Improve cardiopulmonary hemodynamics and prevent right heart failure
- Delay time to clinical worsening
- Reduce morbidity and mortality
TREATMENT

- Lifestyle changes
- Supplemental O$_2$ therapy
- Diuretic therapy
- Vasodilator treatment
- Glycosides
- Anticoagulants
- Surgical treatment
Graded exercise activities such as bike riding and swimming in which patients can gradually increase their workload and limit the extent of their work are safer than isometric activities like lifting weights or stair climbing.
Patients with PAH have a restricted pulmonary circulation. Increased oxygen demand may worsen PAH and right heart failure.

Chronic hypoxemia is due to impaired cardiac output, which results in desaturation of mixed venous blood.

When chronic hypoxemia develops, supplemental oxygen, including ambulatory oxygen therapy, is indicated to maintain arterial oxygen saturation at a level above 90 percent.

DIURETICS

Dramatic clinical improvement in patients with right heart failure can be achieved by instituting diuretic therapy, which reduces right ventricular preload.

The fear that diuretics will induce systemic hypotension is unfounded because the main factor limiting cardiac output is pulmonary vascular resistance and not pulmonary blood flow.

Serum electrolytes should be carefully monitored.

Chest 2004;126:35-62
Role is controversial

However, since neurohormonal sympathetic activation has been demonstrated in pulmonary hypertension, digoxin may be of value because of its sympatholytic properties.

Most useful in cor pulmonale, when left ventricular failure is also present.

Digoxin may also be beneficial in PAH with concomitant intermittent or chronic atrial fibrillation.
### Table 1. History of treatments for pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1950–1980</td>
<td>Empirical/Various vasodilators for acute vasoreactivity testing (tolazoline, acetylcholine, diazoxide, hydralazine, phentolamine, isoproterenol, nitrates, verapamil, nifedipine and diltiazem)</td>
</tr>
<tr>
<td>1970–1980</td>
<td>Uncontrolled trials on long-term vasodilator treatments</td>
</tr>
<tr>
<td>1980–</td>
<td>Oral anticoagulants High-dose calcium channel antagonists (in acute vasoreactivity tests responders) Lung, heart/lung transplantation</td>
</tr>
<tr>
<td>1990–</td>
<td>Intravenous epoprostenol prostacyclin Balloon atrial septostomy</td>
</tr>
<tr>
<td>2000–</td>
<td>New compounds</td>
</tr>
</tbody>
</table>
TREATMENT

Choice of drug therapy depends on:

- Vasoreactive testing
- NYHA stage of disease
- Experience
- Affordability
- Availability of drugs
Options available are –

**Vasodilators:**

- Calcium channel Blockers: Nifedipine, Diltiazem
- Prostanoids
  - Epoprostenol, Trepostinil, Iloprost, Beraprost
- Endothelin receptor antagonist: Bosentan, Ambrisentan, Sitaxsentan
- PDE-5 inhibitors: Sildfenafil
CALCIUM CHANNEL BLOCKERS

- Most successful vasodilators
- Lowers pulmonary blood pressure
- Improve the pumping ability of the right side of the heart
- High dose CCBs - significant survival benefit in properly selected candidates

European Heart Journal 2004;25: 2243-2278
CALCIUM CHANNEL BLOCKERS

- Used in pts with +ve vasoreactivity
- Commonly used: Nifedipine, Diltiazem, Amlodipine
- Side effects: fatigue, flushing, edema, tachycardia, bradycardia
ENDOTHELIN RECEPTORS
ANTAGONISTS

BOSENTAN:

- Improvement in 6 min walk test and dyspnea scores
- Liver function test abnormalities has been reported
- Liver function tests: performed monthly
- Associated with anemia requiring periodic blood count
- Potential teratogenic effects

European Heart Journal 2004;25: 2243-2278
ENDOTHELIN RECEPTORS
ANTAGONISTS

SITAXSENTAN:
- second generation ET-A receptor antagonist
- Improve 6-minute walk test, functional class, and cardiac index
- Adverse event:
  - increased plasma INR in patients taking warfarin
  - Abnormal liver function tests

AMBRISENTAN: ET-A receptor antagonist
- In clinical trials

European Heart Journal 2004;25: 2243- 2278
PHOSPHODIESTERASE INHIBITORS

SILDENAFIL: relaxes pulmonary smooth muscle cells, which leads to dilatation of the pulmonary arteries

- significant improvements in 6-minute walk test, functional class, and hemodynamics
- common side effects
  - headaches, flushing, and dyspepsia
- Contraindicated in patients taking any form of nitrates
PROSTANOIDs

- Derived from prostacyclins
- Vasodilator in pulm and systemic circulation
- Antiplatelet aggregatory activity
- Epoprostenol (Flolan), treprostinil sodium (Remodulin), iloprost (Ventavis), Beraprost

European Heart Journal 2004;25: 2243- 2278
Intravenous prostacyclin (epoprostenol) was first used to treat primary pulmonary hypertension in the early 1980s. Epoprostenol has been approved for the treatment of pulmonary arterial hypertension in North America and in some European countries since the mid-1990s. Continuous intravenous epoprostenol clearly demonstrated clinical benefits for patients in NYHA functional class III or IV.
Epoprostenol can be administered only by continuous intravenous infusion, owing to its short half-life in the circulation (i.e., six minutes) and its inactivation at low pH. For long-term administration, epoprostenol is infused with the use of a portable infusion pump connected to a permanent tunneled catheter inserted in the subclavian vein. Patients are started on a low dose (1-2 ng/Kg/min) and gradually increased based on side effects and tolerance.
SUBCUTANEOUS TREPROSTINIL

- Administered as a continuous subcutaneous infusion
- Improve indexes of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamic measures significantly
- Local pain at the infusion site was a side effect that occurred in 85 percent of the patients
- It is now an approved therapy for pulmonary arterial hypertension in the United States since 2002
INHALED ILOPROST

- A chemically stable prostacyclin analogue that can be delivered by inhaler which improves pulmonary selectivity

- Relatively short duration of action (around 30 min.)

- It must be inhaled as many as 6 to 12 times a day
INHALED ILOPROST

- Side effects included cough and symptoms linked to systemic vasodilatation
- The long-term efficacy of inhaled iloprost remains to be established
- Approved for treating primary pulmonary hypertension in Europe
Absorbed rapidly after the administration of an oral dose under fasting conditions.

Improves exercise capacity in patients with primary pulmonary hypertension and those associated with connective-tissue diseases, congenital left-to-right shunts, portal hypertension, and HIV infection.

Side effects linked to systemic vasodilatation, mainly during the initial titration period.

Beraprost is an approved therapy for pulmonary arterial hypertension in Japan.
ANTICOAGULATION

Recommended as there is
- an increased risk of Thrombosis and Thromboembolism in situ.

Maintain INR of approximately 2.0

Both retrospective and prospective study suggest anticoagulation prolongs life

Should be given in all until unless contraindicated

Chest 2006;130:545–552
Atrial septostomy:
- patients refractory to vasodilator therapy
- aim is to relieve right-sided congestion and augment systemic cardiac output

Pulmonary thromboendarterectomy:
- improve blood flow (in the pulmonary artery) and lung function
Lung transplantation:
Only cure for primary pulmonary hypertension and for advanced pulmonary hypertension (not responsive to medical therapy) The right side of the heart will generally return to normal after the lung/lungs have been transplanted

Heart/lung transplantation:
This type of double organ transplant is very rare but is necessary for all patients who have combined lung and left heart disease

Chest 2004;126:35-62
Predictors of Poor Prognosis

- Poor exercise capacity (6 MWD)
- Cardiopulmonary hemodynamics
  - High right atrial pressure
  - Low cardiac index
  - High mean pulmonary artery pressure
- Enlarged right atrium on echo
- Pericardial effusion on echo
- Absence of anticoagulant use
- Absence of initial acute vasodilator response
Conclusion

- Pulmonary arterial hypertension is a progressive disease with significant morbidity and mortality.

- Right heart failure is an important development which clearly prognosticates and marks disease progression.

- Treatment of right heart failure is essential.

- Therapies with proven benefit in transpulmonary hemodynamics, functional class and exercise tolerance include ET-1 receptor antagonism (bosentan), prostanoids, and oral sildenafil.

- Continuous IV Epoprostenol is reserved for advanced (class IV) disease where there is a proven survival benefit.
All the best..