Pulmonary hypertension

Current perspectives in the diagnosis and management

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PGIMER
• Definition
• Classification
• Pathobiology
• Diagnosis
• Treatment
Evian Nomenclature and Classification of Pulmonary Hypertension (1998) Diagnostic Classification

**Pulmonary artery hypertension**

PPH
- Sporadic
- Familial

Related to:
- Collagen vascular disease
- Congenital systemic to pulmonary shunts
- Portal hypertension
- HIV infection
- Drugs/toxins
- Persistent PH of the newborn

**Pulmonary venous hypertension**

Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease
- Fibrosing mediastinitis
- Adenopathy/tumors
- Pulmonary veno-occlusive disease

**PH associated with disorders of the respiratory system and/or hypoxemia**

- COPD
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilatory disorders
- Long-term exposure to high altitude

**PH due to chronic thrombotic and/or embolic disease**

- Thromboembolic obstruction of proximal pulmonary arteries
- Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)

**PH due to disorders directly affecting the pulmonary vasculature**

- Schistosomiasis
- Sarcoidosis
- Pulmonary capillary hemangiomatosis
Pathobiology of pulmonary hypertension

Pathologic hallmark

- Vasoconstriction
  - Vascular smooth muscle hypertrophy
  - Endothelial cell proliferation
  - Adventitial cell proliferation

Vasoconstriction/Vascular smooth muscle cell hypertrophy

- Vascular endothelial cell dysfunction
- Imbalance between endothelial cell mediators
  - Loss of vasodilators (↓NO, ↓PGI2)
  - Vasoconstrictors (TXA2, ET-1, Serotonin)

- K+ channel dysfunction → ↑Ca++ → Vasoconstriction

- Hypoxia, 5HT, ET-1 → Growth factors for smooth muscle cells
Pathobiology of pulmonary hypertension

- Intermediate cells, pericytes proliferate → Neomuscularisation of distal vessels

2) Endothelial cell proliferation/plexiform lesions

- VEGF, other growth factors → Endothelial cell proliferation

- Mutations in BMPR – II gene, 5HT transporter

  Plexiform lesions – Proliferation of endothelial and smooth muscle cells

  Arterial lumen occlusion, aneurysmal dilatation
Pathobiology of pulmonary hypertension

3) Extra cellular matrix remodeling/adventitial proliferation
   - Increased ECM degradation
     - Elastase, matrix metalloproteiases
     - Perivenular inflammatory cell infiltrate
     - Increased – IL 1B, Increased IL-6

4) Insitu thrombosis
   - Slowing of pulmonary blood flow
     - Altered expression of PGI2, NO.
     - Increased PAI, fibrinopeptide A, increased factor VIII C
Genetic mutation (BMPR2, others)

- ↑ Endothelin-1
- \(\downarrow\) Prostacyclin synthase
  \(\downarrow\) Prostacyclin
- ↑ Serine elastases and MMPs
  ↑ Tenascin-C
- ↑ ACE
  ↑ Angiotensin II
- PAI-1/ fibrinolysis

Modifier genes +/-

+/- Environment

Pulmonary vascular remodelling and vasoconstriction

- ↑ Serotonin transporters
  ↑ Serotonin uptake
- \(\downarrow\) Nitric oxide synthase
  \(\downarrow\) Nitric oxide
- Dysfunctional \(K_{v}\) channels
  VEGF
- Carbamoyl phosphate synthase

Clinical PPH
# Vascular remodelling

<table>
<thead>
<tr>
<th></th>
<th>PAH</th>
<th>PH sec. to lung dis.</th>
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<tbody>
<tr>
<td>1)</td>
<td>Medial smooth muscle HT</td>
<td>++</td>
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<tr>
<td>2)</td>
<td>Distal small vessel neo musc.</td>
<td>++</td>
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<tr>
<td>3)</td>
<td>Adventitial changes</td>
<td>++</td>
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<td>4)</td>
<td>Intimal proliferation</td>
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<tr>
<td>5)</td>
<td>Monoclonal endoproliferation</td>
<td>+</td>
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<tr>
<td>6)</td>
<td>Plexogenic lesions</td>
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<tr>
<td>7)</td>
<td>Insitu thrombosis</td>
<td>common</td>
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</table>
Evaluation of PHTN

PHTN suspected

- NO S/S
- RVSP <36
- TRvel <2.8

CXR, ECG, TT Echo

- RVSP 36-50
- TRvel 2.8-3.4

RVSP >50
- TRvel >3.4

w/u etiology

NYHA 1

Rt heart cath

NYHA 2-4

35-45
25-35

exercise RVSP/PAS

<35
<25

F/U

F/U
Evaluation of PHTN

Confirmed PHTN

- Echo (TEE, contrast) → CHD, LVD, Valvular dis.
- Serology → CTD/HIV
- PFT/ABG/CT Chest/sleep study
- V/Q scan → CTEPH → Pulm angio

Functional assessment – 6 mwt
Rt heart cath

- 30 – 45 PAs → r/o CTD re exam after 1 yr
- 25 – 35 mPap
- >45 PAs → Vasodilator study
- <25 mPap → F/U
- <35 PAs → F/U
Pulmonary hypertension ------- Medical treatment

Progress in pathogenesis paralleled by evolution in therapy

Vasoconstrictive → Vasoproliferative
Vasodilators → Anti proliferative agents

Conventional therapy

Oxygen  | Widely used
Diuretics, Digitalis | Accepted as being important and effective
Anticoagulants
Vasodilators (ca++ channel blockers) | Not supported by RCT’s

Newer therapies

Prostanoids  | RCT’s are available
ET1 receptor antagonists | ongoing
PDE inhibitors
Nitric oxide
Gene therapy
**Vascular Endothelium:**
- Endothelial dysfunction
- Imbalance of vasoactive and mitogenic factors
- Endothelial proliferation
- Plexiform lesions

**Prostacyclin** down

**Endothelin-1** up

**Nitric Oxide** down

**Thromboxane A2** up

**Vascular Smooth Muscle Cells:**
- Vasoconstriction
- Proliferation
- Dysfunction of the voltage-dependent K+ channels and Ca++ channels
Oxygen

- Improves survival in COPD with chronic hypoxia

  MRC (>15 hrs/day) – Ppa not altered in treatment group
  Increased by 2.7 mm Hg / yr control

  NOTT(continuous Vs 10-12 hrs/d) – Ppa decreased 0.4 mm Hg after 6 m

- Decreases progression
  - Might reverse if given continuously ↓2.2 mm Hg/yr (Weitzenblumm et al)
  - Rarely returns to normal values
  - Structural abnormalities of vessels not altered
  - Sub group of pts who are acute responders might have greater benefit

- In other forms of PAH --- To maintain SpO2 > 90%
Diuretics

- Activation of RAS
- ↑ADH

Salt and water retention

- Decrease RV work load
  - Decrease pulm. congestion, ↑ gas exchange
- 2D Echo
  - Septal displacement
  - LV diastolic function

- Compromise adequate filling of RV
  - ↓CO
  - Metabolic alkalosis, ↑ viscosity

↑RV dil → LV comp.
Digitalis
• Inotropic effect on RV modest
  May increase Pap
  Hypoxemia, Hypokalemia increase dig toxicity

• To counteract –ve ionotropic effects of CCB in PPH
• Demonstrable LV dysfunction
• Atrial arrhythmias, Refractory RHF

Anticoagulation
• Sedentary lifestyle, heart failure, venous stasis
• Insitu thrombosis-30-50% in PPH, CTPH
• OAC-doubled survival at 3yrs in pts of PPH(21to49%)
• INR 2-3
Vasodilators

- 25% of pts with IPAH demonstrate acute vasodilator responsiveness
- Such pts have improved survival (94% - 5 yrs) on long term oral vasodilators
- Oral CCB, I.V adenosine, I.V epoprostenol, inhaled NO.

- European Society of Cardiology – consensus definition
  - ↓ mPAP by at least 10 mm Hg to < 40 mm Hg
  - increased / unchanged cardiac output
- Only CCB (in high doses) have demonstrated long term benefit.

- Never been assessed in RCTs.

- High dose CCB → Hypotension and edema.
Prostanoids

- Vasodilation
  - Inhibit platelet aggregation, anti proliferative
  - Increased pulmonary clearance of ET-1
  - Reverse remodeling of pulmonary vessels
  - Non responders to vd testing also respond PG

Epoprostenol

- Prostacyclin (PGI2)

- Improves pulm. haemodynamics, exercise capacity (Barst et al NEJM 1996, Mc laughen et al 1998) and survival in IPAH.

- Found to be efficacious in PAH related to scleroderma (Rubin et al) other CTD (Huebert et al) and in HIV (Farber et al – AJRRCM 2000)

- Need for continuous infusion
Epoprostenol

- Unstable at room temperature and acidic PH.
- Rebound worsening of PAH after abrupt interruption
- Head ache, joint pains, diarrhea, hypotension, high output failure.
- Beneficial effect may be sustained for yrs

Associated with poor outcome

- Right sided failure
- 6 mwd < 250 m
- RAP >12 mm Hg, mPAP > 65 mm Hg
- Absence of fall in PVR by 30%
- Persistence of class III/IV after 3 months
Treprostinil
- I.V or sub cut, stable at room temp
- Haemodynamic effects are similar to epoprostenol
- Studied in NYHA CLASS II – III
- 2 major trials - improvement in 6mwd was less c/w other trails
- Class II ,less ill, CHD
- Effects persist for up to 18 months.

Beraprost
- Orally active ,half life 30-40 mts,chemically stable
- ALPHABET study – 130 pts NYHA – cl II/III
- IPAH/PAH related to other diseases
- 80 microg qid
- No significant improvement in hemodynamics
- Tolerance on long term use.
**Iloprost**

- I.V, oral, aerosol adm, half life 20-25 mts

- Uncontrolled trials - improvement in Hd and exercise capacity

- RCT – AIR study (Aerosolized Iloprost Randomized study)
  class III/IV, IPAH, PAH – CVD, inoperable CTPH
  2.5 to 5 microgm, 6-9 times/day

- Safe, well tolerated

- Being tried in combination with sildenafil and in pulmonary fibrosis
**Endothelin 1 receptor antagonists**

- **ETR**
  - ETa: Vasoconstriction, proliferation of smooth muscle cells
  - ETb: Vasodilatation, clearance of ET1.

**Bosentan** --- dual ETR antagonists

- Sitaxentan – 6000 fold more selective for ETa
- Ambrisentan – ETa selective

**Bosentan**

- Orally active, nonpeptide
- 62.5 mg/ day for 4 wks followed by 125 mg B.D/250 MG B.D for 12 weeks
- Improvement in exercise capacity (6MWD)
- Cardiopulmonary hemodynamics (↓PVR, ↓MPAP, ↓MPAP, ↑CI)
Bosentan

- Improvement in functional class of pt.
- Delayed the time to clinical worsening
- No significant reduction in systemic BP.
- Well tolerated at dose of 125 mg B.D.
- Headache, anemia, syncope, flushing, increased liver enzymes -- dose dependent, transient (2 to 7%)
- First choice for PAH in class III/IV
- LFT to be performed at least monthly
Sitaxentan
- Blocks deleterious effects of ET-1 maintaining beneficial effects.
- 100 mg qd/300 mg qd for 12 wks
- PPH/PAH – CHD, CCF
- High oral bioavailability
- Long duration of action.
- Improved EC and hemodynamics
- Nasal congestion, peripheral edema, increased INR, inhibit cytP450.

Ambrisentan
- ETA selective
- Phase III clinical trails
<table>
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<tr>
<th></th>
<th>Terbogrel</th>
<th>Treprostinil</th>
<th>ALPHABET</th>
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<td>Etio</td>
<td>PPH100%</td>
<td>PPH(58%), CHD, CTD</td>
<td>PPH(48%), CHD, PoPH</td>
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**Nitric Oxide**

- Vasodilator, anti-platelet, anti-inflammatory, anti-oxidant
- Modulates angiogenesis
- Decreased NO synthase in pulm.htn.
- Inhaled NO --- selective pulmonary vasodilator
  - PPHN – FDA approved
  - Potent pulm vasodilator
    - Children with CHD
    - ARDS
    - Post Lung transplantation
- Chronic PAH testing for vasoreactivity
  - acute stabilisation of pts during deteriotation
- Isolated case reports of benefit of long term inhaled NO.
L- Arginine

• Sole substrate for NO synthase
• Exogenous arginine ----- increased NO production
• Short term i.v admn – mixed results – ↓ MPAP by 15%, PVR by 27%
  No benefit
• Oral supplement (1 week) --- Nagaya et al -----↓ MPAP by 9%
  ↓ PVR by 16%
• Lack of RCTs / longterm trials.
Phosphodiesterase inhibitors

• Vasodilator effect of NO depends on cGMP

• cGMP --- activate cGMP kinase – opens K+ channels --- vaso relaxation

• PDE (type5) degrades cGMP.

• PDE 5 inhibitors ---- dipyridamole ---- less potent ,systemic effects
  sildenafil
Sildenafil

- Decreases PAP, decreases PVR
- Augments the effect of NO
- Several non randomized single centre studies showing promising results
- PPH - Indian study – 29 pts --> (25 – 100 mg tds) , 5 – 20 months
  improvement in NYHA class, 6MWT, dyspnoea index

CTEPH

- Role in PHTN due to lung diseases
  Long term combination therapy with prostanoids-

- Minor side effects (head ache, nasal congestion)
- Irreversible retinal damage (PDE6)
- RCTs are in progress
Therapy for PAH
Functional class II/III/IV

General Care
Oral anticoagulants [B for IPAH, E/C for other PAH] + diuretics + oxygen [E/A] + digoxin

Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]

Positive
Oral CCB [B for IPAH, E/B for other PAH]
Sustained Response [3]
Yes: Continue CCB
No:

Functional Class III
Endothelin Receptor Antagonists (Bosentan) [A] or
Chronic IV Epoprostenol [A] or
Prostanoid Analogues
SQ, Inh, Ber

Functional Class IV
Chronic IV Epoprostenol [A]
Bosentan [B]
Traprostiln [B]
Chronic IV Iloprost [C]
No improvement or deterioration

PDE-5 Inhibitors (Sildenafil) [C [4]

Lung Transplantation

Grade of Recommendation: Noted in [1-7]
Pulmonary HTN sec. to lung disease

COPD
• Often mild to moderate, slow progression
• Progression correlates with mortality and PaO2
• Exacerbations in COPD aggravate pulm. HTN
• May be latent and unmasked by exercise
• Vascular changes can be seen in mild COPD

Pathogenesis
• Chronic hypoxemia
• Inflammation
• Smoking
• Mechanical stress

\[ \text{HPVC} \rightarrow \text{Vascular remodeling} \]
Pulmonary HTN sec. to lung disease

- Vasoconstriction
- Endothelial dysfunction \( \downarrow \text{eNOS}, \uparrow \text{ET-1}, \uparrow \text{5 HT transporter} \)
- Hypercoagulable state \( \longrightarrow \) in situ thrombosis
- Smooth muscle proliferation/migration with neo vascularisation of smaller vessels
- Fibrosis of intima
- Increased synthesis of ECM
- Inflammatory cell infiltrate in wall of vessels
- Mechanical stress \( \longrightarrow \) loss of capillary/precapillary arterioles
- Apoptosis
Treatment modalities

• Conventional therapy

• Newer therapies ?? Potential for partial reversibility

Targeting the pathogenetic mechanisms

• Smoking cessation

• LTOT

• Prevention and Rx of acute exacerbations

• Replacing deficient mediators (NO, PGI2)

• Selective pulmonary vasodilatation, ETRA, PDE Inhibitors

• Protease inhibitors
Prostanoids

• Can worsen oxygenation/systemic hypotension

• Inhaled iloprost ---- appears promising
  Pulmonary effects > systemic effects

• Effect of IV PGI2, inhaled NO and aerosolized PGI2, CCB in 8 pts with severe pulmonary fibrosis with pulm HTN were compared (Ghofrani et al AJRCCM 1999)

• NO, PGI2 (aerosolized) \( \rightarrow \) mPAP (44 to 36)  
  \( \downarrow \) PVR

• Systemic BP, SpO2, pulm shunt showed no change

• Long term treatment with inhaled iloprost
Vasodilators

**CCB**  ↓Ppa , ↓CO  
Worsen V/Q relationships by suppressing beneficial effect of HPVC  
slight/no improvement in haemodynamics with worsening clinical status

**Selective pulmonary vasodilators**  
**Nitric oxide** - 40 ppm ----↓Ppa ,↓Pao2  
decreased total amount of NO delivered between V/Q matching

**NO + O2**  - Yoshida et al  
Improvement in pulm. hd and better oxygenation at dose of 5ppm

Difficulty in administration for long term

Benefits need to be confirmed.
Sildenafil

- Used in recent trials as monotherapy or with prostanoids (iloprost/epoprostenol)
- Advantage of oral administration
- Selective ---- pulm > systemic vasodilatation
  Supralselective --- vasodilatation in well ventilated areas

- 16 pts with severe PHTN secondary to lung fibrosis (Ghofrani et al)
  NO(10-20 ppm) $\xrightarrow{i\ v\ PGI2}$
  oral Sildenafil 50 mg

  NO, sildenafil ---- $\downarrow$ PVR, $\downarrow$ Pap
  maintained V/Q matching
  shunt (4%, 3.3% vs 16%)
  $\uparrow$ Pao2

- Amplifies local vasoregulatory mechanisms
Chronic thromboembolic pulmonary hypertension

- 0.1% - 0.4% of Acute PTE
- Honey moon period
- Recurrent TE
- Abnormalities of hemostasis
  - In situ thrombosis
  - Remodeling of vessels in non-occluded
  - Distal vasculopathy in occluded vessels

Pathology

- Loss of intima
- Inflammation of media
- Thrombosis
- Partial recanalization
- Distal occlusion

Worsening pulm. HTN
Chronic thromboembolic pulmonary hypertension

Diagnosis

- 2D Echo
- V/Q scan
- CT chest/pulmonary angio.
- MRI

Evaluation for surgery

- Pulmonary angiography
- Rt. Heart catheterisation
- Fibreoptic pulmonary angioscopy
Chronic thromboembolic pulmonary hypertension

Thromboendarterectomy

- Haemodynamic/ventilatory impairment at rest or with exercise
- Resting PVR > 300 dynes/sec/cm
- Surgical accessibility - Proximal location extends to level of lobar atresia
- Degree of pulm. HTN c/w extent of accessible thromboembolic material
  Central surgical / not surgically accessible  Distal obstruction
  accessible / accessible  Small vessel arteriopathy

- Operative mortality 4 – 10%
- Pulm. HTN persists after surgery – 10%
- Oral anticoagulation/IVC filters
- Prostacyclin, sildenafil
- Ballon angioplasty
- Lung transplantation
**Atrial septostomy**

- Recurrent syncope/RVF despite maximal medical therapy (at least for 6 months)

- Palliative therapy

- Procedure
  - BBAS – Blade ballon atrial septostomy
  - BDAS – Ballon dilatation AS

- Only small series / case reports

- Successful AS - significant clinical improvement
  - beneficial and long lasting hd effects
  - trend towards increased survival

- Procedure related mortality 16%

- CI – Severe RHF , mRAP>20 mm Hg , Spo2<80%
• High level of suspicion for diagnosis
• Identification of etiology using appropriate diagnostic tests
• Better understanding of pathobiology and genetics → Wider therapeutic options
• Conventional therapies --- Role remain controversial, lack RCT.
• Treatment of PHTN advancing rapidly
• Manipulation of disrupted equilibrium between endothelial vd and vc is the best therapeutic option
• Novel agents such as ETRA, sildenafil are being studied by RCTs in PAH and in PHTN secondary to lung disease
• Choosing a drug for a pt to be individualized based on relative benefits, risks and costs.
• Lung transplantation option for non responders

Future directions
• Identification of modifying genes
• Combination treatment of above agents
Thank You