Pulmonary hypertension

Current perspectives in the diagnosis and management

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PGIMER

- Definition
- Classification
- Pathobiology
- Diagnosis
- Treatment

EvianNomenclatureandClassification ofPulmonaryHypertension (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/orhypoxemia

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

} Vascular remodelling

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 I → Growth factors for smooth muscle cells

Pathobiology of pulmonary hypertension

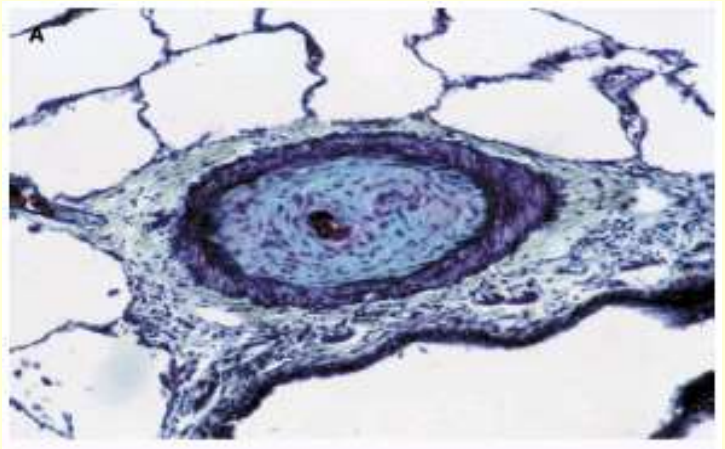
-Intermediate cells, pericytes proliferate ⟶ Neomuscularisation of distal vessels

2) Endothelial cell proliferation/plexiform lesions

- VEGF,other growth factors ⟶ Endothelial cell proliferation
- Mutations in BMPR – II gene,5HT transporter ⟶ Endothelial cell proliferation

Plexiform lesions – Proliferation of endothelial and smooth muscle cells

Arterial lumen occlusion,aneurysmal dilatation



Pathobiology of pulmonary hypertension

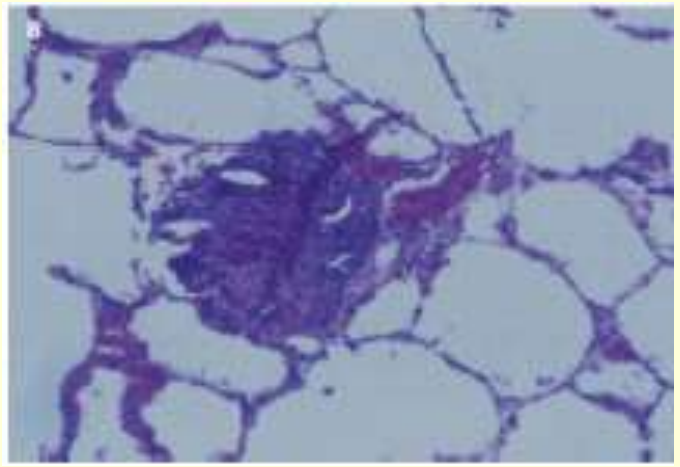
3) Extra cellular matrix remodeling/adventitial proliferation

- Increased ECM degradation

- Elastase,matrix metalloproteiases

- Perivenular inflammatory cell infiltrate

- Increased – IL 1B, Increased IL-6

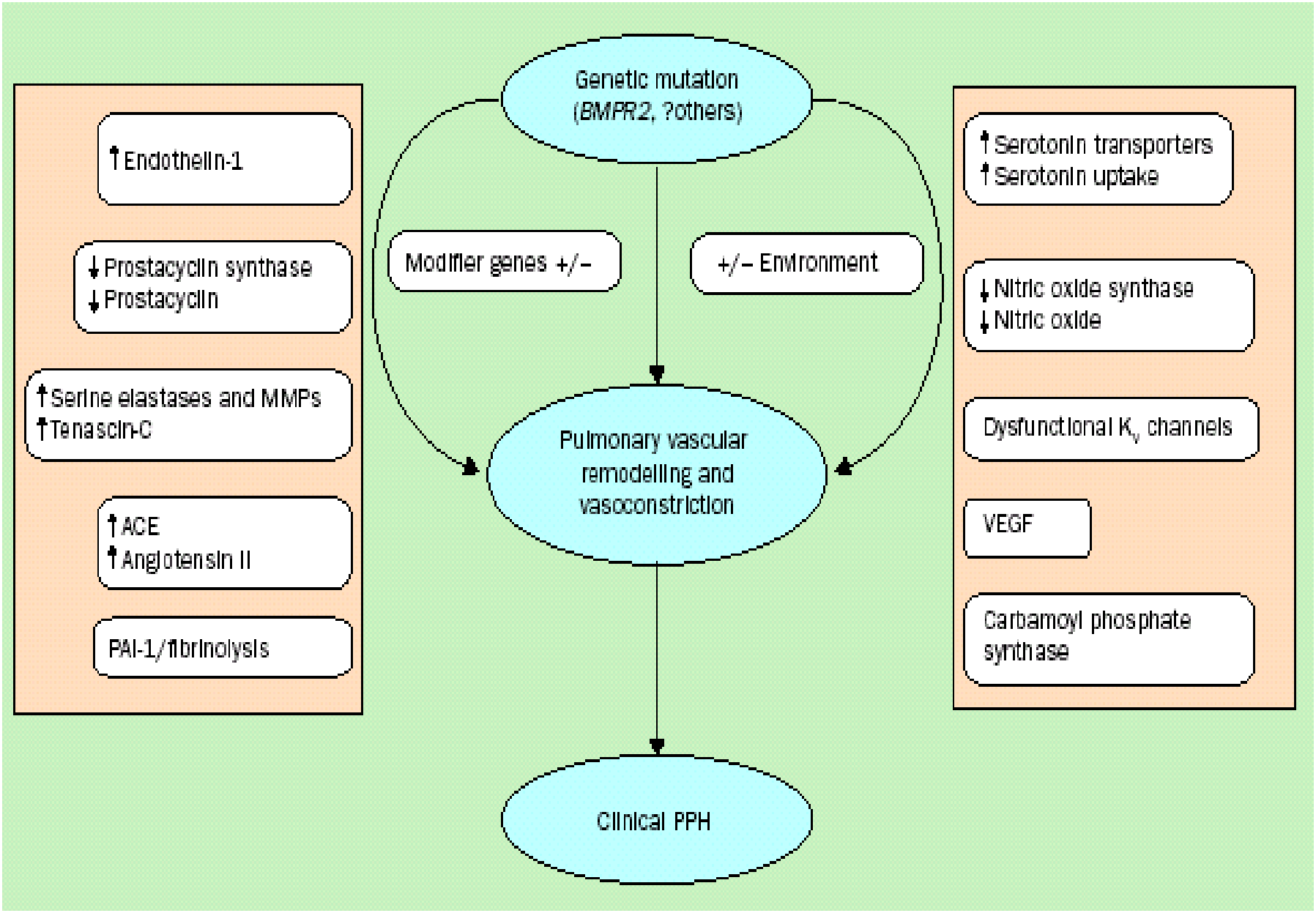


4) Insitu thrombosis

- Slowing of pulmonary blood flow

- Altered expression of PGI2,NO.

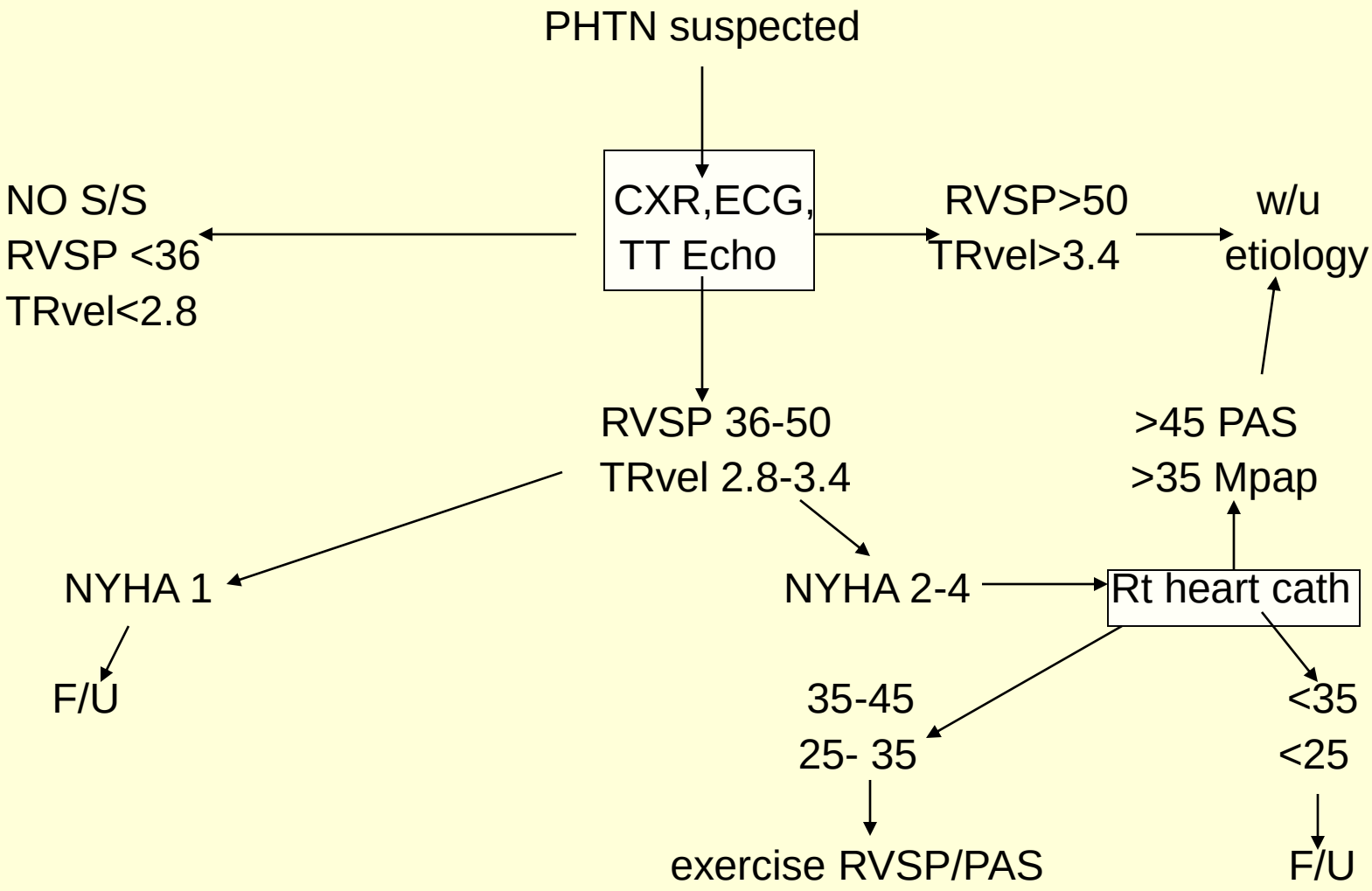
- Increased PAI,fibrinopeptide A,increased factor VIII C


Genetic mutation
(BMPR2, ?others)
Modifier genes +/–
+/– Environment
Pulmonary vascular
remodelling and
vasoconstriction
Clinical PPH
↑Endothelin-1
↓Prostacyclin synthase
↓Prostacyclin
↑Serine elastases and MMPs
↑Tenascin-C
↑ACE
↑Angiotensin II
PAI-1/fibrinolysis
↑Serotonin transporters
↑Serotonin uptake
↓Nitric oxide synthase
↓Nitric oxide
Dysfunctional K_v channels
VEGF
Carbamoyl phosphate
synthase

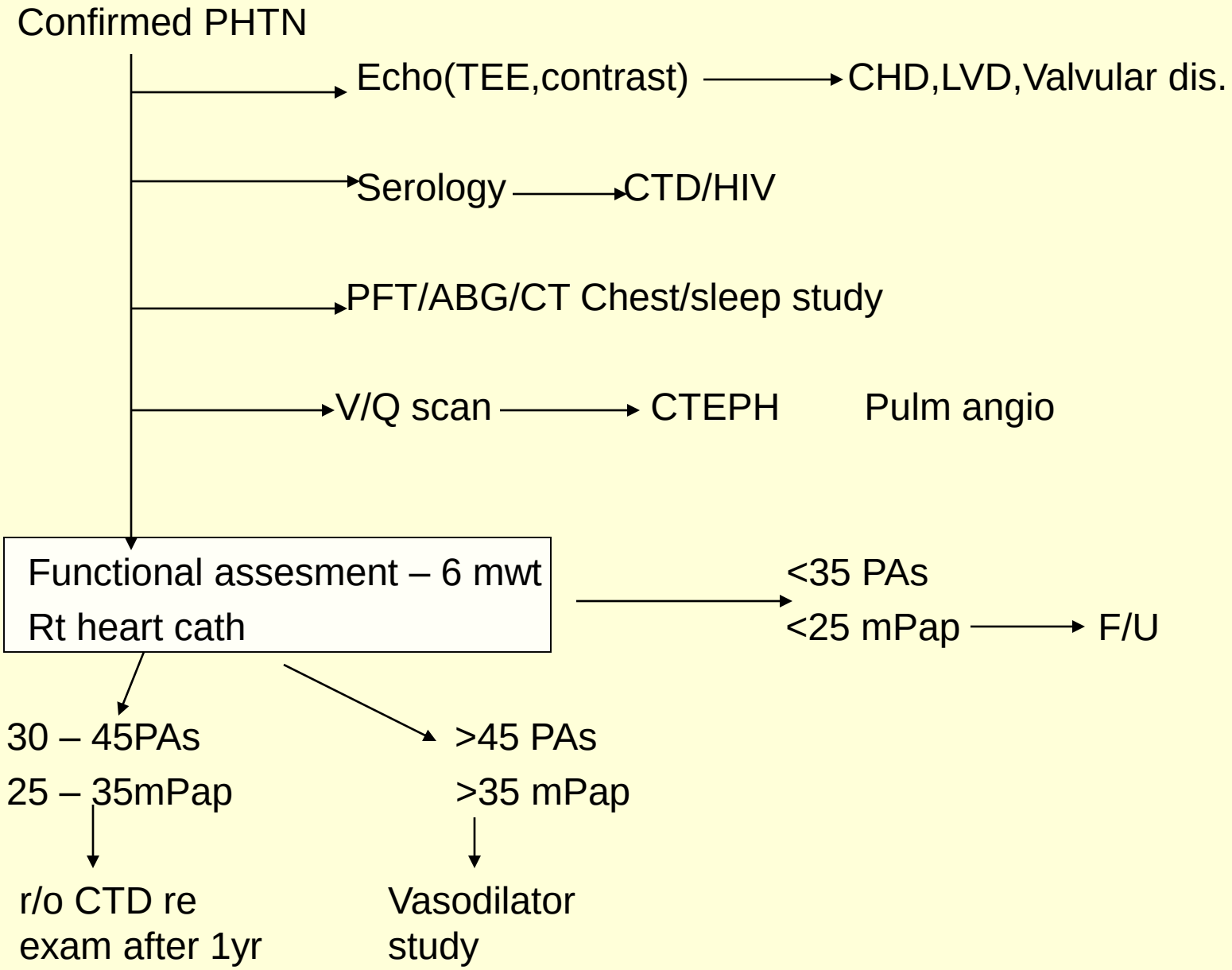
Vascular remodelling

	PAH	PH sec. to lung dis.
1) Medial smooth muscle HT	++	++
2) Distal small vessel neo musc.	++	++
3) Adventitial changes	++	+
4) Intimal proliferation	marked	mild
5) Monoclonal endoproliferation	+	-
6) Plexogenic lesions	+	-
7) Insitu thrombosis	common	rare

Evaluation of PHTN



Evaluation of PHTN



Pulmonary hypertension ------- Medical treatment

Progress in pathogenesis paralleled by evolution in therapy

Vasoconstrictive → Vasoproliferative

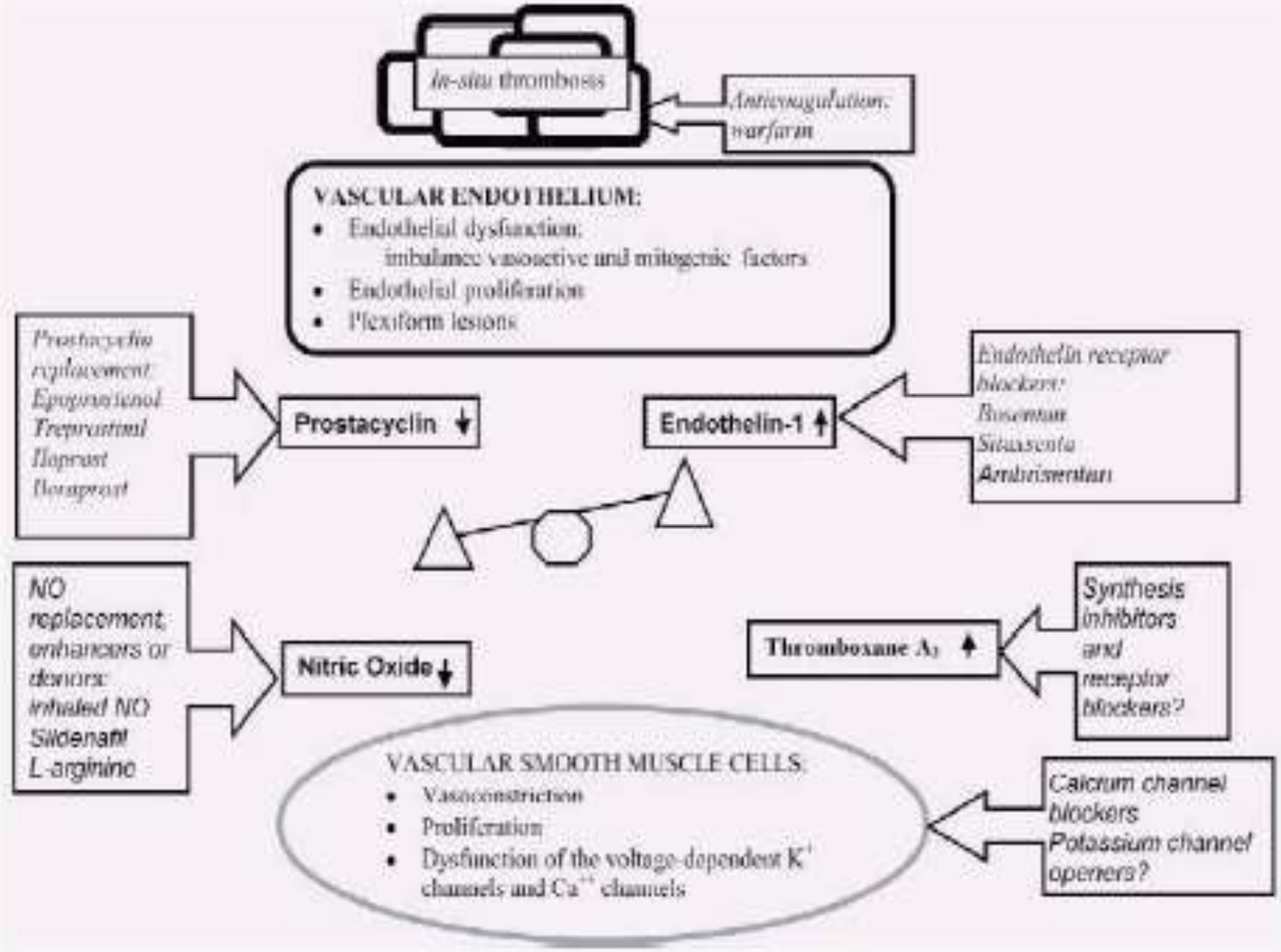
Vasodilators → Anti proliferative agents

Conventional therapy

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

Newer therapies

Prostanoids	RCT's are available
ET1receptor antagonists	ongoing
PDE inhibitors	
Nitric oxide	
Gene therapy	


In-situ thrombosis
Anticoagulation: warfarin
VASCULAR ENDOTHELIUM:
• Endothelial dysfunction: imbalance vasoactive and mitogenic factors
• Endothelial proliferation
• Plexiform lesions
Prostacyclin replacement: Epoprostenol Treprostinil Iloprost Beraprost
Prostacyclin ↓
Endothelin-1 ↑
Endothelin receptor blockers: Bosentan Sitaxsentan Ambrisentan
NO replacement, enhancers or donors: inhaled NO Sildenafil L-arginine
Nitric Oxide ↓
Thromboxane A2 ↑
Synthesis inhibitors and receptor blockers?
VASCULAR SMOOTH MUSCLE CELLS:
• Vasoconstriction
• Proliferation
• Dysfunction of the voltage-dependent K+ channels and Ca++ channels
Calcium channel blockers Potassium channel openers?

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 → ↑RV dil → LV comp.

- Decrease RV work load

  Decrease pulm.congestion, ↑ gas exchange

- 2D Echo
  - RV volumes
  - Septal displacement
  - LV diastolic function

- Compromise adequate filling of RV

  ↓ CO

  Metabolic alkalosis, ↑ viscosity

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 arrythymias, 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 etal**) 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)

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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.
- Head ache, anemia, syncope, flushing, increased liver enzymes -- dose dependent ,transient(2 to7%)
- Approved by FDA – 2001.
- 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

	Terbogrel	Treprostinil	ALPHABET	AIR	Bosentan	BREAT HE1
Pts	46/25	233/236	65/65	101/102	21/11	144/69
Route	Oral bd	S/C continuous	Oral qid	Inhaled 2-4 hrly	Oralbd	Oralbd
Duration m	3	3	3	3	3	4
NYHA class	II/III	III	II/III	III/IV	III	III
Etio	PPH100%	PPH(58%) CHD,CTD	PPH(48%), CHD,PoPH	PPH54 % CTPH, CTD	PPH 85%CTD	PPH-70%, CTD
Mean Pap	55	61	59	53	55	54
6MWT	0 0	16 79	25 45	36 57	76 76	44 52
Hd	⟷	↑	⟷	↑	↑	↑
Clinical event	↑	↑	⟷	↓	↓	delayed

Nitric Oxide

- Vasodilator ,anti platelet, anti inflammatory, anti oxidant
- Modulates angiogenesis
- Decreased NO synthase in pulm.htn.
- Inhaled NO --- selective pulmonary vasodilator
- Potent pulm vasodilator
  - PPHN – FDA approved
  - 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 by15%, 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

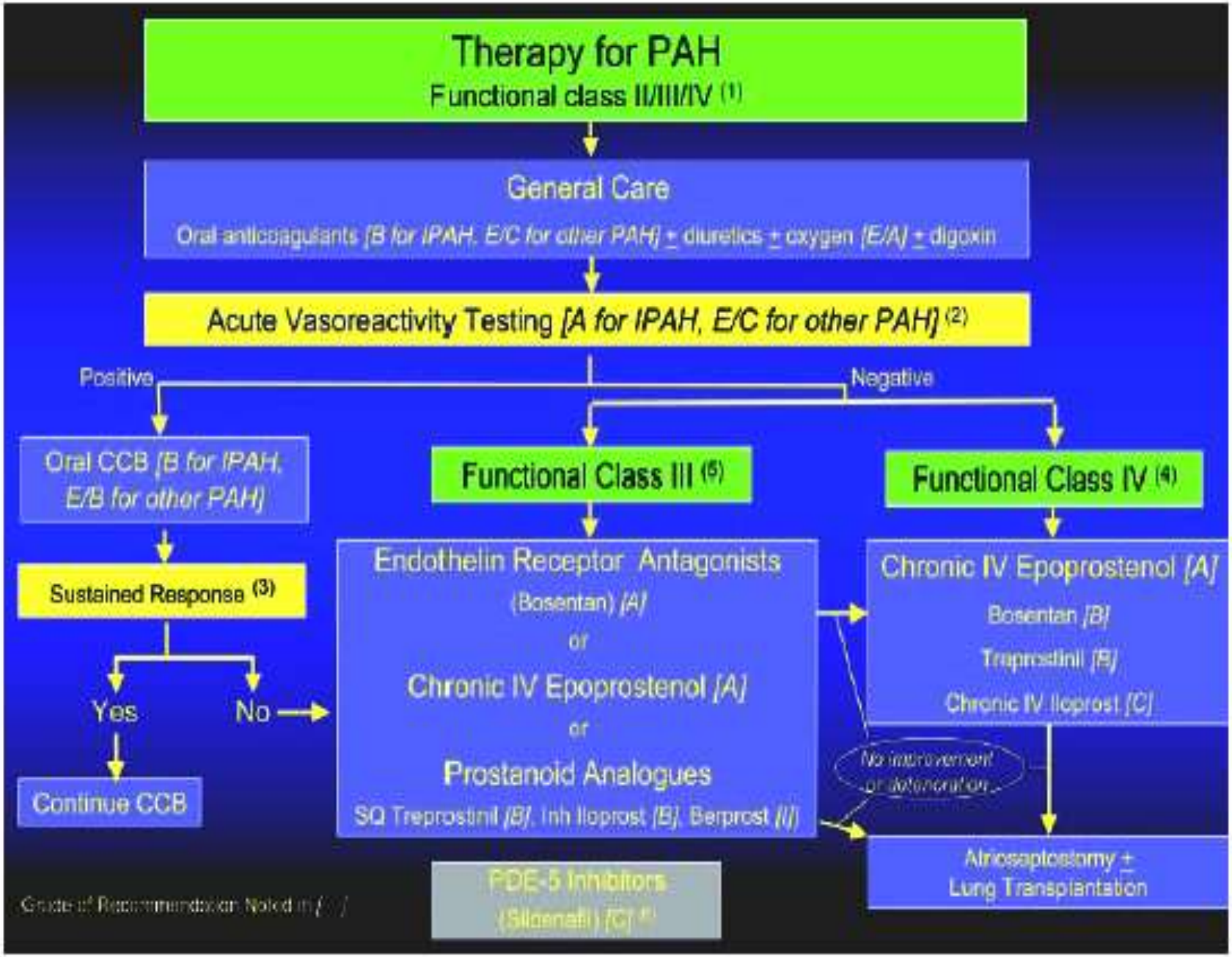
- PDE (type5) degrades cGMP.

- 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
- Role in
  - CTEPH
  - 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 (1)
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] (2)
Positive
Negative
Oral CCB [B for IPAH, E/B for other PAH]
Sustained Response (3)
Yes
No
Continue CCB
Functional Class III (5)
Endothelin Receptor Antagonists
(Bosentan) [A]
or
Chronic IV Epoprostenol [A]
or
Prostanoid Analogues
SQ Treprostinil [B], Inh Iloprost [B], Berprost [I]
Functional Class IV (4)
Chronic IV Epoprostenol [A]
Bosentan [B]
Treprostinil [B]
Chronic IV Iloprost [C]
No improvement or deterioration
Atrioseptostomy ±
Lung Transplantation
PDE-5 Inhibitors
(Sildenafil) [C] *
Grade of Recommendation Noted in ( )

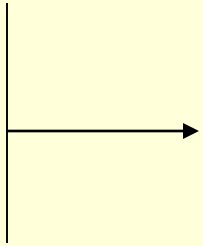
Pulmonary HTN sec. to lung disease

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



HPVC

Vascular remodeling

Pulmonary HTN sec. to lung disease

- Vasoconstriction
- Endothelial dysfunction → ↓eNOS, ↑ET-1, ↑5 HT transporter
- Hypercoagulable state → 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 → 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) ⟶ ↓mPAP (44 to 36)
  ↓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

spiked delivery ------- **Katayama et al (1998**)

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

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

  NO,sildenafil ---- ↓PVR, ↓Pap
  maintained V/Q matching
  shunt (4%,3.3% vs 16%)
  ↑Pao2
- Amplifies local vasoregulatory mechanisms

Chronic thromboembolic pulmonary hypertension

- 0.1% - 0.4% of Acute PTE
- Honey moon period

Recurrent TE
Abn. of hemostasis
In situ thrombosis
Remodeling of vessels in non occluded
Distal vasculopathy in occluded vessels

→ Worsening pulm.HTN

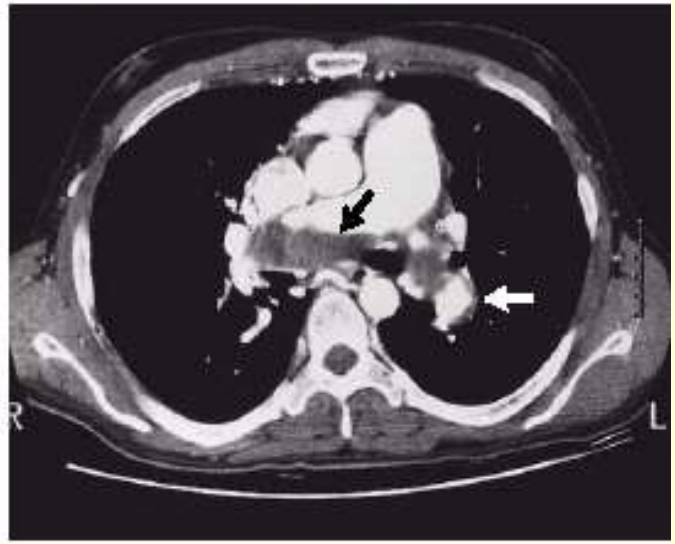
Pathology

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

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 accessible / not surgically accessible < Distal obstruction / 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 lungdisease
- 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


ThankYou