



Pulmonary hypertension



主講藥師：彭春惠

日期：2012/06/17



Introduction

- For a person at rest, blood pressure in a normal pulmonary artery is about **15 mm Hg**.
- In an individual with PH, the average pressure in the pulmonary artery can be more than **25 mm Hg**.
- This increase in pulmonary artery pressure occurs when the small arteries of the lungs become abnormally narrow. This condition can eventually lead to heart failure and death.



Classification of PH

- Previously classified
 - Idiopathic pulmonary arterial hypertension(IPAH, formerly called primary pulmonary hypertension)
 - Secondary PH.

Group 1 PAH

1. Pulmonary **arterial** hypertension (PAH)

1.1. **Idiopathic PAH**

1.2. Heritable

1.2.1. BMPR2

1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)

1.2.3. Unknown

1.3. Drug- and toxin-induced



1.4. Associated with

1.4.1. Connective tissue diseases

1.4.2. HIV infection

1.4.3. Portal hypertension

1.4.4. Congenital heart diseases

1.4.5. Schistosomiasis

1.4.6. Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn

1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

definite risk factors	Aminorex, Fenfluramine, Dexfenfluramine, and toxic rapeseed oil
possible risk factors	Amphetamines, L-tryptophan, Methamphetamines, Cocaine, Phenylpropanolamine, St. John's Wort, Chemotherapeutic agents, SSRIs.

Group 2 PH

2. Pulmonary hypertension owing to **left heart disease**
 - 2.1. Systolic dysfunction
 - 2.2. Diastolic dysfunction
 - 2.3. Valvular disease

Group 3 PH

3. Pulmonary hypertension owing to **lung diseases** and/or **hypoxia**
 - 3.1. Chronic obstructive pulmonary disease
 - 3.2. Interstitial lung disease
 - 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
 - 3.4. Sleep-disordered breathing
 - 3.5. Alveolar hypoventilation disorders
 - 3.6. Chronic exposure to high altitude
 - 3.7. Developmental abnormalities

Group 4 PH

4. Chronic **thromboembolic** pulmonary hypertension (CTEPH)

Group 5 PH

5. Pulmonary hypertension with **unclear** multifactorial mechanisms

5.1. Hematologic disorders: myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis



Epidemiology

Incidence

- Idiopathic pulmonary arterial hypertension
--0.2 cases per 100,000 annually.
- Secondary pulmonary hypertension
--More common; exact incidence unknown.



Pathogenesis

- PAH is a proliferative vasculopathy, characterized by vasoconstriction, cell proliferation, fibrosis, and thrombosis.
- Endothelin levels \uparrow
- Nitric oxide \downarrow
- Prostacyclin levels \downarrow



Common symptoms

- Patients may be asymptomatic initially.
- With disease progression
 - Exertional dyspnea, often with insidious onset
 - Fatigue
 - Angina pectoris (may be caused by right ventricular ischemia)
 - Syncope or near syncope
 - Peripheral edema
 - Tricuspid regurgitation



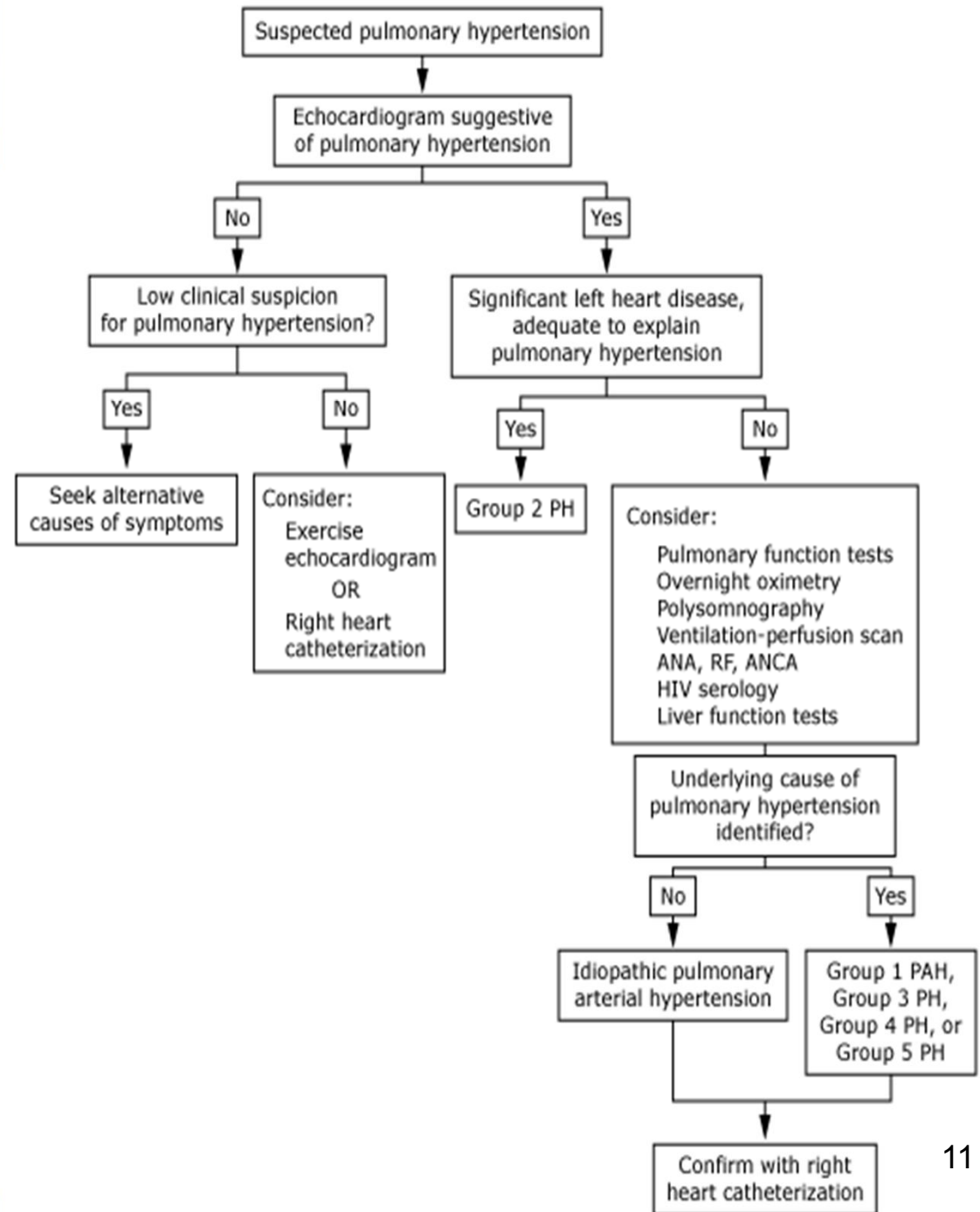
Pulmonary hypertension assessment





Diagnostic evaluation

- ① Chest radiograph
- ② Electrocardiography
- ③ Echocardiography
- ④ Pulmonary function tests
- ⑤ Overnight oximetry
- ⑥ Polysomnography
- ⑦ V/Q scan
- ⑧ Laboratory tests
- ⑨ Exercise testing
- ⑩ Right heart catheterization





Treatment

- Primary therapy
- Advanced therapy





Primary Therapy

Group 1 PAH No effective primary therapies for most types of group 1 PAH.

Group 2 Treatment of the underlying heart disease

Group 3

- 1) Treatment of the underlying cause of hypoxemia
- 2) Correction of the hypoxemia with supplemental oxygen.

Group 4 anticoagulant therapy

Group 5 Treatment of the underlying cause.



Primary Therapy

- **Diuretics**

- Used to treat fluid retention (Grade 2B)

- Caution to avoid decreased cardiac output , arrhythmias induced by hypokalemia, and metabolic alkalosis.

- May need to combine classes (thiazide and loop diuretics)

- Patients often require large doses of diuretics

- **Anticoagulant**

- For IPAH , hereditary PAH, drug-induced PAH, group 4 PH (Grade 2B)

- Wafarin (Coumadin)

- generally keep INR 2.0-2.5



Primary Therapy

- **Digoxin**
 - No data are available on the long-term effects of digoxin in patients with group 1 PAH
 - Improves the left ventricular ejection fraction of patients with group 3 PH
- **Oxygen**
 - For all patients with PH plus hypoxemia
 - In group 3H (Grade 1A), other types (Grade 2B)



Exercise

- Exercise training appears to be beneficial for patients with PH.
- The improved distances exceed those described for all types of advanced therapy.
- Exercise training improved the WHO functional class and peak oxygen consumption.



WHO functional classification for PH

Patients with pulmonary hypertension but without resulting limitations of physical activity.

- I Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.

Patients with pulmonary hypertension resulting in slight limitation of physical activity. They

- II are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.

Patients with pulmonary hypertension resulting in marked limitation of physical activity.

- III They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.

Patients with pulmonary hypertension resulting in inability to carry on any physical activity

- IV without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.



Advanced Therapy

- | | |
|-------------|---|
| Group 1 PAH | Often needed for patients with group 1 PAH because there are no effective primary therapies. |
| Group 2 | For most patients with group 2 PH, advanced therapy should be <u>avoided</u> because it may be harmful. |
| Group 3 | Should only be initiated at specialized centers and administered cautiously due to its potential to worsen ventilation-perfusion mismatch and increase hypoxemia. |
| Group 4 | Who remain WHO functional class III or IV even after anticoagulation or thromboendarterectomy. Pharmacologic therapy can also act as a bridge to surgical intervention. |
| Group 5 | Small studies for patients with PH related to sarcoidosis |



Advanced Therapy

- Patient selection
 - Who have evidence of persistent PH and a WHO functional class II, III, or IV despite adequate primary therapy
- Invasive hemodynamic assessment
 - Acute vasoreactivity test: right heart catheter
 - IV epoprostenol
 - IV adenosine
 - Inhaled nitric oxide



Acute Vasoreactivity test

- Positive
 - Calcium channel blocker : Dihydropyridine or Diltiazem
- Negative
 - Prostanoids
 - Endothelin receptor antagonists(ERAs)
 - Phosphodiesterase 5 inhibitors(PDE 5-I)



Calcium channel blockers

- Prolonged survival, sustained functional improvement, and hemodynamic improvement.
- Titrate up to maximum tolerated dose.
- Systemic hypotension may prohibit use.

long-acting nifedipine (Adalat OROS[®]) 30 ~240 mg/day

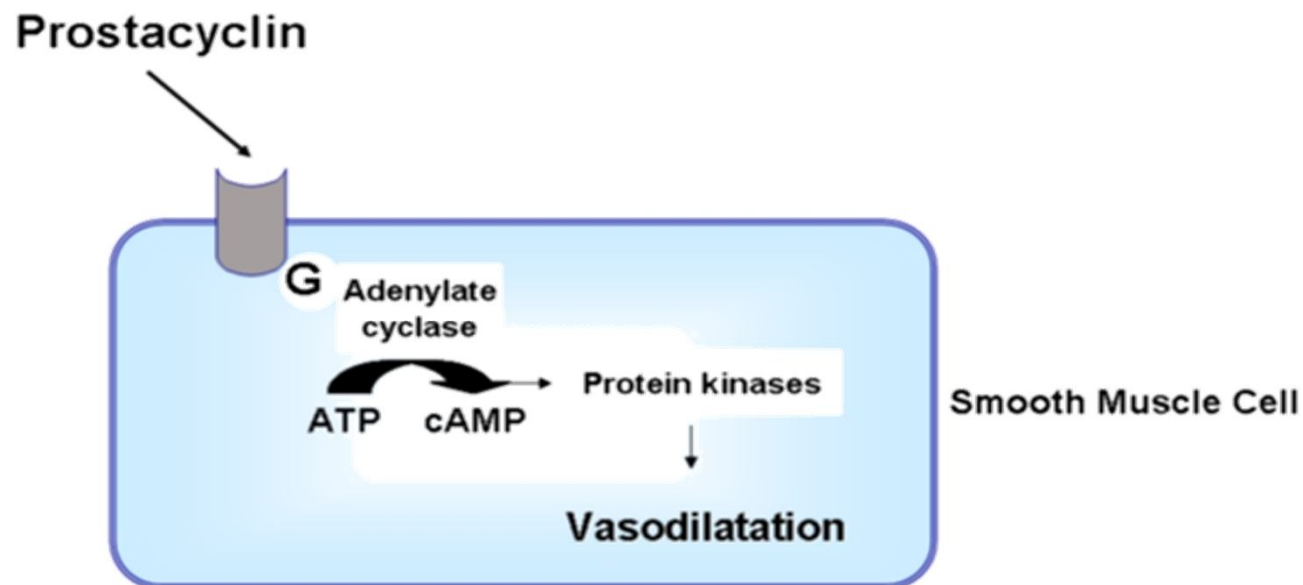
Diltiazem(Diltelan[®], Herbesser[®]) 120 ~ 900 mg/day

Amlodipine(Norvasc[®]) 2.5~20 mg/day



Prostanoids

- Benefits:
 1. Vasodilation, 2. Platelet inhibit,
 3. Anti-proliferative effectives, 4. Inotropic effects.



Ref:http://www.spvu.co.uk/MedicalStaffInformation/Treatment_DiseaseTargetedTherapy.jsp



Prostanoids

- Epoprostenol (Flolan[®]): IV
- Treprostinil (Remodulin[®], Tyvaso[®]): IV, SC, inh
- Iloprost (Ventavis[®]): inh



Epoprostenol (Flolan[®])

- 1) It improves hemodynamic parameters, functional capacity, and survival in patients with IPAH.
- 2) First-line agent in patients with WHO class IV.

使用方式

Delivered continuously through a permanently implanted central venous catheter using a portable infusion pump.

Dose

Initiated: 1 to 2 ng/kg per min.
Increased: by 1 to 2 ng/kg per min every one to two days as tolerated.
Maximal dose: has not been established.

adverse effects

- 1) Headache, flushing, nausea, vomiting, flu-like symptoms, jaw pain, diarrhea, and arthralgias.
- 2) Central venous catheter infection.

Treprostinil (Remodulin[®], Tyvaso[®])

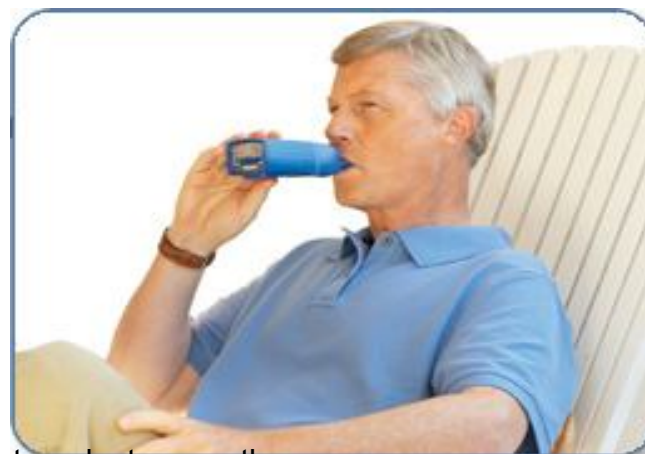
1) Improves hemodynamic parameters, symptoms, exercise capacity, and possibly survival in patients with **group 1 PAH** .

使用方式	<ol style="list-style-type: none">1) IV(Remodulin[®])2) SC: uncommon due to severe pain at the injection site (Remodulin[®])3) INH: recently been approved, specifically for patients with group 1 PAH who are WHO functional class III. (Tyvaso[®])
Dose	2.5 to 5 mcg, six to nine times per day.
Advantage	Compared to epoprostenol: <ol style="list-style-type: none">1) Option of continuous subcutaneous delivery2) A longer half-life that may make interruption of the infusion less immediately life threatening3) No need for refrigeration.

Iloprost(Ventavis® 20ug/2ml/amp)

1) Theoretical advantages in targeting the lung vasculature and does not require intravenous administration.

使用方式	以專用霧化器,避免使用面罩,使用吸嘴吸入即可。
Dose	2.5 to 5 mcg, six to nine times per day. 肝不全: 2.5 ug Q3H, 依據個人耐受性調整 腎不全: creatinine>30 ml/min 不需調整
注意	不可用於收縮壓低於85 mmHg之病患；低血壓病患慎防進一步降低血壓。





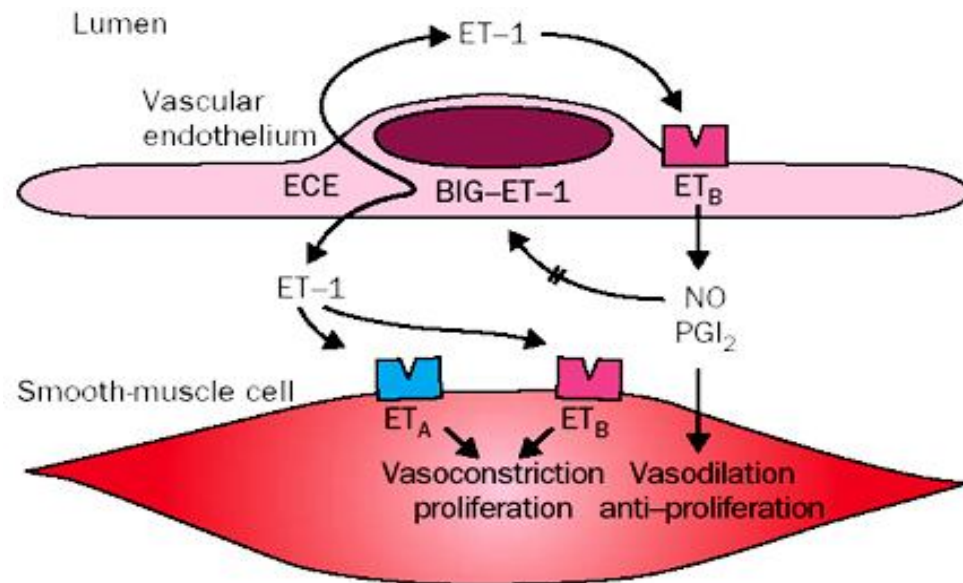
Iloprost (Ventavis)

- 1. Improvements in functional class and hemodynamics observed.
- 2. Safety and side effects
 - Potential for increased hypotensive effect with antihypertensives.
 - Increased risk of bleeding especially with co-administration of anticoagulants.
 - Flushing, increased cough, headache, insomnia, nausea, vomiting, flu-like syndrome.
 - Increased liver enzymes.



Endothelin system in vascular tissue

- Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen.



ET: endothelin-1;BIG-ET-1: proendothelin-1;ECE: endothelin-converting enzyme;
NO: nitric oxide;PGI₂: prostacyclin



Endothelin receptor antagonists (ERAs)

- High concentrations of endothelin-1(ET-1) have been recorded in the lungs of patients with both IPAH and other etiologies of group 1 PAH.
- Endothelin receptor antagonism emerged as an initial therapy for group 1 PAH in the late 1990s.
- Nonselective: Bosentan (Tracleer ®)
- Selective type A ET-1 receptor antagonist
 1. Ambrisentan (Letairis ®)
 2. Sitaxsentan: withdrawn



Bosentan (Tracleer®)

- Dose: 62.5-125 mg BID
- Liver function tests should be monitored monthly during treatment with bosentan

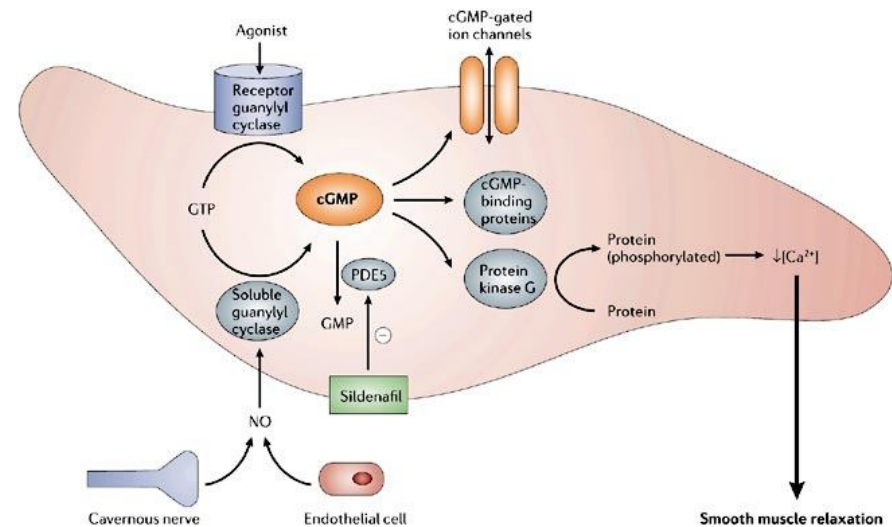
- 禁忌:
 1. 禁用於中度或嚴重肝功能受損者
 2. 禁用於同時使用 cyclosporine A 或 glyburide 者





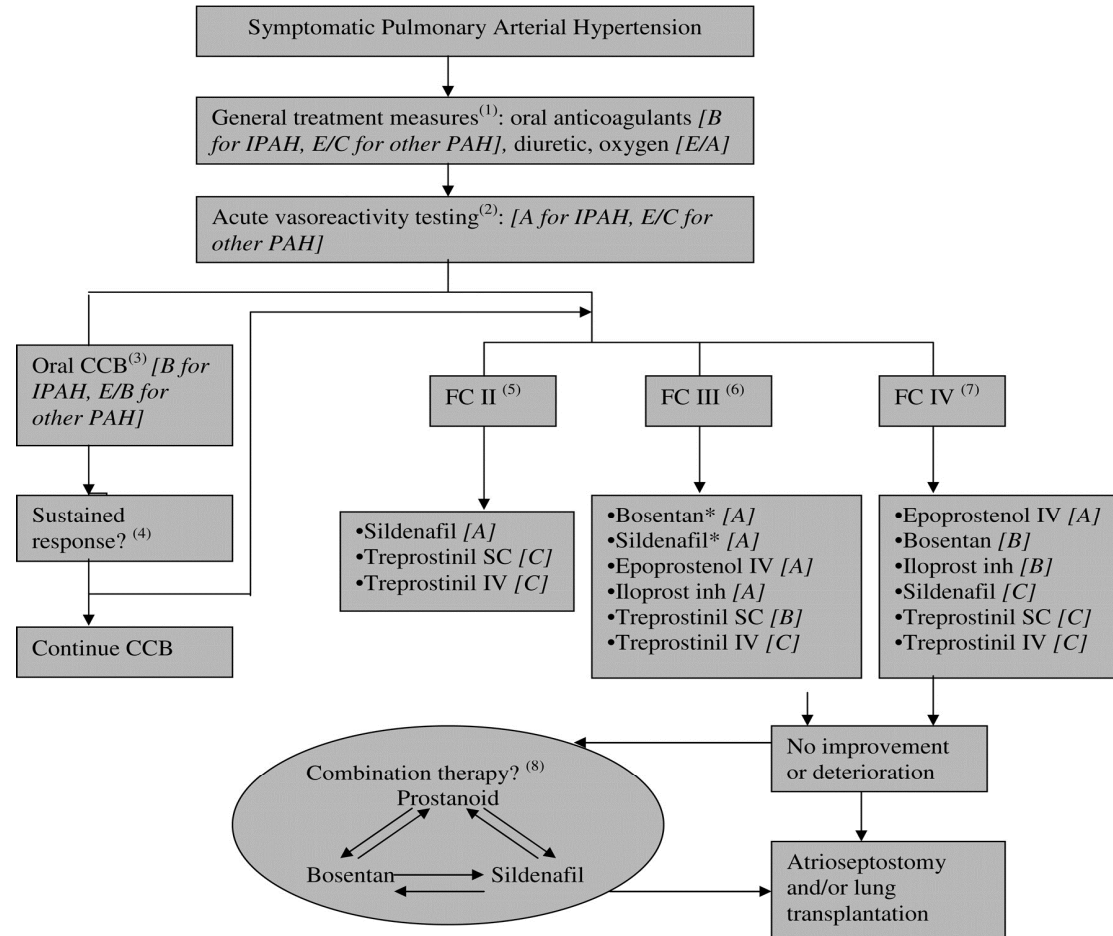
Phosphodiesterase 5 inhibitors (PDE 5-I)

- Sildenafil (Revatio[®])
 - 20mg TID
- Vardenafil (Levitra[®] 20mg/tab)
 - 5 mg once daily for the first 4 weeks, then 5 mg twice daily
- Tadalafil
 - 40mg/day





Treatment algorithm for PAH. The recommended therapies presented in this algorithm have been evaluated mainly in those with IPAH, or PAH associated with connective tissue disease or anorexigen use.



* Not in order of preference.



Summary and recommendations

- Initial therapy should be directed at the underlying cause of the PH. In addition, the need for diuretic, oxygen, and anticoagulant therapy should be assessed.
- Patients with persistent PH whose WHO functional class is II, III, or IV despite treatment of the underlying cause of the PH should be referred to a specialized center to be evaluated for advanced therapy.



Summary and recommendations

- Advanced therapy is widely accepted for many patients with group 1 PAH. In contrast, it must be considered on a case-by-case basis for patients with group 3 PH, group 4 PH, or group 5 PH, after carefully weighing the risks versus the benefits. Advanced therapy should NOT be administered to most patients with group 2 PH.
- All patients selected for advanced therapy should undergo right heart catheterization and most of those who have group 1 PAH should also undergo vasoreactivity testing.



Summary and recommendations

- For patients who have a positive vasoreactivity test, we suggest a trial of calcium channel blocker (CCB) therapy with a dihydropyridine or diltiazem
- For patients with idiopathic pulmonary arterial hypertension (IPAH) who have a negative vasoreactivity test or fail CCB therapy, we recommend advanced therapy with a non-CCB agent (Grade 1A). Non-CCB agents include prostanoids, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors.



Summary and recommendations

- The preferred non-CCB agent is related to the functional severity of disease.
 - For patients who are WHO functional class IV, we suggest intravenous epoprostenol, rather than any alternative agent (Grade 2B). For patients who are WHO functional class II or III, acceptable first-line non-CCB agents include oral ambrisentan, oral bosentan, intravenous epoprostenol, inhaled iloprost, oral sildenafil, oral tadalafil, intravenous treprostinil, or subcutaneous treprostinil.
- Atrial septostomy and lung transplantation are reserved for patients refractory to medical therapy.



References

- Uptodate (©2012 UpToDate® 2012. 03)
- Journal of the American Medical Association. 2009; 302(13): 1490.
- American College of Chest Physicians (ACCP) ©2007 Pulmonary hypertension treatment guidelines.
- http://www.kmuh.org.tw/www/Administration/Pulmonary_Hypertension/index.html

Thank you for your attention !

