



Pulmonary hypertension

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Pulmonary hypertension?

A bad term that should be abandoned

- Systemic arterial hypertension = increased small vessel resistance
- Increased cardiac output or systemic venous pressure do not cause systemic arterial hypertension
- Pulmonary arterial hypertension can be the result of several pathophysiological processes: Increased flow, increased venous pressure, increased arteriolar (rarely venular) resistance and any combination of the above.

Pulmonary hypertension - definition

- Catheterization obtained mean pulmonary artery pressure >25 mmHg, normal or reduced cardiac output and pulmonary vascular resistance > 3 Woods (non indexed)
- Exercise induced mean PA pressure >30 mmHg – very problematic definition
- Suggestion: 20-25 mmHg – borderline

Diagnosis and monitoring

- Systemic arterial hypertension – easy
- Often incidental finding on routine measurement
- Easy to follow up and adjust treatment
- Primary = common
secondary = rare
- Pulmonary hypertension – difficult, no direct access to arterial tree
- Pressure alone is not enough to assess response to treatment
- Primary = rare
secondary = common

Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

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)

2. Pulmonary hypertension owing to left heart disease

- 2.1. Systolic dysfunction
- 2.2. Diastolic dysfunction
- 2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia

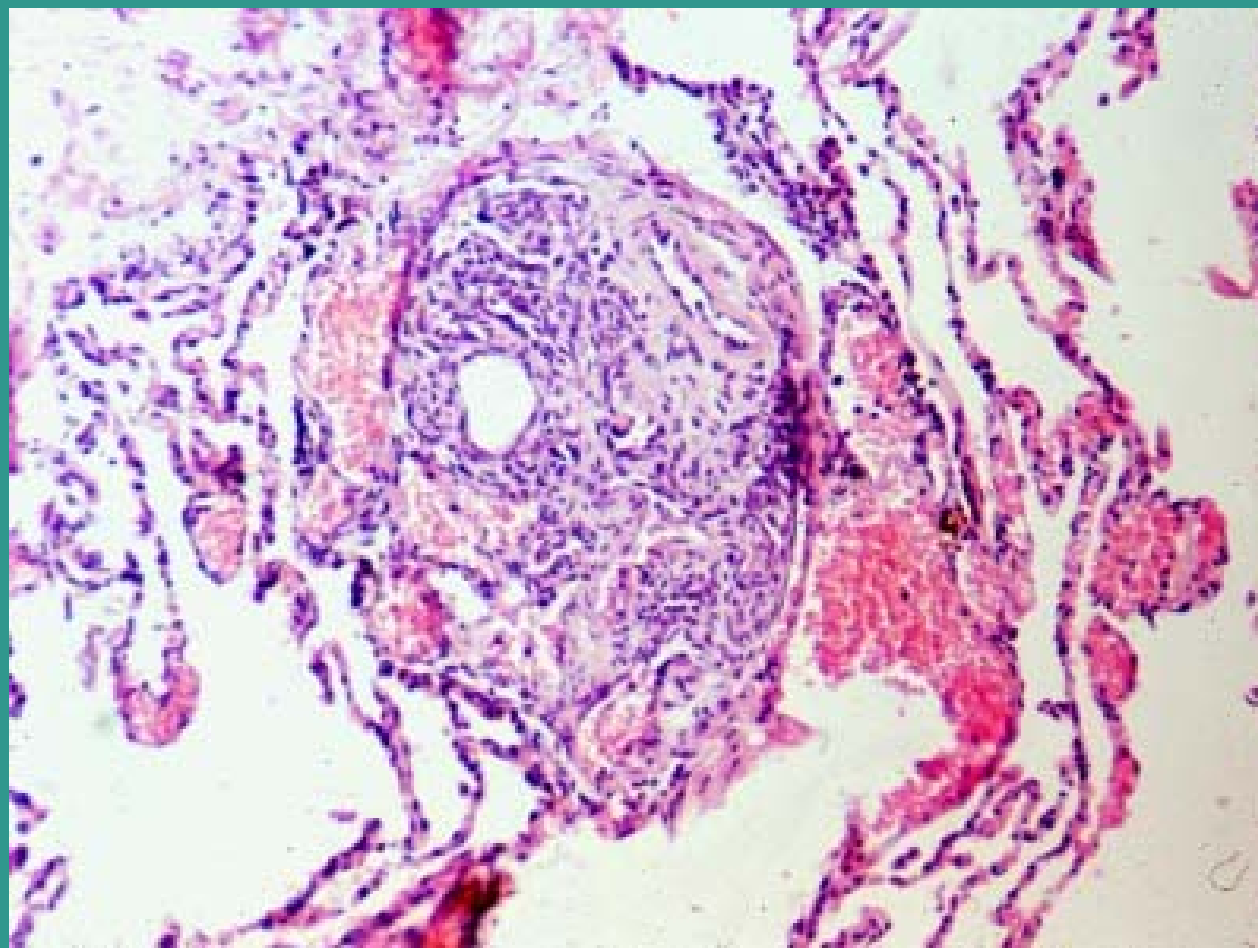
- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep-disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

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

יתר לחץ דם ראתי דרגה IV



Idiopathic pulmonary hypertension

- Not “primary”
- Incidence 2-5/1,000,000
- Females>males
- Median age at diagnosis 37 years
- Familial in 6-10% BMPR2 (TGF-beta)
- Autosomal dominant variable penetrance
- Two hit hypothesis
- Genetic anticipation – children more sick than parents
- Rare – veno-occlusive disease and pulmonary capillary hemangiomatosis

Prognosis – natural history

- Median survival – 2.8 years from diagnosis
- 1 year – 68%, 3 years – 48%, 5 years – 34%
- The heart is the most affected organ. Prognosis worse when RA pressure \uparrow , cardiac index \downarrow , pericardial effusion
- BNP, NT-pro-BNP levels
- FC by 6 minutes walking distance < 380 meters

Diseases and conditions with PH

- Scleroderma – very severe, poor prognosis, histology not inflammatory
- Inflammatory diseases – SLE, mixed
- Liver disease – 4-15% candidates liver transplantation. CI-PA pressure >35 mmHg
- HIV – 1/200
- Drugs – amphetamine derivatives e.g fenfluramine other anorexigens

CHD patients with PHT

- Elevated venous pressure – MS, supra mitral membrane and cor triatriatum: rare and treatable surgically – will not be further discussed
- Malformations with initial left to right shunt and almost inevitable shunt reversal with Eisenmenger syndrome: VSD, PDA, complex CHD with unrestricted pulmonary flow, large surgical central shunts
- Malformations with left to right shunt and occasional development of Eisenmenger syndrome: ASD
- Progressive pulmonary hypertension in repaired shunt lesions.

Bedside diagnosis of pulmonary hypertension

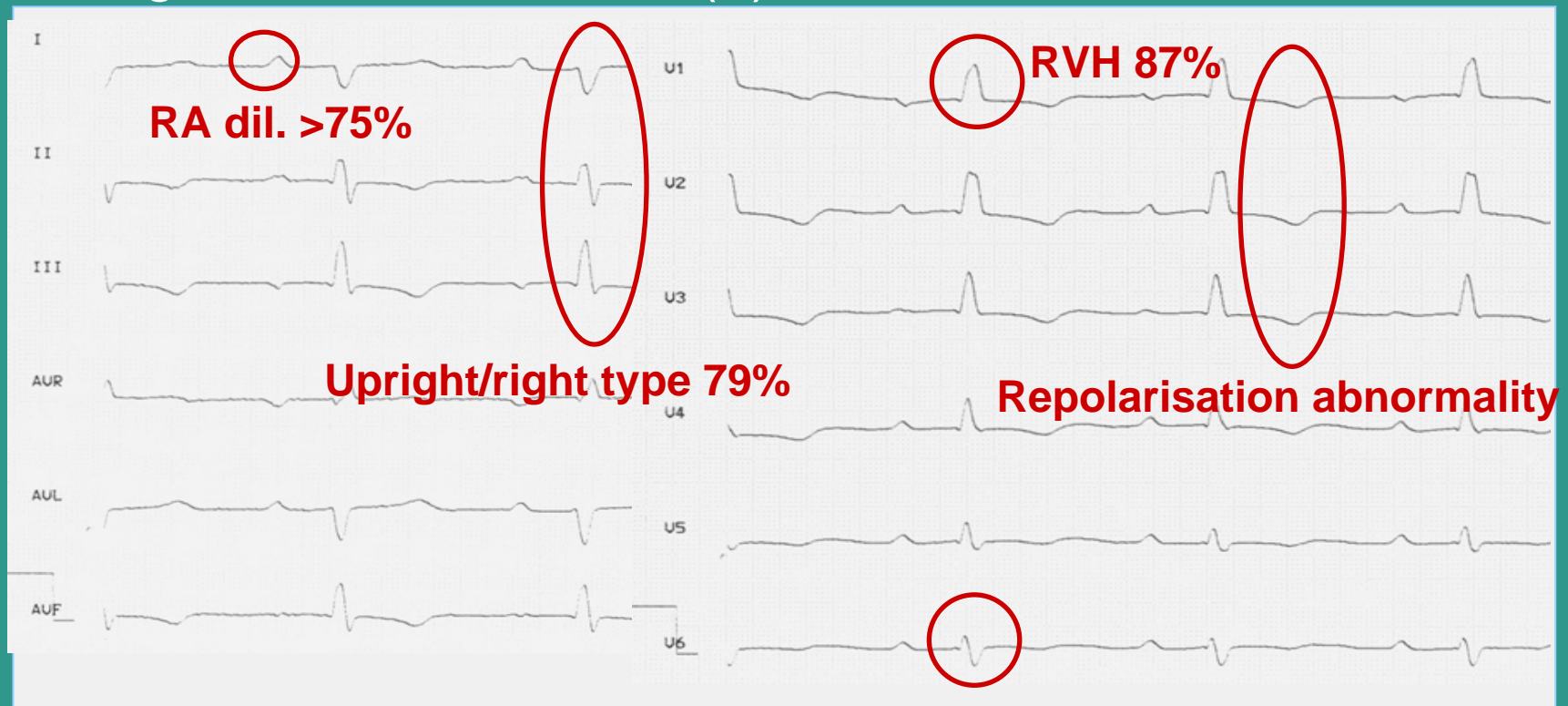
- History – murmur and/or heart failure in childhood, previous operation of lt. rt. shunt lesion, previous palliation with central shunt
- Symptoms - cyanosis on exertion, syncope, declining exercise capacity, angina pectoris, palpitations

Bedside diagnosis (cntd.)

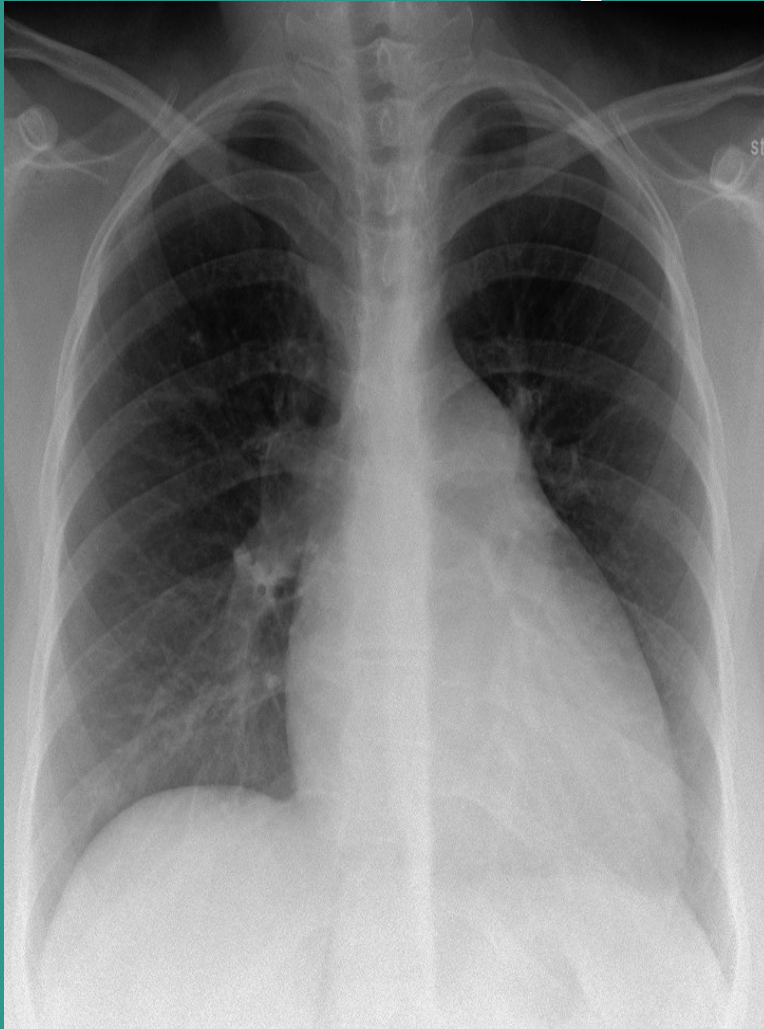
- Physical examination – pulse oximetry arms and legs!!, clubbing, sustained RV heave, loud (single) P2 (dd CTGA), absence of stenotic murmur, absence of continuous murmur, diastolic Graham Steell murmur
- ECG - Right forces
- Chest x-ray: plethora vs. pruning and peripheral oligemia, heart shadow suggestive of CHD, situs anomaly etc.

ECG signs of right heart overload

- Sensitivity: R-type 73 %, RVH 55 %
- Specificity: 70 % (both)
- Prognosis: $P > 0.25$ mV (II) RR 2.8 (Bossone *Chest* 2002)



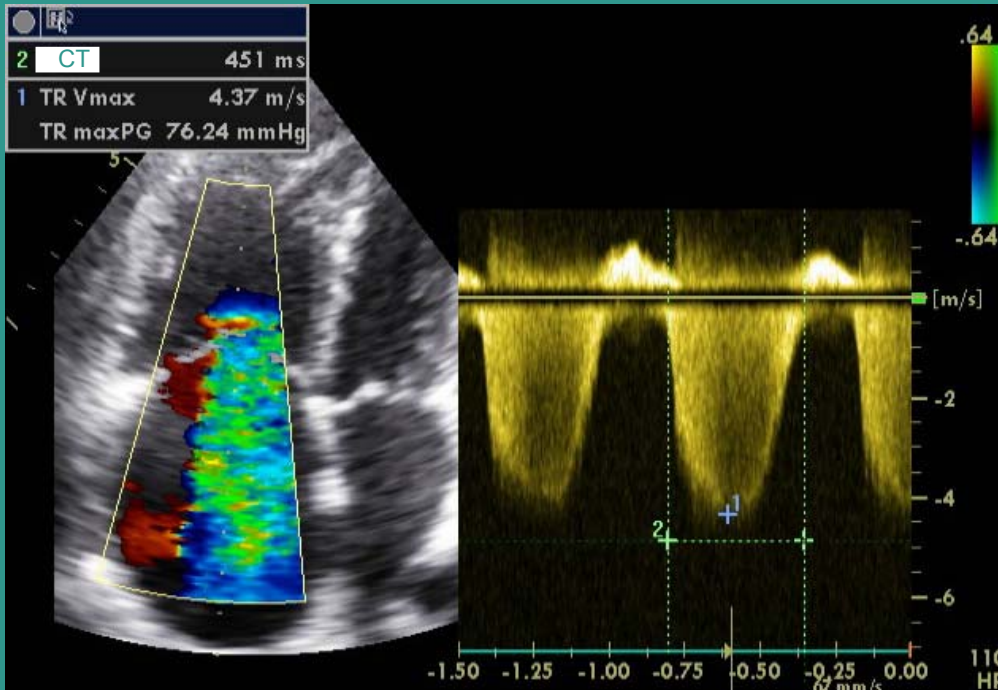
Chest X-Ray



Echocardiography TTE+TEE

- Establish the existence of pulmonary hypertension and assess severity
- Etiology – r/o left heart disease incl. myocardial dysf. – systolic/diastolic mitral stenosis incl. supra-valve membrane and cor triatriatum, pulm. vein stenoses etc., shunt lesions ASD VSD PDA AVSD and complex CHD

Doppler Echocardiography



Courtesy of: R. Voswinckel, Gießen/Germany

Estimation of systolic PAP :

normal	< 2.8 m/s
mild PH	2.8 – 3.4 m/s
moderate PH	> 3.4 m/s

- Measurement of the RV contraction time (RVCT) as a component of the TEI- index ($TEI = [RVCT - RVET] / RVET$)
- TAPSE (tricuspid annular plane systolic excursion)
- Measurement of the RVET in the RV outflow tract by means of pulsed wave doppler echocardiography

Echocardiography (cntd)

- Evaluate impact of PHT on heart structure and function – RV size and function, RVH, tricuspid regurgitation, diastolic interaction with LV, systemic venous hypertension – distention of veins, bulging of interatrial septum, rt. Lt. shunting – PFO or septostomy, thrombosis in situ in pulmonary tree
- Follow up – serial studies, assess effect of treatment, record complications and deterioration

Echocardiography - pitfalls

- In early PPH “normal” (no TR trace) – look for PI, acceleration, septum etc.
- False positive – in pulmonary stenosis, in VSD when cursor cuts TR and VSD jets.
- Pulmonary systolic pressure may be increased in some hyperdynamic conditions with mean pressure still in normal range. (35-55 mmHg TR gradient)
- Missing shunt lesions – sinus venosus defects, anomalous veins, AP-window, PDA (shunt jet is of low velocity). Patients may not be blue yet
- TTE is not enough to r/o CHD. All patients should have TEE before making a diagnosis of PPH

Catheterization

- Should be performed with meticulous attention to details.
- On room air – extensive set of saturations to r/o anomalous veins and unexpected shunt lesions
- In collateral circulation go distal enough
- Try to cross the ias and have an LV cath to write simultaneous pressure with wedge on both lungs
- Repeat measurement on oxygen by mask for 20 minutes and again after potent vasodilator (NO, iloprost inhalation).
- Calculations should include dissolved oxygen.
- Indexed resistances should be the standard

Assessing operability of shunt lesions

- A calculated indexed PVR of up to 7 Woods x msq with oxygen or potent pulmonary vasodilator is usually operable with good chance of resolution
- Indexed PVR >12 Woods x msq is usually considered inoperable
- Indexed PVR 8-12 Woods x msq is less predictable. Some advocate a prolonged trial with medication and repeat study

PHT in repaired CHD

- Assuming the PVR at the time of repair was still in the operable or borderline range, the continuing rise in resistance is an autonomous and unpredictable process, quite similar to that in PPH. Still, the rate of progression is usually far slower, probably because of a more heterogeneous genetic susceptibility
- The pathophysiology is similar to PPH, having two separate circulations, with the systemic circulation being totally dependent on the pulmonary circulation.

שלושת המסלולים לפעולת תכשירים נגד יתר לחץ דם ראתי

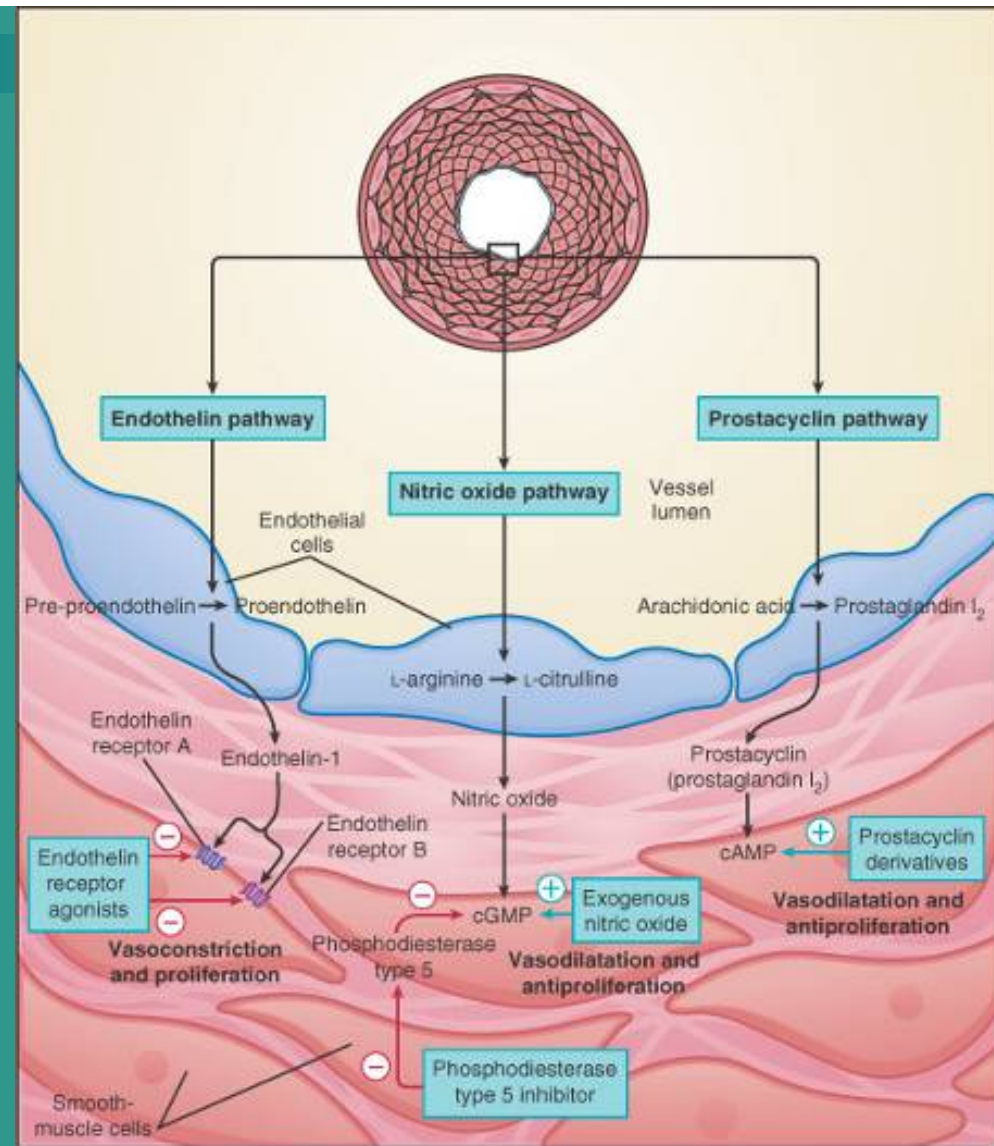


FIGURE 73-9 Targets for current therapies in pulmonary arterial hypertension (PAH). Three pathways involved in the pathogenesis of PAH are shown. These pathways correspond to important therapeutic targets and illustrate how currently approved therapies might work in PAH at the cellular level. Vasoconstriction and cellular proliferation are the dominant processes. There is currently no way of knowing which pathway(s) might be important in any given patient. Although the use of therapies in combination has appeal, there are little data currently indicating that this approach is efficacious.

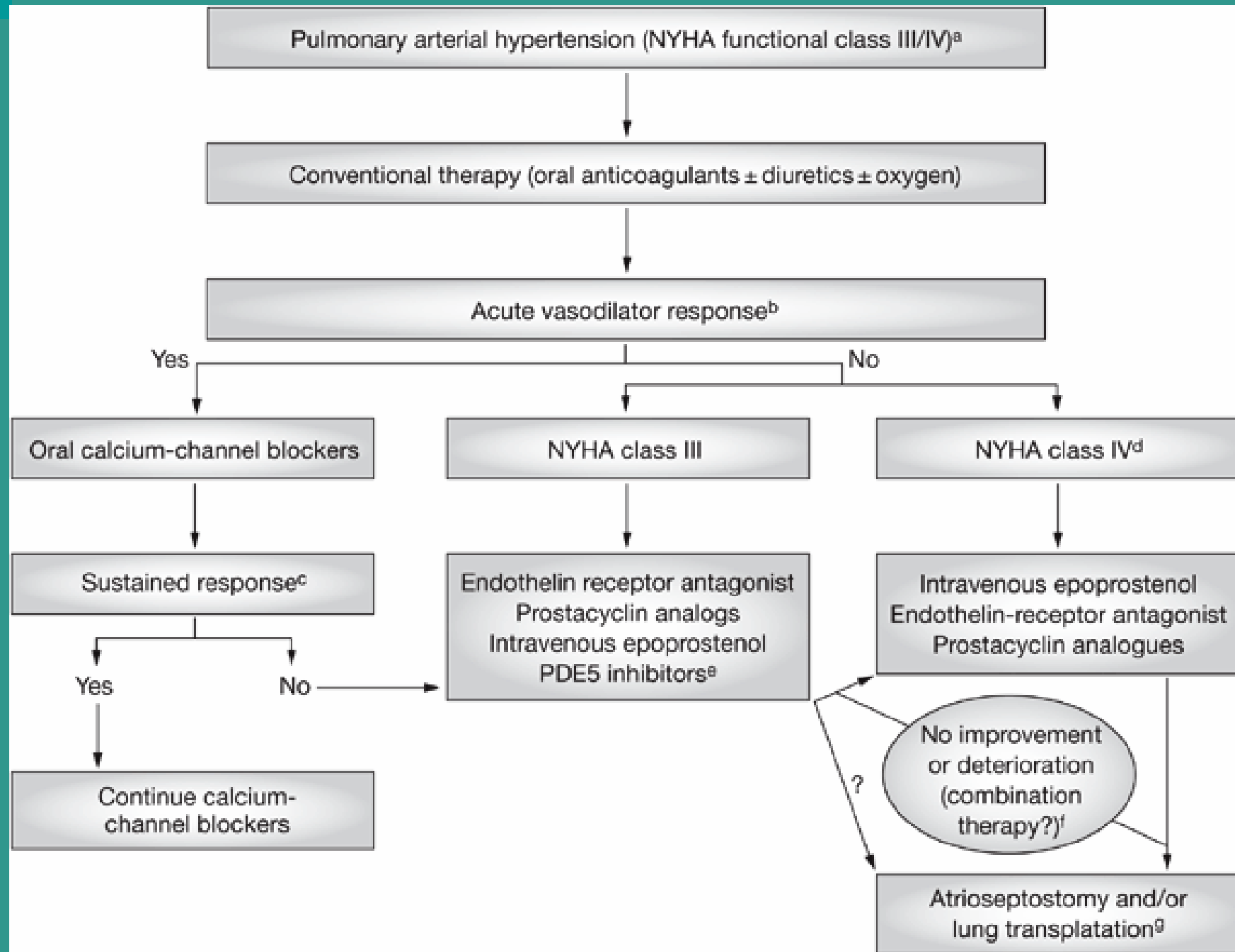
(From Humbert M, Sitbon O, Simonneau G: Treatment of pulmonary arterial hypertension. *N Engl J Med* 351:1425, 2004.)

Drugs – improve functional class, hemodynamics and survival (?)

- Endothelin receptor antagonists – non selective (bosentan) selective – sitaxentan and ambrisentan (no interaction coumadin, less liver toxicity)
- PDE inhibitors – sildenafil and tadalafil
- Prostacycline analogues – epoprostenol (iv only), trepostinil (sc, iv, in testing – inhaled and oral), iloprost (inhaled, iv)
- Rehab programs - physical activity – seems promising alternative

Deteriorating patient and unsettled issues

- Combination therapy (wait for deterioration or initiate early?)
- Atrial septostomy – for syncope
- Lung, double lung, heart lung transplantation (40% 5 year survival)
- Pulmonary thrombendarterectomy (excellent option in good hands – 3% mortality)
- Should we treat FC II patients? (Early study). FDA approval of ambrisentan for class II and III



Paul Wood

The Croonian Lecture

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 20 1958

THE EISENMENGER SYNDROME OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

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Eisenmenger syndrome

- This is the form of PHT that is unique to CHD
- Tissue perfusion is adequate, as systemic circulation is not dependent on pulmonary flow
- The poor oxygen content of the blue blood is compensated for by secondary erythrocytosis
- Except for ASD, pulmonary pressure cannot exceed systemic pressure

Eisenmenger syndrome – the eighth wonder of the world

- Unique pathophysiology, allowing people with the same malignant vascular disease in the lungs that kills PPH patients in 3-5 years, to live up to 50-60 years and sometimes more, with often a reasonable quality of life
- Surprising improved survival over the last decades for an “untreatable disease” – partly due to improved understanding and fewer management mistakes
- Survival is better for simple lesions than complex CHD

Care of Eisenmenger patients –do's

- Close follow up and monitoring of physical findings (edema, saturation) blood tests, functional class, echo – myocardial function and valves (not “pulmonary pressure”)
- Holter monitoring for palpitations and syncope (not routine)
- Therapeutic phlebotomies only for hyper-viscosity symptoms. Proper fluid replacement (preferably colloid)
- Use filters on venous lines
- Hospitalize for hemoptysis and sedate

Care of Eisenmenger patients – don'ts

- Avoid anti aggregants and anti coagulants unless absolute indication
- Avoid unnecessary medical procedures by all means. Prepare thoroughly for unavoidable ones
- Avoid pregnancy which is still considered a major maternal risk
- Avoid dehydration, hot places (disco)
- Avoid long haul flights (split)

Pharmacological intervention in Eisenmenger syndrome

- Simple drugs are helpful: digoxin, careful use of diuretics, amiodarone, oxygen (for symptoms)
- PHT specific medication: early studies included PPH patients and repaired CHD, not Eisenmengers.
- Concern that vasodilators can worsen cyanosis (probably not a problem)
- Long survival with reasonable quality of life; very different from PPH. Treat for thirty years?
- Stopping medication can cause rebound. Therefore timing of intervention is crucial.

PH specific drugs in Eisenmenger

- Breathe 5 - Comparison bosentan vs placebo in Eisenmenger – improved walking distance and hemodynamics
- Naples open label 22 patients – improved everything incl. cath parameters
- India – tadalafil improved everything incl. cath parameters
- Leuven – treatment delays need for transplantation but not death

70 years old Eisenmenger patient

- Large VSD
- Engineer, worked until timely retirement
- On amlodipine for hypertension, digoxin, diuretics
- O2 saturation – 78% Hb – 19g%
- “more difficult to walk recently”
- Has two six minutes tests – walks more than 500 m each time - reassurance
- Than has a chest CT ordered by a pulmonologist



Suggestion

- Congenital heart specialists are the best equipped professionals for the initial evaluation of patients with pulmonary hypertension

Venice classification 2003

1. Pulmonary arterial hypertension (PAH)

1.1. **Idiopathic** (IPAH)

1.2. Familial (FPAH)

1.3. Associated with (APAH):

1.3.1. Collagen vascular disease

1.3.2. Congenital systemic-to-pulmonary shunts**

1.3.3. Portal hypertension

1.3.4. HIV infection

1.3.5. Drugs and toxins

1.3.6. **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)

1.4. **Associated with significant venous or capillary involvement**

1.4.1. Pulmonary veno-occlusive disease (PVOD)

1.4.2. Pulmonary capillary hemangiomatosis (PCH)

1.5. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease

2.1. Left-sided atrial or ventricular heart disease

2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Sleep-disordered breathing

3.4. Alveolar hypoventilation disorders

3.5. Chronic exposure to high altitude

3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1. Thromboembolic obstruction of proximal pulmonary arteries

4.2. Thromboembolic obstruction of distal pulmonary arteries

4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

5. **Miscellaneous**

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)