Teaching Round
14.03.2017

Claudio Sartori

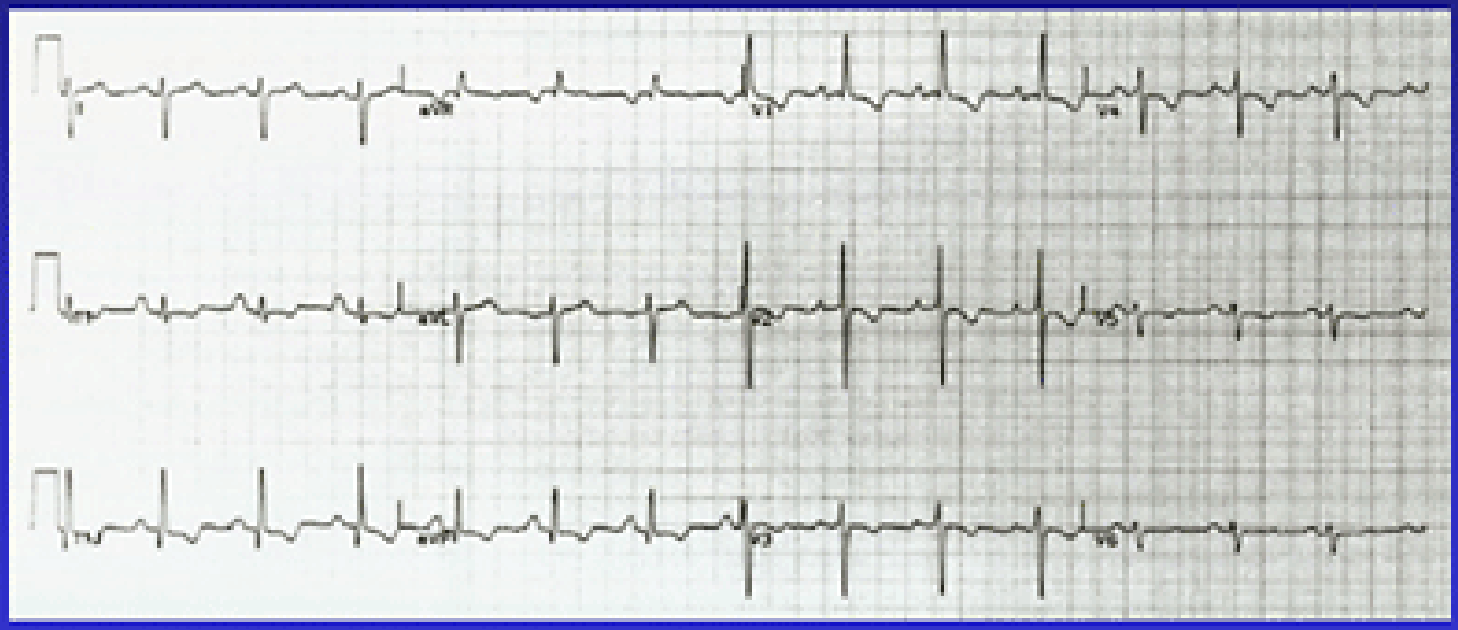
Cas clinique

Femme 47 ans, connue pour un BPCO,
asthénie, douleurs thoraciques, dyspnée à l'effort,
œdèmes membres inférieurs, deux syncopes.

Tabac, BMI 31 kg/m2

Findings on Electrocardiogram

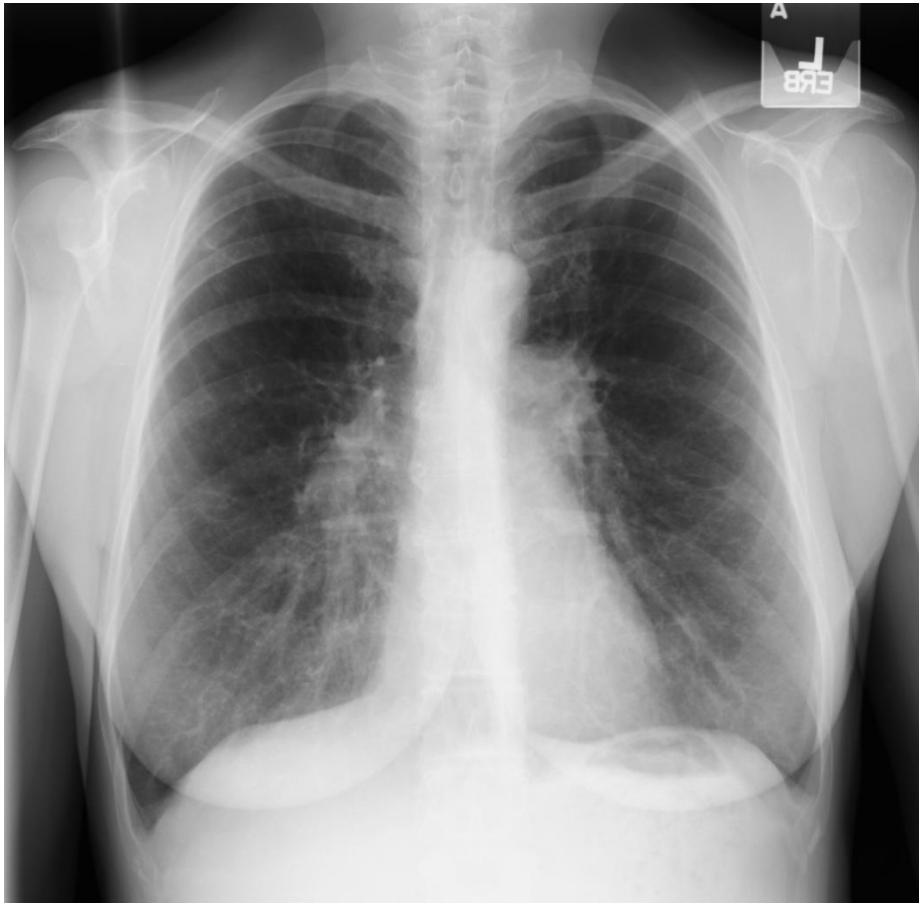
-



ECG abnormalities

- Right heart strain (RVH and RA enlargement)
- Non-specific
- Right axis deviation
- ST depression and T wave inversion V1-V3

MAYO CLINIC



Radiographic findings are subtle and often missed

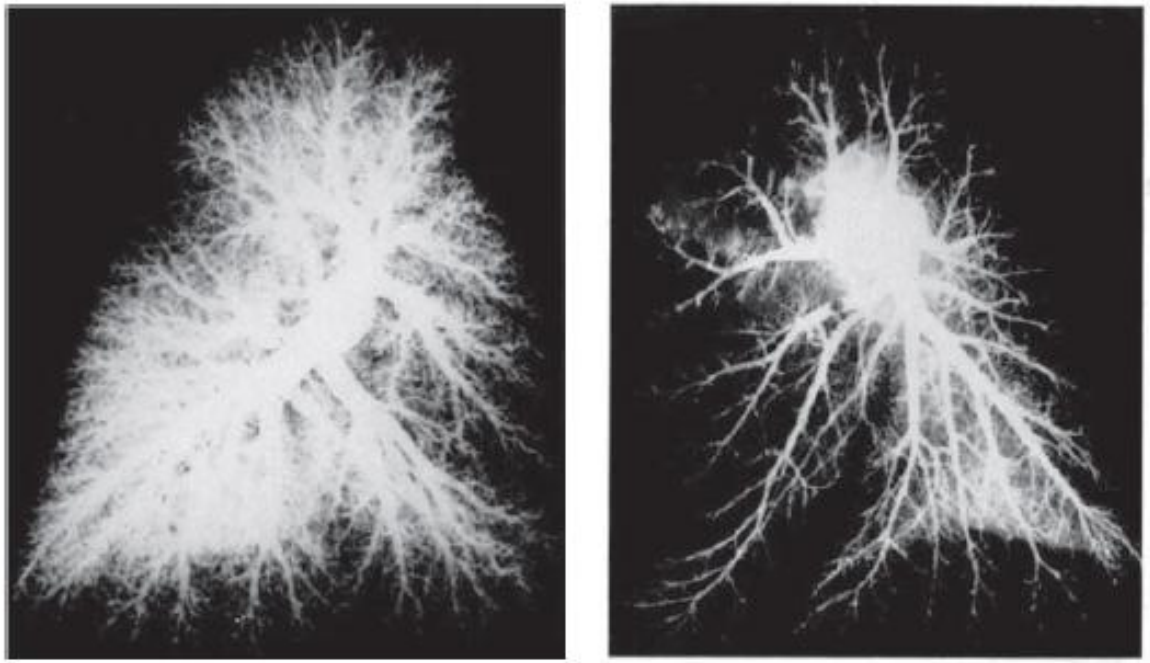
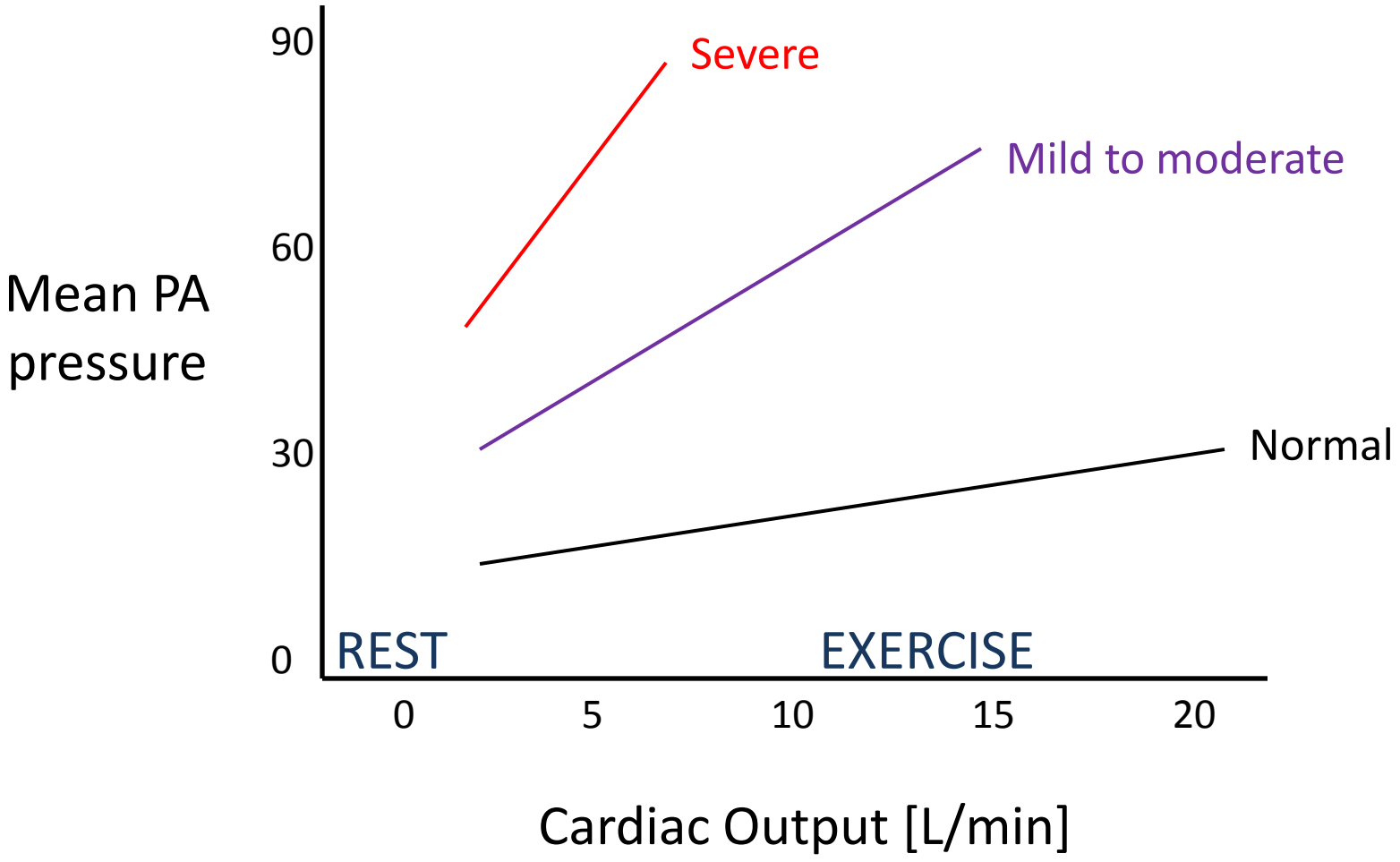


Figure 3. Left, Pulmonary arteriogram from a healthy adult. **Right**, Pulmonary arteriogram from a patient with idiopathic pulmonary arterial hypertension (IPAH) who died within 6 months of

Syncope in patients with PAH

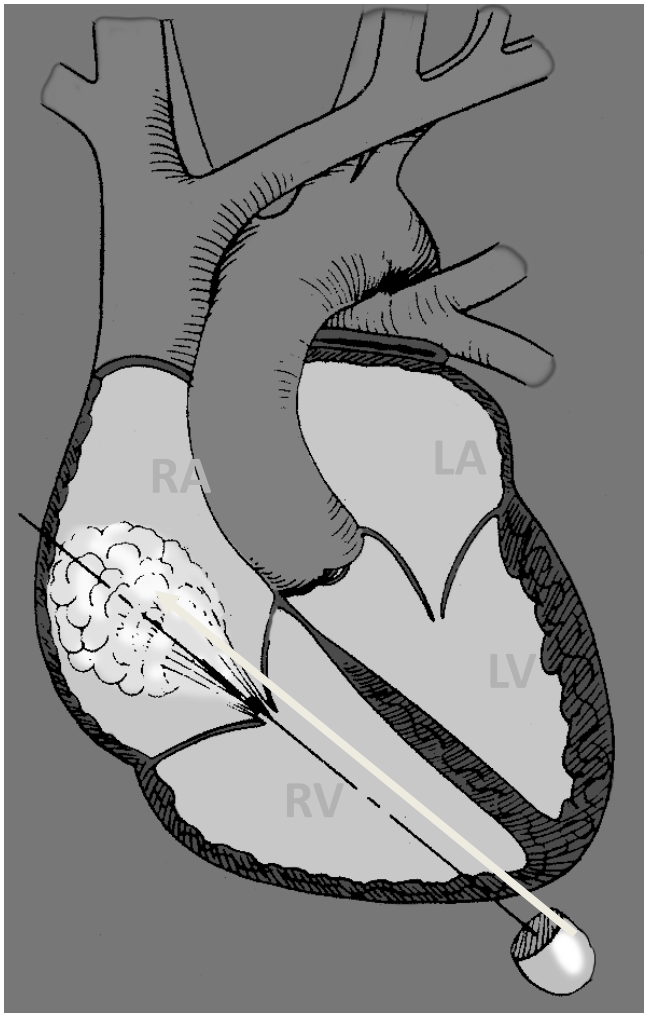
Arrhythmia
Systemic vasodilation
RV failure !
Diastolic ventricular interdependence ?
Extreme elevation of pulmonary artery pressure with exertion !

Mean pulmonary artery pressure and cardiac output relationship



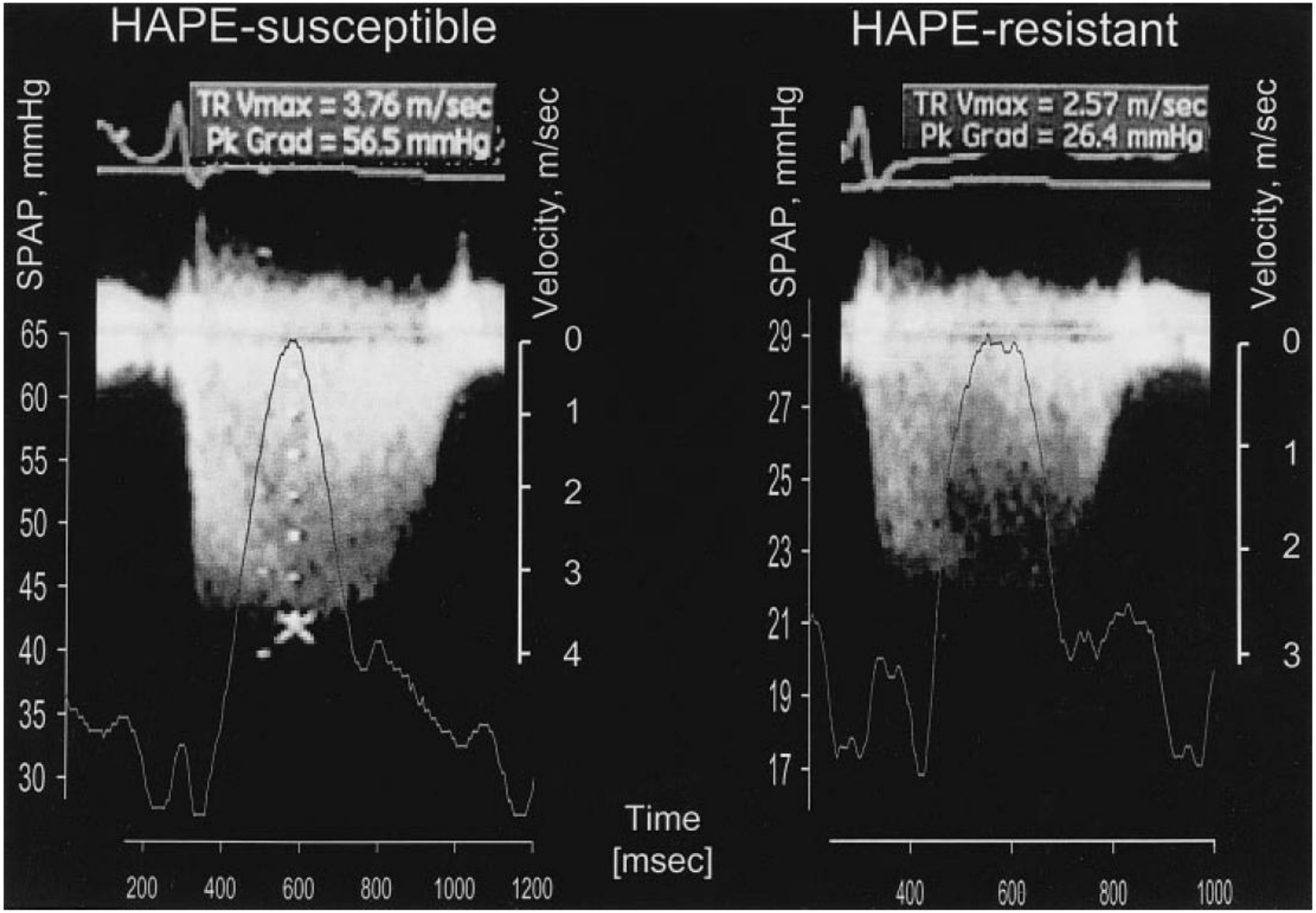
Screening test:
Trans-thoracic echocardiography

$$PASP = (4 \times [TRV]2) + RAP$$



Echocardiography uses Doppler ultrasound to estimate the pulmonary artery systolic pressure

Echo transducer


HAPE-susceptible
TR Vmax = 3.76 m/sec
Pk Grad = 56.5 mmHg
SPAP, mmHg
65
60
55
50
45
40
35
30
Velocity, m/sec
0
1
2
3
4
200
400
600
800
1000
1200
Time
[msec]
HAPE-resistant
TR Vmax = 2.57 m/sec
Pk Grad = 26.4 mmHg
SPAP, mmHg
29
27
25
23
21
19
17
Velocity, m/sec
0
1
2
3
400
600
800
1000

Pulmonary hypertension: Definition

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec and/or midsystolic notching.	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 %with a sniff or <20 % with quiet inspiration).
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole).	Early diastolic pulmonary regurgitation velocity >2.2 m/sec.	Right atrial area (end-systole) >18 cm^2.
	PA diameter >25 mm..	

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Pulmonary hypertension: Classification

1. Pulmonary hypertension
2. PAH due to left heart disease
3. PAH due to lung disease or hypoxia
4. Chronic thromboembolic PAH
5. PAH with unclear multifactorial mechanisms

Table 1. Updated Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
    - 1.1 Idiopathic PAH
    - 1.2 Heritable PAH
        - 1.2.1 BMPR2
        - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
        - 1.2.3 Unknown
    - 1.3 Drug and toxin induced
    - 1.4 Associated with:
        - 1.4.1
        - 1.4.2
        - 1.4.3
        - 1.4.4
        - 1.4.5

1' Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

1'' Persistent pulmonary hypertension of the newborn (PPHN)

3. Pulmonary hypertension due 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 lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Current Clinical Management of Pulmonary Arterial Hypertension

Roham T. Zamanian,* Kristina T. Kudelko,* Yon K. Sung, Vinicio de Jesus Perez, Juliana Liu, Edda Spiekerkoetter

(*Circ Res*. 2014;115:131-147.)

Stanford Approach

Echocardiography: sPAP > 45 mmHg

History

Congenital heart disease
Heart disease
Lung Disease
Sleep-disordered breathing
Thrombo-embolic disease
Liver disease
Autoimmune disease
HIV infection
Drug and toxins

Drug and Toxins

Médicaments et toxiques susceptibles d'induire une HTAP et niveau de risque

Niveau de risque	Définition	Médicaments et toxiques en cause
Certain	Association basée sur l'apparition d'une épidémie ou sur les résultats d'une vaste étude épidémiologique multicentrique	Aminorex Fenfluramine Dexfenfluramine Benfluorex Huile de colza Inhibiteurs sélectifs de la recapture de la sérotonine
Probable	Association basée sur les résultats d'une étude monocentrique cas-témoins ou sur plusieurs séries de cas	Amphétamines, Méthamphétamines L-tryptophane Dasatinib
Possible	Médicaments aux mécanismes d'action similaires à ceux des catégories « certain » ou « probable » mais non encore étudiés	Cocaïne Phénylpropanolamine Millepertuis Agents de chimiothérapie Interféron α et β Dérivés d'amphétamines
Peu probable	Association non confirmée par une étude épidémiologique	Contraceptifs oraux Œstrogènes Tabac

Routine studies

Complete blood count
Metabolic panel
Thyroid function
Pro-BNP
Hepatitis serologies
HIV
Hypercoagulable panel
Screening antinuclear antibodies
(dsDNA, RNP, scl-70, centromere, SSA, SSB)

Examens paracliniques

ECG
Chest Rx
Pulmonary function test
6-minutes walk test
Chest CT-scan
V/Q scan
Sleep apnea screening

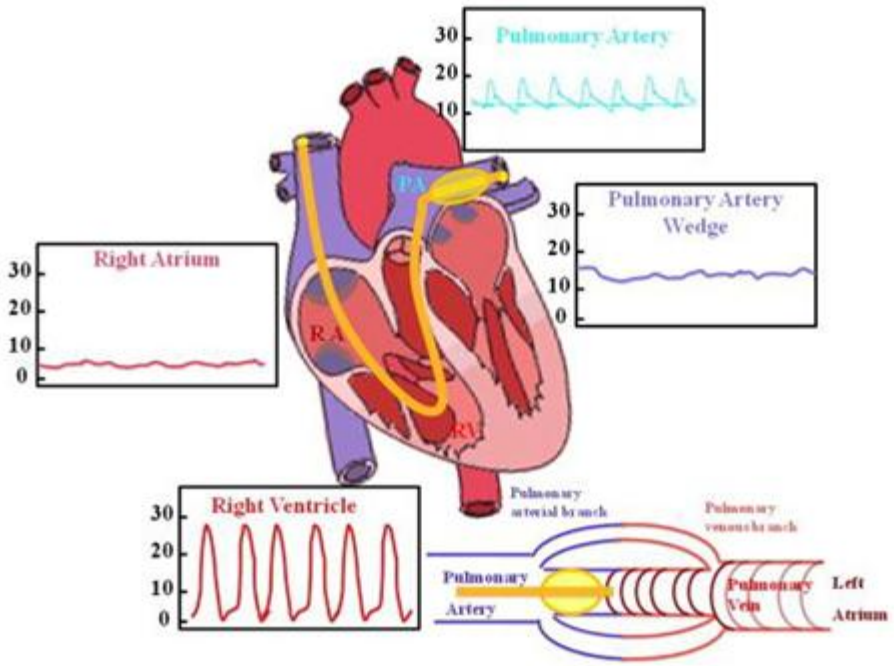
4 weeks appointment

Review of the results

Right heart catheterization

Vasoreactivity challenge with inhaled NO ?
Intracardiac shunt ?
Right ventricular function ?

Pulmonary hypertension diagnosis via right heart catheterization



From Mayo Clinic Right Heart Catheterization Training Manual – Cardiology Rotation

A ***Measurement of Right Ventricular Pressure-Volume Relations***

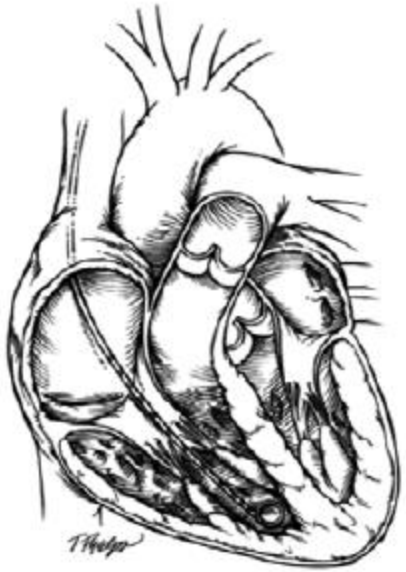
Micromanometer/conductance catheter is inserted into the right ventricle via the right internal jugular vein

Simultaneous measurements of right ventricular pressure and volume are made under steady-state conditions at end-expiration.

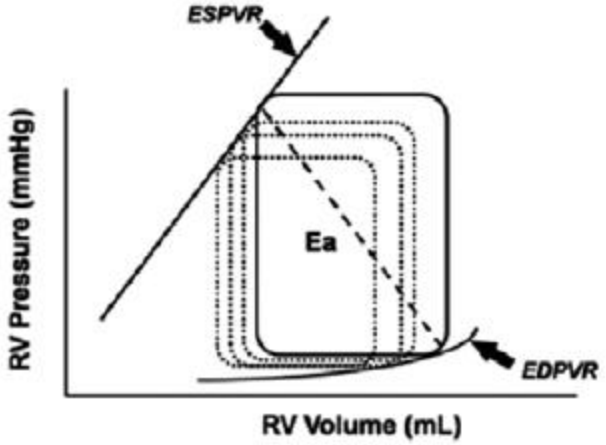
ESPVR is made by reducing RV preload using a balloon inflated in the inferior vena cava or forced Valsalva maneuver.

Pressure-volume relationships are computed using specialized software.

B



C



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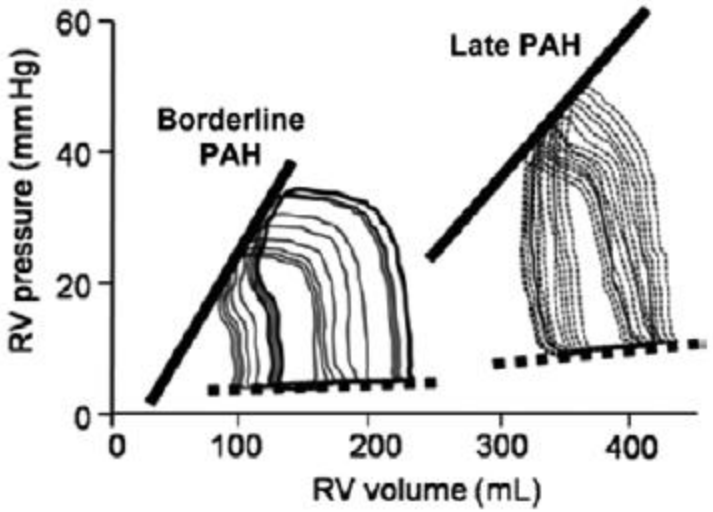


Cardiac MRI

Although echocardiography is the mainstay in the imaging of the right heart in clinical practice, advances in cardiac MRI (CMR) technology have led to the development of more precise techniques for the assessment of hemodynamics in the pulmonary circulation and identification of right ventricular morphological changes. CMR is now regarded as the reference standard in the assessment of RV structure and function via the measurement of RV volumes and ejection fraction, which makes CMR an attractive modality for serial follow-up in PAH management to determine treatment response.[35] In

Vasoreactivity
(iNO, epoprostenol, adenosine, iloprost)

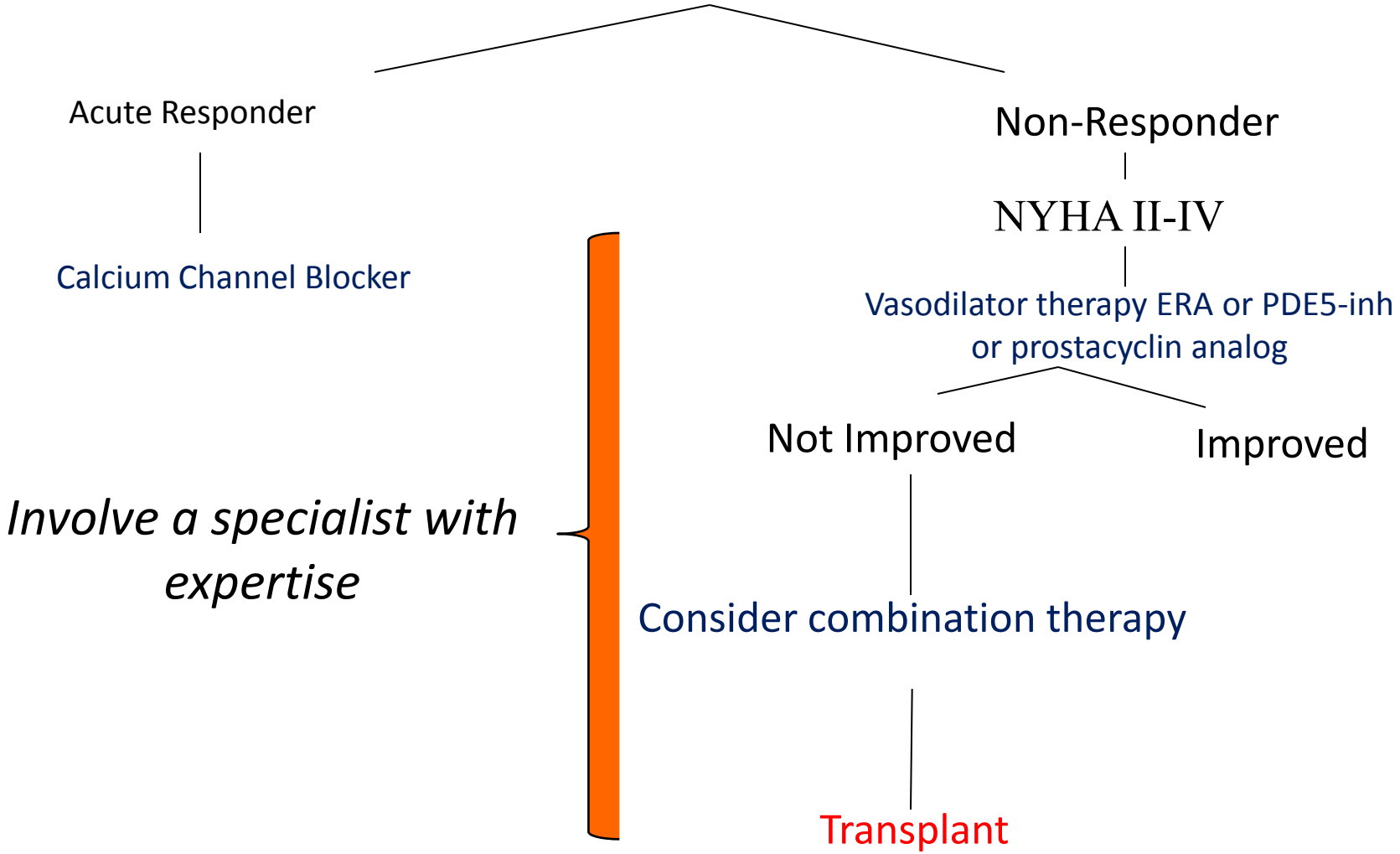
currently accepted criteria for the presence of vasoreactivity is the demonstration of ≥10 mm Hg reduction in mean PA pressure to a value of <40 mm Hg and without a reduction in cardiac output, but these criteria have never been formally validated.[18]

< 15 % are reponders during testing

Only 1/2 of these exhibit long-term responsiveness to CCB

Treatment ?

Right Heart Catheterization and Vasodilator Trial



Calcium Channel Blockers

- PAH therapy is based on severity of disease as determined by right heart catheterization and responsiveness to vasoactivity testing.

- Although not FDA approved for the treatment of PAH, CCBs commonly used are nifedipine, diltiazem, and amlodipine.

- All agents are titrated to clinical effect.

Treatment

Calcium channel blockers: ***nifedipine, amlodipine, diltiazem***
CAVE: verapamil contraindicated !

Phosphodiesterase 5 inhibitors: ***sildenafil, tadalafil***
CAVE: TAS < 100 mmHg
CAVE: nitroglycerin, protease inhibitors

Endothelin Receptor Antagonists: ***bosentan, ambrisentan, macitentan***
Teratogenic
Transaminitis (bosentan)
Anemia
Fluid retention

Soluble guanylate cyclase stimulator: ***riociguat***
3x /day, Hypotension
Teratogenic
CAVE: nitroglycerin

Prostacyclins: ***epoprostenol (IV), treprostinil (iv, sc, inh), iloprost (inh)***

Treatment

Sildenafil	REVATIO
Tadalafil	ADCIRCA
Riociguat	ADEMPAS
Bosentan	TRACLEER
Ambrisentan	VOLIBRIS
Macitentan	OPSUMIT
Epoprostenol	FLOLAN / VELETRI
Trepostinil	REMODULIN
Iloprost	VENTAVIS

PAH (Group 1) Medication Options

	Mild	Moderate	Severe
	25 <MPAP< 35	35 <MPAP< 50	MPAP> 50
Ca^{++} Channel Blocker	X		
Endothelin antagonist	X	X	
PDE-5 inhibitor	X	X	
Prostanoids		X	X
Inhaled iloprost		X	X
SQ treprostinil		X	X
IV epoprostenol		X	X

INTERACTIONS !!!

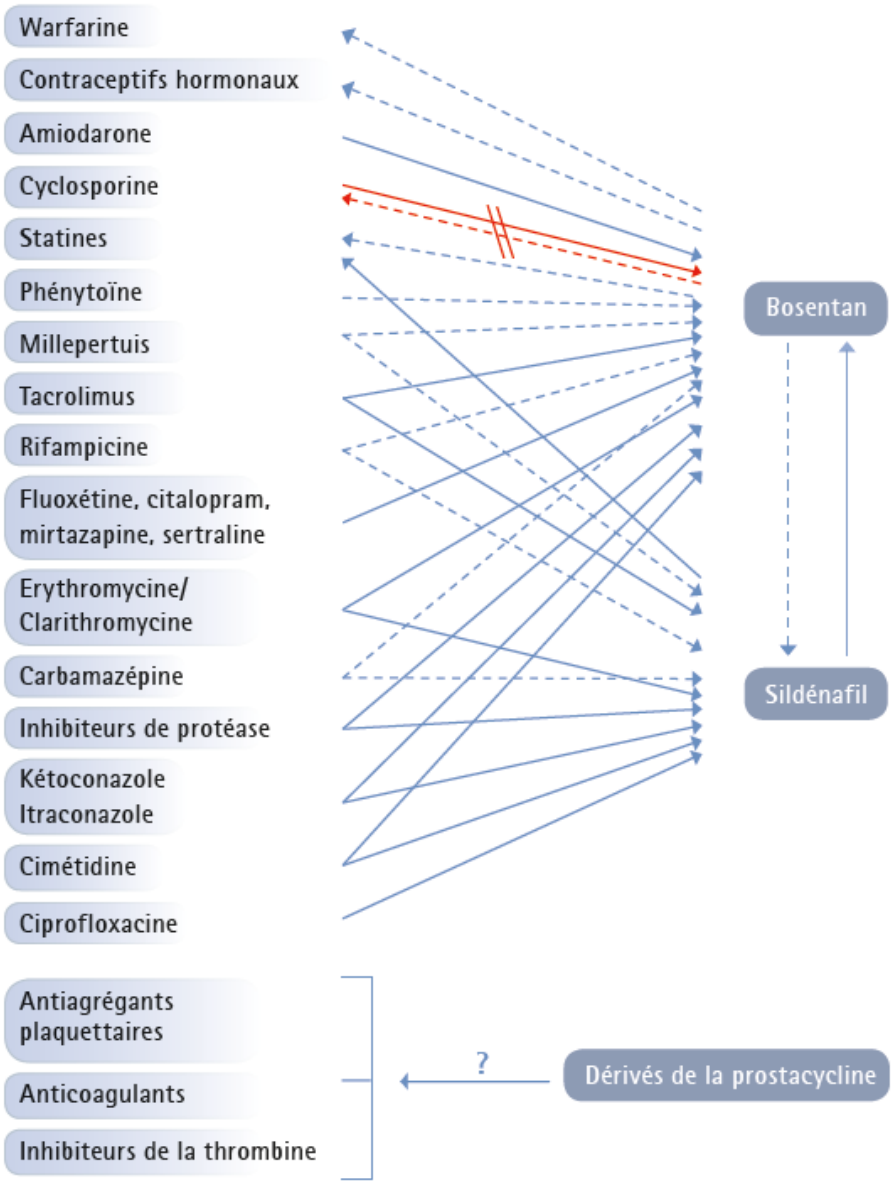


Table 2. Emerging Therapies

Drugs	Proposed Mechanism	NCT Identifier	Clinical Trial
Vasodilators			
Sapropterin dihydrochloride (6R-BH4)	Increase nitric oxide	NCT00435331	Phase I
Selexipag	Non-prostanoid IP receptor agonist	NCT01106014	Phase III
Inhaled nitric oxide	Increase nitric oxide	NCT01457781	Phase II
Beet juice	Increase nitric oxide	NCT02000856	Phase I
Apelin	Increase apelin levels with infusion	NCT01590108	Phase I
Cardizem	Calcium channel blockade	NCT01645826	Phase III
Inhaled nitrite	Increase nitric oxide	NCT01431313	Phase II
Ranolazine	Inhibition of sodium current	NCT01757808	Phase I
		NCT01953965	Phase II
Metabolism			
Dichloroacetate	Inhibition of pyruvate dehydrogenase kinase	NCT01083524	Phase I
Anastrazole	Aromatase inhibitors	NCT01545336	Phase II
Ferinject	Target iron deficiency	NCT01288651	Phase II
Right ventricular remodeling			
Carvediol	HIF activation, NO synthesis, β-adrenergic receptor recovery	NCT01586156	Phase II
Cell damage/endothelial dysfunction			
Coenzyme Q-10	Antioxidant	NCT01148836	Unknown
(–)-Epicatechin	Improvement of endothelial function	NCT01880866	Phase I
Antiproliferative			
Sorafenib	Inhibition of protease-activated receptor	NCT00452218	Phase I
Hydroxyurea	Decrease level of circulating immature bone marrow cells	NCT01950585	Phase 0
Nilotinib	Tyrosine kinase inhibitor	NCT01179737	Phase II
Anti-inflammatory			
Rituximab	Restore B-cell dysregulation	NCT01086540	Phase II
Bardoxolone methyl	Nrf2 and NF-κB suppression	NCT02036970	Phase II
Saquinavir and ritonavir	HIV protease inhibitors	NCT02023450	Phase 0
TheraSorb Ig flex adsorber	Immunoabsorption	NCT01613287	Medical device
BMPR2 modulators			
FK506	Increasing BMPR2 signaling	NCT01647945	Phase II

BMPR2 indicates bone morphogenetic protein receptor 2; HIF, hypoxia inducible factor; IP, prostacyclin receptor; and NO, nitric oxide.

Supportive therapies

Control of volume status
Diuretic
Low sodium diet

Oxygen (at rest and/or exercise)
Exercise training
Pulmonary rehabilitation
Flu and pneumococcal vaccination

Digoxin (?)
Anticoagulation (?)
Beta-blockers (?)

Follow-up

2-6 months
Goal shift from high risk to a lower risk phenotype

(6MWD: > 33 m associated with improvement of quality of life !)

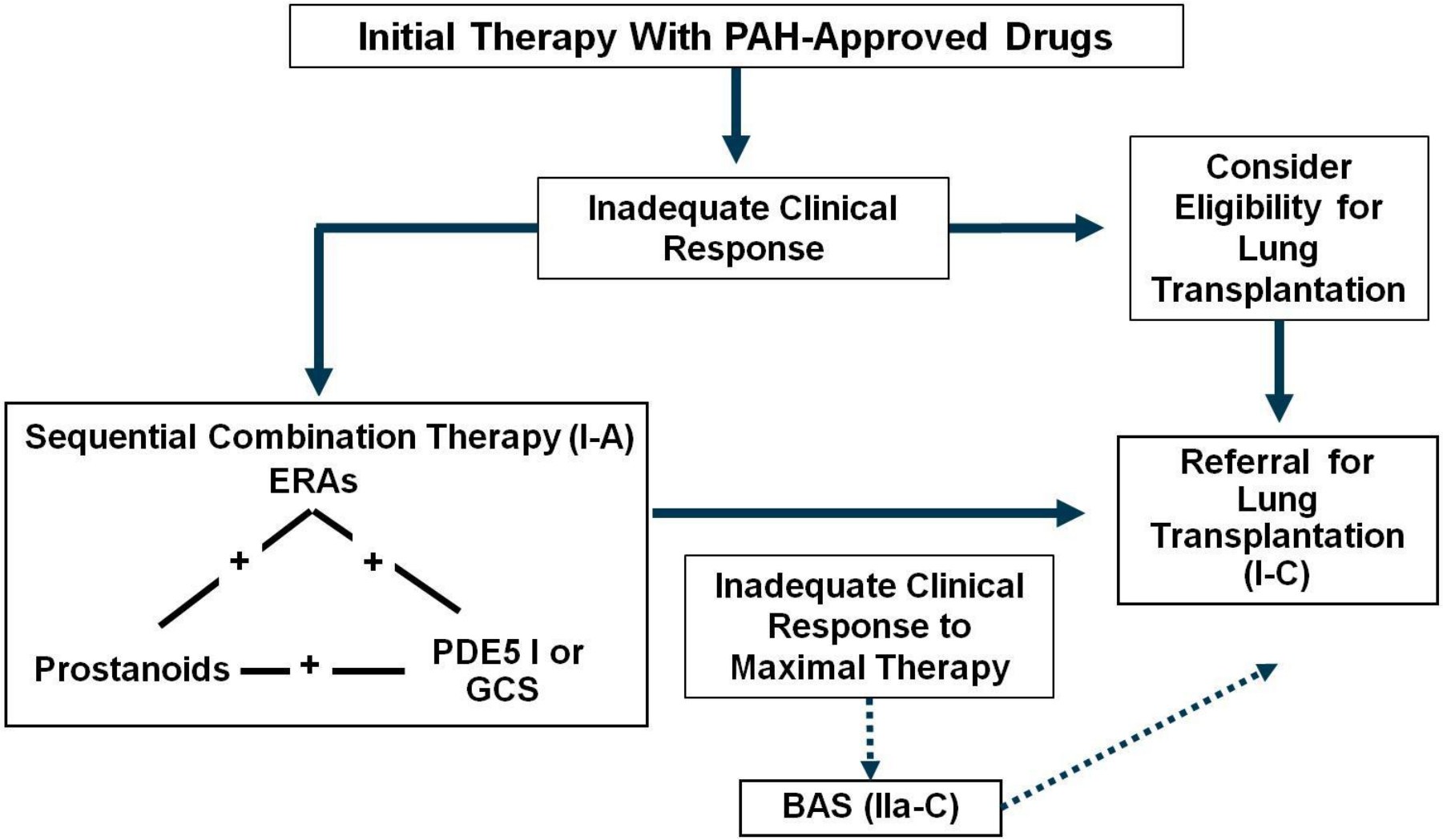
Tableau 4 : Paramètres établis pour déterminer le degré de gravité de la maladie, l'évolution de la maladie et le pronostic chez les patients atteints d'HTAP.[2] TAPSE = tricuspid annular plane systolic excursion

Meilleur pronostic	Paramètre	Moins bon pronostic
Absents	Signes cliniques d'insuffisance cardiaque droite	Présents
Lente	Augmentation des symptômes	Rapide
Non	Syncope	Oui
I, II	WHO-FC	III, IV
Plus longue (> 500 m, en fonction de l'âge)	Test de marche de 6 minutes	Plus courte (< 300 m, en fonction de l'âge)
Consommation max. d'O_2 > 15 ml/kg/min	Spiro-ergométrie	Consommation max. d'O_2 < 12 ml/kg/min
Normales, quasi-normales	NT-proBNP, BNP dans le sang	Très élevées et croissantes
Pas d'épanchement péricardique TAPSE > 2.0 cm	Echocardiographie	Epanchement péricardique TAPSE < 1.5 cm
Pression auriculaire droite < 8 mmHg et index cardiaque ≥ 2.5 l/min/m^2	Hémodynamique	Pression auriculaire droite > 15 mmHg ou index cardiaque ≤ 2.0 l/min/m^2

Table 16 Suggested assessments and timing for the follow-up of patients with PAH

	At baseline (prior to therapy)	Every 3–6 months[a]	3–4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT[b]	✓	✓	✓	✓
Cardio-pulmonary exercise testing[b]	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓[c]		✓[d]	✓[d]

5th World Symposium Treatment Algorithm



Galie N, et al. *J Am Coll Cardiol*. In press.[9]

Balloon atrial septostomy

In patients with RV failure and normal arterial oxygenation

Decompression of the RV

Table 1. Stanford Work-Up Algorithm for Patients With Borderline Elevation in Right Ventricular Systolic Pressure on Echocardiogram

RVSP	RV Size and Function	Symptoms	Risk Factors	Recommended Action
RVSP 35–45 mm Hg	Abnormal	NA	NA	Full work up
	Normal	No symptoms	Any PH risk factors	Repeat echo q6-12 mo
			No PH risk factors	Repeat echo in 12 mo If echo is stable and the patient has no symptoms, discharge from clinic
		(+) Symptoms	Any WHO group 1 risk factors	Full work up
			Diastolic dysfunction	Optimize BP and volume status and recheck echo If optimized, consider full work up
			Valvular heart disease	If MR/AR is >moderate-severe, refer to cardiology and hemodynamics testing, optimize volume status then recheck echo. If optimized, consider full work up
			LV systolic dysfunction	If EF<35%, no further work-up. Refer to cardiology
			COPD	Consider full work-up
			ILD	If FVC/DLCO>1.6, consider full work-up
			OSA	Optimize OSA treatment and repeat echo. If optimized, consider full work-up
			Altitude>3000 ft	Consider full work-up
			Thromboembolic disease	Full work-up
			Any WHO group 5 risk factors	Consider full work-up

AR indicates aortic valve regurgitation; BP, blood pressure; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; EF, ejection fraction; FVC, forced vital capacity; ILD, interstitial lung disease; LV, left ventricle; MR, mitral valve regurgitation; NA, not applicable; OSA, obstructive sleep apnea; PH, pulmonary hypertension; RV, right ventricle; RVSP, right ventricular systolic pressure; and WHO, World Health Organization.

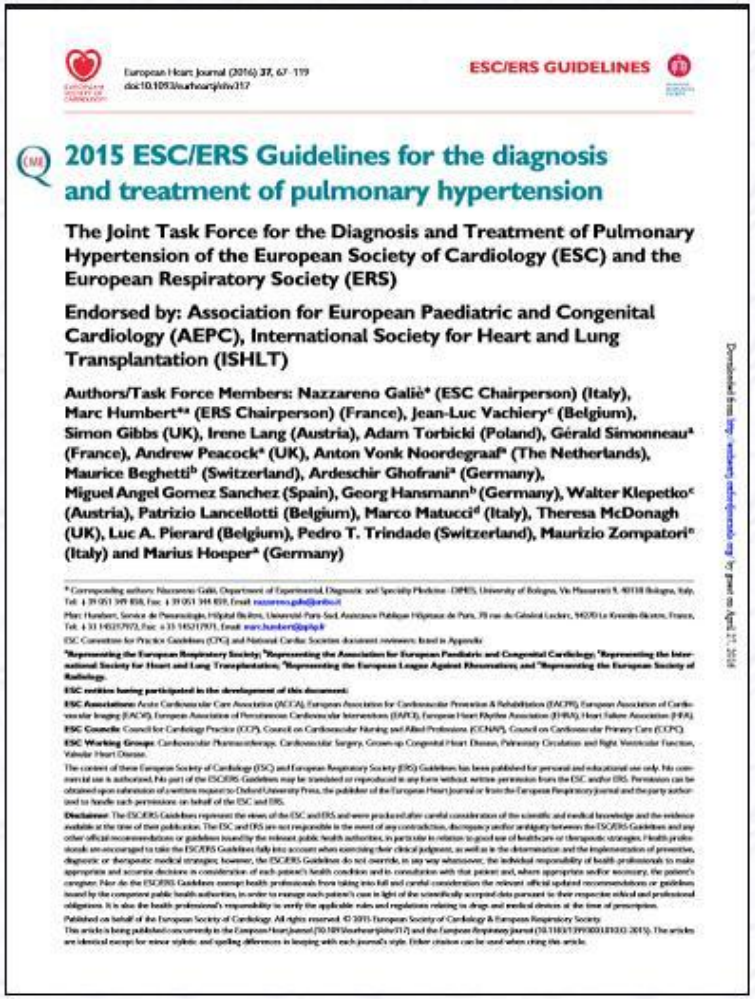
Group 1: “Primary” pulmonary arterial hypertension

- Remember PAH (Group 1) and PH (Groups 2-5) are different entities
- PAH is a progressive disease with a 50% survival at 2.8 years
- Can lead to sudden death
- Often affects young adults: mean age 45 years
- Rarely familial

Final “take home” messages

- New onset exertional dyspnea…think of pulmonary hypertension.
- Screen by Transthoracic Doppler Echo but make sure you tell the cardiologist that you are thinking of PH!
- Definitive diagnosis by right heart catheterization.
- Several pharmacologic options now available: selection a function of PAH severity, expertise, cost assessment, and other factors.
- Pregnancy may cause significant challenges.
- PH patients are increasingly older with potential multiple ongoing diagnoses.

Full Text published in: Eur Heart J & Eur Respir J



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ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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ESC entities having participated in the development of this document:

ESC Associations: Acute Cardiovascular Care Association (ACCA), European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

ESC Councils: Council for Cardiology Practice (CCP), Council on Cardiovascular Nursing and Allied Professions (CCNAP), Council on Cardiovascular Primary Care (CCPC).

ESC Working Groups: Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Grown-up Congenital Heart Disease, Pulmonary Circulation and Right Ventricular Function, Valvular Heart Disease.

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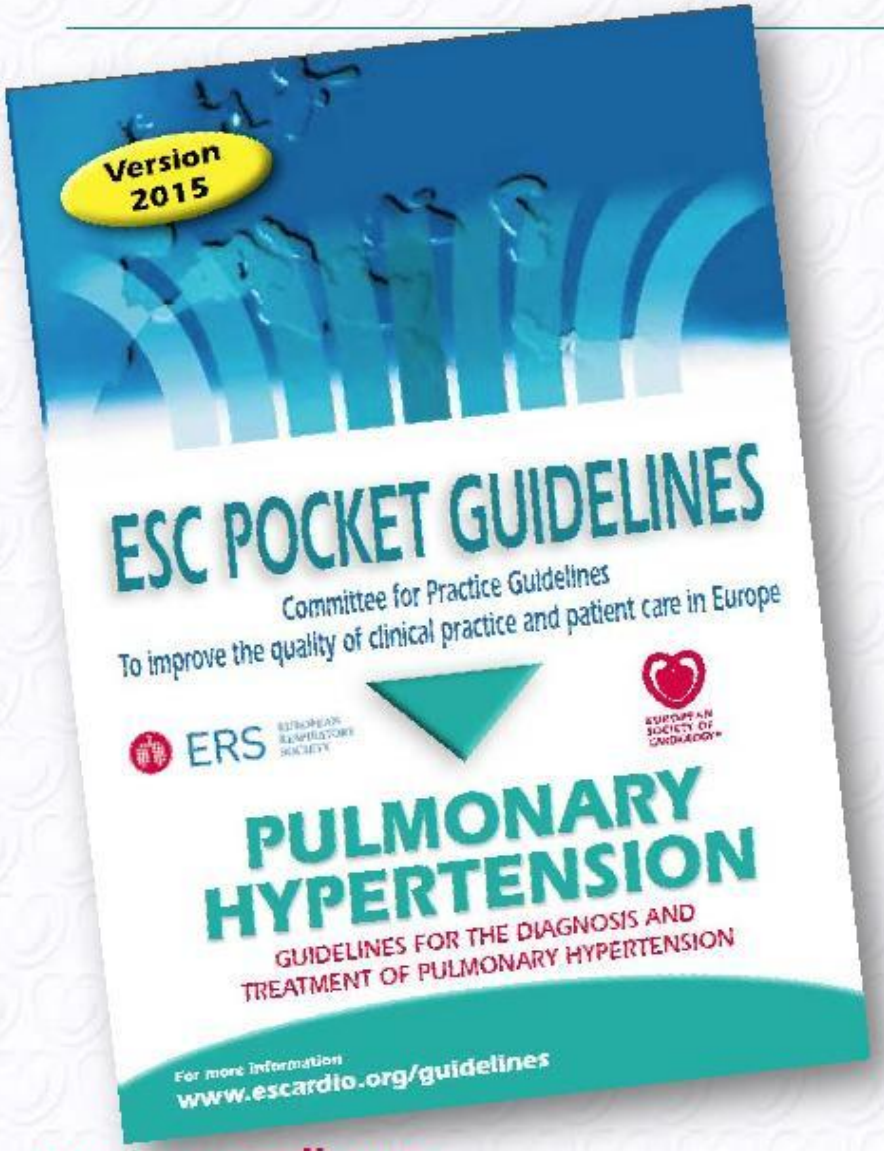
European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Pocket Guidelines and their Interactive App



Free for all users world wide

ESC

ANDROID APP ON Google play

Available on the App Store

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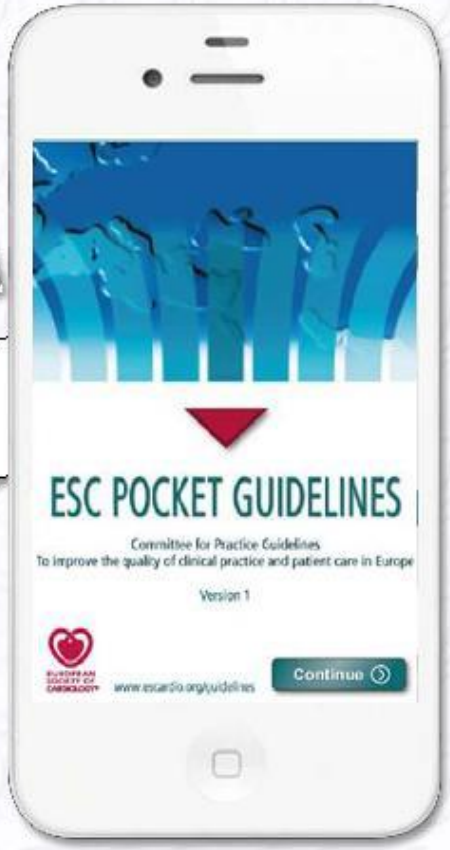


www.escardio.org

Merci pour votre attention

Bonne journée à tous !

Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9, CAV1, KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

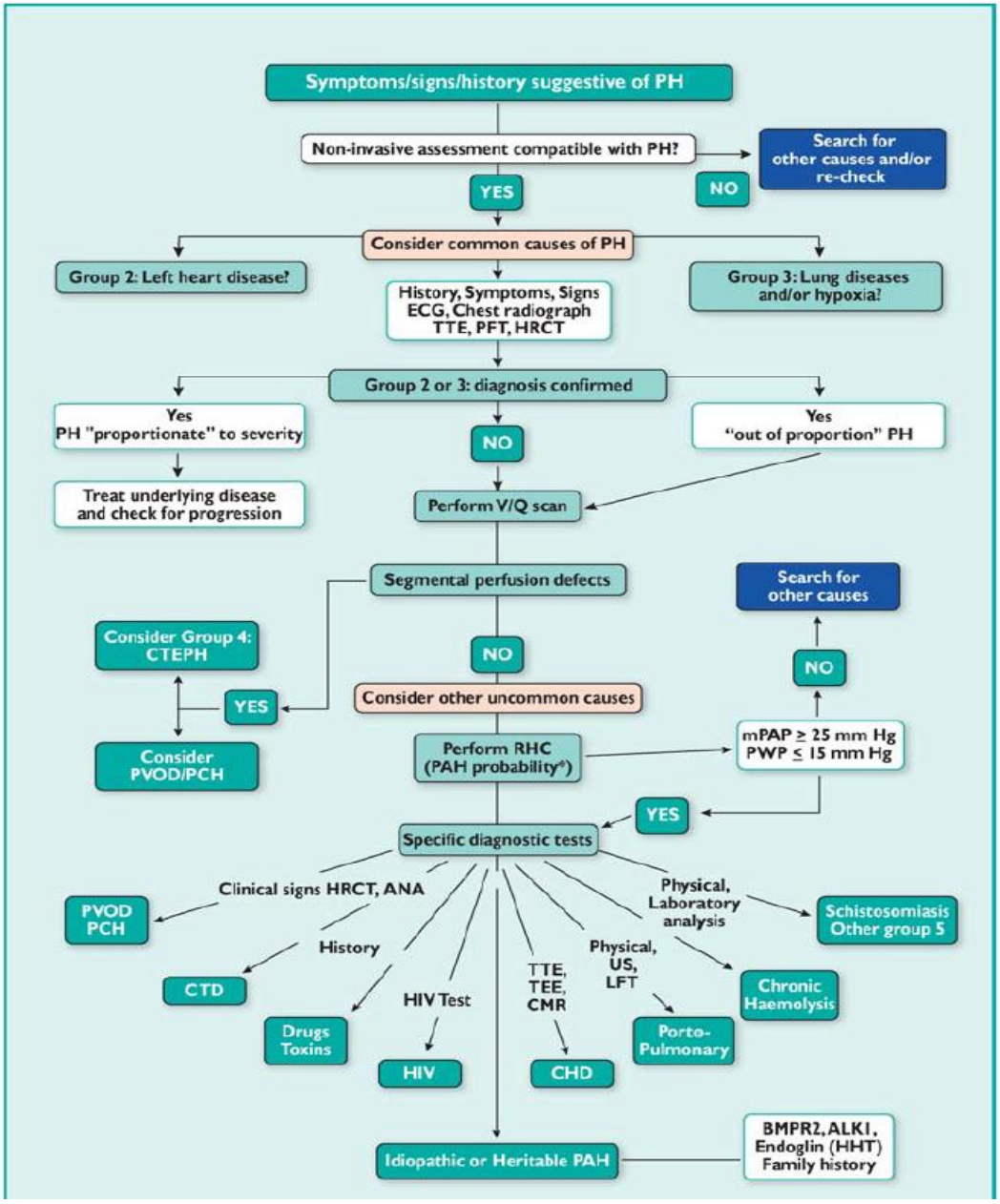
1″. Persistent pulmonary hypertension of the newborn (PPHN)

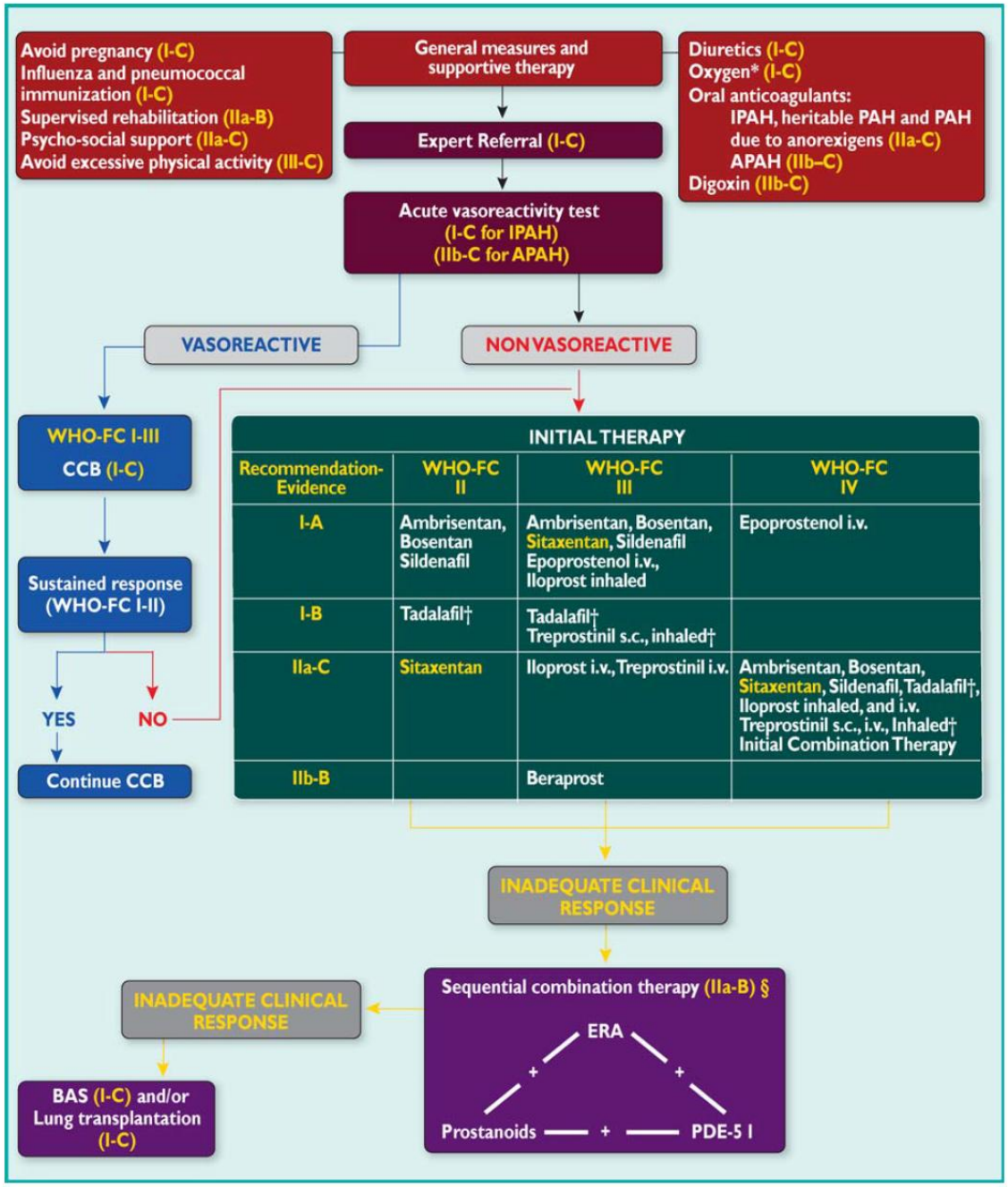
2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - **2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

3. Pulmonary hypertension due 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 lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**


Symptoms/signs/history suggestive of PH
Non-invasive assessment compatible with PH?
Search for other causes and/or re-check
NO
YES
Consider common causes of PH
Group 2: Left heart disease?
History, Symptoms, Signs ECG, Chest radiograph TTE, PFT, HRCT
Group 3: Lung diseases and/or hypoxia?
Group 2 or 3: diagnosis confirmed
Yes PH "proportionate" to severity
NO
Yes "out of proportion" PH
Treat underlying disease and check for progression
Perform V/Q scan
Segmental perfusion defects
Search for other causes
Consider Group 4: CTEPH
NO
NO
YES
Consider other uncommon causes
Consider PVOD/PCH
Perform RHC (PAH probability*)
mPAP ≥ 25 mm Hg PWP ≤ 15 mm Hg
YES
Specific diagnostic tests
Clinical signs HRCT, ANA
Physical, Laboratory analysis
PVOD PCH
Schistosomiasis Other group 5
History
Physical, US, LFT
TTE, TEE, CMR
HIV Test
CTD
Chronic Haemolysis
Drugs Toxins
Porto-Pulmonary
HIV
CHD
Idiopathic or Heritable PAH
BMPR2, ALK1, Endoglin (HHT) Family history


Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)
General measures and supportive therapy
Expert Referral (I-C)
Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)
Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants:
IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
APAH (IIb–C)
Digoxin (IIb-C)
VASOREACTIVE
NONVASOREACTIVE
WHO-FC I-III
CCB (I-C)
Sustained response (WHO-FC I-II)
YES
NO
Continue CCB
INITIAL THERAPY
Recommendation-Evidence
WHO-FC II
WHO-FC III
WHO-FC IV
I-A
Ambrisentan, Bosentan Sildenafil
Ambrisentan, Bosentan, Sitaxentan, Sildenafil Epoprostenol i.v., Iloprost inhaled
Epoprostenol i.v.
I-B
Tadalafil†
Tadalafil† Treprostinil s.c., inhaled†
IIa-C
Sitaxentan
Iloprost i.v., Treprostinil i.v.
Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., Inhaled† Initial Combination Therapy
IIb-B
Beraprost
INADEQUATE CLINICAL RESPONSE
Sequential combination therapy (IIa-B) §
ERA
+
+
Prostanoids
+
PDE-5 I
INADEQUATE CLINICAL RESPONSE
BAS (I-C) and/or Lung transplantation (I-C)