Diagnostic Algorithm For Pulmonary Hypertension

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Agenda

- Definitions and Classifications
- Diagnostic Approach
  - Clinical
  - Imaging
  - Hemodynamic assessment
- Risk Assessment

Definitions

- PH is defined as an increase in **mean pulmonary arterial pressure** (PAPm) ≥25 mmHg **at rest** as assessed by **RHC**

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	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	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

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

Classification

1. Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

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
- 2.5 Congenital /acquired pulmonary vein stenosis

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 11)

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)

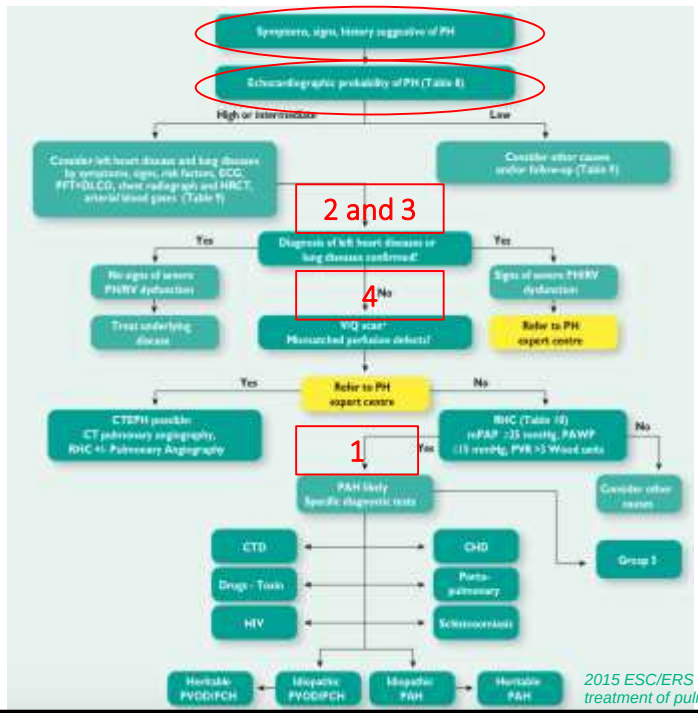
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Diagnosis

- **Clinical suspicion** based on symptoms and physical examination
- A comprehensive **set of investigations** to
- Haemodynamic criteria are met

➢Etiology

➢Functional and Haemodynamic severity



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

Clinical presentation

Initial symptoms are typically induced by exertion

- Shortness of breath
- Fatigue
- Syncope
- Angina

Clinical presentation

Less commonly

-Dry cough

-Exercise-induced nausea and vomiting

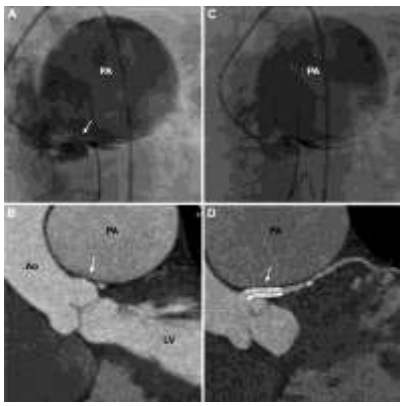
-Rupture of hypertrophied bronchial arteries

-Compression

Left recurrent laryngeal nerve

airway compression

LMT compression



Clinical Examination

- **Signs PH**
- Signs suggestive of the **etiology**
- Telangiectases-Sclerodactyly: **Scleroderma**
- Inspiratory crackles : interstitial lung disease
- Digital clubbing : **cyanotic CHD**-interstitial **lung disease**-**liver** disease-**PVOD**
- Spider naevi, and palmar erythema: liver disease.
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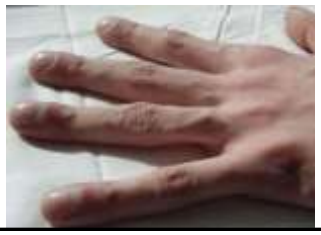
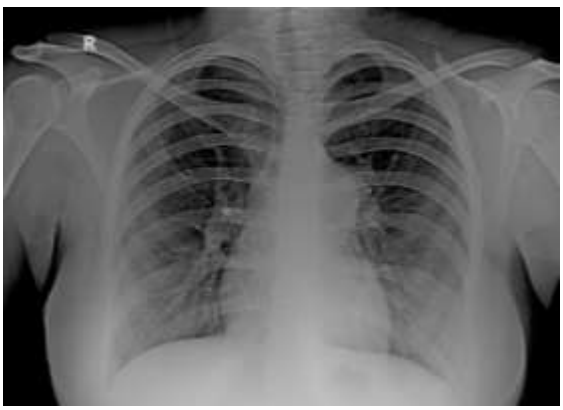


Chest Radiograph

- Abnormal at the time of diagnosis in **90%**
- The degree of PH in any given patient **does not** correlate with the extent of radiographic abnormalities



Echocardiography Probability for PH

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	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	

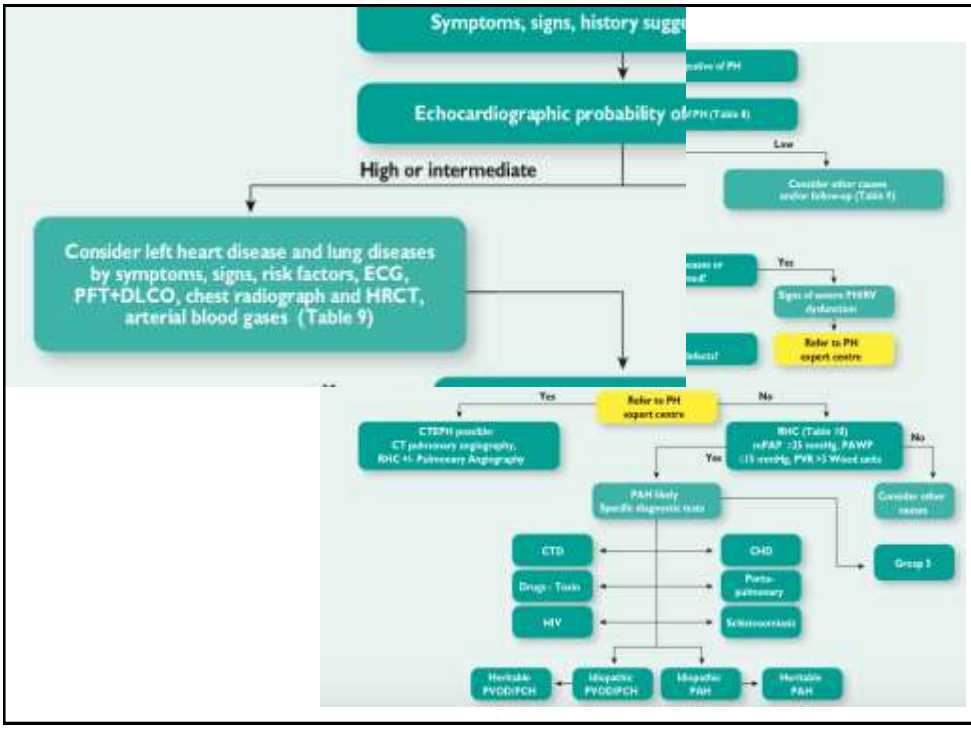
A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<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.	

Echocardiography Probability for PH

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[a]	Class[b]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[a]	Class[b]	Level[b]	Ref[c]
Low	Alternative diagnosis should be considered	IIa	C	Echo follow-up should be considered	IIa	C	
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C	Further assessment of PH including RHC should be considered[d]	IIa	B	45, 46
	Further investigation of PH may be considered[d]	IIb					
High	Further investigation of PH (including RHC[d]) is recommended	I	C	Further investigation of PH[a] including RHC is recommended	I	C	

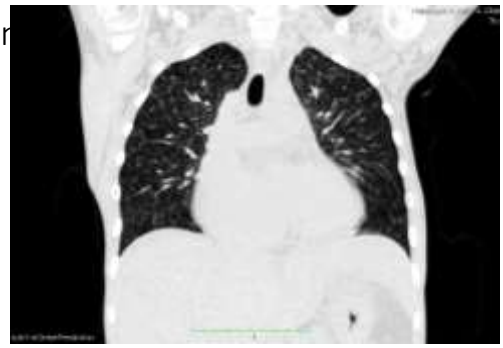
Echocardiography

- Left heart disease
- Congenital heart disease (TTE-TEE)
- Limitations:
- Underestimate : severe tricuspid regurgitation, TRV may be significantly underestimated and cannot be used to exclude PH
- Overestimation: not suitable for screening for mild, asymptomatic PH
- Repeat ECHO measurements alone are not sufficient to monitor change in PASP or progression of PAH.



High-Resolution CT

- Chest diseases
- **Ground-glass** abnormalities are also preser
  in PAH (**>1/3 of cases)**



- PVOD
- Pulmonary capillary haemangiomatosis

Pulmonary function tests and arterial blood gases

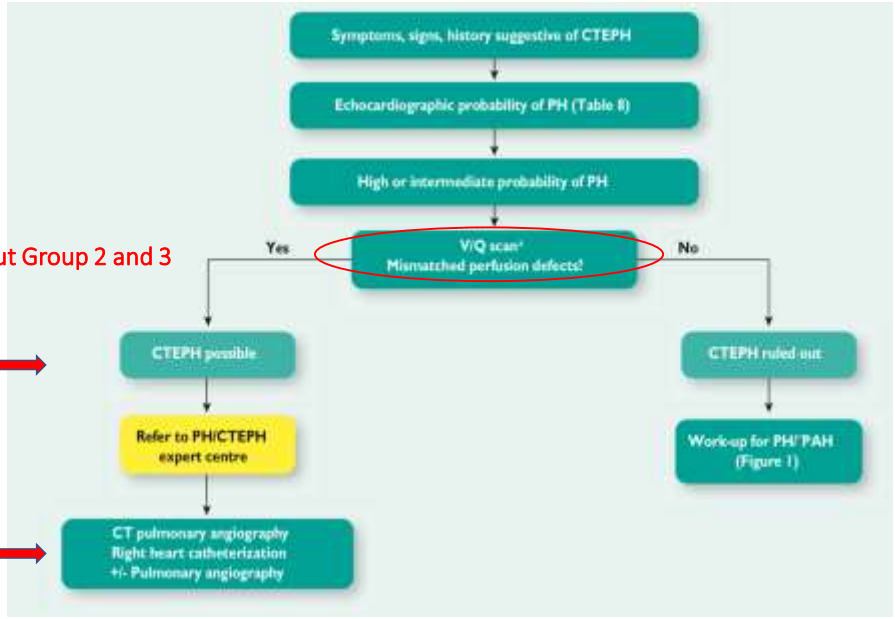
➢Lung Volumes

1. Chest diseases
2. PAH: mild to moderate reduction of lung volumes

➢Lung diffusion capacity

1. Parenchymal lung disease
2. Usually normal in PAH – Abnormal: PVOD, Scleroderma

After ruling out Group 2 and 3

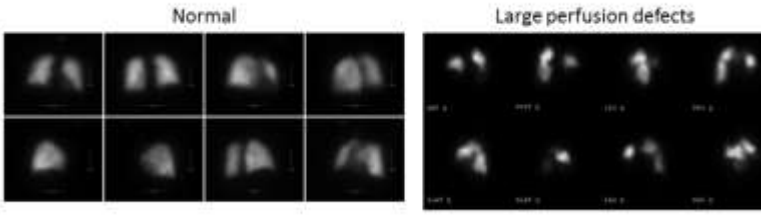


Ventilation/perfusion lung scan

- **Screening** method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary angiogram (CTPA), especially in inexperienced centers
- A normal- or low-probability V/Q scan **excludes** CTEPH with a

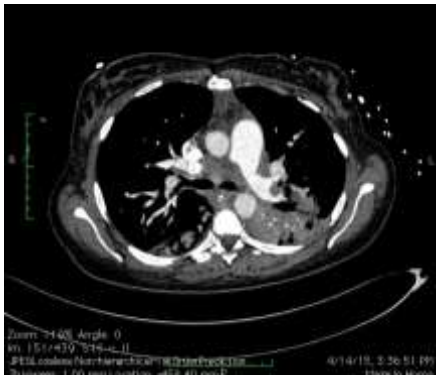
  sensitivity of 90 – 100% specificity of 94 – 100%
- Caveat:

PVOD: Small peripheral unmatched non-segmental defects in perfusion

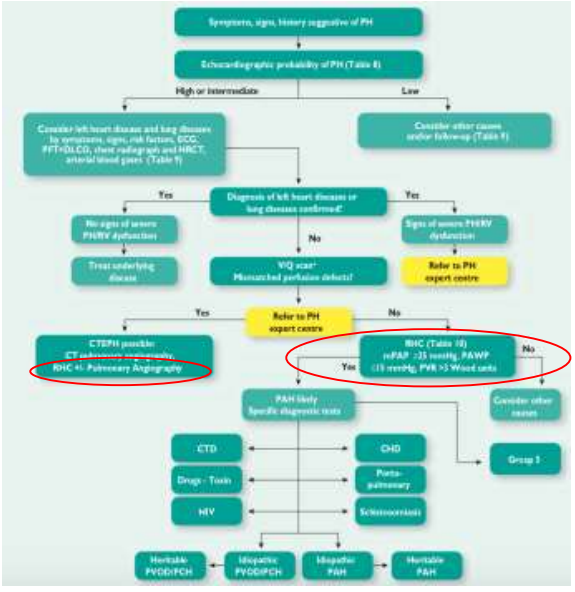


CT Pulmonary Angiography

- Diagnosis (less sensitive than V/Q)
- Surgical accessibility



Right Heart Catheterization



Right Heart Catheterization

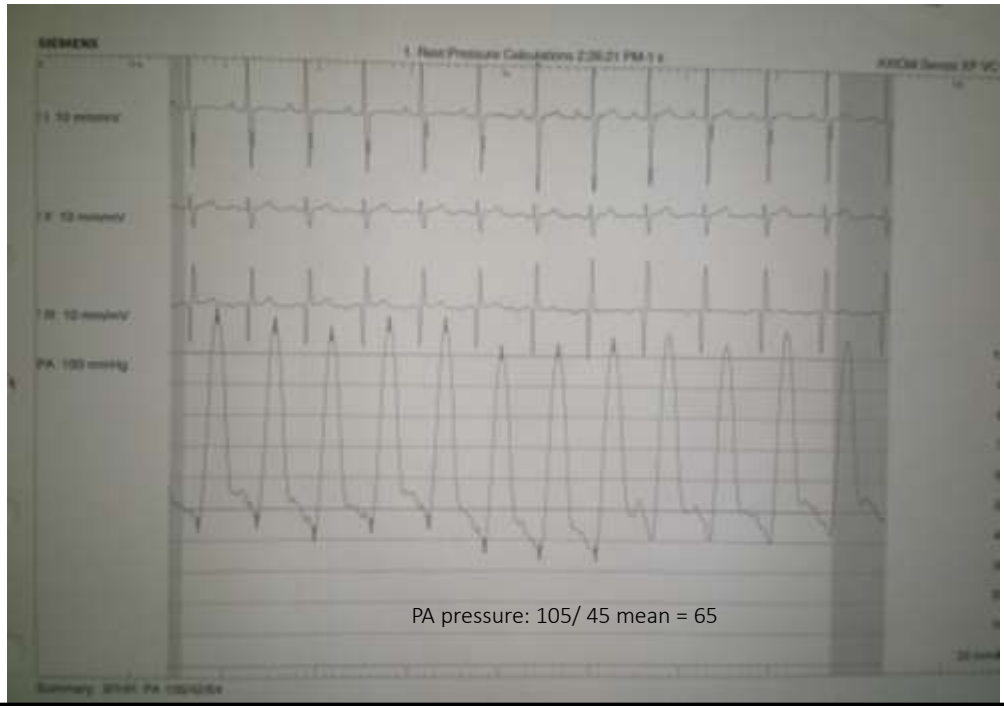
1. Confirm
2. Vasoreactivity (only for IPAH, HPAH and PAH associated with drugs)
3. Stratification
4. Follow Up

- At expert centers, these procedures have
  Low morbidity (1.1%)
  Very mortality (0.055%)

Vasoreactivity Testing

Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP $\geq$10 mmHg to reach an absolute value of mean PAP $\leq$40 mmHg with an increased or unchanged cardiac output	I	C

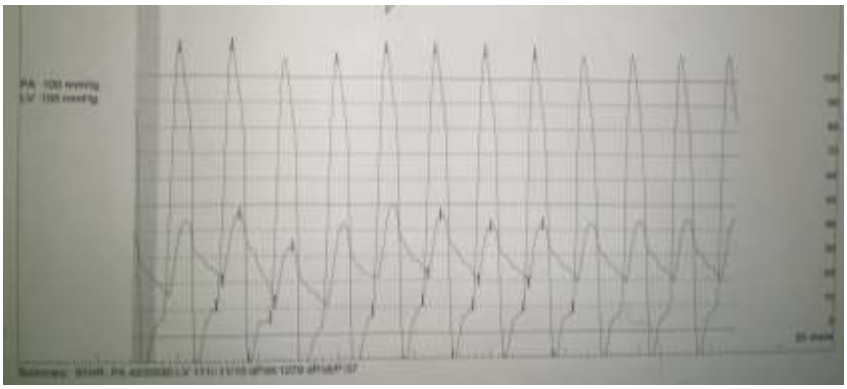
Nitric oxide is recommended for performing vasoreactivity testing	I
Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative	I
Adenosine should be considered for performing vasoreactivity testing as an alternative	IIa
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative	IIb



PA pressure: 105/ 45 mean = 65

Vasoreactivity (Adenosine 500 u/kg/min)

Mean PAP dropped to 30 mmHg
PVR dropped from 12 wood units to 3 woods units
Cardiac index increased from 2.18 L/min/m^2 3.6 L/min

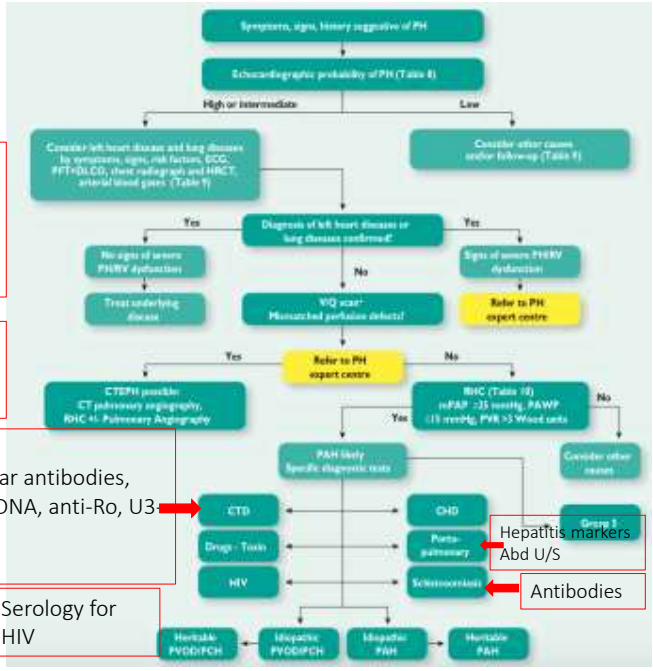


1. Routine biochemistry (liver, kidney)
2. CBC
3. Thyroid function
4. NT-proBNP

Thrombophilia screening in CTEPH

Serology for CTD.....Scleroderm antinuclear antibodies, including anti-centromere, dsDNA, anti-Ro, U3-RNP, B23, Th/To and U1-RNP

Serology for HIV



Blood tests and immunology

- Routine biochemistry (liver, kidney)
- CBC
- Thyroid function
- NT-proBNP
-
- Thrombophilia screening in CTEPH

Serology for

- **CTD**.....Scleroderm antinuclear antibodies, including anti-centromere, dsDNA, anti-Ro, U3-RNP, B23, Th/To and U1-RNP
- **hepatitis and HIV**

Caveat: **40% of patients with IPAH have ANA usually in a low titre (1:80)**

Evaluation of severity

- Clinical parameters
- Imaging
- Hemodynamics
- Biochemical markers

Risk Assessment In PAH

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[b]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Risk Assessment In PAH

- **WHO-functional class** despite its interobserver variability, remains one of the most powerful predictors of survival
- **RV function** is a key determinant of exercise capacity and outcome in patients with PH
- Estimated PASP at rest is usually **not prognostic** and **not relevant** for therapeutic decision making
- An **increase** in PAPs **does not** necessarily **reflect disease progression** and a **decrease** in PAPs **does not** necessarily signal **improvement**

Conclusions

- The diagnostic process starts with **clinical suspension** and **echocardiographic probabilities**
- Identify the more common clinical groups of PH (**2 ,3 then group 4** and finally makes the diagnosis and recognizes the different types in **group 1** and the rarer conditions in group 5.
- **V/Q scan** is the screening method of choice for CTEPH
- **RHC** is an essential tool for diagnosis, risk stratification and follow up
- **Vasoreactivity** testing is mandatory before CCBs
- Use a multidimensional approach for **severity evaluation**

Thank You