Pulmonary Hypertension - A Distinct Perspective

Ankit Kumar Sahu[1], Sudeep Kumar[2]

[1, 2] Department of Cardiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

ABSTRACT

In this review, we have discussed pulmonary hypertension including definition, classification, pathophysiology, epidemiology, diagnosis and treatment of each class of PH as per latest available data and guidelines. Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure of ≥ 20 mmHg at rest. The clinical classification of pulmonary hypertension (as per world health organization) includes five different classes constructed on the basis of clinical causes of pulmonary hypertension. The main pathophysiology involved in the development of pulmonary hypertension of all types is prolonged pulmonary vasoconstriction caused by multiple factors which ultimately leads to pulmonary vascular remodelling (structural as well as functional). The primary treatment of pulmonary hypertension comprises of correction/control of underlying cause of pulmonary hypertension. The prevalence of pulmonary hypertension is increasing in developed as well as developing countries and thus its awareness is important for timely diagnosis and management of this chronic condition. The main aim of our review is to provide all the necessary information regarding pulmonary hypertension in one document.

KEYWORDS

Pulmonary Hypertension, Chronic Thromboembolism, Left Heart Disease, Lung Disease, Pulmonary Arterial Hypertension

Corresponding Author:
Dr. Ankit Kumar Sahu,
Department of Cardiology,
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Lucknow - 226014, Uttar Pradesh, India.
E-mail: ankitsahu.md@gmail.com

DOI: 10.18410/jebmh/2021/438

How to Cite This Article:
Sahu AK, Kumar S. Pulmonary hypertension - a distinct perspective. J Evid Based Med Healthc 2021;8(26):2349-2362. DOI: 10.18410/jebmh/2021/438

Submission 12-03-2021,
Peer Review 22-03-2021,
Acceptance 13-05-2021,
Published 28-06-2021.

BACKGROUND

Pulmonary circulation, involving pulmonary arteries (carrying deoxygenated blood from heart to lungs) and pulmonary veins (carrying oxygenated blood from lung to heart), performs various important functions such as pulmonary gas-exchange, serves as a blood reservoir for the left ventricle, provides nutrition to alveoli and alveolar ducts and removes excess fluid from the alveoli.[1,2] Pulmonary circulation in adults is a high flow, low pressure, and low resistance circuit. In adults, normal pulmonary vascular bed offers 10 % resistance as compared to systemic circulation.[3] The normal pulmonary vascular resistance (PVR) in adults is 67 ± 23 dyne – sec/cm^5 (1 - 3 wood units). Normal mean pulmonary artery pressure (mPAP) at rest is 14.0 ± 3.3 mmHg and varies slightly with age (< 30 years: 12.8 ± 3.1 mmHg, 30 - 50 years: 12.9 ± 3.0 mmHg, > 50 years: 14.7 ± 4.0 mmHg).[4] An elevated blood pressure in the pulmonary circulation results in development of "Pulmonary Hypertension", which is a pathophysiological disorder characterized by extensive remodelling of the pulmonary circulation predominantly in the distal pulmonary arteries and arterioles and can complicate the majority of cardiovascular and respiratory diseases.[5,6]

DEFINITION AND CLASSIFICATION

Pulmonary hypertension (PH) a haemodynamic state found in multiple clinical conditions, is defined as increase in mPAP of ≥ 20 mmHg at rest as assessed by right heart catheterisation (RHC).[7,8] In normal conditions, at rest mPAP is 14 ± 3 mmHg. During exercise, mPAP is up to 35 mmHg and 30 mmHg can be considered normal in individuals ≤ 50 years and > 50 years, respectively.[4,9]

PH is hemodynamically classified into three class :[10]

1. Pre-capillary PH (mPAP ≥ 20 mmHg, PVR ≥ 3 Wood units and pulmonary capillary wedge pressure, PCWP ≤ 15 mmHg) which may be due to primary pulmonary arterial pressure (PAH), lung disease, chronic thromboembolism or any unclear or/and multifactorial mechanism.
2. Isolated post-capillary PH (mPAP ≥ 20 mmHg, PVR < 3 Wood units and PCWP > 15 mmHg) which may be due to left heart disease (LHD) or any unclear or/and multifactorial mechanism.
3. Combined Pre and Post-Capillary PH (mPAP ≥ 20 mmHg, PVR ≥ 3 Wood units and PCWP > 15 mmHg)

PH is clinically classified into five different groups to categorize multiple clinical conditions based on their clinical presentation, pathological findings, haemodynamic characteristics, and treatment strategy.[10,11] The detailed clinical classification of PH is displayed in Figure 1.

GROUP-I: PULMONARY ARTERIAL HYPERTENSION (PAH)

PAH is a clinical condition defined by the presence of pre-capillary PH and PVR > 3 Wood units, in the absence of other causes of pre-capillary PH such as lung diseases, chronic thromboembolism, or other rare diseases.[10,12]

Pathophysiology

An increase in mPAP is associated with irreversible remodelling of the pulmonary vascular bed, predominantly of the distal pulmonary arteries and arterioles. According to recent evidences, the pathogenesis of PAH involve miscommunication between cells within the vascular wall such as pulmonary vascular endothelial and smooth muscle cells, myofibroblasts and pericytes and sustained inflammatory reactions and altered immunity; altered energy metabolism; inhibition of apoptosis, and excessive activation of some growth factor-stimulated signalling pathways and; interaction of systemic hormones, local growth factors, cytokines, and transcription factors.[11,13,14] (Figure 2a).

Epidemiology

PAH affects about 35,000 - 1,00,000 individuals worldwide. In general population, the overall prevalence of PAH is about 15 per million adults and idiopathic PAH (IPAH) is 6 per million adults. In Asian population, PAH most commonly develops due to congestive heart disease (CHD, 40%) followed by idiopathic IPAH (38 %), connective tissue disease (CTD, 15 %), human immunodeficiency virus (HIV, 5 %) and portal hypertension (2 %).[7,10,14]

Clinical Presentation

PAH most commonly presents with progressive exertional breathlessness. Other symptoms are fatigue, weakness, angina, syncope/dizziness, peripheral oedema and abdominal distension. Raynaud's phenomenon and Ortner's syndrome may rarely develop in advance stage of PAH. The physical signs of PAH include left parasternal lift, an accentuated pulmonary component of S2, a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and right ventricular S3. Jugular vein distension, hepatomegaly, peripheral oedema, ascites, and cool extremities characterize patients in a more advanced stage.[15,16]

Diagnosis[10]

Electrocardiogram (ECG)

ECG may provide suggestive or supportive evidence of PH by demonstrating RV hypertrophy and strain, and right atrial dilatation. The absence of these findings neither excludes the presence of PH nor does it correlate with the hemodynamic severity of the disease.

Chest Radiograph

Most of the patients with IPAH have abnormal chest radiograph at the time of diagnosis. Findings include central pulmonary arterial dilatation and right atrium and ventricle enlargement in more advanced cases. The chest radiograph also helps to exclude associated lung diseases (Group - III) or pulmonary venous hypertension due to LHD (Group - II).

Pulmonary Function Tests and Arterial Blood Gases

Abnormalities in pulmonary function test and arterial blood gas analysis may indicate respiratory pathology. An abnormally decreased lung diffusing capacity of carbon monoxide (DLCO), is associated with a poor outcome. The differential diagnosis of a low DLCO in PAH includes pulmonary veno-occlusive disease (PVOD), PAH associated with scleroderma and parenchymal lung disease. Patients with PAH show a typical pattern with a low-end tidal partial pressure of carbon dioxide (Pco2), high ventilatory equivalents for carbon dioxide (VECO2), low oxygen pulse and low peak oxygen uptake (peak VO2). As the prevalence of nocturnal hypoxaemia and central sleep apnoea is high in PAH (70 – 80 %), polysomnography and overnight oximetry should be considered in those with symptoms suggestive of obstructive sleep apnoea or other forms of sleep disordered breathing. Six-minute walk test is the most common to assess functional exercise capacity which is important to have a baseline measurement and response to PAH therapy.

Echocardiography

In presence of a clinical suspicion of PAH, trans-thoracic echocardiography is often the first examination to be performed. Pulmonary arterial systolic pressure can be determined by measuring the peak tricuspid regurgitation velocity (TRV) and considering right atrial pressure. Contrast echocardiography should be considered when peak TRV is technically difficult to measure in order improve the doppler signal during measurement. The echocardiographic probability of PH has been judged based on TRV as:

1. Low (≤ 2.8 m/s or not measurable and absence of other echo PH signs),
2. Intermediate (≤ 2.8 m/s with other echo PH sign or 2.9 - 3.4 m/s without other echo PH signs)
3. High (2.9 - 3.4 m/s with other echo PH signs or > 3.4 m/s).

However, one cannot completely rely on cut-off values of TRV as it may underestimate or overestimate the probability of PH. Thus, several additional echocardiographic signs are proposed in addition to TRV which include right and left ventricle basal diameter ratio (> 1.0) and flattening of the interventricular septum (left ventricular eccentricity index > 1.1 in systole and/or diastole), right ventricular outflow doppler acceleration time (< 105 m/sec) and/or mid - systolic notching, early diastolic pulmonary regurgitation velocity (> 2.2 m/sec), diameter of the pulmonary artery (> 25 mm), inferior cava diameter > 21 mm with decreased inspiratory collapse (< 50 % with a sniff or < 20 % with quiet inspiration) and right atrial area (end-systole) > 18 cm2. In addition, echocardiography can be helpful in detecting the cause of suspected or confirmed PH.

Ventilation / Perfusion Lung Scan

PAH patients except chronic thrombo embolic pulmonary hypertension (CTEPH) usually have normal ventilation/perfusion lung scan, but it sometimes may show small peripheral unmatched and non-segmental perfusion defects (mosaic pattern) typical for CTEPH.

High – Resolution / Contrast - Enhanced Computed Tomography (CT)

CT imaging provides essential information on vascular, cardiac, parenchymal and mediastinal abnormalities. It may suggest the diagnosis of PH and provide clues to the form of PAH (e.g. oesophageal dilation in systemic sclerosis, congenital cardiac defects such as anomalous pulmonary venous drainage or chronic pulmonary thromboembolism) and also provide prognostic information.

Cardiac Magnetic Resonance (CMR) Imaging

CMR imaging is accurate and reproducible in the assessment of right ventricle size, morphology and function and allows non-invasive assessment of blood flow, including stroke volume, cardiac output, pulmonary arterial distensibility and right ventricular mass. CMR provides useful prognostic information in patients with PAH both at baseline and at follow-up.

Blood Tests and Immunology

Blood and immunological tests are required to identify the cause of PAH. Routine biochemistry, haematology and thyroid and liver function tests along with other specific blood tests are required in all PAH patients. Serological testing is required to detect underlying CTD, hepatitis and HIV. Immunological testing is required as PAH is associated with various autoimmune disorders such as scleroderma (anti - centromere, dsDNA, anti - Ro, U3 - RNP, B23, Th / To and U1 - RNP), acquired immunodeficiency syndrome and systemic lupus erythematosus (anti - cardiolipin antibodies). Around 40 % of patients with IPAH have elevated antinuclear antibodies albeit in a low titre (1 : 80).

Abdominal Ultrasound Scan

Abdominal ultrasound may be helpful for identification of some of the aetiological factors connected with PAH (Porto - pulmonary hypertension, hepatic schistosomiasis, etc) and the systemic effect of chronically elevated systemic venous pressure (cardiac cirrhosis).

Echocardiography		Likelihood	
Parameters	**Findings**	**PH - LHD**	**PAH**
Ejection fraction	< 50 %	↑	↓
Left atrial size	LAD > 40 mm LAVI > 28 mm/m^2	↑	↓
LV wall thickness	➢ 11 mm	↑	↓
Trans-mitral doppler	Grade II / III diastolic dysfunction	↑	↓
Mitral regurgitation	Severe MR > 1	↑	↓
RV size	RV to LV area > 1	↓	↑
Inter-ventricular septum	Systolic flattening Lateral - septal TDI disparity	↓	↑
Inter-atrial septum	Bulging into LA	↓	↑
RV systolic function	TAPSE < 1.5 cm	↓	↑
RVOT doppler	Notching	↓	↑

Table 1. Echocardiographic Differentiation between Group - I and Group - II Pulmonary Hypertension

PH – LHD: pulmonary hypertension due to left heart disease ; PAH : pulmonary arterial hypertension ; LAD : left atrial diameter ; LAVI : left atrial volume indexed ; LV : left ventricular ; RV : right ventricular ; TDI : tissue doppler imaging ; TAPSE : tricuspid annular plane systolic excursion ; RVOT : right ventricular outflow tract.

Right Heart Catheterization and Vasoreactivity

RHC is required to confirm the diagnosis of PAH, to assess the severity of haemodynamic impairment and for vasoreactivity testing of the pulmonary circulation in

selected patients. Cardiac catheterization should be performed if there is discordance between clinical and echocardiographic findings with regards to aetiology or severity of PH [e.g. large silent patent ductus arteriosus (PDA) with Eisenmenger syndrome or poor echo window in chronic obstructive pulmonary disease (COPD) patients]. Vasoreactivity testing, usually using inhaled nitric oxide, intravenous epoprostenol or intravenous adenosine can identify patients with IPAH who may respond to long-term high dose calcium channel blockers (CCB). A positive response is defined as a reduction in mPAP of at least 10 mmHg, to less than 40 mmHg, without a fall in cardiac output. Only about 7 % of patients with IPAH meet these criteria. Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, heritable pulmonary arterial hypertension (HPAH) and PAH associated with drugs use.

The risk (low < 5 %, intermediate 5 - 10 % and high > 10 %) assessment of PAH based on all the diagnostic test is displayed in Table 2.

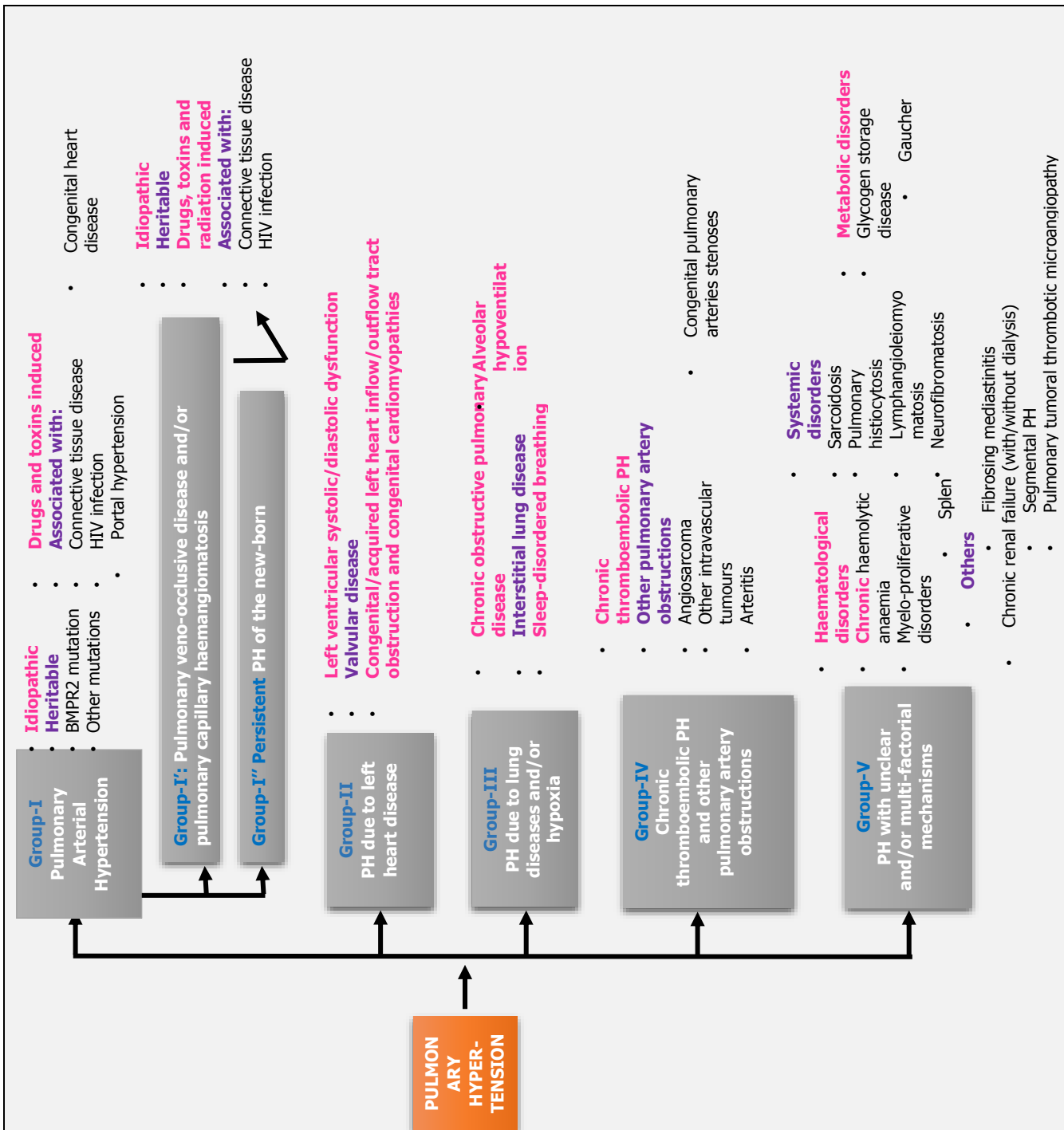

Figure 1. WHO Clinical Classification of Pulmonary Hypertension (BMPR2: Bone Morphogenetic Protein Receptor Type - 2 Gene; HIV : Human Immunodeficiency Virus; PH Pulmonary Hypertension)

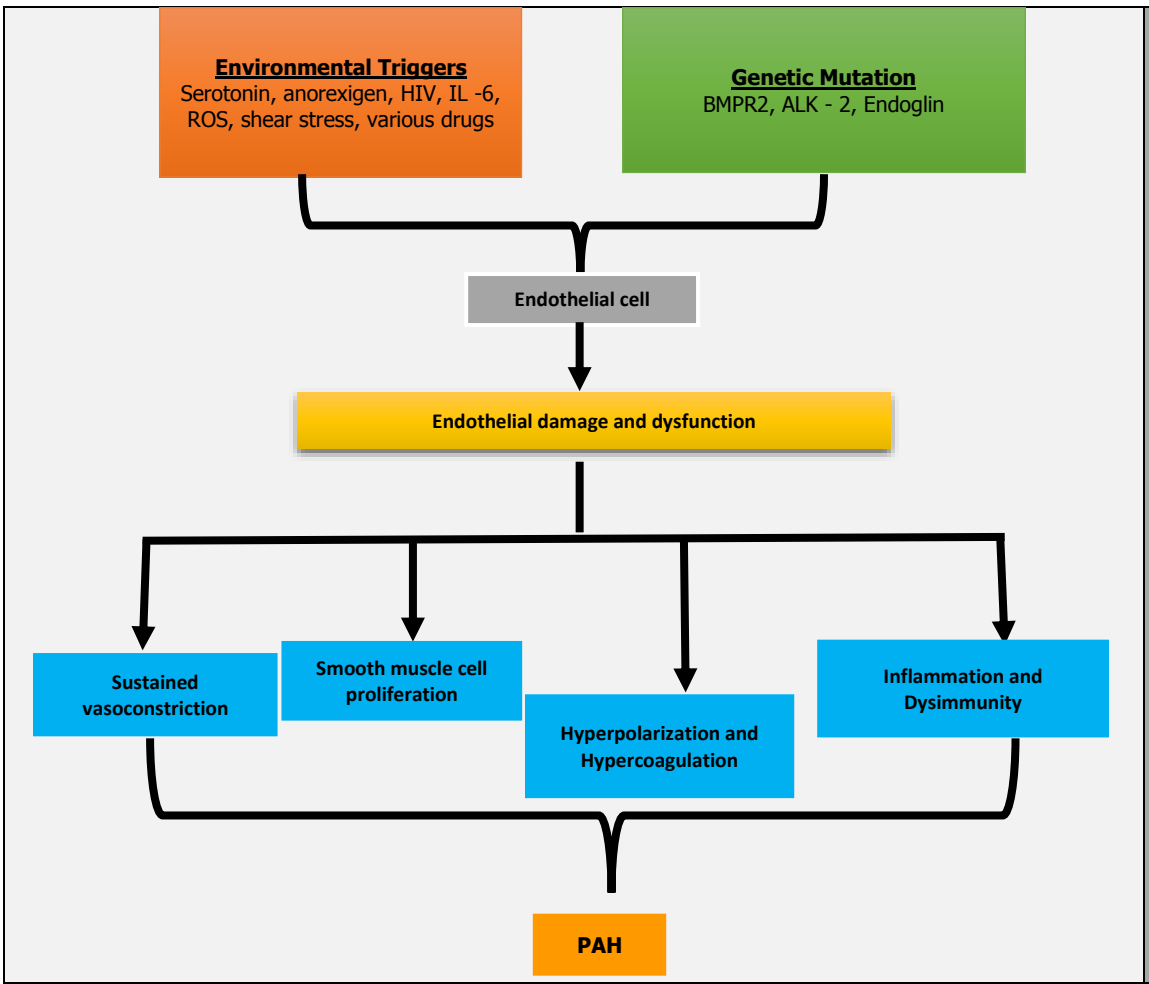

Figure 2a. Pulmonary Arterial Hypertension (Group - I)

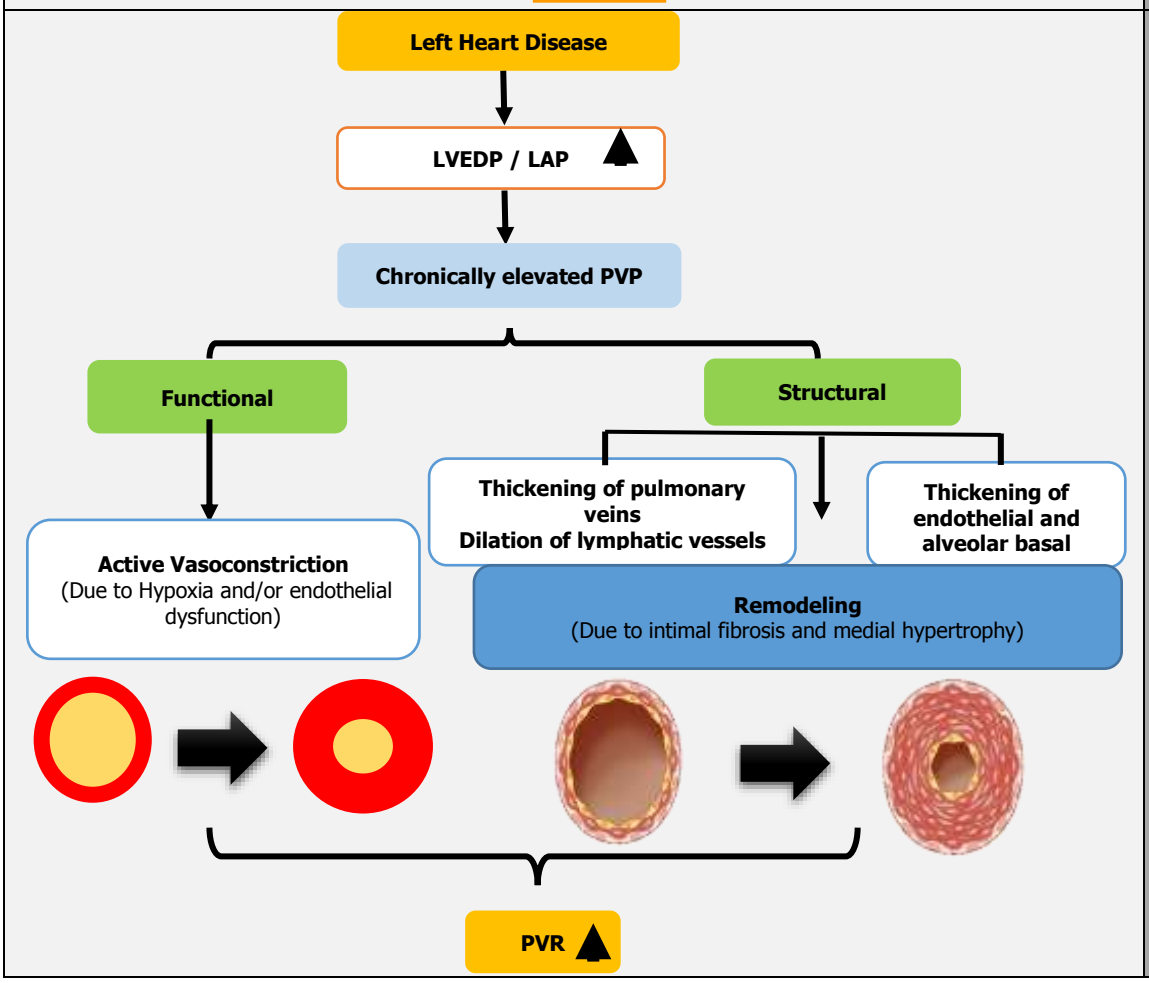

Figure 2b. Pulmonary Hypertension due to Left Heart Disease (Group - II)

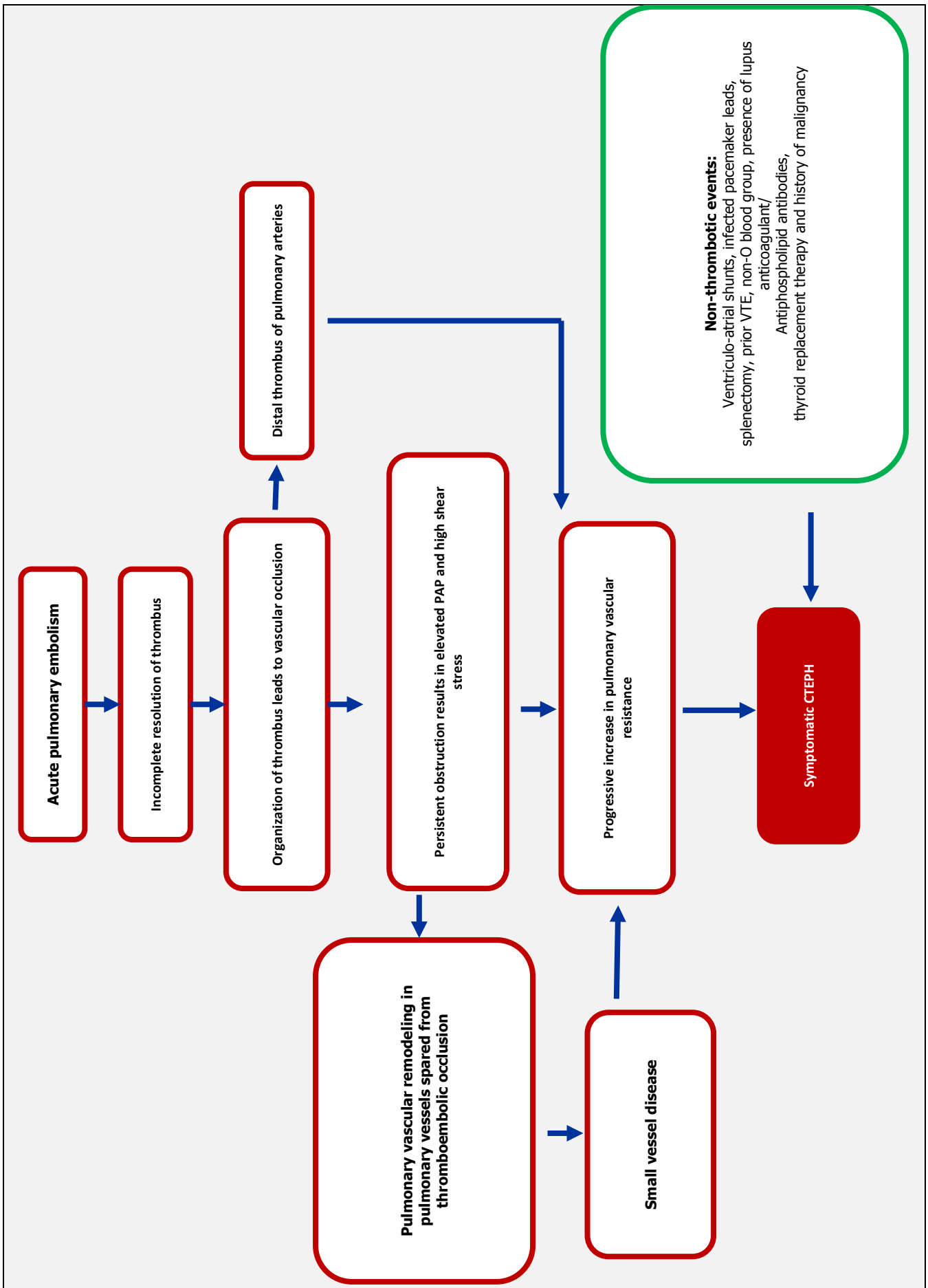

Figure 2c. Chronic Thromboembolic Pulmonary Hypertension (Group - IV)

Figure 2. Pathophysiology

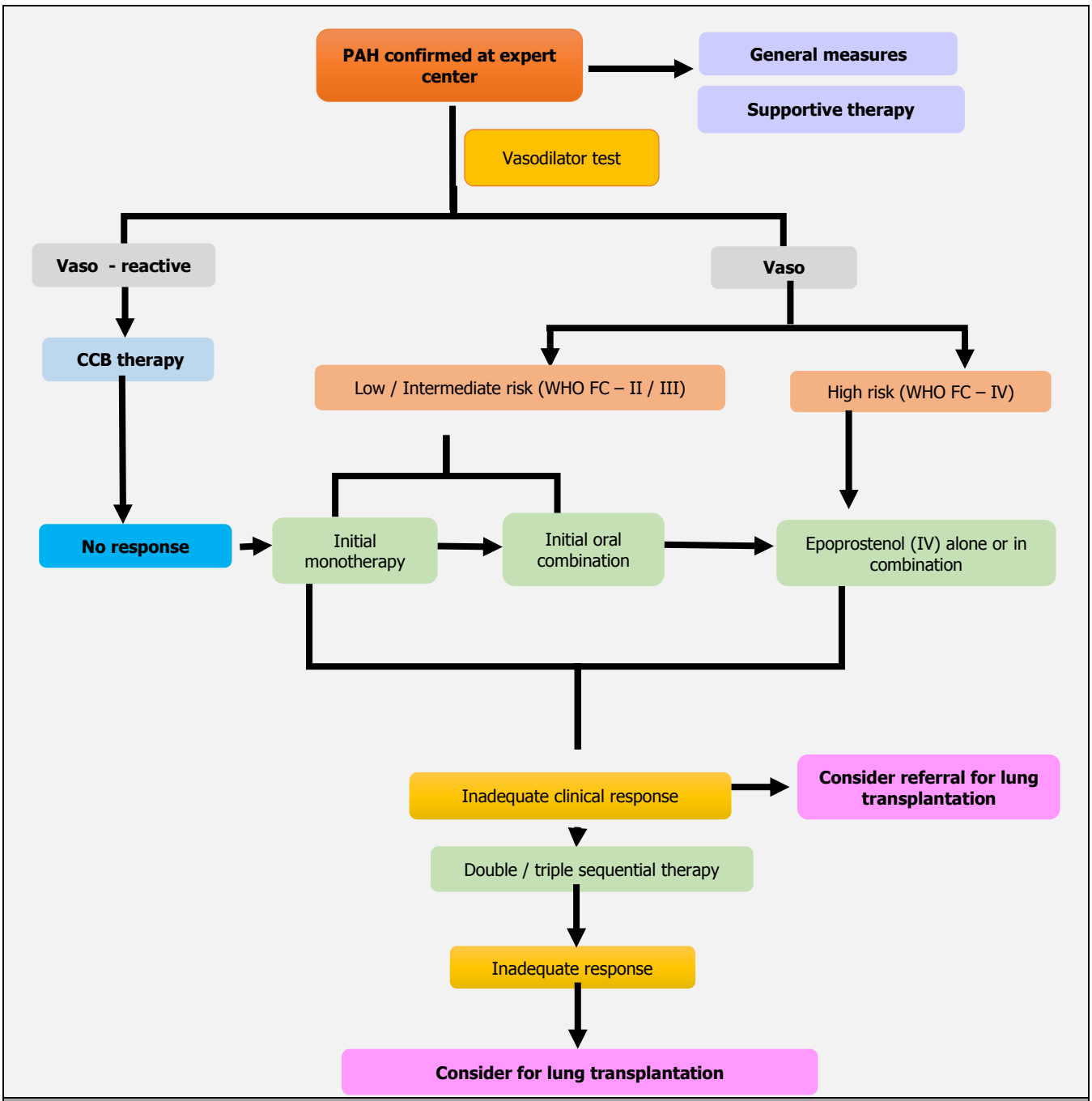

Figure 3a. Pulmonary Arterial Hypertension (Group - I)

Determinants of Prognosis	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	Repeated
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	Peak VO_2 11 – 15 ml/min/kg	Peak VO_2 < 11 ml/min/kg
NT-proBNP plasma levels	BNP < 50 ng / I NT - proBNP < 300 ng/l	BNP 50 – 300 ng/l NT - proBNP 300 –1400 ng/l	BNP > 300 ng/l NT - proBNP > 1400 ng/l
Imaging (echocardiography, CMR	RA area < 18 cm^2 No PE	RA area 18 – 26 cm^2 No / minimal PE	RA area > 26 cm2 PE present
Haemodynamic	RAP < 8 mmHg CI ≥ 2.5 I/min/m2 SvO2 > 65 %	RAP 8 – 14 mmHg CI 2.0 – 2.4 l/min/m2 SvO2 60 – 65%	RAP > 14 mmHg CI < 2.0 l/min/m2 SvO2 < 60 %

Table 2. Risk Assessment of Pulmonary Arterial Hypertension Based on Diagnostic Test

HIV: human immunodeficiency virus; IL – 6: interleukin – 6; ROS: reactive oxygen species; BMPR2: bone morphogenetic protein receptor type - 2 gene; ALK - 2 : activin receptor - like kinase - 2 gene; PAH: pulmonary arterial hypertension; LVEDP / LAP: left ventricular end -diastolic pressure / left atrial pressure; PVP: pulmonary venous pressure; PVR: pulmonary vascular resistance; PAP: pulmonary arterial pressure; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; 6MWD: 6 - minute walking distance; VO2: oxygen consumption; NT – proBNP: N - terminal pro - brain natriuretic peptide; CMR: cardiac magnetic resonance; RA: right atrium; PE: pericardial effusion; RAP: right atrial pressure; CI: cardiac index; SvO2: mixed venous oxygen saturation

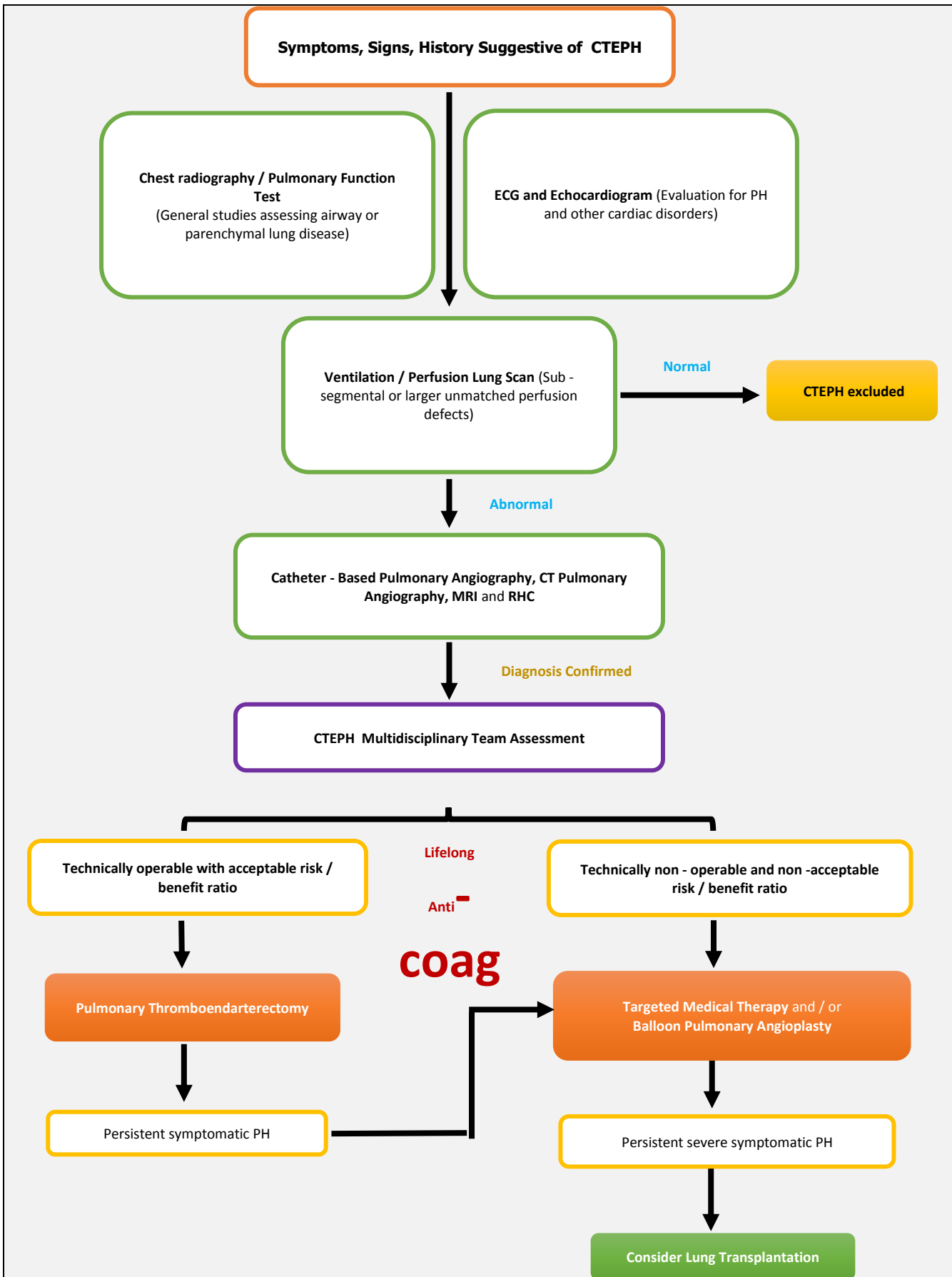

Figure 3b. Chronic Thromboembolic Pulmonary Hypertension (Group - IV)

Figure 3. Algorithm for the Treatment

(PAH: pulmonary arterial hypertension; CCB: calcium channel blocker; WHO FC: world health organization functional classification; iv: intravenous; CTEPH: chronic thromboembolic pulmonary hypertension; ECG: electrocardiogram; PH: pulmonary hypertension; CT: computed tomography; MRI: magnetic resonance imaging; RHC: right heart catheterization.

TREATMENT[10]

General Measures

- Isometric exercises and excessive physical activity that leads to distressing symptoms (breathlessness, exertional dizziness, or chest pain) should be avoided. Patients should be advised of mild physical activity within symptoms limit. Supervised exercise rehabilitation should be advised for physical conditioning of symptomatic WHO class II - III patients.
- Avoid pregnancy and elective surgery in patients with PAH. Epidural anaesthesia is probably better tolerated than general anaesthesia in these patients.
- Exposure to high altitudes (> 1500 - 2000 m), travel in unpressurized aircraft must be avoided.
- Genetic counselling should be offered to select PAH patients (e.g. BMPR2 mutation).
- Phlebotomy may be needed in patients with symptomatic secondary polycythaemia.
- Use of nitroglycerine for angina is avoided because it may worsen the pain.
- Vaccination against influenza and pneumococcal pneumonia is recommended in PAH patients as they are more prone to pneumonia.
- Physiological, social as well as emotional support is required to improve quality of life.
- Medical treatment adherence is important and should be checked periodically.

Supportive treatment

- Diuretic treatment is recommended if signs of right ventricular failure and fluid retention are observed.
- O2 administration should be considered for patients in WHO - FC III and IV and those with arterial blood O2 pressure consistently < 8 kPa (60 mmHg).
- Oral anticoagulants may be considered due to use of anorexigens in such patients.
- Anaemia and/or iron status should be corrected.

Specific Drug Treatment

1. CCBs

High doses of CCBs (Nifedipine, Diltiazem and Amlodipine) are recommended in PAH patients who respond to vasoreactivity test performed at the time of RHC.

2. Endothelin Receptor Antagonists (ERA)

In PAH patients, activation of the endothelin system has been demonstrated in both plasma and lung tissue which leads to endothelin-1 production and exerts vasoconstrictor and mitogenic effects. Ambrisentan, bosentan and macitentan are the three endothelin receptor antagonists used in PAH patients.

3. Phosphodiesterase Type - 5 (PDE - 5) Inhibitors and Guanylate Cyclase Stimulators

PDE-5 is an enzyme which degrade cyclic guanosine monophosphate (cGMP) in the nitric oxide / cGMP pathway in the smooth muscle cells lining the blood vessels supplying various tissues including pulmonary vasculature. Inhibition of these enzyme block degradation of cGMP and thus results in vasodilation. Sildenafil, tadalafil and vardenafil are three PDE-5 inhibitors that are approved for the treatment of PAH. Riociguat is a stimulator of guanylate cyclase and thus enhances cGMP production which results into vasodilation and is approved for PAH treatment.

4. Prostacyclin Analogues and Prostacyclin Receptor Agonists

Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation mainly synthesised by endothelial cells in vascular walls. As impairment in prostacyclin synthesis and metabolism has been observed in PAH patients, various prostacyclin analogues and prostacyclin receptor agonist are used in the treatment of PAH. Beraprost, epoprostenol, iloprost, treprostinil are prostacyclin analogues and selexipag is a prostacyclin receptor agonist which are approved for the treatment of PAH.

Combination therapy, either sequentially or initially (upfront), using two or more classes of drugs simultaneously has been considered as an effective option for management of PAH. If the outcomes of medical treatment in patient of PAH remain uncertain or patients fail to medical therapy, then transplantation (heart–lung or double-lung transplantation) should be considered. The algorithm for the treatment PAH is described in Figure 3a.

SUBSETS OF PAH

1. Paediatric PAH[10]

There is no standard age for development of PAH, it can occur at any age from the neonatal to adulthood. Syncope is more common presenting symptom in children, and other common symptom include dyspnoea, fatigue and failure to thrive. Unlike adult PAH, right ventricular failure is a late event in paediatric PAH and child may die due sudden death before its occurrence. Diagnosis of paediatric PAH must be confirmed by heart catheterization, and should be followed by vasoreactivity testing. The similar treatment algorithm including combination therapy and heart-lung transplantation, as that of adult PAH patients, is recommended for children but the dose of each drug should be altered (Figure 3a).

2. PAH Associated with Adult CHD[10,17,18]

Patients with CHD, particularly systemic-pulmonary shunts most probably leads to PAH if left untreated. The clinical class of PAH-CHD include PAH associated with Eisenmenger's syndrome (CHD with initial large systemic – to - pulmonary shunt which results into reversal of shunt and systemic cyanosis), PAH with small / coincidental defects and persistent PAH after defects correction. Dyspnoea, fatigue and syncope are the common symptoms and patients with Eisenmenger's syndrome usually present with cyanosis, haemoptysis, stroke, brain abscesses, coagulation abnormalities and even sudden cardiac death. Treatment should be individualized based on patient's condition

including targeted therapy and various supportive/general measure. If no improvement is noted with medical therapy, even with combination therapy, then heart-lung transplantation should be considered.

3. PAH Associated with CTD[10]

CTDs such as systemic sclerosis, systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis and Sjogren's syndrome may lead to development of PAH. Female with age > 60 years are more prone to CTD associated PAH (Female : Male – 4 : 1). Systemic sclerosis represents the main CTD associated with PAH in western population, while systemic lupus erythematosus is more common in Asia. Symptoms and clinical presentation are analogous to IPAH. In asymptomatic patients with systemic sclerosis, annual resting echocardiography, DLCO and biomarkers are recommended for screening of PAH. RHC should be performed in all cases of clinically suspected and ECHO inconclusive PAH associated with CTD. Immunosuppressive therapy in combination with glucocorticosteroids and cyclophosphamide is recommended to improve clinical condition. Treatment of patients with CTD and PAH is similar to IPAH treatment described in Figure 3a.

4. PAH Associated with Portal Hypertension (PoPH)[10]

Liver cirrhosis is the most common cause of PoPH and around 1 - 5 % patients with portal hypertension develop PAH. The pathogenetic association between portal hypertension and PH not clear yet. The clinical signs, symptoms, diagnosis and treatment of PoPH are similar as the other forms of PAH, however the co-existence of portal hypertension and severity of liver disease should be kept in mind. Anticoagulants should be avoided as the patients with PoPH have a higher risk of bleeding and beta-blockers (generally used to treat portal hypertension) should also be avoided as they worsen haemodynamic condition of PoPH patients. The hepatotoxicity of drugs should be noted before prescribing them to PoPH patients. Liver transplantation is contraindicated in patients with significant PAH however, pre-treatment of these patients for PAH might improve the outcomes after liver transplantation. On the contrary, simultaneous liver and bilateral lung transplant confers definitive cure.

5. PAH Associated with HIV Infection[10]

The modern HIV management technique HAART (highly active anti-retroviral therapy) has decreased incidence of HIV - associated PAH and also resulted in improved survival rate. An indirect action of HIV infection on inflammatory reactions and growth factors may act as a trigger for development of PAH as no evidence of viral particles were found in the complex plexiform lesions in HIV - PAH patients. The clinical presentation of HIV - PAH is similar to IPAH. Echocardiography is recommended in patients with unexplained dyspnoea in order to detect HIV related cardiovascular complications such as myocarditis, cardiomyopathy or PAH. The RHC must be performed to confirm the diagnosis of HIV - PAH and the absence of LHD. The treatment of HIV - PAH follows the same treatment algorithm as that for PAH (Figure 3a), along with HAART. Anticoagulation (due to increased risk of bleeding, compliance issues and drug interactions) and CCBs (as non - responders to acute vasodilator) are not recommended in patients with HIV - PAH.

Group I': Pulmonary veno-occlusive disease (POVD) and pulmonary capillary haemangiomatosis (PCH)[10]

The true incidence of PVOD/PCH remains unknown because many cases are still misclassified as PAH due to similarities in pathological and clinical characteristics. In contrast to IPAH, there is a male predominance in PVOD and the prognosis appears to be worse. The diagnosis of PVOD/PCH can be established with a high probability by the combination of clinical suspicion, physical examination, bronchoscopy and radiological findings. In heritable cases, identification of a bi-allelic EIF2AK4 mutation is sufficient to confirm a diagnosis of PVOD/PCH without histological confirmation. Most patients complain of dyspnoea on exertion and fatigue, clinical presentations that are indistinguishable from PAH. Physical examination may reveal digital clubbing and bi-basal crackles on lung auscultation, which is unusual in PAH. High resolution CT thorax is the investigation of choice. Typical findings suggestive of PVOD/PCH include presence of subpleural thickened septal lines, centrilobular ground-glass opacities and mediastinal lymphadenopathy.

There is no established medical therapy for PVOD/PCH. Most importantly, vasodilators and in particular, intravenous epoprostenol must be used with great caution because of the high risk of severe drug-induced pulmonary oedema. High dose diuretics, O2 therapy and gradual increase in epoprostenol doses are recommended. Therefore, therapy for PVOD/PCH should be undertaken only at centres with extensive experience in the management of PH and patients should be fully informed about the risks. The only curative therapy for PVOD/PCH is lung transplantation, and there are no reports of recurrence of disease following transplantation.

GROUP-II: PH DUE TO LEFT HEART DISEASES (PH-LHD)

Definition and Classification

The Haemodynamic Classification of PH - LHD:[10,19,20]

1. Post-capillary PH: mPAP ≥ 25 mmHg and PAWP > 15 mmHg. Passive PH–LHD: normal trans-pulmonary pressure gradient (TPG: ≤ 12 mmHg) and PVR (≤ 3 Woods units)
2. Isolated post-capillary PH: Diastolic pressure gradient (DPG) < 7 mmHg and/or PVR ≤ 3 Wood Units.
3. Combined post-capillary and pre-capillary PH: DPG ≥ 7 mmHg and / or PVR > 3 Woods units. Reactive PH–LHD: TPG > 12 mmHg and PVR ≥ 3 Woods units.

Reactive Reversible PH-LHD
Normalization of the TPG and PVR during vasodilator challenge, suggesting a predominance of functional over structural abnormalities of the pulmonary arterial vascular bed.

Reactive irreversible PH-LHD
Not responsive to vasodilators and/or inodilators suggesting a structural over functional abnormalities of the pulmonary arterial vascular bed.

The Clinical Classification of PH-LHD Include Three Main Entities: [21,22]

1. PH due to heart failure with preserved ejection fraction (HFpEF, EF > 50 %)
2. PH due to heart failure with reserved ejection fraction (HFrEF, EF ≤ 50 %)
3. PH due to valvular heart disease (VHD)

Pathophysiology

Left ventricular systolic/diastolic dysfunction, valvular disease, congenital left ventricular outflow tract obstruction, cardiomyopathies or congenital/acquired pulmonary vein stenosis are responsible for increase in left atrial pressure causing backward transmission of filling pressures to pulmonary vasculature and ultimately leads to PH.[22,23] The pathophysiology of PH-LHD is outlined in Figure 2b.

Epidemiology

Patients with severe left ventricular systolic dysfunction may develop PH in around 60 % of cases and patients of HFpEF may present with PH in up to 70 % of cases. The likelihood of presence of reactive PH-LHD increases with increase in severity of heart failure. In left sided valvular diseases, the prevalence of PH increases with the increase in disease severity. Almost all patients with severe symptomatic mitral valve disease and up to 65 % of patients with symptomatic aortic stenosis present with PH.[10,19,20]

Clinical Presentation and Diagnosis

Diagnosis of PH-LHD is often a challenging task as the symptoms are nonspecific to interpret, which may lead to misdiagnosis of PAH. Compared with PAH, patients with PH-LHD (in HFpEF) are often older (> 65 years), female, diabetic, hypertensive, have coronary artery disease, arrhythmias, sleep disordered breathing and have the features of metabolic syndrome. Upon physical examination, the features such as pulmonary crackles, left sided S3 or S4, left sided murmurs, or irregular heart sounds consistent with arrhythmia point towards the presence of LHD. The patients with reactive PH-LHD may present with orthopnoea and paroxysmal nocturnal dyspnoea which are not found in other forms of PH. Additional pulmonary vascular congestion, pleural effusion, and left ventricle hypertrophy may also be observed in such patients in chest radiogram and ECG.[8,20,24]

For the evaluation of any type of PH, chest X-ray and ECG should be performed. Echocardiography is the most convenient non-invasive modality as it immediately points towards LHD as a cause of PH and also help to differentiate PH-LHD and PAH (Table 1). CMR is useful tool to spot structural abnormalities of the left ventricle and atrium, to assess left ventricular systolic function, to detect presence of CHD, myocardial fibrosis or infiltrative disease, right ventricular enlargement and systolic function and, hypertrophy. RHC should be performed to confirm the diagnosis of PH-LHD and help to optimize the medical therapy. RHC also help to assess risk in patients being considered for transplantation and mechanical circulatory support. In case if diagnosis of LHD could be missed and patients are inappropriately diagnosed with PAH at resting condition, provocative test (with exercise or volume loading), especially echocardiographic findings associated with HFpEF, should be considered.[10,20,22]

Treatment

The main treatment of PH-LHD is the management of the underlying cardiac disease (heart failure or valvular disease) as no specific treatment to treat PH is available. Therapy should include treatment with appropriate diuretics, vasodilators, and neurohormonal antagonists, as well as with device and surgical therapies. Comorbidities that may contribute to PH such as sleep apnea, pulmonary embolism, and COPD as well as risk factors of cardiovascular disease such as diabetes, hypertension and features of other metabolic disorders should be identified and aggressively managed. Heart transplantation along with left ventricular assist device improves the pulmonary haemodynamics in reactive PH-LHD patients and also improves operability and post-transplant outcomes in these patients. There is no definite evidence supporting the use of PAH therapies in patients with PH-LHD.[10,12,19,21]

GROUP-III: PH DUE TO LUNG DISEASES AND/OR HYPOXIA

Definition and Classification[10,12,25]

COPD, interstitial lung disease (ILD) and combined pulmonary fibrosis and emphysema (CPFE) are the most common lung diseases leading to the development of PH. On the other hand, Langerhans cell granulomatosis, sarcoidosis, obstructive sleep apnea and obesity hypoventilation syndrome are the rare conditions causing PH.

The haemodynamic classification of PH associated with lung disease is:

- COPD / IPF / CPFE without PH: mPAP < 20 mmHg
- COPD / IPF / CPFE with PH: mPAP = 21 - 24 mmHg with PVR ≥ 3 Wood units, or mPAP 25 - 34 mmHg
- COPD / IPF / CPFE with severe PH: mPAP > 35 mmHg, or mPAP ≥ 25 mmHg in the presence of a low cardiac output (CI < 2.0 L/min/m2), not explained by other causes and PVR > 6 Wood units

Pathophysiology

Group-III PH caused by various respiratory disorders (COPD and various interstitial lung disease such as idiopathic pulmonary fibrosis, auto - immune related fibrosis, sarcoidosis, systemic sclerosis, lymphangioleiomyomatosis, Langerhans cell histiocytosis and hypersensitivity pneumonitis), high altitude hypoxia, obesity hypoventilation syndrome and obstructive sleep apnoea involves multiple pathophysiological mechanisms. Pulmonary acute hypoxia leads to vasoconstriction which is a common physiological process, however, persistent hypoxia causes pulmonary vascular remodelling due to activation of various intracellular mediators which leads to elevation of PVR and ultimately results in PH. Other factors involved in development of Group-III PH are mechanical stress, inflammation, pulmonary vascular endothelial dysfunction and chronic injury to alveolar capillary membrane.[26-29]

Epidemiology

Among patients with COPD, the estimated prevalence of PH is 10 - 30 %.[30] The prevalence of PH in idiopathic pulmonary fibrosis is 8 - 85 % depending on the severity of the disease.[31,32] There is partial susceptibility of development of PH in patients with CPFE with a prevalence of 30 – 50 % Around 15 - 53 % patients with any sleep-related breathing disorder develop PH and in patients with sarcoidosis, the chance of development of PH ranges from 5.7 to 74 %.[33]

Clinical Presentation and Diagnosis

It may be very difficult to identify specific signs and symptoms of PH in patients with severe lungs diseases, however if patient's symptoms and pulmonary function tests derangements are disproportionate to the underlying lung pathology then echocardiography should be performed to identify associated PH or LHD. RHC should not be performed in patient with lung disease with suspected PH, unless lung transplant or alternative diagnosis is contemplated (Group-I or Group-IV).[12,25,33]

Treatment

At present, there is no specific therapy for PH associated with lung diseases and thus the fundamental goal is to manage underlying lung disease with optimized treatment strategy. Administration of supplemental O2 in patient with COPD associated PH with hypoxemia has partially reduce the progression of disease. The use of PAH drugs is not recommended for patients with Group-III PH.[10,12,25]

GROUP-IV: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

Definition and Epidemiology

CTEPH, a pre-capillary PH, is the result of obstructive pulmonary artery remodelling due to incomplete resolution of pulmonary thrombo emboli (despite of ≥ 3 months of curative anticoagulation) and formation of a chronic, fibrotic, flow-limiting thrombus within the pulmonary vascular bed.[10,34,35] Hemodynamic findings includes mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, and PVR ≥ 3 Wood units.

Pathophysiology

Multifactorial mechanisms are involved in development of Group-IV PH. Unresolved thrombo emboli is considered as the prime cause of CTEPH, however small vessel disease due to pulmonary vascular remodelling in non-obstructed vessels, infection and various inflammatory reactions (due to autoimmune and haematological disorders) also play significant role in development of CTEPH.[34,36] Detailed pathophysiology of CTEPH is described in Figure 2c.

Clinical Presentation and Diagnosis

Patients with CTEPH usually present with progressive dyspnoea on exertion (NYHA class III / IV), haemoptysis, and/or signs of right heart dysfunction including fatigue, palpitations, syncope, or oedema at an advanced stage of the disease. Several signs of right heart failure such as extended neck (jugular) veins, severe peripheral oedema, ascites, hepatomegaly and acrocyanosis, may indicate a lethal state of the disease. The other physical findings at the time of presentation includes left parasternal heave, fixed splitting of the S2 heart sound, right ventricular S3, and systolic murmur of tricuspid regurgitation. Early diagnosis of CTEPH is a challenging task as the median time reported between the development of acute event and clinical signs is 14 months.[10,12,36]

The algorithm for the diagnosis of CTEPH is presented in figure 3b. The chest radiography, ECG and echocardiogram are performed at an initial stage of diagnosis to exclude various other possibilities. However, planer lung ventilation/perfusion imaging and modern multi-detector CT pulmonary angiography have been used to confirm CTEPH. Once confirmed, RHC should be performed to determine PVR to predict the prognosis of the disease. At last, selective catheter-based pulmonary angiography should be performed for technical assessment of the operability.[10,35,37]

Treatment

After diagnosis, patient should be transferred to PH referral center for further management. The treatment algorithm of CTEPH is presented in figure 3b. Pulmonary thromboendarterectomy should be performed in all patients who are eligible for surgery extracorporeal membrane oxygenation should be used as a standard of care post-surgery in severe cases optimal management of patients with CTEPH include of lifelong anticoagulation (even after pulmonary thromboendarterectomy) and diuretics, and in cases of heart failure / hypoxemia O2 should be used.[10,34,35,37] Although pulmonary thromboendarterectomy is a standard treatment for CTEPH, around 40 % of patients are inoperable (inaccessible vascular obstruction, PAP out of proportion).

Thus, such patients should be treated either with targeted medical therapy or balloon pulmonary angioplasty

(BPA) or with both depending on the severity. PAH - targeted therapy (off-label use) should be considered in symptomatic CTEPH patients who are ineligible for surgery.

Riociguat (guanylate cyclase stimulator) is the only drug approved for inoperable CTEPH or for patients with persistent/recurrent PH even after surgery. BPA also improve haemodynamic state, symptoms, exercise capacity and right ventricular function, however it may lead to various complications and thus should be performed by experts in only few selected cases. If symptoms persist with deteriorative condition of patient even after all these treatments, then lung transplantation should be considered.[10,12,35,37]

GROUP-V: PH WITH UNCLEAR AND/OR MULTIFACTORIAL MECHANISMS

This group of PH is known as miscellaneous group as the exact pathophysiology of PH is poorly understood and involves multifactorial mechanisms. PH may be caused by multiple mechanisms such as pulmonary vasoconstriction, proliferative vasculopathy, extrinsic compression, intrinsic occlusion, thrombus formation, high-output cardiac failure, vascular obliteration and left heart failure due to various severe disorders.[10,38]

The main goal of the treatment includes management of underlying causes rather than focusing on controlling PH. There is lack of studies specifying use of PAH drugs for Group-V PH and thus each patient should be carefully diagnosed and treated.[10,39]

Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Comroe JH Jr. The main functions of the pulmonary circulation. Circulation 1966;33(1):146-158.
[2] Demello DE, Reid LM. Embryonic and early fetal development of human lung vasculature and its functional implications. Pediatr Dev Pathol 2000;3(5):439-449.
[3] Suresh K, Shimoda LA. Lung circulation. Comprehensive Physiology 2016;6(2):897-943.
[4] Kovacs G, Berghold A, Scheidl S, et al. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34(4):888-894.
[5] Jutant EM, Humbert M. Pulmonary hypertension: definition, classification and treatments. Biologie Aujourdhui 2016;210(2):53-64.
[6] Hoeper MM, Ghofrani HA, Grünig E, et al. Pulmonary hypertension. Deutsches Ärzteblatt International 2017;114(5):73.
[7] Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. The Lancet Respiratory Medicine 2016;4(4):306-322.
[8] Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest 2014;146(2):449-475.
[9] Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(Suppl 25):D42-D50.
[10] Galiè N, Humbert M, Vachiery JL, et al. 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). Eur Heart J 2016;37(1):67-119.
[11] Sysol J, Machado R. Classification and pathophysiology of pulmonary hypertension. Continuing Cardiology Education 2018;4(1):2-12.
[12] Barberà JA, Román A, Gómez-Sánchez MÁ, et al. Guidelines on the diagnosis and treatment of pulmonary hypertension: summary of recommendations. Archivos de Bronconeumología (English Edition) 2018;54(4):205-215.
[13] Guignabert C, Tu L, Girerd B, et al. New molecular targets of pulmonary vascular remodeling in pulmonary arterial hypertension: importance of endothelial communication. Chest 2015;147(2):529-537.
[14] Prins KW, Thenappan T. WHO Group I pulmonary hypertension: epidemiology and pathophysiology Cardiology Clinics 2016;34(3):363-374.
[15] Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987;107(2):216-223.
[16] Gaine SP, Rubin LJ. Primary pulmonary hypertension. The Lancet 1998;352(9129):719-725.
[17] Galie N, Manes A, Palazzini M, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs 2008;68(8):1049-1066.
[18] D'Alto M, Mahadevan VS. Pulmonary arterial hypertension associated with congenital heart disease. Eur Respir Rev 2012;21(126):328-337.
[19] Barnett CF, Selby VN. Overview of WHO group 2 pulmonary hypertension due to left heart disease. Adv Pulm Hypertens 2015;14(2):70-78.
[20] Vevecka AH, Ũerban M, Jurcuţ R, et al. Reactive pulmonary hypertension in left heart disease "Post-capillary PH with a pre-capillary component". Romanian Journal of Cardiology 2015;25(2):147-152.
[21] Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53(1):1801897.
[22] Rosenkranz S, Bonderman D, Buerke M, et al. Pulmonary hypertension due to left heart disease: updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011;(154 Suppl 1):S34-S44.

[23] Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology and emerging clinical perspectives. J Am Coll Cardiol 2017;69(13):1718-1734.
[24] Pugh ME, Sivarajan L, Wang L, et al. Causes of pulmonary hypertension in the elderly. Chest 2014;146(1):159-166.
[25] Olschewski H, Behr J, Bremer H, et al. Pulmonary hypertension due to lung diseases: updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol 2018;(Suppl 272):63-68.
[26] Dunham-Snary KJ, Wu D, Sykes EA, et al. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest 2017;151(1):181-192.
[27] Weir EK, López-Barneo J, Buckler KJ, et al. Acute oxygen-sensing mechanisms. N Engl J Med 2005;353(19):2042-2055.
[28] Fein DG, Zaidi AN, Sulica R. Pulmonary hypertension due to common respiratory conditions: classification, evaluation and management strategies. J Clin Med 2016;5(9):75.
[29] Harari S, Elia D, Humbert M. Pulmonary hypertension in parenchymal lung diseases: any future for new therapies? Chest 2018;153(1):217-223.
[30] Elwing J, Panos RJ. Pulmonary hypertension associated with COPD. Int J Chron Obstruct Pulmon Dis 2008;3(1):55-70.
[31] Raghu G, Nathan SD, Behr J, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J 2015;46(5):1370-1377.
[32] Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respiration 2008;76(3):288-294.
[33] Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J 2019;53(1):1801914.
[34] Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26(143):160112.
[35] Mahmud E, Madani MM, Kim NH, et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. J Am Coll Cardiol 2018;71(21):2468-2486.
[36] Hoeper MM, Mayer E, Simonneau Gr, et al. Chronic thromboembolic pulmonary hypertension. Circulation 2006;113(16):2011-2020.
[37] Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53(1):1801915.
[38] Kalantari S, Gomberg-Maitland M. Group 5 pulmonary hypertension: the orphan's orphan disease. Cardiology Clinics 2016;34(3):443-449.
[39] Weatherald J, Savale L, Humbert M. Medical management of pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5): Is there a role for pulmonary arterial hypertension medications? Current Hypertension Reports 2017;19(11):86.