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Advanced Cardiovascular Medicine



Editors
Ashok Seth
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2

Pulmonary Hypertension: Evaluation and Optimizing Therapy in the Present Era

Neeraj Awasthy

INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery (PA) pressure of ≥25 mm Hg at rest. Pulmonary arterial hypertension has varied etiology and clinical features. Underlying etiology of PAH determines the natural history of the disease and response to therapy. Early identification of PAH is suggested because advanced disease may be less responsive to therapy.[1–3] Although pulmonary hypertension (PH) being a vast topic in itself, it is important to understand that this chapter does not discuss the various definitions, classifications, epidemiology, pathogenesis, clinical manifestations, natural history, and prognosis. This chapter mainly discusses about how to proceed with a patient of PAH and its management. Management is essentially diagnosing the patient with PAH followed by treatment. Treatment involves the primary therapy and advanced therapy. Primary therapy is directed at the underlying cause of the PAH and advanced therapy is the therapy directed at the PAH itself. Advanced therapy includes treatment with prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or, rarely, certain calcium channel blockers (CCBs).

CLASSIFICATION

The World Health Organization (WHO) classifies patients with PH into five groups based upon etiology: Dana Point, 2008 (Table 2.1). While patients in group 1 are considered to have PAH, patients in the remaining four groups are considered to have PH. When all five groups are discussed collectively, PH is generally used. We adhere to this nomenclature in the discussion that follows.

CLINICAL PRESENTATION

The early symptoms of PH are often mild and may be overlapped with many other conditions. These symptoms include dyspnea, dizziness, and fatigue. At rest there may be no symptoms and no apparent signs of illness. As a result there is a lag period of about 2 years from the onset of symptoms to the diagnosis of disease.[1,2] PAH is thus frequently not recognized until the disease is relatively advanced. Insidious presentation with exercise induced dyspnea that may be progressive. Angina generally late presentation may be because of right ventricular (RV) ischemia in a hypertrophied ventricle. Syncope or near syncope occurs once the RV output becomes fixed. Once the right ventricle fails, it may present with systemic congestion. Presence of orthopnea and paroxysmal nocturnal dyspnea signifies left-sided dysfunction. Presence of chronic cough signifies pulmonary pathology. Causes of hemoptysis include underlying thromboemolism, lung infarction, superadded infection, deranged coagulation, and bleeding parameters secondary to chronic hypoxia and secondary to pulmonary edema in left-sided diseases. Hoarseness of voice may be secondary to paralysis of left laryngeal nerve by dilated pulmonary arteries.

Patients with high-risk factors and associated condition such as family history, connective tissue diseases, congenital heart disease, or a history of intake of drugs or toxins should be proactively investigated for the presence of PAH.

Clinical Signs

Physical signs of PAH include large "a" wave in jugular venous pulse, a low volume carotid arterial pulse with normal upstroke, left parasternal (or RV) lift, a systolic pulsation of the dilated pulmonary arteries may be seen in second intercostal space, an accentuated pulmonary component of second heart sound, a diastolic murmur of pulmonary insufficiency (starting with a gap from the second heart sound), and RV S3 and fourth heart sound of RV origin. In advanced disease with RV failure, there may be jugular venous distension, hepatomegaly, lower limb edema, ascites, and cool extremities.

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Table 2.1 The classification of PAH as per WHO (Dana Point 2008)

Group 1	**Pulmonary arterial hypertension (PAH)** Idiopathic pulmonary hypertension (IPH) Heritable pulmonary hypertension (HPH) Bone morphogenetic protein receptor type 2 (BMPR2) Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without hemorrhagic telangiectasia) Unknown Drug- and toxin-induced *Associated with pulmonary hypertension (APH):* – Connective tissue diseases – Human immunodeficiency virus (HIV) infection – Portal hypertension – Congenital heart disease (CHD) – Schistosomiasis – Chronic hemolytic anemia – Persistent pulmonary hypertension of the newborn (PPHN) – Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
Group 2	**Pulmonary hypertension due to left heart diseases** Systolic dysfunction Diastolic dysfunction Valvular disease
Group 3	**Pulmonary hypertension due to lung diseases and/or hypoxemia** Chronic obstructive pulmonary disease (COPD) Interstitial lung disease (ILD) Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental abnormalities
Group 4	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
Group 5	**Pulmonary hypertension with unclear multifactorial mechanisms** *Hematological disorders*: Myeloproliferative disorders, splenectomy *Systemic disorders*: Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis *Metabolic disorders*: Glycogen storage disease, Gaucher's disease, thyroid disorders *Others*: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BASIC INVESTIGATIONS

Polycythemia may be seen in chronic hypoxia secondary to lung pathology or chronic right-to-left shunt lesions. Test to detect hypercoagulable state, platelet number and function should be done in appropriate patients. Abnormal liver function test (LFT) may be present in RV dysfunction. Uric acid levels are elevated in PAH. There is increased incidence of thyroid diseases in PAH.

Electrocardiogram

Electrocardiogram (ECG) changes including RV hypertrophy and right atrial overload correlate well with a diagnosis of RV hypertrophy but are not sensitive or specific for PAH. Presence of prominent left ventricular (LV) forces or left atrial overload suggests LV disease and mitral valve disease, respectively. The ECG abnormalities are relatively less pronounced in obstructive pulmonary disease because in

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these patients PH shows increased modest increase and also because of associated hyperinflation.

Chest Radiograph

Dilated central pulmonary arteries, with peripheral pruning of blood vessels are a classical chest X-ray finding. Right atrial and RV dilatation may be seen in advances disease. The other important features which may be seen in individual types include the following:[4-6]

- *Group 2*: Pulmonary venous hypertension may point to the left heart disease.
- *Group 3*: This may show evidence of lung disease, these may be associated with kyphoscoliosis.
- In pulmonary veno-occlusive disease, there are enlarged central pulmonary arteries with septal lines and normal left-sided chambers.
- In pulmonary capillary hemangiomatosis, there are bilateral bibasilar reticular or reticulonodular opacities with enlarged central pulmonary arteries and septal lines, and pleural effusions are unusual as compared to pulmonary veno-occlusive disease.
- In chronic thromboembolic pulmonary hypertension (CTEPH), there may be irregular shaped and asymmetrically enlarged proximal vessels and regional differences in pulmonary vascularity.

Echocardiography

Echocardiography is particularly helpful in evaluating the following aspects of PH:

1. Estimation of PA pressure to determine, if PH is present
2. Assessment of cardiac cause of pulmonary hypertension
3. Assessment of severity of RV dysfunction
4. Assessment of prognostic variables.

Estimation of PA Systolic Pressure to Determine if PH is Present

Doppler Echocardiography

It is the most commonly used modality for the estimation of PA pressures. It enables the reliable estimation of PA pressures, because in the absence of pulmonary outflow obstruction, tricuspid regurgitation peak velocity (TRV) and RV outflow tract acceleration time have linear positive and negative correlations, respectively, with systolic pulmonary artery pressures (SPAP) and mean pulmonary artery pressures (MPAP) measured by right heart catheterization (RHC).[6]

Tricuspid Regurgitation Peak Velocity (Fig. 2.1)

Tricuspid regurgitation peak velocity is estimated by calculating systolic transtricuspid gradient using modified Bernoulli equation[7] and then adding an assumed or calculated right atrial pressure (RAP).[8-14] The RAP can be calculated as in Table 2.2 (Fig. 2.2). Echocardiographic Doppler estimated RV systolic pressure has good correlations with invasively measured pressures. False positive of TRV may be seen in the following circumstances:

- Physiologic range of SPAP is dependent on age and body mass index (BMI). It may be as high as 40 mm Hg in older (age >50 years) or obese (BMI >30 kg/m^2) subjects. It is more common in patients with diabetes and is likely due to PA noncompliance or abnormal LV diastolic filling pressures occurring with aging and systemic hypertension.
- *Flow-dependent variable*: In hyperdynamic states such as in hypothyroidism, anemia, dobutamine infusion, a TRV of 3 m/s is achieved easily; on the other hand, in low output states the velocity can be underestimated.
- Agitation can give falsely high value of TRV. This is very important in children, they should be quite comfortable and hence preferably sedated.
- Multiple views searching for the best envelope and maximal velocity should be taken for TRV estimation, as TRV velocity measurements are angle dependent.
- From the apical four chamber view the position of the transducer must be angled more medially and inferiorly particularly to avoid mitral valve signal.
- Color flow Doppler is recommended to obtain the best alignment between regurgitant flow and the Doppler signal.
- The injection of contrast agents (agitated saline, sonicated albumin, air–blood–saline mixture) may be required to achieve clear delineation of the tricuspid regurgitation (TR) jet envelope. Potential overestimation of Doppler

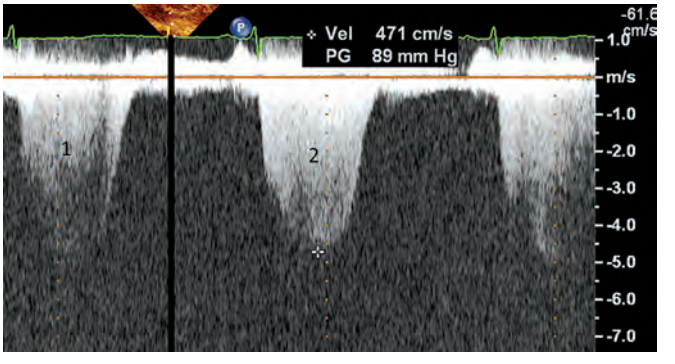


Fig. 2.1 2D Echocardiography with continuous flow Doppler across the tricuspid valve showing TR Max PG= 89 mm Hg, suggestive of significant PAH

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Table 2.2 Evaluation of RAP by echocardiography

Inferior vena cava diameter	*Change with respiration*	*Estimated right atrial pressure (mm Hg)*
Small, 1.5 cm	Collapse	0
Normal, 1.5–2.5 cm	Decrease by > 50%	5
Normal	Decrease by < 50%	10
Dilated >2.5 cm (Fig. 2.2)	Decrease by < 50%	15
Dilated with dilated hepatic veins	No change	20 or more

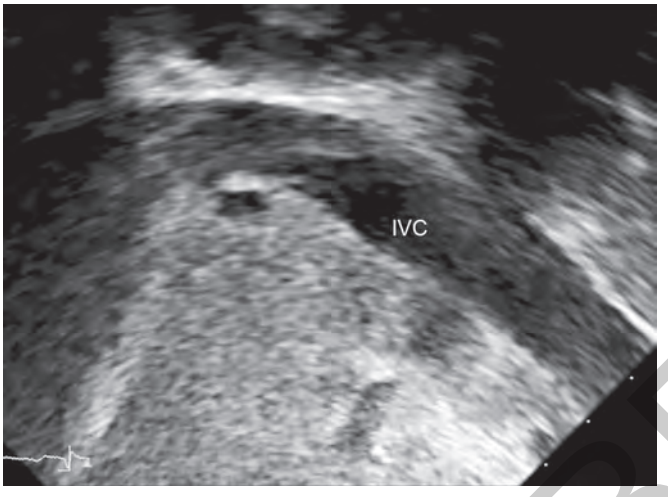


Fig. 2.2 2D echocardiography with subcoastal bicaval view showing dilated inferior vena cava (IVC). IVC may be measured in this view

European Society of Cardiology guidelines for the echocardiographic diagnosis and treatment of PH suggest the following:

1. PH unlikely for TRV <2.8 m/s, SPAP <36 mm Hg (assuming RAP of 5 mm Hg), and no additional echocardiographic signs of PH
2. *PH possible for:*
   a. TRV ≤2.8 m/s and SPAP ≤36 mm Hg but the presence of additional echocardiographic signs of PH
   b. TRV of 2.9–3.4 m/s and SPAP of 37–50 mm Hg with or without additional signs of PH
3. PH likely for TRV >3.4 m/s and SPAP >50 mm Hg with or without additional signs of PH[15]

Abbreviations: TRV, tricuspid regurgitation peak velocity; PH, pulmonary hypertension; SPAP, systolic pulmonary artery pressures

velocities should be taken into account because of contrast artifacts.

- In severe TR because of early equalization of RV pressure and RAP, the peak velocity may not reflect the true RV–RAP gradient. So, the observed values have to be interpreted in the context of the clinical scenario.
- At the time of definitive diagnosis, many patients with PH show at least moderate TRV, because of annular dilation, altered RV geometry, and apical displacement of the tricuspid leaflets. The degree of TR cannot be used as a surrogate for the degree of PAP elevation.
- Another important variable of TR is d*p*/d*t*. RV d*p*/d*t* was assessed using spectral Doppler recordings from the TR signal at a sweep speed of 200 mm/s by measuring the time interval in which the regurgitant velocity increased from 0.5 m/s to 2 m/s (1–16 mm Hg). A value of <410 ms was considered a poor prognostic marker in PH. Various objective parametrs are summarized in Table 2.3.

Pulmonary Regurgitation Velocity (Fig. 2.3)

Pulmonary valvular regurgitation is common in PH. Peak velocity of the pulmonary regurgitation signal gives an estimate of mean PAP and end-diastolic velocity can give an estimate of pressure difference between the PA diastolic and right ventricle end-diastolic pressures. Mean PAP and pulmonary end-diastolic pressure are not routinely used in the diagnosis or follow-up of PH, but may be useful when TR is absent or unreliable.

Acceleration Time (Fig. 2.4)

Pulsed-wave Doppler interrogation of the RV outflow tract in a patient of PH usually reveals an acceleration time of <100 ms, which reflects abnormal MPAP. It may be used when the tricuspid velocity cannot be measured.

- *Notching of the flow velocity envelope* may also be seen in PH. A notch seen in mid-systole is associated with severe PH and RV dysfunction.
- PVR may be calculated on echocardiography, but a PVR calculated by these methods has its limitations as compared to those calculated by cardiac catheterization.

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Table 2.3 The various objective parameters for pulmonary hypertension assessment

Parameter	*Normal*		*Abnormal*
TRV (m/s)	<2.6		2.6 2.8 in obese subjects 2.9 in patients >60 years
RVOT acceleration time ms	>110	105–110	<105
RA volume index mL/m^{-2}	≤34 in males ≤27 in females		>34 in males >27 in females
RV fractional area change (%)	32–60		≤32
LV eccentricity index	1		>1 at end-diastole indicates volume loading of the RV >1 at end-systole indicates pressure loading of the RV
RV MPI (Tei index)	<0.28	0.28–0.32	>0.32
S' wave of tricuspid annulus (cm/s)	>12	11.5–12	<11.5
IVRT (s)	<75		≥75
TAPSE (ms) (for children use charts) (Fig. 2.8)	≥20	16–20	<16
Estimated PVR wood units	<1	1–3	>3

Abbreviations: TRV, tricuspid regurgitation peak velocity; TAPSE, tricuspid annular plane systolic exertion; RA, right atrial; RV, right ventricular; LV, left ventricular; RVOT, right ventricular outflow tact; PVR, pulmonary vascular resistance; IVS, interventricular septum; IVRT, isovolumic relaxation time.

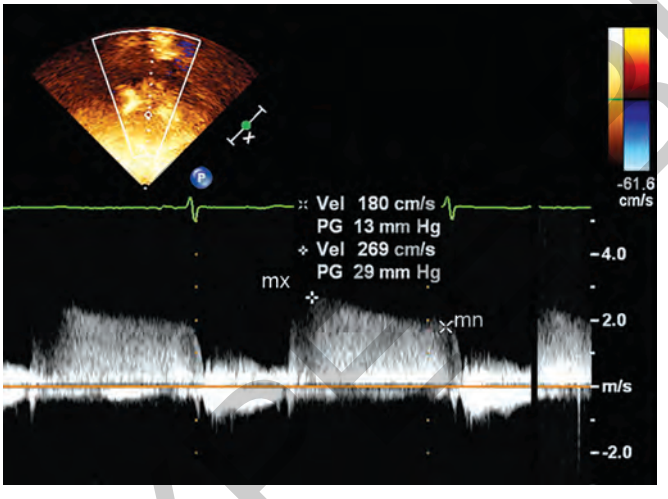


Fig. 2.3 2D echocardiography with continuous flow Doppler across the pulmonary valve measuring pulmonary regurgitation jet velocity. PR max PG of 29 mm Hg and end diastolic gradient of 13 mm Hg

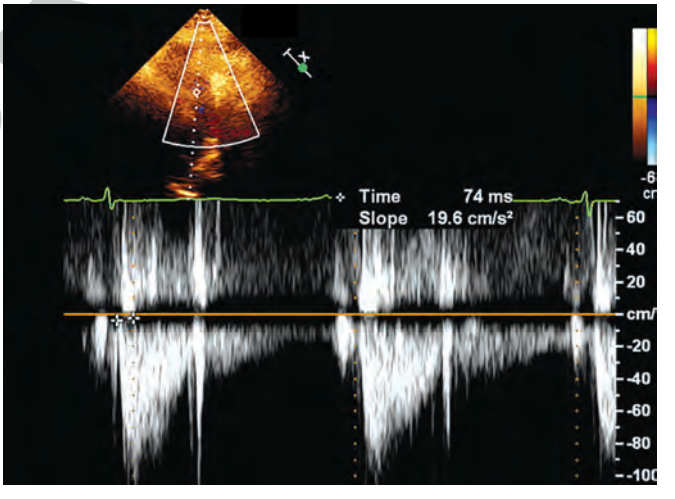


Fig. 2.4 Acceleration time

Other features of PH include (non-Doppler features of PH) the following (Figs 2.5 to 2.8):

- Enlarged right-sided chambers
- RV hypertrophy
- Increased interventricular septal thickness
- An abnormal interventricular septum/posterior LV wall ratio (>1)
- Reduced global RV systolic function

Table 2.3 summarizes various objective parameters for PH assessment:

- In a case of PH high RV pressure results in shape distortion and motion of the interventricular septum ("flattening"), which persists throughout the cardiac cycle (Fig. 2.5). As a consequence, the left ventricle appears D-shaped, with reduced diastolic and systolic volumes but preserved global systolic function.[5–8]
- Pericardial effusion (Fig. 2.8) and mitral valve prolapse have also been described in patients with PH. Pericardial effusion may be a because of impaired venous and

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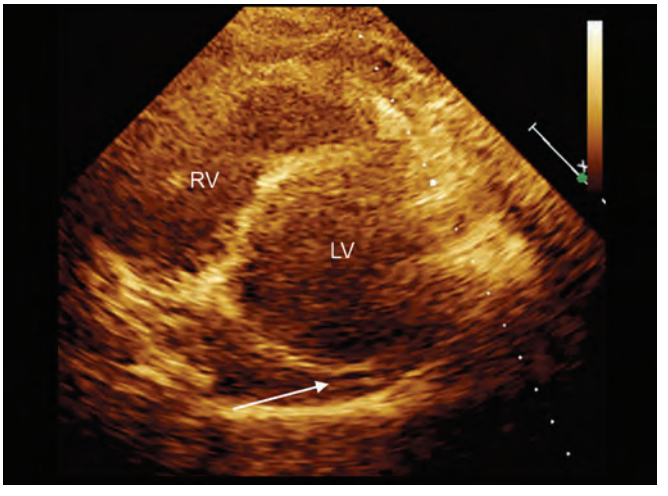


Fig. 2.5 2D echocardiography with parasternal short axis view at the level of the papillary muscles showing the flattened septal motion and presence of mild pericardial effusion (marked by arrow) in a patient with severe PAH

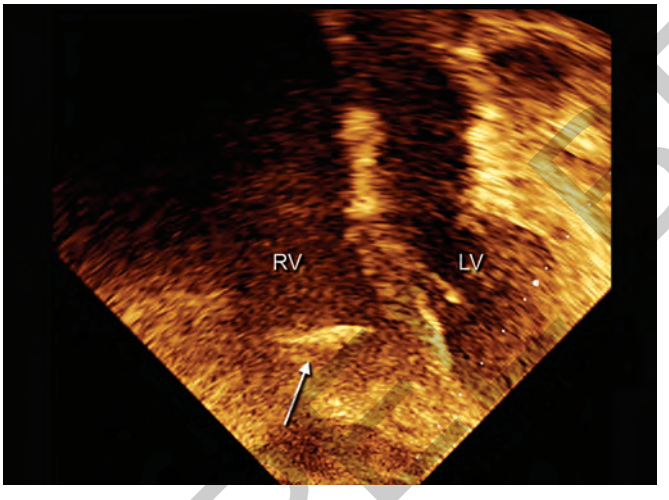


Fig. 2.6 Apical 4c view in a patient with severe PAH showing the hypertrophied RV with prominent moderator band (marked by arrow)

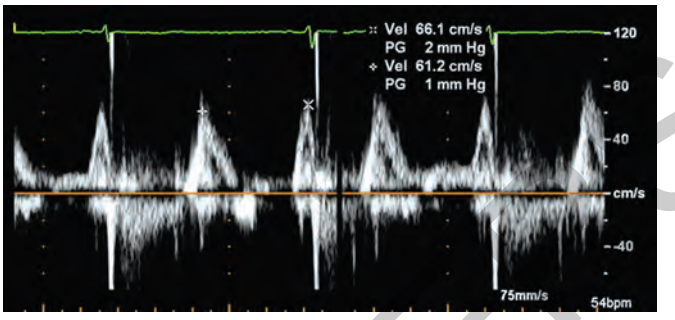


Fig. 2.7 Doppler flow echocardiography with cursor across the mitral inflow in a patient of pulmonary artery hypertension showing diastolic dysfunction of the left ventricle

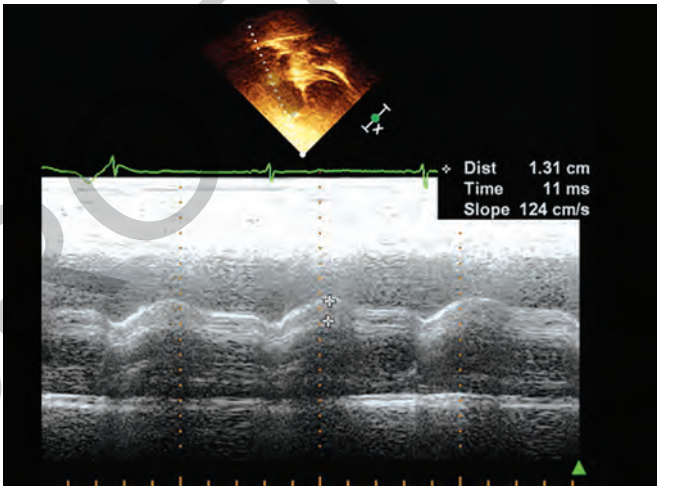


Fig. 2.8 TAPSE signal taken across the lateral annulus of the TV (as detailed in the text) showing borderline RV diastolic dysfunction with TAPSE of 13 mm in a 60-year-old lady

lymphatic drainage secondary to increased RAP. Mitral valve prolapse is related to a small left ventricle and the possible involvement of valve leaflets affected by associated connective tissue disorders, valvular heart disease.

- Because of altered RV–LV interaction, LV diastolic dysfunction may be characterized by a marked dependence of LV filling on atrial contraction, thus atrial fibrillation may not be well tolerated and vasodilating therapy may have detrimental effects on diastolic LV loading.
- Left ventricular eccentricity index is the ratio of the major axis of the LV parallel to the septum (D2) divided by the minor axis perpendicular to the septum (D1). It is measured in the parasternal short-axis view at the level of the LV papillary muscles in both end diastole and end systole.
- In a purely pressure-loaded RV, flattening of the IVS occurs in end systole, resulting in an increased end-systolic LV eccentricity index. Conversely, the eccentricity index will be increased in end diastole in pure volume loading of the RV. Left ventricular diastolic eccentricity index has been shown to be of prognostic significance particularly in patients with idiopathic PH who also have reduced RV function [tricuspid annular plane systolic exertion (TAPSE) <15 mm] (Fig. 2.8).
- Right atrial volume index is calculated from the apical four-chamber view or from the subcostal view and is measured at maximum atrial volume at the end systole.

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The single plane area—length method—is used and right atrium volume is measured using the area and the long-axis length of the atrium.[24–26]

Right atrium volume index = (0.85 $A2/L$)/BSA,

where A is the atrium area in any view (cm^2), L is the long-axis atrium length (cm), and BSA is body surface area.

- Stroke volume, cardiac output, and pulmonary vascular resistance calculated on echocardiography are not considered to be mandatory measures in PH.

Qualitative Assessment of the RV

Right ventricular dilation is assessed in multiple views including the parasternal long-axis, short-axis, and the apical four-chamber views. With chronically elevated PA pressures the RV walls become hypertrophied. Right ventricular hypertrophy is defined by RV free wall thickness of ≥0.5 mm on the apical four-chamber view. One of the first anatomical elements to become hypertrophied is the moderator band (Fig. 2.6). In contrast to other conditions affecting the RV (e.g. RV infarction or arrhythmogenic RV cardiomyopathy) where there will be regional wall motion abnormalities, contractility assessment in PH shows global RV impairment. Dilation of the RV has been shown to be linked to adverse clinical outcome and mortality.[27]

M-Mode in PH

M-mode echocardiography at the level of pulmonary valve may show diminution of a wave, fast deceleration slope, and mid-diastolic closure.

Computerized Tomography

Spiral chest computerized tomography (CT) scan is important to diagnose chronic thromboembolic PH. Besides thrombi in the pulmonary vasculatures, a mosaic pattern of variable attenuation compatible with variable pulmonary perfusion can be seen on nonenhanced CT scan. Marked variation in the size of pulmonary arteries is also a feature of chronic thromboembolism. CT scan is also important to exclude pulmonary cause of PAH.

Cardiac Catheterization

Cardiac catheterization not only establishes the severity of the disease, it is also important to adjust the response to therapy. Pulmonary artery wedge pressures are classically normal in PAH except in advanced stages when left-sided dysfunction sets in. Response to vasodilator therapy (as discussed later) is an important parameter.

Pulmonary Artery Wedge Angiogram

Pulmonary artery angiography should be done with caution with adequate precautions such as maintenance of adequate oxygenation and prevention of vasovagal reactions and rapid treatment of those that occur with intravenous atropine. Features on the wedge angiogram include the following:

- Sparsity of arborization of the pulmonary tree
- There is abrupt termination of arteries measured by measuring the length of segment over which lumen diameter narrows from 2.5 to 1.5 mm
- Tortuosity and narrowing of the small arteries
- Reduced background capillary filling.

There are certain pitfalls in the interpretation of wedge angiogram:

- In advanced vascular disease because of intimal hyperplasia there is diffuse narrowing and hence abrupt tapering may not be observed; however, background haze is absent and pulmonary circulation time is prolonged.
- The background may appear dark if the whole vessel is not filled with contrast.
- Incomplete occlusion by the balloon may also give the false impression of a dense background.
- Pulmonary stenosis or presence of previous band may give the false impression of rapid tapering.

With the advent of CT scan and the risk involved in PA wedge angiogram, it is less commonly used modality.

Other investigations summarizing the treatment of patients are given in Table 2.4.

PH Evaluation and Classification (Type, Functional Capacity, Hemodynamics)

Once the diagnosis of PH is established next step in the management involves the initiation of the therapy. Prior to initiation of the treatment a baseline investigations aimed at assessing the severity of the lesion are helpful and these would in turn aid in monitoring the response to therapy.

BASELINE ASSESSMENT

Key determinants of disease severity are functional impairment and hemodynamic derangement. The functional significance of the PH is determined by measuring exercise capacity. From the exercise capacity, the patient's WHO functional class can be determined (Table 2.5).[4]

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Table 2.4 Investigations which rule out the selective subsets of pulmonary hypertension

Exclusion of group 2 (left heart disease) and group 3 (lung diseases):

- Clinical evaluation, electrocardiogram, chest radiograph, echocardiogram, pulmonary function tests, and high-resolution computed tomography (HRCT):
  - ECG may provide suggestive or supportive evidence of pulmonary hypertension by demonstrating right ventricular (RV) hypertrophy and strain, and right atrial dilatation.
  - Doppler echocardiography provides several variables that correlate with right heart hemodynamics—Doppler echocardiography should always be performed in the case of suspected pulmonary hypertension.
  - Chest radiography may show cardiomegaly and enlarged pulmonary arteries, allows the reasonable exclusion of associated moderate to severe lung diseases (Group 3) or pulmonary venous hypertension due to left heart disease (Group 2).
  - Pulmonary function tests and arterial blood gas samples to identify contribution of underlying airway or parenchymal lung disease.
  - HRCT provides evaluation of lung parenchyma. It facilitates the diagnosis of interstitial lung disease and emphysema.

Exclusion of group 4:

- If pulmonary hypertension groups 2 or 3 are not found less common causes of pulmonary hypertension should be looked for:
  - *A ventilation/perfusion lung scan:* Where there is evidence of multiple segmental perfusion defects, a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) should be suspected.
  - The final diagnosis of CTEPH requires CT pulmonary angiography, right heart catheterization, and selective pulmonary angiography.

If a ventilation/perfusion scan is normal, or shows only subsegmental patchy perfusion defects, a tentative diagnosis of Group 1 (pulmonary hypertension) or the rarer condition of Group 5 PH is made.

- A CT pulmonary angiography may also show signs suggestive of Group 1′ pulmonary veno-occlusive disease (PVOD).
- Additional specific diagnostic tests including hematology, biochemistry, immunology, serology, and ultrasonography will allow the final diagnosis to be refined:
  - Cardiac magnetic resonance (CMR) imaging provides a direct evaluation of RV size, morphology, and function, and allows noninvasive assessment of blood flow including stroke volume, cardiac output (CO), distensibility of pulmonary artery, and RV mass; CMR is also used to distinguish pulmonary hypertension associated with congenital heart disease.
  - Blood, immunology, and serological tests are important to detect underlying connective tissue disease, human immunodeficiency virus (HIV) infection, and hepatitis; liver function tests and hepatitis serology should be examined, if clinical abnormalities are noted.
  - An abdominal ultrasound scan can reliably exclude liver cirrhosis and/or portal hypertension.
  - Right heart catheterization (RHC) represents the diagnostic gold standard for the confirmation of a diagnosis of pulmonary hypertension, and usually includes vasoreactivity testing.

Table 2.5 Functional classification for pulmonary hypertension

Functional class	*Symptomatic profile*
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

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Cardiopulmonary Exercise Testing (CPET)[15-20]

It has become the gold standard for assessing a patient's exercise capacity and maximal cardiovascular response. It is a maximal stress test—the patient exercises at a workload that progressively increases to their symptom tolerance (i.e. the maximum workload the patient can tolerate). As such, it is difficult to perform in patients with severe disease.

Pulmonary hypertension patients show reduced peak Vo_2 and this measurement correlates with a patient's prognosis. Cardiopulmonary exercise testing with measuring of the $VO_{2\ max}$ offers some advantages over the 6-minute walk test (6MWT) in terms of sensitivity, but these tests are more difficult to perform and require specialist equipment. As they are a maximal stress test, they are not suitable for more severe patients who may not be able to tolerate the exercise and may be exposed to risk of syncope and discomfort. Routine tredmill test with Naughton protocol in less symptomatic patients and 6 MWT in symptomatic patients may be used.

Biochemical Markers

Serum levels of N-terminal pro-hormone brain-type natriuretic peptide (NT-pro BNP) have been shown to be associated with prognosis in PH.[1] A level of serum NT-pro BNP below 1,400 pg/mL seems to identify patients with good prognosis.

Primary therapy is initiated after determining the severity of the disease; however, RHC is often deferred until advanced therapy is indicated because it is an invasive procedure.[24,25]

***Primary therapy*:** It refers to treatment directed at the underlying cause of the PH. The disease severity should be reassessed following primary therapy in order to determine whether advanced therapy is indicated:

- *Group 1 PH*: There are no effective primary therapies for most types of group 1 PH. As a result, advanced therapy is often needed.
- *Group 2 PH*: These have PH secondary to left heart disease and hence treatment is aimed at treatment of the underlying heart disease, which is discussed in detail separately.
- *Group 3 PH*: Patients in group 3 have PH secondary to various pulmonary causes and the management consist of treatment of the underlying cause of hypoxemia and correction of the hypoxemia with supplemental oxygen. Oxygen is the only modality with proven mortality benefit in some patients with group 3 PH.
- *Group 4 PH*: In the patients with thromboembolic occlusion. Anticoagulation is primary medical therapy.
- Surgical thromboendarterectomy is primary surgical therapy for selected patients with thromboembolic obstruction of the proximal pulmonary arteries.[8] Perioperative mortality for this procedure is <10%, and hemodynamic response may be dramatic and sustained. Prior to proceeding with this invasive approach, a 3-month period of anticoagulation is required.
- *Group 5 PH*: Group 5 PH is uncommon and includes PH with unclear multifactorial mechanisms (Table 2.1). Primary therapy is directed at the underlying cause.

General Care

This includes care in all patients such as avoiding pregnancy, prevention and prompt treatment of chest infections, and awareness of the potential effects of altitude.[1,5,6]

Supportive Care

They include oxygen, diuretic, anticoagulant, and digoxin therapy, as well as exercise.

***Oxygen therapy*:** Continuous oxygen administration remains the corner stone of therapy in patients with group 3.[1,9,10] The flow of oxygen needed to correct hypoxemia should be determined by measurement of the oxygen saturation. Oxygen is administered at 1–4 L/min generally via nasal prongs and adjusted to maintain the oxygen saturation above 90% at rest and, if possible, with exercise and sleep.[11]

Supplemental oxygen will not significantly improve the oxygen saturation of patients who have congenital heart disease with a right-to-left shunt (Eisenmenger physiology).

***Diuretics*:** It will diminish hepatic congestion and peripheral edema.[9] But overuse can decreased cardiac output (due to decreased RV and/or LV preload), arrhythmias induced by hypokalemia, and metabolic alkalosis. Fluid can also be removed by dialysis or ultrafiltration if necessary.

***Anticoagulation*:**[21,22] Patients with PH are at increased risk for intrapulmonary thrombosis and thromboembolism due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis, and a sedentary lifestyle. Even a small thrombus can produce hemodynamic deterioration in a patient with a compromised pulmonary vascular bed that is unable to dilate or recruit unused vasculature.

It is generally accepted that anticoagulation is indicated in patients with idiopathic PH, hereditary PAH, drug-induced PH, or group 4. Limited experience with newer anticoagulants makes *warfarin* the anticoagulant of choice, with a therapeutic goal of an international normalized ratio (INR) of approximately two.

The risk of bleeding on vitamin K antagonists may differ among patients with different types of PH. A retrospective study of 198 patients with PH receiving anticoagulation reported major bleeding events in 23%. Patients with PH frequently have other risk factors for thromboembolism (e.g. atrial fibrillation, severe left heart failure) that may warrant anticoagulation.

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***Digoxin*:**[23] Digoxin therapy has been shown to have both beneficial effects and drawbacks:

- *Digoxin* improves the RV ejection fraction of patients with group 3. This group of patient may be more sensitive to digitalis toxicity and thus require close monitoring.
- *Digoxin* helps control the heart rate of patients who have supraventricular tachycardias associated with RV dysfunction. *Verapamil* may be used for multifocal atrial tachycardia, unless there is concurrent LV failure.

***Exercise*:** Exercise training appears to be beneficial for patients with PH. Exercise training does not improve hemodynamic abnormalities, but there is data to suggest that skeletal muscle training may play a major role in the treatment of patients with PH. Exercise is known to elevate PA pressures so graded exercises such as bike riding in which patients can gradually increase their workload are considered safer then isometric exercises.[15–20]

Pregnancy Issues

Changes occurring during pregnancy may be detrimental to mother and the fetus. The changes in blood volume, increased oxygen consumption, circulating procoagulant factors and risk of pulmonary embolism from deep veins and amniotic fluid are additional risk factors. Thus, the subject needs to be discussed with women of childbearing age with appropriate contraceptive advice.

Advanced Therapy

Advanced therapy is directed at the PH irrespective of the underlying cause. It includes treatment with prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or, rarely, certain calcium channel blockers (CCB).

***Patient selection*:** Advanced therapy is considered for patients who have evidence of persistent PH and a functional class II, III, or IV despite adequate primary therapy.[24-26] There are special considerations for each group of PH.

- *Group 1 PH*: There are no effective primary therapies, so advanced therapy is often needed for patients with group 1 PAH.
- *Group 2 PAH*: Treatment is directed toward the primary cause, yet there are a few conditions where advanced therapy may be considered:
  - Patients with persistent PH due to mitral stenosis who have undergone mitral valve replacement.
  - However, for most patients with group 2 PH, advanced therapy should be avoided because it may be harmful.[3,4]
- *Group 3 PH*: Advanced therapy is occasionally considered for patients in group 3, who remain WHO functional class III or IV despite correction of hypoxemia and optimization of the underlying disease, especially if the severity of PH is out of proportion to the severity of the parenchymal lung disease. The tendency of advanced therapy to worsen ventilation-perfusion mismatch and increase hypoxemia in patients with group 3 PH may be formulation- and disease-specific.
- *Formulation-specific effect*:
  - *Epoprostenol* may increase hypoxemia in patients who have pulmonary fibrosis. Inhaled nitric oxide, inhaled *Iloprost*, and oral *Sildenafil* may be used as they do not appear to have this effect.[26,27] All of these agents decrease the pulmonary vascular resistance.
- *Evidence of a disease-specific effect*: Oral *Sildenafil* did not appear to worsen hypoxemia in pulmonary fibrosis,[26] but was associated with worsened hypoxemia due to chronic obstructive pulmonary disease.[28] In both diseases, oral Sildenafil decreased the PA pressure.
- *Group 4 PH*: Advanced therapy can be considered for patients with group 4 who remain WHO functional class III or IV even after anticoagulation or thromboendarterectomy. Pharmacologic therapy can also act as a bridge to surgical intervention.
- *Group 5 PH*: Few studies have shown role of advanced therapy related to sarcoidosis. A series of eight patients described a favorable response to intravenous *Epoprostenol* in most patients,[29] while another study reported that carefully selected patients can be transitioned from prostanoid infusion to oral *Bosentan.*[30]

General Approach

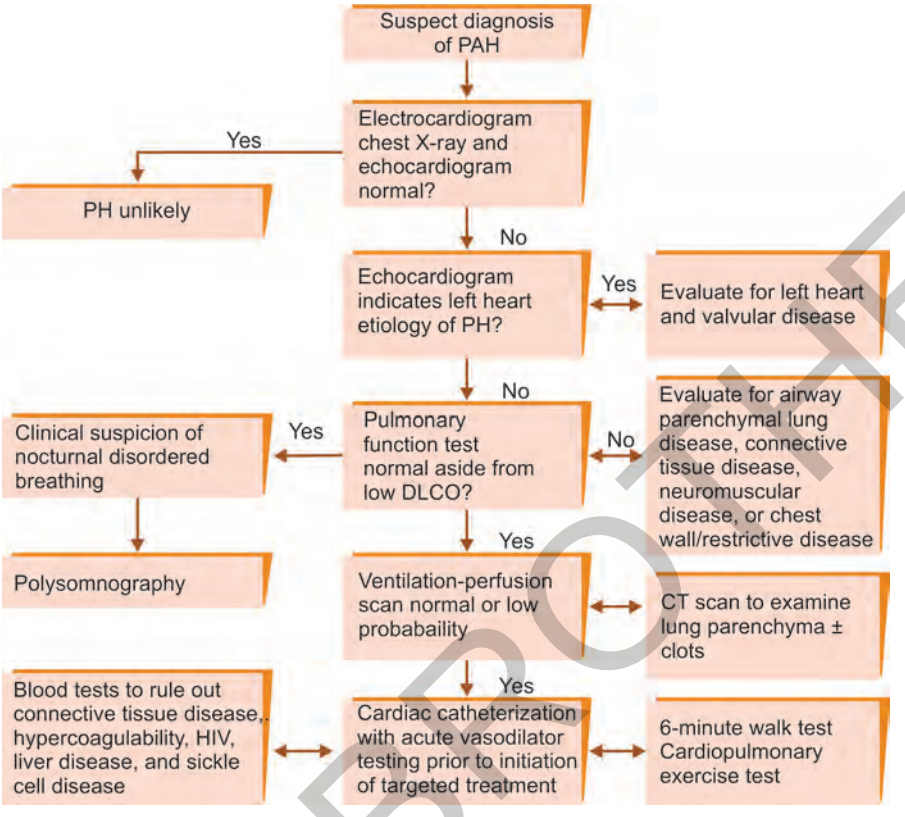
Patients with PH who are selected for advanced therapy should undergo an invasive hemodynamic assessment and should undergo a vasoreactivity test (detailed below). Patients with positive vasoreactivity test are candidates of oral CCB therapy with a dihydropyridine or *diltiazem*. Patients with a negative vasoreactivity test require advanced therapy with a prostanoid, endothelin receptor antagonist, or phosphodiesterase type 5 inhibitor. Combination therapy may be appropriate in refractory cases. In patients with treatment refractory to medical therapy lung transplantation or creation of a right to left shunt by atrial septostomy may be considered.[8] An algorithm for advanced therapy is shown in Flow chart 2.1.

***Vasoreactivity test*:** Patients of group 1 PAH should undergo a vasoreactivity test with *Epoprostenol*, adenosine, or inhaled nitric oxide[31]:

- *Epoprostenol*: Infusion is started at 1–2 ng/kg per minutes, increased gradually by 2 ng/kg per minute every 5–10 minutes until a clinically significant fall in blood pressure, an increase in heart rate, or adverse symptoms (e.g. nausea, vomiting, and headache) develop.
- Adenosine is administered intravenously at 50 μg/kg per minute and increased every 2 minutes to a maximal dose of 200–350 μg/kg per minute. As a practical guide starting

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Flow chart 2.1 An algorithm for advanced therapy



the undiluted adenosine (1 mL = 3 mg) at the body weight per mL gives the requisite dose at 50 µg/kg per minute, e.g. for a 60 kg adult 60 mL/h of adenosine (strength 1 mL = 3 mg) gives 50 µg/kg per minute. This starting dose can be appropriately increased.

- Inhaled nitric oxide is administered at 10–20 ppm may be used.[31–36]
- Vasoreactivity test is considered positive if mean PA pressure decreases at least 10 mm Hg and to a value <40 mm Hg, with an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure. Patients with porto-PH should not undergo vasoreactivity testing, as they are at increased risk of adverse sequelae from pure vasodilator therapy.

Calcium-channel blockers (CCB):[37-42] Patients with reactive vasodilator response may be considered for treatment with CCBs like dihydropyridine or *diltiazem*.[12,37–39] The CCB therapy can be initiated with either long-acting *nifedipine* (30 mg/day) or *diltiazem* (120 mg/day), and gradually increased to maximal dose. Systemic blood pressure, heart rate, and oxygen saturation should be carefully monitored during titration. Long-acting dihydropyridine like *amlodipine* is a useful alternative for patients who are intolerant of the other agents. Patients who respond to CCB therapy with a dihydropyridine or *diltiazem* (defined as asymptomatic or minimal symptoms) should be reassessed after 3–6 months of treatment. Patients on CCB have been shown to have better quality of life with improved functional class and survival than nonresponders.

***Prostanoids*:** Prostanoid formulations include intravenous *Epoprostenol* (prostacyclin), intravenous *treprostinil*, subcutaneous treprostinil, inhaled treprostinil, and inhaled Iloprost.[43,44] All of the prostanoid formulations have the limitations of a short half-life and a heterogeneous response to therapy.

***Epoprostenol (Flolan)*:** It is available for intravenous use. It improves hemodynamic parameters, functional capacity, and survival in patients with idiopathic pulmonary arterial hypertension (IPAH).[45–49] It is delivered continuously through an implanted central venous catheter using a portable infusion pump, usually initiated at doses of 1–2 ng/kg per minute and increased as per tolerance by 1–2 ng/kg per minute every 1–2 days. Once an initial level of 6–10 ng/kg per minute is achieved (usually within 1–2 weeks), most patients require dose increases of 1–2 ng/kg per minute every 2–4 weeks to sustain the clinical effect. In children,

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the maintenance dosage is higher than in adults. A maximal dose has not been established.[50-54] Side effects include jaw pain, foot pain, poorly defined gastropathy, diarrhea, and arthralgias. Also are the side effects of the delivery systems including thrombosis, pump malfunction, and interruption of the infusion. Central venous catheter infection can also contribute to the morbidity and mortality of continuous *Epoprostenol* therapy.[55,56]

***Treprostinil (Remodulin)*:**[57-63] It is administered intravenously, subcutaneously and recently inhaled. Subcutaneous administration is uncommon due to severe pain at the injection site. It improves hemodynamic parameters, symptoms, exercise capacity, and possibly survival in patients with group 1.[44,57-59] It has not been evaluated in patients with other types of PH.

There are no available trials comparing *Epoprostenol* to *treprostinil*. Advantages of parenteral treprostinil, compared to Epoprostenol, include the option of continuous subcutaneous delivery, a longer half-life (4 hours) that may make interruption of the infusion less immediately life-threatening, and no need for refrigeration. All of these advantages allow more flexibility and easier administration. For patients who desire the advantages associated with treprostinil administration, it can be offered as first-line therapy. Based upon preliminary results, patients who are already receiving Epoprostenol generally can be transitioned to treprostinil (subcutaneous or intravenous) without a significant loss of clinical efficacy.[60,61] Reciprocally, Epoprostenol can be given if the desired effect is not achieved with treprostinil.

Iloprost (Ventavis)[64] is administered via inhalational route. It is thus selective to lung vasculature without systemic side effects, but it requires frequent administration (6–9 up to 12 times per day).

***Beraprost*:** It is orally active prostacyclin analog. In a large European trial (ALPHABET), it improved exercise capacity over 12 weeks period, but large scale trials are needed especially for children.

Endothelin Receptor Antagonists

Endothelin-1 is a smooth muscle mitogen and a potent vasoconstrictor.[65-67] The endothelin receptor antagonists improved exercise capacity, dyspnea, and hemodynamic measures (PA pressure, pulmonary vascular resistance, and cardiac index).

Bosentan (Bosentas) is a nonselective endothelin receptor antagonist.[68–71] It is administered orally. In BREATHE-1 trial, Bosentan improved symptoms, the 6-minute walking distance, and the WHO functional class.

Selective agents include type A endothelin-1 receptor antagonists administered orally including *ambrisentan* (Volibris, Endobloc) and Sitaxsentan. The ARIES-1 and ARIES-2 trials suggest that ambrisentan[72–74] and sitaxsentan[75–78] improve exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PH. Hepatotoxicity is the main adverse effect of some endothelin receptor antagonists. It was for this reason the sitaxsentan was withdrawn from the market.[79–81] Liver function tests should be monitored monthly during treatment with Bosentan, but monitoring of LFTs is no longer required for patients treated with ambrisentan. Side effects include peripheral edema. Mild cases of edema can be managed with diuretics, but more severe cases warrant discontinuation of the medication. Endothelin receptor antagonists are also potent teratogens hence requiring meticulous contraception in childbearing age group.[82]

***PDE5 inhibitors*:** *Sildenafil* (Assurans, Viagra, Revatio), *Tadalafil* (Cialis, Adcirca), and *Vardenafil* (Levitra) are orally administered cyclic GMP phosphodiesterase type 5 (PDE5) inhibitors.

- *Sildenafil* improves pulmonary hemodynamics and exercise capacity in patients with group 1.[83–86] In SUPER-1 trial the Sildenafil demonstrated significant improvement in hemodynamics and 6-minute walk distances, which persisted during 1 year of follow-up.[85] Mortality was not reported. In SUPER-2 trial,[87] there was persistent improvement in the 6-minute walk distance and WHO functional class of 46% and 29% of patients, respectively, compared with the baseline values measured prior to the SUPER-1 trial. The estimated 3-year survival rate was 79%. *Tadalafil* and *Vardenafil* also appear to improve outcomes in patients with group 1. The PHIRST done with Tadalafil (40 mg) showed significantly increased the 6-minute walk distance and the time to clinical worsening, while decreasing the incidence of clinical worsening and improving health-related quality of life. This improvement of the 6-minute walk distance was sustained for an additional 52 weeks in the PHIRST-2 trial, an uncontrolled extension trial. Similar response has been shown with Vardenafil.[88-90]

***Guanylate cyclase stimulant*:** Stimulators of the nitric oxide receptor, soluble guanylate cyclase (sGC) have dual mode of action. They increase the sensitivity of sGC to endogenous nitric oxide (NO), a pulmonary vasodilator, and they also directly stimulate the receptor to mimic the action of NO.

Riociguat[91] had a favorable safety profile and was well tolerated, with dyspepsia, headache, and hypotension as the most frequent side effects. Preliminary results from phase III randomized placebo-controlled trials of riociguat in patients with PAH (PATENT-1) and inoperable CTEPH (CHEST-1), also suggest similar benefit.[92–94]

Dosage of various drugs is tabulated in Table 2.6.

Combination Therapy

Combining pharmacologic agents with different mechanisms of action may produce an additive effect as under:

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Ashok Seth is the Chairman, Interventional Cardiology, Fortis Escorts Heart Institute and Research Center, New Delhi, India; and Head, Cardiology Council, Fortis Group of Hospitals. During his career span of 26 years, he has pioneered numerous angioplasty techniques—Directional Atherectomy, Angioscopy, Stents, Thrombectomy Devices and Drug-eluting Stents, Use of Impella Heart Support Device Failing Heart, Bioabsorbable Stents and Transcatheter Aortic Valve Implantation (TAVI) and implemented it successfully both in India and other regions in Asia Pacific. He has performed one of the highest number of angiographies and angioplasties which has been mentioned in the 'Limca Book of Records'.

He has been a part of the Focused Advisory Group and seminal studies for development and clinical applicability of Bioresorbable Scaffold (BRS) stent, which is highly recognized technique worldwide.

For his unique achievements and contributions, he has been honored with the prestigious National Honor of Padma Bhushan and Padma Shri Award by the President of India in 2015 and 2003 respectively, the National Award of Republic of Spain Officer's Cross Order of Isabella the Catholic in 2010, 'Mason Sones Award' from SCAI (USA) in 2010 and numerous other awards.

He has been the President of the Cardiological Society of India and Vice President of the Asian Pacific Society of Cardiology. He was elected Board of Trustee of SCAI (USA) for the period 2007–2010, and is presently a member of the SCAI Nominating Committee and Voting Selector of the MSCAI Nominating Committee. He has been invited to lecture on and demonstrate complex angioplasty techniques in more than 400 international training courses and meetings across the globe including live transmissions of complex cases from India to the TCT and EuroPCR Meetings. He is on the Editorial Board of JACC—Cardiovascular Interventions, Catheterization and Cardiovascular Interventions (CCI), Euro Intervention, Indian Heart Journal and others.

He has been honored Doctorate from four prestigious Universities in India. He has more than 250 publications to his credit in prestigious Indian and International medical journals, written and edited chapters in 10 textbooks of Cardiology and Medicine and edited two books in Cardiology. He has trained more than 350 cardiologists from India and abroad in advance techniques of angioplasty.



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