Chapter 27

Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a syndrome resulting from decreased flow of blood in the pulmonary vasculature due to increased vascular resistance. There are an intimal hyperplasia, medial hypertrophy and adventitial proliferation. The revised World Health Organization (WHO) Classification has divided pulmonary hypertension (PH) into five types. The incidence of PAH is 15/million in the population. The diagnosis of PAH is established by clinical examination, Doppler echocardiography and right heart catheterization (RHC). Acute vasodilator testing is done to assess the responsiveness of calcium channel blockers. In high-risk patients intravenous prostanoids should be started as an initial therapy followed by endothelin receptor antagonists. In the low-risk patients, oral endothelin receptor antagonists may be started, failing which intravenous prostanoids may be replaced. Phosphodiesterase-5 (PDE-5) inhibitor may be used as additional agents.

In severely ill patients with advanced right heart failure invasive therapies like atrial septostomy, heart-lung transplantation, pulmonary thromboembolectomy and right ventricular assist device may be tried.

INTRODUCTION

Pulmonary arterial hypertension is a syndrome resulting from restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance (PVR) and ultimately right heart failure. Multiple pathogenic pathways have been implicated in the development of PAH including those at molecular and genetic levels, in the smooth muscles, endothelial cells and adventitia. The imbalance in the vasoconstrictor and vasodilator milieu has served as the basis for current medical therapies. Recent advances have led to increased recognition and new therapies. While some data exist to form guidelines, other areas have been inadequately explored.

PATHOLOGY AND PATHOGENESIS

Pulmonary arterial hypertension is associated with increased PVR resulting from loss of vascular luminal cross-section due to vascular remodeling produced by excessive cell proliferation and reduced rate of apoptosis, although excessive vasoconstriction plays a significant role in approximately 20% of patients.

Pulmonary arterial hypertension is a panvasculopathy predominantly affecting small pulmonary arteries (resistant vessels). Pulmonary arterial hypertension is characterized by a variety of arterial abnormalities including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation and plexiform arteriopathy. An individual patient may manifest all these lesions and the distribution of the lesion may be diffuse or focal.

Right ventricle (RV) function is a major determinant of functional capacity and prognosis in PAH (1) while RV hypertrophy and dilatation is initiated by increased after load, the adequacy of RVs compensatory response is quite variable amongst individuals. Right ventricle function could potentially be improved by effective therapies to regress pulmonary vascular obstruction or by directly improving RV contractile function.

Pulmonary arterial hypertension is characterized by endothelial dysfunction, a decreased ratio of apoptosis/proliferation in pulmonary artery smooth muscle cells (PASMCs) and thickened disordered adventitia in which there is excessive activation of adventitial metalloproteases. It is a multigenic disorder particularly familial PAH (FPAH). Two genes like bone morphogenetic protein receptor type 2 (BMPR-2) and activin like kinase-1 have been implicated in the pathogenesis of FPAH. In the vascular lumen, PAH is characterized by platelets that are depleted of serotonin and elevation of plasma serotonin. In PAH, endothelial dysfunction is characterized by increased production of vasoconstrictor/mitogenic compounds such as endothelin and thromboxane and deficient production of vasodilators like prostanoids. In PAH, there is increased production of thromboxane A2 and deficient prostacyclin leading to thrombosis, proliferation and vasoconstriction. Endothelin-1 level is also increased in PAH. Decreased level of endothelial nitric oxide (NO) has been observed in PAH as it is quickly inactivated by PDE-5. Autoantibodies/proinflammatory cytokines and inflammatory infiltrates have been observed in some cases of PAH suggesting that inflammation may contribute to the development of some forms of PAH. The PASMCs in PAH also display excessive proliferation in response to transforming growth factor-β, and this propensity to accumulate unwanted cells is exacerbated by impaired smooth muscle cell apoptosis. In PAH, the adventitia is fragmented, permitting cell migration and creating mitogenic peptides such as tenoscin.

CLASSIFICATION

Revised WHO classification of PH is illustrated in Table 1.

Epidemiology

Prevalence of PAH is about 15/million and IPAH is 6/million. Familial PAH is found in 6–10% of PAH. The incidence of PAH in human immunodeficiency virus (HIV) individual is 0.5% or 6–12 times that of general population. The prevalence of PAH in patients...
of cirrhosis is 2–6%. The prevalence of PAH in sickle cell disease is about 30%. The prevalence of PAH in systemic sclerosis 32–3%. From India, Rahul Mehrotra, et al. 2012 reported 57 patients of PH. Type-I was the most common (72%) and Type-II are the second most (16%), common form of PH in their registry. Type-III and Type-IV were less common (5 and 7% respectively) whereas no patient was found in Type-V PH.

### DIAGNOSIS

**Detection**

- **Symptom evaluation:** Symptoms that suggest PH are exertional dyspnea, fatigue or weakness, angina, syncope, peripheral edema and abdominal distension
- **Screening of susceptible persons:** With a known genetic mutation with PAH or first degree relative of IPAH, scleroderma spectrum of diseases, patient with congenital heart disease and patient with portal hypertension
- **Incidental history:** During Doppler echocardiography pulmonary artery systolic pressure (PASP) greater than 35 mm Hg or mean greater than 25 mm Hg, one can go for RHC.

### DETECTION ASSESSMENT

**Physical Examination**

Left parasternal lift, accentuated pulmonary component of P2, tricuspid regurgitation murmur, pulmonary early diastolic murmur, right ventricular S3, raised jugular venous pressure (JVP), hepatomegaly, peripheral edema and ascites with abnormal chest X-ray, electrocardiography (ECG) and Doppler echocardiography. Transthoracic Doppler echocardiography estimates PASP and can provide additional information about the cause and consequences of PH.

### ESSENTIAL TESTS

Certain tests are essential to characterize potential substrates to determine severity and prognosis accurately and to settle treatment.

### PROGNOSTIC FACTORS ASSESSMENT (TABLE 2)

**Functional class:** New York Heart Association (NYHA) functional class III and IV have lower survival than class I and II, i.e. 2.5 years versus 6 years. Six-minute work test was found to be an independent predictor of survival leading to use of this test as the primary end point for many prospective trials. The three hemodynamics variables were associated with increased risk of death like increased mean pulmonary artery pressure (MPAP), increased mean right atrial pressure (RAP) and cardiac index. The presence of any degree of pericardial effusion and Doppler echocardiographic index (Tei-index) is predictive of an adverse outcome. Brain natriuretic peptide and N-terminal-pro brain natriuretic peptide (NT-pro BNP) are better independent predictors of survival. Increased uric acids, detectable troponin T also independently correlate with mortality.

### Acute Vasodilator Testing

The rational for vasodilator testing in the diagnostic evaluation of PAH patients is based on two factors: (1) Acute vasodilator responsiveness identifies patients with a better prognosis and (2) Responders are more likely to have a sustained beneficial response to oral calcium channel blockers than nonresponders and would be treated with these less expensive drugs.

### Agents for Acute Vasodilator Testing

Agents for acute vasodilator testing are: Nitric oxide: 20–40 ppm for 5 minutes, intravenous epoprostenol, intravenous adenosine, American College of Clinical Pharmacy (ACCP) guidelines proposed that an acute response to vasodilator testing be defined as a decrease
in MPAP by at least 10 mm Hg or an absolute level of less than 40 mm Hg without a decrease in cardiac output (CO).

**TREATMENT GOALS**

The treatment goal is to improve patient symptoms, enhance functional capacity (lower MPAP) and normalize CO, to reverse or at least prevent progression of the disease and improve survival (Flow chart 1).

**General Measures**

Patients are advised to have low-graded exercise such as walking as tolerated. Avoid heavy physical exertion, avoid exposure to high altitude, sodium-restricted diet less than 2.4 gm/day, immunization against influenza and pneumococcal pneumonia, anticoagulation—international normalized ratio (INR) 1.5–2.5 with warfarin, diuretics in RV volume overload, O₂ supplementation to keep O₂ saturation greater than 90%, digoxin in right heart failure, low CO states and atrial arrhythmias.

**Calcium Channel Blockers**

Patients of IPAH who have a good vasodilator response may be treated with calcium channel blockers. If the patient does not improve to functional class I-III on calcium-channel blocker therapy, the patient should not be considered a chronic responder and alternative or additional PAH therapy should be instituted long-acting nifedipine, diltiazem or amlodipine are the most commonly used calcium-channel blockers.

**Prostanoids**

Prostacycline synthetase is reduced in PAH patients, resulting in inadequate production of prostacyclin I₂, a vasodilator with antiproliferative effects. There are three commercially available prostanoids: (1) Epoprostenol; (2) Trepostinil and (3) Iloprost.

**Epoprostenol**

Epoprostenol improves function class, exercise tolerance, hemodynamics and survival in IPAH. In the series of 178, functional class III and IV IPAH patients, Sitbon et al.²⁹ reported improved survival with intravenous (IV) epoprostenol compared to historical controls with 1, 2, 3 and 5 years survival rates of 86%, 70%, 63% and 55% respectively. Intravenous epoprostenol has also been evaluated in PAH associated with scleroderma spectrum of diseases. The drug should be delivered by continuous intravenous infusion in the hospital at a dose of 2 ng/kg/min and the dose is further adjusted based on symptoms of PAH and side effects of the drugs. Optimal dose range for chronic therapy is between 25 and 40 ng/kg/min for most adult patients. Side effects are headache, jaw pain, flushing, nausea, diarrhea, skin rash and musculoskeletal pain.

**Trepostinil**

Trepostinil used in II, III and IV functional class of PAH. Tapson et al.²⁹ reported 82% improvement of 6MWT in 16 functional class III or IV PAH patients treated with intravenous trepostinil as monotherapy. In 2004, Food and Drug Administration (FDA) approved the use of intravenous trepostinil in functional class II, III and IV PAH patients. Side effects are similar to intravenous epoprostenol.

**Iloprost**

Iloprost is a prostanoïd drug given by adaptive aerosol device. In a more recently, trial Opitz et al.³⁰ reported event free survival rate of 53%, 24% and 20% at 1, 2 and 3 years respectively in IPAH patients treated with iloprost monotherapy. Common side effects include cough, headache and flushing and jaw pain. It was approved for functional class III and IV PAH by FDA in 2004.

**Endothelin Receptor Antagonists**

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH.

**Bosentan**

In a double blind controlled study³¹ of 32 functional classes of III or IV IPAH and other PAH were randomized to receive bosentan and placebo. After 12 weeks, the 6MWT improved by 70 M in the bosentan arm whereas no improvement was seen in the placebo. FDA approved the dose of bosentan 12.5 mg twice daily. It is currently widely used in patients with PAH. Food and Drug Administration recommends LFT be checked monthly and hematocrit 3 monthly.

**Sitaxsentan**

It is more selective for endothelin A (ETA) receptor. In a randomized placebo controlled double blind trial [sitaxsentan to relieve impaired exercise 1 (STRIDE-1)], 178 NYHA functional class II, II and IV patients with either IPAH, PAH related to connective tissue disease or congenital shunt equally randomized to receive placebo. Sitaxsentan 100 mg or sitaxsentan 300 mg orally once daily. Sitaxsentan improved exercise capacity as assessed by 6MWT and functional class after 12 weeks of treatment. The incidence of liver function abnormalities
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were more favorable for the 100 mg dose. In an earlier study, sitaxsentan was associated with fatal hepatitis when used at higher dose.20

**Ambrisentan**
It is a relative selective antagonist of ETA receptor. Two phase-II pivotal trials of ambrisentan in PAH have been completed and randomized 202 and 192 patients with PAH respectively to placebo or ambrisentan. Dose of 5 and 10 mg ambrisentan was compared with placebo in ARIES. After 12 weeks, there were improvements in primary end points of 6MWT in both studies. The change in mean 6MWT in ARIES-1 was plus 22.8 M and plus 43.6 M for the 5 and 10 mg doses respectively and minus 7.8 M in the placebo group. In the ARIES-2, it was plus 22.2 M and plus 49.4 M for the 2.5 mg and 5 mg doses respectively and minus 10.1 M in the placebo group. Ambrisentan was approved by FDA in June 2007 for PAH patients with functional class II or III symptoms.

**Phosphodiesterase Inhibitors**
Nitric oxide activates guanylate cyclase which increases cyclic guanosine monophosphate (GMP) production. Cyclic GMP causes vasorelaxation but its effects are short-lived due to the rapid degradation by PDE-5. Therefore, PDE-5 inhibitor such as sildenafil and tadalafil might be expected to enhance or prolong the effects of these vasodilating cyclic nucleotides.

**Sildenafil**
The super-1 study was randomized double-blind, placebo controlled trial that assigned 278 patients with PAH to placebo or sildenafil (20, 40 or 80 mg) orally 3 times daily for 12 weeks.21 The 6MWT increased from base line in all sildenafil groups with mean placebo-corrected treatment effects of 45, 46 and 50 M for 20 mg, 40 mg and 80 mg doses of sildenafil, respectively. There was little change in the placebo group. Food and Drug Administration approved dose of sildenafil in patients with PAH is 20 mg administered orally 3 times daily.

In the study of BK Sastry et al. 2007, 39 patients of IPAH receiving conventional therapy were compared with 139 patients of IPAH receiving additional sildenafil. The survival was 89%, 43% and 19% in the control group vs 93%, 75% and 54% in the sildenafil group at the end of 1, 3 and 5 years respectively. There was improvement of symptoms.22

**Tadalafil**
It has been approved by FDA for erectile dysfunction. It is a PDE inhibitor and its role in PAH is under evaluation.

**Combination Therapy**
The goal is to maximize efficacy and minimize toxicity. Most recently the addition of sildenafil or placebo was evaluated in 207 PAH patients who remained symptomatic with a 6MWT of 100–450 M while on a stable dose of intravenous epoprostenol for at least 3 M.23 Patients treated with sildenafil experienced a placebo-adjusted improvement 6MWT of 288 at 16 weeks as well as improvement in MPAP, CO and time to clinical worsening. So many randomized studies are going on for further opinion.

**Invasive Therapies**
Despite advances in the medical management of PAH many patients experience progressive functional decline, largely related to worsening of right heart failure. In these patients surgical therapies may be considered like atrial septostomy, heart and lung transplantation, surgical thromboendarterectomy.24 Other surgical approach like BV mechanical assistance is under investigation.

**Atrial Septostomy**
Atrial septostomy creates a right to left interatrial shunt, decreasing right heart filling pressures and improving right heart function and left heart filling. The CO improves by 15–60% in some series,
besides improvement of NYHA class and 6MWT.²⁵ Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure.

**Lung and Combined Heart-Lung Transplantation**

Currently, 1,700 single lung, double lung and combined heart and lung transplants annually performed would aid in adults are for primary indication of PAH.²⁶ The survival rate were 1, 3, 5 and 10 years in 66%, 57%, 47% and 27% respectively in PAH patients undergoing transplantation. Single lung transplantation (SLTx) and double lung transplantation (DLTx) is done in patients with PAH with better cardiac performance. In patients with severe cardiac decompensation or with coronary heart disease (CHD) and heart-lung transplantation (HLTxs) is preferred.

**Pulmonary Thromboendarterectomy**

If CTEPH is the cause of PAH and patients are evaluated by angiogram to have surgical accessible disease, then they can undergo thromboendarterectomy. The goal of pulmonary thromboendarterectomy (PTE) is to remove sufficient material from pulmonary arteries to substantially lower PVR and improve CO. This is done in high-volume centers.²⁷

**Right Ventricular Assist Device**

Development of refractory, right heart failure portends a grave prognosis in patients with PAH. Preclinical studies are suggested the usefulness of right ventricular assist support in model of PH.²⁸²⁹

**REFERENCES**