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Primary pulmonary hypertension and its management: A complete review

[1]Dr.SUMIT PRATAP SINGH, [2]Dr.MAYANK YADAV, [3]Dr.BHARAT SIDDHARTH, [4]Dr.MOHD AZAM HASEEN, [5]Dr.RENU YADAV

[1]Assistant Professor, [2]Assistant Professor, [3]Senior Resident, [4]Associate Professor, [5]Senior Resident

[1]JNMC,AMU,Aligarh,

[2]JNMC,AMU,Aligarh,

[3]AIIMS,New Delhi,

[4]JNMC,AMU,Aligarh,

[5]VMMC,New Delhi

Abstract

Idiopathic pulmonary arterial hypertension (IPAH) can present at any age from infancy to adulthood and remains a progressive fatal disease. Right ventricular (RV) function is the most important determinant of the prognosis. Although there is no curative treatment available for IPAH, the therapeutic options available are pharmacological treatment with drugs, surgical treatment with lung or heart- lung transplantation and the newly devised interventional therapy includes the Potts shunt(PS). Potts shunt has emerged as a new surgical alternative to lung or heart-lung transplantation with prolonged survival and persistent improvement in functional capacities. This article will highlight the current status of different treatment options available for IPAH with their results.

Key words- primary pulmonary hypertension, potts shunt, lung transplant

Introduction

Pulmonary artery hypertension(PAH) is a progressive pulmonary vasculopathy which if left untreated has got very poor prognosis both in terms of morbidity and mortality[1].

Definition

The definition of pulmonary hypertension (PH) is usually defined as a mean pulmonary artery pressure (mPAP) greater than 20 mm Hg at rest as per the Sixth World Symposium on Pulmonary Hypertension in 2018[2], >25 mm Hg at rest (according to the 2015 European Society of Cardiology European Respiratory Society guidelines[3], measured by cardiac catheterization. PAH is the precapillary PH—that is, a pulmonary artery pressure >25 mmHg with a normal pulmonary artery occlusion pressure or left atrial pressure (<15 mmHg)[4].

Pathophysiology

The basis of PH pathophysiology can be defined as a lethal viscous cycle starting with increased pulmonary vascular resistance leading to increased right ventricular performance and oxygen consumption with resultant right ventricular hypertrophy and dilatation, leading to decreased cardiac output and eventual right ventricular failure (Figure 1)[5,6]. To maintain the cardiac output, the right ventricle pressure increases in response to the increase in the pulmonary circulation resistance. Progressive remodeling of pulmonary vascular system occurs over course of time which further promotes PH. The anatomical structure and geometry of RV is designed in such a manner that it can adapt to a wide range of variation in preload but it does not respond adequately to increase in afterload. Right ventricular hypertrophy due to increased wall stress occurs in response to chronic pressure overload (Laplace's Law)[6]. With increasing afterload, right ventricular stroke volume decreases linearly and eventual ventricular dilatation occurs leading to decrease in right ventricular coronary blood flow, when oxygen consumption is increased[7]. Furthermore, right ventricular dilatation shifts the interventricular septum to the left, decreasing left ventricular preload and compliance and thus cardiac output leading to inadequate right ventricular coronary blood and ultimately right ventricular failure [7].

Presenting signs and symptoms

Exertional dyspnea is the most frequent symptom in patients with PH although patients may present with a myriad of cardiopulmonary symptoms. In early stages PH is usually asymptomatic and later may present as chest pain and syncope. Symptoms like peripheral edema or ascites develops once RV dilatation and right heart failure sets in. Physical examination findings include increased jugular venous pressure, a reduced carotid pulse, and a palpable right ventricular impulse. An increased pulmonic component of the second heart sound, a right sided fourth heart sound, and murmur of tricuspid regurgitation can be heard.

Diagnosis

Right heart catheterization in PH not only confirms the diagnosis but also quantifies the degree of pulmonary hypertension (measurement of pulmonary artery pressure, cardiac output, and left ventricular filling pressure, underlying cardiac shunt) and can undertake acute vasodilator testing. Acute vasodilator testing, during catheterization defines the extent of pulmonary vasodilator reactivity and helps to decide suitable treatment plan. Inhaled nitric oxide (NO) is usually used as pulmonary vasodilator (10-80 ppm)[8]. A positive vasodilator response is defined as a decrease of at least 10 mmHg in mean PAP and achieving a mean PAP <40 mmHg, an increase or no change in cardiac output with no significant fall in blood pressure[9]. Patients who respond to acute vasodilator therapy can often be treated with calcium channel blockers and have a more favorable prognosis[10]. Echocardiography is also helpful in confirming the diagnosis and excluding left-sided lesions as the cause of PH but is not specific enough to confirm a diagnosis of PH alone.

Severity of disease

Severity of disease is determined according to World Health Organization (WHO) functional class. Patients in functional class IV have lower exercise capacity (as measured by the 6-min walking distance (6MWD)), higher right atrial pressure (RAP), lower cardiac index, increased pulmonary vascular resistance index and lower peak oxygen consumption compared with patients in functional class I–III[11,12].

Prognosis

RV function is the most important determinant of the prognosis in patients with PAH[13-15]. The degree to which the right ventricle responds to such changes is dependent upon the age of the patient and rapidity of onset of PH.

The natural history of PH is dismal, with a reported median survival rate of 2.8 years when untreated[16]. Functional class remains a strong predictor of survival, with patients who are in NYHA functional class IV having a mean survival of less than six months. The cause of death is usually right ventricular failure, which is manifest by progressive hypoxemia, tachycardia, hypotension, and edema.

Treatment strategies :

The aim of current treatment strategies is to preserve the RV function by reducing the pulmonary vascular resistance and RV load. Here, we review the treatment options in patients with severe PAH, the assessment and selection of suitable treatment strategy and the various bridging techniques to lung transplant available.

At the 5th World Symposium on Pulmonary Hypertension 2013 in Nice, France, a consensus algorithm for the treatment of pediatric IPAH/familial PAH was published as shown below[1](figure 2).

Pharmacological therapy:

In the last two decades there has been marked advancement in the medical management with significant improvement in the survival of patients with pulmonary hypertension, which can be seen by the ever-decreasing number of patients with PH who ultimately undergo transplantation. In 1990, approximately 10.5% of all lung transplants were for patients with PH whereas in 2001 only 3.6% of all lung transplants were performed in patients with this condition and most recently, 3.3% as reported by the ISHLT Transplant Registry in 2010[17,18].

Currently available oral and parenteral drugs mainly targets the three pathways:

I. Nitric oxide (NO) pathway

II. Endothelin pathway

III. Prostacyclin pathway

Phosphodiesterase 5 inhibitors

Sildenafil is an orally active, potent, and selective inhibitor of phosphodiesterase 5, resulting in vasodilatation and antiproliferative effects through the nitric oxide–cGMP (cyclic guanosine-3′,5′-monophosphate) pathway within the pulmonary vasculature and has shown beneficial effects on exercise capacity, symptoms, and haemodynamics after numerous retrospective, observational as well as small, nonrandomized, prospective studies[19,20].

As phosphodiesterase 5 is highly expressed in the hypertrophied human right ventricle, sildenafil have positive ancillary effects on the right ventricular myocardium in PAH as validated by various studies[21,22].

Tadalafil, a selective phosphodiesterase 5 inhibitor has longer duration of action than that of sildenafil, thus once-daily dosing is required. It has shown to improve exercise capacity and quality-of-life measures and to reduce clinical worsening[23].

Endothelin-receptor antagonists

In PAH endothelin system activates, resulting in vasoconstrictor and mitogenic effects[24]. Bosentan is an orally active, dual endothelin A-receptor and endothelin B-receptor antagonist, and has shown improvements in exercise capacity, WHO functional class, haemodynamics, echocardiographic variables, and time to clinical worsening[25-27]. Elevation in hepatic aminotransferases can occur as an adverse effect, but more rarely than in adults.

Ambrisentan is a selective endothelin A-receptor antagonist used in adult patients with PAH and was found to improve

symptoms, exercise capacity, haemodynamics, and time to clinical worsening[28,29]. An increased incidence of peripheral oedema has been reported, but the adverse effect on liver-function tests was not noted[30]. It is safe in paediatric patients with similar pharmacokinetics to those in adult[31].

Prostanoids

Prostacyclin is expressed in vascular endothelial cells and is a potent vasodilator, and might also have cytoprotective and antiproliferative effects. Epoprostenol is a synthetic prostacyclin with a short half-life (3–5 min), administered intravenously by an infusion pump via a central venous catheter, and has been shown to improve symptoms, exercise capacity, and haemodynamics in patients with PAH[32-34]. Continuously applied intravenous epoprostenol is still considered the most effective drug to treat severe PAH in children[32,34].

Iloprost is a chemically stable prostacyclin analogue available in intravenous, oral, and inhalative administration. Inhaled iloprost in adults with PAH is associated with improved symptoms, pulmonary vascular resistance and exercise capacity[35].

RECENT DRUG DEVELOPMENT FOR PAH THERAPY

Continious advancement in the pharmacological therapy has led to the development of new drugs for improved outcome in patients with PAH.

Macitentan, a novel dual endothelin-receptor antagonist developed by modifying the structure of bosentan, has improved receptor-binding capacity and fewer drug–drug interactions than bosentan[36,37]. It has shown to reduce the morbidity and mortality in adult patients with PAH significantly. The drug is associated with the risk of anaemia, however no liver toxicity was observed[38].

Riociguat, an oral agent which acts in synergy with endogenous nitric oxide and also directly stimulates soluble guanylyl cyclase independently of nitric oxide availability, has shown to improve haemodynamics, WHO functional class, and time to clinical worsening[39].

Imatinib is an antiproliferative agent that target tyrosine kinase, has shown to improve exercise capacity and haemodynamics, although the long-term safety of imatinib in patients with PAH is unclear[40].

Selexipag is an orally active, selective prostacyclin-receptor agonist with high functional selectivity for the receptor. Selexipag has shown to reduce pulmonary vascular resistance after 17 weeks, compared with placebo[41].

β-blockers seems to have an indirect beneficial role in PAH patients by improving ventricular filling by decreasing heart rate and extending the duration of diastole[42,43]. Although its negative inotropic effect is a potential concern, requiring further research for its use in patients with PAH[44].

Interventional and surgical therapies

Although there has been significant improvement in the survival as well as quality of life due to the marked advancement in the medical management of PAH, progression of the disease in some patients still leads to overt right ventricular failure, a low systemic cardiac output, recurrent syncope, and even death[16]. For these refractory PAH cases various intervention options have been propose based on the idea that patients with Eisenmenger syndrome often have better right ventricular function and longer survival than patients with severe IPAH[45,46]. Thus, conversion of these patients to an Eisenmenger physiology can be achieved by creating a right to left shunt in the form of atrial septostomy or pott's shunt, with the aim of decompressing right heart structures and increasing systemic cardiac output. These transcatheter or surgical interventions are currently performed as life saving palliative procedures, or for bridging to lung or combined heart lung transplantation.

Atrial Septostomy

Atrial septostomy is an interventional technique that can be used as a palliative therapy in the management of patients with advanced PH with a failing right ventricle[47,48] already on combined medical therapy, as well as a palliative bridge to transplantation to increase the likelihood of survival while waiting for a donor organ[49-51]. Austen[93] first proposed that the surgical creation of an ASD should be performed for the management of patients with primary pulmonary hypertension (PPH), after which Rich and Lam[52] were the first to perform this intervention nonsurgically, since then continuous improvements in transcatheter techniques have been made.

By creating an interatrial communication, a right to left shunt will occur leading to decompression of the right atrium and ventricle[52]. This acute pressure unloading shifts the right ventricular pressure-volume loop to the left, increases left ventricular preload and systemic output, and thereby avoids a potentially fatal deterioration in right ventricular performance. Pulmonary haemodynamics-pulmonary artery pressures and pulmonary vascular resistance-are not affected by this intervention, but sympathetic overactivity will decrease[51,53]. Besides these acute haemodynamic effects, the long-term benefit of atrial septostomy includes the relief of syncope and an increase in exercise capacity by maintaining systemic blood pressure during exercise and pulmonary hypertensive crisis[48,51].

As spontaneous closure of the created defect occurs in ~10% of patients, the procedure can be repeated, and stent devices can be implanted to keep the communication patent[47,48,50].

Procedure-related mortality across centers worldwide was reported to be quite high (7.1% at 24 h and 14.8% at 1 month; median survival 60 months)[50]; however, in expert centers and selected patients on PAH-targeted therapy, AS-related mortality was <1% [54,55].

Reverse Potts shunt

The original procedure, described by Willis J. Potts of Chicago in 1946, was developed for palliation of cyanotic patients, as a connection between the left pulmonary artery (LPA) and the descending aorta (DAO)[56].

In an attempt to convert PAH with suprasystemic pulmonary arterial pressure into Patent Ductus Arteriosus -Eisenmenger physiology, Blanc et al[57] developed a novel application of the Potts shunt created with a side-to-side anastomosis from the left pulmonary artery to descending aorta in pediatric patients.

The use of a reverse Potts (LPA/DAO) shunt in suprasystemic PAH is considered advantageous compared with atrial septostomy, as it provides highly oxygen-saturated blood for the coronary arteries and the central nervous system, only causes desaturation of the lower body, and additionally lowers the risk of fatal paradoxical embolisms. The reverse Potts shunt equalizes pulmonary arterial and aortic pressure, and unloads the RV in systole, with a subsequent reduction in shifting of the interventricular septum toward the LV, and thus improvement in systolic and diastolic LV performance[58]. The LPA-DAO shunt can be achieved either by a direct side-by-side anastomosis or by using a synthetic graft tube/prosthesis.

Such a connection should be about the size of the DAO to allow sufficient decompression of the RV, whereas an oversized Potts shunt resulting in decreased pulmonary perfusion, underfilling of the LV, extreme desaturation of the lower body, and subsequent undersupply of the myocardium and the brain should be avoided. As the experience with the Potts shunt procedure is nearly exclusively available in children, these data cannot be extrapolated to severely ill adults, who may have a considerably higher periprocedural risk[59]. The Potts shunt procedure may be considered in patients with suprasystemic PH refractory to any medical treatment, including combined therapy (intravenous prostacyclin analogs) presenting in New York Heart Association/World Health Organization functional class III or IV. The largest published series so far consists of 24 children with drug-refractory PAH in which a permanent Potts shunt was created (19 surgical LPA-DAO, 6 via stenting of a PDA)[60]; 21 survivors showed persistent improvement in functional capacities without syncope or RV failure, after a mean follow-up of more than 2 years, six patients experienced severe post-operative complications, and 3 early deaths related to low cardiac output occurred[60]. This procedure often results in significant improvement in functional class, exercise tolerance, and reduced levels of natriuretic peptides in survivors[60,61].

PDA Stenting

The favourable results of Potts shunt has led to the development of new interventional strategies in creating a connection between the left pulmonary artery and descending aorta. The most elegant method is the implantation of a stent in a still-patent persistent ductus arteriosus (PDA). Ductal stenting is an established method in CHD with duct-dependent circulation, and can be established with considerably low periprocedural risk in experienced centers[62-64].

Trans Catheter Potts Shunt

There are now some clinical data on a transcatheter Potts shunt (TPS) in which percutaneous catheter placement is used to connect the left pulmonary artery to the descending aorta. A recent study described the creation of a transcatheter Potts shunt with iCAST 7x22 mm covered stent (Atrium Medical, Hudson, NH, USA), using fluoroscopically guided retrograde needle perforation of the descending aorta at the site of apposition to the left pulmonary artery[59]. Three patients underwent successful transcatheter Potts shunt creation, two patients demonstrated improvement in symptoms with no late complications with a follow-up of 10 and 4 months, respectively; one patient died due to comorbidities.

Bleeding (massive hemothorax) is the most feared complication of TPS, making thoracic computed tomography an investigation of choice to select the ideal candidate for surgery[65]. Two types of relationships between left lower pulmonary artery and descending aorta has been described; in type 1, there is practically no distance between the vessels, and in type 2 the gap between the structures is greater, as such making type 1 patients the ideal candidates for TPS anastomosis.

A radiofrequency-assisted perforation approach is yet another refinement to try to improve the safety and efficacy of TPS creation[66].

Modified Potts Shunt

Other development in the Potts procedure include the implantation of a unidirectional valve within the Potts anastomosis, which can be considered for patients with PH and subsystemic or isosystemic pulmonary artery pressures who exhibit suprasystemic pulmonary artery pressures during exercise, and in patients in whom bidirectional shunting occurs after decompression of the right ventricle[67].

Combined Potts Shunt With Atral Septostomy

In patients with severe PH owing to left heart disease with or without an additional precapillary component, a combination of Potts shunt and atrial septostomy might be more favourable than either procedure alone, in patients with a restrictive and borderline left ventricle and disproportionate PH[68,69].

Aortic Banding

Experimental observations have shown that ventricular-ventricular interactions induced by moderate banding of the aorta might have therapeutic potential in imminent chronic right ventricular failure. The rationale behind this was rightward mechanical shift of the inter-ventricular septum, thereby improving right ventricular end-diastolic volume and pressure via improved Frank Starling effects and filling dynamics, respectively. The additional beneficial effects of ventricular-ventricular interactions have also been reported on a histological and molecular level[70]. Hence moderate aortic banding might be an

option for the treatment of end-stage PAH. Although the clinical studies are lacking, but a similar approach using banding of the pulmonary trunk in children with left ventricular failure owing to dilated cardiomyopathy has shown promising results[71].

Lung transplantation

Despite the marked advancement in the medical therapies for PH which has reduced patient referral for lung transplant programs, transplantation remains the gold standard for patients who fail medical therapy[50].

IPAH is the second most common indication for lung transplantation in paediatric patients[72]. Reported survival post transplant is 87% at 1 year, 60% at 3 years, and 49% at 5 years[73]. In general, referral for transplantation assessment is advisable when patients have a less than 50%, 2- to 3-year predicted survival or NYHA class III or IV level of function, or both[49].

Absolute contraindications for lung transplantation include severe organ dysfunction, chronic non-curable infection and recent malignancy[74]. Selection of patients for transplantation referral is also influenced by the underlying aetiology of PAH[75], like patients with PAH associated with connective tissue disease[76], pulmonary veno-occlusive disease[77], and pulmonary capillary haemangiomatosis have worse prognosis and should be referred for transplantation at earliest. Bilateral lung transplant accounts for 91% of transplants performed for PH and the remaining 9% consist of single lung transplant[78].

Conclusion

Pulmonary arterial hypertension is a rare but severe disease, with limited treatment options available, that too in the form of palliation. Although the need for lung transplant has reduced markedly due to the advancement in these management strategies, but still there exist a huge potential in further advancement in the management of pulmonary hypertension, especially in the pediatric patients.

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Legends

Figure-1: Pathophisiology of PAH

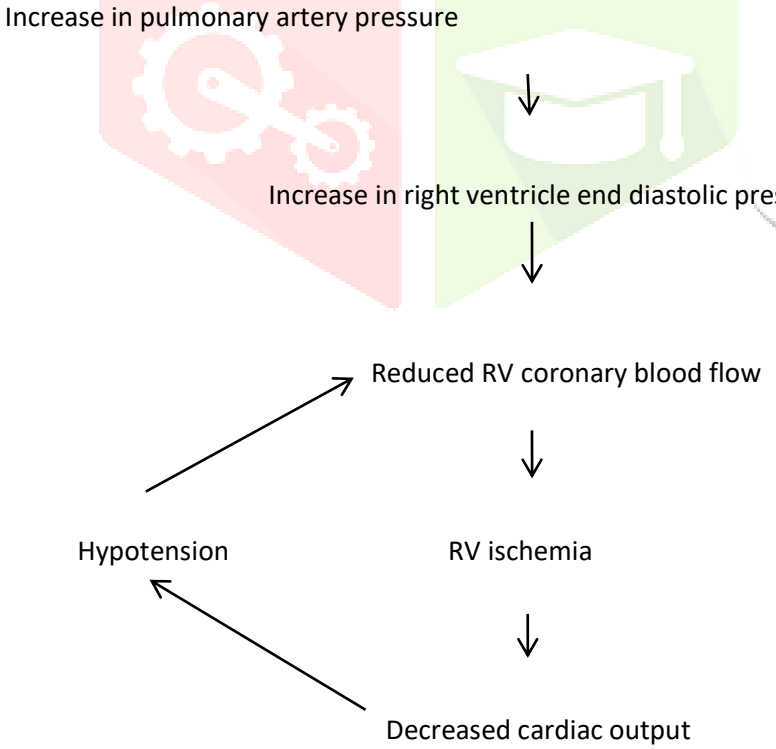

Figure 2- Treatment algorithm for IPAH; WHO FC- World health organization Functional class, CCB- Calcium channel blocker, i.v PCA- Intravenous prostacycline analogue, AS- Atrial septostomy, PS- Pott's shunt