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Pulmonary Hypertension: Diagnosis, Management, and Treatment

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ABSTRACT

Pulmonary hypertension (PH) is a hemodynamic state that is characterized by a resting mean pulmonary artery pressure ≧ 25 mmHg. The common forms of PH are pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), PH caused by left-heart disease, and PH due to lung disease. Previously regarded as untreatable, the treatment of PAH has dramatically advanced since the introduction of the drug epoprostenol in 1999, with three-year survival rates improving from 30%–40% to over 85%. Drugs available for the specific treatment of PAH include endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogs, and prostacyclin-receptor agonists. In the past decade, management and treatment of CTEPH have also improved. While pulmonary endarterectomy used to be the only option for the treatment of CTEPH, newer treatments include a soluble guanylate cyclase stimulator, which has proven to be an efficacious targeted therapy. Other cases benefit from balloon pulmonary angioplasty.

Keywords: Pulmonary hypertension, pulmonary arterial hypertension, pulmonary hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH)

Abbreviations:
BMPR2: bone morphogenetic protein receptor type II
BPA: balloon pulmonary angioplasty
CTEPH: chronic thromboembolic pulmonary hypertension
mPAP: mean pulmonary artery pressure
PAH: pulmonary arterial hypertension
PAWP: pulmonary arterial wedge pressure
PDE-5: phosphodiesterase type 5 inhibitor
PEA: pulmonary endarterectomy
PH: pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is a severe clinical condition that is characterized by an increase

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in pulmonary vascular resistance leading to right ventricular failure and premature death.[1] Prior to the development of epoprostenol, which was the first drug approved in 1999 in Japan for the treatment of PAH,[2] the life expectancy of patients with PH was less than three years.[3] The treatment of PH has advanced significantly since 1999, specializing in its management.[4,5] Early diagnosis is key for the successful treatment of PH. However, early-stage PH is often overlooked because the presenting symptoms are non-specific. These may include fatigue, weakness, shortness of breath upon exertion, and impaired ability to perform physical activities such as climbing stairs. Abnormal physical findings such as elevated jugular venous pressure, a pronounced pulmonic component of the second heart sound, hepatomegaly, ascites, and lower extremity edema may also be present. Syncope should not be overlooked because it indicates the presence of a life-threatening state. Herein, we review current methods for the diagnosis, management, and treatment of PH in Japan.

CLASSIFICATION OF PH

Elevated pulmonary artery pressure, which may have a variety of causes, is defined as mean pulmonary arterial pressure (mPAP) ≧ 25 mmHg as determined by supine resting right-heart catheterization.[6] PH is categorized on the basis of pathological and hemodynamic characteristics and is clinically classified into one of the following five groups, according to the consensus of the Fifth World Symposium on Pulmonary Hypertension held in 2013 in Nice, France: pulmonary arterial hypertension (PAH; Group 1), PH caused by left-heart disease (Group 2), PH caused by chronic lung disease or hypoxia, or both (Group 3), chronic thromboembolic PH (CTEPH; Group 4), and PH caused by unclear multifactorial mechanisms (Group 5) (Table 1).[1] At the Sixth World Symposium on Pulmonary Hypertension held in 2018 in Nice, France, a new proposal suggested that the threshold to diagnose PH should be lowered to an mPAP of 20 mmHg for promoting early patient care. In the following sections, we will discuss the diagnosis, management, and treatment of PAH and CTEPH, the two key subgroups of PH.

EPIDEMIOLOGY

Although exact numbers are unknown because of undiagnosed or misclassified cases, the estimated prevalence of PAH is 5–25 cases per million worldwide.[7,8] In Japan, all patients with PAH and CTEPH are registered in the Specified Disease Treatment Research Program. In 2014, 2,946 patients were treated for PAH and 2,511 patients were treated for CTEPH (total population of Japan, 127 million). The incidence of PAH favors women to men by 1.7-fold, and that of CTEPH favors women to men by more than twofold.[9]

PROGNOSIS

The prognosis for patients with idiopathic PAH has dramatically improved over the past 20 years. PAH, previously known as primary PH, was regarded as an untreatable disease; the three-year survival rate was 30%–40% with the use of digitalis, diuretics, and anticoagulants.[10] Since the introduction of the first PAH-specific therapies in 1999 in Japan, however, the three-year survival rate has improved to over 85%.[11-13] Similarly, the prognosis for CTEPH was poor without intervention and depended on the hemodynamic severity of the PH; the cumulative survival of patients with mPAP >30 mmHg was significantly lower than that of patients with mPAP ≤30

mmHg. Those with signs of right heart failure survived an average of 1.7 years. In patients with mPAP >50 mmHg, 2-year survival was 20%[14,15] However, appropriately treated patients now have a three-year survival rate of over 90%.[16]

HISTOPATHOLOGIC FEATURES

In PAH, the small pulmonary arteries (diameter <500 μm) are affected by vascular lesions, including medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with perivascular inflammatory infiltrates, plexiform lesions, and thrombotic lesions.[17] Pulmonary vasoconstriction is usually observed and is associated with the overproduction of vasoconstrictors (endothelin-1) or the reduced production of vasodilators such as nitric oxide or prostacyclin, or both. The proliferation, migration, and apoptosis of smooth muscle cells, endothelial cells, and fibroblasts may be stimulated by interleukin-1, interleukin-6, and tumor necrosis factor α; in addition, it may be induced via growth factors, serotonin, angiogenic factors, and members of the transforming growth factor β superfamily.[18,19] Mutations of bone morphogenic protein receptor type II (BMPR2) are the most common cause of heritable PAH.[20] Anorexigens, portal hypertension, connective tissue disease, human immunodeficiency virus, and congenital heart disease (Eisenmenger's syndrome) also cause PAH.1

CTEPH is characterized by the presence of obstructive, non-resolving fibrotic thrombi. Prominent obstructions are present in the larger vessels and arteriopathy is present in microvessels. The pathophysiology of CTEPH is complex and not yet fully understood. Our current understanding is that CTEPH could result from recurrent pulmonary embolism or in situ thrombosis in the lung resulting from arteriopathy.[21]

DIAGNOSIS

The signs and symptoms of early-stage PH are frequently non-specific and may not be observed until the condition has progressed. Symptoms include dyspnea, initially while exercising and eventually while at rest, accompanied by fatigue, exhaustion, chest pressure, or syncope. The presence of exertional dyspnea and exercise intolerance can aid in the diagnosis of PH. Dilated jugular veins, hepatomegaly, ascites, and lower extremity edema appear as PH progresses. Abnormal findings on cardiac examination include a pronounced pulmonic component of the second heart sound (P2) and a systolic murmur at a left parasternal location upon tricuspid regurgitation.

Electrocardiographic and chest radiographic signs are also useful in the diagnosis of PH. The signs frequently observed in patients with PH include P pulmonale, R wave to S wave ratio >1 in the V1 lead, and right ventricular strain and an S1Q3T3 pattern on electrocardiogram; right atrial enlargement and dilated pulmonary arteries are observed on chest radiogram.

Echocardiography is indicated for suspected PH for identifying the condition and determining the cause(s). Left-heart disease (Group 2) is a common cause of PH that can be inferred using echocardiography. Chest X-ray, electrocardiography, arterial blood gas analysis, pulmonary function testing (including determination of lung diffusion capacity using carbon monoxide), and chest computed tomography are useful means of determining whether pulmonary disease is the cause of the PH (Group 3). When left-heart disease and pulmonary disease are less likely, ventilation/perfusion scintigraphy can be used for diagnosing thromboembolic PH, and pulmonary angiography can be used for diagnosing CTEPH (Group 4). PAH (Group 1) is diagnosed only after excluding PH in Groups 2, 3, and 4 (Figure).[22]

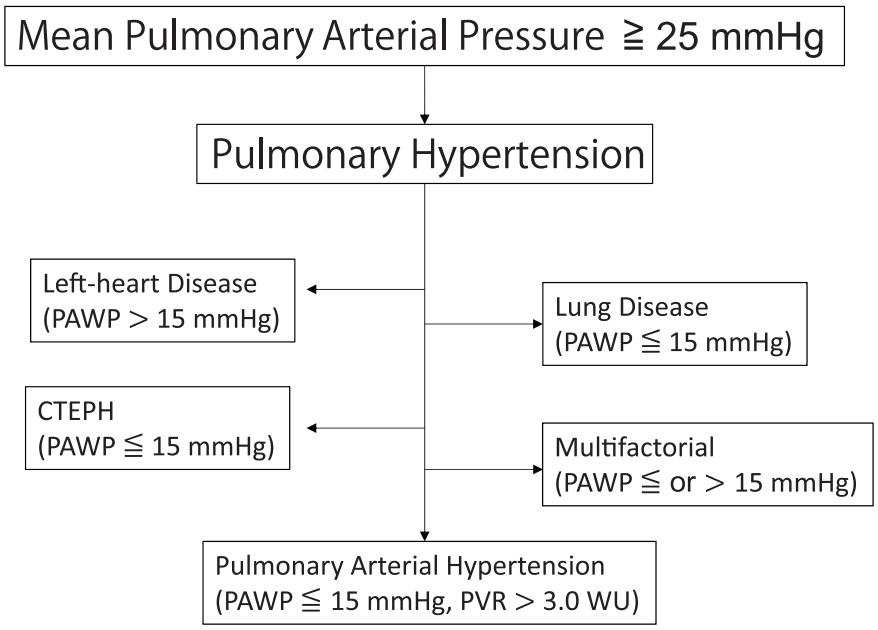

Fig. 1 Diagnostic algorithm for pulmonary arterial hypertension
Differential diagnosis of pulmonary arterial hypertension based on mean pulmonary arterial pressure, pulmonary arterial wedge pressure (PAWP), and pulmonary vascular resistance (PVR). CTEPH: chronic thromboembolic pulmonary hypertension. WU, Wood units

PAH (Group 1) includes idiopathic PAH, heritable PAH, drug- or toxin-induced PAH, and PAH associated with connective tissue disease, human immunodeficiency virus infection, portal hypertension, or congenital heart disease. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are categorized in Group 1′ (Table 1). In all cases, right-heart catheterization should be conducted to confirm the patient's mPAP. A diagnosis of PAH should be considered not only in patients with mPAP ≥ 25 mmHg, but also in those with pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance > 3.0 Wood units.[4] Vasoreactivity testing during right-heart catheterization is recommended for identifying patients with a good response to calcium channel blockers; however, there are few such patients in the Japanese population.

At the Sixth World Symposium on Pulmonary Hypertension (2018), PAH with vasoreactivity was proposed for inclusion in a subgroup of Group 1. Additionally, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis were proposed for inclusion within Group 1 rather than within Group 1′, and PH caused by simple congenital heart disease with a shunt was proposed to remain in Group 1. PH caused by complex congenital heart disease was proposed for inclusion in Group 5.

Presently, a resting mPAP of 20 mmHg is considered the upper level of normal, and a resting mPAP ≥ 25 mmHg is the cutoff value for a diagnosis of PH; therefore, how patients with a mPAP between 21 and 24 mmHg (referred to as so-called borderline PH) can be classified and managed remains unclear.[23] In some circumstances, the borderline PH—particularly in patients with PH caused by the scleroderma spectrum of diseases—an mPAP from 21 to 24 mmHg is associated with a high risk of future development of manifest PAH.[24]

Physicians must be aware of the presence of left-heart disease when diagnosing PAH in

Table 1 Fifth World Symposium on Pulmonary Hypertension Classification (Nice, France, 2013)

1. Pulmonary arterial hypertension
1.1. Idiopathic pulmonary arterial hypertension
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3
1.2.3. Unknown
1.3. Drug- or toxin-induced pulmonary arterial hypertension
1.4. Pulmonary arterial hypertension associated with
1.4.1. Connective tissue diseases
1.4.2. Human immunodeficiency virus infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″ Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left-heart disease
2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital/acquired left-heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure

ALK1 = activin receptor-like kinase 1; BMPR2 = bone morphogenetic protein receptor type II; CAV1 = caveolin 1; ENG = endoglin; KCNK3 = potassium channel subfamily K member 3; SMAD9 = mothers against decapentaplegic homolog 9

patients whose PAWP is between 13 and 18 mmHg because PAWP can vary depending on the use of diuretics. Patients taking diuretics may be misdiagnosed with PAH (Group 1) if their mPAP is >25 mmHg and their PAWP is ≤15 mmHg. Notably, PAWP can be reduced by diuretics and in some cases may increase to exceed 15 mmHg without diuretics.

EVALUATION OF SEVERITY

Baseline evaluation of severity is important for predicting prognosis in PAH. A single parameter is not a reliable prognostic indicator; thus, a systemic evaluation is necessary. The baseline evaluation determines the initial therapy, and follow-up assessments are important for evaluating response to treatment. Useful markers for the determination of initial therapy and the evaluation of response to therapy are the World Health Organization functional class; hemodynamic variables evaluated by right-heart catheterization, such as mPAP, pulmonary vascular resistance, mean right atrial pressure, cardiac index, mixed venous oxygen saturation, systolic blood pressure, and exercise tolerance evaluated by 6-min walk distance or cardiopulmonary exercise testing; and echocardiographic parameters such as the presence of pericardial effusion or right atrial area in end-systole >18 cm^2.

Brain natriuretic peptide and uric acid can be used as biomarkers during follow-up. Brain natriuretic peptide can be elevated when patients with PH have right ventricular overload, and its level predicts prognosis. Uric acid level increases when venous congestion causes tissue hypoxia. Brain natriuretic peptide and uric acid values differ in PH from that in left-sided heart failure. Additionally, brain natriuretic peptide levels do not increase in some patients despite the presence of right ventricular failure. In CTEPH, mPAP > 30 mmHg or increased pulmonary vascular resistance indicates a poor prognosis.[15,25]

ETIOLOGY/GENETICS

A germline mutation coding the *BMPR-2* gene, which is part of the transforming growth factor β superfamily of receptors, is implicated in 70% of patients with heritable PAH and in as many as 40% of patients with idiopathic PAH.26 However, approximately 80% of carriers of the *BMPR-2* mutation are positive for the genotype and negative for the phenotype. Genes coding activin receptor-like kinase 1 (*ALK1*), endoglin, SMAD family member 9 (*SMAD9*), caveolin 1 (*CAV1*), and potassium channel subfamily K member 3 (*KCNK3*) cause PAH. Mutations in eukaryotic translation initiation factor 2α kinase 4 (*EIF2AK4*) have been identified as causing heritable pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.[27,28]

In CTEPH, thrombophilia caused by mutations in protein C, protein S, or antithrombin should be checked. Lupus anticoagulant and antiphospholipid antibodies are associated with CTEPH. CTEPH may also be more common in people with non-O blood groups.[29] A significantly higher frequency of HLA-B*5201 than in normal controls has been observed in Japanese patients with CTEPH. HLA-B*5201-positive patients are predominantly female.[30]

TREATMENT OF PAH

General management

Exercise should be limited to a symptom-free level for maintaining adequate skeletal muscle conditioning. Activities such as climbing and running should be limited. However, despite the potential risks associated with exercise, studies indicate that physical and respiratory rehabilitation improves exercise capacity and quality of life in patients with PAH. Further studies are required for determining the program of exercise training that will lead to the best prognosis.[31] Pregnancy should be avoided owing to the high risk of mortality of the mother or the exacerbation of PH when pregnant.[32] When right-heart failure supervenes, cardiotonic drugs such as digoxin and dobutamine, or diuretics, or both, should be administered. When hypoxemia with arterial

pO2 < 60 mmHg is noted, ambulatory oxygen therapy is indicated. Anticoagulants were once considered to be effective in improving prognosis in patients with PAH, but are now considered harmful when administered together with contemporary pulmonary vasodilators. Anemia or iron deficiency should also be corrected.

Targeted therapy

Patients who have been newly diagnosed with idiopathic, heritable, or drug-related PH that are identified as responders by vasoreactivity testing should be treated with a calcium antagonist. For non-responders, PAH-specific drugs should be considered. PAH-specific drugs target the endothelin, nitric oxide, or prostacyclin pathways. These pathways are associated with abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries in patients with PAH. Several therapies targeting these three pathways are presently available, including endothelin-receptor antagonists, nitric oxide, phosphodiesterase type 5 (PDE-5) inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogs, and prostacyclin-receptor agonists.[33] Drugs approved for use in PAH and CTEPH are summarized in Table 2.

Bosentan is an orally active dual endothelin-receptor antagonist against both endothelin-receptor A (vasoconstrictive) and B (vasodilatory). Liver dysfunction, leuko- and thrombocytopenia, and drug interactions are problematic side effects.[34] Ambrisentan is an endothelin-receptor A antagonist that occasionally induces edema and the aggravation of interstitial pneumonitis.[35] Macitentan is a novel dual endothelin-receptor antagonist with sustained receptor binding and enhanced tissue penetration. In the SERAPHIN trial, the risk of morbidity and mortality was significantly reduced by 45% in patients with PAH receiving 10 mg of macitentan ($p < 0.001$) compared with in those receiving placebo.[36]

Nitrous oxide secreted from vascular endothelium increases the expression of cyclic guanosine monophosphate, which acts on vascular smooth muscle to induce vessel dilatation. The breakdown of cyclic guanosine monophosphate is inhibited by PDE-5, which is abundant in pulmonary vessels. Sildenafil and tadalafil are reversible competitive inhibitors of PDE-5. Improvement in exercise capacity and hemodynamics has been reported with sildenafil.[37,38] Tadalafil is a long-

Table 2 Approved Drugs for PAH and CTEPH

Mechanism of Action	Drug Name	Indication	Route
Endothelin-receptor antagonists	Bosentan	PAH	Oral
	Ambrisentan	PAH	Oral
	Macitentan	PAH	Oral
Phosphodiesterase type 5 inhibitors	Sildenafil	PAH	Oral
	Tadalafil	PAH	Oral
Guanylate cyclase stimulators	Riociguat	PAH	Oral
		CTEPH	
Prostacyclin analogues	Epoprostenol	PAH	Intravenous
	Iloprost	PAH	Inhaled
	Treprostinil	PAH	Subcutaneous
			Intravenous
	Beraprost	PAH	Oral
Prostaglandin I2 receptor agonists	Selexipag	PAH	Oral

CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension

acting PDE-5 inhibitor that is also useful in improving symptoms associated with PAH and avoiding clinical worsening.[39]

Riociguat is an oral soluble guanylate cyclase stimulator. It has a dual mode of action—it increases the sensitivity of soluble guanylate cyclase to nitric oxide and directly stimulates soluble guanylate cyclase independently of nitric oxide. Riociguat increases levels of cyclic guanosine monophosphate, resulting in vasorelaxation of the pulmonary artery. It also significantly improves exercise capacity.[40,41] However, its use is associated with adverse events in patients with PH, complicating idiopathic interstitial pneumonia.

Epoprostenol is an analog of the naturally occurring eicosanoid prostacyclin (prostaglandin I2 or PGI2). It is continuously administered via a central vein. Prostacyclins have direct and potent vasodilatory effects; they inhibit platelet aggregation and thrombus formation and have antiproliferative and anti-inflammatory actions. These effects are mediated via G-protein-coupled prostacyclin receptors in blood vessels. Epoprostenol is expensive and requires special handling to perform the mixing procedure, but it is the most effective PAH-specific drug currently available, and it remains the most recommended drug for the treatment of severe PAH worldwide. Another prostanoid therapy, treprostinil, is also available; treprostinil can be delivered via cutaneous or intravenous infusion.

Iloprost is an inhaled prostanoid therapy. Patients require 6–9 inhalations per day.[42] A new oral selective prostacyclin-receptor agonist, selexipag, delays disease progression and reduces the risk of hospitalization for PAH.[43] In Japan, beraprost is another orally available prostaglandin; however, the beneficial effects of beraprost are modest and are observed only during the early phases of treatment.[44]

MANAGEMENT OF PAH

PAH-specific drugs can be used alone or in combination. Combination therapy, administered either in sequence or upfront, can improve long-term outcomes in patients with PAH.[45] Dual combination therapy with a PDE-5 inhibitor and an endothelin-receptor antagonist is the most widely utilized regimen. When considering the use of combination therapy, classification on the basis of the expected one-year mortality (as determined by considering clinical, hemodynamic, biochemical, and echocardiographic data) is often used: low (<5% per year), intermediate (5%–10% per year), and high (>10% per year) risk. Combination therapy is recommended for patients with newly diagnosed PAH and with low or intermediate risk. Initial combination therapy may be more effective than sequential therapy in patients with PAH at intermediate risk. Intravenous prostacyclin analog administration is recommended for patients at high risk. Achieving a low clinical risk is the treatment goal; it is defined as a 6-min walk distance greater than 440 m, peak VO2 > 15 mL/min/kg, and cardiac index > 2.5 L/min/m^2.

Lung transplant

When the treatment response is inadequate despite maximal medical therapy, referral for lung transplant evaluation should be considered. The preferred procedure in patients with PAH is a double-lung transplant. In Japan, living-donor lobar lung transplantations are performed more frequently than cadaveric lung transplantations because of the difficulty in obtaining brain-dead donors.[46] The outcome of lung transplants has improved, and the one-year survival rate in experienced centers is more than 90%.[47]

TREATMENT OF CTEPH

Medical treatment

All patients should be treated using life-long anticoagulant therapy, i.e. vitamin K antagonists, with a target international normalized ratio of 1.5–2.5.[22] Current evidence is insufficient for recommending the use of new oral anticoagulants in patients with CTEPH. Pulmonary vasodilators are used for treating patients with inoperable CTEPH, on the basis of findings that similar histopathological changes are observed in the distal pulmonary arteries of both patients with CTEPH and those with PAH. The soluble guanylate cyclase stimulator riociguat is licensed for the treatment of CTEPH.[40]

Pulmonary endarterectomy

Pulmonary endarterectomy (PEA) is the standard of care for patients with operable CTEPH. PEA should be considered in all patients whose lesions are deemed accessible. The operability assessment should be performed by a multidisciplinary CTEPH team. PEA involves the removal of thickened endothelia under deep hypothermia and extracorporeal circulation with extra low-temperature cooling. The procedure is usually performed for the removal of thromboembolic lesions, primarily in the proximal main artery. In some expert centers, distal lesions in the mid-segmental and sub-segmental branches can be targeted by PEA. Presently, PEA provides a 10-year survival rate of 72%.[16] However, the present in-hospital death rate is 5%–8%, which suggests that PEA remains a high-risk procedure in some patients.[48]

Balloon pulmonary angioplasty

Balloon pulmonary angioplasty (BPA) is another treatment option for patients who are technically inoperable or for those in whom the risk-benefit ratio for PEA is unacceptable. BPA is performed by dilating stenotic lesions and breaking intraluminal webs and bands in the distal pulmonary arteries. Unlike PEA, which requires a single procedure, multiple BPA sessions are required for obtaining adequate blood flow; however, BPA is less invasive than PEA. BPA was first performed in the United States but has been further developed by centers in Japan.[49-52]

CONCLUSION

Since 1999, PAH has become a treatable cardiovascular disease with improved survival and decreased morbidity. The exact classification of PH is important because prognosis and treatment responses differ among different groups of patients. Combination therapy in patients with newly diagnosed PAH should be considered for treatment, and re-evaluation during follow-up is essential. Although medication for CTEPH is now available, PEA remains the preferred treatment option. BPA is another treatment option for patients with CTEPH.

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CONFLICT OF INTEREST

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