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Update

An update on pulmonary arterial hypertension

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Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure of more than 25 mm Hg at rest or 30 mm Hg with exercise.[1] It is characterized by vascular proliferation and growth, leading to increased vascular resistance and right heart dysfunction. Normal pulmonary artery pressure in a person living at sea level has a peak systolic value of 18 to 25mmHg, an end-diastolic value of 6 to 10mmHg and a mean value ranging from 12 to 16mmHg.[2] The diagnostic criteria used in the National Institute of Health (NIH) registry include a mean pulmonary-artery pressure of more than 25mm Hg at rest, or more than 30 mm Hg with exercise, and the exclusion of left-sided cardiac valvular disease, myocardial disease, congenital heart disease, and any clinically important respiratory, connective tissue, or chronic thromboembolic diseases.[3]

The classification of pulmonary hypertension is mainly based on the anatomy or the etiology. Pulmonary hypertension due to cardio-respiratory condition is quite common but primary pulmonary hypertension is rare. Idiopathic or Primary pulmonary hypertension is a condition characterized by sustained elevation of pulmonary artery pressure without a demonstrable cause. Primary pulmonary hypertension (PPH) has an incidence of one to two cases per million people per year in Western populations.[4] It is a progressive disease usually affecting the arterial side of the pulmonary circulation and, if untreated, progresses to severe pulmonary hypertension and, finally, right heart failure.

Classification of pulmonary hypertension:

Pulmonary hypertension had been classified as either idiopathic (IPAH) also called primary pulmonary hypertension (PPH) or secondary [5]. A wide-ranging number of causes such as hypoxic lung disease, left to right shunt, left heart dysfunction, and liver disease were included in secondary pulmonary hypertension. The identical pathologic features as well as similar treatment in patients with a severe pulmonary hypertension from whatever the cause represent a strong rationale for categorizing all the above conditions in a single group of diseases defined according to the new World Health Organization classification as pulmonary arterial hypertension [6]. The new classification proposed at the WHO meeting in 1998 is shown in Table 1.

Table 1 WHO new diagnostic classification[6]

1. Pulmonary arterial hypertension
1.1 Primary pulmonary hypertension
(a) Sporadic
(b) Familial
1.2 Related to:
(a) Collagen vascular disease
(b) Congenital systemic to pulmonary shunts
(c) Portal hypertension
(d) HIV infection
(e) Drugs/toxins
(1) Anorexigens
(2) Others
(f) Persistent pulmonary hypertension of the newborn
(g) Others

2. Pulmonary venous hypertension
2.1 Left sided atrial or ventricular heart disease
2.2 Left sided valvular heart disease
2.3 Extrinsic compression of central pulmonary veins
(a) Fibrosing mediastinitis
(b) Adenopathy/tumours
2.4 Pulmonary veno-occlusive disease
2.5 Others

3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Sleep disordered breathing
3.4 Alveolar hypoventilation disorders
3.5 Chronic exposure to high altitude
3.6 Neonatal lung disease
3.7 Alveolar-capillary dysplasia
3.8 Others

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1 Thromboembolic obstruction of proximal pulmonary arteries
4.2 Obstruction of distal pulmonary arteries
(a) Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
(b) In situ thrombosis
(c) Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature

5.1 Inflammatory
(a) Schistosomiasis
(b) Sarcoidosis
(c) Others

5.2 Pulmonary capillary haemangiomatosis

Based on exercise performance, graded I–IV in a manner analogous to the New York Heart Association grade, each patient is further classified according to the degree of functional disturbance, (Table 2).

Table 2 ***Functional classification of pulmonary hypertension (modified after the NYHA functional classification according to the WHO 1998)***

(A) Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

(B) Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(C) Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

(D) Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Pathology of pulmonary hypertension

The pathological picture of pulmonary arterial hypertension as has been defined as proliferative and obstructive pulmonary vascular disease is characterised by cellular proliferation that involves the intima, media, and adventitia of the small pulmonary arteries and arterioles. Plexiform lesions that are considered as a proliferation of endothelial cells, smooth muscle cells, and myofibroblasts with formation of microvessels are often present. Thrombosis in situ, typically involving the small arteries or veins, can co-exist with any of the previous findings. This picture is characteristic not only of PPH but is present in other conditions with pre-capillary pulmonary hypertension—for example, congenital systemic to pulmonary shunts, collagen vascular disease, portal hypertension, and HIV infection. Though pulmonary vasculature has anatomical similarities to the systemic circulation with similar arterial structure of intima, media and adventitia, there are several important differences between the two circulations. The major difference is that the pulmonary circulation is a high flow, low pressure system with a remarkable degree of compliance to cope with cardiac outputs that may rise six-fold with heavy exercise and the pulmonary vessels must be thin walled to allow gas exchange with the need to be sufficiently well supported so as not to rupture. A further important difference between the two circulations is the response to hypoxia. The systemic circulation dilates to hypoxia whereas the pulmonary circulation constricts. Hypoxic pulmonary vasoconstriction is a reflex that has been known since 1946. So is the relationship between the vasoconstriction/remodeling that occurs following hypoxia and that, which accompanies IPAH.[7—9]

Familial PAH is an autosomal dominant disorder with reduced penetrance and genetic anticipation, and has been mapped to a locus designated PPH1 on chromosome 2q33. In the future genetic analysis can help us to identify patients at the very early stages of the disease. Familial PPH has an incidence of at least 6% among all cases of PPH [10].

Screening for Pulmonary Arterial Hypertension (PAH)

This can be done by a sequential approach in four stages

1. Clinical suspicion of PAH
2. Detection of PAH
3. Identification of Clinical class
4. Evaluation for the type of PAH, functional capacity of the patient and haemodynamics.

Clinical Suspicion of PAH

Most patients present with a complain of exertional dyspnoea, exertional chest pain and syncope. Signs of right ventricular strain like parasternal heave, loud P2, pansystolic murmur of tricuspid regurgitation, early diastolic murmur of pulmonary regurgitation, right ventricular S3, raised JVP and oedema may be present. Family history of PAH[10], connective tissue disease[11], past history of thromboembolic disease, drug history including use of appetite suppressants[12, 13] and L-tryptophan, 5-hydroxytrptamine uptake inhibitors, presence of portal hypertension[14-17], HIV infection[18, 19], and congenital heart disease may lead to early recognition of PAH. Similarly chest X-Ray, Echocardiography or ECG done for other conditions may also give rise to suspicion of PAH.

Detection of PAH

ECG: may give evidence of haemodynamically significant PAH, such as right ventricular hypertrophy, right axis deviation or right atrial enlargement [20].

Chest x-ray: may reveal enlarged hilar and main pulmonary artery shadow with peripheral pruning and also give evidence of coexisting conditions like obstructive airway disease, interstitial lung disease[20].

Doppler echocardiography (DE): studies show good correlations between Doppler based estimation of pulmonary arterial systolic pressure and direct measurement of by right heart catherization. DE fairly estimates pulmonary arterial systolic pressure (PASP), which is equivalent to right ventricular systolic pressure (RVSP) in absence of RV outflow obstruction and tricuspid stenosis. RVSP is calculated by measuring the systolic regurgitant tricuspid flow velocity v and an estimate of right atrial pressure (RAP),value obtained from jugular veinous distention or a standardized value and then applying the formula: $RVSP=4V^2 + RAP$. RAP can also be gauged by a decreased inspiratory collapse of IVC and its enlargement. Echocardiography also provides evidence of left ventricular function and associated heart disease as a cause of pulmonary arterial hypertension[20-26].

Clinical class (IPAH or SPAH) identification

Clinical class identification can be done based on the following investigations.

DE (grade of PAH and functional status of heart), pulmonary function test(severity and type of respiratory disease causing PAH), pulse oximetry(overnight monitoring show frequent desaturation in Sleep apnoea syndrome causing PAH)and confirmed by polysomnography, ABG test, ventilation perfusion scan of lung in PAH suspected to be due to thromboembolism along with spiral CT and pulmonary angiography[27].

Evaluation of PAH (type, functional capacity, haemodynamics)

Type

Serological markers for: connective tissue diseases, HIV, autoimmune liver disease.

Abdominal ultrasound: Cirrhosis and portal hypertension

Functional capacity

Exercise capacity predicts survival in PAH. The six minute walk test (6MWT) is a very useful simple test. Reduction of arterial saturation > 10% during 6MWT increases the mortality by 2.9 % in a 26 months follow up period.

Haemodynamics

Though right heart catheterization confirms the presence of PAH, establishes its cause, assess severity and guide therapy by vasoreactivity test [22-24], echocardiography (table 3) estimates PASP quite reliably. Moreover it can be repeated frequently to monitor therapy. Out of the many drugs available, inhaled iloprost and nitric oxide are often used for this purpose. Nitric oxide is the substance of choice to test for acute vasoreactivity, as calculation of the true effect on vascular tone is more reliable. Real-time Doppler echocardiography performed during inhalation of nitric oxide or iloprost will be able to identify "true" responders, represented by patients in whom the acute fall of both pulmonary artery pressure and pulmonary vascular resistance is in the range of 30–50%

Table 3: ***Echo-cardiographic measurements used in pulmonary hypertension*** [22-24]

Qualitative assessment
Enlarged right atrium and ventricle
Right ventricular hypertrophy
D shaped left ventricular cavity with flattening of the IV septum in systole
Diminished/absent atrial wave of pulmonary valve
Mid systolic closure or notching of pulmonary valve
Haemodynamic assessment
Tricuspid regurgitation velocity*
Right ventricular outflow tract flow acceleration time
Pulmonary artery systolic flow acceleration time
Right ventricular ejection time
Right ventricular index of myocardial performance
Timing of mid systolic deceleration of right ventricular ejection
Right ventricular long axis function (marker of overall right ventricular systolic function)

*Most accurate echocardiographic technique for assessing pulmonary artery pressure.

Table 4: Investigations recommended in the assessment of pulmonary hypertension [5, 6]

Imaging:
Chest x-ray
Echocardiogram
Ventilation perfusion scan
High-resolution CT lungs
Contrast helical CT pulmonary arteries with pulmonary angiography (in selected cases)
Abdominal ultrasound

Respiratory:
Arterial blood gases in room air
Lung function (including FEV1, FVC, TLC, VA, TLCO, KCO)
Nocturnal oxygen saturation monitoring

Cardiac:
ECG
Submaximal exercise test (six minute walk or incremental shuttle test)
Cardiac catheterisation (including right heart catheterisation with saturations and haemodynamics, and acute pulmonary vasoreactivity study)

Blood investigations include:
Routine biochemistry and haematology
Thrombophilia screen
Thyroid function
Autoimmune screen (including anti-centromere antibody, anti-SCL70 and RNP, phospholipid antibodies)
Hepatitis serology
Serum angiotensin converting enzyme
HIV

Urine:
beta-HCG (women)

CT: computed tomographic; FEV1: forced expiratory volume in one second; FVC: forced vitalcapacity; TLC: total lung capacity; VA: alveolar volume; TLCO: carbon monoxide transfer factor; KCO: carbon monoxide transfer factor corrected for alveolar volume; RNP: ribonuclear protein; HIV: human immunodeficiency virus.

Management

Treatment of pulmonary arterial hypertension should ideally be followed in an evidence based manner [25,26].

Classes of Recommendation

Class I: Evidence and / or general agreement that a given treatment is beneficial, useful or effective

Class II: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment

Class IIa: Weight of evidence is in favour of the treatment

Class IIb: usefulness less well established by evidence /opinion

Class III: Evidence or general agreement that the treatment is not useful or effective and may in fact be harmful.

Levels of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analysis

Level of Evidence B: Data derived from a single randomized clinical trial or large non-randomized studies.

Level of Evidence C: Consensus of opinion of the experts and /or small studies, retrospective studies, registries.

Medical Therapy

Anticoagulation

All patients with primary or thromboembolic pulmonary hypertension should be treated life-long with warfarin to achieve an international normalized ratio (INR) of 1.5-2.5. Warfarin should be seriously considered in other types of pulmonary arterial hypertension where there is no contraindication, such as gastrointestinal haemorrhage, significant haemoptysis or liver disease with coagulation abnormalities.[1,27,28] For Idiopathic PAH: Class of recommendation (CR) = IIa, Level of evidence(LE) =C. For other PAH CR= IIb, LE= C

Oxygen Therapy

Patients with pulmonary hypertension should undergo nocturnal oxygen saturation monitoring. Controlled oxygen therapy may be indicated for those patients with sustained nocturnal hypoxaemia where arterial oxygen saturations are below an average of 90% on air and are corrected on controlled supplemental oxygen.[27-29] CR= IIa, LE= C

Supportive Medical therapy

Right heart failure gives rise to fluid retention, which is improved by diuretics. Digoxin has been shown to improve cardiac output acutely in primary pulmonary hypertension. Its efficacy when administered chronically in this condition is unknown although it improves symptoms and reduces hospital admissions without increased mortality in patients with chronic heart failure.

Diuretics are indicated to control fluid retention. For diuretics CR = I and LE = C. Digoxin may be considered in patients who remain symptomatic on medical therapy.[30-34] CR = IIa. LE= C

Vasodilator therapy [35-60]**:**

The rationale for vasodilators is based on the importance of vasoconstriction in the pathogenesis of pulmonary hypertension. Vasodilator therapy with calcium antagonists may improve symptoms, haemodynamics, and survival in pulmonary arterial hypertension. Since this treatment can result in rapid clinical deterioration, it should only be used in patients with a positive acute vasodilator study and a cardiac index > 2.1 l/min/m2. The systemic use of vasodilators in patients with pulmonary venous hypertension may cause pulmonary oedema by increasing pulmonary blood flow in the presence of downstream obstruction. Vasodilators are also contraindicated in patients with hypoxic pulmonary hypertension caused by chronic lung disease or interstitial lung disease who are prone to worsening hypoxaemia with vasodilator therapy caused by ventilation perfusion mismatch. Calcium antagonists should not be started before performance of an acute vasodilator study. For patients with a cardiac index > 2.1 l/min/m2 and/or mixed venous oxygen saturation > 63%, and/or right atrial pressure < 10 mm Hg, and with a positive response to acute vasodilator challenge, a calcium antagonist should be initiated. Diltiazem or nifedipine are appropriate unless right ventricular function is impaired when amlodipine should be considered. Calcium antagonists should be commenced in hospital where they should be uptitrated according to symptoms, blood pressure, oxygen saturation, and exercise tolerance. Recommendation for Calcium channel antagonist.CR for IPAH =I, LE= C. For other PAH CR=IIb and LE=C

Long term prostaglandin therapy

Patients with pulmonary hypertension, which is primary, familial or caused by anorectic agents, connective tissue diseases, shunts, associated with congenital heart disease, portal hypertension, sarcoidosis, HIV or chronic thromboembolic disease (either inoperable or as a bridge to pulmonary thromboendarterectomy), in modified NYHA functional classes III and IV, with a cardiac index < 2.1 l/min/m^2 and/or pulmonary arterial oxygen saturation < 63% and/or right atrial pressure > 10 mm Hg should be considered for long-term intravenous infusion of prostaglandins. This is regardless of whether they have any evidence of vasodilator capacity at cardiac catheterisation. Prostaglandin therapy should be considered in all patients who do not respond to conventional medical therapy before proceeding to lung transplantation. The drug should not be discontinued because of the risk of death from rebound pulmonary hypertension. The starting dose of epoprostenol is 2 ng/kg/min and that of iloprost is 1 ng/kg/min. After initiation of therapy these drugs should be uptitrated over one week to the maximum tolerated dose while the patient remains in hospital. Patients should be instructed in sterile techniques for handling drugs, catheter care, preparation of dressings and drug administration. Appropriate support must be provided at home. Conventional medical therapy should be continued after commencing prostaglandins. Calcium antagonists should be withdrawn on starting prostaglandins if there is evidence of clinical deterioration before this. The dose of prostaglandins should be increased any time the patient has a return of symptoms attributable to pulmonary hypertension. Specialist care in a pulmonary vascular unit is required for this technically challenging treatment (Fig 1). For Epoprostenol for IPAH and PAH due to connective tissue disease CR= I, and LE= A. Other PAH CR= IIa , LE= C. For Iloprost CR= IIa and LE= B for IPAH. For Beraprost which is first oral analog CR = IIb and LE= B

Nitric oxide: More useful for vasodilator test than for therapy. No significant trial for recommendation.

Endothelin receptor Antagonists: Endothelin 1 (ET-1) is potent vasoconstrictor and smooth muscle mitogen that may contribute to increased vascular tone and proliferation in PAH. Two types of endothelin receptors ET-A and ET- B are known. ET-B counteracts the action of endothelin -1. ET-1 expression , production and concentration in plasma and lung tissue are elevated in PAH and level correlate with disease severity.

Bosentan

It is dual ET-1 and ET-2 receptor antagonist. An International placebo controlled trial with oral bosentan (62.5mg BID for 4 weeks followed by 125mg for 12 weeks in 144 patients of PAH showed significant improvement in 6MW, haemodynamics and functional class [61,62]. For IPAH CR= I and LE= A.

Phosphodiesterase-5 Inhibitors (PDE5): may be useful as the PDE5 is strongly expressed in lung and their activities are increased in PAH which leads to rapid metabolism of potent vasodilator nitric oxide (NO)

Sildenafil [63, 64]

This may be useful at average dose of 7.5-100mg starting with lower dose. CR= I and LE= A

Atrial Septostomy

Atrial septostomy [65,66] may be considered in severe pulmonary hypertension refractory to prostaglandin therapy particularly if it is associated with recurrent syncope. It is not indicated in the critically ill with severe right ventricular failure or in patients with impaired left ventricular function. Atrial septostomy should only be performed by physicians with experience in performing this procedure with low morbidity and in a centre with expertise in pulmonary hypertension. CR=IIa and LE= C.

Table 5: Dose ranges, routes of administration, and half-lives of the most frequently used vasodilators in patients with ipah [26, 27].

DRUG	ROUTE	DOSE RANGE	HALF-LIFE
Epoprostenol*	Intravenous	2–20 ng/kg of body weight/min	3 – 5 min
Adenosine	Intravenous	50 –200 mcg/kg of body weight/min	5 –10 sec
Nitric oxide	Inhaled	5 –80 ppm	15 –30 sec
Nifedipine	†Oral	30 –240 mg/day	2–5 hr
Diltiazem	†Oral	120 –900 mg/day	2–4.5 hr

*The dose range shown is for a short-term infusion; the dose range for long-term infusions often exceeds 100 to 150 ng per kilogram per minute.
†The half-life shown refers to conventional preparations; sustained-release preparations may be administered once daily.

Surgical Therapy

Thromboendarterectomy

Patients of any age with chronic proximal pulmonary thromboembolic disease should be considered for pulmonary thromboendarterectomy [67, 68]. Patients with coronary artery or valvular heart disease may also be considered. Significant lung disease (forced expiratory volume in one second (FEV_1) < 30% predicted) is a contraindication. Patients with ventriculo-atrial shunts for hydrocephalus may not be suitable because they develop distal embolic disease not amenable to surgical removal.[69-72]

Lung transplantation

Lung or heart lung transplantation is indicated in patients with pulmonary hypertension with symptomatic progressive disease, which, despite optimal medical and/or surgical treatment, leaves the patient in modified NYHA functional classes III or IV. The six-minute walk test is a useful tool in the assessment of when to list patients for transplantation. Patients with a six-minute walk test result of < 400 meter should be considered for transplantation. Candidates should meet the internationally agreed guidelines for lung transplantation. Haemodynamic indications comprise a cardiac index < 2.1 l/min/m2, and/or pulmonary arterial oxygen saturation < 63%, and/or right atrial pressure > 10 mm Hg, and/or mean pulmonary artery pressure > 55 mm Hg.[69,70]

Prognosis

Survival of untreated PPH patients in the National Institute of Health (NIH) Registry was a median of 2.8 years after diagnosis, but patients may survive for lengthy periods, particularly with the use of newer means of treatments. Predictors of survival in IPAH include indicators of the severity of disease as assessed by measurement of haemodynamic characteristics (mean pulmonary-artery pressure, right atrial pressure, cardiac index, and mixed venous oxygen saturation), functional class, exercise tolerance (Six minute walk test is useful in the assessment of functional impairment and prognosis, and in the evaluation of long term therapeutic response),anticoagulant therapy, and the response to vasodilators.[71,72] Most patients succumb to progressive right-sided heart failure, but sudden death accounts for approximately 7 percent of deaths.

Conclusion

Pulmonary arterial hypertension is frequently encountered by practicing physicians. The diagnosis can be established by DE non-invasively. Quite effective drugs have been introduced in the management of PAH in recent years. All important aspects of PAH has been addressed in this review article.

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