

CLINICAL STUDY

Pulmonary arterial hypertension – contemporary management strategy

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Abstract: Pulmonary arterial hypertension (PAH) is a severe chronic disorder of pulmonary arteries with progressive precapillary pulmonary hypertension, characterized by poor life quality and very poor prognosis. Unless treated, it causes death within 2–3 years from diagnosis. PAH affects mainly younger women. The treatment of PAH should not only be symptomatic, but also directed towards the improvement in patient's survival and quality of life. Many novel drugs putting together so called specific PAH therapy (endothelin receptor antagonists, prostanoids, phosphodiesterase – 5 inhibitors) were tested in randomized trials. PAH management requires a highly individualized approach, state of the art knowledge and adequate experience. Patients therefore should be referred to specialized PAH centers providing both complete diagnosis and therapy. In our region a close co-operation between Czech and Slovak PAH centers has also proved to be profitable. Data sources.

Literature retrieval was accessed through MEDLINE using the terms pulmonary hypertension, PAH, diagnosis, treatment. Reference citations from publications identified were reviewed (Ref. 47). Full Text (Free, PDF) www.bmj.sk. Key words: pulmonary arterial hypertension, conventional therapy, specific therapy.

Pulmonary arterial hypertension (PAH) is a diverse etiology group of diseases affecting small pulmonary arteries. It is defined by mean pulmonary arterial pressure more than 25 mmHg at rest or more than 30 mmHg with exercise, with concomitant pulmonary capillary wedge pressure of less than 15 mmHg and pulmonary vascular resistance more than 3 WU. Progressive increase of pulmonary vascular resistance leads to right ventricular failure and ultimately to death.

Idiopathic PAH is relatively rare, with estimated incidence of 1–2 per million. PAH associated with other conditions is more common. The most common association is with connective tissue diseases, especially with limited scleroderma. Other conditions include congenital systemic to pulmonary shunts, portal hypertension and HIV infection (1). If we include all PAH categories, the minimal prevalence has been estimated to 15 cases per million (2, 3). PAH affects mainly younger women and unless treated causes death within 2–3 years of diagnosis (4).

Diagnosis of PAH

The diagnostic process of PAH includes clinical suspicion, detection of pulmonary hypertension and identification of pulmo-

nary hypertension clinical class (5, 6). A close and exact evaluation of all clinical signs and diagnostic findings is necessary, so as to enable the precise categorization of PAH. In patients with generally very poor prognosis it is so possible to sort out those with i.e. chronic thromboembolic pulmonary hypertension (CTEPH) that can be potentially curable (7–10).

PAH can be **suspected** when symptoms (dyspnoea, fatigue, weakness, angina, syncope on exercise, abdominal tension) and physical signs (accented pulmonary components of S2, systolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, jugular vein distension, hepatomegaly, peripheral oedema, ascites, cyanosis) are present in subjects without specific heart or lung disease or in subjects with illness that can be associated with PAH such as connective tissue disease, portal hypertension, HIV infection and congenital heart disease (11).

Detection phase of PAH diagnostic approach include electrocardiography, chest radiography and echocardiography.

– The electrocardiogram can show signs of right ventricular hypertrophy. This shows high specificity but low sensitivity. Right bundle branch block, ST and T wave abnormalities and signs of right atrial enlargement may be present (12).

– Chest X-ray may present enlargement of the central pulmonary arteries with pruning of the peripheral blood vessels. The right ventricle and atrium may also be enlarged. Chest radiography can exclude emphysema, pulmonary fibrosis and thoracic cage abnormalities.

– Transthoracic echocardiography (TTE) is excellent non-invasive screening test in patients with suspected pulmonary hypertension. TTE estimates pulmonary artery systolic pressure (PASP) by summing the systolic regurgitant tricuspid flow ve-

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locity (v) and right atrial pressure (RAP) estimated from characteristics of the inferior vena cava applied in the formula: $PASP = 4v^2 + RAP$. When poor images make obtaining the estimates of peak tricuspid regurgitation velocities difficult, saline contrast medium enhancement should be used to improve the accuracy of the measurements (13). The presence of a pericardial effusion confers a poor prognosis of PAH. Echocardiography will rule out left-sided myocardial and valvular diseases responsible for pulmonary venous hypertension and congenital heart diseases. Echocardiographic screening for the detection of pulmonary hypertension has been suggested to be performed yearly in asymptomatic patients with the scleroderma spectrum of diseases and only in presence of symptoms in other connective tissue diseases. We should screen first-degree relatives of those with pulmonary hypertension and patients with suspected portopulmonary hypertension if being considered for transplantation (14).

The next step after the pulmonary hypertension detection is the **confirmation** of its clinical class.

– Pulmonary functional tests will identify the contribution of underlying airway or parenchymal lung disease (15). In idiopathic PAH the vital capacity may be reduced to approximately 80 % of predicted. The diffusing capacity for carbon monoxide (DLCO) is mildly reduced to approximately 60 to 80 % of predicted. Approximately 20 % of patients with systemic sclerosis have an isolated reduction in DLCO which may be associated with the development of PAH. The degree of arterial hypoxemia is often slight to moderate.

– Polysomnography should be considered to assess a possible contributory role of sleep apnea syndrome in pulmonary hypertension.

– Ventilation and perfusion lung scintigraphy can eliminate the diagnosis of CTEPH (16).

– High resolution computerized tomography (CT) of the lungs can eliminate interstitial lung disease and emphysema. Contrast-enhanced spiral CT can visualize central chronic pulmonary thromboemboli.

– Pulmonary angiography is more accurate in the identification of distal obstructions. It is required to confirm CTEPH and assess operability (7–10, 17). Visualization of bronchopulmonary collaterals by bronchial arteriography or CT angiography helps to distinguish patients with CTEPH from those with PAH. Large bronchopulmonary collaterals are found in patients with CTEPH.

– Magnetic resonance imaging is used for the evaluation of pathological and functional changes of heart and pulmonary circulation.

– Blood tests such as for antinuclear antibody, rheumatoid factor, human immunodeficiency virus, hepatitis, aspartate aminotransferase and alanine aminotransferase levels can identify causes of PAH such as lupus, scleroderma, rheumatoid arthritis, acquired immunodeficiency syndrome, and liver disease. The lack of an identifiable cause confers the term “idiopathic” on this condition.

For PAH **evaluation** exercise capacity testing and right heart catheterization is required.

– Exercise testing in PAH is useful to allow objective assessment of the severity of symptoms and follow success of therapy. Exercise testing has been shown to also be predictive of survival. Six-minute walk test is simple and inexpensive. It is usually combined with the Borg score of dyspnoea level (18). Cardiopulmonary exercise testing is technically more difficult than six-minute walk test. It allows measurement of ventilation and pulmonary gas exchange during exercise.

– The diagnosis of PAH cannot be confirmed without right heart catheterization. Not only other causes of PAH can be excluded but in addition it also establishes the severity of the disease and allows an assessment of prognosis. Measurements of all right-sided pressures are made at end expiration to avoid incorporating negative intrathoracic pressures. Acute vasodilator testing should be performed whenever PAH is discovered or confirmed during right heart catheterization (19). The acute pulmonary effect of short-acting vasodilators (intravenous epoprostenol, inhaled nitric oxide, intravenous adenosine) predicts the hemodynamic response to long-term calcium-channel blockers. A positive acute vasodilator test is defined as a reduction of mean pulmonary artery pressure >10 mmHg to reach an absolute value of mean pulmonary artery pressure <40 mmHg with an increase or unchanged cardiac output. Patients with a positive acute response to vasoreactivity tests have a better prognosis when compared to nonresponders.

– Biomarkers, such as brain natriuretic peptide and troponin, are also used to monitor clinical course.

Principles of therapy of PAH

The aims of PAH treatment should be directed not only towards symptomatic benefits, but should also lead to improvements in survival and quality of life for the patients (20). Over the last years great advances were made in the PAH management. Many novel drugs (endothelin receptor antagonists, prostanoids, phosphodiesterase-5 inhibitors) were tested in randomized trials (21). The grading system for the level of evidence is based on the number of randomized controlled clinical trials (RCT) with a given treatment (level of evidence A – data from multiple RCT or meta-analyses, level of evidence B – data from a single RCT, level of evidence C – consensus of opinion of the experts). The grade of recommendation is based on the level of clinical efficacy that is expected from the therapeutic procedure (class I – strong recommendation, class IIa – moderate recommendation, class IIb – weak recommendation, class III – negative recommendation).

Before embarking on long-term therapy for PAH, the reversibility testing should be performed to identify the small group of responders benefiting from calcium channel blockers. However, the vast majority of patients with PAH will not fulfill the criteria for calcium channel blockers treatment. Those patients should receive specific therapy (22). Specific PAH therapy is based on functional status. It should be instituted at the time of diagnosis. In NYHA class III (and class II) oral drugs are preferred. Bosentan, dual endothelin-1 receptor antagonist is first-

line therapy. In NYHA class IV intravenous prostanoids, lung transplantation and atrial septostomy remain the therapies of choice (23).

Pregnancy is contraindicated in patients with PAH. Consequently, safe and effective contraception is always recommended for women of childbearing potential. Patients should receive annual immunization against influenza.

Conventional therapy of PAH

Oral **anticoagulant** therapy is widely recommended for patients with PAH. It has been shown to improve survival in patients with idiopathic PAH and PAH associated to anorexigens (24). The rationale for the use of anticoagulant treatment is based on the demonstration of thrombophilic predisposition in patients with pulmonary hypertension. The target international normalized ratio between 1.5 and 2.5 is recommended.

Calcium channel antagonists cause pulmonary and systemic vasodilatation. They are effective in the presence of vasoconstriction but not in its absence. Thus patients who benefit are those with a positive acute vasodilator response. The response rate to acute vasodilators is 10–15 %. The response rate to long term therapy with calcium-channel blockers is less than 7 percent (25). Long term use of high dose diltiazem (up to 720 mg/day) and nifedipine (up to 180 mg/day) reduces pulmonary artery pressure and mortality (26).

Diuretics are indicated to control fluid retention. Their traditional role has been limited to patients manifesting right ventricular failure and systemic venous congestion. Various diuretics are used in patients with PAH, including furosemide, hydrochlorothiazide, and spironolactone. Careful monitoring of blood pressure, fluid status, serum electrolyte levels and renal function is critical in treated patients.

Digitalis may be used in PAH patients with atrial fibrillation to slow ventricular rate. Short term administration produces a modest increase in cardiac output and reduction in circulating norepinephrine levels (27). No data are available on the effects of long term treatment.

Most patients with PAH present with only mild degrees of arterial hypoxaemia. Patients with severe right-sided heart failure and resting hypoxaemia resulting from markedly increased oxygen extraction at rest should be treated with continuous **oxygen therapy** to maintain their arterial oxygen saturation above 90 %.

Specific therapy of PAH

Prostanoids

Prostaglandin I₂ (prostacyclin) is the main product of arachidonic acid in the vascular endothelium. It is a potent vasodilator in both the pulmonary and systemic circulation and has antiplatelet, antiproliferative and direct inotropic activity. The synthesis of prostacyclin is markedly diminished in patients with PAH (28).

Intravenous prostacyclin-epoprostenol has a short half-life in the circulation (3–5 min). This explains why it needs to be

administered by continuous intravenous route by means of infusion pumps and permanent tunnelized catheters. Infusion of epoprostenol should be kept cool by using cold ice-packs. Epoprostenol was first used to treat pulmonary hypertension in the early 1980s. In a 12-week prospective RCT of 81 patients with PAH in functional class III and IV was demonstrated an improvement in hemodynamics, exercise capacity and survival in epoprostenol-treated patients (29). The experience with epoprostenol in PAH for more than 10 years has been reported. Survival rates over 5 years were markedly improved compared to historical controls (30, 31). Epoprostenol is usually started at a dose 2 ng/kg/min and this dose is gradually increased. The average dose at 1 year is 20–30 ng/kg/min. Adverse effects of epoprostenol include headache, jaw pain, nausea, diarrhoea, hypotension and leg pain. Pump failure and catheter dislocation may cause rapid and life-threatening hemodynamic deterioration. The most relevant complication related to the delivery system is sepsis. Intravenous epoprostenol is the treatment of first choice in functional class IV.

Treprostinil is a stable prostacyclin derivative. Its pharmacologic properties allow it to be administered through continuous subcutaneous infusion. The largest RCT performed so far in patients with PAH included 470 patients in functional class II, III and IV (32). There were improvements in exercise capacity, hemodynamics and clinical events in the treprostinil group. There was a clear dose-effect relationship. Infusion site pain is the most common side effect of subcutaneous treprostinil. It was reported in 85 % of patients exposed to the drug. Intravenous treprostinil was recently approved for PAH therapy. Preliminary data about the possibility of successful transition from intravenous epoprostenol to intravenous treprostinil were provided. Long-term therapy with treprostinil appears to improve exercise tolerance, symptoms and survival in patients with PAH (33).

Iloprost is a stable prostacyclin analog with longer serum half-life of 20–30 minutes. Administration by inhalation has been suggested to cause selective pulmonary vasodilatation. Inhaled iloprost has advantages over intravenous prostanoids in that it does not require a central venous catheter, or infusion pump system. However, due to short duration of action after a single inhalation, it requires frequent inhalations (from 6 to 12 times daily). In a 12-week multicenter RCT of 203 patients with PAH and CTEPH, 2.5 or 5 µg iloprost administered six or nine times daily improved the 6-min walking distance, functional class and hemodynamics (34). As no studies have yet evaluated the mortality benefits of iloprost, it should be considered second-line therapy.

Endothelin-1 receptor antagonists

Endothelin-1 (ET-1) is potent vasoconstrictor and mitogen for vascular smooth muscle cells and fibroblasts. ET-1 binds to two types of receptors, ETA and ETB. ET-1 plasma levels are increased in patients with PAH and correlate with severity of disease and with survival.

Bosentan is a dual ETA/ETB receptor antagonist. In a 12-week RCT of 32 patients with PAH bosentan was superior to

placebo in increasing 6-minute walking distance, Borg dyspnoea index, functional class and hemodynamics (35). A large 16-week RCT included 213 patients with idiopathic PAH and PAH associated with connective tissue disease (36). Patients were randomized into three groups: bosentan dosage titrated to 125 mg twice/day, bosentan dosage titrated to 250 mg twice/day, or placebo. At the end of 16 weeks, the 6-minute walking distance was significantly improved in the bosentan groups compared with the placebo group. The difference between the bosentan groups was not significant (+54 m for 250 mg dose group and +35 m for 125 mg dose group). In the scleroderma patients bosentan prevented 6-minute walking distance deterioration. Dose-dependent and reversible increase in hepatic aminotransferases occurred in 10 % of the subjects. It was more frequent and severe in the 250 mg dose group. On the basis of these data, bosentan was approved at the target dose 125 mg. The first ever multicenter RCT of 54 patients with PAH related to Eisenmenger's syndrome patients significantly increased their exercise capacity and decreased pulmonary vascular resistance under treatment (37). Bosentan may also be effective and safe in patients with Child A cirrhosis and portopulmonary hypertension, PAH related to HIV infection and in selected patients with CTEPH (38). Favorable survival rates with first-line bosentan therapy were reported. In a study of 169 patients with idiopathic PAH, survival rates at 1, 2 and 3 years were 96, 89 and 86 %, respectively. These survival rates were not achieved with bosentan therapy alone because 23 % of the patients eventually required addition of or transition to other PAH therapies (39). Non-invasive bosentan treatment is first-line therapy for PAH patients in functional class III.

Sitaxsentan is a selective ETA receptor antagonist. In RCT of 178 patients with PAH sitaxsentan given orally once daily improved exercise capacity, hemodynamics and clinical events (40).

Like sitaxsentan, **ambrisentan** is a selective ETA receptor antagonist. In RCT ambrisentan improved 6-minute walking distance, hemodynamics and WHO functional class in patients with PAH (41). Elevated hepatic aminotransferases concentrations more than three times the upper limit of normal value were observed in 3.1 % of the patients.

Phosphodiesterase-5 inhibitors

Production of nitric oxide is impaired in patients with PAH, resulting in decreased production of cyclic guanosin monophosphate (cGMP). The vasodilatory effects of cGMP are short-live, due to the rapid degradation of cGMP by phosphodiesterases (PDE). The isoform PDE5 is abundantly expressed in the lung.

Sildenafil is selective PDE5 inhibitor. The drug at the dose ranging from 20 to 80 mg 3 times daily appears to improve exercise capacity and hemodynamics in patients with PAH (42). There were no serious adverse events related to sildenafil treatment. Favourable survival rates with sildenafil were also published. These data have led to the approval of sildenafil at dose 20 mg 3 times daily for the treatment of PAH.

Tadalafil was recently registered at a dose of 40 mg once daily for PAH therapy.

Combination therapy

Treatment of PAH is evolving towards combination therapy with the aim of simultaneously targeting more than one pathogenetic pathway. The evidence that combination therapy with prostanoids, endothelin receptors antagonists and PDE5 inhibitors is safe and effective comes mostly from uncontrolled studies and several double-blind, placebo-controlled trials (43). Addition of bosentan to patients receiving inhaled, subcutaneous, or intravenous prostanoids improves exercise capacity and haemodynamics. The combination of intravenous epoprostenol and sildenafil compared to intravenous epoprostenol alone, improves exercise capacity in patients with PAH (44). A large clinical programme assessing potential synergistic effect in managing patients with PAH by combining bosentan and sildenafil has been initiated.

New developments

Several new compounds are in various phase of development, including rho kinase inhibitors, serotonin transporter inhibitors, statins, and vasoactive intestinal peptide. Imatinib, a tyrosine kinase inhibitor, reversed monocrotaline-induced pulmonary hypertension presumably by blocking platelet-derived growth factor signaling (45).

Interventional therapy of PAH

Balloon atrial septostomy and lung transplantation are indicated for refractory PAH or where medical treatments are unavailable (46).

Atrial septostomy is used as a palliative treatment or as bridge to lung transplantation in patients with advanced PAH to decompress failing right ventricle and increase cardiac output. Procedural mortality ranges from 5 to 50 %.

Lung transplantation is the final option in the management of PAH. Most centers prefer bilateral lung transplantation. Patients should be considered for transplantation when they are WHO functional class III or IV despite medical therapy. The 1-year survival rate is between 70 and 75 %, the 2-year survival rate is between 55 and 60 %, and the 5-year survival rate is between 40 and 45 %.

Comprehensive management of PAH

The management of patients with PAH should be concentrated in specialized centers that can provide both complete diagnosis and therapy of PAH (10, 47). PAH centers need to have sufficient experience especially with right heart catheterization and acute vasodilatation testing as well as with other intervention methods. During the last years a close regional co-operation between Czech and Slovak PAH centers has proved to be greatly profitable.

To the PAH center should be referred all patients with the gradient on tricuspid regurgitation (TR) more than 40 mmHg when left heart lesions causing pulmonary venous hypertension and lung diseases are excluded. Also border-line patients with

the gradient of TR 30–40 mmHg should be referred when their symptoms or echocardiographic features suspicious from pulmonary hypertension are progressive. Asymptomatic patients with the gradient of TR 30–40 mmHg need a regular 6 months follow-up at his regional cardiologist.

Conclusions

The right diagnostic proceeding as well as adequate management of patients with PAH requires a close collaboration of experienced cardiologists, pneumologists, rheumatologists, radiologists etc. Establishing an accurate and timely diagnosis of PAH and initiating appropriate treatment represent the major clinical challenges in the management of this disease.

The treatment of PAH has evolved considerably and the outlook for patients has subsequently improved due to a remarkable amount of research including RCT that have been realized over the last few years. But none of the currently available therapies is perfect and the regression of advanced pulmonary vascular remodeling is still a wishful thinking. Nowadays the combination therapy of PAH seems to be a promising course. For the future novel therapies studied in experimental models and human tissue appear to prevent and reduce pulmonary arterial medial hyperplasia through their anti-proliferative and/or pro-apoptotic effects. These agents have to be tested in patients with PAH.

The comprehensive management of patients with PAH should be reserved for specialized centers.

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