REVIEW ARTICLE

Contemporary Prospects for the Diagnostics and Treatment of Chronic Pulmonary Hypertension

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SUMMARY

Jansa P., Aschermann M., Lindner J. et al.: Contemporary Prospects for the Diagnostics and Treatment of Chronic Pulmonary Hypertension

Pulmonary hypertension is defined as a rise of mean pressure in the pulmonary artery over 25 mmHg at rest or over 30 mmHg during activity with accompanying increase of pulmonary vascular resistance over 3 WU (Wood's unit). According to the recent WHO classification from 2003, pulmonary hypertension can be further categorized as pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic pulmonary hypertension, chronic thromboembolic pulmonary hypertension and pulmonary hypertension from other causes. Since symptoms of pulmonary hypertension are non-specific, the diagnosis is frequently late. Patients with a higher risk of pulmonary hypertension require frequent echocardiographic examination. Treatment of pulmonary hypertension is rather complex and financially demanding. It should therefore be centralized in specialized units. The choice of pharmacotherapy is based on the acute pulmonary vasodilatation test. Only patients with a positive test (10% of patients) are indicated for treatment with calcium channel blockers. In the case of a negative test, the treatment of choice in NYHA III class is bosentam *per os*, in the NYHA IV class it is epoprostenol intravenously. In patients with chronic thromboembolic pulmonary hypertension, organized thrombotic material should be surgically removed together with the layer of the pulmonary artery (pulmonary endarterectomy) after preceding anticoagulation treatment lasting at least three months.

The Pulmonary Hypertension Center at the Cardiocenter of the General Teaching Hospital is the only unit in the Czech Republic which, in addition to the complex therapy of the pulmonary arterial hypertension, can also employ surgical treatment of chronic thromboembolic pulmonary hypertension.

Key words: pulmonary hypertension, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, calcium channel blockers, bosentan, epoprostenol, anticoagulation treatment, pulmonary endarterectomy.

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Pulmonary hypertension is a syndrome characterized by increased mean pulmonary arterial pressure over 25 mm Hg at rest or over 30 mmHg during activity and increased pulmonary vascular resistance over 3WU (Wood's units). The cause can range from simple transmission of elevated pressure in the left heart to complicated primary disease of the pulmonary arteries, which often progresses quickly and may have a fatal outcome several years after the first symptoms appeared.

Increased interest in primary pulmonary blood vessel diseases led to establishment of a new, so-called clinical classification of pulmonary hypertension (Venezian classification) (1). This classification categorizes pulmonary hypertension in five categories (Tab. 1). Clinical units in each category are characterized by similar pathogenesis, histological image, clinical symptoms and treatment. The classification omits functional and genetic factors. On the other hand, it allows clear communication on the topic of pulmonary hypertension, standardization of diagnostics and treatment, preparation of clinical studies and research of pathophysiological mechanisms in clearly defined populations of patients.

The major advances in the pharmacotherapy of pulmonary arterial hypertension (PAH) which we have experienced in the last few years, and the possibility of curative surgical intervention in the chronic thromboembolic pulmonary hypertension (CTEPH), have essentially changed the situation of patients with these previously incurable diseases.

ETHIOLOGY, PATHOGONESIS, EPIDEMIOLOGY

The main changes in the pulmonary blood vessels in patients with chronic pulmonary hypertension include vasoconstriction, blood vessel remodeling and thrombosis. These changes are probably caused by endothelial dysfunction associated with overproduction of vasoconstriction, growth and thrombogenic factors (endothelin-1, thromboxan) compared to factors with vasodilatation, antiproliferation and antithrombotic properties (prostacyclin, NO) (2).

PAH comprises a group of diseases characterized by severe precapillary pulmonary hypertension associated with primary disease

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Table 1. Clinical classification of pulmonary hypertension – Venice 2003

1. Pulmonary arterial hypertension (PAH)
- 1.1. Idiopathic (IPAH)
- 1.2. Familiar (FPAH)
- 1.3. Associated with (APAH):
  - 1.3.1. Connective tissue disease
  - 1.3.2. Congenital systemic to pulmonary shunts
  - 1.3.3. Portal hypertension
  - 1.3.4. HIV infection
  - 1.3.5. Drugs and toxins
  - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliterative disorders, splenactomy)
- 1. 4. Associated with significant venous or capillary involvement:
  - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
  - 1.4.2. Pulmonary capillary haemangiomatosis (PCH)
- 1. 5. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension associated with left heart diseases
- 2.1 Left-sided atrial or ventricular heart disease
- 2.2.Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung respirastory diseases and/or hypoxia:
- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Sleep disorded breathing
- 3.4. Alveolar hypoventilation disorders
- 3.5. Chronic exposure to high altitude
- 3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease:
- 4.1. Thromboembolic obstruction pf proximal pulmonary arteries
- 4.2. Thromboembolic obstruction of distal pulmonary arteries
- 4.3. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscelaneous:

Sarcoidosis, histocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

of the pulmonary arteries. Histological images show characteristic plexiform arteriopathy. The PAH includes most of all the idiopathic PAH where the inciting factor is still unknown. This factor leads to endothelial dysfunction and further on to blood vessel remodeling. In a familiar form, we also do not know the inciting factor. The disease is associated with a heterozygotic mutation of a receptor gene BMPR II (bone morphogenic protein) (3). Further on, the PAH group includes diseases similar to the idiopathic PAH; the inciting factor is considered to be systemic connective tissue diseases, an inborn heart defect, portal hypertension, anorectics abuse or HIV infection. The PAH prevalence is estimated to be 60-80 cases per 1 million inhabitants. It should be mentioned that there is a high occurrence of PAH in people with systemic sclerodermia (4).

Chronic obstruction pulmonary disease (COPD) is the most common cause of hypoxic pulmonary hypertension. Approximately 8-10 percent of patients with COPD suffer from pulmonary hypertension. In patients with interstitial pulmonary disease in its terminal stage, pulmonary hypertension is present in 60-70 percent of cases. Pulmonary hypertension is also present in 20-40 percent of patients with sleeping obstruction apnea syndrome.

CTEPH is a result of a so-called macroform or microform of repeated pulmonary embolism. The macroform takes a form of repeated fits of acute pulmonary embolia, while the clinical picture of the microform is initially silent and is manifested by progressive effort dyspnea, usually in the severe stage of pulmonary hypertension. CTEPH is characterized by intraluminal organized thrombi, multiple stenosis and occlusions of pulmonary artery branches. Pulmonary hypertension is not only a result of chronic mechanic obstruction of pulmonary arteries but also a result of blood vessel remodeling in the perfused regions. It is estimated that CTEPH develops in a course of 2 years in up to 4 percent of patients surviving acute pulmonary embolism. (5). The cause is not entirely clear. Hypercoagulation state can be diagnosed in a minority of cases.

CLINICAL PICTURE

Most symptoms in patients with chronic pulmonary hypertension are associated with increased pressure in the pulmonary artery. They are not specific for individual categories of pulmonary hypertension and they quite often do not occur until the pulmonary artery pressure reaches double the normal values (6). These nonspecific symptoms often result in late diagnosis.

Progressive stress dyspnea and fatigue are the most frequent symptoms. The severity of dyspnea significantly correlates with the prognosis. Anginous chest pain is a result of the right ventricle ischemia, while syncopes and presyncopes are symptoms of a low

cardiac output. Less frequent symptoms of this disease include hoarseness caused by recurrent laryngeal nerve compression due to the dilated pulmonary artery trunk, coughing and hemoptysis.

Objective findings are associated with the severity of pulmonary hypertension. Accentuated second heart sound over the pulmonary artery, the fourth heart sound and a gallop rhythm are often present. The third heart sound is present in severe cases of the disease. Murmur of tricuspid and pulmonary regurgitation may also be present. Most patients present with increased filling of neck veins and a palpable systolic pulse in the precordial region or in the epigastrium due to right ventricle hypertrophy. Severe stages are then characterized by peripheral edema and cyanosis.

DIAGNOSIS

The goal of diagnostic examinations is to prove or exclude pulmonary hypertension, assessment of etiology and the level of severity.

Echocardiography is the key non-invasive diagnostic tool (7). It provides an assessment of the size, shape, hypertrophy, and function of the right ventricle and an estimate of the pressure in the pulmonary artery. Further on, echocardiography is essential to exclude a shunt defect, valve or myocardial defects as a cause of the pulmonary artery hypertension. Doppler echocardiography is essential for evaluating the level of pulmonary hypertension. Prognostically unfavorable echocardiographic signs in pulmonary hypertension include dilatation of the right ventricle and presence of precardial exudation. Patients with a high risk of developing PAH (especially patients with sclerodermia) need to undergo echocardiography regularly.

ECG signs of the right ventricle hypertrophy as well as increased heart rate at rest are considered to be independent negative prognostic factors. Signs of right ventricle hypertrophy are specific for the pulmonary artery hypertrophy, but they are a little sensitive (8).

A chest X-ray usually reveals dilatation of the pulmonary artery trunk. Further findings may help in classification of the type of pulmonary hypertension.

Ventilation and perfusion scintigraphy is essential in the diagnosis of pulmonary embolism and CTEPH.

A spiral CT may, for example, reveal thrombo-embolic disease (after the contrast matter application) or an interstitial pulmonary disease.

Magnetic resonance imaging allows us to assess not only the morphological but also the functional parameters of the pulmonary circulation. We can evaluate the surface and volume of individual heart compartments and the pressure in the pulmonary artery. In routine care of patients with the pulmonary artery hypertension, however, magnetic resonance imaging is not necessary. All relevant information may be obtained using other tests and examinations.

Polysomnography should be performed in patients with a risk of the syndrome of obstructive sleep apnea (obese patients and those with excessive day sleepiness and snoring at night).

Pulmonary artery angiography is essential for establishing a precise diagnosis of the CTEPH before performing pulmonary endarterectomy. The angiographic finding of the bronchial-pulmonary collaterals helps in differentiating between CTEPH and PAH.

Right heart catheterization with hemodynamic evaluation provides a definite diagnosis of pulmonary hypertension. It further provides information regarding the precise quantification of the pulmonary hypertension, assessment of the heart output, pulmonary vascular resistance and measurement of the vasodilatation response in the test of acute pulmonary vasodilatation (9).

The simplest, cheapest and most easily-repeated stress test is the six-minute walk test. The results well correlate with the severity of pulmonary hypertension and the prognosis of the disease (10).

Pulmonary tissue biopsy is indicated only when diagnosis is unclear in order to exclude vasculititis or an interstitial lung desease as a cause of pulmonary hypertension.

TREATMENT

The prognosis of untreated symptomatic chronic pulmonary hypertension is very unfavorable. While patients with the NYHA class I or II have an average survival time of 5 years, in the NYHA stage III it is only 2.5 years and in the NYHA class IV it is only 6 months (11, 12). An essential breakthrough in the unfavorable prognosis of patients with pulmonary hypertension has been brought about by new possibilities of effective treatment, especially in the last decade. In PAH, medical treatment leads to dramatic improvement in life prognosis, while in CTEPH surgical therapy is often curative. The possibilities of drug therapy in hypoxic pulmonary hypertension are also being investigated.

The goal of drug therapy in PAH is to affect 3 elementary pathophysiological mechanisms that cause the initiation and development of the disease (vasoconstriction, proliferation, procoagulation) and to influence the symptoms and prognosis of the patients. In addition to conventional therapy, including administration of anticoagulation agents, vasodialatation using calcium blockers and treatment of heart failure, there are many specific drug agents such as prostanoids, endotelin-1 receptor antagonists and inhibitors of the phosphodiesterase available.

Calcium channel blockers are indicated in only 10% of patients with PAH with preserved vasoreactivity (13). All patients with PAH who do not have any contraindication should be treated with anticoagulants (14). The target INR in the treatment using vitamin K antagonists should be around 2.

Prostanoids are indicated in patients with the PAH in the NYHA class III and IV if they are non-responders in the test of acute pulmonary vasoreactivity (15). Epoprostenol is a synthetic analogue of prostacyclin that needs to be administered continuously for a longer period via a central venous catheter due to its short biological half-life. The vasodilatation effect of epoprostenol on pulmonary circulation in patients with advanced PAH is not important. The antiproliferative, antiaggregation and positive ionotropic effects are especially important. Epoprostenol improves functional efficiency, hemodynamic parameters, quality of life and most of all prognosis in the patients. Today it is the first-line treatment and the most effective alternative to transplantation in patients with PAH in the NYHA class IV. Treprostinil is a stable prostacyclin analogue. It can be administered subcutaneously or intravenously; inhalation is also being tested. Subcutaneous infusion is less demanding compared to intravenous infusion concerning the infusion pump and helps avoid complications associated with the central venous catheter. Beraprost is a peroral stable analogue of prostacyclin. It is effective in early stages of the PAH. Iloprost is a stable prostacyclin analogue used in the treatment of the PAH. It is either inhaled or administered intravenously. The disadvantage of inhalation is the need for ultrasound nebulization 6-9 times per day. The inhalation form of administration avoids systemic side effect of the drug; however, long-term treatment leads to stabilization of the disease in only a small number of patients.

Selective or dual antagonists of the endotelin-1 receptor are used in the treatment of the PAH. An essential advantage of the endotelin receptor antagonists is the possibility of *per os* administration; the disadvantage is a dose-dependent liver toxicity (16). Bosentan is a dual endotelin-1 antagonist with a high affinity to the ET_A receptor. The effect of bosentan treatment in the PAH is well documented in

patients with idiopathic PAH and in patients with PAH associated with scleroderma, HIV infection and PAH resulting from inborn heart shunt defects. As well as a significant functional improvement and hemodynamic parameters improvement, bosentan also leads to improvement of the patients' prognosis. Bosentan is the drug of choice in patients with PAH in the NYHA class III. Selective antagonists, sitaxsentan and ambrisentan are still not available in clinical practice.

Sildenafil is a peroral selective phosphodiesterase 5 inhibitor. Sildenafil treatment of PAH leads to improved functional efficiency, hemodynamics and prognosis (17). It can be expected that sildenafil will become the treatment of choice for some patients.

Non-pharmacological modalities in the treatment of the PAH include balloon atrial septostomy and lung transplantation (18). Atrial septostomy, a palliative interventional method, creates an artificial communication between the atria resulting in a right-left shunt. The goal of the intervention is to increase the cardiac output. Lung transplantation is an effective method in patients in the terminal stage of the PAH when all other available therapeutic methods are ineffective.

The pulmonary artery endarterectomy is a potentially curative method for patients with CTEPH, especially when the central branches of the pulmonary artery are affected (19). The principle of the surgery is not embolectomy but rather endarterectomy, i.e. removing the organized fibrin thrombus with a part of the blood vessel wall of the pulmonary artery. The procedure is performed via sternotomy in extracorporeal circulation and deep hypotheramia. Visualization of the distal branches of the pulmonary artery is essential in order to perform successful surgery. In the case of CTEPH it is complicated by a significant collateral flow from the bronchial arteries. That is why the endarterectomy, which lasts 20-30 minutes on the right side and 20-30 minutes on the left side, takes place in a complete circulation arrest. Hypothermia then serves as a brain protection mechanism. Key parameters for selecting the patients include functional efficiency, level of pulmonary hypertension and surgical access to the thrombotic obstruction. Symptomatic patients with a pulmonary blood vessel resistance of 800 dyn.s.cm^{-5} (10 WU) are indicated for surgery. Prior to surgery it is necessary to undergo at least three months of anticoagulation therapy. In patients with CTEPH who are not candidates for surgery, specific pharmacotherapy, percutaneous balloon atrial septostomy or lung transplantation may present alternative forms of treatment. More experience is needed, however.

SITUATION IN THE CZECH REPUBLIC

The issue of pulmonary circulation has been dealt with at several departments in the Czech Republic. At present the 2nd Medical Department of the 1st Medical Faculty and the General Teaching Hospital in Prague place the most intensive focus in this issue. The Center for Pulmonary Hypertension of the General Teaching Hospital provides not only pharmacotherapy, but it is also the only center in the Czech Republic to deal with surgical treatment of the CTEPH (20).

From 1998 to November 2005 PAH was diagnosed in 92 patients. Next to conventional treatment, all other key specific preparations are used (epoprostenol, treprostinil, iloprost, bosentan, sildenafil). There was one successful case of balloon atrial septostomy. A program of pulmonary artery endarterectomy has been under development in cooperation with Professor Eckhard Mayer from Mainz at the Cardiocenter of the GTH since 2004. 17 successful surgeries have been performed so far. We expect to indicate 20-30 patients for pulmonary artery endarterectomy in the Czech Republic. It is rational to maintain 1 center in the Czech Republic.

CONCLUSION

Despite all the medical advances, PAH still remains an incurable disease. Current pharmacotherapy is able to relieve the symptoms, influence the hemodynamics parameters and improve the quality of life and the patients' prognosis. The treatment is, however, extremely costly and - especially in parenteral drug administration - complicated by many side effects. There is great hope for the development of peroral treatment. It is, however, limited in its application and often remains ineffective in patients with disease progression. Combined treatment seems to be very promising.

CTEPH represents one of the few types of the chronic pulmonary hypertension that can be treated surgically. Precise diagnostics and localization of the thrombotic obstruction is essential. Close interdisciplinary cooperation between the cardiosurgeon, intensive care specialist, cardiologist and radiologist is necessary.

The unfavorable prognosis in patients with pulmonary hypertension, complicated differential diagnosis and complicated and very expensive treatment all suggest the need to concentrate the patients in specialized centers. This is the only way to provide them with optimal and complex care and gain maximum experience with treating this disease.

Abbreviations
CT – computer tomography
CTEPH – chronic thromboembolic pulmonary hypertension
COPD – chronic obstructive pulmonary disease
INR – International Normalized Ratio
PAH – pulmonary arterial hypertension
NO – nitric oxide
WU – Wood's unit

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