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REVIEW

Pulmonary hypertension: its diagnosis and management, a multidisciplinary approach

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ABSTRACT

Pulmonary hypertension is a devastating complication of various, but rare diseases and can also occur as an isolated entity. It causes morbidity and mortality in all patients. Ongoing research has provided some insight into the pathophysiology and clinical manifestations, and new therapeutic options have recently become available for some types of pulmonary hypertension. In order to provide optimal care for an individual patient it is mandatory to establish the type and severity of the pulmonary hypertension in each patient. The diagnostic protocol used in our hospital is presented along with a description of two case histories. An algorithm of the different therapeutic strategies now available is given as well as recommendations for follow-up.

KEYWORDS

Diagnostic protocol, pulmonary hypertension, systemic sclerosis, unexplained breathlessness

INTRODUCTION

Pulmonary hypertension is a life-threatening condition which can occur either as an isolated entity or as a complication of various diseases. If left untreated, it causes increasing breathlessness and eventually death in all cases. Pulmonary hypertension is defined as a mean pulmonary artery pressure of >25 mmHg at rest or >30 mmHg during exercise, measured during right heart catheterisation.[1]

The most common symptoms of pulmonary hypertension are breathlessness, fatigue and (near) syncope.[2] Since these symptoms are nonspecific, pulmonary hypertension is often overlooked or diagnosed only in advanced stages. Pulmonary hypertension is a well-known complication of connective tissue diseases such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD). Because of the physical limitations arising from these underlying diseases, patients with pulmonary hypertension as a complication of these diseases complain of shortness of breath at a later stage than the normal population. Deaths that have previously been assigned to heart attacks may in fact have been caused by pulmonary hypertension. Pulmonary hypertension usually occurs late in the course of collagen vascular diseases. Since the majority of these patients are seen at regular intervals by rheumatologists or internists, this presents us with an opportunity to screen for pulmonary hypertension at an earlier stage, thus making it possible to start a therapy that may prevent progression of pulmonary hypertension and premature death. Although pulmonary function testing and echocardiography are widely used as screening tests and can identify patients with advanced pulmonary hypertension, these tests cannot be considered to be adequate for the exclusion of pulmonary hypertension in breathless patients. Therefore, a clinical history of longstanding dyspnoea should potentially be regarded as a sign of pulmonary hypertension, irrespective of the findings of pulmonary function testing and echocardiography,[3] and should prompt a right heart catheterisation, the gold standard for the assessment of pulmonary hypertension.

In 2003, the World Health Organisation (WHO) proposed a new classification for pulmonary hypertension. The basis of this new classification (*table 1*) is the notion of common pathophysiological processes involving the pulmonary blood vessels in all forms of the disorder.[4] These pathophysiological processes include (i) endothelial dysfunction which results in exaggerated vasoconstriction and impaired vasodilatation, promoting vascular remodelling of all layers of the vessel wall;[5] (ii) proliferation of the adventitia limiting vascular elasticity; (iii) hypertrophy of the medial smooth muscle promoting vasoconstriction and (iv) occlusion of the vascular lumen due to intima proliferation and *in situ* thrombosis. The availability of new therapies that have been shown to slow down or prevent progression of pulmonary hypertension has caused a growing interest among physicians to diagnose pulmonary hypertension at an early stage. Since various specialities can be confronted with patients with pulmonary hypertension, we started a multidisciplinary pulmonary hypertension outpatient clinic (MPHO clinic), comprising a rheumatologist/internist, pulmonologist, cardiologist and a specialised nurse, in order to facilitate early and fast diagnosis according to a protocol, and to institute the best therapies currently available.

In this paper we describe two patients who presented to this MPHO clinic, to illustrate the different diagnostic procedures of our protocol and the instituted therapies.

Table 1 *Revised WHO clinical classification of pulmonary hypertension (Venice 2003)*[6]

Group 1: Pulmonary arterial hypertension
Idiopathic
Familial
Associated with
- Collagen vascular disease
- Congenital systemic to pulmonary shunts
- Portal hypertension
- HIV infection
- Drugs/toxins
- Other

Associated with significant venous or capillary involvement
- Pulmonary veno-occlusive disease
- Pulmonary capillary haemangiomatosis

Persistent pulmonary hypertension of the newborn

Group 2: Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease

Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxaemia
Chronic obstructive lung disease
Interstitial lung disease
Sleep disorder breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumour, parasites, foreign material)

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

CASE REPORT 1

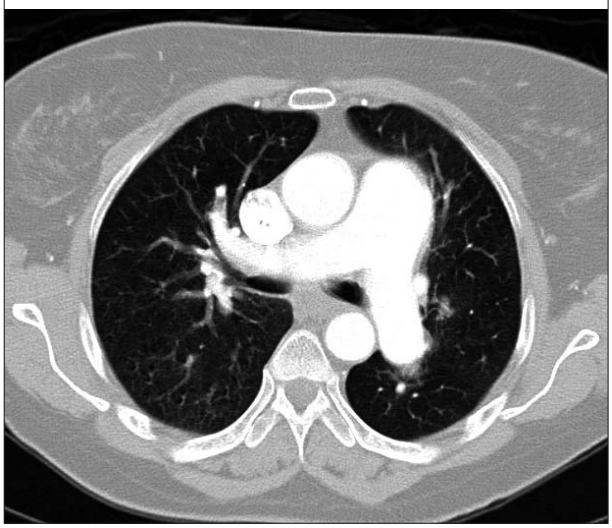
A 22-year-old Asian female was referred to our outpatient clinic. She had been diagnosed with SLE seven years before with symptoms of fever, Raynaud's phenomenon, pericarditis, pleuritis, ANA and anti-dsDNA positivity, and at a later stage also with arthritis of the knees. From the onset of her disease she had been treated with low-dose prednisone and azathioprine until three years ago when her SLE was considered to be in remission. On presentation she reported a two-year history of shortness of breath on exertion with an inability to exercise. Symptoms of right-sided heart failure were not present. On physical examination she was dyspnoeic while undressing, with an unremarkable internal and rheumatological examination. The electrocardiogram (ECG) revealed right ventricular hypertrophy. The results of the laboratory investigations were unremarkable except for ANA positivity with anti-SM autoantibodies and anti-dsDNA antibodies 10 IU/ml present. Pulmonary function testing showed no evidence of restrictive or obstructive lung disease, but a marked decrease in diffusion capacity was present: carbon monoxide transfer (DLCO) 60% of predicted. The echocardiogram showed pulmonary hypertension with normal left ventricular function. A right heart catheterisation revealed a pulmonary artery pressure of 79/37 mmHg with a mean of 54 mmHg. Right atrial pressure was 12 mmHg (normal), and the cardiac index was 2.9 l/min/m^2. The pulmonary vascular resistance was increased to 781 dynes.sec.cm^{-5}. Since pulmonary hypertension was established, a vasodilator test was performed. First the patient breathed 100% oxygen, and the measurement of the pulmonary artery pressure was repeated and found to be unchanged. Next prostacyclin up to 12 ng/kg/min was used to determine vasoreactivity of the pulmonary arteries, that is a significant decrease in pulmonary artery pressure, which was not present in this case. A ventilation/perfusion scan was negative for pulmonary embolism, as was the ultrasound of the abdomen for portal hypertension. A six-minute walk test (6-MWT) was performed. This is the distance a patient can walk in six minutes with encouragement, in a standard-

ised setting.[7] A healthy person has a 6-MWT of 650 to 750 meters. This patient had a 6-MWT of 505 m. She was diagnosed with pulmonary arterial hypertension, WHO group I, related to autoimmune disorder (*table 1*), NYHA functional class III. Treatment was started with bosentan, an oral dual endothelin receptor antagonist, 62.5 mg twice daily during the first four weeks, and 125 mg twice daily thereafter. Bosentan was well tolerated and after three months of treatment her NYHA functional class had improved from III to II and her 6-MWT was 537 m. The treatment was considered successful and continued. Until now, 18 months later, our patient is doing well and still on the same medication.

CASE REPORT 2

A 57-year-old Caucasian woman was referred for a second opinion. Her medical history was unremarkable until eight years ago, when a gradual progression of shortness of breath occurred. Because the echocardiogram was suggestive of pulmonary hypertension the patient was referred to the MPHO clinic for further evaluation. On physical examination she was dyspnoeic while undressing. Internal and rheumatological examinations were unremarkable; in particular there were no signs of right-sided heart failure present. Laboratory evaluation was normal. Pulmonary function testing revealed only a slight reduction in the diffusion capacity (DLCO was 79% of predicted), without signs of restrictive or obstructive lung disease. Blood gas analysis showed hypoxaemia, with PaO_2 of 5.9 kPa at room air. The echocardiogram performed in our hospital was also suggestive of pulmonary hypertension, which was confirmed with right heart catheterisation. Her pulmonary artery pressure was 104/55 mmHg, with a mean of 69 mmHg. The pulmonary vascular resistance and the cardiac index were 787 dynes.sec.cm^{-5} and 1.87 l/min/m^2 respectively. Vasoreactivity testing was negative. A ventilation/perfusion scan was negative for pulmonary embolism, as was the ultrasound of the abdomen for portal hypertension. The CT angiography of the lungs revealed dilated central pulmonary arteries and was otherwise unremarkable (*figure 1*). Her 6-MWT was 397 m. The diagnosis of idiopathic pulmonary arterial hypertension NYHA functional class III was made and treatment was started with bosentan. After three months she had improved to NYHA class II and her 6-MWT improved to 462 m.

Figure 1 *CT angiography of case 2, showing dilated central pulmonary arteries*



DIAGNOSIS OF PULMONARY HYPERTENSION: A DIAGNOSTIC PROTOCOL

Pulmonary hypertension should be suspected in any patient with unexplained shortness of breath. Next, two noninvasive tests can be performed to obtain further indications of pulmonary hypertension: pulmonary function testing and echocardiography. A decreased diffusion capacity with signs of mild restrictive lung disease is suggestive of pulmonary hypertension.[8] With transthoracic echocardiography an estimation of the systolic pulmonary artery pressure from the tricuspid regurgitation jet velocity and the jugular venous pressure can be made.[9] The diagnosis of pulmonary hypertension should be confirmed by right heart catheterisation, widely considered the gold standard for the diagnosis of pulmonary hypertension. During right heart catheterisation direct measurements of pulmonary artery pressure, right heart pressures, mixed venous oxygen saturation, cardiac output, pulmonary vascular resistance, and response to vasodilator drugs can be made. Also, right heart catheterisation is mandatory to measure the pulmonary wedge pressure to exclude left-sided heart disease as a cause of pulmonary hypertension. Once diagnosed, pulmonary hypertension should be classified according to the WHO classification and to the degree of functional disability, based on exercise performance, according to the New York Heart Association (NYHA) criteria (*table 2*), in order to establish the best treatment options.[1] The differential diagnosis of pulmonary hypertension can be extracted from the WHO classification. For the analysis of patients with pulmonary hypertension we designed a protocol that is performed in each patient with suspected pulmonary hypertension. These patients are seen at a special outpatient clinic, the MPHO clinic, where they are examined by a multidisciplinary team consisting of a rheumatologist/internist, pulmonologist, cardiologist and a specialised nurse. Prior to the diagnostic work-up, a careful history of each patient is taken, with special attention for the symptoms of dyspnoea, symptoms related

Table 2 *Modified New York Heart Association functional classification*[1]

Class I
Patients with pulmonary hypertension in whom there is no limitation to usual physical activity. Ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or near syncope.

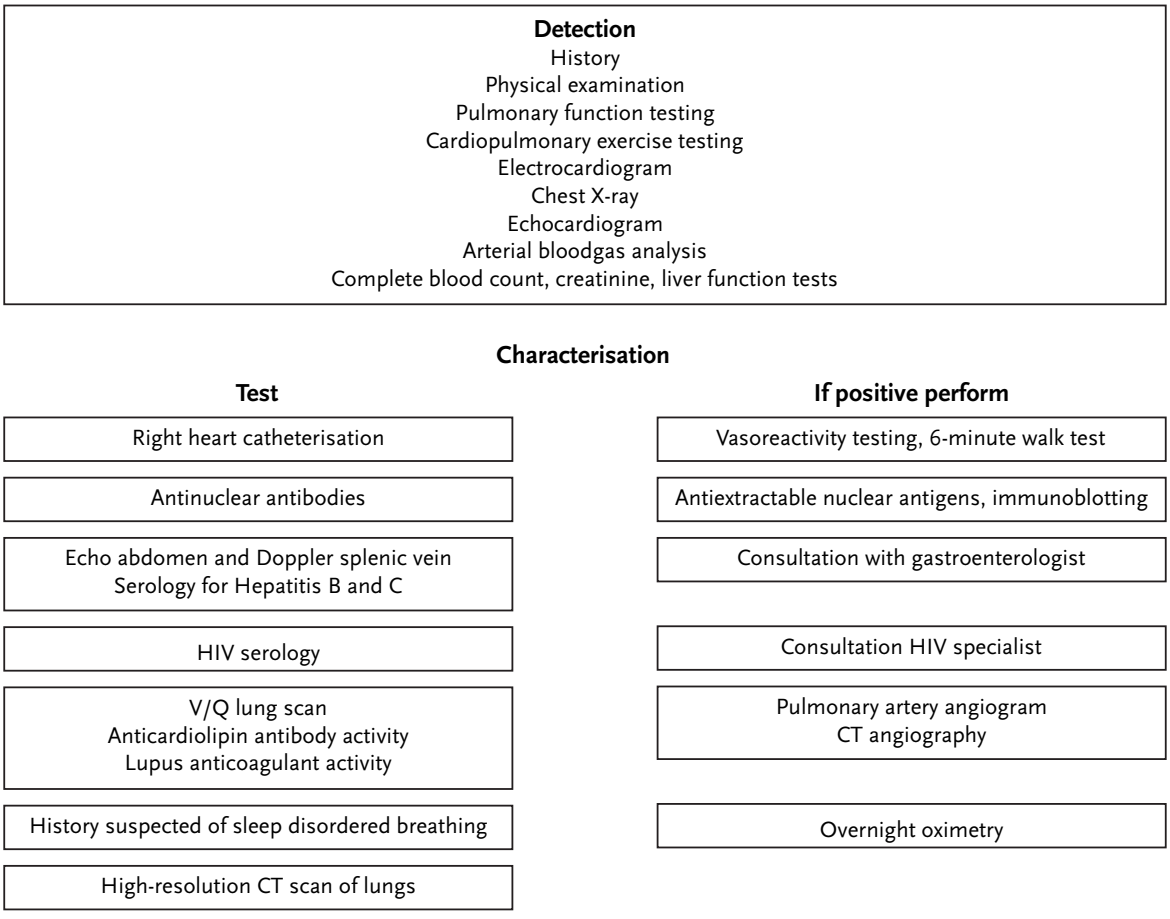
Class II
Patients with pulmonary hypertension who have a mild limitation of physical activity. They are comfortable at rest. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or near syncope.

Class III
Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary physical activity causes increased dyspnoea, fatigue, chest pain, or near syncope.

Class IV
Patients with pulmonary hypertension who are unable to perform any physical activity without symptoms and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

to autoimmune disorders, and prior drug and toxin use. A routine internal and rheumatological examination is performed, focussed on signs and symptoms of pulmonary hypertension and diseases known to be complicated by pulmonary hypertension. Furthermore, pulmonary function testing, including exercise tests, namely a 6-MWT and if possible a symptom limited exercise test on a cycle ergometer, chest X-ray, ECG, echocardiography and blood analysis are performed directly following the consultation. When the results of history and examinations are further indicative of pulmonary hypertension, right heart catheterisation is carried out, and if pulmonary hypertension is confirmed vasoreactivity tests are performed. The protocol used by our multidisciplinary team is schematically shown in *figure 2*. This approach consists of both essential tests, which are performed on each patient, and complimentary tests. After the results of the tests have become available the patients are discussed by the multidisciplinary team and the appropriate treatment is chosen and proposed to the patient during a follow-up visit. Patients with pulmonary hypertension are included in a prospective follow-up study.

Figure 2 *Diagram showing analysis of pulmonary hypertension*



TREATMENT STRATEGIES

General treatment

The general therapeutic options for pulmonary hypertension include oxygen therapy in patients with hypoxaemia, anticoagulant drugs if there are no contraindications and digoxin and diuretics in cases of right-sided heart failure. If the pulmonary vasoreactive tests are positive, the treatment of choice is high-dose calcium channel blockers. Vasoreactivity is considered to be present when the mean pulmonary artery pressure has decreased by at least 10 mmHg to 40 mmHg or less with normal or high cardiac output after intervention with pulmonary vasodilators, such as 100% oxygen, nitric oxide inhalation or intravenous prostacyclin.[1] Only 10 to 15% of the idiopathic pulmonary arterial hypertension patients meet these criteria.[10] The percentage of vasoreactive patients in the group with pulmonary arterial hypertension associated with autoimmune disorders is unknown, but believed to be even lower. Favourable clinical and prognostic effects of high-dose calcium channel blockers in vasoreactive patients have been shown in nonrandomised, noncontrolled studies.[11,12] The occurrence of side effects such as oedema, headache, tachycardia and hypotension limits the use of high-dose calcium channel blockers. If there is no vasoreactivity present or high-dose calcium channel blockers have to be discontinued because of side effects, the next treatment steps are based upon the WHO classification and functional NYHA classification.

Specific treatment

Specific treatment is available for some of the causes of pulmonary hypertension, for example pulmonary arterial hypertension, WHO group I. Bosentan, an oral endothelin antagonist, has been approved for pulmonary arterial hypertension, NYHA class III. The efficacy of bosentan has been established in two randomised placebo-controlled trials in which a significant improvement in the 6-MWT occurred after 12 weeks of treatment.[13,14]
Epoprostenol has been approved for the treatment of patients of the same WHO group I, in NYHA class III but also NYHA class IV. In several randomised controlled trials in idiopathic pulmonary hypertension the beneficial effects of epoprostenol were proven on survival, exercise tolerance, functional class and pulmonary vascular haemodynamics.[15-17] In pulmonary arterial hypertension (PAH) occurring in association with autoimmune disorders, a randomised controlled study showed a significant improvement in exercise capacity and haemodynamics in the treatment group.[18]
Recently, sildenafil, an oral phosphodiesterase inhibitor, has been shown to be effective in pulmonary arterial hypertension patients, both in patients with idiopathic PAH and in patients with PAH associated to autoimmune disorders, with an improvement in symptoms and exercise capacity[19-21] and a large placebo-controlled phase III trial is pending.
Other new drugs, such as treprostinil, a subcutaneously administrated prostaglandin, and sitaxsentan, a selective endothelin-A receptor antagonist, have given promising results in randomised clinical trials.[22]

When pulmonary arterial hypertension is diagnosed but patients are in NYHA class I or II, they are evaluated again after six months or sooner if there are signs of clinical deterioration. If a patient is in NYHA class III, the treatment of choice is bosentan. At the start of this therapy the patient is also informed about treatment possibilities when bosentan fails, including (heart) lung transplantation. The efficacy of bosentan is evaluated after three months and every three months thereafter. The treatment is considered effective if the 6-MWT is at least stable. If the treatment with bosentan fails, the next treatment option is continuously intravenously administered epoprostenol. This is also the treatment of choice for patients in NYHA class IV.
Other therapeutic options include combination therapies with epoprostenol and bosentan[23] and/or sildenafil.[24]
Atrial septostomy, a surgical procedure to create a right-to-left shunt that increases the cardiac output in cases of right-sided ventricular failure can also be considered.[25-27] Current indications for this procedure are limited and considered a bridging therapy to transplantation.
Treatment for the other causes of pulmonary hypertension, namely the WHO group II to V, is mainly supportive, and is focussed on the underlying disease. Physicians should pay special attention to pulmonary hypertension WHO group IV, chronic thrombotic and/or embolic diseases, because bilateral pulmonary thromboendarterectomy can be a curative treatment for these patients.[28]

CONCLUSION

Patients with pulmonary hypertension have a life-threatening disease. In order to provide adequate care for these patients it is necessary to perform a complete analysis to rule out the other differential diagnostic possibilities and to establish the type of pulmonary hypertension. We have described the protocol for pulmonary hypertension in our hospital, including treatment and follow-up strategies. Collaboration of a multidisciplinary team of rheumatologists/internists, pulmonologists, cardiologists and specialised nurses accounts for the most optimal diagnostic and therapeutic procedures.

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