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CLINICAL STUDY

The long-term response to treatment with calcium channel blockers in a patient with idiopathic pulmonary arterial hypertension.

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Abstract: Pulmonary arterial hypertension (PAH) is a disease characterised by a gradual increase in resistance of pulmonary circulation leading to right ventricular failure and death. In only 10 % of cases, there is a response to acute vasoreactivity testing with a significant reduction in mean pulmonary artery pressure (PAP), while in this group of patients, less than one half of cases benefit from long-term treatment with calcium channel blockers (CCB). This paper describes a case report of a young patient with dyspnoea and suspicion of pulmonary hypertension who was referred to a specialised centre. The complex evaluation of her clinical state led to confirmed diagnosis of idiopathic pulmonary arterial hypertension (IPAH). Because there was a positive response to vasoreactivity testing, the treatment for IPAH was initiated with a high dose of CCB. This treatment markedly improved her clinical state as well as echocardiographic and hemodynamic findings.
In this study, the authors present a diagnostic algorithm in pulmonary hypertension and emphasise the role of CCB in treatment of PAH in carefully selected patients *(Tab. 1, Fig. 5, Ref. 7)*. Full Text in PDF *www.elis.sk.*
Key words: pulmonary hypertension, pulmonary arterial hypertension, acute vasoreactivity testing, treatment, calcium channel blockers.

Pulmonary arterial hypertension (PAH) is a serious disease resulting from restriction of flow through the pulmonary arterial circulation. There is a variety of pulmonary arterial abnormalities including endothelial dysfunction, excessive vasoconstriction, intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis *in situ*, plexiform lesions and varying degrees of inflammation. These changes lead to pulmonary arteriopathy resulting in a progressive increase in pulmonary vascular resistance, pressure-overload and failure of right ventricle, and death (1, 2). The prognosis for severe stages of PAH is often worse than that for many malignancies (3, 4). Early diagnosis and correct treatments are among the ways of positively affecting the prognosis of patients. Until recently, there was only one treatment modality, namely comprised of an empiric use of CCB and nonspecific treatment of right heart failure. Due to new therapeutic modalities that specifically affect the pathophysiological processes of clinically manifested PAH, the progression and prognosis of patients with this rare disease are more favourable (5). Hence, there is a small group of patients (about 10 %) who are indicated for CCB treatment while in case of long therapeutic response of the disease to this treatment, the prognosis is relatively favourable (6).

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This study describes a case of a young woman who was referred to a specialised PAH centre with dyspnoea and suspicion for pulmonary hypertension. A diagnostic algorithm in pulmonary hypertension is presented, and the position of CCB in the treatment of PAH of carefully selected patients was emphasised.

Case report

A 21-year-old woman was referred to PAH centre by a pneumologist for effort dyspnoea and suspicion for pulmonary hypertension.

The patient had no history of any diseases and never had a serious health problem. However, when she was fourteen, she experienced syncope during exercise. Since that time, she has been observing a slow decline in her physical condition.

She has been frequently suffering from shortness of breath, increased fatigue and dizziness. At the time of her referral, she was working in an office while studying at a university and thought that the worsening of her condition resulted from lack of physical exercise. With regard to the experienced syncope, she was frequently examined by an internist and neurologist but they did not reach any relevant conclusions. It was assumed that her syncope resulted from hypotension. Because of effort dyspnoea, she was also examined by a pneumologist. As her basic spirometry was normal, a possibility of interstitial lung disease was predicted. The lungs were examined by computerised tomography (CT). This procedure showed no pathology in pulmonary interstice but surprisingly it documented a severe dilatation of the pulmonary

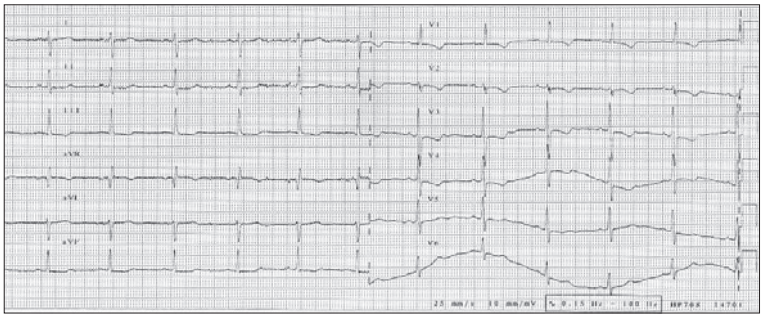

Fig. 1. ECG. Right ventricular hypertrophy and overload.

trunk. Therefore, the patient was referred to echocardiography. The results demonstrated a dilatation of the right ventricle and a typically D-shaped left ventricle, thus showing a dilatation of the pulmonary trunk with an estimation of systolic PAP of approximately 70 mmHg. She was then referred to a specialised centre with suspicion of PAH. It took seven years from her first syncope to her admission to specialised centre.

At admission, she complained of fatigue and shortness of breath when climbing stairs to the first floor. She was of asthenic habitus, with a body mass index (BMI) of 17.6. Her systemic blood pressure was 120/65 mmHg, and her resting heart rate was 80 beats/min. There was an accentuated pulmonary compound of S_2 and permanent cleft of S_2 audible over the pulmonary artery. The remaining physical examination was physiological.

There was no abnormality in complete blood cell count or in haemocoagulation including the screening for hereditary coagulopathy. Complex biochemistry revealed abnormalities in bilirubin values (total bilirubin 18.1 μmol/l, direct bilirubin 5.1 μmol/l) and cholesterol (3.2 mmol/l). The value of NT-proBNP was normal (98.9 μg/l). In addition, blood pH was within the physiological range.

ECG showed a sinus rhythm, domination of right ventricle, and its hypertrophy with overload (Fig. 1). Chest X-ray showed a prominence of the pulmonary arch, dilatation of the right descendent pulmonary artery and pruning of peripheral vasculature. The shadow of the heart was not enlarged (Fig. 2). Echocardiography documented a dilatation of the right ventricle (diastolic diameter 42 mm) with well-preserved systolic function (TAPSE 18 mm). There was a tricuspid regurgitation of first degree, and the estimation of systolic PAP (60 mmHg) was derived from tricuspid regurgitation peak jet velocity. Flow velocity in the right outflow tract measured by pulsed-wave Doppler was 100 cm/s, and acceleration time (ACT) was 80 msec. Left ventricle was not enlarged, displayed good systolic function with an index of deformity of 0.74. There was a leftward septal shift at end-systole and early diastole.

Because transoesophageal echocardiography has not been performed due to the patient's intolerance, we performed contrast echocardiography examination with agitated saline contrast ("bubble study"). We did not show proof of a shunt at the level of interatrial septum. All ventilatory parameters during spirometry were within the physiological range: forced vital capacity (FVC) was 89 % of reference value adjusted for patient's age, and forced expiratory volume in one second (FEV1/FVC) was 121 %. Peak oxygen consumption (peak VO_2) during spiroergometry was 20.4 ml/kg/min, and anaerobic threshold was achieved at VO_2 17.3 ml/kg/min. The ECG signs of right ventricle overload were marked during this examination, and there was an absence of adequate increase in systolic blood pressure during exercise (six-minute walking distance was 540 metres).

Right heart catheterisation (RHC) measures and calculations are as follows: systolic/diastolic/mean PAP (PAP s/d/m) = 72/37/53 mmHg, pulmonary artery wedged pressure (PAWP) = 11 mmHg, central venous pressure (CVP) = 6 mmHg, cardiac output (CO) = 4.5 l/min, cardiac index = 2.9 l/min/m^2. The transpulmonary pressure gradient (TPG) was 42 mmHg, and the pulmonary vascular resistance (PVR) was 9.3 Wood units. Vasoreactivity testing was done with intravenous (i.v.) adenosine (total dose 100 μg/kg/min). The values of PAP decreased to 49/22/37 mmHg, CO increased to 7.5 l/min, TPG decreased to 27 mmHg and PVR decreased to 3.6 Wood units. These findings indicated a precapillary PAH reversible in vasoreactive testing.

To identify potential causes of PAH, other tests were performed. Serology showed negative antibody reactivity against HIV as well as negative reactivity of anti-nuclear and anti-centromeric antibodies used to screen for connective tissue disease. Ultrasound of the abdomen showed physiological findings in abdominal organs, and there were no signs of portal hypertension.

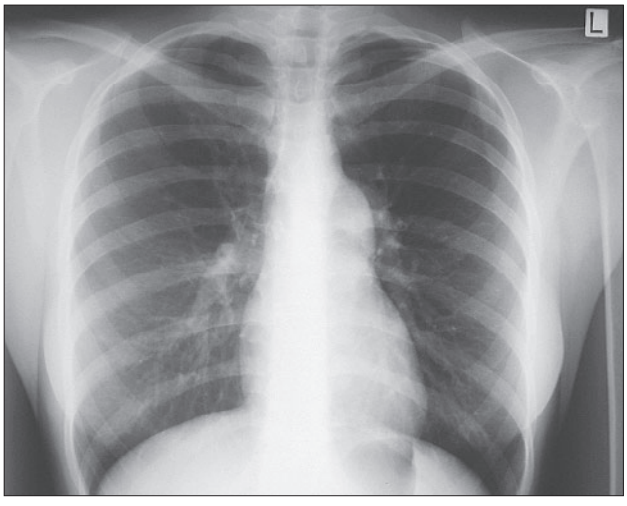

Fig. 2. Chest X-ray: Pruning of peripheral vasculature; prominence of the pulmonary arch; dilatation of the right descendent pulmonary artery.

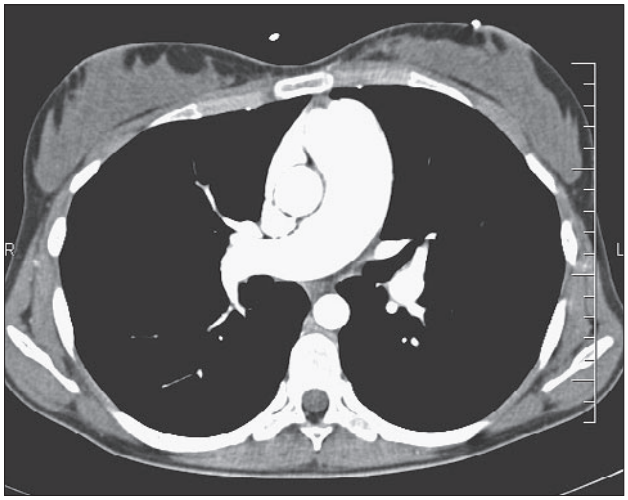

Fig. 3. Pulmonary trunk dilatation on CT imaging.

Doppler ultrasound of venous system of lower extremities and CT pulmonoangiography excluded thromboembolic affliction. CT documented severe dilatation of pulmonary trunk (35 mm) and pulmonary arteries (Fig. 3). Simultaneously, high resolution CT did not provide proof of pulmonary interstice affliction.

On the grounds of all above-mentioned examinations, the clinical state was classified as idiopathic pulmonary hypertension (IPAH) of a severe degree that was reversible in acute vasoreactive testing. The following pharmacological treatment included amlodipine at 20 mg/day and warfarin at 3 mg/day (to achieve a value of 2.0–2.5 international normalised ratio (INR).

The patient was regularly examined at the outpatient department, and during these visits, her clinical state was both subjectively and objectively evaluated as improved. The dose of amlodipine was increased to 25 mg per day while the dose of warfarin was stabilised at 6 mg daily. Ten months after the diagnosis of IPAH, complex re-evaluation of the clinical state was performed.

The patient herself characterised her clinical state as being considerably improved. Without dyspnoea, she was able to walk upstairs to the fourth floor without becoming short of breath or tired during housekeeping.

In every physical examination, the observation of asthenic habitus was consistent (BMI 18). Blood pressure was 115/65 mmHg, and resting heart rate was 100 beats/min. There were no signs of right heart failure. There was an accentuated pulmonary compound of S2 over the pulmonary artery. The overall results of the physical examination were physiological.

Tab. 1. Right heart catheterisation. Results before and after treatment with CCB.

	baseline	After 10 months of treatment with 20 mg of amlodipine
PAP s/d/m (mmHg)	72/37/53	32/18/25
PAWP (mmHg)	11	8
CVP (mmHg)	6	7
CO (l/min)	4,5	8,4
CI (l/min/m2)	2,9	5,5
TPG (mmHg)	42	17
PWR Wood units	9,3	2

Biochemistry results indicated hypocholesterolemia (3.7 mmol/l) and anaemia of a mild degree (Hb 105 g/l). The value of NT-proBNP was normal (28.4 pg/ml), and all other complex biochemistry tests did not show abnormalities.

ECG and chest X-ray indicated no significant change compared to previous findings.

Echocardiography indicated a normal diameter of the right ventricle (in diastole 28 mm) and good systolic function (TAPSE 20 mm). Tricuspid regurgitation was not detected. The diameter of left ventricle in diastole was 41 mm, it was circular in shape, and its systolic function was normal. The six-minute walking distance was 700 metres.

Right heart catheterisation revealed a mean PAP of 25 mmHg while PVR was 2 Wood units (Tab. 1).

In the context of all the above-mentioned examinations, the treatment with CCB was considered successful, and it was concluded that this IPAH patient is a long-term responder to this therapy.

Over the subsequent one-year period, the patient's clinical and echocardiographic state remained unchanged. The patient expressed interest in having a child. The course of PAH is unpredictable, especially in light of the changed circulatory conditions during pregnancy. It may require high doses of drugs with dangerous teratogenic risk potential.

At the time of publishing of this article (3 years after the diagnosis), patient is asymptomatic, mPAP is only mildly elevated. She receives and tolerates 20 mg of amlodipin daily a she decided to adopt a baby.

Discussion

Despite significant development in the knowledge of pathophysiological processes that cause pulmonary hypertension and despite new therapeutic modalities, the prognosis of patients with PAH is poor. With regard to this unfavourable prognosis and to clinical manifestation of severe disease, PAH is considered a malignant disease. PAH stays a disease, which diagnosis and consecutive therapy is due to non-specific symptoms very late. Data from the French national registry show that in 75 % of patients, PAH is diagnosed at a later stage in functional class WHO (World Health Organization) III or IV 7 (Fig. 4). The diagnostic algorithm in PAH is difficult and complex.

The present case report confirms the key role of right heart catheterisation in the diagnosis of PAH; it also emphasises the importance of acute vasoreactivity testing for making the right decision during the therapeutic approach. Pursuant to the actual Guidelines of European Society of Cardiology (ESC) for the diagnosis and treatment of PAH, vasoreactivity testing may be performed using one of three substances, namely epoprostenol, nitric oxide or adenosine.1 At the Department of Heart Failure and Transplantation, i.v. adenosine is used up to the entire dose of 350 μg/kg/min.

A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged CO (1). In this case report, these criteria of vasoreactivity were executed (reduction of mean PAP from 53 to 37 mmHg, CO increased from

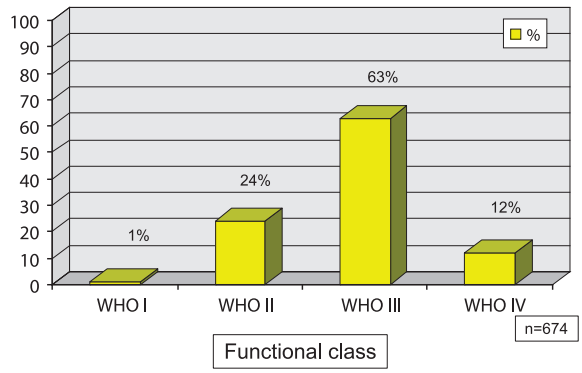

Fig. 4. WHO functional class at time of PAH diagnosis – data from French National Registry (6).

4.5 to 7.5 l/min). In this way, right heart catheterisation clearly confirmed pulmonary arterial (precapillary) hypertension (PAP 11 mmHg) and simultaneously its reversibility was shown. These results indicated the initiation of treatment with CCB for the patient. The indispensable part of PAH treatment is anticoagulation therapy because the formation of *in situ* microthrombi in pulmonary arterial circulation can lead to disease progression (1).

Only 10 % of patients may be classified as acute responders in acute vasoreactivity testing in IPAH. From this small group, approximately one-half of all patients are long-term responders to CCB treatment while long-term treatment of PAH with CCB is indicated exclusively in the latter patients. These patients experience long-term benefits from this treatment. Subjective and objective aspects of their improvement sustain, and their prognosis is the most auspicious among all types of PAH 6 (Fig. 5). In the present case report, the good effect of treatment sustained for more than 14 months. However, it is necessary to regularly monitor this positive response to treatment. In cases when the background disease progresses, a decision must be made about administering specific treatment (phosphodiesterase type-5 inhibitors, endothelin receptor antagonists, prostanoids).

Conclusion

Diagnosis and treatment of PAH are difficult processes, and there is a need for clinical experience and assembly of patients to specialised centres. Only an accurately diagnosed type of PAH and correctly guided therapeutic strategy will have a positive effect on unfavourable prognoses of patients. In the last decade, new molecules were introduced that target different pathophysiological mechanisms of the development and progression of PAH, and they dramatically changed the fate of patients with PAH. Despite this discovery, there is still room for CCB therapy for carefully selected patients, and the testing of pulmonary vasoreactivity should remain a part of the routine protocol of RHC.

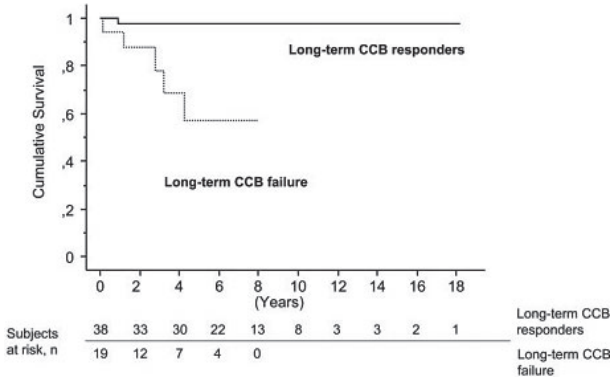

Fig. 5. Prognosis of long-term CCB responders (5).

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