CLINICAL STUDY

Initial experiences with novel therapy for pulmonary hypertension in Slovakia

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Abstract

Pulmonary hypertension (PH) is the most serious and potentially devastating chronic disorder of the pulmonary circulation with diverse etiologies and pathogenesis characterized by abnormal increased vasoconstriction and vascular remodelling. Current specific therapy of PH is based on an understanding of its pathogenesis and is acting through pathogenic pathways and therefore changes therapeutic strategy, effectively improves clinical course and prolongs life. The authors discuss the actual classification, pathogenesis in short and particularly actual treatment modalities and the impact on the natural history of this disorder. In chronic thromboembolic pulmonary hypertension is pulmonary endarterectomy if correct indicated the curable method, warranted substantial improvement of life quality and survival. These novel therapies of PH were absent in Slovakia until recently. The authors present initial experiences, results of PH management up to date on the basis of cooperation with PH centres in Austria and Czech Republic *(Tab. 1, Fig. 6, Ref. 32)*.

Key words: pulmonary hypertension, specific therapy, pulmonary endarterectomy.

Pulmonary hypertension (PH) is the most serious and potentially devastating chronic disorder of the pulmonary circulation with diverse etiologies and pathogenesis. Untreated, it is characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular failure and death. This haemodynamic abnormality is delineated as mean pulmonary arterial pressure (PAP) >25 mmHg at rest or >30 mmHg after exercise. The pathophysiologic pathways of chronic PH are multiple (genetic mutations, inflammation, pulmonary venous hypertension, hypoxemia, mechanical obliteration of pulmonary arteries by thrombi and emboli), they appear in combination. The recent clinical classification of PH established during the 3rd World Symposium on Pulmonary Hypertension in Venice (2003) consists of five categories (Tab. 1) (1). The present work deals with the problems concerning the first and the fourth category.

The first category – pulmonary arterial hypertension (PAH) includes a variety of diseases with different etiologies but similar clinical presentation, morphologic findings and response to medical treatment. In the two subgroups – idiopathic PAH (IPAH), former primary pulmonary hypertension, and familiar PAH there is not any identifiable cause, but there have been identified mutations in the gene encoding the BMPR2 in about 25 % and 50 % of cases respectively. The third subgroup covers a number of conditions of known cause.

Regardless of their known or unknown etiology all forms of PAH share similar pathophysiologic features. The keystone of PAH is the progressive rise of PVR caused by vasoconstriction, inflammation, thrombosis, particularly obstructive remodelation of pulmonary arteries (hypertrophy, proliferation, fibrosis). In the background of these processes lies the basic pathobiologic mechanism – endothelial dysfunction, which leads to impaired production of vasodilators such as nitric oxid and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1, serotonin, thromboxan. This humoral disbalance causes over-

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Tab. 1. Clinical Classification of Pulmonary Hypertension (Venice 2003) (1).

1.	**Pulmonary arterial hypertension**
1.1	Idiopathic (IPAH)
1.2	Familial (FPAH)
1.3	Associated with
1.3.1	Collagen vascular 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 disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4	Associated with significant venous or capillary involvement
1.4.1	Pulmonary veno-occlusive disease
1.4.2	Pulmonary capillary hemangiomatosis
1.5	Persistent pulmonary hypertension of the newborn
2.	**Pulmonary hypertension with left heart disease**
2.1	Left-sided atrial or ventricular heart disease
2.2	Left-sided valvular heart disease
3.	**Pulmonary hypertension associated with lung diseases and/or hypoxemia**
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	Developmental abnormalities
4.	**Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
4.1	Thromboembolic obstruction of proximal pulmonary arteries
4.2	Thromboembolic obstruction of distal pulmonary arteries
4.3	Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5.	**Miscellaneous**: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

weight of processes of vasoconstriction, proliferation and procoagulation in the pulmonary vascular bed and produces the characteristic histologic picture of pulmonary arteriopathy. This is medial hypertrophy of muscular arteries, thickening of intima (concentric, laminar, eccentric or concentric nonlaminar) and adventitia, thrombosis in situ or in about 50 % of cases complex lesions (plexiform lesions, dilation lesions, arteritis).

The fourth category chronic thromboembolic pulmonary hypertension (CTEPH) is an under-diagnosed consequence of unresolved acute or recurrent pulmonary embolism (PE) mostly due to insufficient therapy. This condition is relative rare, because in the vast majority of patients (75–85 %) with PE endogenous fibrinolysis together with anticoagulation therapy results in complete or near-complete clot lysis within a few weeks. However, for unknown reasons, some patients will have insufficient clot lysis and the obstructing material becomes organized in the vessel walls. It is characterized by intraluminal thrombus fibrous organization, leading to stenosis or complete obstruction of pulmonary artery branches. Pulmonary hypertension develops and affects also those areas of the pulmonary vascular bed which originally have not been affected by thromboembolism. The process of progressive pulmonary vascular remodelling and enhanced reactivity in nonoccluded vessels sets in motion and guarantees the steady increase in PVR, right ventricular overload and failure (2). Histologically, microvascular changes in patients with advanced CTEPH look very similar to the lesions observed in IPAH.

From the pathophysiologic point of view the PH is an irreversible proliferative and obliterative process resulting into obstruction and restriction of the pulmonary artery bed and right ventricular pressure overload, hypertrophy and finally into failure. Untreated, the progression of PVR increase is sustained and fast, the prognosis is poor. Due to complicated and complex etiopathogenesis the management of PH has been problematic in the past and presents a diagnostic and therapeutic challenge still nowadays.

The treatment induction of PH follows exact definition of PH category, of underlying causes and contributing factors. The clinical assessment consists in careful and detailed history, in physical examination (signs of PH and right ventricular pressure overload) and in a bright scale of diagnostic tests (3). Echocardiography is the key method providing the diagnosis and quantification of PH, the cardiac consequences of PH, allows estimation of some causes of PH (congenital heart diseases, left heart diseases), and brings prognostic information. The form and the etiology of PH identify following diagnostic procedures: car-

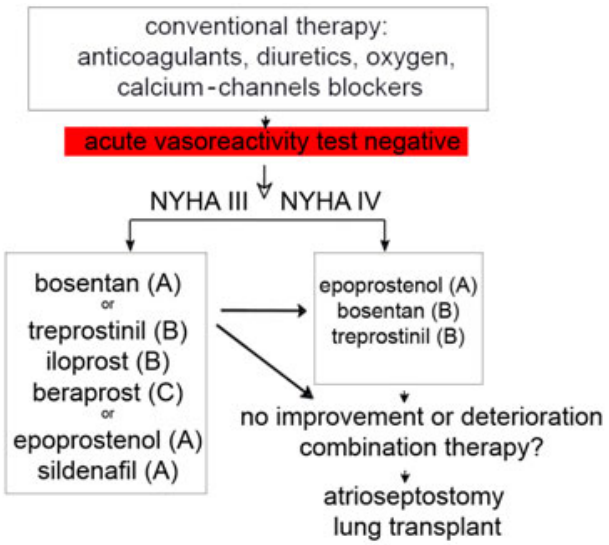

Fig. 1. Treatment algorithm. Modified according to (3).

diac catheterisation, acute testing of pulmonary vasoreactivity, lung scintigraphy, spiral chest CT, pulmonary angiography, pulmonary function tests). The management of PH patients requires exercise testing (6-minute walk test, ergospirometry). The diagnostic process is completed and the diagnosis of PH is established, the patient should be treated according to the current evidence. The current therapy consists of following modalities:

– Lifestyle changes: physical activity should be limited, stay in high altitude, pregnancy or hormonal contraception should be avoided; influenza vaccination

– Medical therapy:

a) Conventional therapy (vasodilator therapy by calcium-channel blockers, anticoagulants, supplemental oxygen therapy, diuretics, digitalis)

b) Unconventional/specific therapy

(further prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase-5 inhibitors).

– Nonpharmacologic invasive techniques:

a) atrial septostomy a transplantation

b) pulmonary endarterectomy.

The target of medical therapy is inhibition of pathogenetic mechanisms of the disease (vasoconstriction, obstructive remodelation, thrombosis of pulmonary arteries) and is oriented to the broad spectrum of diseases in the first category – pulmonary arterial hypertension. The role of medical therapy in CTEPH is marginal, in this group the leading treatment method is pulmonary endarterectomy.

The medical treatment in the 1980s was limited to anticoagulants, symptomatic therapy (digitalis, diuretics, oxygen) without influence on prognosis, as well as to various vasodilators, calcium-channel blockers in the main. Right using high doses calcium-channel blockers sustained reduction of pulmonary arterial pressure, improvement of symptoms and survival could have been achieved, but only in the minority of patients with positive vasoreactivity test (cca 13 %) (4). In the 1990s the unconventional, specific therapy (continuous intravenous administration of epoprostenol) was established and improved symptoms and survival. That was the crucial step in the development of therapeutic options for PH, showing dramatic and progressive changes in the past few years. Therapeutic algorithm is conditioned by the vasoreactivity test. Patients with positive test are treated with calcium-channel blockers and anticoagulants. In the case of negative test of pulmonary vasoreactivity the treatment regime follows the scheme present in Figure 1 (3).

Prostacyclin (prostaglandin I_2), a metabolit of arachidonic acid is endogenously produced by vascular endothelium. In PAH there is a relative deficiency of prostacyclin, a fact playing important role in the pathogenesis. Prostacyclin is not only a potent vasodilator in the pulmonary and systemic circulation, but a strong antiproliferative factor, has antiplatelet aggregatory activity and inotropic effect. The treatment of PAH takes advantage of this multifactorial way of effect. Epoprostenol is stabil analogue of prostacyclin, in the human medicine used for the first time in 1984 (Higenbottam), has very short half-life (<6 min), is unstable at room temperature and should be kept cold prior to and during the infusion. Therefore the therapy requires continuous 24 hours i.v. infusion via central catheter. Patient are usually begun on a low dosage (2 ng/kg/min) and gradually titrated upward based upon side effects and tolerance. The "plateau" dose is varying between 20–40 ng/kg/min. Side effects of epoprostenol therapy include flush, headache, jaw pain, nausea, diarrhea, hypotension and line-related complications (from tunnel infections to sepsis, malfunction of the pump or clearness of the catheter with rebound fenomenon). Abrupt interruption of the epoprostenol infusion may lead to a rebound worsening of PH with symptomatic deterioration and perhaps even death. The treatment can be offered only to a cooperating patient with social background. The long-term epoprostenol therapy according to EBM improves in broad spectrum of PAH patients exercise capacity, hemodynamic parameters, life quality as well as survival (5, 6) and is considered as reference therapy of PAH in patients with negative test of vasoreactivity in functional class NYHA III–IV. The nature of the delivery system of the successful and effective epoprostenol therapy has inspired the development of prostacyclin analogues with alternative routes of delivery. Treprostinil, a stable prostacyclin analogue, shares pharmacologic actions similar to epoprostenol, but differs in that it is stable in room temperature with longer half-live (2–4 hours). There is not necessary to keep the solution cold. Manipulation is therefore simple-handle, the risk of rebound fenomenon falls off. The solution can be applied intravenously or subcutaneously and in both forms is bioequivalent. Nowadays the inhaled treprostinil is tested in study TRIUMPH. The initial dose 1.25 ng/kg/min should be titrated upward to average dose of 15–25 ng/kg/min. The side effects are similar to epoprostenol, but the infusion-site pain in subcutaneous delivery in about 80 % of patients. The presence of pain is very individual and not dose-dependent. The therapy in PAH patients was associated with significant haemo-

dynamic improvement and exercise capacity (7) and better survival (70 % vs expected 46 %) during three years (8). Iloprost, a stable prostacyclin analogue in room temperature with half-life of 20–25 min can be delivered via inhalation or intravenously. Inhaled therapy for PH may provide selectivity of the hemodynamic effects to the pulmonary vasculature, thus avoiding systemic side effects. The condition for the delivery system is to produce aerosol particles of appropriate size (3–5 μm) to ensure deposition to the alveolar surfaces. The relative short duration of action is the major disadvantage of this form of treatment, because 6–12 inhalations per day may be needed to maintain the desired clinical effect. Each inhalation requires 10–15 min. The iloprost therapy in PAH and CTEPH patients improved exercise capacity and haemodynamic parameters without differences in mortality rate (9). The pulmonary selectivity of inhaled iloprost provides therapeutical option in patients who are prone to decrease systemic arterial pressure (portopulmonary hypertension) and in emergency situations. The chronic inhaled therapy is considered for patients with disease in class NYHA III, if they are willing to accept the inconveniences of repeated daily inhalations. Long-term survival data are needed. Beraprost is the first orally active prostacyclin analogue with chemical stability. It is rapidly absorbed: peak plasma concentrations are reached within 30 min and the half-life is 30–40 min. On the basis currently available experience (exercise capacity improved without any significant changes in haemodynamics, functional class or survival) beraprost is considered for patients with less severe PH and is approved for treatment of PAH in Japan (10).

Endothelin receptor antagonists (ERAs) are due to the prominent role of endothelin in the pathogenesis of pulmonary vascular disease promising agents in the treatment of PAH. Endothelin-1 mediates vasoconstriction and smooth muscle cell proliferation through endothelin-A (ET_A) receptors, but it can induce vasodilation through endothelial ET_B receptors. Endothelin levels have been shown to correlate with pulmonary hemodynamics in IPAH, in PAH due to congenital cardiac disease or in CTEPH. Bosentan, is oral nonselective, dual ERA ($ET_A + ET_B$) with higher affinity for ET_A. In IPAH and associated forms of PAH (scleroderma, congenital heart disease) bosentan could improve exercise capacity, hemodynamics and in IPAH survival (11, 12). The target dose of bosentan is 125 mg twice a day for patients with PAH in class NYHA III or IV with negative test of pulmonary vasoreactivity. Side effects of bosentan therapy include a dose-dependent increase in hepatic transaminases in about 10 % of treated patients, fully reversible after withdrawal, a small incidence of anaemia. Because bosentan is teratogenetic (craniofacial abnormalities), reduces the effect of hormonal contraceptives, a reliable form of contraception should be used.

Phosphodiesterase (PDE) inhibitors, particularly type 5 produce pulmonary vasodilation by promoting an enhanced and sustained level of cyclic GMP, an identical effect to inhaled NO. Sildenafil, is potent and highly specific PDE type 5 inhibitor approved in treatment for erectil dysfunction. When tested as single oral agent, sildenafil have been shown to be selective pulmonary vasodilator, blocks acute hypoxic pulmonary vasoconstriction, in patients with PAH reduces PAP, PVR and improves functional class and exercise capacity (13, 14).

Combination therapy takes advantage of various mechanisms of action, some agents might have additive effects or enhance and prolong the effects of others. The combination permits lower dosage, thereby minimizing toxicity, but enhances significantly therapy costs.

Atrial septostomy, a palliative transcatheter treatment method, is indicated in patients with failure of medical therapy, with persisting of right ventricular failure and/or syncope and represents bridging to transplantation. Lung and heart-lung transplantation is the final option in the management of PAH in patients with failure of available therapeutic options, fulfilling the indication criteria (15). Pulmonary endarterectomy (PEA) is in patients with CTEPH nowadays generally accepted treatment method providing a potential surgical cure. The PEA must be distinguished from acute embolectomy for massive pulmonary embolism. PEA involves a true endarterectomy (dissection of organized tromboembolic material + part of the intimal layer of pulmonary arterial wall). The prognosis of CTEPH patients without perspectives of PEA is poor, depends on severity of PH (16). Precise diagnostic investigations are needed before the indication for PEA. The first step method for PH diagnosis is echocardiography, then haemodynamic measurements and lung scintigraphy. The key methods for evaluation of PH are spiral CT and pulmonary angiography. The last one is the "gold standard" showing the exact localisation and the type of PA obstructions, in the vast majority bilateral (2). The angiograms examination and decision making for PEA requires specific experience, particularly of surgical team. With growing experience endarterectomy of subsegmental PA braches is possible. The presence of concomitant microvasculopathy or inaccessible distal disease may limit the response to PEA. The patient selection for PEA is further made based on the degree of PH (PVR >300 dyne.s.s.cm^{-5}, PAP >40 mmHg) and functional impairment (class NYHA III or IV) and on global risk of surgery (no severe comorbidities) (15). The operation is more than 30 years old procedure made via median sternotomy in extracorporeal circulation and circulatory arrest under deep hypothermia. The tricuspid valve incompetence returns after successful PEA, the repair is not necessary. Jamieson introduced an intraoperative classification of CTEPH (17). According to this the surgical treatment is possible in type I (central thrombus) and type II (thickening intima, fibrous webs and bands), in type III (occlusions in segmental and subsegmental branches) only by adequate surgical experience with dissection within peripheral PA. Type IV (secondary in situ thrombosis, peripheral involvement like in primary PH) is contraindicated for surgery. The outcomes are very optimistic concerning functional status (III/IV class NYHA returning to I/II class NYHA postoperatively), haemodynamics and right ventricular function (significant improvement) and survival (75 % 6-year) (18). The suboptimal outcome of surgery could be due to inadequate endarterectomy or significant secondary small vessel vasculopathy in nonoccluded vascular bed present in many patients with CTEPH. This cohort of CTEPH patients is characterized by pro-

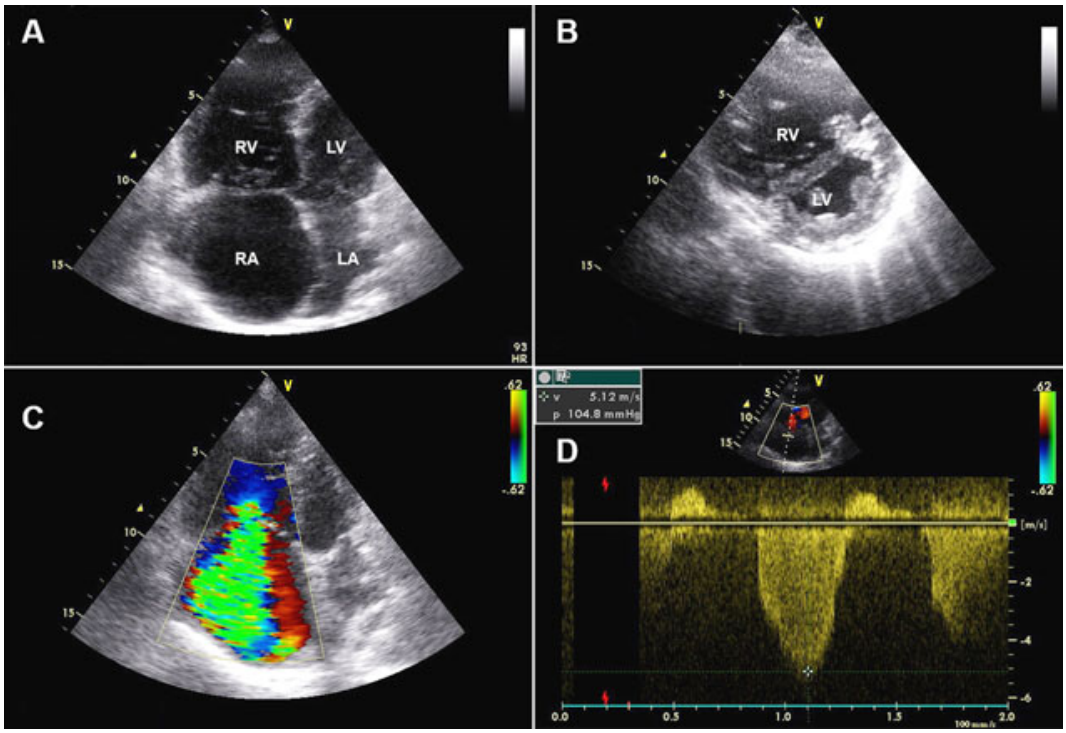

Fig. 2. Transthoracic echocardiography. 2A) 4chamber view, severe dilation of right ventricle (RV) and atrium (RA), displacement of interatrial septum toward right atrium 2B) D shape of left ventricle (LV), large right ventricle, 2C) severe tricuspid regurgitation, 2D) continuous Doppler echocardiography – transtricuspid regurgitation gradient of 105 mmHg (approximation of systolic pulmonary pressure of 120 mmHg).

gressive PH despite long-term medical and surgical therapies including anticoagulation. The process of preoperative patient evaluation, selection, surgery and postoperative management requires multidisciplinary approach.

In nonsurgical patients (type III/IV) or high-risk surgical candidates, there are 3 treatment options: medical therapy, balloon pulmonary angioplasty or transplantation. The rationale of medical therapy is based on the presence of small vessel vasculopathy and enhanced reactivity in nonoccluded vessels that can limit the hemodynamic improvement following pulmonary trombendarterectomy. Positive experiences with prostanoids and sildenafil (reduction of PAP, PVR, increase in cardiac index and 6MWT distance) (19, 20) and ongoing study with bosentan (BENEFIT) are promising for patients with inoperable CTEPH.

Pulmonary hypertension is accounted a devastated progressive disease usually with very poor life quality and prognosis. The natural history of the disease is very heterogeneous – patients with IPAH survive after the diagnosis in average 30 months, patients with Eisenmenger syndrome decades. Prognosis is depending in the main on the type of PH, further on symptoms duration, functional class, haemodynamics and particularly on treatment modality (21). Major advances in understanding of the mechanisms of the disease development as well as the entrenchment of the modern diagnostic imaging and therapeutic surgical modalities opened new horizons of therapeutic consequences. Unconventional specific therapy of PAH is medical treatment, acting through pathogenic pathways and therefore changes therapeutic strategy, effectively improves clinical course and prolongs life. Pulmonary endarterectomy is in the case of correct indication curative method, warranted substantial improvement of life quality and survival in CTEPH. Modern treatment of PAH in Slovakia was absent until recently. We present two cases of PH management in collaboration with PH centres in Prague and Vienna, as well as cardiothoracic surgery in Vienna up to date.

Case reports

Case 1

Patient, a 55-year old woman without any singularity as well in her family as her own history, her problems – effort related symptoms: dyspnea, fatigue, angina – started 5 years ago (autumn 2001). She was managed like chronic obstructive pulmonary disease. Later on the symptoms got worse – dyspnea during conversation and the signs of right ventricular failure (hepatomegaly, lower extremity edema) associate. In 2004 the diagnosis of pulmonary hypertension was established, she got anticoagulants, diuretics, digoxin and she was referred to our hospital. At the admission she complained of expressive dyspnea and fatigue, she was cyanotic, blood pressure 120/75 mmHg, HF 88/min reg., systolic murmur in the tricuspid area, complete clinical picture of marked right ventricle failure was present (hepatomegaly, ascites, lower extremity edema). She underwent complete diag-

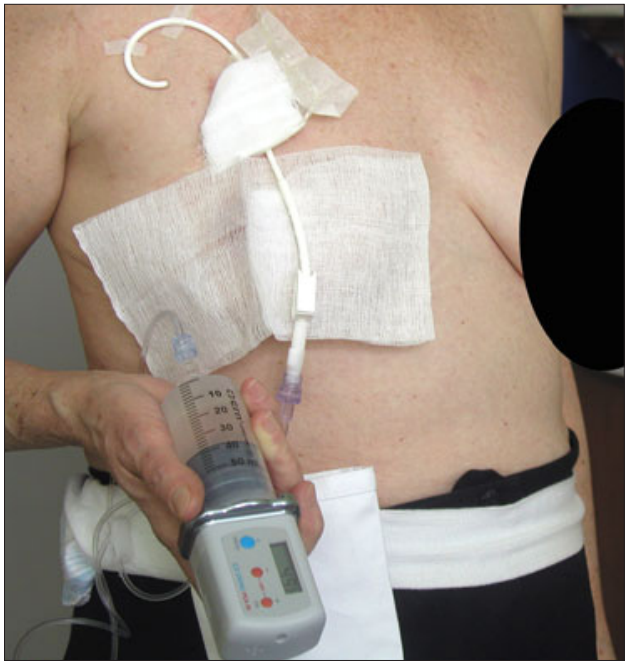

Fig. 3. The delivery system: tunelized central venous catheter, ambulatory infusion pump.

nostic algorithm (see above) with conclusion of idiopathic pulmonary arterial hypertension – severe and fixed (negative test of vasoreactivity) with dysfunction and failure of right ventricle, class NYHA III. The most important findings were as follows.

– The haematologic and biochemical results normal with the exception of hyperbilirubinemia

– ECG: right axis deviation, right ventricular hypertrophy and strain

– Echocardiography (Fig. 2): severe dilation of right ventricle and atrium, D shape of left ventricle and paradox motion of interventricular septum (sign of right ventricular overload), systolic and diastolic dysfunction of right ventricle, severe tricuspid regurgitation, transtricuspid regurgitation gradient 105 mmHg (approximation of systolic pulmonary pressure of 120 mmHg), a. pulmonalis dilation, small pericardial effusion

– Haemodynamics: cardiac index 2.4 l/min/m^2, a. pulmonalis pressure 122/33/67 mmHg, pulmonary capillary wegde pressure 6–7 mmHg, right atrium pressure 16 mmHg, right ventricle enddiastolic pressure 22 mmHg, PVR 17 Wood units = 1379 dyne.s.s.cm^{-5}, O_2 saturation 91 %.

– Pulmonary angiography: large central pulmonary arteries with marked typical peripheral vascular tapering and pruning.

– 6 minutes walking test: 228 m, Borg scala 4, O_2 saturation 89 % before, 88 % after walking.

Patient according to the diagnosis and the findings fulfilled criteria for unconventional, specific therapy of IPAH. In December 2005 continuous i.v. treprostinil therapy via tunelized central venous catheter was initiated. The catheter was surgically implanted, the infusion is delivered by an ambulatory infusion pump. The delivery system is complex (Fig. 3) and required the patient to learn the techniques of sterile drug preparation, operation of the pump and care of the intravenous catheter. She does it in few days. The starting dose was 2 ng/kg/min and later on was titrated upward. Within 4 months the dose reached the bottom border of the usual average dose of 15 ng/kg/min. The above mentioned symptomatology moderated astonishing quickly — during week. The improvement of exercise capacity checked by 6 MWT was after 1 months of therapy +70 m (up to 298 m), Borg scala 6 with further increasing of the distance to 312 m in 2 months, Borg scala 8. The 6 minute distance about 310–320 m remains after 4 months of therapy. The functional class NYHA improved too (-I grade). The decrease of systolic pulmonary pressure could be confirmed by Doppler echocardiography (-15 mmHg). Other echocardiographic parameters did not change substantial. The dose of diuretics could be reduced. She masters very well the infusion preparation, pump operation or catheter care. The patient considers substantial improvement of life quality despite the dependency on continuous infusion therapy.

Case 2

Patient, a 40-year old man with negative family history, without any problems until March 2004, when effort dyspnea, fatigue, cough and epigastric pain started. He was managed like coronary heart disease. Later on he was hospitalised because of symptoms aggravation and the diagnosis of recurring pulmonary embolism was established. The asymptomatic left popliteal and femoral flebothrombosis as the source of the pulmonary embolism was diagnosed. An oncologic process as well as trombofilia was excluded. He got anticoagulants and diuretics. In January 2005 signs of dysfunction and failure of right ventricle appeared, his functional class NYHA was III. In June 2005 he was admitted to our hospital in order to undergo the diagnostic procedures. The most important findings were as follows.

– Clinical status: BP 120/80 mmHg, HF 95/min, central cyanosis, systolic murmur in the tricuspid area, hepatomegaly. The haematologic and biochemical results were normal with the exception of hyperbilirubinemia and acquired APC-R resistance in association with elevated level of factor VIII (300 IU/dl). Hereditary trombofilia was excluded.

– ECG: right axis deviation, right bundle branch block.

– Echocardiography (Fig. 4 before): severe dilation of right ventricle and atrium, severe systolic and diastolic dysfunction of the right ventricle, paradox motion of intervetricular septum, preserved systolic function, but diastolic dysfunction of the left ventricle, moderate tricuspid regurgitation, transtricuspid regurgitation gradient 85 mmHg, a. pulmonalis dilation, small pericardial effusion.

– Haemodynamics: cardiac index 1.8 l/min/m^2, a. pulmonalis pressure 75/27/44 mmHg, pulmonary capillary wegde pressure 7 mmHg, right atrium pressure 15 mmHg, right ventricle enddiastolic pressure 17 mmHg, PVR 11 Wood units = 876 dyne.s.s.cm^{-5}, O_2 saturation 93 %.

– Pulmonary angiography (Fig. 5): large central pulmonary arteries, status post recurring pulmonary embolism with occlusions – right: a. lateralis lob. med., tr. intermedius, a. medialis, posterobasalis, a. laterobasalis lob. inf. and left: a. apicalis lob.

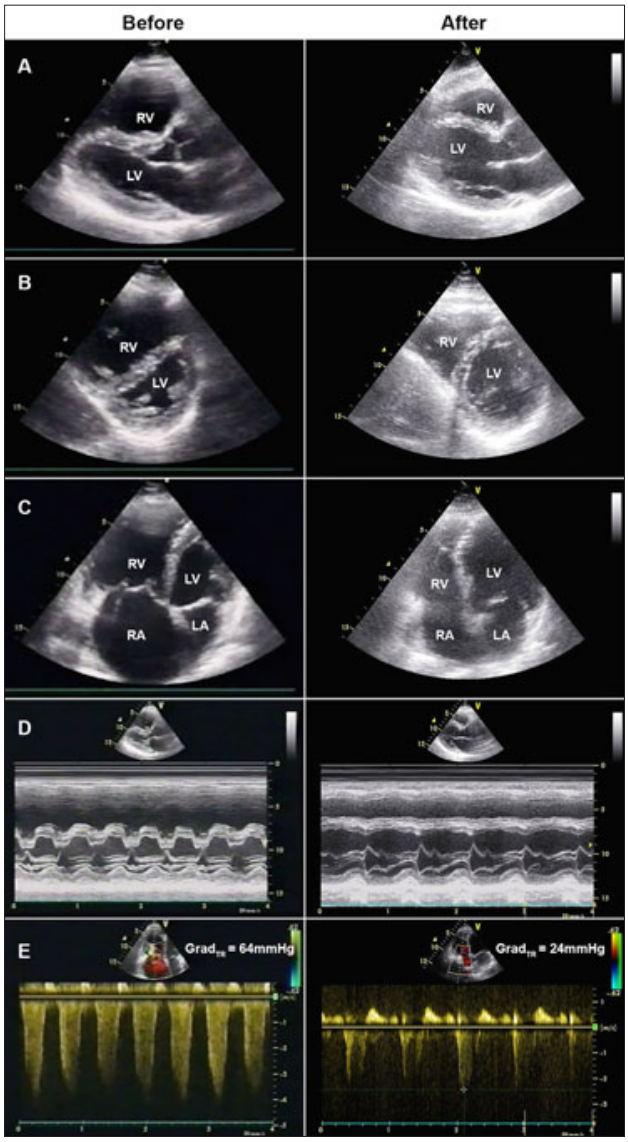

Fig. 4. Transthoracic echocardiography. 4A–C before: Severe dilation of right ventricle (RV) and atrium (RA), displacement of interatrial septum toward right atrium, D shape of left ventricle (LV)(4B before). 4D before: Mmode echocardiography – paradox motion of intervetricular septum. 4E before: Continuous Doppler echocardiography – transtricuspid regurgitation gradient of 64 mm Hg (approximation of systolic pulmonary pressure of 80–85 mm Hg). 4A–C after: total regression of right ventricular overload, of dilation of RV and RA, normalization of the shape of left ventricle (4B after). 4D after: Mmode echocardiography – normalization of interventricular septum motion. 4E after: Continuous Doppler echocardiography – transtricuspid regurgitation gradient of 24 mmHg (approximation of systolic pulmonary pressure of 35 mmHg), e.i. normalization of pulmonary pressure.

sup., a. post. lob. sup., a. lingul. sup. et inf. lob. sup. and perif. a. anterior lob. sup.

– Duplex sonography of leg veins: dilation of vv. iliacae bilateralis, tricuspid flow, residuum of thrombosis in v. poplitea l. sin.

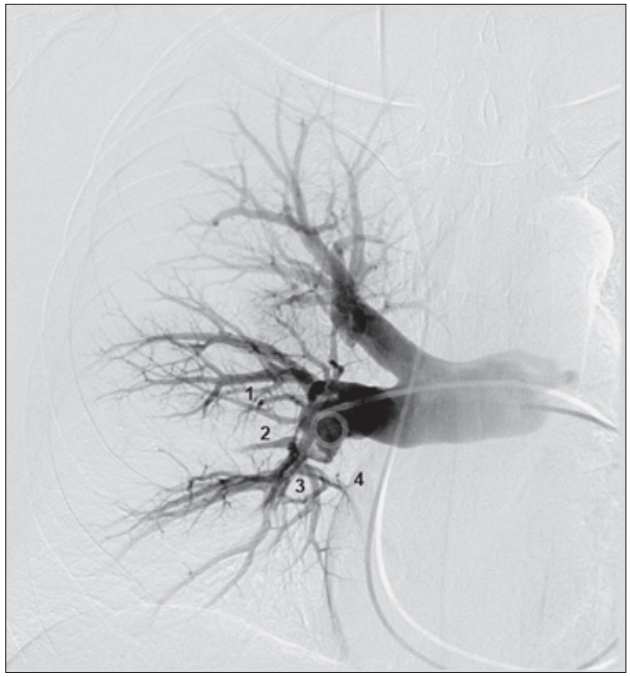

Fig. 5. Right pulmoangiography with multiple occlusions: 1 – a. lateralis lobi medii, 2 – a. laterobasalis lobi inferioris, 3 – a. medialis lobi inferioris, 4 – a. posterobasalis lobi inferioris.

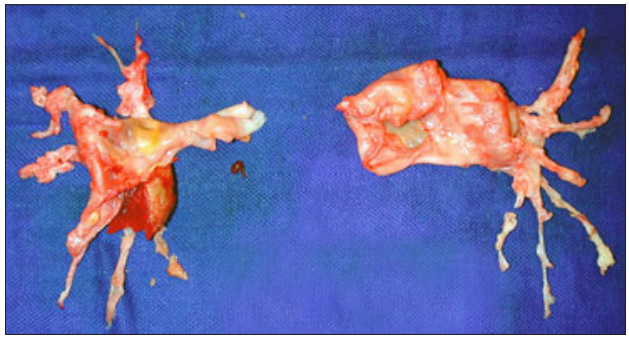

Fig. 6. Specimen of pulmonary endarterectomy.

– 6 minutes walking test: 450 m, Borg Scala 7, O_2 saturation 94 % before, 94 % after walking.

Patient according to the diagnosis and the findings fulfilled criteria for CTEPH type II, suitable for surgical treatment. In October 2005 he underwent pulmonary endarterectomy without any complication in the postoperative course. Material removed from the pulmonary bed shows Figure 6. Within 2 months the symptoms of exercise intolerance, dyspnoe, fatigue disappeared, the improvement of exercise capacity checked by 6MWT was after 2 months of therapy +170 m (up to 620 m), Borg scala 10. In 3 months we detected further increasing of the distance in 6 min to 650 m, Borg scala 10. The echocardiogram showed total regression of right ventricular overload, dilation and dysfunction, of pulmonary hypertension, paradox motion of intervetricular septum disappeared, the pulmonary pressure completely normalized (Fig. 4 after). The work disability of patient

was stopped ten weeks after surgery and he started his full time job again. From the medical therapy he takes just anticoagulants.

Discussion

The treatment of PAH nowadays and in the future is based on the pathophysiologic pathways of the disorder. According to the rapid progress in understanding of the disease mechanisms the treatment alternatives are advancing rapidly too. Results of EBM have provided a basis for current recommended treatment algorithm (Fig. 1). Recommended therapy obviously needs to be applied in light of the individual patient. Anticoagulants are according to the pathomechanisms (in situ thrombosis) and to the risk of thromboembolism in failing right heart as well as in CTEPH the fixed component of the therapy of PH. Improved survival has been reported with oral anticoagulation (4).

While oral calcium-channel blockers and continuous intravenous epoprostenol have been used successfully for over a decade, novel treatment options – including prostacyclin analogs, ERAs, and PDE-5 inhibitors – change the course of this disease. Using high doses calcium-channel blockers in the long-term therapy benefit could have been achieved only in the half (about 7 %) of patients with positive vasoreactivity test (cca 13 %) (4). Continuous intravenous epoprostenol is considered as reference therapy of PAH in patients with negative test of vasoreactivity in functional class NYHA III–IV improving quality and duration of life (5). Epoprostenol therapy is complicated beside the adverse effects by the a sophisticated delivery system (complex pump system, necessity of cooling) and the risk of local and systemic infection (2–3x per year in each patient) and rebound fenomenon due to the delivery system malfunction. Prostacyclin analogs offer the benefit over continuous intravenous epoprostenol of an alternative delivery system. Treprostenil continuous infusion compares favourable with reference i.v. epoprostenol therapy (8), has some technical advantages. There is no need for cooling, the pump is simpler, so the portable delivery system is miniature. The rebound fenomenon in intravenous treprostenil is not imminent. Our experience with intravenous treprostinil corresponds with published data (7, 8, 22, 23). We could detect the improvement of exercise capacity (+ 92 m in 4 months), quality of life (-I class NYHA), reduction of PAP (-15 mmHg), reduction of diuretic dosage. The incidence and extent of adverse effects are acceptable and are temporary connected with the dose elevation. There were not yet any infectious complications. Inhaled prostanoids have a great advantage – nonivasive delivery system. Iloprost needs about 6–9 inhalations per day to achieve satisfactory clinical results, treprostinil due to longer half-life 4 inhalations. The indication is functional class NYHA III. At present long-term survival data are needed.

Oral ERAs for the therapy of PAH according their direct impact on crucial pathogenetic mechanism appear to have great promise. Bosentan is an antiproliferative, vasodilating agent approved for the therapy of PAH, functional class NYHA III. In several RCTs with bosentan improvement of hemodynamics, exercise capacity, functional status and clinical outcome has been shown (11, 12, 24, 25). Questions that remain to be answered and are the topics of ongoing studies: the role of bosentan in functional class NYHA I–II, in combination therapy and in CTEPH.

CTEPH is a serious consequence of PE associated with considerable morbidity and mortality. It develops in about 0.5–5 % among patients who survive a PE. The following increased the risk of CTEPH: a previous PE, younger age, a larger perfusion defect, idiopathic PE at presentation (26). No predisposing factors or medical conditions have been identified, with the exception of antiphospholipid antibodies in 10–20 % and plasma factor VIII >230 IU/dl in 39 %. Splenectomy, ventriculo-atrial shunts, chronic inflammation, i.e. osteomyelitis, haemolytic anemia and trauma are considered to be independent risk factors (26, 27, 28). Pulmonary endarterectomy has been regarded as a promising, potentially curative surgical procedure in type I and II. Type III is operable in centres with great skill. Type IV is for PEA contraindicated (17). There are about 20 centres worldwide. The University of San Diego has extensive surgical experience (treated above 2000 patients). In our geographic region the important centres are in Vienna, Austria and in Mainz, Germany. Recently a centre in Prague, Czech republic has got very good experiences (29). However, PEA is associated with specific postoperative complications, such as reperfusion pulmonary edema and persistence of PH, leading to a considerable mortality of 7–24 %. Survival of operated patients is 75–80 %. Successful PEA results in a significant improvement of symptoms, pulmonary haemodynamics (cardiac output, pulmonary hypertension, right ventricle function) and clinical status that is unprecedented with any other treatment modality for PH. This is the case of our patient with disappearance of symptomatology and clinical features of right ventricular failure, with normalisation of pulmonary haemodynamics as well as echocardiographic parameters. From the risk factors for thromboembolism we could find elevation of factor VIII, present in almost 40% of patients with CTEPH (28). Until now in our institution we have indicated 4 patients for PEA, 3 are still operated, one is waiting for the procedure. The result of two operated patients is excellent the third patient has residual PH and is planned for specific therapy.

Conclusion

The management of patients with PH, making an accurate diagnosis at all requires collaboration of experienced cardiologists, pneumologist, rheumatologist, radiologists, and in the case of CTEPH cardiothoracic surgeons and experts in intensive medicine. In our country an essential condition in the enhancement of PAH patient management is the improvement of the education, i.e. to learn the basics of ESC Guidelines (3) and to recognize the particularity in our region (30, 31) and to continue in cooperation with PH centres in Vienna and Prague. PAH despite of actual therapeutic modalities is progressive disorder with poor prognosis and stays untreatable. Promising seems to be the combination therapy. For the future novel therapies studied in animal models and human tissue appear to prevent and reduce pulmo-

nary arterial medial hyperplasia through their anti-proliferative and/or pro-apoptotic effects: serotonin transporter inhibitors by blocking serotonin uptake; dichloroacetate by activating voltage-gated potassium channels; and simvastatin by preventing activation of small GTPases (32). CTEPH is the rare condition among disorders associated with PH, which could be cured by sophisticated surgical procedure. The crucial in the management is correct diagnosis and classification.

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