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REVIEW

Why is pulmonary hypertension so frustrating?

Kaldararova M

National Institute of Cardiovascular Diseases, Children's Cardiac Center, Bratislava, Slovakia.
kaldararova@dkc-sr.sk

Abstract: Pulmonary hypertension (PH) is a relatively uncommon but on the other hand all too frequently fatal disorder of the pulmonary arteries with diverse etiology. Vascular remodeling leads to increased pulmonary vascular resistance and this again to right ventricular overload and failure.
Discussed are the current classification, pathogenesis and particularly treatment possibilities and contemporary trends, as well as the impact on the natural history of this disorder.
The effect of conventional PH management of the past decades was insufficient. Understanding the pathophysiological mechanisms of the disease development was the greatest progress made in the last years. Targeting the pathogenic pathways of endothelial function is now being utilized in the so called specific therapy, which to some point improves patients' clinical course and life expectancy. The therapy of PH today seems to have the potential to slow down the progression of the disease and with some new promising molecules on the horizon there might be hope even to reverse the entire disease process. On the whole though, PH treatment remains frustrating because the majority of up-to-date managed and treated patients have still low exercise tolerance, unacceptable hemodynamics, suboptimal life quality and their mortality stays high.
Despite all the advances, still the most important goal remains a wide-spread early detection of PH patients and associated conditions leading to PH (e.g. congenital heart defects and connective tissue diseases) and a centralized management of the disease in highly specialized expert centers *(Tab. 1, Fig. 4, Ref. 36)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: pulmonary hypertension, classification, pathophysiology, specific therapy, management perspectives.

Pulmonary hypertension represents a long-lasting problem that brought-up many questions and far too few answers. During the last decades there was perhaps no other topic in cardiology that would be more frustrating because of the painful effort to understand its complex pathophysiology and to find a way to overcome the poor disease prognosis. Last pieces of knowledge dramatically changed the clinical insight and management strategies of pulmonary hypertension. The so called specific therapy brought an improvement of patient's life quality and a new hope for their life expectancy. So the logical today's headline question would be: Is this now just a too optimistic boom, or is the specific therapy really the beginning of a new modern era that will bring a turnover in pulmonary hypertension curability at last?

Historical milestones

Although the presence and clinical significance of pulmonary changes for the heart were known from the 16th century, the scientific history of pulmonary vascular pathology begun with the Romberg's first description of "sclerotic" changes of the arteries in the lungs in 1891 (1). It took though another 60 years till Dresdale in 1951 gave the first clinical definition of pulmonary hypertension (PH) (2) and Wood in 1958 confirmed the presence of elevated pulmonary arterial pressure by direct invasive measurements (3). Since then it was still a long way to understand this complicated problem. It passed another 15 years till in Geneva in 1973 the first WHO classification was established, trying to differentiate all the known causal influences for progressing to PH. From that time the classification underwent 3 revisions (although the last published one was back in 2003 and is known as the Venice classification (4)) implementing new up to date facts in etiology and pathobiology of pulmonary vascular changes.

The treatment strategies of PH started with the first heart-lung transplantation by Shumway and Reitz in 1981 (5), followed by medical vasodilatation therapy in the mid 1980-ties (6). Better understanding of pathophysiological pathways of pulmonary vascular changes have led to the so called specific therapy strategy in the 1990-ties (7) that opened a new era for the treatment of PH (Fig. 1) (8) and brought for patients hope for better prognosis and improvement of life quality.

The historical background of PH management in Slovakia is based on a 30-year tradition of the Institute of Cardiovascular Diseases (ÚKVCH), continued at present at the National Institute of Cardiovascular Diseases (NÚSCH) in Bratislava, in cooperation with other Slovak cardiovascular, as well as pulmonary centers. Already in the 1990-ties the problem of pulmonary circulation alterations and secondary deteriorated pulmonary

National Institute of Cardiovascular Diseases, Children's Cardiac Center, Bratislava, Slovakia

Address for correspondence: M. Kaldararova, MD, National Institute of Cardiovascular Diseases, Children's Cardiac Center, Limbova 1, SK-833 51 Bratislava, Slovakia.
Phone: +421.2.59371864

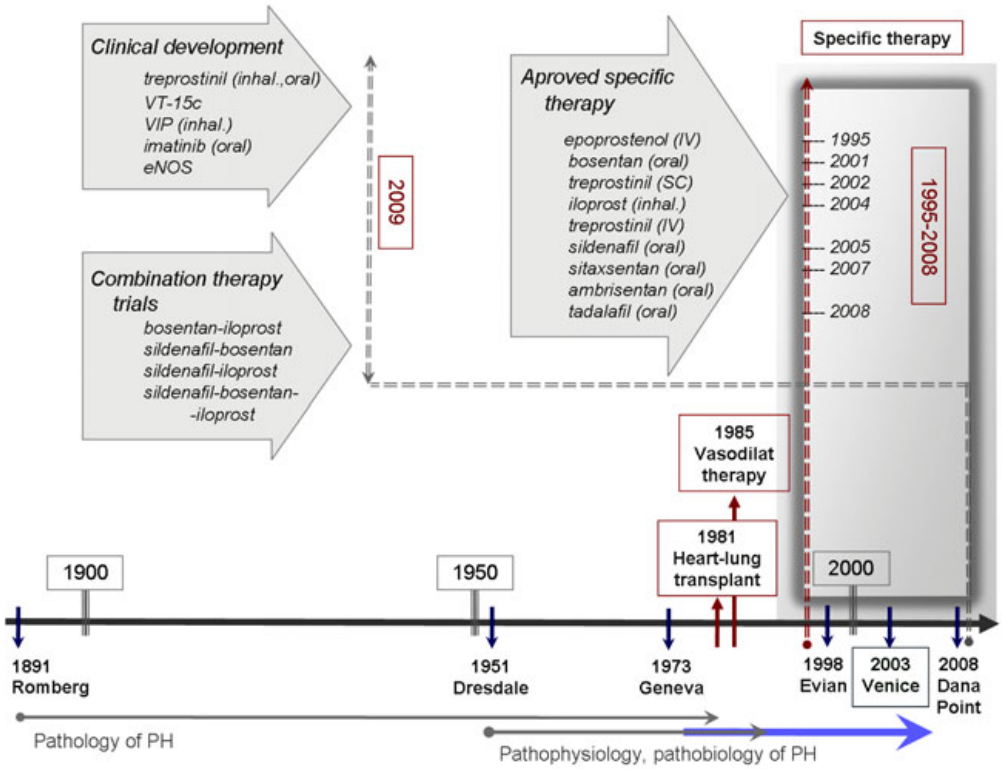

Fig. 1. Historical milestones in pulmonary hypertension (PH – pulmonary hypertension, IV – intravenous, SC – subcutaneous, inhal. – inhalative, Geneva – Ist WHO pulmonary hypertension meeting in 1973, Evian – 2nd WHO pulmonary hypertension meeting in 1998, Venice – 3rd WHO pulmonary hypertension meeting in 2003, with last published results, Dana point – 4th World pulmonary hypertension symposium in 2008, not yet published at time of paper submitting, modified from: Barst RJ et al (8).

function in cardiac patients, especially due to mitral valve disease and cardiac surgery, was in Slovakia closely studied and published (9–11).

Definition

Pulmonary hypertension is defined by elevated mean pulmonary arterial pressure (mPAP) >25 mmHg at rest or >30 mmHg during exercise. It is a widely heterogeneous group of diseases, with various underlying causes, all characterized by a similar reaction of the pulmonary vascular bed. From the pathophysiological point of view it is from a certain point an irreversible process characterized by proliferation and obliteration of the small pulmonary arteries. In PH it comes to a progressive increase in pulmonary arterial pressure and pulmonary vascular resistance that is leading to right ventricular failure and to death.

Classification – bringing order into diversity

According to the 2003 Venice classification (4, 12, 13) there are 5 main groups of PH (Tab. 1). It is important to distinguish the underlying causes in each group, as it means other diagnostic protocols with different treatment possibilities and especially entirely different prognostic outcome of these patients.

Group 1 in the Venice classification is *pulmonary arterial hypertension (PAH)*, still a very heterogeneous group – including idiopathic pulmonary arterial hypertension (IPAH), familiar pulmonary arterial hypertension (FPAH) and forms associated with various other conditions, like connective tissue diseases (14, 15) and congenital systemic to pulmonary shunts, or human immunodeficiency virus (HIV) infections.

The "true disease" in this sense is IPAH, where it is very trying to understand all the mechanisms that lead to pulmonary hypertension. The role of genetics in the development of PH is also still not completely cleared, though the familiar occurrence (FPAH) emphasizes the suspicion that a genetic susceptibility may be present. A mutation of BMPR2 gene was reported in up to 55 % of patients with FPAH and in more than one-fourth of patients with IPAH (4). On the other hand it is believed that in a vulnerable cell phenotype an exogenous injury or a triggering stimulus is the key that is initiating the whole cascade of pulmonary vascular changes that lead to progression of the disease.

Other forms of PAH differ according to the underlying cause and the prognosis of PH is depending on the management, therapy possibilities and prognosis of the primary disease.

A very specific group is PAH as a result of congenital heart defects. These defects enable a systemic to pulmonary (or left to right, L-R) shunting with increased pulmonary blood flow.

Tab. 1. WHO Classification of Pulmonary Hypertension – Venice 2003 (4).

1. Pulmonary arterial hypertension
   - Idiopathic
   - Familiar
   - Associated with
     - Collagen vascular disease
     - Congenital systemic to pulmonary shunt disease
     - Portal hypertension
     - Infection with human immunodeficiency virus
     - Drugs and toxins
     - Other
   - Associated with substantial venous or capillary involvement
     - Pulmonary veno-occlusive disease
     - Pulmonary capillary hemangiomatosis
   - Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - Left-sided atrial or ventricular heart disease
   - Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung disease or hypoxemia
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic or embolic disease
   - Thromboembolic obstruction of proximal pulmonary arteries
   - Thromboembolic obstruction of distal pulmonary arteries
   - Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
   - Sarcoidosis, pulmonary Langerhans-cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

A long-term volume and even more pressure overload of the pulmonary circulation leads to reactive pulmonary vascular changes, at some point irreversible (Eisenmenger's syndrome). Vascular changes conclude in increased vascular resistance and this again leads to elevation of pulmonary vascular pressure. When the pulmonary pressure exceeds systemic pressure, the shunt across the defect turns right to left (R-L), which is manifesting as systemic desaturation and central cyanosis of the patient.

Unique in congenital heart defects is that PAH here is preventable – when the defect is closed soon enough, PH in most cases will not even develop. Due to this experience and due to advances in pediatric cardiology (early diagnosis as well as successful surgical and interventional treatment possibilities) the number of patients with Eisenmenger's syndrome is constantly decreasing. On the other hand, also as a result of new surgical techniques, many patients with complex congenital defects are now surviving into adulthood. Especially patients with a so called single ventricle physiology are very sensitive to any pulmonary vascular changes. As they have no ventricle to pump the blood through the pulmonary circuit, for them even a trivial elevation of pulmonary resistance can be fatal, not to forget the high risk of thrombosis in any part of their venous system, due to the very slow blood flow and alterations in their hemocoagulation profile.

Group 2 in the Venice classification represents the most frequent cause of mild to moderate PH – due to left heart diseases. The pulmonary vascular changes are in these cases not so outstanding and after releasing the heart problem the elevated pulmonary pressure tends to decrease.

Group 3 PH covers a broad spectrum of lung disorders and altitude sickness causing mild to moderate PH. The management is entirely in hands of pneumologists.

Group 4 is a special group of PH. *Chronic thromboembolic pulmonary hypertension (CTEPH)* is caused by a combination of exo- and endogenous factors. The management of these patients is complex, including the treatment and prevention of deep venous thrombosis, as well as the management of pulmonary complaints.

Group 5 includes rare or extrapulmonary causes of elevated pulmonary vascular pressure.

Understanding the pathophysiology

The process of pulmonary hypertension evolvement is a very complex cascade (Fig. 2) of pathophysiological changes of small diameter (<500 μg) pulmonary arteries (16–18). A cross interaction of diffuse distal arterial vasoconstriction, perivascular inflammatory reaction and in situ thrombosis lead to progressive pulmonary vascular remodeling that includes hypertrophy, proliferation and fibrosis. In this process all three layers and each type of pulmonary vessel cells (endothelial cells, smooth muscle cells and fibroblasts) are involved.

Extensive vasoconstriction is supposed to be an early component of PH. The experimental findings of variations in expression and activity of calcium and potassium channels in pulmonary arteries smooth muscle cells indicate that some cases of pulmonary hypertension may represent a form of a channelopathy (19).

The crucial role though seems to play endothelial dysfunction with chronically impaired production of pulmonary vasodilatators (i.e. nitric oxide (NO) and prostacyclin (PGI_2)) and/or an increased production of pulmonary vasoconstrictors (i.e. endothelin-1 (ET-1)). Understanding the activation pathways of the above mentioned three mediators enabled for the first time targeted specific therapy of PH (20) (Fig. 3).

On the other hand the process of pulmonary vascular regulation is much more complex than that (21). A number of other endothelial cell- and/or platelet-mediators and growth factors (serotonin, vascular endothelial growth factor (VEGF), platelet derived growth factor (PDEF), thromboxan A2 (TXA_2), platelet activating factor (PAF), von Willebrand factor (vWF) etc.) have shown to be involved in the pulmonary vasoconstriction-dilation regulation mechanism. Also the effect of these factors on endothelial cell damage, local platelet regulation failure (with increased chemotaxia, aggregation and adhesion) and local inflammatory reaction is being studied. Pathological neo-angio-

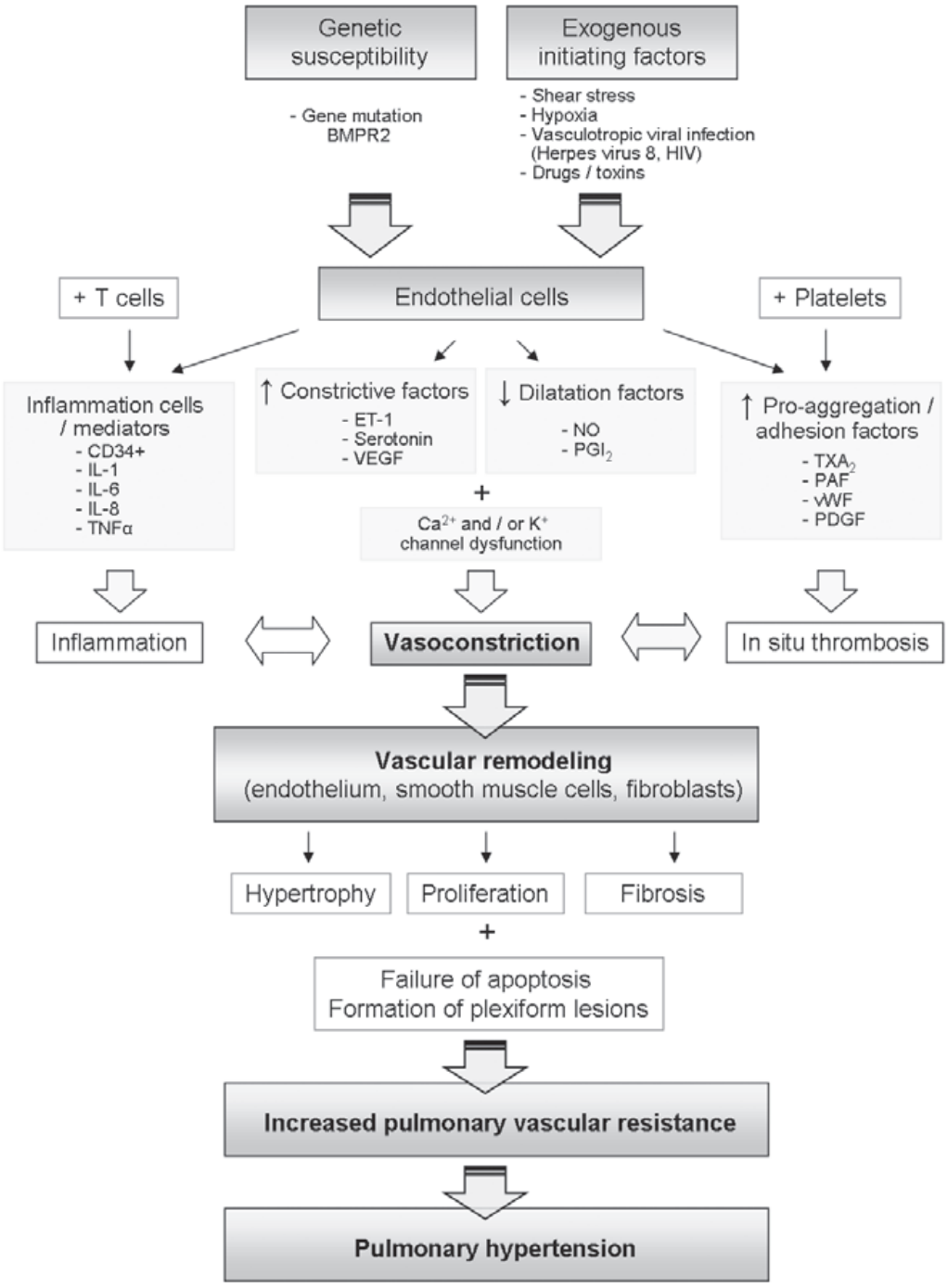

Fig. 2. Pathophysiology of pulmonary hypertension (ET-1 – endothelin 1, VEGF – vascular endothelial growth factor, NO – nitric oxide, PGI_2 – prostaglandin I_2, CA^{2+} – calcium channels, K^+ – potassium channels, TXA_2 – thromboxan A2, PAF – platelet activating factor, vWF – von Willebrand factor, PDGF – platelet derived growth factor).

genesis with plexiform lesions formation as the failure of normal apoptosis in pulmonary arteries is supposed to play an important role in PH evolvement as well (22).

The complexity of normal pulmonary vascular regulation and pathological regulation mechanisms in pulmonary hypertension need to be explained in detail. Understanding the role and importance of any factor gives us a key for potential new targeted therapeutical options. Understanding the whole pathophysiology is though the only hope for the future for the possibility to reverse the pulmonary hypertension process.

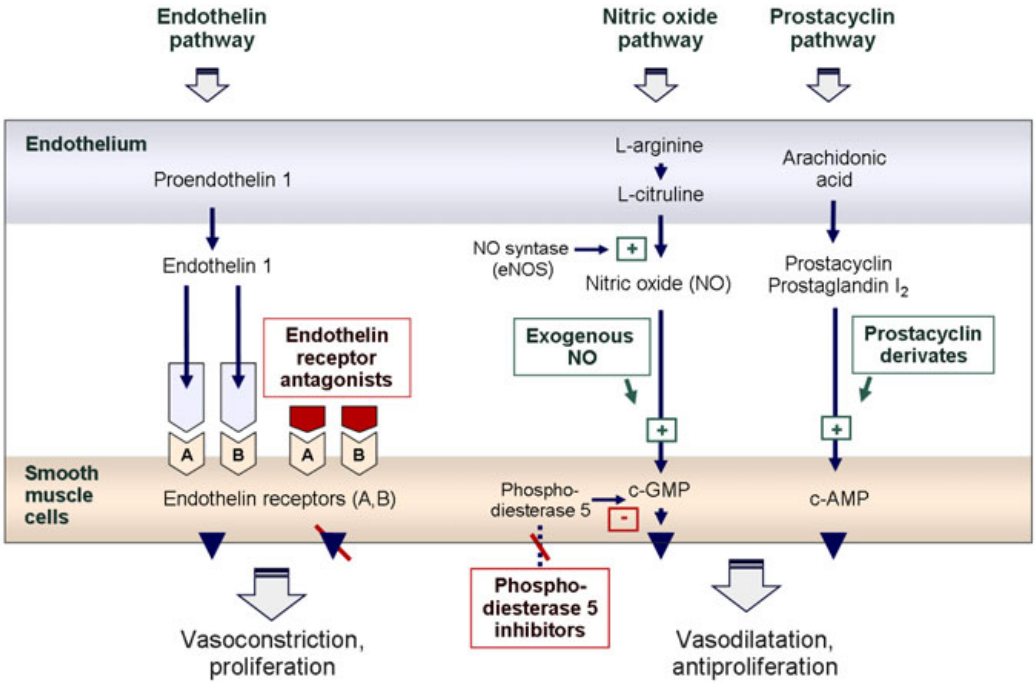

Fig. 3. Endothelial function – 3 target pathways for current treatment options, modified from: Humbert M et al (15) (NO – nitric oxide, eNOS – endothelial NO syntase, c-GMP – c-guanidin monophosphate, c-AMP – c-adenosine monophosfate).

How "rare" and how "bad"?

The prevalence of PAH in Europe is established to about 15 patients per million inhabitants (23), but the number of patients may be underestimated. Out of all PH about 40 % are patients with IPAH, 15 % associated with connective tissue diseases and 11 % due to congenital systemic to pulmonary shunt defects.

Transferring this to the Slovak population, it means about 75–100 expected patients with PAH (24) and 1/3–1/2 of them are supposed to be symptomatic according to the New York Heart Association (NYHA) in functional class II.–IV.

Due to sustained, fast and progressive increase of pulmonary vascular resistance the prognosis is often very poor. Many forms of PAH (like IPAH) have a life-expectancy of 2.8 years from time of diagnosis (25), in children it may be even less then 1 year. Untreated 1-year survival rate is 68–88 % and a 5-year survival only 34 %.

The crucial role in the poor prognosis of IPAH seems to play the early progressive deterioration of right ventricular function with low cardiac output (26) (Fig. 4). This can be testified in forms of PH with preserved right ventricular function (like in patients with congenital shunt defects in Eisenmenger's syndrome) where a much better long-term survival (27, 28) is experienced.

Clinical features

The first manifestation of PH clinical symptoms may have a sneaking onset and are very non specific. Very often it takes 1–2 years from onset of symptoms till the right diagnosis is made. Fatigue and decreased exercise tolerance are usually the first signs, followed later by progressive dyspnoea and/or syncope. Symptoms like chest pain or peripheral edema are less frequent.

Cyanosis is usually a late symptom, most markedly expressed in Eisenmenger's syndrome. Progressive long-term cyanosis may lead to a complex of secondary complications, associated with polycytemia or hyperviscose syndrome. The most serious problem is an extremely high risk of thrombosis and thromboembolic complications and on the other hand also bleeding disorders, not to forget as well other organs' affection (liver, kidneys, bones etc.).

It is very important to think also about other diseases (like connective tissue or liver diseases), as PH may be the first sign of a different primary disease. In this case naturally the only relevant treatment of PH is managing the underlying cause.

Diagnostic tools

First it is necessary to establish the diagnosis of elevated pulmonary arterial pressure and its severity. In this echocardiography plays a crucial role. According to tricuspid regurgitation gradient (in the absence of right ventricle outflow obstruction or pulmonary stenosis) the systolic pulmonary arterial pressure can be approximated. Also the degree of right ventricular dilatation and right ventricular function as a prognostic factor is important to consider. And of course the left heart diseases as a cause of PH must be ruled out.

As the next step in the diagnosis of PH an invasive confir-

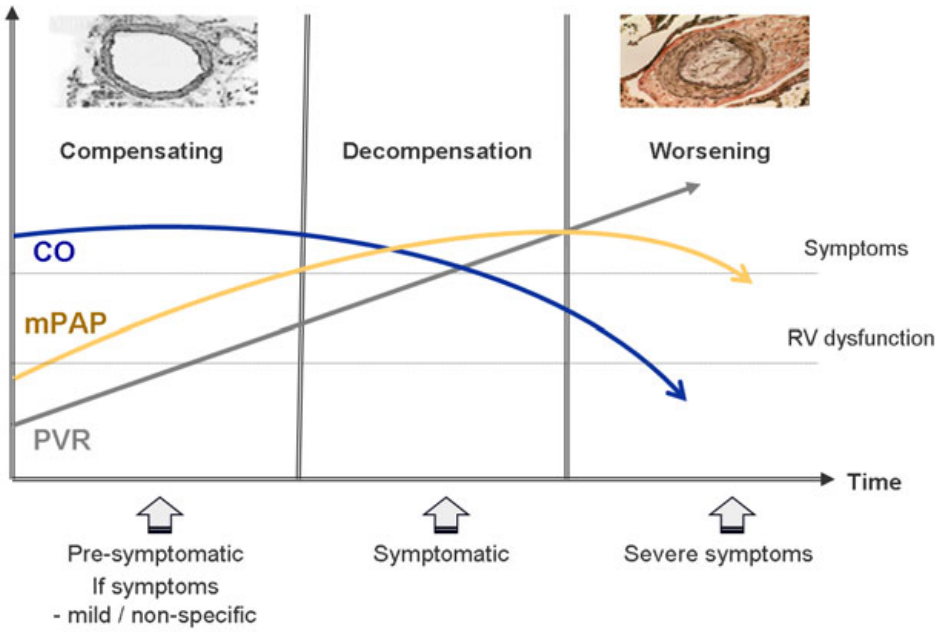

Fig. 4. Clinical symptoms of pulmonary hypertension according to hemodynamic parameters (CO – cardiac output, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance).

mation of pulmonary arterial pressure is necessary, as well as a test of vasoreactivity.

Other diagnostic methods (like computer tomography angiography (CTA), ventilation/perfusion scintigraphy, etc.) help in differentiating and classifying the type of PH and other methods again (ergospirometry and 6 minute walking test (6MWT)) to establish the patient's functional status.

For a complete diagnosis also laboratory parameters and other diagnostic tools need to be examined to rule out other systems (liver, kidney etc.) possible affection.

Therapy – still a nightmare or a breakthrough at last?

Due to a very complex etiopathogenesis of PH and in the absence of satisfactory explanations of pulmonary circulation pathophysiological regulatory mechanisms the management of PH patients has been insufficient and frustrating in the past and according to numerous recent studies still remains a great challenge for today and for the near future.

In the last two decades as the heart-lung transplantation from the long-term view has shown so far quite disappointing results, so this option remains reserved only for the most severe PH patients. All the more wide-spread activities are presently oriented to the possibilities of medical therapy.

The standard – conventional therapy of PH includes anticoagulants, diuretics and oxygen therapy. It moderates the RV failure symptoms, though has no significant influence on prognosis. In the 1980-ties very promising seemed vasodilatation therapy with calcium channel blockers but showed to be effective in only about 10 % of patients, so called long-term responders.

In the 1990-ties a breakthrough in PH therapy was achieved. A so called specific therapy gave during the last 10 years PH patients a new hope. Better understanding of the pathophysiology of the endothelial function enabled targeted therapeutical impact of three pathways (12, 18, 29). Intravenous prostacyclin (epoprostenol) and other prostanoid analogues (beraprost, treprostinil, iloprost) affect the prostacyclin pathway, endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan) affect the endothelin pathway and phosphodiesterase-5 antagonists (sildenafil, tadalafil) affect the nitric oxide pathway. In Slovakia these novel therapeutical modalities were implemented into the PH management protocols since 2005 (30, 31).

As a success of the specific therapy many short-term studies showed better survival of PH patients and especially an increase of their functional capacity. On the other hand, from the long-term point of view, patients' clinical improvement and life prolongation on specific therapy is still not as optimistic as it was hopefully expected. After the first-line rapid improvement there is often a clinical worsening experienced.

This clinical practice confirms the assumption that in such a complex pathophysiology influencing only one pathway may not be sufficient. Treatment strategies at present tend to shift toward a combination therapy, with the logical mean to attack more pathophysiological pathways at the same time. Though it has to be kept in mind that none of these impacts mean a cure yet, as they cannot reverse the process of PH, they can merely slow-down the progression of irreversible pulmonary vascular changes. In this context for achieving best results it is important to start treating the patient as soon as possible.

As regarding other – non medication – treatment possibilities,

CTEPH represents a specific category of PH. The prognosis of CTEPH patients as a whole is poor (like in IPAH) and depends on severity of PH. Though in contrast to other forms of PH, there is a subgroup of patients where a surgical therapeutic option can be applied. For CTEPH patients with proximal pulmonary arteries affection without significant secondary distal microvasculopathy a so called pulmonary endarterectomy (PEA) is a very promising new and curable strategy (32, 33). The process of preoperative patient evaluation, selection, surgery and postoperative management requires a multidisciplinary approach. In the management of Slovak CTEPH patients a close and very successful co-operation with the Czech Republic was established (34–36).

The perspectives

The first and most important goal is still an **early detection** of patients with PH, especially those with idiopathic or familiar forms. To think of this diagnosis is the crucial message for all the family– and first contact doctors who come across patients with nonspecific but progressive PH symptoms. It often takes too much time till the diagnosis of PH is recognized. Due to the very poor prognosis every day that the patients with PH are treated according to the right diagnosis can be very beneficial for them.

Also very useful turned out to be a targeted *screening for PH* in high risk population groups – in patients with connective tissue diseases, especially with sclerodermia. A close co-operation of cardiologists and rheumatologists in this field is required.

Due to the *advances in pediatric cardiology and cardiac surgery* in the last decades there was a great progress achieved in diminishing PH associated with congenital heart defects. This is the only group of patients where the development of PH is avoidable: So an early closure of systemic to pulmonary shunts means for the future a decreasing number of patients with irreversible pulmonary vascular changes (Eisemengers' syndrome). On the other hand, as another success of pediatric cardiology there is a growing adult patients population with single ventricle physiology, with no functional subpulmonary ventricle that could be pumping blood into the pulmonary circuit. These patients represent a very high risk group with many potential problems and complications. Therefore their pulmonary circulation needs to get a close and continual attention and in these patients it has to be taken very good care of all, even trivial, pulmonary pathology.

The screening and first-line detection of PH should be as wide-spread as possible. On the other hand, as pulmonary hypertension is not a very frequent problem, the complex management of these patients should be concentrated in highly **specialized expert centers** – with an experienced stuff and all the necessary diagnostic and therapeutic modalities available.

In the *diagnostic process and in differential diagnosis of PH* should all possible diagnostic tools and methods be effectively used. Emphasized should be the important role of echocardiography as a noninvasive and highly sensitive method that can be used very well for screening, as well as for long-term monitoring of patients with PH. Catheterization is the golden standard for exact measurements of pulmonary arterial pressure and pulmonary vascular resistance, as well as for pulmonary vasoreactive testing. Other diagnostic methods help in differentiating the underlying causes of PH or establishing the patient's contemporary functional status.

The *classification* of patients with PH helps to see the diversity of processes that can lead to the same outlying picture. On the other hand, the same clinical picture does not mean the same prognosis, or the same treatment protocol. This is why it is so important to think about all possible (and especially all potentially curable) causes of PH.

Understanding the molecular pathophysiology of pulmonary vascular changes, the various pathways of regulation mechanisms and their interaction is the key for a successful **targeted therapeutic impact** in the management of PH. During the last years the specific therapy gave new hope for PH patients as many studies have shown improved functional status and better survival after using medication influencing one of the endothelial regulation pathways. The followed parameters often showed though only temporary improvement and also it can be a point for discussion how significant is for the patient for example an improvement of 20–50 m in a 6MWT. In light of these experiences there is a tendency to start the medication sooner (already in NYHA class II patients) when the morphological changes of pulmonary arteries are less prominent. Other contemporary and a most logical trend in PH management is the combination therapy, influencing 2 or more pathways at the same time. There are also some perspective new molecules tested in experimental studies that are trying to influence other endothelial regulatory mechanisms.

Conclusions

In spite of the visible progress achieved in the PH management during the last couple of years it is necessary to stay on the ground. No matter how optimal and up-to-date the current management is, in approximately 50 % of the treated patients still their exercise tolerance and functional capacity stays low (6MWT <400–450 m, NYHA class III.–IV.), their hemodynamic parameters are unacceptable (mean pulmonary artery pressure ~50–55 mmHg), life quality is suboptimal and annual mortality is high (>5–10 %).

The specific targeted impact is definitely the right way in treatment strategies for PH. It seems to be the beginning of an extensive way though, till it will be possible to influence successfully and with a long-term outcome such a complex pathophysiological problem. And hopefully in the future a way will be found not only to slow down the progress of the disease like it is done today but also to come to an effective reversal of already present morphological changes of the pulmonary vascular bed. Only then would pulmonary hypertension be a curable disease and would stop to be a nightmare at last.

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