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PATHOPHYSIOLOGY ADVANCES IN THE TREATMENT OF PULMONARY HYPERTENSION

Abstract: *Pathophysiology advances in the treatment of pulmonary hypertension*

The pulmonary hypertension (PH) is the disease with still not clear pathophysiology. The possibilities of current pharmacological treatment of this disorder are unfortunately relatively small, thus the advances in searching of new agents effective in this disease are in progress. The article briefly discusses the present PH classification, its basic etiopathogenesis description and the current and potential possibilities of the pharmacological intervention.

Key words: pulmonary hypertension, pulmonary hypertension pathophysiology, pulmonary hypertension treatment
Słowa kluczowe: nadciśnienie płucne, patofizjologia, leczenie nadciśnienia płucnego

INTRODUCTION. BASIC DEFINITION AND CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition occuring in multiple clinical conditions. According to latest ESC/ERS (European Society of Cardiology and European Respiratory Society) guidelines form 2009, it is regarded to be an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest, demonstrated during right heart catheterisation. Normal mPAP at rest is about 14 ± 3 mm Hg, with upper limit of about 20 mm Hg, thus value of 25 mm Hg has been chosen as a significant marker of PH (the significance of mPAP between 21–24 is unclear and requeires further evaluation in epidemiological studies) [1].

Previously PH was mostly described as either a systolic pulmonary artery pressure (PAP) of ≥ 35 mm Hg or alternatively as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest or ≥ 30 mm Hg with exertion in the pres-

ence of normal or reduced cardiac output [2–4]. However, the PH definition based on the exercise PAP assessement is not supported at the present, because of the findings showing that healthy individuals can achieve even higher values. Thus, the only accepted PH definition is this one due to the resting PAP estimation [1].

Pulmonary hypertension was first described in 1865 by the German physican Klob, who reported in his autopsy of a patient who died at age 59 presenting progressive ankle oedemas, dyspnoea and cyanosis, findings of narrowing of the finer branches of the pulmonary artery with arteriosclerosis. The similar clinical course in 24 years old patient reported Romberg in 1891, who also observed massive right ventricular hypertrophy. The next, recurrent cases of these kind of abnormalities resulted in "Ayerza's disease" defining in 1913 by argentinean physician Arrillaga, who honoured in this way his Professor name, also working on this research area [5].

For many years, the explanation of pulmonary hypertension remains mysterious and this clinical entity was regarded to be a result of unknown either primary or secondary factors. In 1957, PH was divided into 5 classes, according to the predominance cause and histopathological features: chronic bronchitis and emphysema, left to right shunt, primary pulmonary hypertension, primary pulmonary arteriosclerosis and pulmonary embolismus [5]. The progress in PH understanding that had been made over the years resulted in renewed division. The current PH classifications take various aspects of this disease into account. There is a pathophysiological PH division into three main classess: pre-capillary, post-capillary and mixed ones, based both on anatomical features and haemodynamic findings of the major parameters: mPAP, PWP (pulmonary wedge pressure) and CO (cardiac output). The pre-capillary PH is characterized by resting mPAP ≥ 25 mm Hg (in accordance with general definition) and PWP ≤ 15 mm Hg with normal or reduced CO. Contrary to the above, post-capillary PH is diagnosed on the basis of PWP > 15 mm Hg and the same other abnormalities (resting mPAP ≥ 25 mm Hg, CO normal or reduced) [1]. The most used PH classification, however, is the clinical one. The actual version, established at Dana Point meeting, is a slightly modificated Evian-Venice classification proposed in 1998 and 2003. The conditions proceeding with PH are divided into five groups, according to the clinical and therapeutical options (Table 1). The comparison of the both pathophysiological and clinical PH division indicates, that PH patients classified according to clinical description to group 1, 3, 4 and 5, are mostly suspected to develop pre-capillary mechanisms of PH, while those ones suffering from PH due to left heart disease — group 2, are meeting the criteria of post-capillary PH [1].

Table 1 — Tabela 1

Clinical classification of pulmonary hypertension (Dana Point, 2009) [1]

Kliniczna klasyfikacja nadciśnienia płucnego według ustaleń IV Światowego Sympozjum Nadciśnienia Płucnego (Dana Point, 2009) [1]

1. Pulmonary arterial hypertension (PAH)	1.1. Idiopathic 1.2. Heritable 1.3. Drugs and toxins 1.4. Associated with (APAH) — connective tissue diseases — HIV infection — portal hypertension — congenital heart disease — schistosomiasis — chronic haemolytic anaemia 1.5. Persistent pulmonary hypertension of the newborn 1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2. Pulmonary hypertension due to left heart disease	2.1. Systolic dysfunction 2.2. Diastolic dysfunction 2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1. Chronic obstructive pulmonary disease (COPD) 3.2. Interstitial lung disease 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4. Sleep-disordered breathing 3.5. Alveolar hypoventilation disorders 3.6. Chronic exposure to high altitude 3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension	
5. Pulmonary hypertension with unclear and/or multifactoral mechanisms	5.1. Haematological disorders: myeloproliferative disorders, splenectomy 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4. Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

EPIDEMIOLOGY AND SYMPTOMATOLOGY OF PULMONARY HYPERTENSION

The epidemiological data on the prevalence of the different PH types are not available. However, there are reports about PAH prevalence, revealing that this rare clinical condition is about 15 cases/million adult population (incidence 2,4 cases/million adult population/year) [1, 6]. Several risk factors for PAH development have been identified, including pharmacological agents. They were classified as definite (usage of anorexic drugs, mainly derivatives of fenfluramine), likely (amphetamine, metamphetamine), possible (cocaine, some chemiotherapeutic agents, selective serotonin reuptake inhibitors, pergolid) and unlikely (oral contraceptives, estrogens), according to the strength of their association with PAH and their probably causal role [1]. Contrary to PAH, PH resulting from left heart diseases is estimated to be high; up to 60% of patients with severe left ventricular systolic dysfunction and up to 70% of patients with diastolic left ventricular failure present PH development. Moreover, all patients with severe mitral valve disease and up to 65% of those with symptomatic aorta stenosis demonstrate PH progression [1].

Similarly, PH due to lung diseases prevalence is also high; in advanced chronic pulmonary obstructive disease (COPD), PH is observed in about > 50% of patients, while in interstitial lung diseases it is in range between 32–39% [1].

The general PH symptoms, shared with all PH forms, include breathlessness, exertional exacerbations, fatigue, weakness, angina, syncope [1, 2]. The permanent consequence of an increase in pulmonary pressure, due to elevated pulmonary resistance and impedance of flow, is right ventricle strain resulting in right ventricle volume and pressure overload. It must be emphasized that right ventricle demonstrates a heightened sensitivity to changes in both pre- and afterload. Furthermore, this pathophysiological conditions lead to right ventricle dilation (and eventually hypertrophy), but also result in encroaching on the left ventricle. That is why progressive right ventricular dysfunction contributes to low cardiac output and hypotension in patients with PH. Additionally, increased right ventricle wall strength predisposes to its ischaemia. Tricuspid regurgitation develops as a result of right ventricle dysfunction. There are also neurohormonal compensatory reaction observed in right-sided failure, involving atrial and B-type natriuretic peptides elevation in patients with PH and right ventricle failure. These peptides promote not only diuresis but also inhibit further pulmonary vasoconstriction. The final common pathway for haemodynamic deterioration is an isolated right ventricular failure or because of the ventricular interdependence, both right and left ventricular insufficiency leading to death [3].

PULMONARY HYPERTENSION PATHOPHYSIOLOGY

Despite close connection and joint classification, the underlying mechanisms responsible for PH development in particular Dana Point classes are completely different. Thus, there is no common treatment option in various PH groups. However, whatever the predominance pathophysiological initiating event is, the progressive increase in pulmonary vascular resistance develops.

In PAH, a multifactoral pathophysiology involving various biochemical pathways and cells is discussed. The initiative factor is still elusive, however, it is thought that endothelial dysfunction plays a key role in disease development [7]. Whatever the primary event is, it leads to variable vasoconstriction, vascular smooth muscle and endothelial cells proliferation and in-situ thrombosis. Additionally, apart from vascular medial smooth muscle, endothelial-dependence proliferation, the extracellular matrix also participates in pulmonary vessels remodelling. Tenascin-C, elastin, fibronectin, produced in increased amounts together with collagen, highly expressed in medial layer, also cause vascular stiffness and lead to smooth muscles proliferation. These all mechanisms are responsible for pulmonary vessel narrowing and vascular resistance increase. Pulmonary endothelium is also regarded to contribute in PH development because it regulates resistance through a complex balance between vasodilatators (prostacyclins, nitric oxide) and vasoconstrictors (endothelin-1, thromboxane A2, serotonin), that is disturbed in PH. Moreover, pulmonary endothelium also mediates growth factors inhibitors, antithrombotic mediators versus mitogens and prothrombic determinants, respectively [4]. As mentioned previously, endothelial dysfunction predisposes to an imbalance in the vasodilators and vasoconstrictors production and to oversecretion of the thrombotic and inflammatory agents [4, 7].

The most important advancement in PAH pathophysiology in recent years was the revealing of mutations involving transforming growth factor beta superfamily receptors. It was discovered that in familial PAH, germline mutations in the bone morphogenetic protein receptor II (BMPR-II) gene occurs in about 70% of cases. BMPR-II mutations were also detected in 11–40% of spontanic, sporadic PH cases. Moreover, other mutations in the endoglin receptor and activin-like receptor 1 (ALK-1), associated with hereditary haemorrhagic telangiectasia, have also been thought to be characteristic for PAH phenotype in some families. That is why these findings seem to be one of the most important genetic factors predisposing to PAH, especially when revealed that proteins encoded by these genes are also involved in control of vascular cell proliferation. It is interesting, however, that the response of vascular endothelial and smooth muscle cells to bone morphogenetic protein 2 (BMP2) depends on the anatomical localisation of the cells — those ones located in large arteries are inhibited, while peripheral artery smooth muscle

cells enhance proliferation. BMP2 proteins also regulate endothelial cells functions by their protection from the apoptosis. Thus, reduced BMP2 function in BMPR-II receptor mutations, leads to increased endothelial apoptosis with subsequent damage of the endothelial barrier allowing the ingress of serum factors, promoting smooth muscle and myofibroblasts proliferation and changes in the matrix [7].

There are also reports that PAH is related to the auto-antibody diseases. About 15% of PAH patients have a connective tissue disturbances. It seems that an intact immune system is necessary for the protection against PAH. In animal models, disease progression was revealed to rely on inflammation that is implicated in repair and misrepair in vascular remodelling (Il-1, Il-6, RANTES, fractalkine were demonstrated to be upregulated). Disturbed immunity is regarded to be a "second hit" and cause of the worsened PAH pathophysiology [7].

The mechanisms of other PH types can be explained by several multiple mechanisms. PH due to left heart diseases develops mostly as a result of the passive, background transmission of the pressure elevation (post-capillary PH), but pathophysiology of this PH form may also include vasoconstrictive reflexes arising from stretch receptors located in the left atrium and pulmonary veins and endothelial dysfunction of pulmonary arteries leading to vessel remodelling.

PH resulting from lung diseases or hypoxia is caused by hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of capillares, inflammation and toxic effects of cigarette smoking. The endothelial derived imbalance between vasoconstrictory and vasodilatatory agents secretion is also possible. PH observed in pulmonary embolism depends on the mechanical obstruction of pulmonary arteries. The clotting formation is associated with coagulation process disturbances together with platelet and fibrinolysis dysfunction, that enable the local procoagulation environment. It is aggravated by inflammatory infiltration that is found in pulmonary endarterectomy specimens. The pathophysiology of PH classified as group 5th, according to Dana Point grading (pulmonary hypertension with unclear and/or multifactoral mechanisms) is unclear and multifactoral [1].

CURRENT TREATMENT OF PULMONARY HYPERTENSION

Treatment of pulmonary hypertension is complex, involving both symptomatic and — in selected PH group — specific and causative agents. Available specific drugs are currently approved for the treatment of patients suffering from PAH. However, patients with hypoxia-induced PH or those ones with chronic thromboembolic PH may also benefit from these treatment. This specific PAH management address three main aspects: 1. pulmonary vasoconstriction 2. vascular

obstruction by recurrent embolism or local thrombosis 3. pulmonary vascular remodelling, that is the most difficult to treat [8].

Basic rules should be introduced in all PH patients, regardless from the detailed pathomechanisms. Patients should keep their active lifestyle to maintain their psychological well-being and to prevent physical de-conditioning, but on the other hand they should avoid events leading to significant shortness of breath. Episodes of dizziness, near-fainting or syncopes must be considered as alarming signs of right ventricular insufficiency progression and require restriction of physical activity to level that prevents these symptoms. Female patients should be advised to use contraceptives as pregnancy may induce rapid PH deterioration. In the case of chronic hypoxia (PaO_2 < 60 mm Hg), long term oxygen treatment must be implemented to prevent hypoxic pulmonary vasoconstriction. Moreover, patients should not exceed altitudes of 1500 m above sea level and supplemental oxygen is recommended for airplanes travel [8].

At present, there is neither specific therapy for PH due to the left heart disease nor for PH associated with COPD or interstitial lung disease. The management should be aimed at the optimal treatment of the underlying disease. In patients suffering from PH secondary to left heart disease, angiotensin converting enzyme inhibitors or angiotensin AT1 receptor antagonists in combination with diuretics can be used to promote left ventricular re-compensation. Other drugs (nitrates, inotropic agents) and interventions (valvular surgery, resynchronisation therapy, left ventricle device implantation or heart transplantation) are also to be considered. The treatment of choice for patients with COPD or interstitial lung disease and associated hypoxemic PH is long term oxygen therapy. Treatment with conventional vasodilators is not recommended because they may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction. Patients with chronic thromboembolic pulmonary hypertension should receive life-long anticoagulation, usually oral vitamin K antagonists adjusted to a destination INR between 2 and 3 [1, 8].

The administration of — so called — specific drugs dedicated for pulmonary hypertension treatment is restricted to pulmonary artery hypertension — PAH. This specific therapy contains various agents, such as: inhalatory nitric oxide, calcium channel blockers (CCB), prostacyclin and prostacyclin derivatives, phosphodiesterase –5 and –3 inhibitors and endothelin receptor antagonists ("sentans"). These pharmacological agents address the main pathophysiological PAH aspect — pulmonary vasoconstriction [7].

The inhalatory nitric oxide (INO) causes selective pulmonary vasodilatation, lowering the PAP and pulmonary vascular resistance (PVR). NO administration activates guanylate cyclase and increases guanosine 3,5-monophosphate (cGMP) level, resulting in pulmonary vascular smooth muscles relaxation. INO is a therapeutic option in short-term high pulmonary pressure restraint in critically ill adults, in management of acute, refractory hypoxia related to ADRS

and in short-term management of pulmonary hypertension in pediatric population. INO administration is associated with some side effects, including methemoglobinemia and carboxyhemoglobinemia [7, 9].

Inhibition of cGMP degradation by phosphodiesterase-5; PDE5 (and to a lesser extend, phosphodiesterase-3; PDE3) is an alternative pharmacological approach to enhance pulmonary vasodilatation. Additionally, PDE5 inhibitors are also suspected to exert antiproliferative effects. All PDE5 inhibitors approved for erectile dysfunction treatment cause significant pulmonary vasodilatation [1, 9–11]. They are mentioned in Table 2 below.

The earliest traditional vasodilators used since the 1980s were calcium channel blockers and nifedipine, diltiazem and amlodipine were predominantly used. The choice of selected CCB is based on patient's baseline heart rate — a relative bradycardia favours nifedipine or amlodipine while patient with resting tachycardia starts with diltiazem. Limiting factors reported to be the most frequent adverse effects were systemic hypotension and lower limb peripheral oedema [1, 7, 10, 11].

The rationale for prostacyclin usage in PAH treatment is based upon the physiological features of this compound — it induces potent vasodilatation of all vascular beds and is the most potent endogenous inhibitor of platelet aggregation. Moreover, it appears that prostacyclin has both cytoprotective and antiproliferative properties. At present, there are few prostacyclin analogues clinically used, that possess different pharmacokinetic profile but similar pharmacodynamic effects [1, 7, 9–11]. They are shortly described in Table 2 below.

The endothelin-1 receptor antagonists are used in PAH treatment due to data supporting a prominent role of the endothelial system in PAH pathogenesis mentioned above. Endothelin-1 (ET1) exerts vasoconstrictor and mitogenic effects by binding to ETA receptors. There are also ETB ones but their activation lead to the opposite effects (vasodilatatory and antiproliferative), counterbalancing the deleterious effects of ET1 mediated via ETA receptors. From this reason, there were attempts to introduce ETA receptor selective antagonists, since selective ETA antagonist may have advantages over non-selective inhibition. Undoubtedly, there are no premises to apply selective ETB receptor antagonists [12, 13]. However, despite potential differences in receptor isoforms activity, the efficacy of both selective and non-selective ET1 receptor antagonists estimated in several studies appeared to be similar. The ETA/ETB receptor antagonists (sentans) introduced to PAH therapy are given in table 2 below [1, 7, 9–11].

Table 2 — Tabela 2

Current pharmacological options in PAH treatment [1, 7, 9, 10]

Obecne możliwości farmakoterapii nadciśnienia płucnego [1, 7, 9, 10]

Group	Mechanism of action	Pharmacological agents	Remarks
Nitric oxide (NO)	Activation of vascular smooth muscles soluble guanylate cyclase resulting in increased cGMP production, leading to diminishing calcium-dependent calmodulin activity with subsequent myosin light chains phosphorylation decrease and relaxation	INO	increased risk of methemoglobinemia and/or carboxyhemoglobinemia requires a closed inhalation circuit and may be associated with significant PH rebound increased cost of therapy
Phosphodiesterase-5 inhibitors (PDE5-Inhibitors)	Inhibition of cGMP degradation, resulting in cGMP increased level — thus these agents act via the same mechanism as that exerted by NO	sildenafil tadalafil vardenafil	sildenafil — orally active, administrated twice daily tadalafil, vardenafil — once-daily dispensed most of side effects were related to potent vasodilatation (headaches, flushing, epistaxis, hypotension)
Calcium channels blockers (CCB)	Blockade of calcium channels, leading to diminishing calcium-dependent calmodulin activity with subsequent myosin light chains phosphorylation decrease and relaxation	nifedipine amlodipine diltiazem	patients should undergo vasoreactivity test prior to starting CCB since CCB treatment results in survival advantage among patients with chronic PAH and positive vasodilator response compared to nonrespondens
Prostacyclins	Activation of adenylate cyclase resulting in increased cAMP production, acting similar to cGMP and finally leading to relaxation	epoprostenol treprostinil beraprost iloprost	epoprostenol — only for i.v. infusion, short half-life time (3–5 min) treprostinil — administrated by the i.v. as well as s.c. route (via microinfusion pump and small subcutaneous catheter)

Table 2 — Tabela 2

Group	Mechanism of action	Pharmacological agents	Remarks
			beraprost — first chemically stable and orally active prostacyclin analogue (data suggesting that improvement in exercise capacity persists only up to 3–6 months when administrated chronically iloprost — avaiaible for i.v., oral and aerosol administration; inhaled drug dose is considerably lower compared to other routes of administration Most observed side effects: flushing, headaches, diarrhoea, leg/jaw pain, infusion local pain
Endothelin-1 receptor antagonists ("sentans")	Blockade of ETA receptors for ET-1, resulting in decreased phosphatidylinositol (PIP) and inositol 1,4,5-triphosphate pathway, leading to diminished RhoA (ras homolog gene family) and ROCK (RhoA kinases) activity, leading to relaxation	bosentan tezosentan ambrisentan sitaxentan	bosentan, tezosentan — dual ETA/ETB receptor antagonists ambrisentan, sitaxentan — selective ETA receptor antagonists The most significant side effects were related to dose-dependent hepatic aminotransferases increases — for this reason liver function tests should be performed monthly ambrisentan — an increased incidence of peripheral oedema was reported bosentan — an inducer of cyp3A4 and cyp2C9 — increased risk of pharmacokinetic drug interactions! sitaxentan — an inhibitor of cyp2C9 and weak inhibitor of cyp3A4, cyp2C19 and cyp2C8 increased risk of pharmacokinetic drug interactions!

PATHOPHYSIOLOGICAL PREMISES OF FUTURE PULMONARY HYPERTENSION TREATMENT

All of the current therapies that have been approved for PAH treatment, are focused on the vasoactive mechanisms. From the pathophysiological point of view, the future PAH pharmacological opportunities should be concentrated not only on the next generation of vasodilators but also on anti-proliferative agents introduction, according to the demonstrated heightened proliferation of smooth muscle in the small pulmonary resistance arteries. However, the advances in agents reversing and preventing from the vascular remodelling development are still insufficient, since the therapy of vascular remodelling is the most difficult feature to treat [1, 7].

The future antiproliferative agents include factors blocking growth factors. It was shown that several growth factors (platelet derived growth factor; PDGF, basic fibroblast growth factor; b-FGF, epithelial growth factor; EGF) are implicated in the abnormal proliferation and migration of vascular smooth muscle cells. They also act as potent mitogen and chemoattracant for vascular smooth muscle cells. Growth factors activate their receptors (e.x. PDGFR) belonging to a family of transmembrane receptor tyrosine kinases that are autophosphorylated after ligand bindings. Imatinib, is a selective inhibitor of tyrosine kinase that was initially designed for blocking breakpoint cluster region Abelson (bcr-abl oncogen). Thus, this agent was approved for treatment of chronic myeloid leukaemia, however, it also displayed efficacy in two animal models of PAH, showing desired pulmonary hemodynamics and vascular remodelling improvement. These findings made imatinib an attractive antiproliferative agent in a number of settings [7, 10].

Recent advances have also identified GTP-ase RhoA kinase and its effector protein — rho kinase that play role in vascular tone and structure maintenance. In pulmonary vessels, rho-kinase phosphorylates and inactivates myosin light chain phosphatase, causing vasoconstriction. Thus, inhibition of RhoA/rho kinase system promotes vasodilatation. The experimental studies demonstrated that treatment with fasudil — rho kinase inhibitor lead to sustained pulmonary vasodilatation in fetal sheep [14, 15].

The other directions focused on the next generation of vasodilatators research, mostly acting via soluble guanylate cyclase (sGC). Both stimulators (augment the NO effects on the enzyme) and activators (mediate via NO independent mechanisms) of sGC are studied. Riociguat (sGC stimulator) underwent first clinical trials demonstrating significant improvement in pulmonary haemodynamic parameters in patients with PAH. The observed effects were greater than those noted by inhaled NO. Other vasodilatators such as vasoactive intestinal peptide (VIP) are also particularly of interest. VIP and related peptides exert biological effects via specific receptors VPAC-1 and 2, with sig-

nalling pathways involving cAMP and cGMP, both of which induce relaxation of vascular smooth muscle cells. Therefore VIP seems be also potential PAH treatment target, however, clinical data are lacking and controlled studies are required [7, 10].

On a margin it should be noticed that pulmonary hypertension development was also observed after some anorexigenic agents (aminorex), as it was mentioned earlier. It became a background of serotonin PAH hypothesis, originated in the 1960s when the relationship between anorexigenic drugs and increased PAH risk development was revealed for the first time. In the early 1980s the similar findings were displayed for patients receiving fenfluramine. These agents are serotonin transporter substrates and increase extracellular serotonin level — the appetite-suppressant effects of fenfluramine and its derivatives is regarded to be depended on the increased serotonin release and augmented serotonin receptors stimulation [16]. Serotonin is thought to induce pulmonary hypertension by acting on specific serotonin transporters resulting in pulmonary arterial fibroblast and smooth muscles proliferation enhancement. It leads to the thickening of the medial layer and a narrowing of the pulmonary arteries lumen, contributing to the vascular remodelling and in consequence resulting in vasoconstriction and pulmonary resistance increase. The experimental data confirm serotonin role in PAH development — this compound can potentiate the development of hypoxia-induced PAH in rats. The exact mechanism by which serotonin induces PAH has not been clearly described so far, however the interactions between serotonin and BMP system have been reported — increased serotonin signalling may provide a second risk factor which can mediate PAH in patients with a mutation in BMPR-II gene [16]. It is unknown, if agents changing serotonin transporters functioning (selective serotonin reuptake inhibitors?), may be valuable in PAH — therapeutic approaches that challenge the function of the serotonin transporters and receptors in PAH patients have not been tested [16–19].

There are also interesting reports suggesting the potential benefit role of dehydroepiandrosterone (DHEA) in PAH. DHEA is a steroid hormone derived from cholesterol in adrenal glands. In contrast to other steroid hormones, no selective receptor for DHEA has been found. DHEA is converted into androgens/estrogens, thus it is unknown if DHEA can exert its effects through these receptors directly or by its metabolites, however, the common belief exists that DHEA is a poor agonist of estrogen receptors. Pharmacodynamic studies revealed that this hormone hyperpolarizes the membrane affecting K Ca channel and acts as a BK Ca opener. Moreover, in experimental studies it was shown that DHEA induces the up-regulation of pulmonary artery soluble guanylate cyclase protein expression and increases pulmonary artery vasodilator responsiveness to nitric oxide. DHEA also decreases the hypoxia-induced factor 1 (HIF-1α) in pulmonary vascular smooth muscle cells. There are also experimental preliminary

results demonstrating that chronic (three weeks and more) DHEA administration in rats prevented RhoA kinase overactivity. Thus, it seems be possible that DHEA may be included into new class of pharmacological agents applying in PAH treatment — inhibitors of RhoA kinase system [20].

In summary, current pharmacological directions in searching of new agents in PAH treatment are listed in table 3 below.

Table 3 — Tabela 3

Future possible pharmacological options in PAH treatment

Przyszłe możliwe opcje farmakoterapii nadciśnienia płucnego

Group	Pharmacological agents under invastigations
Phosphodiesterase-3 inhibitors (PDE3-Inhibitors)	minrinon
Soluble guanylate cyclase (sGC) activators	riociguat
Inhaled vasoactive intestinal peptide	in experimental studies at present
tyrosine kinase inhibitors (platelet-derived growth factor inhibitors)	imatinib
vascular endothelial growth factor receptor inhibitors	in experimental studies at present
Rho-kinase inhibitors	fasudil
selective serotonin reuptake inhibitors (SSRI)	in experimental studies at present

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PATOFIZJOLOGICZNE POSTĘPY W LECZENIU NADCIŚNIENIA PŁUCNEGO

Streszczenie

Nadciśnienie płucne jest chorobą o wciąż nie w pełni poznanej patofizjologii. Możliwości aktualnego leczenia farmakologicznego w tym zaburzeniu są, niestety, relatywnie niewielkie, dlatego trwają poszukiwania nowych związków skutecznych w leczeniu tego schorzenia. Artykuł krótko przedstawia obecną klasyfikację nadciśnienia płucnego, główne elementy jego etiopatogenezy oraz aktualne i potencjalne możliwości interwencji farmakologicznej.

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