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New Agents in the Treatment of Pulmonary Hypertension

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Pulmonary Hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). As stated in the European Society of Cardiology (ESC) 2009 guidelines, it can be classified into 5 main categories, presented in Table 1. Pulmonary arterial hypertension is a rare disease with a prevalence of 15 cases /million adult population and an incidence of 2.4 cases/million adult population/year.[1,2] The pathophysiology of PH is complex and it has not been elucidated in detail since it involves various biochemical pathways and cell types. Vasoconstriction, remodeling with extensive proliferation of the vessel wall cells causing progressive obstruction, inflammation and thrombosis have been implicated. Structural or functional abnormalities of potassium channels in the smooth muscle cells and endothelial dysfunction characterized by impaired nitric oxide (NO) and prostacyclin production or increased expression of thromboxane A2 and endothelin-1are thought to underlie the cellular changes.[3]

Although groups two and three account for the majority of the cases, the trials testing and validating therapeutic options involve mostly patients with group one PH (Pulmonary Arterial Hypertension-PAH). Apart from conventional therapy including diuretics, oral anticoagulants, calcium channel blockers in case of established vasoreactivity, digoxin, oxygen administration and exercise –rehabilitation programs, specific drugs have emerged and gradually find their place in the management of PAH during the last decade. *Prostanoids* such as intravenous (IV) epoprostenol, iloprost inhaled and IV and treprostinil subcutaneously (SC) or IV have been established agents in the management of PAH, improving performance ability and survival (epoprostenol). *Beraprost* has shown promising albeit short –term results in the ALPHABET trial.[4-10] *Phosphodiesterase (PDE) type-5 inhibitors (sildenafil, tadalafil)* and *endothelin receptor antagonists (bosentan, ambrisentan*) improve exercise capacity and hemodynamic parameters and are widely used in the treatment of PAH.[11-16] Sitaxentan demonstrated favourable results initially [17, 18] but was subsequently withdrawn in early 2011 due to a few cases of fatal hepatic toxicity considered to be idiosyncratic, unpredictable and thus unpreventable.

Table 1. Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension (PAH)	**PH due to Lung Diseases &/or Hypoxia**
Idiopathic (IPAH)	Chronic obstructive pulmonary disease (COPD)
Heritable/familial (FPAH)	Interstitial lung disease
BMPR2 ALK1, Endoglin Unknown	Other pulmonary diseases with mixed restrictive & obstructive pattern
Drug and toxin-induced	Sleep disordered breathing
Associated with APAH	Alveolar hyperventilation dis.
Connective tissue disorders	Chronic exposure of high altitude
HIV infection	Developmental abnormalities
Portal hypertension	
Congenital heart diseases	**Chronic Thromboembolic PH (CTEPH)**
Schistosomiasis	
Chronic hemolytic anemia	**PH with Indistinct, Multi-factorial Mechanisms**
Persistent PH of the newborn (PPHN)	Hematological dis. (e.g. myelo-proliferative dis., splenectomy, hemoglobinopathies)
Pulmonary Veno-Occlusive Disease (PVOD) & Pulmonary Capillary	Systemic dis. (e.g. sarcoidosis, pulmonary Langerhans cell histocytosis, lymphangiomatosis)
	Metabolic dis. (e.g. glycogen storage disease, Gaucher's disease, thyroid disorders)
PH with Left Heart Disease	
Systolic dysfunction	
Diastolic dysfunction	Others (e.g. tumoural obstruction, fibrosing mediastinitis, chronic renal failure & dialysis)
Valvular disease	

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; dis. = disorders; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

In spite of the remarkable progress in the management of PAH, the response cannot yet be characterized satisfactory. Moreover, the cost of specific treatment is still considerably high. Thus, the need for novel medical approaches is still present. New agents of the already used categories are tested. *Macitentan*, a novel endothelin (ET)-A/ET-B receptor antagonist, is being evaluated in

the SERAPHIN trial, after producing a promising hemodynamic profile in a previous phase II study. [19,20]

The signaling pathways of cyclic (c) GMP play a cardinal role in the pathogenesis of PAH. cGMP levels are decreased in the pulmonary vascular bed either through impairment of NO bioavailability, guanylyl cyclase inactivation or enhanced cGMP degradation by PDEs.[21,22] Consequently, augmentation of cGMP signaling is a pathophysiologically reasonable therapeutic target. PDE-5 inhibitors are currently a useful option, but their effects on pulmonary artery pressure (PAP) are small (approximately 5 mmHg reduction), a significant number of patients do not respond well and there is often a dose-dependent systemic hypotensive effect that limits the drug's utility. Novel attempts focus on NO enhancement. NONOates, stable NO donor forms, which spontaneously release defined amounts of NO when exposed to physiological pH are tested as inhaled preparations with promising results though in animal models so far.[23,24]

Another way to increase cGMP signaling is by enhancing endothelial NO synthase (eNOS). Tetrahydrobiopterin (BH4), a key co-factor of eNOS, is frequently reduced in patients with PAH and its supplementation may increase the enzyme's activity. [25] Moreover, cicletanine, an 'eNOS coupling agent' has beneficial effects in patients with secondary PH. [26] This agent probably acts by coordinating eNOS activity with BH4 supply/binding, while it may also enhance the endogenous formation of prostaglandin (PG) I2 and natriuretic peptides. Cicletanine is currently under phase II evaluation in patients with PAH. Finally, the Pulmonary Hypertension and Cell Therapy trial aims at testing the safety and tolerability of autologous progenitor cell-based gene delivery of human eNOS in PAH patients, since endothelial progenitor cells are thought to play a role in the pathogenesis of the disease [27] and it is currently recruiting participants.

Furthermore, soluble Guanyl-cyclase (sGC) agonists have been recently developed, which stimulate sGC, both independently of the endogenous vasodilator NO and in synergy with NO. [28,29] *Riociguat* is a sGC stimulator or haem-dependent activator which works in synergy with NO and activates Fe2+-sGC complex. *Cinaciguat* and *ataciguat* activate the haem-free form of the enzyme and act additively with NO. [30,31] The sGC stimulators enhance the action of NO and therefore their effect may lack pulmonary selectivity, a characteristic which may not be the case when the NO independent activators are used. However, all agents have been evaluated in phase II trials [32] and are currently undergoing further testing in various clinical settings in relation with PH. [33,34,35] Unfortunately, cinaciguat although exhibiting promising results in cases of PH due to left-sided heart failure, when given in patients with decompensated heart failure, it did not improve their clinical condition and was also held responsible for episodes of significant hypotension. [33,35]

Novel therapeutic targets in PH include also several proliferative pathways. A significant number of growth factors are implicated in the pathogenesis of the disease with PDGF, FGF-2, EGF, VEGF being among them. These substances act on the pulmonary vascular bed as potent mitogens and chemoattractants, and through the tyrosine kinase receptor pathways activate the *ras*-mitogen activated protein kinase (MAPK) cascade, resulting in proliferation, migration and resistance to apoptosis. Interruption of these hyperplastic procedures can be attempted by interfering in various sites of the biochemical pathway. Tyrosine-kinase inhibitors such as imatinib (Gleevec) have been attributed a favourable effect [36,37] and the results of a phase III trial (IMPRES) are awaited. Other similar molecules (sunitinib and sorafenib) which block PDGF, VEGF and other proproliferative signalling pathways are under evaluation for safety and tolerability in Phase I studies. [38]

Another important pathway involved in the vascular changes underlying PH is the Rho kinase pathway which mediates vasoconstriction and smooth muscle cell proliferation, through a complicated metabolic process involving 5-HT and Bone Morphogenetic Protein Receptor (BMPR). Rho-kinase inhibitor fasudil has been shown to reduce PH and pulmonary vascular resistance in animal models and in humans, [39,40] but it has to be administered by nebulization, in order to avoid systemic hypotension. [41]

The Bone Morphogenetic Protein Receptor system is involved in the pathogenesis of PAH, especially in inheritable forms, and it has recently emerged as a potential therapeutic target. PMPR2, a serine-threonine kinase and a member of the TGFb superfamily is mostly implicated, which activates the Smad protein signaling sequence and the MAP kinase pathways. In PAH mutations of BMPR2 leading to diminished expression or dysfunction have been reported. [42,43] Gene therapy using viral vectors is under investigation . [44]

Serotonin is another molecule which plays a role in the pathobiology of PAH. Its contribution was discovered when PAH secondary to anorexigen use was studied. 5-hydroxy-tryptamine (HT; serotonin) is a potent vasoconstrictor and a mitogen for smooth muscle cells and fibroblasts. [45] At the time several agents targeting serotonin signaling mechanisms are under evaluation (serotonin receptor inhibitors terguride and re-uptake inhibitor escitalopram).

Finally, new evidence is gathered regarding well known and established treatment options. The Renin-Angiotensin-Aldosterone System is activated in cases of PH and its inhibition with captopril is not a new idea. [46] However, the discovery of the sybtype 2 of the Angiotensin Converting Enzyme (ACE2) has provided new insights since its role is vasoprotective and anti-mitogenic. Stimulation of ACE2 expression either by lentiviral gene delivery or XNT, an ACE2 activator, can potentially reverse experimental PH. [47] Statins may also prove useful due to their antiproliferative, anti-thrombotic, anti-inflammatory and antioxidant actions. Simvastatin has been efficient in decreasing pulmonary pressure in animal models. [48]

In conclusion, significant progress has been made in recent years with regard to the treatment of PAH. Nevertheless, efficient therapy has not been achieved yet and there is plenty of room for novel therapeutic approaches. New drugs are developing on the basis of the specific pathobiology of the disease and older agents find new indications thanks to the elucidation of the complex molecular and pathophysiological aspects of this debilitating disease.

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IMAGES IN CARDIOLOGY

Catheter Ablation of Incessant Ventricular Tachycardia in a Patient With Coronary Artery Disease

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A 67-year-old male with known coronary artery disease was referred to our hospital for catheter ablation of incessant ventricular tachycardia (VT). Transthoracic echocardiography revealed severe wall motion abnormalities of the left ventricle along with an apical aneurysm. Left ventricular voltage mapping showed a region with low voltage (<1.5 mV) at the left ventricular apex. Propagation mapping revealed a macro-reentry circuit around the apical aneurysm. Mid-diastolic potentials were recorded during the VT (**Fig**. 1, left panel, arrows), while entrainment mapping was excellent. The first radiofrequency energy application terminated the tachycardia. A circumferential lesion around the aneurysm was finally performed (**Fig**. 1, right panel, red dots). Ventricular tachycardia became non-inducible, and the patient is free from arrhythmic events during the last six months.