

Review

Hypoxia- and non-hypoxia-related pulmonary hypertension — Established and new therapies

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Abstract

Pulmonary hypertension can occur as an isolated disease affecting the lung vessels only, in association with underlying hypoxic lung disorders, or due to chronic thromboembolic disease. Pulmonary hypertension caused by pulmonary venous congestion will not be focused on in this review. Regardless of the underlying disease, chronic cor pulmonale is associated with progressive clinical deterioration and a poor prognosis in most cases. The aim of specific therapies for pulmonary hypertension is to reduce pulmonary vascular resistance and thereby improve right ventricular function. Currently, three classes of drugs (prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors) are approved for the treatment of pulmonary arterial hypertension (PAH) in a defined patient population (group I according to the recent WHO classification). However, these medications may also lower pulmonary vascular resistance in patients with associated lung diseases (e.g. chronic obstructive pulmonary disease or lung fibrosis) and significant pulmonary hypertension, for whom these drugs are not yet approved. As non-selective vasodilators may induce gas-exchange disturbances, which preclude their long term use in these patients, such substances should be avoided in the hypoxemic patient. In this article we provide an update of the current understanding of hypoxia- and non-hypoxia-related pulmonary hypertension, addressing both the pathophysiological understanding of different disease aetiologies as well as the therapeutic options currently available.

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1. Classification and aetiology

1.1. Hypoxia-related pulmonary hypertension

Pulmonary hypertension associated with hypoxia or chronic diseases of the respiratory system is regarded as separate entity according to the recent WHO classification. It includes chronic obstructive pulmonary disease (COPD), interstitial lung diseases, sleep disordered breathing, but also chronic exposure to high altitude and some rare neonatal

diseases [1]. While hypoxia has major impact on the pulmonary circulation, other factors such as hypercapnia or polycythemia seem to play a minor role for the development of pulmonary hypertension [2,3]. Adaptation of perfusion to ventilation is one of the most important features of pulmonary physiology. The key regulator of this phenomenon is hypoxic pulmonary vasoconstriction, originally described by Von Euler and Liljestrand [4], which ensures an optimized gas exchange [5,6]. In their original study Von Euler and Liljestrand could for the first time describe pulmonary vasoconstriction as a response to hypoxic breathing in cats. This physiological response is operative in most mammals and assures that pulmonary blood flow is directed preferentially to well ventilated areas of the lung, at rest as well as during exercise. As changes in the distribution

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of blood flow to different areas of the lung must occur rapidly (e.g. when changing from prone to supine position, or when stressing the pulmonary circulation upon exercise) adjustments of vessel diameter in the respective regions of the lung must be regulated immediately [5,7,8]. A key molecule for this fast response, which links alveolar ventilation (and thus the degree of regional oxygenation) to local lung perfusion is nitric oxide [5]: It has been conclusively shown that the fall in lung NO production precedes the rise in pulmonary pressure upon induction of acute experimental hypoxic pulmonary vasoconstriction, as well as that lung NO production is closely related to the degree of alveolar ventilation [9]. Thus, while regional acute hypoxic pulmonary vasoconstriction is crucially required to assure optimized adaptation of the perfusion to ventilation, chronic general hypoxia is one of the most frequent inducers of chronic pulmonary hypertension. Furthermore, structural changes in pulmonary arteries are described in early chronic obstructive pulmonary disease (COPD), emphysema and interstitial lung diseases [10].

1.1.1. Pulmonary hypertension associated with interstitial lung disease

Patients with pulmonary arterial hypertension associated with collagen vascular diseases (CVD, e.g. scleroderma) are classified as PAH based on the actual WHO classification. Many of these patients have a minor to moderate degree of interstitial lung disease. While clinical efficacy of specific PAH treatment has been proven in CVD associated PAH this has not yet been shown in other forms of interstitial lung disease associated pulmonary hypertension. Interstitial lung diseases lead to dyspnea of the patient due to a combination of restrictive changes of the parenchyma and gas-exchange deterioration. Relevant pulmonary hypertension may develop and significantly contribute to dyspnea at rest or under exercise. The molecular and cellular mechanisms that trigger and expedite the development of pulmonary hypertension in interstitial lung diseases are not well understood. Historical observations suggested a correlation of vital capacity and DLCO with severity of pulmonary hypertension in IPF patients [11]. Recent data no longer supports a direct correlation of lung function tests to the existence of pulmonary hypertension [12,13], which implicates the necessity of focused diagnostic procedures (echocardiography, right heart catheter) to rule out pulmonary hypertension in patients with interstitial lung disease. Elevated levels of brain natriuretic peptide may be a useful plasma marker to detect patients with pulmonary hypertension in this collective [13]. Pulmonary hypertension has an impact on mortality in idiopathic pulmonary fibrosis [14,15] and interstitial lung disease associated with scleroderma [16]. Therefore, manifest pulmonary hypertension in patients with ILD warrants treatment in order to improve exercise capacity, dyspnea and survival. Due to the pre-existing gas-exchange problems of these patients, the ideal drug to treat pulmonary hypertension should introduce an intrapul-

monary selective vasodilatation, i.e. vasodilatation selectively in well ventilated areas of the lung in order to maintain optimal gas exchange. In patients with idiopathic pulmonary fibrosis, inhaled nitric oxide – the prototype of an intrapulmonary selective vasodilator – and sildenafil were shown to act as intrapulmonary selective vasodilators, whereas intravenous prostacyclin leads to increase in shunt flow fraction and increased hypoxemia [17]. Comparable pulmonary and intrapulmonary selective vasodilatation was shown for inhaled iloprost [18]. Comparable data does not yet exist for the endothelin receptor antagonist bosentan. Long term clinical experience with bosentan does not suggest a negative impact on gas exchange as this drug is supposed to lack acute vasodilatory capacity. Controlled trials addressing the use of these drugs in pulmonary hypertension associated with interstitial lung disease are still missing. In cases where severity of pulmonary hypertension appears to be inappropriate to the extension of ILD, specific treatments for PAH may be used in the attempt to improve symptoms. However, due to lack of controlled clinical trials, specific treatment currently cannot be generally recommended.

1.1.2. Pulmonary hypertension associated with chronic obstructive pulmonary disease (COPD)

In COPD, pulmonary hypertension has been found in about one third of patients, however exercise induced pulmonary hypertension may affect up to 91% of all patients [19,20]. Interestingly, early structural changes in the pulmonary vasculature have even been described in smokers, irrespective of the presence of changes in the airways [21]. Occurrence of severe PH is less frequently reported in COPD and might develop in acute exacerbation of the underlying respiratory disease; on the other hand, in late stages of COPD chronic right heart failure, the classical so called *cor pulmonale* is a common finding in most of the patients. Overall, about 5–20% of patients with chronic obstructive respiratory diseases are currently estimated to develop severe PH without any other major contributing factor [22,23]. It is an interesting finding that many COPD patients with severe pulmonary hypertension have a rather moderate degree of airway obstruction, more pronounced hypoxemia and less hypercapnia. This recently leads to the assumption that these patients may represent a distinct subgroup of COPD associated pulmonary hypertension associated with significantly impaired survival [24]. The importance of the issue is displayed by the fact, that COPD is worldwide one of the most frequent diseases with a considerable increase in incidence over the next decade [25]. Although long term oxygen therapy (LTOT) improves survival in patients with COPD, prognosis of patients with COPD and a mean pulmonary artery pressure >25 mm Hg is still poor despite this measure [26]. Due to possible co-morbidities in this patient population, additional cardiovascular disorders such as left heart disease or thromboembolic pulmonary hypertension should be considered.

1.2. Non-hypoxia-related pulmonary hypertension

1.2.1. Pulmonary arterial hypertension (PAH)

The recent WHO conference on pulmonary hypertension (PH) has defined five main classes of chronic pulmonary hypertension [1]. This classification was mainly based on clinical and therapeutic similarities between the rather heterogeneous groups of underlying diseases. Group I of this classification, the so called pulmonary arterial hypertension (PAH), is composed by pulmonary vascular diseases with predominantly pre-capillary vascular remodelling, and includes idiopathic and familial PAH (former primary pulmonary hypertension), pulmonary hypertension associated with collagen vascular diseases (e.g. lupus erythematosus, scleroderma, CREST syndrome, Sjögren syndrome), PH associated with congenital heart disease (left to right shunt, Eisenmenger syndrome), PH associated with primary liver disease, and PH associated with HIV-infection or drugs and toxins (e.g. anorexigens). Furthermore, diseases that comprise significant histopathological involvement of the capillary or postcapillary vasculature like pulmonary capillary haemangiomatosis and pulmonary veno-occlusive disease (PVOD) are also classified as PAH. In addition rare storage diseases (Gaucher's disease, type-1 glycogen storage), haemoglobinopathies, splenectomy or myeloproliferative disorders may lead to pulmonary hypertension and are classified as PAH. In the paediatric field, persistent pulmonary hypertension of the newborn comprises histopathological and clinical similarities to the adult disease and therefore belongs to the same group.

The best known PAH subgroup is the idiopathic and/or familial pulmonary arterial hypertension (iPAH/fPAH), although the incidence is rather low with about 3–5 cases per million/year. The diagnosis of iPAH is made in the absence of any underlying disease. The same applies to fPAH with the difference that other family members have also been affected by the disease. Significant efforts have been made in the past to understand the pathogenesis of this fatal disease. The linkage of mutations in the gene of the bone morphogenetic protein receptor-2 (BMPR-2) to the disease in 50% of the families as well as in about 25% of the sporadic patients with iPAH was a breakthrough [27,28]. Most of these mutations are point mutations (with more than 50% located in the kinase regions of the receptor), but larger mutations leading to a lack of one or several exons of the BMPR-2 gene have also been described [29,30]. All mutations supposedly lead to malfunction of BMPR-2, which signals through a highly conserved signalling pathway via SMAD proteins and via alternative pathways. However, it is still not well understood how loss of BMPR-2 signalling leads to vascular remodelling exclusively in the lung. BMPR-2 mutation has also been described for a patient suffering from PVOD, suggesting a close pathogenetic link of iPAH and PVOD [31]. BMPR-2 belongs to the superfamily of transforming growth factor receptors. Mutations of two other receptors out of this superfamily (Alk-1,

endoglin) also lead to vascular malformation and disease, the hereditary hemorrhagic teleangiectasia (HHT) [32,33]. Interestingly, Alk-1 mutations may also be associated with pulmonary hypertension and the general features of dominant autosomal inheritance, disease penetrance in heterozygous patients (homozygous mutations are lethal) and high variability of phenotype even with the same genotype are shared by iPAH and HHT. The lack of BMPR-2 mutations in a significant number of iPAH and fPAH patients as well as the variations in onset, progress and severity of disease is currently not understood but implicates the existence of additional genetic mutations and contributing factors.

The human immunodeficiency virus infection can induce a severe form of PH and it has been hypothesized that viral products *per se* are a driving force of the disease [34]. Histopathological similarities between the highly vascularised Kaposi sarcoma, which was linked to the angiogenic HIV tat-protein and the Kaposi sarcoma associated herpesvirus (HHV-8), and the pathognomonic plexiform lesions in iPAH exist [35]. The importance of infection of pulmonary vessels with HHV-8 in iPAH patients is however currently controversially discussed [36].

Many other factors have been identified that contribute to the pathogenesis of PH in patients and animal models. Established mediators of pulmonary vascular remodelling are e.g. endothelin-1 (ET-1), thromboxane, platelet derived growth factor (PDGF), transforming growth factor beta (TGF beta), epidermal growth factor (EGF), serotonin, inflammatory cytokines, hypoxia, increased shear stress and vessel wall tension. Putative regulators of vascular “anti-remodelling” are prostacyclin, nitric oxide and vascular endothelial growth factor. Several of the above mentioned players are actually targeted by current therapies of PAH, as it will be described below in more detail.

1.2.2. Chronic thromboembolic pulmonary hypertension

There is growing interest in the medical treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH, group IV of the WHO classification of pulmonary hypertension). Only a minor fraction of these patients is eligible for therapy with surgical desobliteration by pulmonary endarterectomy (PEA). Nevertheless, the determination of eligibility for PEA is mandatory in every patient presenting with thromboembolic disease as this is the only causal therapy at hand. The risk and benefits of PEA have to be balanced for each patient and the decision should be made by expert centers for pulmonary hypertension in close collaboration with specialized cardiothoracic surgeons [37–39]. As a prerequisite for this approach, the vascular obstruction has to be located in the proximal (down to sub-segmental) pulmonary arteries [40]. Once a substantial percentage of the pulmonary vasculature is occluded by thromboembolic material, secondary – putatively shear stress-related – mechanisms of vascular remodelling may be triggered in the non-occluded vascular bed, which result

in a progressive increase in total lung vascular resistance independent of additional events of embolic occlusion of vessel lumen [41–43]. Finally, in patients having undergone surgical desobliteration without satisfactory resolution of pulmonary hypertension (PH), medical treatment of PH may represent the only therapeutic option. Evidence from experimental studies suggests that systemic or inhaled vasodilators may reduce pulmonary vascular resistance in pulmonary embolism models, however, these investigations were restricted to the early post-embolic period [44,45]. Several clinical trials suggest that specific treatments for PAH may exert beneficial effects in patients with CTEPH [46–49].

2. Treatments of pulmonary hypertension

The European Society of Cardiology (ESC) as well as the American College of Chest Physicians (ACCP) recently generated clinical guidelines on the diagnosis and treatment of pulmonary arterial hypertension [50,51]. Current treatments of pulmonary hypertension address mainly three aspects of the disease: 1. pulmonary vasoconstriction, 2. vascular obstruction by recurrent embolism and/or local thrombosis, and 3. vascular remodelling, being the most difficult feature to treat. Based on the previous considerations the use of vasodilators, some of which may also have some anti-proliferative effects, and anti-coagulants has been established for many forms of chronic pulmonary hypertension. Very recently, the first pre-clinical and clinical data were presented indicating the efficacy of purely anti-proliferative substances for the treatment of severe pulmonary hypertension (see Future therapies). Available specific drugs for the treatment of pulmonary hypertension are currently only approved for the treatment of patients suffering from PAH. However, patients with hypoxia-related pulmonary hypertension or chronic thromboembolic pulmonary hypertension may also benefit from these treatments. With regard to hypoxia-related pulmonary hypertension eligible vasodilator therapies are those that can reduce pulmonary vascular resistance without worsening gas exchange through the induction of ventilation/perfusion mismatch. The same may be of relevance for patients with chronic thromboembolic pulmonary hypertension in which gas-exchange disturbances may accompany the rise in pulmonary vascular resistance. In the following we will mainly focus on the currently approved therapies for the treatment of pulmonary arterial hypertension and only briefly summarize which of these specific therapies have shown efficacy in patients with associated forms of pulmonary hypertension in early clinical studies.

2.1. Basic therapy

Before treating patients with specific therapies for PAH some basic rules should be followed. An active lifestyle is important for the psychological well being of the patient as

well as to prevent physical de-conditioning. Patients should be advised to perform according to their individual capabilities but to strictly avoid events that lead to significant shortness of breath. Episodes of dizziness, light-headedness, near-fainting or syncopes should be considered as alarming signs of severe right ventricular insufficiency and require consequent restriction of physical activity to a level that prevents these symptoms. Female patients of childbearing potential should be advised to use safe contraceptive measures as pregnancy may often induce rapid disease progression that may not be stabilized with current therapies. In cases of chronic hypoxemia ($\text{PaO}_2 < 60$ mm Hg) long term oxygen treatment (LTOT) should be implemented to prevent hypoxic pulmonary vasoconstriction. Patients should not exceed altitudes of 1500 m above sea level and supplemental oxygen is recommended for airplane travels. Moderate oral anti-coagulation (target INR 2.0) should be introduced in all patients (in the absence of contraindications) to avoid in situ thrombosis or recurrent embolic events [52,53], while in patients with proven CTEPH target INR ranges between 2.5 to 3.5. In case of fluid retention diuretics reduce right ventricular preload and -dilation and help to reduce right ventricular failure. Therefore many patients benefit significantly from diuretics. Beta-blocker therapy is contraindicated in PH patients as these drugs prevent adaptive increases in heart rate and myocardial inotropy, both of which represent important compensatory mechanisms of the failing right ventricle. In addition they may lead to pulmonary vasoconstriction. In patients with pulmonary hypertension due to left heart failure, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists in combination with diuretics can be used to promote left ventricular re-compensation. Angiotensin converting enzyme inhibitors and angiotensin receptor antagonists are not indicated for isolated right heart failure. Cardiac glycosides should not be prescribed as inotropes to support right ventricular contractility, however they may be considered in cases of atrial fibrillation.

2.2. Specific therapy

Calcium channel blockers may provide excellent outcome in a small subset of PAH patients (~7%). However, only such patients that show marked reduction in their pulmonary pressure and resistance upon vasoreactivity testing during right heart catheterization will respond favourably to high dose calcium channel blockers in the long term. Response criteria are defined as a decrease of the mean pulmonary arterial pressure of more than 10 mm Hg under an absolute level of 40 mm Hg and a normal cardiac output during the acute administration of short acting vasodilators such as inhaled nitric oxide or iloprost, i.v. adenosine or i.v. prostacyclin [54–56]. Patients lacking significant response during vasoreactivity testing will not benefit from calcium channel blockers. Moreover, the use of calcium channel blockers is restricted in patients with severe

gas-exchange disturbances as they may induce unselective intrapulmonary vasodilatation and concomitant ventilation/perfusion mismatching.

2.3. Prostacyclin and prostacyclin derivatives

2.3.1. Intravenous prostanoids

Prostacyclin is a potent endogenous vasodilator that is mainly produced by vascular endothelium [57]. In PAH patients the ratio of vasodilative prostacyclin and vasoconstrictive thromboxane production is shifted towards the latter mediator. Prostacyclin induces an intracellular increase of its second messenger cAMP via activation of the adenylate cyclase with subsequent smooth muscle cell (SMC) relaxation, inhibition of SMC proliferation and platelet aggregation [58,59]. Intravenous prostacyclin has been shown to improve hemodynamics, exercise capacity and survival in PAH patients [60], and has therefore been approved by the FDA in 1995 (NYHA class III–IV). As prostacyclin has a short half-life and is only stable in a basic solution, it must be administered continuously via a central venous line by use of an infusion pump. Due to the short half-life, discontinuation of infusion due to catheter defects, pump malfunction or operating errors can lead to rebound pulmonary hypertension and death of the patient. Intravenous administration of prostacyclin analogues with improved stability and longer half-life like iloprost or treprostinil may potentially reduce the risk of rebound pulmonary hypertension.

The systemic application of prostacyclin or its stable analogues aims for pulmonary vasodilatation to reduce pulmonary vascular resistance and to improve right ventricular performance. However, due to the intravenous route of administration non-selective vasodilatation in both the pulmonary as well as the systemic circulation may occur [17]. To gain maximum clinical efficacy, the i.v. prostanoid dose is initially up-titrated over the first few days up to a maximal tolerable dose which is limited by the occurrence of adverse events. Typical side effects are flushing, headache, nausea, diarrhoea, yaw- and leg-pain. Considerable tachyphylaxia is observed with i.v. prostanoids that often requires several-fold dose increases over time. Continuous intravenous treatment is associated with the risk of catheter related infections and life threatening sepsis, the incidence of the latter ranging from 0.1 to 0.6 cases per patient/year.

Little experience has been gained in the treatment of other forms of pulmonary hypertension than PAH with the continuous infusion of prostacyclin. In patients with COPD and pulmonary hypertension i.v. epoprostenol administration resulted in deterioration of gas exchange and was considered as a non-beneficial treatment in a placebo controlled trial [61]. When used in patients suffering from CTEPH as a preoperative treatment before thromboendarterectomy i.v. epoprostenol did not show overall good efficacy, however in selected patients some clinical impro-

vement was observed [62]. If associated with underlying interstitial lung disorders, medical treatment of pulmonary hypertension may be complicated by the possible induction of ventilation/perfusion mismatch upon administration of non-selective vasodilators. This has been shown for the acute administration of i.v. epoprostenol in patients with lung fibrosis and pulmonary hypertension, where significant reductions in arterial oxygenation were observed [17,18].

2.3.2. Subcutaneous treprostinil

In order to avoid catheter associated complications, the subcutaneous application of the stable prostacyclin analogue treprostinil was developed. Significant improvements in exercise capacity, dyspnea index, signs and symptoms of PAH as well as hemodynamics were shown after 3 months of treatment in a randomized controlled trial [63]. As a specific side effect, local pain at the infusion site was observed in about 85% of patients the occurrence of which may have hampered optimal dosing in some cases. However, recent reports state that site pain is not dose related. Subcutaneous treprostinil is approved in the US, Canada and Australia for PAH (NYHA class II–IV) and France for iPAH (NYHA class III). Intravenous treprostinil is approved in the US, Canada and Israel for the treatment of PAH.

2.3.3. Oral beraprost

Beraprost is a stable and orally active prostacyclin analogue. The elimination half-life of beraprost after oral intake is about 35 min, the peak plasma levels are reached after 30 min. Systemic side effects of beraprost are common and comparable to those of intravenous prostacyclin. A 12 week double blind, placebo controlled trial showed significant improvement of a 6 minute walking distance in PAH patients with NYHA functional class II and III [64]. Idiopathic PAH patients improved significantly whereas the other forms of PAH did not. Pulmonary hemodynamics were not significantly changed. A consecutive 12 month trial could not show that long term therapy with oral beraprost has sustained efficacy, as initial improvements in six-minute walking distance levelled off after 9 months of treatment [65]. This first documented observation of a loss of drug effect over time underlines the importance of long term studies for PAH therapies. Beraprost is currently approved only in Japan and Korea.

2.3.4. Inhaled iloprost

To combine the beneficial effects of prostanoids with a safer way of administration and a pulmonary selective mode of action inhalation of nebulised prostacyclin and its derivatives had been developed over the last decade. With this approach a high drug concentration can be administered directly to the alveolar space into direct proximity to the pulmonary resistance vessels. Iloprost was the first stable prostacyclin analogue used for inhalative therapy of PAH. The overall drug dose delivered as an aerosol to the lung is

considerably lower when compared to the intravenous application (5–10% of the daily i.v. dose), leading to less systemic side effects nevertheless providing comparable efficacy. Iloprost inhalation induces substantial, pulmonary selective vasodilatation [66]. It was also the first nebulised vasodilator which shared similarities with inhaled nitric oxide (NO) with regard to intrapulmonary selective vasodilatation, preferentially operative in well ventilated areas [18]. The relatively short half-life of iloprost, however, explains the necessity of 6 to 9 inhalations per day to achieve an effective treatment. Iloprost inhalation has shown to improve exercise capacity, hemodynamics, and survival after 3 months in a randomized controlled trial (AIR-1 study) with a sustained effect after 24 months of treatment (AIR-2), however addition of another agent was necessary in a fraction of patients (similar to the long term treatment with bosentan) [46]. Different nebulisers are currently in use, all of which produce aerosol particles (2.5–5.0 μm) that are suited to reach the peripheral air spaces and with which the duration of drug administration ranges between 5 and 15 min. Interestingly, the discontinuous application of iloprost as an aerosol circumvents tachyphylaxia and therefore dose escalations are not required as often as with systemic prostanoid administration. Iloprost inhalation is approved for treatment of PAH (NYHA class III–IV) in the US and for iPAH (NYHA class III) in Europe. In addition, inhaled iloprost is the only therapy currently approved for the treatment of CTEPH in Australia and New Zealand. In patients with lung fibrosis and pulmonary hypertension inhaled iloprost selectively reduced pulmonary vascular resistance and did not deteriorate ventilation/perfusion matching, thereby leaving arterial oxygenation unaltered [18]. However, controlled trials addressing the long term benefit of this therapy in fibrosis patients are currently missing.

2.3.5. Inhaled treprostinil

Treprostinil sodium is currently the most stable prostacyclin analogue available with an elimination half-life of 4.5 h after intravenous administration [67]. The inhalation of treprostinil leads to equipotent — but significantly prolonged vasodilatation after a single inhalation manoeuvre, when compared to inhaled iloprost [68]. The clinical efficacy of inhaled treprostinil is currently under investigation in a randomized, controlled trial (TRIUMPH-1) using only 4 inhalations per day. Already, open label studies in a small number of patients ($n=25$) demonstrated beneficial clinical effects of inhaled treprostinil as monotherapy as well as in combination with bosentan or sildenafil. Notably, treprostinil can be applied in doses up to 15-fold higher than inhaled iloprost and the inhalation time can be reduced to even one single breath without the occurrence of systemic side effects. These unexpected features illuminate the notable pulmonary selectivity of inhaled treprostinil and are a prerequisite for a possible future administration by the use of metered dose inhaler.

2.4. Phosphodiesterase-5 inhibitors

2.4.1. Sildenafil

Nitric oxide (NO) is the central stimulus for cyclic guanosine monophosphate (cGMP) generation via activation of the soluble guanylate cyclase in pulmonary vascular smooth muscle cells. NO is produced by endothelial cells and is an important regulator of pulmonary vascular tone [69]. NO production is oxygen dependent and lack of NO production under hypoxic conditions contributes to acute and chronic hypoxic pulmonary vasoconstriction. The enzymatic counterpart of NO is the cGMP degrading enzyme phosphodiesterase-5 (PDE-5) [70,71]. In parallel to the prominent expression and activity of the NO/cGMP/PDE-5 axis in the penile corpus cavernosum, a high abundance can be detected exclusively in lung tissue [72]. This implicated the use of selective PDE-5 inhibitors for the treatment of pre-capillary pulmonary hypertension. Despite the oral route of administration sildenafil is a potent pulmonary- and intrapulmonary-selective vasodilator [73], which maintains (and might even improve) ventilation/perfusion matching and oxygenation [17]. Sildenafil, taken as tablets (20–80 mg TID), improved exercise capacity, hemodynamics and NYHA functional class in a 3 month randomized controlled clinical trial in patients with PAH in functional classes II–IV (SUPER-1) [74]. The positive effects of sildenafil were sustained after more than one year of treatment in a long term open label extension study (SUPER-2). Sildenafil is currently approved for the treatment of PAH in the US (NYHA class II–IV) and in Europe (NYHA class III). Results from smaller studies, which were not powered to show clinical efficacy, indicated clinical improvement due to this approach in patients suffering from pulmonary hypertension associated with interstitial lung disease [17] and CTEPH [47,75]. A study on 6 patients with PH associated with COPD was also promising [76]. Future controlled clinical trials have to confirm the rationale to use this approach in the aforementioned secondary forms of pulmonary hypertension for which currently approved therapies are lacking.

2.4.2. Tadalafil and vardenafil

Tadalafil and vardenafil are further selective PDE-5 inhibitors, currently approved for use in erectile dysfunction only. A direct comparison of both drugs with sildenafil with respect to acute effects on pulmonary hemodynamics and gas exchange showed that pulmonary selective vasodilatation was achieved mainly with sildenafil and tadalafil and to a lesser extent with vardenafil. In the same study, sildenafil appeared to be the only PDE-5 inhibitor with some intrapulmonary selectivity as displayed by an improved arterial oxygenation, while the other PDE-5 inhibitors left gas exchange more or less unaffected [77]. The chronic use of tadalafil as a new treatment for PAH is currently under investigation in a controlled clinical trial.

2.5. Endothelin receptor antagonists (non-selective and selective)

Endothelin-1 is a potent vasoconstrictor. It is thought to be involved in the pathogenesis of pulmonary arterial hypertension by inducing both vasoconstriction and proliferation of vascular smooth muscle cells [78,79]. Endothelin-1 mediates its signalling via two receptors, endothelin-receptor A (ET_A) and ET_B. ET_A and ET_B are expressed on smooth muscle cells and endothelial cells. Because endothelin binding to ET_B has been described to be beneficial in vascular remodelling processes [80,81], a selective inhibition of ET_A may have advantages over non-selective inhibition of both receptors.

2.5.1. Bosentan

The non-selective endothelin receptor antagonist bosentan was investigated in two randomized, placebo controlled trials, in patients with iPAH or PAH associated with collagen vascular diseases [82,83]. Patients received 62.5 mg BID in the initial 4 weeks followed by 125 mg or 250 mg BID for additional 12 weeks if the initial dose was tolerated. Bosentan significantly improved the primary endpoint (6 minute walking distance) as well as the time to clinical worsening when compared to placebo. A better effect was observed with the higher dose, however, liver toxicity as the main side effect occurred more frequently in the 250 mg BID than in the 125 mg BID group. Bosentan was therefore approved in a dosage of 125 mg BID for the treatment of PAH in functional classes III–IV in North America, and class III in Europe. A long term follow up study showed a 91% survival after 2 years with bosentan treatment in a group of 134 PAH patients in functional class III. This rate was comparable to a historic control of i.v. prostacyclin treated patients, however, in the bosentan treated cohort only 75% of the patients remained on monotherapy after 2 years [84]. In a second long term observational study, 103 patients in functional classes III and IV were followed over a mean period of 2 years. In this study an 87% survival after 1 year was reported. Intravenous prostacyclin needed to be introduced to 44% of the patients during the observation time.

Investigations addressing the impact of bosentan on ventilation/perfusion matching in patients with pulmonary hypertension associated to ventilatory disorders have not yet been published.

2.5.2. Ambrisentan and sitaxsentan

The selective ET_A receptor antagonist ambrisentan was investigated in two randomized, controlled trials with doses of 2.5 mg or 5 mg (ARIES-2) and 5 mg or 10 mg ambrisentan (ARIES-1) given once daily in patients with PAH (NYHA class I–IV). Though not yet published in a peer reviewed journal the top line results of the ARIES-1 and -2 trials were recently presented (<http://investor.myogen.com/phoenix.zhtml?c=135160&p=irol-news>). According to these

reports, ambrisentan showed a very good clinical efficiency with a clear dose effect relationship. Interestingly, no liver toxicity was observed with this compound (defined by a more than 3-fold elevation of liver enzymes) in the trials using doses of 2.5 mg to 10 mg ambrisentan. A study that switched 36 patients who encountered liver toxicity with bosentan ($n=34$) or sitaxsentan ($n=5$) to a treatment with 5 mg ambrisentan showed recurrence of liver toxicity in only one patient over a mean exposure of 6 months. Recently ambrisentan received an expedited review status by the FDA and approval.

Another selective ET_A inhibitor, sitaxsentan, was investigated in two randomized, double blind, placebo controlled trials [85–87]. In the first trial (STRIDE-1) sitaxsentan did not significantly improve the primary endpoint (improvement of oxygen uptake during cycle ergometry). However, secondary endpoints (6 minute walking distance, improvement of NYHA functional class) were improved in the active treatment group as compared to placebo. The subsequent study (STRIDE-2) compared doses of 50 mg and 100 mg sitaxsentan once daily with the administration of 125 mg bosentan BID and placebo. The primary endpoint (this time 6 minute walking distance) was met in the 100 mg group (placebo-corrected increase in 6 minute walking distance 31.4 m) but not in the 50 mg group. The effect of bosentan was not significantly different to 100 mg sitaxsentan (29.5 m placebo-corrected increase in 6 minute walking distance), but the incidence of liver enzyme elevations 3-fold greater than the upper normal with sitaxsentan was only 3% as compared to 11.5% in the bosentan group. At the time of writing the manuscript the drug company has received a positive opinion recommending the approval of the drug by the Committee for Medicinal Products for Human Use (CHMP) of the European Agency for the Evaluation of Medicinal Products (EMA).

2.6. Possible future therapies

2.6.1. Platelet derived growth factor receptor (PDGFR) — inhibition

Several growth factors have been implicated in the abnormal proliferation and migration of vascular smooth muscle cells (SMC), including platelet derived growth factor (PDGF), basic fibroblast growth factor (b-FGF), and epithelial growth factor (EGF) [88–91]. In vitro studies established that PDGF acts as a potent mitogen and chemoattractant for SMC [92]. PDGF activates cell surface receptors. The PDGF receptors (PDGFRs) belong to a family of transmembrane receptor tyrosine kinases (RTKs) that are autophosphorylated upon ligand binding. Imatinib, a selective inhibitor of the RTKs c-kit, bcr-abl and PDGFR, was approved for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumor [93]. The application of imatinib in two animal models of pulmonary hypertension showed excellent effects on pulmonary hemodynamics, survival and vascular remodelling [94].

Compassionate use of imatinib in patients in need for rescue therapy due to disease progression (despite ongoing maximized combination treatment with approved PAH drugs) provided promising results with regard to disease regression [95]. Drugs like imatinib, which target the process of uncontrolled proliferation in pulmonary hypertension, may in the future facilitate reverse remodelling of the pulmonary vessels.

2.6.2. Vasoactive intestinal peptide

The biological effects of vasoactive intestinal peptide (VIP) are transduced via specific receptors (VPAC-1 and VPAC-2) that signal via cAMP and cGMP, both of which induce relaxation of vascular SMCs. VIP interferes with platelet aggregation. A study of inhaled VIP (50 µg QID) in 8 patients showed favourable effects on exercise capacity [96]. However, data on acute hemodynamic effects upon VIP-inhalation are lacking and controlled studies are needed to assess clinical efficacy and the respective safety of this therapeutic principal.

2.6.3. Selective serotonin reuptake inhibitors

Serotonin (5-hydroxytryptamine [5-HTT]) has been shown to play a role in the pathogenesis of experimental and clinical pulmonary hypertension. Key players in this context were the 5-HT-transporter (5-HTT) as well as to the 5-HT receptors in the membrane of SMC, leading to increased proliferation of these cells [97,98]. Therapeutic approaches that challenge the function of the 5-HTT or the 5-HT receptors have not yet been tested in PH patients.

2.7. Combination therapies

Combination therapies targeting different regulatory mechanisms of vasomotion or proliferation are already used in many patients with pulmonary hypertension in order to maximize clinical benefit and to stabilize the disease on a favourable prognostic level.

The combination of a sub-threshold dose of the phosphodiesterase (PDE)-3/4 inhibitor tolfenetrine (which inhibits the degradation of the second messenger of prostanoids cAMP) with inhaled iloprost amplified and prolonged the iloprost effects without resulting in increased incidence of adverse events [99]. Unfortunately, such PDE-3/4 inhibitors are currently not at hand for clinical use, but based on the initial encouraging experimental and clinical results further clinical studies are warranted.

The combination of a PDE-5 inhibitor with prostanoids has the potential to augment both the cGMP and cAMP pathways, synergistically inducing relaxation and possibly reduced proliferation of vascular SMC. The inhalation of iloprost or treprostinil when added to sildenafil induced significant additional pulmonary vasodilatation without loss of pulmonary selectivity [73,100]. Adjunct treatment with sildenafil in 14 patients who experienced disease progression despite ongoing inhaled iloprost therapy resulted in signifi-

ficant and sustained improvement of exercise capacity and functional class [101].

The addition of sildenafil to the therapy of 9 patients who deteriorated despite an ongoing bosentan treatment resulted in favourable clinical improvement over an observation period of one year [102]. The combination of bosentan with pre-existing oral or inhalative prostanoid therapy was addressed in 20 patients. Bosentan in this study induced a significant improvement of exercise ability and resulted in sustained clinical stabilization [103].

These early studies exemplify the benefit that can be gained by combinations of drugs currently approved for PAH. However, the question which combination is optimal for which form of pulmonary hypertension is still unanswered. In addition, it is unclear whether first line combination therapy is superior to a stepwise escalation of PAH therapies (the latter procedure is currently followed in most specialized PH-centers). Both aspects need to be addressed in randomized controlled studies in the future.

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