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Nitric Oxide Pathway and Phosphodiesterase Inhibitors in Pulmonary Arterial Hypertension

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Pulmonary hypertension (PH) is a disease of various origins. Nitric oxide—a potent vasodilator—is a key player of pulmonary vasoregulation. Nitric oxide signaling is mainly mediated by the guanylate cyclase/cyclic guanylate monophosphate pathway. The effects of this second messenger system are limited by enzymatic degradation through phosphodiesterases (PDEs). Recently, beneficial effects of the oral PDE-5 inhibitor sildenafil (originally approved for the treatment of erectile dysfunction) were reported for the treatment of PH. We provide a brief overview of the experimental and clinical application of PDE inhibitors in the field of PH. In particular, studies reporting the clinical effectiveness of sildenafil are highlighted. This agent, despite oral application, displays characteristics of a pulmonary selective vasodilator. In addition, evidence shows that sildenafil is operative mainly in the vasculature of well-ventilated areas of the lung. However, to date, controlled randomized trials proving the efficacy of this approach for the treatment of pulmonary arterial hypertension are lacking. The results of such studies have to confirm the current encouraging findings before recommendations regarding the use of PDE-5 inhibitors as a new treatment for PH can be made. (J Am Coll Cardiol 2004;43:68S–72S) © 2004 by the American College of Cardiology Foundation

Nitric oxide (NO) is constitutively produced in the lung by NO synthases. The main cellular sources of lung NO production are the vascular endothelium and the airway epithelia (1,2). Local NO production regulates pulmonary perfusion depending on alveolar ventilation to assure optimized ventilation/perfusion distribution (3,4). Nitric oxide synthase activity is regulated on transcriptional and post-translational redox-based modulation level (5). The common signaling pathway of endogenous vasodilators, such as NO, prostaglandins, and natriuretic peptides, engage cyclic nucleotides (cyclic adenylate monophosphate [cAMP] and cyclic guanylate monophosphate [cGMP]) (Fig. 1). These second messengers are mainly produced by activation of adenylate-cyclase and guanylate-cyclase (GC) (6). Phosphodiesterases (PDEs) represent a superfamily of enzymes, with PDE-1 through PDE-11 being currently known, that inactivate cAMP and cGMP, with different tissue distribution and substrate specificities (6,7). Owing to the stabilization of these second messengers, PDE inhibitors differentially regulate levels of cAMP and/or cGMP, depending on their selectivity profile. Therefore, they might offer as therapeutic tools to augment and prolong prostanoid- and NO-related vascular effects. The efficacy of this approach has been proven in several experimental studies (8,9). Interestingly, the major cGMP-degrading PDE, PDE-5, is abundantly expressed in lung tissue (7). The orally administered selective PDE-5 inhibitor sildenafil has been approved for the treatment of erectile dysfunction (10). Despite the broad use in healthy men and in patients with a variety of underlying diseases, sildenafil displays an excellent safety profile (11).

CURRENT TREATMENTS FOR PULMONARY ARTERIAL HYPERTENSION (PAH)

Continuous infusion of prostacyclin has been shown to be a life-saving therapy in severe primary pulmonary hypertension (PPH) (12) and to improve exercise capacity in collagen vascular disease-associated pulmonary hypertension (PH) (13). There are, however, drawbacks of this therapy, including substantial systemic side effects due to lack of pulmonary selectivity of the prostanoid, the need of progressive dosage increase, and septic complications of the intravenous line. To preserve the advantageous effects of prostacyclin, and avoid several of these side effects, the concept of aerosolized iloprost for treatment of PAH was developed (14,15). Recently, the results of a double-blind, placebo-controlled multicenter study demonstrated that daily inhaled iloprost significantly improved exercise capacity, New York Heart Association (NYHA) functional classification, dyspnea scoring, and event-free survival over a three-month obser-

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Abbreviations and Acronyms

cAMP = cyclic adenylate monophosphate
cGMP = cyclic guanylate monophosphate
GC = guanylate cyclase
HIV = human immunodeficiency virus
NO = nitric oxide
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PDE = phosphodiesterase
PH = pulmonary hypertension
PPH = primary pulmonary hypertension

vation period in patients with selected forms of PAH and chronic thromboembolic PH (16).

Another promising approach to medical treatment of PAH is the use of the nonselective oral endothelin receptor antagonist bosentan. In a controlled phase III study, bosentan showed beneficial effects on exercise tolerance in patients with PPH and those with PH associated with collagen vascular disease (17). However, liver toxicity was documented in a minor percentage of patients, and long-term experience will have to elucidate the occurrence of this complication during chronic treatment of a substantial number of patients.

The search continues for an "ideal" pulmonary vasodilator that combines pulmonary selectivity with simplicity of administration and reduced side effects. Recently, the

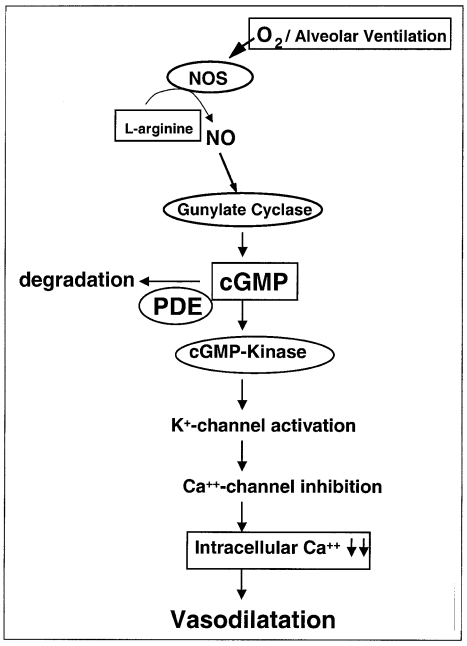

Figure 1. Scheme of nitric oxide (NO) metabolism pathway. In this diagram the nitric oxide (NO) pathway is depicted. In presence of oxygen (O_2) and/or alveolar ventilation, NO synthases (NOS) are activated and produce NO from L-arginine via L-citrulline. The NO activates soluble- and membrane-bound guanylate cyclases, which synthesize cyclic guanylate monophosphate (cGMP), which subsequently activates cGMP-kinase. This enzyme—by activation of K^+-channels and subsequent Ca^{++}-channel inhibition—evokes a reduction of intracellular Ca^{++} concentration, finally resulting in vasodilation. The downstream effects of NO are limited by phosphodiesterase (PDE)-induced degradation of cGMP.

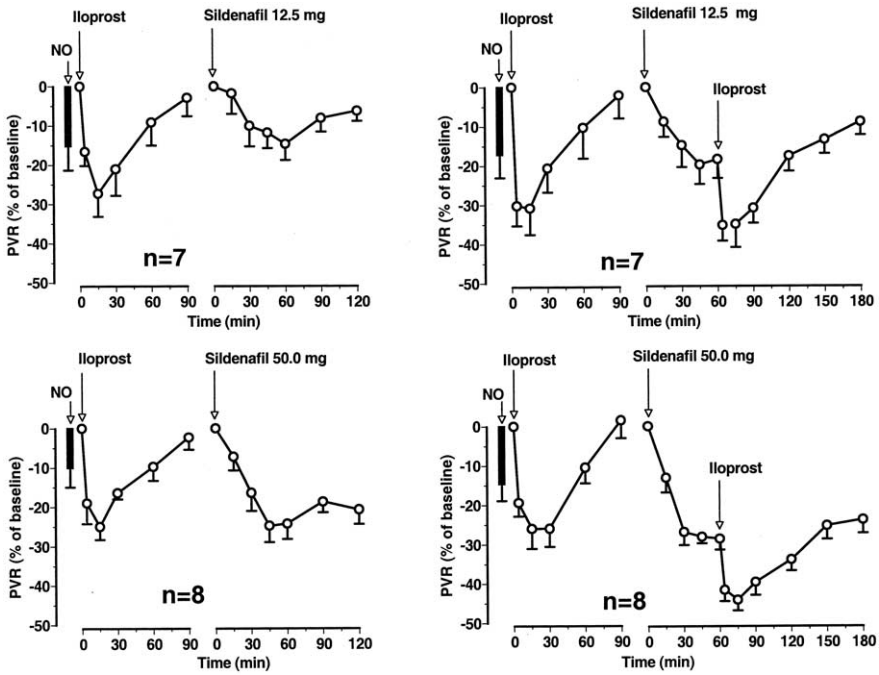

Figure 2. Comparison of pulmonary vasodilative potency of oral sildenafil, inhaled nitric oxide (NO), and inhaled iloprost. Comparative vasodilator testing was performed in 30 patients with precapillary pulmonary hypertension. In each group, the effect of inhaled NO on pulmonary vascular resistance (PVR) was compared with that of sildenafil, inhaled iloprost, or a combination of both. In the **upper left figure,** inhaled NO and iloprost were compared with a low dose of sildenafil (12.5 mg), while in the **upper right** figure a combination of sildenafil and iloprost was tested. The **lower left figure** summarizes the effects of 50 mg sildenafil compared to NO and iloprost, and the **lower right figure** shows the data of a combination of high-dose sildenafil with iloprost (adapted from Ghofrani et al., Ann Intern Med 2002;136:515–22).

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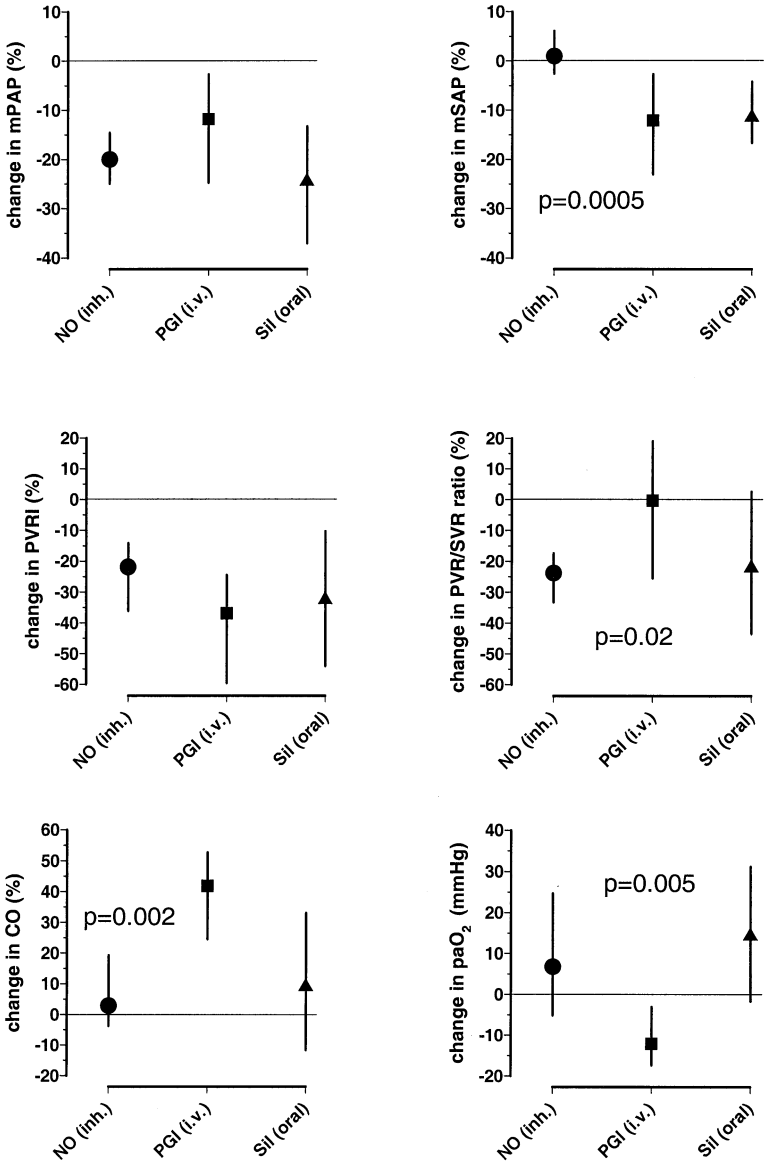

Figure 3. Hemodynamic and gas-exchange response to inhaled nitric oxide (NO), infused PGI_2, and oral sildenafil in patients with lung fibrosis and pulmonary hypertension. Deviations from preintervention baseline are displayed for inhaled NO, infused prostacyclin (PGI iv), and oral sildenafil (Sil oral). CO = cardiac output; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; Pa_{O_2} = partial pressure of arterial oxygen (changes in mm Hg); PVRI = pulmonary vascular resistance index; PVR/SVR ratio = ratio of pulmonary to systemic vascular resistance (adapted from Ghofrani et al., Lancet 2002;360:895–900).

PDE-5 inhibitor sildenafil has come into the focus of investigation.

SILDENAFIL IN EXPERIMENTAL PH

In animal experiments, several PDE inhibitors displayed favorable pulmonary vasodilatory potential (8,18,19). Sildenafil in such a setting proved to be a potent and pulmonary-selective vasodilator (9). Most interestingly, this agent was also able to reduce hypoxia-induced PH in man and in an experimental animal model (20). The effects of sildenafil on chronic remodeling processes in the pulmonary vasculature are not yet well known. It is hoped that future results derived from long-term experimental models of PH will provide insight into these mechanisms.

CLINICAL EXPERIENCE WITH SILDENAFIL FOR THE TREATMENT OF CHRONIC PH

The vasodilatory effects of NO administered by inhalation are restricted to the pulmonary vasculature. Nitric oxide has a very short half-life, is used as a screening agent for lung vasoreactivity (21), and is effective for improving gas exchange in selected patients with the adult respiratory distress syndrome (22). Weaning from chronic NO treatment in patients with the adult respiratory distress syndrome was

found to be facilitated by oral sildenafil (23). In patients with PAH, short-term application of sildenafil during right heart catheterization showed the potential to reduce pulmonary vascular resistance in a dose-dependent manner. Interestingly, the vasodilatory effects were mainly operative in the pulmonary circulation and were significantly stronger than the effects seen with inhaled NO (24). In combination with another pulmonary selective vasodilator, inhaled iloprost, augmentation of the pulmonary vasodilatory effect of each single agent was noted (24,25) (Fig. 2). In patients with deteriorating severe PAH despite ongoing prostanoid treatment, long-term adjunct oral sildenafil improved exercise capacity and pulmonary hemodynamics (26). The combination of prostanoids and sildenafil could prove to be an appealing concept for future treatment of PH. Numerous reports about the clinical use of sildenafil in PAH as short-term application and long-term treatment in uncontrolled trials have been published (24,27–34).

Interestingly, sildenafil also appears to be effective for treating patients with PH of origin other than PPH. In patients suffering from human immunodeficiency virus (HIV)-related PH, sildenafil was similarly effective in reducing pulmonary vascular resistance as in PPH (35). Moreover, this therapeutic approach has been reported to be effective in pediatric patients (36). In the presence of interstitial lung disease, systemic administration of vasodilators regularly increases the blood flow to low or nonventilated lung areas by interfering with the physiological hypoxic vasoconstrictor mechanism, thereby worsening preexistent ventilation/perfusion mismatch and shunt flow. The decrease in arterial oxygenation and the wasting of the small ventilatory reserve of these patients are the negative consequences of this effect. Most interestingly, oral sildenafil was found to cause pulmonary vasodilation in patients with lung fibrosis and PH, with the overall vasodilatory potency corresponding to that of intravenous prostacyclin. Notably, in contrast to the infused prostanoid, selectivity for well-ventilated lung areas was demonstrated for sildenafil, resulting in an improvement rather than deterioration of gas exchange (37) (Fig. 3). Also, recent data suggest beneficial long-term effectiveness in patients with nonoperable chronic thromboembolic PH (38). The importance of this finding is the fact that there are few therapeutic options that can be offered to these patients (except lung transplantation).

Conclusions. The NO/cGMP axis represents a pivotal signaling pathway for the lung circulation. Phosphodiesterases, as regulators of the second messenger response to endogenous NO, are thus of great therapeutic potential for the treatment of lung circulatory disorders. Among the clinically available PDE inhibitors, sildenafil is a most promising agent for pulmonary vasodilation and long-term antiremodeling in the lung vasculature of PAH patients. Although orally administered, sildenafil does possess features of pulmonary selectivity. It may be favorably combined with other vasodilative and antiproliferative agents. Large trials, including a placebo-controlled phase III trial with sildenafil in patients with PAH, are currently underway.

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