

Combination Therapy with Oral Sildenafil and Inhaled Iloprost for Severe Pulmonary Hypertension

Hossein Ardeschir Ghofrani, MD; Ralph Wiedemann, MD; Frank Rose, MD; Horst Olschewski, MD; Ralph Theo Schermuly, PhD; Norbert Weissmann, PhD; Werner Seeger, MD; and Friedrich Grimminger, MD

Background: Inhalation of the stable prostacyclin analogue iloprost is being studied for treatment of pulmonary hypertension. The selective phosphodiesterase-5 inhibitor sildenafil has been reported to cause pulmonary vasodilatation.

Objective: To evaluate the safety and effectiveness of oral sildenafil, alone and in combination with inhaled iloprost, for treatment of pulmonary hypertension.

Design: Randomized, controlled, open-label trial.

Setting: Intensive care unit.

Patients: 30 patients with severe pulmonary arterial hypertension ($n = 16$), chronic thromboembolic pulmonary hypertension ($n = 13$), or pulmonary hypertension due to aplasia of the left pulmonary artery ($n = 1$), all classified as New York Heart Association class III or IV.

Intervention: All patients received inhaled nitric oxide and aerosolized iloprost (inhaled dose, 2.8 μg). They were then randomly assigned to receive 12.5 mg of oral sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost, or 50 mg of sildenafil plus inhaled iloprost.

Measurements: Systemic and pulmonary arterial pressure, pulmonary arterial occlusion pressure, cardiac output, central venous pressure, peripheral arterial oxygen saturation, and arterial and mixed venous blood gases were measured during right-heart catheterization by using a Swan-Ganz catheter.

Results: In rank order of pulmonary vasodilatory potency (maximum reduction of pulmonary vascular resistance and increase in cardiac index), 50 mg of sildenafil plus iloprost was most effective, followed by 12.5 mg of sildenafil plus iloprost. Iloprost alone and 50 mg of sildenafil were almost equally effective but were less potent than the combination regimens, and the least potent treatments were 12.5 mg of sildenafil and nitric oxide. In patients who received 50 mg of sildenafil plus iloprost, the maximum change in pulmonary vasodilatory potency was -44.2% (95% CI, -49.5% to -38.8%), compared with -14.1% (CI, -19.1% to -9.2%) in response to nitric oxide. With administration of 50 mg of sildenafil plus iloprost, the area under the curve for reduction in pulmonary vasodilatory resistance surpassed that of administration of 50 mg of sildenafil alone and iloprost alone combined, the vasodilatory effect lasted longer than 3 hours, and systemic arterial pressure and arterial oxygenation were maintained. No serious adverse events occurred.

Conclusion: Although limited by the small sample and lack of long-term observations, the study shows that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost to cause strong pulmonary vasodilatation in both severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Ann Intern Med. 2002;136:515-522.

www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

Severe pulmonary hypertension is a debilitating disease with short life expectancy that often affects young people. Continuous intravenous administration of epoprostenol has been used for pulmonary vasodilatation and was shown to improve exercise capacity and survival in patients with primary pulmonary hypertension (1). However, this therapy is limited by serious infectious complications of the intravenous line, systemic side effects due to the nonselectivity of the vasodilator response, and very high costs incurred because of tachyphylaxis with long-term administration.

The vasodilatory effects of nitric oxide administered by inhalation are restricted to the pulmonary vasculature. Nitric oxide has a very short half-life and is used as a screening agent for lung vasoreactivity (2). Inhalation

of aerosolized iloprost, a long-acting prostacyclin analogue, causes strong preferential pulmonary vasodilatation in both primary and secondary pulmonary hypertension (3–6). Long-term use of nebulized iloprost was shown to be beneficial in severe primary pulmonary hypertension and overt right-heart failure (7, 8), but because the drug wears off in about 60 minutes, patients must take 6 to 12 inhalations daily to achieve sustained relief of pulmonary hypertension.

Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, the second messengers of prostacyclin and nitric oxide. The phosphodiesterases have different tissue distributions and substrate affinities (9); in particular, phosphodiesterase-5 is abundantly ex-

Context

Common therapies for pulmonary hypertension have disadvantages: Continuous intravenous epoprostenol may cause sepsis, hypotension, and tachyphylaxis; nitric oxide requires continuous inhalation; and inhaled iloprost requires up to 12 doses per day. Phosphodiesterase in lung tissue (PDE-5) inhibits the action of these therapies by inactivating the second messengers of prostacyclin and nitric oxide (cyclic adenosine monophosphate and cyclic guanosine monophosphate). Because sildenafil blocks the action of PDE-5, thereby causing vascular dilatation, it could be useful in treating pulmonary hypertension.

Contribution

This randomized, controlled trial of low- or high-dose sildenafil, with or without inhaled iloprost, showed dose-dependent improvement in mean pulmonary artery pressure and hemodynamics with sildenafil alone. Iloprost amplified the effects.

Implications

Sildenafil may enhance the management of pulmonary hypertension.

—The Editors

pressed in lung tissue (10). Inhibition of phosphodiesterase may augment and prolong prostanoid- and nitric oxide-related vascular effects.

The novel selective phosphodiesterase-5 inhibitor sildenafil has been approved for treatment of erectile dysfunction. Sildenafil causes only very minor systemic hemodynamic effects in healthy humans (11). Data from an experimental model of pulmonary hypertension (12) and two recent case reports (13, 14) suggested that sildenafil might be an effective pulmonary vasodilator.

We compared the pulmonary vasodilatory effect of sildenafil with that of inhaled nitric oxide and aerosolized iloprost in 30 patients with severe pulmonary hypertension. We evaluated dose-response characteristics of sildenafil alone and in combination with inhaled prostanoid during right-heart catheterization.

METHODS**Patients**

Thirty patients (23 women and 7 men) with severe pulmonary hypertension (mean pulmonary arterial pressure > 40 mm Hg) were included. Sixteen patients had

pulmonary arterial hypertension, as defined by the World Health Organization World Symposium on Primary Pulmonary Hypertension (15); of these patients, 10 had primary pulmonary hypertension and 6 had calcinosis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (the CREST syndrome). One patient had aplasia of the left pulmonary artery. Thirteen patients had chronic thromboembolic pulmonary hypertension and were not candidates for surgery.

All patients were admitted for testing of pulmonary vasoreactivity and evaluation of therapeutic options. Seventeen patients were tested for the first time and had not been previously treated with inhaled iloprost. Thirteen patients had been tested at least 3 months after previous vasodilator testing; 11 of these patients were receiving long-term therapy with inhaled iloprost.

Exclusion criteria were pulmonary hypertension secondary to chronic obstructive pulmonary disease, pulmonary venous congestion, congenital heart disease, acute or chronic inflammatory lung disease, pregnancy or insufficient contraceptive measures, or previous treatment with phosphodiesterase inhibitors, including theophylline preparations. The individual response to vasodilators, including inhaled nitric oxide, was neither an inclusion nor an exclusion criterion.

Treatment

The study protocol was approved by the Justus-Liebig-University Ethics Committee, and each patient gave written informed consent.

A 7.5-French Swan-Ganz fiberoptic thermodilution pulmonary artery catheter (93A-754H, Baxter Healthcare, Irvine, California) was inserted via the right jugular vein by using standard techniques. Each patient received short-term inhaled nitric oxide; the maximum vasodilator response to this agent required nitric oxide, 20 to 40 parts per million. If necessary, patients received nasal oxygen throughout the test to achieve arterial oxygen saturation greater than 88%. After hemodynamic values returned to baseline, inhaled iloprost was delivered by using an ultrasonic nebulizer (Multisonic compact [Otto Schill GmbH, Probstzella, Germany]; mass median aerodynamic diameter, 3.9 μm ; duration of inhalation, 4 minutes; total inhaled dose, 2.8 μg) (16). Hemody-

Table. Baseline Hemodynamic Data*

Group (Patients)	Heart Rate	Mean Systemic Arterial Pressure	Mean Pulmonary Arterial Pressure	Cardiac Index	Pulmonary Vascular Resistance	Arterial Oxygen Saturation	Mixed Venous Oxygen Saturation
	beats/min	mm Hg	mm Hg	L/min per m ²	dyne/s per cm ⁻⁵	%	%
Sildenafil, 12.5 mg (<i>n</i> = 7)	73 ± 10.1	89 ± 14.6	53 ± 11.9	1.86 ± 0.8	1325 ± 728	95 ± 5.0	60 ± 12.4
Sildenafil, 50 mg (<i>n</i> = 8)	73 ± 16.7	100 ± 11.9	57 ± 16.4	1.95 ± 0.3	1262 ± 735	96 ± 2.0	59 ± 10.7
Sildenafil, 12.5 mg, plus iloprost (<i>n</i> = 7)	67 ± 6.9	93 ± 7.4	53 ± 11.6	1.86 ± 0.5	1230 ± 521	94 ± 3.7	60 ± 10.6
Sildenafil, 50 mg, plus iloprost (<i>n</i> = 8)	82 ± 12.4	98 ± 14.1	59 ± 11.6	1.63 ± 0.3	1471 ± 577	94 ± 3.4	51 ± 11.6

* Data are presented as the mean ± SD.

dynamic and gas exchange variables were measured at 5, 15, 30, 60, and 90 minutes after iloprost inhalation.

At the end of a 2-hour observation period, when hemodynamics had returned to baseline values, patients were randomly assigned to one of four treatment groups: 12.5 mg of oral sildenafil alone (*n* = 7); 12.5 mg of oral sildenafil, followed by 2.8 μg of inhaled iloprost 1 hour later (*n* = 7); 50 mg of oral sildenafil alone (*n* = 8); or 50 mg of oral sildenafil, followed by 2.8 μg of inhaled iloprost 1 hour later (*n* = 8). Patients were assigned to the therapeutic regimens by using computerized randomization in groups of four; no more than two patients in a row were assigned to one group.

Hemodynamic measurements and blood sampling were performed at 15, 30, 60, 90, and 120 minutes (and at 150 and 180 minutes in the group receiving 12.5 mg of sildenafil plus iloprost and in the group receiving 50 mg of sildenafil plus iloprost) after administration of oral sildenafil. To assess the overall vasodilator response, the area under the curve (AUC) of reduction in pulmonary vascular resistance was calculated as the integral of the difference between preintervention baseline values until pulmonary vascular resistance again reached 95% of baseline values or 120 minutes.

Statistical Analysis

Data are given as the mean and 95% CIs. For every variable, the response to vasodilator treatment was considered significant if the 95% (*P* < 0.05), 99% (*P* < 0.01), or 99.9% (*P* < 0.001) CI of the difference between pretreatment and post-treatment values did not overlap with zero. Two-way analysis of variance (ANOVA) was performed to test for significant differences and possible interaction of vasoreactivity to different vasodilators with underlying disease. One-way

ANOVA with the Scheffé post-test was used to determine hemodynamic responsiveness to the vasodilator regimens when two-way ANOVA indicated that underlying disease was a significant factor.

RESULTS

Baseline Hemodynamics

The Table shows baseline hemodynamics in all treatment groups. All patients had severe pulmonary hypertension and low cardiac index values. No pulmonary venous congestion was observed, as indicated by low pulmonary arterial occlusion pressure (8.7 ± 0.6 mm Hg). On ANOVA, the groups did not differ significantly in any baseline characteristic.

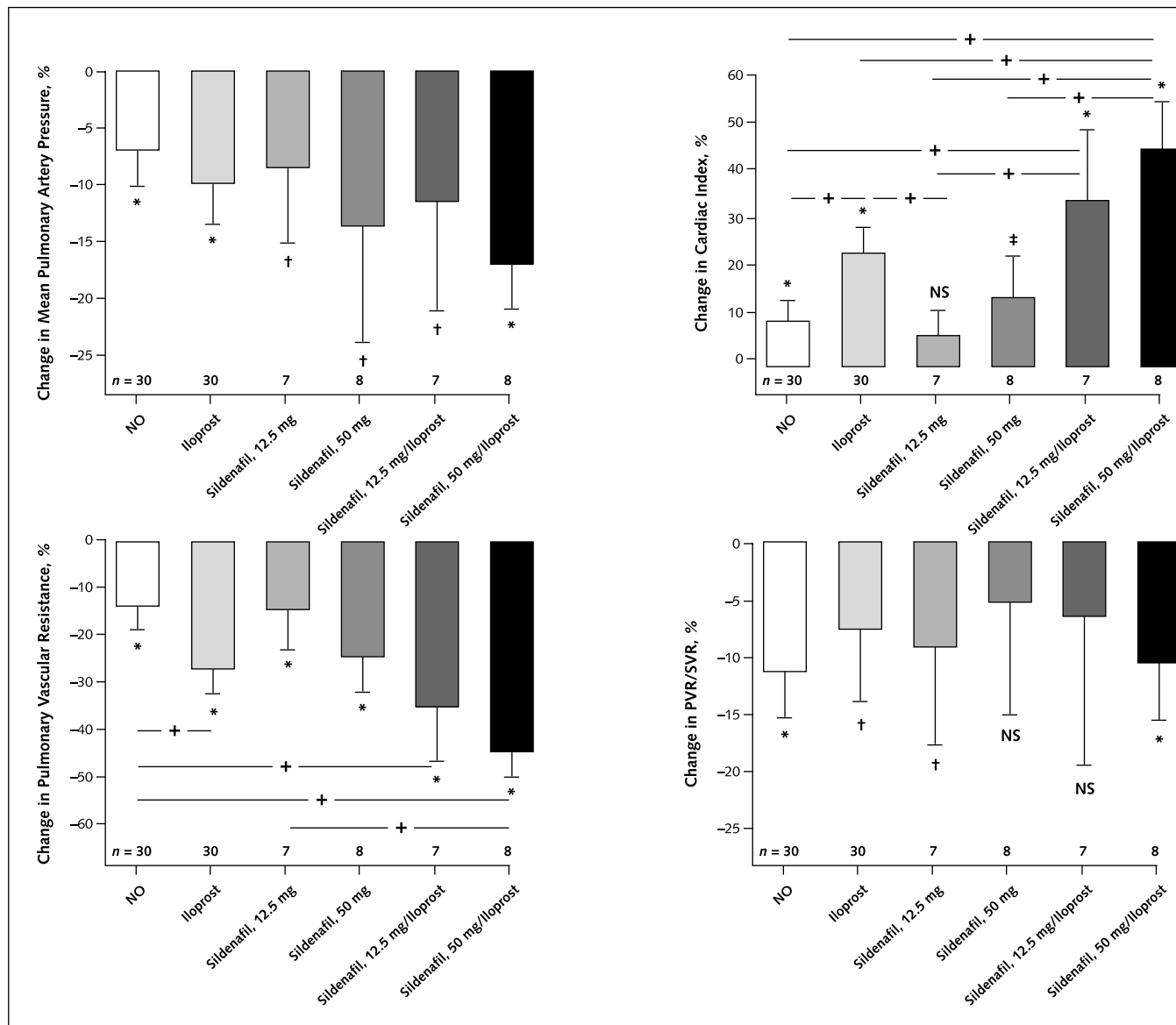
Inhaled Nitric Oxide

Inhalation of nitric oxide decreased mean pulmonary arterial pressure (change, -7.0% [95% CI, -3.8% to 10.2%]), increased the cardiac index (change, 7.9% [CI, 3.4% to 12.5%]), and decreased pulmonary vascular resistance (change, -14.1% [CI, -19.1% to -9.2%]) (Figure 1). The pulmonary selectivity of the vasodilatory effect was indicated by a significant reduction in the ratio of pulmonary to systemic vascular resistance. The decrease in pulmonary vascular resistance in response to inhaled nitric oxide did not differ significantly among groups (Figure 2). The effects of nitric oxide wore off within 15 minutes.

Inhaled Iloprost

Aerosolized iloprost decreased the pulmonary vascular resistance by 27.1% (CI, 22.2% to 32.1%) and increased the cardiac index by 22.8% (CI, 17.6% to

Figure 1. Hemodynamic responses to vasodilators.



Bars show the maximum changes from preintervention baseline values; error bars represent CIs. Analysis of variance with the Scheffé post-test for intergroup comparison indicated significant differences ($P < 0.001$); plus signs bracketed by horizontal bars show these relationships. NO = nitric oxide; NS = not significant; PVR/SVR = ratio of pulmonary vascular resistance to systemic vascular resistance. * $P < 0.001$, † $P < 0.05$, ‡ $P < 0.01$ for differences between pretreatment and post-treatment values.

27.9%) (Figure 1). The decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pulmonary vasodilatation. No significant differences among groups in the vasodilator response to inhaled iloprost were observed (Figure 2). The effects of iloprost wore off within 60 to 90 minutes.

Oral Sildenafil

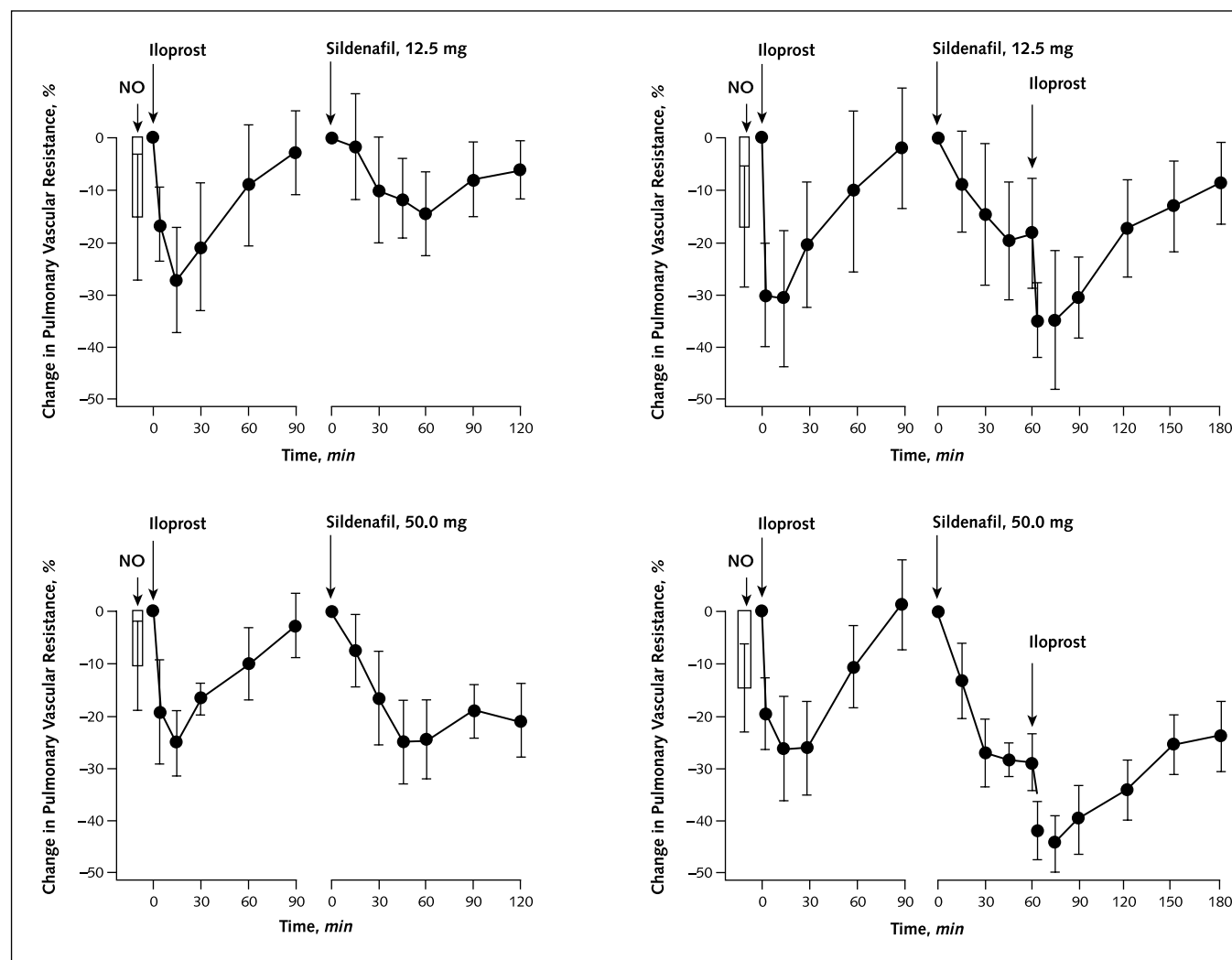
Administration of 12.5 mg or 50 mg of sildenafil decreased mean pulmonary arterial pressure in a dose-dependent manner (change, -8.5% [CI, -15.1% to -1.9%] and -13.5% [CI, -23.8% to -3.2%], respectively) (Figure 1). The cardiac index increased by 5.0%

(CI, -0.5% to 10.5%) and 13.2% (CI, 4.3% to 22.2%), and pulmonary vascular resistance decreased by 14.7% (CI, 6.6% to 22.7%) and 24.3% (CI, 16.7% to 31.8%). The decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pulmonary vasodilatation. Arterial oxygen did not decrease significantly (data not shown), and no adverse events were observed. The vasodilatory response to sildenafil began within 15 minutes of administration and reached a plateau after 45 to 60 minutes; the 50-mg dose of sildenafil was still effective after 120 minutes (Figure 2).

Combination Therapy

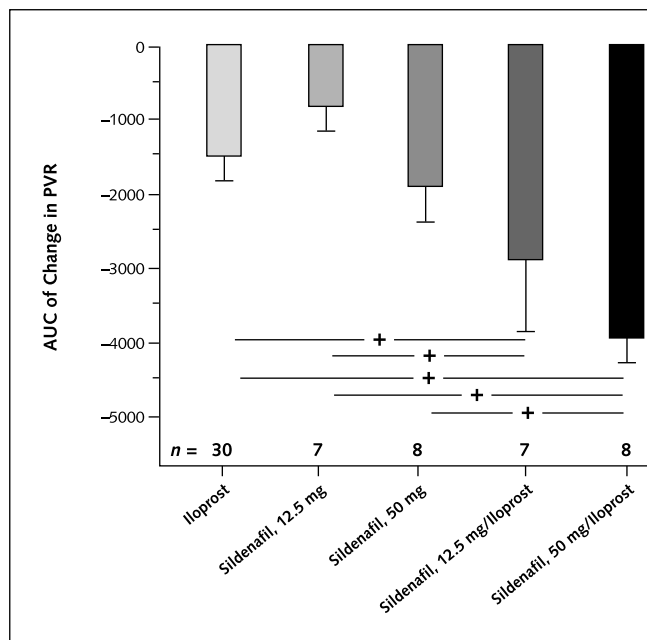
Inhalation of iloprost 1 hour after oral intake of 12.5 mg or 50 mg of sildenafil significantly increased the pulmonary vasodilator response compared with each single intervention (Figures 1 and 2). It also decreased pulmonary vascular resistance ($P < 0.001$, ANOVA) and increased cardiac index ($P < 0.001$, ANOVA) to a significantly greater extent than did the single interventions and maintained good pulmonary vasodilatation. The maximum reduction in pulmonary vascular resistance was most pronounced in patients who received 50

Figure 2. Time to decrease in pulmonary vascular resistance in response to vasodilator challenge.



Data are presented as the mean; error bars indicate CIs. Arrows indicate administration of therapy. The bars at the left of each panel show the maximum reduction in pulmonary vascular resistance caused by initial nitric oxide (NO) inhalation. Pretreatment baseline values are set at 100%.

Figure 3. Area under the curve (AUC) of reduction in pulmonary vascular resistance (PVR) in response to therapy.



To assess mean AUCs and CIs (indicated by the error bars), we calculated the integral of difference between preintervention baseline values until pulmonary vascular resistance again reached 95% of baseline values or 120 minutes had passed. Analysis of variance with the Scheffé post-test for intergroup comparison indicated significant differences ($P < 0.001$); plus signs bracketed by horizontal bars demonstrate these relationships.

mg of sildenafil plus iloprost (change, -44.2% [CI, -49.55% to -38.8%]). The overall vasodilatory response to the combined interventions lasted beyond the 180-minute observation period. The AUC for reduction in pulmonary vascular resistance after combination therapy was greater than the sum of the AUCs for each single intervention, at either dose of sildenafil plus iloprost ($P < 0.001$, ANOVA) (Figure 3). No significant decrease in arterial oxygen saturation (data not shown) and no adverse events occurred during combination therapy.

Subgroup Analysis

Baseline hemodynamic values did not significantly differ between patients with primary pulmonary hypertension and those with chronic thromboembolic pulmonary hypertension. On two-way ANOVA to assess the effect of diagnosis on hemodynamic responsiveness to

monotherapy and combination therapy, no significant difference could be detected on the basis of diagnosis. Furthermore, no interaction was seen when patients with primary pulmonary hypertension were compared with all other patients and with those who had chronic thromboembolic pulmonary hypertension.

DISCUSSION

Lung tissue is a rich source of phosphodiesterases. Phosphodiesterase-3 and phosphodiesterase-4 by hydrolyzation assist in degradation of cyclic adenosine monophosphate, and phosphodiesterase-5 assists in decay of cyclic guanosine monophosphate. The actions of these phosphodiesterases limit the vasodilatory effects of adenylylate cyclase stimuli (such as prostanoids) and guanylate cyclase stimuli (such as nitric oxide) (17). Crosstalk between the cyclic adenosine monophosphate and the cyclic guanosine monophosphate pathways has been demonstrated; inhibition of phosphodiesterase-3 by cyclic guanosine monophosphate is the most prominent example (9). Moreover, phosphodiesterases may be up-regulated in response to increased second messenger levels as a negative feedback loop (9).

We found that the phosphodiesterase-5-selective inhibitor sildenafil caused strong dose-dependent pulmonary vasodilatation, even in the absence of exogenous nitric oxide administration, in patients with pulmonary arterial hypertension (many of whom had primary pulmonary hypertension) and those with chronic thromboembolic pulmonary hypertension. Only 3 of 30 patients were considered responsive to nitric oxide, on the basis of reduction of pulmonary arterial pressure by more than 20% and a decrease in pulmonary vascular resistance of more than 20% (18). However, in accordance with our findings and those of other investigators (5, 7), inhaled iloprost provoked substantially stronger pulmonary vasorelaxation in most of these patients. This was also true for the subgroup of patients with chronic thromboembolic pulmonary hypertension, in whom marked lung vasodilatation was observed in response to aerosolized prostanoid (7). Most surprising, as seen in an experimental model of pulmonary hypertension (12), the maximum vasodilatory response to sildenafil markedly surpassed that provoked by nitric oxide in the same patients, and the decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pul-

monary vasodilatation despite oral administration of the phosphodiesterase inhibitor. Thus, substantial baseline stimulation of guanylate cyclase in the lung vasculature of patients with hypertension may be assumed and is only partly attributable to nitric oxide; thus, strong pulmonary vasodilatation results when phosphodiesterases block the breakdown of the second messenger, cyclic guanosine monophosphate.

Administration of oral sildenafil plus inhaled iloprost produced a much greater vasodilatory response than did each single agent. The AUC of the reduction in pulmonary vascular resistance with 12.5 mg or 50 mg of sildenafil plus iloprost exceeded the summed AUCs from patients receiving sildenafil alone at either dose or iloprost alone. The decrease in the ratio of pulmonary to systemic vascular resistance in the combination-therapy groups again indicated preferential pulmonary vasodilatation over systemic vasodilatation, and arterial oxygenation did not worsen. Of note, the maximum decrease in pulmonary vascular resistance in patients with chronic pulmonary hypertension approached nearly 50% in response to 50 mg of sildenafil plus iloprost, although this group did not include classic responders to vasodilator treatment, as indicated by the moderate effect of nitric oxide inhalation. The extent to which a cyclic guanosine monophosphate-linked inhibition of phosphodiesterase-3 and, thus, prolongation of prostanoinduced cyclic adenosine monophosphate contribute to this synergism, and whether additional mechanisms are at work, are yet to be elucidated.

Our study had limitations. Because our sample was small and long-term observations are lacking, our current data are too preliminary to allow recommendations for new therapeutic strategies. Furthermore, no definitive conclusion about the influence of etiology of the disease or differences in baseline characteristics can be made at this stage. Further controlled studies in larger samples are needed to address these issues.

We conclude that oral sildenafil is an effective pulmonary vasodilator in both pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In combination with inhaled iloprost, this treatment has synergistic hemodynamic effects with no loss of selectivity for the pulmonary vasculature. Combined administration of oral sildenafil and inhaled iloprost may become a novel approach to achieve pulmo-

nary vasodilatation and long-term antiremodeling in pulmonary hypertension of various causes.

From University Hospital, Justus-Liebig-University, Giessen, Germany.

Acknowledgments: The authors thank Dr. R.L. Snipes for linguistic editing of the manuscript and George Afram for technical assistance.

Grant Support: By the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 547).

Requests for Single Reprints: Hossein Ardeschir Ghofrani, MD, Department of Internal Medicine, University Hospital, Justus-Liebig-University, Klinikstrasse 36, 35392 Giessen, Germany; e-mail, ardeschir.ghofrani@innere.med.uni-giessen.de.

Current Author Addresses: Drs. Ghofrani, Wiedemann, Rose, Olschewski, Schermuly, Weissmann, Seeger, and Grimminger: Department of Internal Medicine, University Hospital, Justus-Liebig-University, Klinikstrasse 36, 35392 Giessen, Germany.

Author Contributions: Conception and design: H.A. Ghofrani, R. Wiedemann, H. Olschewski, W. Seeger, F. Grimminger.

Analysis and interpretation of the data: H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, F. Grimminger.

Drafting of the article: H.A. Ghofrani, H. Olschewski, W. Seeger, F. Grimminger.

Critical revision of the article for important intellectual content: H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, F. Grimminger.

Final approval of the article: H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, F. Grimminger.

Provision of study materials or patients: H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, W. Seeger, F. Grimminger.

Statistical expertise: H.A. Ghofrani, H. Olschewski, N. Weissmann, W. Seeger.

Obtaining of funding: H.A. Ghofrani, W. Seeger, F. Grimminger.

Administrative, technical, or logistic support: H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, F. Grimminger.

Collection and assembly of data: H.A. Ghofrani, R. Wiedemann, F. Rose, R.T. Schermuly, W. Seeger, F. Grimminger.

References

1. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996;334:296-302. [PMID: 8532025]
2. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet*. 1991;338:1173-4. [PMID: 1682593]

3. Olschewski H, Walrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med.* 1996;124:820-4. [PMID: 8610951]
4. Olschewski H, Ghofrani HA, Walrath D, Schermuly R, Temmesfeld-Wollbrück B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med.* 1999;160:600-7. [PMID: 10430735]
5. Hoepfer MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. *J Am Coll Cardiol.* 2000;35:176-82. [PMID: 10636277]
6. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. *Circulation.* 2000;101:2388-92. [PMID: 10821815]
7. Olschewski H, Ghofrani HA, Schmehl T, Winkler J, Wilkens H, Höper MM, et al. Inhaled iloprost to treat severe pulmonary hypertension. An uncontrolled trial. German PPH Study Group. *Ann Intern Med.* 2000;132:435-43. [PMID: 10733442]
8. Hoepfer MM, Schwarze M, Ehlerding S, Adler-Schuermeier A, Spiekerkoetter E, Niedermeyer J, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med.* 2000;342:1866-70. [PMID: 10861321]
9. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. *Physiol Rev.* 1995;75:725-48. [PMID: 7480160]
10. Ahn HS, Foster M, Cable M, Pitts BJ, Sybertz EJ. Ca/CaM-stimulated and cGMP-specific phosphodiesterases in vascular and non-vascular tissues. *Adv Exp Med Biol.* 1991;308:191-7. [PMID: 1666264]
11. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, et al. Use of sildenafil (Viagra) in patients with cardiovascular disease. Technology and Practice Executive Committee. *Circulation.* 1999;99:168-77. [PMID: 9884398]
12. Weimann J, Ullrich R, Hromi J, Fujino Y, Clark MW, Bloch KD, et al. Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension. *Anesthesiology.* 2000;92:1702-12. [PMID: 10839922]
13. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. *Heart.* 2000;84:E4. [PMID: 10908271]
14. Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension [Letter]. *N Engl J Med.* 2000;343:1342. [PMID: 11183578]
15. Rich S, ed. Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998, Evian, France, 6–10 September 1998. Available at www.who.int/ncd/cvd/pph.html. Accessed on 1 July 2001.
16. Gessler T, Schmehl T, Hoepfer MM, Rose F, Ghofrani HA, Olschewski H, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Eur Respir J.* 2001;17:14-9. [PMID: 11307743]
17. Rabe KF, Tenor H, Dent G, Schudt C, Nakashima M, Magnussen H. Identification of PDE isozymes in human pulmonary artery and effect of selective PDE inhibitors. *Am J Physiol.* 1994;266:L536-43. [PMID: 7515580]
18. Sitbon O, Brenot F, Denjean A, Bergeron A, Parent F, Azarian R, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. A dose-response study and comparison with prostacyclin. *Am J Respir Crit Care Med.* 1995;151:384-9. [PMID: 7842196]