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Differences in Hemodynamic and Oxygenation Responses to Three Different Phosphodiesterase-5 Inhibitors in Patients With Pulmonary Arterial Hypertension

A Randomized Prospective Study

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OBJECTIVES We sought to compare the short-term impact of three different phosphodiesterase-5 (PDE5) inhibitors on pulmonary and systemic hemodynamics and gas exchange parameters in patients with pulmonary arterial hypertension (PAH).

BACKGROUND The PDE5 inhibitor sildenafil has been reported to cause pulmonary vasodilation in patients with PAH. Vardenafil and tadalafil are new PDE5 inhibitors, recently being approved for the treatment of erectile dysfunction.

METHODS Sixty consecutive PAH patients (New York Heart Association functional class II to IV) who underwent right heart catheterization received short-term nitric oxide (NO) inhalation and were subsequently assigned to oral intake of 50 mg sildenafil (n = 19), 10 mg (n = 7) or 20 mg (n = 9) vardenafil, or 20 mg (n = 9), 40 mg (n = 8), or 60 mg (n = 8) tadalafil. Hemodynamics and changes in oxygenation were assessed over a subsequent 120-min observation period.

RESULTS All three PDE5 inhibitors caused significant pulmonary vasorelaxation, with maximum effects being obtained after 40 to 45 min (vardenafil), 60 min (sildenafil), and 75 to 90 min (tadalafil). Sildenafil and tadalafil, but not vardenafil, caused a significant reduction in the pulmonary to systemic vascular resistance ratio. Significant improvement in arterial oxygenation (equally to NO inhalation) was only noted with sildenafil.

CONCLUSIONS In PAH patients, the three PDE5 inhibitors differ markedly in their kinetics of pulmonary vasorelaxation (most rapid effect by vardenafil), their selectivity for the pulmonary circulation (sildenafil and tadalafil, but not vardenafil), and their impact on arterial oxygenation (improvement with sildenafil only). Careful evaluation of each new PDE5 inhibitor, when being considered for PAH treatment, has to be undertaken, despite common classification as PDE5 inhibitors. (J Am Coll Cardiol 2004;44:1488–96) © 2004 by the American College of Cardiology Foundation

In recent years, several new drugs have been developed for the treatment of pulmonary arterial hypertension (PAH), including continuous intravenous epoprosterenol (1), inhaled iloprost (2), subcutaneous trepostinil (3), oral bosentan (4), and oral beraprost (5,6). In addition, there is increasing evidence for the therapeutic effectiveness of the phosphodiesterase-5 (PDE5) inhibitor sildenafil in PAH (7–9). Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, the second messengers of prostacyclin and nitric oxide (NO) (Fig. 1). The phosphodiesterases have different tissue distributions and substrate affinities (10). Interestingly, PDE5 is abundantly expressed in lung tissue (11), thus offering as target molecule for PAH treatment concepts.

Recently, the new PDE5 inhibitors vardenafil and tadalafil have been approved for the treatment of erectile dysfunction. These PDE5 inhibitors share major properties with sildenafil, including mechanisms of action and preferential though not fully selective inhibition of PDE5. The clinical efficacy and safety profiles of these medications are linked to their molecular mode of action, their selectivity for PDE5, and their pharmacokinetic properties (12). However, all investigations performed so far have mainly focused

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Abbreviations and Acronyms

cGMP = cyclic guanosine monophosphate
CI = confidence interval
mPAP = mean pulmonary arterial pressure
NO = nitric oxide
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PDE = phosphodiesterase
PVRI = pulmonary vascular resistance index
SVRI = systemic vascular resistance index

on comparing the effects of these substances on erectile dysfunction. No data exist addressing the efficacy and safety of vardenafil and tadalafil, as opposed to sildenafil, on pulmonary and systemic hemodynamics in patients with PAH.

In the present study, we characterized the hemodynamic profile of different doses of vardenafil and tadalafil in patients with PAH. Response profiles were compared with those of inhaled NO (20 to 40 ppm) and sildenafil (50 mg), serving as reference agents, as previously described (7,9,13,14). Dosing of vardenafil and tadalafil was based on the labeling of these substances in their original indication, as well as preliminary investigations of our own group (data not published) addressing dose-response profiles of these agents.

METHODS

Patients. Overall, 82 patients were screened, of whom 22 were excluded (12 did not meet inclusion criteria, seven did not provide consent, and three were clinically unstable between screening and study onset). Sixty patients (39 women and 21 men) with chronic PAH, as defined by the recent World Conference on Pulmonary Hypertension (15), were included: 46 with idiopathic PAH, seven with Eisenmenger's disease, four with CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), two with porto-pulmonary hypertension, and one with human immunodeficiency virus associated.

All patients were admitted to our pulmonary hypertension center for testing of pulmonary vasoreactivity and evaluation of therapeutic options. Diagnostic procedures preceding patient recruitment included clinical chemistry, immunologic analysis, chest X-ray, lung function testing, echocardiography, and a high-resolution computed tomographic scan of the lung. In all cases, perfusion scintigraphy, spiral computed tomography, and, in selected cases, pulmonary angiography were performed to exclude chronic thromboembolism as the underlying reason for pulmonary hypertension. All patients were tested for the first time and had not been previously treated with pulmonary vasodilators, except for 14 of the patients receiving low-dose calcium channel blocker therapy.

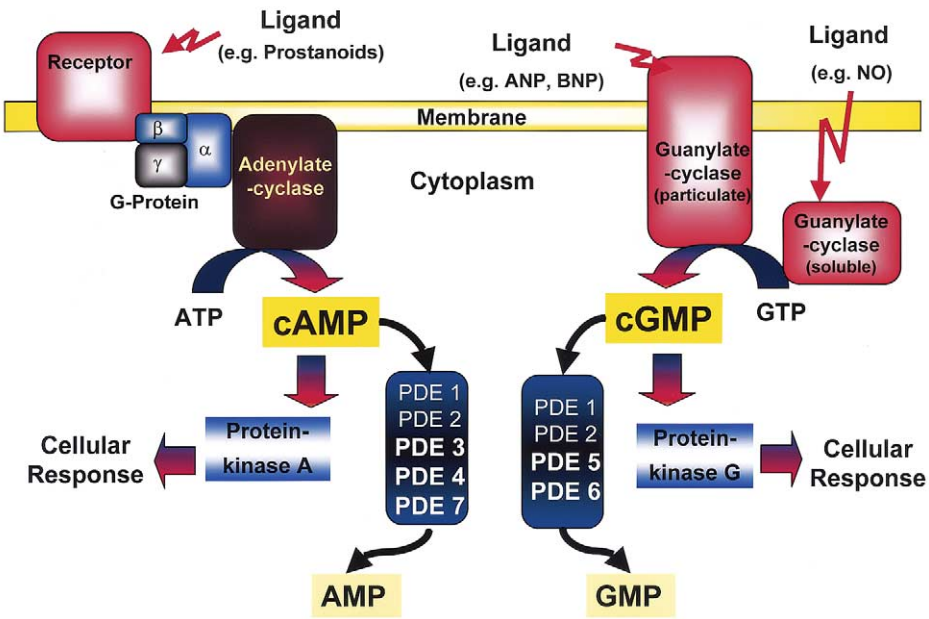

Figure 1. Intracellular signaling pathway of nitric oxide (NO), prostanoids, and natriuretic peptides: role of phosphodiesterases (PDEs). Ligands (i.e., NO, atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], and prostanoids) activate membrane-bound or soluble cyclases. Guanylate and adenylate cyclases generate cyclic guanosine monophosphate (cGMP) and adenosine monophosphate (cAMP) from GTP and ATP. These intracellular second messengers, via activation of protein kinases, induce cellular responses (i.e., vasodilation and anti-proliferation). Phosphodiesterases limit the effects of the ligands by degradation of second messengers cGMP and cAMP into inactive GMP and AMP. Thus, by inhibition of the PDEs, the PDE inhibitors augment and prolong the cellular responses to NO, prostanoids, and natriuretic peptides.

Exclusion criteria were pulmonary hypertension secondary to chronic obstructive or restrictive pulmonary disease, recurrent pulmonary embolism, pulmonary venous congestion, acute or chronic inflammatory lung disease, pregnancy or insufficient contraceptive measures, and previous treatment with PDE inhibitors. The individual response to vasodilators, including inhaled NO, was neither an inclusion nor an exclusion criterion. The study protocol was approved by the Justus-Liebig-University Ethics Committee, and each patient gave written, informed consent. The procedures followed were in accordance with institutional guidelines.

A fiberoptic thermodilution pulmonary artery catheter (Edwards Swan-Ganz, 93A-754H 7.5-F; Baxter Healthcare, Irvine, California) was used to measure central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, cardiac output, and mixed venous oxygen saturation. Patients received continuous nasal oxygen throughout the entire test procedure if initial arterial oxygen saturation was below 88%.

Treatment. After assessment of baseline hemodynamic values, each patient received short-term inhaled NO; the maximum vasodilator response to this agent required 20 to 40 ppm NO. When hemodynamic parameters had returned to baseline values after cessation of NO inhalation, patients received one oral dose of a PDE5 inhibitor. In the first 19 patients presenting with PAH, 50 mg sildenafil was orally administered. Subsequently, PAH patients were randomly assigned to receive either 10 mg (n = 7) or 20 mg (n = 9) oral vardenafil or 20 mg (n = 9), 40 mg (n = 9), or 60 mg (n = 8) oral tadalafil (Fig. 2). Patients were assigned to the therapeutic regimens by using computerized randomization in groups of five; no more than two patients in a row were assigned to one group. Hemodynamic measurements were performed at baseline, during maximum effect of inhaled NO, and 15, 30, 45, 60, 90, and 120 min (and, in selected cases, after 150 min) after ingestion of each PDE5 inhibitor. Calculations were made at peak reduction of pulmonary vascular resistance (PVR).

Statistics. All baseline data are given as the median and range (minimum to maximum). Hodges-Lehmann point estimates of median difference and exact 95% confidence intervals (CIs) are presented for the response of each parameter to each vasodilator challenge (pre- and post-intervention values). One-way analysis of variance with the Scheffé post-test for multiple comparisons was used to seek for statistical differences between hemodynamic and gas exchange variables in the different treatment groups at baseline and to analyze for statistical differences regarding the responsiveness to each vasodilator.

Role of funding source. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Functional classification and baseline hemodynamics. According to clinical criteria, nine patients were classified as being in New York Heart Association (NYHA) functional class II, 35 patients in class III, and 16 patients in class IV. The mean pulmonary artery pressure (mPAP) was markedly elevated (53.0 mm Hg [range 30 to 87 mm Hg]), and the cardiac index was in the lower normal range (2.2 l/min per m^2 [range 1.0 to 4.0 l/min per m^2]), with a correspondingly increased PVRI (PVRI 1,569 dynes/cm^{-5} per m^2 [range 402 to 4,099]). Distribution to functional classes, to PAH subgroups, as well as baseline hemodynamics did not significantly differ between the treatment groups (Table 1).

Nitric oxide inhalation. Inhalation of NO caused a rapid decrease in mPAP by −9.8% (CI −7.2 to −13.4), accompanied by a median increase in the cardiac index by 6.0% (CI 2.6 to 9.4), resulting in a PVRI reduction of −15.5% (CI −11.0 to −19.3) (Table 2, Fig. 3). Pulmonary selectivity of the vasodilatory effect was reflected by a reduction of −13.8% (CI −10.5 to −17.9) in the PVR/systemic vascular resistance (SVR) ratio. Concomitantly, a significant increase in arterial pO_2 of 9.6% (CI 1.6 to 19.0) was noted. All NO-induced changes returned to baseline within <10 min after stopping inhalation of this agent.

Sildenafil. Fifty mg of oral sildenafil caused a significant decrease of mPAP by −16.2% (CI −11.6 to −21.5), accompanied by a median increase in the cardiac index by 13.2% (CI 9.9 to 17.1), resulting in a PVRI reduction of −28.0% (CI −26.1 to −31.2) (Fig. 3). A peak vasodilatory effect was noted at 60 min (CI 52.0 to 67.5) after drug intake (Fig. 4). Despite systemic administration, pulmonary selectivity of the vasodilatory effect was reflected by a −15.5% (CI −11.1 to −21.3) reduction in the PVR/SVR ratio. As with inhaled NO, a concomitant significant increase in arterial pO_2 of 8.9% (CI 1.2 to 22.9) was noted. No adverse events were reported during this short-term vasodilatory testing procedure on intake of sildenafil.

Vardenafil. Oral vardenafil at doses of 10 mg and 20 mg caused a significant decrease of mPAP of −14.3% (CI −5.6 to −23.1) and −12.1% (CI −7.3 to −15.8), respectively. A median increase in the cardiac index of 9.3% (CI 1.8 to 18.7) was noted after 10 mg vardenafil and of 18.4% (CI 9.8 to 25.1) after 20 mg vardenafil, respectively. The PVRI was reduced by −21.6% (CI −10.2 to −32.3) and −26.3 (CI −22.8 to −29.2), respectively (Fig. 3). Peak vasodilatory effect was noted at 41.3 min (CI 22.5 to 60.0) after intake of 10 mg vardenafil and at 45 min (CI 37.5 to 60.0) of 20 mg vardenafil (Fig. 4). By contrast with inhaled NO and oral sildenafil, vardenafil caused almost an equipotent reduction of SVR and PVR, as reflected by the PVR/SVR ratios of −6.9 (CI −24.8 to 15.2) for 10 mg and −0.1 (CI −8.2 to 4.2) for 20 mg of this substance. Arterial oxygenation remained virtually unchanged with both concentrations of this agent (Fig. 3). Despite the lack of pulmonary selectivity, only minor adverse events (such as flushing and

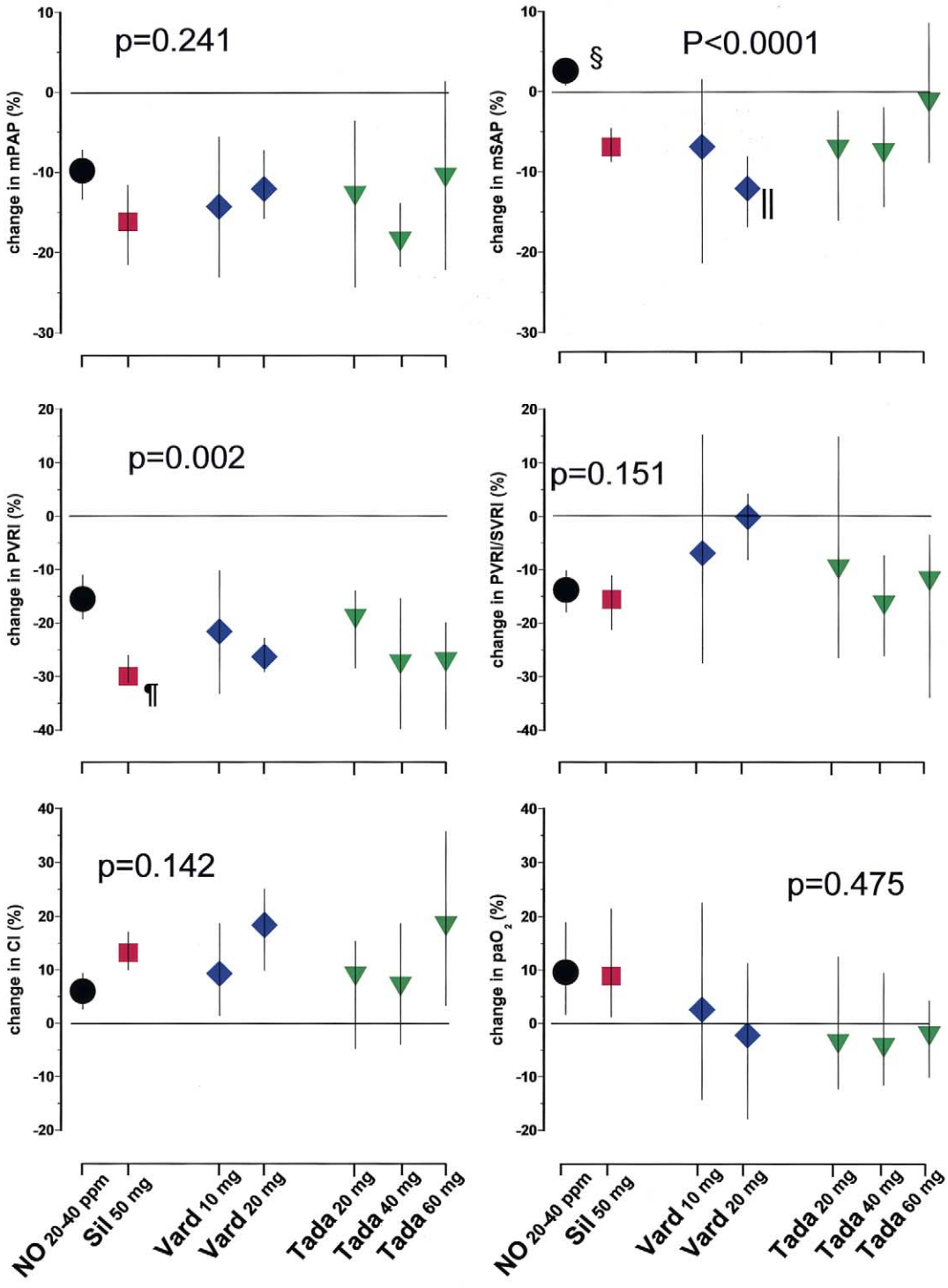

Figure 2. Hemodynamic and oxygenation response to inhaled nitric oxide (NO), oral sildenafil, oral vardenafil, and oral tadalafil. Deviations from the pre-intervention baseline value are displayed (point estimates of median difference [percentage of baseline = **symbols**], with exact 95% confidence intervals [**bars**] for inhaled NO [NO 20 to 40 ppm = **solid circles**], oral sildenafil [Sil 50 mg = **red squares**], 10 and 20 mg oral vardenafil [Vard 10 mg and Vard 20 mg = **blue diamonds**], and 20, 40, and 60 mg oral tadalafil [Tada 20 mg, Tada 40 mg, Tada 60 mg = **green inverted triangles**]). mSAP = mean systemic arterial pressure; CI = cardiac index; pO_2 = partial pressure of arterial oxygen. The p values indicate significant differences of treatment effects, as determined by one-way analysis of variance. ¶Different from NO. ‖Different from tadalafil 60 mg ($p < 0.05$, Scheffé post-test).

a light headache in three of nine patients in the 20-mg group) were reported after intake of vardenafil.

Tadalafil. Oral tadalafil, given at doses of 20, 40, and 60 mg, caused a significant decrease of mPAP of −12.6% (CI −3.6 to −24.4), −18.3% (CI −13.9 to −21.8), and −10.0% (CI −22.2 to 1.1), respectively. Median increases in the cardiac index of 9.3% (CI −4.8 to 15.4), 7.5% (CI −4.0 to 20.7), and 18.8% (CI 3.3 to 36.7) were noted for

Table 1. Baseline Hemodynamic and Gas Exchange Variables

Treatment Group	Baseline/NO (n = 60)	Sildenafil 50 mg (n = 19)	Vardenafil 10 mg (n = 7)	Vardenafil 20 mg (n = 9)	Tadalafil 20 mg (n = 9)	Tadalafil 40 mg (n = 8)	Tadalafil 60 mg (n = 8)	p Value*
Age (yrs)	51 (18 to 81)	54 (18 to 81)	46 (37 to 78)	51 (31 to 74)	42 (28 to 67)	64 (33 to 70)	44 (39 to 69)	0.334
PAH origin, A/B/C/D/E	46/7/4/2/1	14/4/0/0/1	5/2/0/0/0	7/0/0/2/0	7/0/2/0/0	6/1/1/0/0	7/0/1/0/0	NA
Patients receiving oxygen (n)	30	10	3	4	4	5	4	NA
NYHA class distribution, II/III/IV	10/34/16	0/12/7	2/4/1	3/5/1	1/4/4	2/6/0	2/3/3	0.121
Heart rate (beats/min)	82 (55 to 108)	83 (63 to 96)	76 (62 to 107)	90 (72 to 108)	82 (61 to 105)	69 (55 to 89)	81 (57 to 106)	0.105
Mean systemic arterial pressure (mm Hg)	88 (64 to 140)	95 (79 to 125)	78 (74 to 110)	86 (70 to 123)	91 (77 to 140)	86 (64 to 99)	90 (76 to 116)	0.331
Mean pulmonary arterial pressure (mm Hg)	53 (30 to 87)	56 (43 to 74)	61 (31 to 87)	48 (30 to 79)	45 (31 to 84)	48 (31 to 55)	46 (36 to 78)	0.233
Cardiac index (l/min per m^2)	2.2 (1.0 to 4.0)	2.1 (1.0 to 3.5)	2.9 (1.8 to 4.0)	2.4 (1.7 to 3.9)	2.0 (1.2 to 2.8)	2.1 (1.8 to 2.6)	2.5 (1.0 to 3.8)	0.116
Systemic vascular resistance index (dynes/cm^{-5}/m^2)	3,222 (1,463 to 6,316)	3,854 (1,728 to 6,316)	1,860 (1,737 to 4,303)	2,735 (1,463 to 5,158)	3,383 (2,235 to 3,337)	2,735 (2,458 to 3,328)	2,555 (1,929 to 4,150)	0.038
Pulmonary vascular resistance index (dynes/cm^{-5}/m^2)	1,569 (402 to 4,098)	1,811 (949 to 4,098)	1,369 (586 to 3,280)	1,647 (402 to 2,659)	1,336 (753 to 3,337)	1,303 (750 to 1,969)	1,011 (572 to 3,986)	0.212
Mixed venous oxygen saturation (%)	62.9 (30.7 to 81.1)	60.5 (44.2 to 71.8)	68.3 (61.8 to 72.6)	62.5 (49.1 to 72.3)	65.8 (39.9 to 81.1)	61.1 (51.4 to 78.8)	61.4 (30.7 to 74.6)	0.265
Partial pressure of arterial oxygen (mm Hg)	69.9 (47.8 to 166.0)	70.5 (50.0 to 147.0)	76.7 (49.0 to 82.0)	68.5 (56.3 to 135.7)	81.0 (54.0 to 166.0)	62.8 (47.8 to 101.0)	66.1 (64.0 to 72.3)	0.330
Partial pressure of carbon monoxide (mm Hg)	33.3 (22.0 to 59.4)	29.5 (23.6 to 40.0)	38.4† (29.4 to 55.7)	34.0 (29.7 to 37.9)	35.7 (23.5 to 59.4)	33.2 (22.0 to 39.0)	34.2 (27.8 to 41.0)	0.007

*Analysis of variance was used to seek significant intergroup variances. †Different from sildenafil 50 mg group ($p < 0.05$, Scheffé post-test). Hemodynamic and gas exchange variables at baseline for the entire patient population (baseline/NO) and for the subgroups (after assignment to different treatments) are presented in this table. Data are presented as the median value (range) or number of subjects.

NA = not applicable; NO = nitric oxide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAH origin: A = idiopathic pulmonary arterial hypertension; B = Eisenmenger's disease; C = CREST syndrome; D = porto-pulmonary hypertension; E = HIV associated.

Table 2. Peak Effects of Pharmacologic Interventions on Hemodynamics and Gas Exchange Variables

Treatment Group	Baseline/NO (n = 60)	Sildenafil 50 mg (n = 19)	Vardenafil 10 mg (n = 7)	Vardenafil 20 mg (n = 9)	Tadalafil 20 mg (n = 9)	Tadalafil 40 mg (n = 8)	Tadalafil 60 mg (n = 8)	p Value*
Heart rate (beats/min)	0.6 (−1.6 to 2.9)	−4.9 (−10.3 to 0.1)	4.2 (−6.3 to 22.1)	4.4 (−3.4 to 8.8)	−5.4 (−17.9 to 7.6)	−1.2 (−7.7 to 14.4)	3.1 (−7.7 to 14.8)	0.06
Mean systemic arterial pressure (mm Hg)	2.6†‡ (0.8 to 4.2)	−6.9§ (−4.5 to −8.8)	−6.9 (−17.1 to 1.5)	−12.1§# (−8.1 to −16.9)	−6.9† (−0.8 to −16.1)	−7.3† (−0.9 to −14.4)	−1.1 (−8.6 to 8.5)	<0.0001
Mean pulmonary arterial pressure (mm Hg)	−9.8§ (−7.2 to −13.3)	−16.2§ (−11.6 to −21.4)	−14.3§ (−5.6 to −23.1)	−12.1§ (−7.3 to −15.8)	−12.6† (−2.8 to −24.4)	−18.3§ (−13.3 to −21.8)	−10.0 (−22.2 to 2.0)	0.241
Cardiac index (l/min per m^2)	6.0† (2.6 to 9.4)	13.2§ (10.0 to 17.1)	9.3† (1.8 to 18.7)	18.4§ (9.8 to 25.1)	9.4 (−4.8 to 15.4)	7.5 (−4.0 to 20.7)	18.8† (3.3 to 36.7)	0.142
Systemic vascular resistance index (dynes/cm^{-5}/m^2)	−1.2 (−4.3 to 2.3)	−14.3§¶ (−11.0 to −18.2)	−14.8§ (−7.1 to −28.0)	−26.4¶§ (−17.5 to −29.9)	−11.5 (−25.0 to 3.1)	−14.0‖ (−0.3 to −22.7)	−12.0 (−25.6 to 2.0)	<0.0001
Pulmonary vascular resistance index (dynes/cm^{-5}/m^2)	−15.5§ (−11.0 to −19.3)	−28.0§¶ (−26.1 to −31.1)	−21.6§ (−10.2 to −32.3)	−26.3§ (−22.8 to −29.2)	−18.6§ (−14.4 to −28.4)	−27.1§ (−14.2 to −39.8)	−26.7§ (−19.9 to −39.8)	0.002
PVR/SVR ratio	−13.8§ (−10.2 to −18.0)	−15.5§ (−11.1 to −21.2)	−6.9 (−24.8 to 15.2)	−0.1 (−8.2 to 4.2)	−9.3 (−26.5 to 14.9)	−16.0§ (−7.1 to −26.1)	−11.5‖ (−2.8 to −33.9)	0.151
Mixed venous oxygen saturation (%)	3.6† (1.7 to 5.8)	8.4§ (4.4 to 13.0)	4.8 (−0.2 to 9.7)	6.1 (−0.8 to 21.2)	0.7 (−6.9 to 12.0)	0.6 (−3.5 to 5.1)	4.6 (−1.1 to 23.2)	0.465
Partial pressure of arterial oxygen (mm Hg)	9.6† (1.6 to 19.0)	8.9‖ (1.2 to 22.9)	2.6 (−11.4 to 22.5)	−2.2 (−17.9 to 13.5)	−3.2 (−12.3 to 12.5)	−3.9 (−11.6 to 9.6)	−1.7 (−10.1 to 4.5)	0.475
Partial pressure of carbon monoxide (mm Hg)	0.6 (−1.1 to 2.1)	2.2 (−1.1 to 5.2)	−3.3‖ (−0.1 to −6.4)	−0.9 (−5.4 to 3.8)	−0.2 (−3.4 to 3.5)	0.0 (−10.0 to 3.1)	−1.7 (−6.2 to 1.0)	0.882

Hemodynamic and gas exchange variables at baseline for the entire patient population (baseline/NO) and for the subgroups (after assignment to different treatments) are presented in this table. *Analysis of variance was used to seek significant intergroup variances. Symbols indicate significant differences for each variable as compared with pre-intervention baseline values: †$p < 0.01$; §$p < 0.001$; ‖$p < 0.05$. ‡Different from all groups except tadalafil 60 mg. #Different from tadalafil 60 mg. ¶Different from NO ($p < 0.05$, Scheffé post-test). Data are presented as the median value (range).

NO = nitric oxide; PVR/SVR = pulmonary to systemic vascular resistance.

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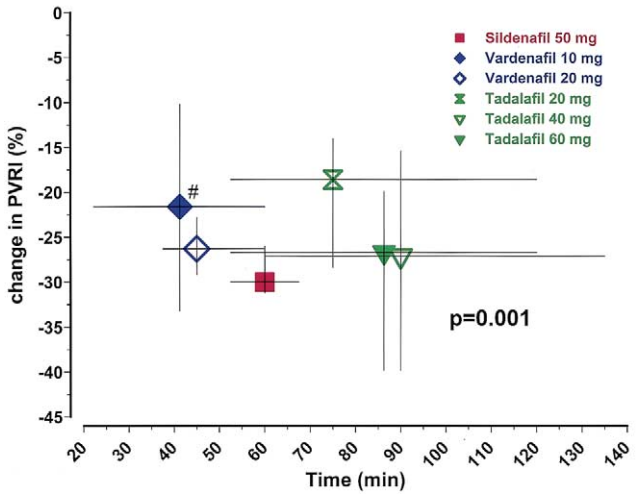

Figure 3. Kinetics of peak pulmonary vasodilatory effects of the different phosphodiesterase-5 (PDE5) inhibitors. Deviations from the pre-intervention baseline values (point estimates of median difference [percentage of baseline = **symbols**], with exact 95% confidence intervals [CIs] [**vertical bars**]) for PVRI over time; also displayed are point estimates of median difference effects (percentage of baseline = **symbols**), with exact 95% CIs (**horizontal bars**). The changes are noted in response to sildenafil (Sil 50 mg = **red square**), vardenafil (Vard 10 mg = **solid blue diamond**; Vard 20 mg = **open blue diamond**), and tadalafil (Tada 20 mg = **green hourglass**; Tada 40 mg = **open green inverted triangle**; Tada 60 mg = **solid green inverted triangle**). The p value indicates significant difference of time to peak pulmonary vasodilation between the different therapeutic agents, as determined by analysis of variance (#different from Tadalafil 40 mg group; $p < 0.05$, Scheffé post-test). There was no difference in the magnitude of response among the treatment groups ($p = 0.185$). PVRI = pulmonary vascular resistance index.

20, 40, and 60 mg of tadalafil. The PVRI was reduced by −18.6% (CI −14.0 to −28.4), −27.1% (CI −14.2 to −39.8), and −26.7 (CI −19.9 to −39.8), respectively (Fig. 3). A peak vasodilatory effect was noted at 75 min (CI 52.5 to 120) after intake of 20 mg, at 90 min (CI 60 to 120) with 40 mg, and at 86.3 min (CI 52.5 to 135) with 60 mg of tadalafil, respectively (Fig. 4). Interestingly, even at the highest dosage of 60 mg tadalafil, selectivity for the pulmonary circulation was reflected by a significant reduction of the PRV/SVR ratio of −11.4% (CI −2.8 to −33.9). As with oral vardenafil, arterial oxygenation remained virtually unchanged with all concentrations of tadalafil employed (Fig. 3). No adverse events were reported after intake of oral tadalafil.

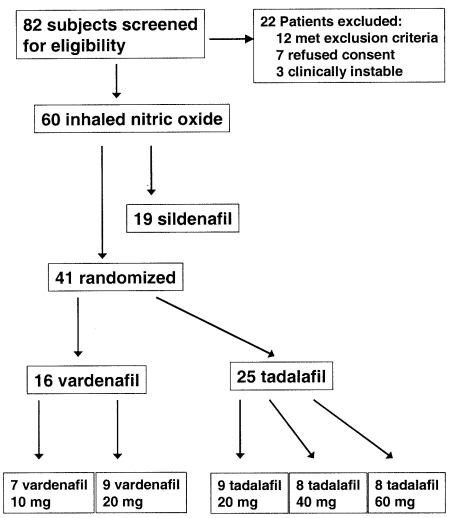

Figure 4. Flow chart of participants. The design of the study and assignment of subjects to the therapeutic interventions are shown in this flow chart.

DISCUSSION

Our data show that despite sharing structural and pharmacologic similarities with sildenafil, vardenafil and tadalafil differ substantially from sildenafil in their effects on the pulmonary circulation.

Lung tissue is a rich source of phosphodiesterases, including PDE5, the major function of which is acceleration of the decay of cyclic guanosine monophosphate (cGMP) (11). Thereby, PDE5 limits the vasodilatory effects of guanylate cyclase stimuli, such as NO and atrial natriuretic peptides (10). Inhaled NO is a widely accepted vasodilatory agent frequently used for the assessment of pulmonary vascular reactivity in patients with chronic pulmonary hypertension (16,17). The rate of so-called responders to this agent (definition for response: fall in mPAP and PVRI of more than 20%; 11 of 60 patients in the current study) is well in line with previously published reports (13,14).

We and others recently showed that the PDE5-selective inhibitor sildenafil causes strong and dose-dependent pulmonary vasodilation (7–9). Notably, even at the high dose of 50 mg sildenafil, the characteristics of preferential pulmonary over systemic vasodilation were found to be preserved in those preceding studies. Based on these results, we employed 50 mg oral sildenafil as a reference agent in the current study. The profile of preferential pulmonary vasodilation was well reproduced, with a maximum PVRI reduction of ~30% and a reduction of PVRI/SVRI ratio of ~15% (Fig. 3). At the time being, our best explanation for the preferential pulmonary vasodilatory effect of sildenafil derives from the assumption of a substantial baseline stimulation of guanylate cyclase in the lung vasculature of patients with chronic pulmonary hypertension, attributable to ongoing pulmonary NO production (18–20) and to circulating natriuretic peptides such as atrial and brain natriuretic peptide (21–23).

Most interestingly, sildenafil not only displays characteristics of pulmonary selectivity but also appears to ameliorate ventilation-perfusion matching ("intrapulmonary selectivity"), thereby improving arterial oxygenation. This has previously been shown in patients with lung fibrosis and secondary pulmonary hypertension, in whom sildenafil simultaneously reduced PVR and improved gas exchange properties (24). In the currently tested patients, ventilation-perfusion matching was not directly assessed, but intrapulmonary selectivity of sildenafil is again indicated by a significant increase of arterial oxygenation. It may be speculated that sildenafil does not act as a nonspecific vasodilator

in this vascular bed, but rather amplifies local cGMP-based vasoregulatory loops, thereby improving rather than disturbing adaptation of perfusion to ventilation distribution.

The newly introduced PDE5 inhibitors vardenafil and tadalafil have both been reported to be equally effective as sildenafil with regard to the treatment of erectile dysfunction (25,26). The main differences described so far are related to the rapidity of the onset of effects and to the duration of effects. Furthermore, several reports indicate a slightly different side-effect profile of vardenafil, tadalafil, and sildenafil (27–29). Currently, most authors explain these differences by the different selectivities of sildenafil, vardenafil, and tadalafil for the various PDE subgroups: sildenafil's 50% inhibitory capacity values for PDE5 (3.5 nmol), PDE6 (37 nmol), PDE1 (281 nmol), and PDE11 A (2,730 nmol) indicate a high selectivity for PDE5, but not an exclusive effect on this PDE (25). Similarly, vardenafil's selectivity for PDE5 over PDE6, PDE1, and PDE11 A is 25-fold, 500-fold, and 1,160-fold, respectively. By contrast, tadalafil is considerably more selective for PDE5 than for PDE6 (187-fold) but has significantly less selectivity for PDE11 A (fivefold selectivity for PDE5 over PDE11 A). In addition, there are major differences in mean half-lives: 3 to 4 h for sildenafil and vardenafil (30) and ~18 h for tadalafil (31).

Our current observations regarding peak hemodynamic effects being reached after ~40 min with vardenafil, ~60 min with sildenafil, and ~90 min with tadalafil are well in agreement with previous reports addressing kinetics of effects in the erectile dysfunction area (31). However, despite sharing many similarities with sildenafil in terms of structure and pharmacologic properties, vardenafil was found to lack pulmonary selectivity in our currently investigated patient cohort. This observation was true for both the 10-mg and 20-mg vardenafil group, as indicated by virtually equivalent reductions of PVR and SVR in response to both dosages. Further studies are needed to address the question of whether this surprisingly different profile, as compared with sildenafil, is due to the minor differences in the PDE inhibition pattern or to PDE's unrelated, currently unknown modes of actions.

Tadalafil is currently approved for the treatment of erectile dysfunction in dosages of 10 mg and 20 mg per tablet (32). However, in studies investigating the effects of tadalafil on cardiac and circulatory function, single doses up to 50 mg have been reported to be safe in terms of an absence of significant systemic vasodilation (33). In preceding pilot studies in PAH patients (data not given), up to 60 mg tadalafil was found to be well tolerated, without major systemic side effects. Based on these data, we decided to use 20, 40, and 60 mg of oral tadalafil in the current investigation in a randomized fashion. Most interestingly, tadalafil displayed selectivity for the pulmonary circulation, even in the 60-mg group. As expected from previous pharmacokinetic data, the peak hemodynamic effects of tadalafil were noted after ~90 min. We have not extended the observation period over 120 min (and in selected cases up to 150 min), as the entire catheterization and vasoreactivity testing procedure exceeded 6 h on average. Pharmacokinetic studies characterizing the maximum duration of PDE5 effects will be subject to forthcoming investigations.

By contrast with inhaled NO and sildenafil, neither vardenafil nor tadalafil improved arterial oxygenation. As multiple inert gas elimination measurements were not performed in the present study, the underlying mechanisms may not be fully resolved. There was no difference in cardiac output increase between sildenafil on the one side and both vardenafil and tadalafil on the other, and it is thus highly unlikely that differences in central venous oxygen saturation are responsible for the differences in arterial oxygenation. Thus, it may be assumed that sildenafil, as mentioned earlier, exerted a favorable impact on ventilation-perfusion matching, but this was not the case for vardenafil and tadalafil. It is presently fully unknown whether the discussed differences in the PDE inhibition pattern or PDE's unrelated modes of actions of sildenafil may be responsible for this interesting difference.

Conclusions. The present study is the first to compare the short-term hemodynamic profiles of three different PDE5 inhibitors—sildenafil, vardenafil and tadalafil—in a well-defined patient collective suffering from chronic PAH. Although vardenafil showed the most rapid onset of effects, this substance lacked selectivity for the pulmonary circulation, which was demonstrated for sildenafil and tadalafil, even at high doses of the latter agent. The pulmonary vasodilatory response to tadalafil appeared to be the most long-lasting, as anticipated from previous studies in the field of erectile dysfunction. By contrast with sildenafil, vardenafil and tadalafil did not improve arterial oxygenation. Obviously, we cannot translate short-term effects into long-term effects, because we know that long-term effects may be significantly more efficacious than short-term effects, such as has been observed with epoprostenol; however, the converse may also occur. These findings thus strongly support the notion that careful evaluation of the pulmonary hemodynamic and gas exchange effects of each new PDE inhibitor focusing on cGMP decay is to be undertaken, despite common classification as PDE5 inhibitors.

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