Sildenafil Inhibits Altitude-induced Hypoxemia and Pulmonary Hypertension

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Exposure to high altitude induces pulmonary hypertension that may lead to life-threatening conditions. In a randomized, double-blind, placebo-controlled study, the effects of oral sildenafil on altitude-induced pulmonary hypertension and gas exchange in normal subjects were examined. Twelve subjects (sildenafil [SIL] n = 6; placebo [PLA] n = 6) were exposed for 6 days at 4,350 m. Treatment (3 × 40 mg/day) was started 6 to 8 hours after arrival from sea level to high altitude and maintained for 6 days. Systolic pulmonary artery pressure (echocardiography) increased at high altitude before treatment (+29% versus sea level, $p < 0.01$), then normalized in SIL (−6% versus sea level, NS) and remained elevated in PLA (+21% versus sea level, $p < 0.05$). Pulmonary acceleration time decreased by 27% in PLA versus 6% in SIL ($p < 0.01$). Cardiac output and systemic blood pressures increased at high altitude then decreased similarly in both groups. Pa_{O_2} was higher and alveolar-arterial difference in O_2 lower in SIL than in PLA at rest and exercise ($p < 0.05$). The altitude-induced decrease in maximal O_2 consumption was smaller in SIL than in PLA ($p < 0.05$). Sildenafil protects against the development of altitude-induced pulmonary hypertension and improves gas exchange, limiting the altitude-induced hypoxemia and decrease in exercise performance.

Keywords: cardiac output; exercise; gas exchange; hypoxia

Exposure to high altitude leads to hypoxemia, which induces several physiologic or pathophysiologic responses in normal humans. Among those, the hypoxic pulmonary vasoconstriction leads to an increase in pulmonary artery pressure (Ppa), which may have adverse consequences. High Ppa has been recognized to be one of the main causing factors of high-altitude pulmonary edema (HAPE), a serious acute condition that has a mortality rate of 44% in untreated patients (1, 2). Moreover, ventilation–perfusion mismatch has been correlated to increasing Ppa at high altitude, probably by the development of interstitial and perivascular edema, aggravating the hypoxemia (3). In the early phase of exposure to high altitude, signs of acute mountain sickness (AMS) may develop and have been shown to be worsened by aggravating hypoxemia, although the precise mechanisms of AMS have not been elucidated (4). Altitude hypoxia induces a dramatic decrease in physical aerobic performance, as assessed by the maximal O_2 consumption (4). Several steps in the oxygen transport from the ambient air to the cell can be responsible for the limitation in aerobic performance, among which O_2 transfer within the lungs, cardiac output, and tissue diffusion of O_2 may play an important role (5). Altogether, acute altitude-induced hypoxemia leads to an adverse condition where, at least, overall well-being is altered by AMS and reduction in performance, and life is possibly threatened by the development of high Ppa and HAPE. Any treatment or condition that limits the increase in Ppa and reduces the altitude-induced hypoxemia may be beneficial for humans acutely exposed to high altitude.

The treatment currently recommended for HAPE is rapid reoxygenation combined with a calcium-channel blocker (6, 7). The partial efficacy of this treatment and its systemic adverse effects (hypotension), however, limit its use. Inhalation of nitric oxide has also been used, and has demonstrated its efficacy in this condition, but its use in the field is difficult (8). L-Arginine supplementation has also been found to improve gas exchange at high altitude, further suggesting that the nitric oxide synthase (NOS)–nitric oxide system is involved in the hemodynamic changes in the lungs (9). Recently, sildenafil, a selective inhibitor of type-5 phosphodiesterase, has been shown to lower Ppa and was used successfully in the treatment of severe primary or secondary pulmonary hypertension (10–18). In most cases, sildenafil was not given as a unique treatment but associated with inhaled nitric oxide, intravenous epoprostenol, or inhaled iloprost. Only two studies have evaluated the effect of oral sildenafil (50–100 mg, single dose) in normal subjects exposed to acute hypoxia, in a randomized double-blind study (13, 14): hypoxia-induced increase in Ppa was almost abolished with sildenafil and no important effect on systemic circulation was observed. Deleterious effects of high altitude occur after several hours of exposure, however, and no double-blind controlled study has evaluated the effect of sildenafil on the adverse effects of prolonged altitude exposure in normal humans. Sildenafil has also been reported to increase arterial Po_2 (17) and improve physical performance (14, 15, 18) in various cases of severe pulmonary hypertension, but no study has explored the effect of a several-day treatment by sildenafil on these variables in normal subjects exposed to altitude conditions.

The objective of the present study was to explore the effects of oral sildenafil in normal subjects exposed for 6 days to an altitude of 4,350 m, in a randomized double-blind placebo-controlled manner. The hypothesis was that sildenafil would reduce the hypoxia-induced increase in Ppa and ameliorate the pulmonary hemodynamics and gas exchange conditions, increasing the arterial Po_2, alleviating the clinical symptoms, and limiting the reduction in aerobic performance. Some of the results of this study have been previously reported in the form of abstracts (19, 20).

METHODS

Subjects

Twelve male normal subjects (aged 29 ± 6 years) participated in the study. Anthropometric characteristics were as follows: height 181 ± 6 cm, body weight 79 ± 11 kg. They were healthy, unacclimatized to

(*Received in original form June 24, 2004; accepted in final form October 24, 2004*)

Supported by a grant from Pfizer S. A. France.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171. pp 275–281, 2005
Originally Published in Press as DOI: 10.1164/rccm.200406-804OC on October 29, 2004
Internet address: www.atsjournals.org

altitude, moderately trained subjects, with no particular medical history, and no previous episode of severe altitude sickness. They gave their informed consent to participate in the study, which was approved by the Ethics Committee of Necker Hospital, Paris.

Procedure

The following evaluations were performed during the 11-day experimental period from Days −3 to 8 (Figure 1). Sea-level Petit-Ebersviller measurements were performed in Bobigny (60-m altitude); then subjects were transported to Chamonix (1,035 m) for 1 day and to Observatoire Vallot (4,350 m) by helicopter (21). Additional details on the methods and equipment used are provided in an online data supplement.

Clinical Questionnaire and Systemic Hemodynamic Parameters

A daily questionnaire was filled three times a day (8:00–9:00 A.M., 1:00–2:00 P.M., and 6:00–7:00 P.M.), including the Lake Louise consensus questionnaire, to evaluate the symptoms of AMS (22), and some specific questions related to the possible adverse effects of sildenafil (headache, muscle pain, dyspepsia, flushing). A score of sleep disturbances was evaluated in the morning (from 0, normal sleep, to 3, very poor sleep). Ataxia and dyspnea were also evaluated (from 0 to 3) according to the Lake Louise consensus (22). At the same moment, heart rate and O_2 saturation were evaluated by pulse oximetry (Ohmeda Biox 3740; Medical Supplies & Equipment Co.), and systemic systolic and diastolic blood pressure were evaluated in a supine position by sphygmomanometry.

Echocardiography

Subjects were examined by two observers on left decubitus or supine position, using a portable ultrasound system equipped with a 2.5-MHz probe (Cypress; Acuson/Siemens, Erlangen, Germany). Complete two-dimensional, time movement (TM)-echography and Doppler parameters for left cardiac function were recorded following classical procedures. Systolic pulmonary arterial pressure (sPpa) was calculated from the tricuspid gradient. The acceleration time of the pulmonary flow was taken as an index of pulmonary vascular resistance (23). At each examination, all parameters were measured at least three consecutive times and the subjects were examined three times on baseline on Days −3, −2, and −1; five times during the altitude exposure on Days 1, 2, 3, 5, and 6; and at recovery on Day 8 (sea level postexposure). Baseline normoxic values (sea level preexposure) were taken as the mean of values obtained at Days −2 and −1. Values at Days −2 and −3 were pooled and considered as initial values after 1 to 2 days of treatment; values at Days 5 and 6 were pooled and considered as final values after 4 to 5 days of treatment.

Maximal Exercise Test

Maximal aerobic performance was evaluated through a step-by-step progressive exercise test performed on a bicycle ergometer (Monark, Vansbro, Sweden) until exhaustion, at Days −3, 2, 5, and 8. ECG was monitored continuously (Life Scope 6; Nihon Kohden, Tokyo, Japan) and arterial O_2 saturation was obtained by ear oximetry (Ohmeda Biox 3740) on an ear lobe previously vasodilated by a capsaicin cream. Pa_{O_2}, Pa_{CO_2}, and pHa were measured by means of a blood gas apparatus (Model 220; Bayer Diagnostics, Leverkusen, Germany) from an arterialized blood sample. Cardiac output and an intrathoracic fluid index were measured continuously by transthoracic impedencemetry (Physioflow PF-05 lab1; Manatec, France), from electrodes placed on the base of the neck and on the medial line under the xyphoid (24, 25).

Color Vision Test

Modifications in color vision in the red-green axis have been observed at high altitude and correlated with severity of AMS (26). Transient, fully reversible, impairment of color discrimination has also been noticed as a side effect of treatment with sildenafil (27). Color vision was evaluated in the present study, using the Lanthony 15-Hue Desaturated Test at Days −1, 3, 5, and 8. A color confusion index was calculated. The greater the number and importance of mistakes, the higher the color confusion index value (28).

Cyclic Guanosine Monophosphate and Sildenafil

Blood sampling was performed at rest from an antecubital vein at Days −1, 3, 6, and 8 to measure cyclic guanosine monophosphate (cGMP), sildenafil concentration, and hematocrit, 1 to 2 hours after oral administration. cGMP was measured by radioimmunoassay (cGMP RIA kit; Immunotech, Marseille, France). Sildenafil plus desmethylsildenafil concentration was measured by a liquid chromatography–tandem mass spectrometry method (29). Hematocrit was measured immediately by means of a microcentrifuge (Sigma 112, Osterode-am-Harz, Germany).

Treatment

Subjects were randomly assigned to a placebo- (PLA, n = 6) or sildenafil- (SIL, n = 6) treated group. Treatment (40 mg) started on Day 1 at 4,350 m at 8:00 P.M., 6 to 8 hours after arrival at Observatoire Vallot. Treatment then was taken (40 mg orally) three times a day (8:00 A.M., 2:00 P.M., and 8:00 P.M.) from Days 2 to 6. Sildenafil and placebo were provided by Pfizer.

Statistics

Values are presented as mean ± SD. A Mann-Whitney *U* test was performed to compare the two groups and analyze the effects of treatment in each condition (symbol #). Values obtained at high altitude after treatment (from Days 2–6) have also been compacted and analyzed with a Mann-Whitney *U* test to evaluate the overall effect of treatment at high altitude (symbol +). A Wilcoxon paired test was used between each condition and sea level to evaluate the effect of altitude exposure on each group (symbol *). Values of the two groups were pooled at Day 1 to evaluate, by a Wilcoxon paired test, the overall effect of hypoxia before treatment (symbol §). The symbols #, +, *, and § appear in tables and figures. A p value less than 0.05 was considered as significant.

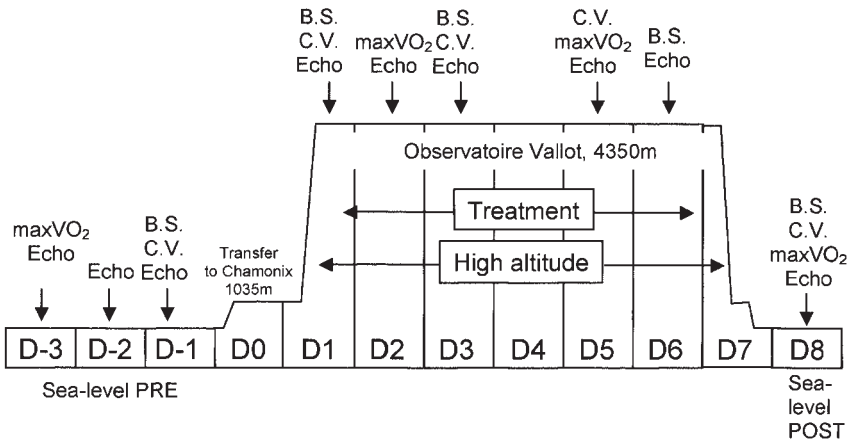

Figure 1. Schematic diagram of the procedure. The whole study lasted 12 days, from Day −3 to Day 8. Vo_2max = maximal exercise test; Echo = echocardiographic examination; B.S. = blood sampling; C.V. = color vision test; D = day.

RESULTS

Tolerance

Exposure to high altitude and treatment were well tolerated by all subjects. Subject 4 (PLA) showed some low values of Sa_{O_2} (under 60%) at various occasions at high altitude, without any abnormal clinical symptoms, except moderate headache and fatigue. His cardiac and lung auscultation and neurologic examination were strictly normal. He was maintained in the study and given inhaled O_2 (1 L/minute) for 4 hours during sleep from Days 4 to 5, at distance from any test involved in the study. It is noteworthy that the significance of all results presented is not modified if Subject 4 is excluded from the study. Frequency of expected adverse events was not different between the two groups: one SIL and two PLA subjects suffered from dyspepsia; three SIL and one PLA subjects showed flushing of the face; muscle pain was noticed by two SIL and three PLA subjects. All these complaints were occasional. Sildenafil treatment had no effect on color vision. Acute exposure to high altitude (Day 1) was associated with a slight alteration in color vision score in both groups (Day 1 versus sea level pre, $p < 0.05$); then values returned to normal levels (Table 1).

Clinical Evaluation

Subjects suffered from AMS until Day 4; then the Lake Louise score was not significantly different from normoxic baseline. Lake Louise score tended to be lower in SIL group at Day 1 ($p = 0.054$) before treatment and thereafter at Days 5 and 6, but the difference did not reach significance. Among clinical symptoms, gastrointestinal symptoms and dizziness were similar in the two groups (results not shown). Headache, which is both a symptom of AMS and a possible adverse effect of sildenafil, was not significantly modified by the treatment. Fatigue score seemed slightly higher in PLA than in SIL, even after the return to normoxia, but the differences did not reach significance. Sleep was significantly altered during the first 2 nights at high altitude, with no effect of sildenafil. Only scarce cases of ataxia or dyspnea scores different from zero were noticed, with no effect of sildenafil (results not shown) (*see* Table 1).

Systemic Hemodynamic Parameters

Mean daily heart rate increased in both groups at high altitude (Figure 2A). Heart rate in SIL was significantly lower than in PLA from Days 2 to 6 ($p < 0.01$). Systolic and diastolic systemic arterial pressure increased transiently from Days 1 to 4, but was not modified by the treatment (Figure 2B). Sa_{O_2} decreased at high altitude and was clearly higher in SIL than in PLA from Days 2 to 6 ($p < 0.001$ [Figure 2C]).

Echocardiography

As expected, sPpa increased with acute exposure to high altitude (Day 1) before treatment (Figure 3). After 1 to 2 days of treatment (Days 2–3), sPpa was significantly lower in SIL than in PLA ($p = 0.025$). After 4 to 5 days of treatment (Days 5–6), sPpa was lower in SIL than in PLA ($p < 0.05$). At Days 5 to 6, when compared with sea level, sPpa increased by 21% in PLA ($p = 0.03$) and decreased by 6% in SIL (not significant [NS]). Pulmonary acceleration time decreased in both groups at Day 1 (before treatment) and returned to basal normoxic values in SIL but stayed low in PLA at high altitude ($p = 0.001$, PLA versus SIL). All other echocardiographic parameters, especially those exploring left ventricular function, were strictly normal and similar in the two groups (Table 2). The diameter of the left ventricle slightly decreased in diastole and systole, leading to a transient increase in shortening fraction. Left atrium diameter and mitral early to late peak velocity ratio (E/A) progressively decreased with exposure to high altitude. Cardiac output measured by Doppler increased from sea level at Day 1 and Days 2 to 3 in both groups ($p < 0.05$), then returned to basal values, with no significant effect of treatment.

Aerobic Performance and Gas Exchange

As expected, maximal O_2 consumption decreased at high altitude (Day 2) and slightly (NS) increased with acclimatization (from Days 2–5) (Table 3 and Figure 2). The altitude-induced mean decrement in maximal O_2 consumption was smaller in SIL (−29% at Day 2, −25% at Day 5) than in PLA (−39% at Day 2, −35% at Day 5) ($p < 0.01$, SIL versus PLA, Figure 2D). At high altitude, Pa_{O_2} was higher in SIL than in PLA, either at rest ($p < 0.05$ at Days 5–6) or at exercise ($p < 0.01$ at Days 5–6). Alveolar–arterial difference in Po_2 at rest and at exercise decreased in both groups at high altitude, but the decrease was lower in PLA than in SIL ($p < 0.001$ at rest, $p < 0.05$ at exercise). On return to sea level, at rest, Pa_{O_2} was lower and alveolar–arterial difference in Po_2 higher than in basal level values. As expected, Pa_{CO_2} decreased and pHa increased at high altitude (hyperventilation-induced hypocapnia and alkalosis); no difference was found between the two groups. Cardiac output at rest, measured by transthoracic impedencemetry, transiently increased at high altitude ($p < 0.05$) and was similar in the two groups. At ventilatory threshold, cardiac output was modified, neither by altitude nor by treatment. Heart rate at ventilatory

TABLE 1. CLINICAL SYMPTOMS AND COLOR VISION

		Sea Level Pre	D1	D2	D3	D5	Sea Level Post
Lake Louise score, a.u.	PLA	0.1 ± 0.1	2.8 ± 1.6*	1.8 ± 1.4*	1.3 ± 0.8*	0.9 ± 1.1	0.3 ± 0.4
	SIL	0.1 ± 0.1	1.0 ± 0.7*,§§	1.9 ± 1.3*	1.3 ± 0.5*	0.3 ± 0.3	0.0 ± 0.0
Headache score, a.u.	PLA	0.0 ± 0.1	1.2 ± 0.6*	0.8 ± 0.5*	0.7 ± 0.4*	0.3 ± 0.4	0.0 ± 0.0
	SIL	0.0 ± 0.1	0.7 ± 0.5*,§§	1.1 ± 0.5*	0.9 ± 0.2*	0.2 ± 0.3	0.0 ± 0.0
Fatigue score, a.u.	PLA	0.1 ± 0.1	0.6 ± 0.5*	0.6 ± 0.7*	0.6 ± 0.5*	0.4 ± 0.6	0.3 ± 0.4
	SIL	0.0 ± 0.1	0.2 ± 0.3§	0.4 ± 0.5	—	0.1 ± 0.1	0.0 ± 0.0
Sleep score, a.u.	PLA	0.6 ± 0.5	2.0 ± 1.1*	1.0 ± 0.9	0.7 ± 1.0	0.4 ± 0.5	0.5 ± 0.8
	SIL	0.3 ± 0.4	1.6 ± 0.5*,§	0.9 ± 0.9	0.5 ± 0.8	0.6 ± 1.2	0.3 ± 0.8
Color confusion index, a.u.	PLA	1.21 ± 0.18	1.51 ± 0.39*	—	1.26 ± 0.27	1.26 ± 0.24	1.27 ± 0.24
	SIL	1.28 ± 0.32	1.51 ± 0.39*	—	1.31 ± 0.13	1.34 ± 0.21	1.22 ± 0.46

Definition of abbreviations: a.u. = arbitrary units; D1 to D5 = first to fifth day at 4,350 m; PLA = placebo; sea level post = return to normoxic conditions; sea level pre = basal normoxic condition; SIL = sildenafil.

* $p < 0.05$ versus sea level pre.

§ $p < 0.05$, D1 versus sea level pre for the whole group (placebo + sildenafil).

§§ $p < 0.01$, D1 versus sea level pre for the whole group (placebo + sildenafil).

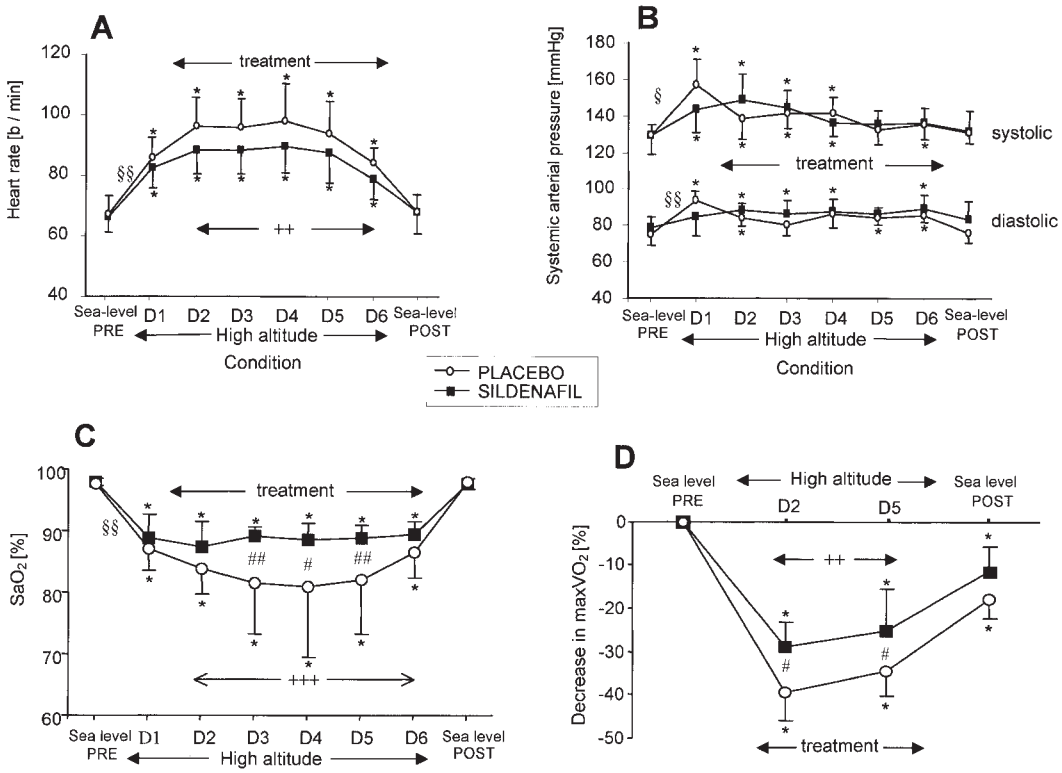

Figure 2. Systemic hemodynamic parameters and exercise performance. *$p < 0.05$ versus sea level pre; #$p < 0.05$, ##$p < 0.01$ sildenafil versus placebo; §$p < 0.05$, §§$p < 0.01$ D1 versus sea level pre for the whole group; ++$p < 0.01$, +++$p < 0.001$ sildenafil versus placebo for pooled high altitude with treatment values.

threshold and at maximal exercise decreased at high altitude in both groups. After the return to sea level, maximal heart rate remained lower than before the hypoxic exposure. The intrathoracic fluid index increased in both groups at high altitude (Day 2), then decreased only in SIL and stayed elevated in PLA ($p < 0.05$ SIL versus PLA).

Acclimatization to High Altitude

The physiologic parameters, characteristics of acclimatization to high altitude (Pa_{CO_2}, pHa, heart rate), were modified from Days 2 to 5 as expected. No difference was found between SIL and PLA. Pa_{CO_2} at rest and at the ventilatory threshold decreased from Days 2 to 5 (SIL: $p < 0.03$, PLA: NS); pHa at the ventilatory threshold increased (SIL: $p < 0.03$, PLA: NS). Heart rate at the ventilatory threshold and at maximal exercise decreased from Days 2 to 5 ($p < 0.05$ for PLA and SIL). Sildenafil treatment had no effect on these parameters (Table 3).

Serum cGMP, Serum Sildenafil, and Hematocrit

Serum cGMP increased from sea level at Day 1 before treatment, then by 165% ($p < 0.05$) and 42% (NS) at Day 6 in SIL and PLA, respectively ($p < 0.05$ SIL versus PLA) (Figure 4). Serum sildenafil plus desmethylsildenafil concentration was below detectable limit at Day −1 and Day 1 and increased in the SIL group to 10.3 ± 6.7 ng/mL and to 254 ± 146.3 ng/mL at Day 2 (cumulative dose of sildenafil ingested, 36 hours after first pill: 160 mg) and Day 6 (cumulative dose of sildenafil ingested, 108 hours after first pill: 520 mg), respectively. Hematocrit was not modified by the treatment. In the whole group, mean hematocrit increased from 43.2 ± 2.6% at sea level (Day −1) to 46.1 ± 1.8 at Day 3 ($p < 0.001$); 45.3 ± 1.3 at Day 6 ($p < 0.01$); and was still high at Day 8 (45.9 ± 2, $p < 0.001$).

DISCUSSION

This is the first double-blind controlled study evidencing the beneficial effect of oral sildenafil (3 × 40 mg/day for 6 days) in

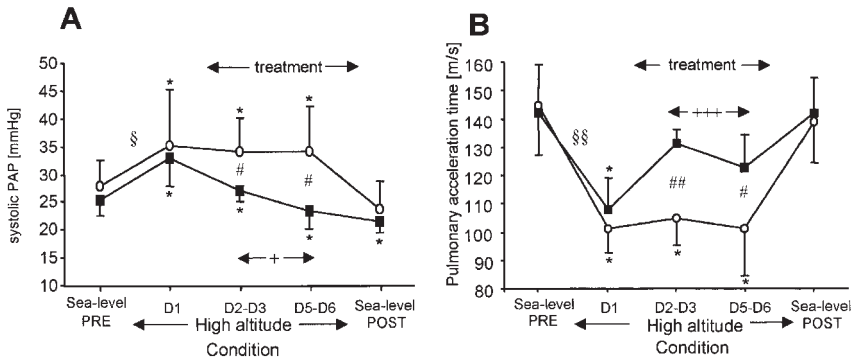

Figure 3. Echocardiographic evaluation of pulmonary hemodynamics. PAP: pulmonary artery pressure. *$p < 0.05$ versus sea level pre; #$p < 0.05$, ##$p < 0.01$ sildenafil (*filled squares*) versus placebo (*open circles*); §$p < 0.05$, §§$p < 0.01$ D1 versus sea level pre for the whole group; +$p < 0.05$, +++$p < 0.001$ sildenafil versus placebo for pooled high altitude with treatment values.

TABLE 2. ECHOCARDIOGRAPHIC PARAMETERS

		Sea level pre	D1	D2–D3	D5–D6	Sea level post
Left ventricle diameter in diastole, mm	PLA	52.2 ± 3.8	52.8 ± 5.7	49.1 ± 4.0*	49.4 ± 3.8*	51.4 ± 4.2
	SIL	50.9 ± 2.4	48.1 ± 1.5*,§§	47.4 ± 2.1*	48.9 ± 1.6*	50.5 ± 0.8
Left ventricle diameter in systole, mm	PLA	30.7 ± 4.8	32.6 ± 3.8	27.5 ± 3.8*	28.2 ± 2.5	30.8 ± 3.9
	SIL	29.6 ± 1.9	28.9 ± 1.8	26.3 ± 2.8*	28.4 ± 2.4	30.7 ± 2.2
Shortening fraction, %	PLA	40.6 ± 4.6	39.0 ± 3.6	44.0 ± 4.2*	43.1 ± 3.1	40.0 ± 5.2
	SIL	40.5 ± 3.6	40.1 ± 4.3	46.0 ± 5.2*	42.3 ± 3.9	39.8 ± 4.6
Mitral E/A wave ratio	PLA	2.0 ± 0.4	1.4 ± 0.3*,§	1.4 ± 0.2*	1.4 ± 0.1*	1.8 ± 0.4
	SIL	1.8 ± 0.3	1.6 ± 0.3	1.3 ± 0.2*	1.4 ± 0.2*	1.5 ± 0.4
Left atrium diameter, mm	PLA	36.1 ± 3.6	33.2 ± 3.4*,§	33.4 ± 3.4*	32.4 ± 5.0*	32.2 ± 4.9
	SIL	36.7 ± 3.4	35.0 ± 3.8	31.4 ± 5.2*	32.3 ± 3.9*	30.1 ± 4.5*
Cardiac output, L/min	PLA	5.09 ± 0.55	6.45 ± 1.30	6.86 ± 1.97*	6.16 ± 1.38	5.10 ± 0.96
	SIL	4.75 ± 0.59	6.15 ± 0.77§	6.05 ± 0.69	5.19 ± 0.50	4.42 ± 0.65

Definition of abbreviations: D1 to D6 = first to sixth day at 4,350 m; PLA = placebo; sea level post = return to normoxic conditions; sea level pre = basal normoxic condition; SIL = sildenafil.

* $p < 0.05$ versus sea level.

§ $p < 0.05$, D1 versus sea level pre for the whole group (placebo + sildenafil).

§§ $p < 0.01$, D1 versus sea level pre for the whole group (placebo + sildenafil).

normal subjects exposed to prolonged high-altitude hypoxia. High-altitude hypoxia induces a specific pulmonary vasoconstriction and an acute sympathetic activation. Hence, after acute exposure to 4,350 m all the subjects exhibited a decrease in Sa_{O_2} and the expected changes in cardiac hemodynamics with an increase in heart rate, cardiac output, and systemic and pulmonary pressures. Acclimatization then occurred with a decrease in heart rate and an increase in ventilation.

The main observed effect of sildenafil was a suppression of the hypoxia-induced increase in Ppa, associated with an increase in blood oxygenation. No adverse effect, such as systemic hypotension or alteration in color vision, was noticed. Only minor adverse effects (muscle pain, dyspepsia) have been recorded. Lastly, sildenafil hampered the hypoxia-induced decrease in exercise performance and did not interfere with acclimatization.

The effect of sildenafil on Ppa, already observed in humans suffering from primary or secondary pulmonary hypertension (10–13, 15–18), has been found in normal subjects exposed to altitude-induced hypoxia. No adjunct treatment, such as nitric oxide or epoprostenol, has been used in the present study sug-

TABLE 3. EXERCISE AND GAS EXCHANGE DATA

			Sea Level Pre	D2	D5	Sea Level Post
Pa_{O_2}, mm Hg	Rest	PLA	95.8 ± 5.3	47.7 ± 9.1*	46.0 ± 7.2*	90.1 ± 5.1*
		SIL	94.7 ± 4.5	49.4 ± 4.1*	52.2 ± 2.6*,#	88.3 ± 8.7*
	Smax exercise	PLA	89.1 ± 7.0	39.9 ± 3.9*	39.5 ± 3.0*	90.5 ± 8.9*
		SIL	91.4 ± 4.1	41.8 ± 2.6*	44.8 ± 0.9*,##	98.2 ± 3.2*
P_A-Pa_{O_2}, mm Hg	Rest	PLA	17.4 ± 5.4	12.0 ± 2.8	14.4 ± 5.2	30.4 ± 5.4*
		SIL	18.2 ± 3.2	8.6 ± 2.0*,#	8.4 ± 2.9*,#	30.8 ± 5.1*
	Smax exercise	PLA	23.2 ± 5.2	23.8 ± 4.3	27.8 ± 6.0	32.1 ± 5.2
		SIL	22.9 ± 5.3	21.0 ± 3.8	22.0 ± 2.7#	23.2 ± 3.8#
Pa_{CO_2}, mm Hg	Rest	PLA	37.8 ± 2.1	26.5 ± 2.8*	26.3 ± 3.0*	35.3 ± 1.9
		SIL	38.2 ± 3.5	28.4 ± 1.7*	24.6 ± 1.6*	33.3 ± 2.5*
	Smax exercise	PLA	37.7 ± 3.4	26.3 ± 2.4*	24.2 ± 1.2*	33.5 ± 3.5*
		SIL	38.7 ± 2.3	26.6 ± 1.6*	24.0 ± 0.9*	32.4 ± 1.9*
pHa	Rest	PLA	7.44 ± 0.02	7.50 ± 0.04*	7.49 ± 0.01*	7.44 ± 0.02
		SIL	7.43 ± 0.01	7.49 ± 0.02*	7.52 ± 0.02*	7.44 ± 0.02
	Smax exercise	PLA	7.35 ± 0.01	7.43 ± 0.04*	7.46 ± 0.04*	7.37 ± 0.03
		SIL	7.37 ± 0.01	7.43 ± 0.04*	7.47 ± 0.03*	7.36 ± 0.04
Cardiac output, L/min	Rest	PLA	4.7 ± 0.9	7.7 ± 2.0*	6.3 ± 1.8*	5.4 ± 0.8
		SIL	5.4 ± 0.8	7.1 ± 1.4*	6.7 ± 1.4*	5.2 ± 0.8
	Smax exercise	PLA	15.6 ± 1.8	17.5 ± 2.0	14.6 ± 2.7	15.0 ± 1.3
		SIL	15.6 ± 2.4	17.3 ± 4.6	14.9 ± 4.1	16.0 ± 1.9
Heart rate, b/min	Smax exercise	PLA	173 ± 12	170 ± 15*	158 ± 12*	167 ± 15
		SIL	171 ± 11	163 ± 11*	151 ± 11*	161 ± 6
	Max exercise	PLA	192 ± 14	184 ± 12*	175 ± 13*	187 ± 15*
		SIL	194 ± 6	181 ± 9*	173 ± 8*	187 ± 6*
ΔIFT index, %	Rest	PLA	0	17.7 ± 9.1*	22.5 ± 17.1*	2.8 ± 16.3
		SIL	0	15.5 ± 11.5*	2.8 ± 11.3†	−3.7 ± 14.1

Definition of abbreviations: ΔIFT index = variation of intrathoracic fluid from sea level pre; D2, D5 = second and fifth day at 4,350 m; Pa_{O_2}, Pa_{CO_2}, pHa = arterialized blood gases; P_A-Pa_{O_2} = alveolar-arterial difference in P_{O_2}; PLA = placebo; sea level post = return to normoxic conditions; sea level pre = basal normoxic condition; SIL = sildenafil; Smax exercise = ventilatory threshold.

* $p < 0.05$ versus sea level pre.

# $p < 0.05$, SIL versus PLA.

$p < 0.01$, SIL versus PLA.

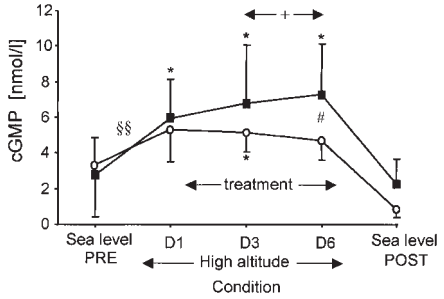

Figure 4. Serum cGMP. *$p < 0.05$ versus sea level pre; #$p < 0.05$ sildenafil (*filled squares*) versus placebo (*open circles*); §§$p < 0.05$ D1 versus sea level pre for the whole group. +$p < 0.05$ sildenafil versus placebo for pooled high altitude with treatment values.

gesting that the inhibition of PDE5 by itself can have a vasodilatory effect on pulmonary circulation, probably by increasing the availability of cGMP within the pulmonary vasculature (13). In the present study, plasma level of cGMP increased with sildenafil and was associated with a decrease in Ppa without significant decrease in cardiac output. This is in accordance with a direct effect of cGMP on pulmonary vascular smooth muscle cell rather than an effect on cardiac function. Increase in Ppa at high altitude was also confirmed by the decrease in pulmonary acceleration time, as shown at Day 1, which has been considered as an index of pulmonary hypertension (23). Sildenafil restored this index to basal values as soon as in Days 2 to 3, whereas it stayed low in PLA during the whole stay at high altitude. Although present at Days 2 to 3, the overall hemodynamic effects of sildenafil on pulmonary circulation were more marked on Days 5 to 6 when the plasma concentration of the drug was increased 25-fold.

All parameters of left ventricular systolic function (Table 3) were not modified by the treatment, confirming that sildenafil has no effect on cardiac contractility and left ventricular afterload. Furthermore, sildenafil has been shown to have no or modest effects on systemic vasculature after a single dose of less than 100 mg (30). In the present study, sildenafil had no significant effect on systemic circulation because systemic arterial pressure and cardiac output transiently raised then returned to baseline values similarly in the two groups. Lastly, despite a lower heart rate in the treated group, cardiac output did not significantly change suggesting a lack of negative effect of sildenafil on cardiac inotropism. The lowering effect on heart rate may be indirect, by increasing Sa_{O_2}, or direct through a negative chronotropic effect by increased cGMP (31). The decrease in E/A ratio, an index of left ventricular relaxation, observed in the two groups with exposure to high altitude was probably caused by a decrease in left ventricular filling as shown by the associated decrease in left arterial and systolic and diastolic left ventricular diameters. This phenomenon is probably linked to a lower venous return caused by an altitude-induced decrease in plasma volume previously observed in the same conditions (32). In the present study, plasma volume was not measured but indirect evidence can be drawn from the acute increase in hematocrit from 43 to 46%.

The increase in Pa_{O_2} and Sa_{O_2} observed at rest and exercise, associated with a lower alveolar-arterial O_2 difference and an unchanged Pa_{CO_2}, is particularly interesting because it evidences a better oxygen transfer within the lungs, probably because of a better ventilation-perfusion adequacy or a decrease in lung diffusion impairment. Hypoxia-induced increase in Ppa has been shown to be one of the main mechanisms responsible for the development of the alveolar edema in HAPE (1, 2). Even in normal subjects, ventilation-perfusion mismatch has been shown to increase at high altitude with increasing Ppa, either by a nonuniform pulmonary vasoconstriction or by increasing the interstitial and perivascular edema (3). By lowering Ppa, sildenafil could reduce the pulmonary capillary leak and limit the development of interstitial edema. The observed decrease in intrapulmonary fluid index with sildenafil is in favor of this hypothesis. This amelioration of blood oxygenation, in turn, can have a beneficial effect on pulmonary vasculature, enhancing the effect of the drug. On return to sea level, all parameters tended to return to sea level basal values. In both groups at rest, however, Pa_{O_2} was lower and the alveolar-arterial difference in P_{O_2} (A) higher than in basal conditions. This may not be linked to hypoventilation because P_{CO_2} was not elevated. It could be related to a slight persistent interstitial edema or ventilation-perfusion mismatch after altitude exposure.

No significant adverse event was evidenced and the treatment was well tolerated. The dose used (120 mg/day) is comparable with what is now commonly used (100–150 mg) in prolonged treatment of pulmonary hypertension (15, 18). No clear effect has been shown on the clinical signs of AMS, even if a tendency to lower the Lake Louise score was shown after 4 days of altitude exposure. Headache being a possible adverse effect of sildenafil, however, its probable increase in treated subjects may have jeopardize a possible beneficial effect on overall AMS score because of a better blood oxygenation. The indication of sildenafil in the treatment of HAPE has not been addressed in the present study because none of the subjects suffered from this severe condition. The beneficial effect on Ppa strongly suggests, however, that this drug could be highly effective in this condition, without adverse systemic effect, contrary to the classically proposed calcium blockers (6, 7).

The beneficial effects of sildenafil on pulmonary circulation and gas exchange have been sufficient to limit the altitude-induced decrease in maximal aerobic performance. To the authors' knowledge, no pharmacologic treatment has been previously shown to reduce this disabilitating effect of prolonged high-altitude exposure. Sildenafil treatment did not interfere with the usual physiologic characteristics of acclimatization to high altitude. The decrease in Pa_{CO_2} and increase in pHa indicating a process of ventilatory acclimatization and the decrease in maximal heart rate, attributable to a progressive desensitization of cardiac β-receptors (33), observed in the present study from Days 2 to 5, were not modified by the treatment. Similarly, an acute altitude-induced decrease in plasma volume probably accounts for the slight increase in hematocrit, without any significant effect of treatment.

Sildenafil, by its vasodilating effect on pulmonary circulation, (*1*) suppresses the altitude-induced pulmonary hypertension; (*2*) ameliorates pulmonary hemodynamics and gas exchange, limiting the altitude-induced hypoxemia and favoring cardiovascular adaptation to exercise; and (*3*) does not alter the normal physiologic processes of acclimatization. Further studies will determine if sildenafil can replace calcium blockers in the treatment of HAPE.

Conflict of Interest Statement: J.-P.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; I.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.J.-L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.B. does not have a financial relationship with a commercial entity that has an interest

in the subject of this manuscript; J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors are grateful to Eric Jaudinot and Véronique Chauveau (Pfizer France), Ghazwan Butrous (Pfizer Sandwich) for supporting the project and providing sildenafil citrate, and Richard Hucker (Pfizer Sandwich) for the dosage of sildenafil. The authors thank all the volunteers for their participation in this study at Observatoire Vallot, the Laboratoire de Glaciologie et Géophysique de l'Environnement for the use of the facilities, Acuson/Siemens for providing the echocardiographic device (Cypress), and Bayer Diagnostics for providing the blood gases analyzer.

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