

Sildenafil Increased Exercise Capacity during Hypoxia at Low Altitudes and at Mount Everest Base Camp

A Randomized, Double-Blind, Placebo-Controlled Crossover Trial

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Background: Alveolar hypoxia causes pulmonary hypertension and enhanced right ventricular afterload, which may impair exercise tolerance. The phosphodiesterase-5 inhibitor sildenafil has been reported to cause pulmonary vasodilatation.

Objective: To investigate the effects of sildenafil on exercise capacity under conditions of hypoxic pulmonary hypertension.

Design: Randomized, double-blind, placebo-controlled crossover study.

Setting: University Hospital Giessen, Giessen, Germany, and the base camp on Mount Everest.

Participants: 14 healthy mountaineers and trekkers.

Measurements: Systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximum exercise capacity on cycle ergometry 1) while breathing a hypoxic gas mixture with 10% fraction of inspired oxygen at low altitude (Giessen) and 2) at high altitude (the Mount Everest base camp).

Intervention: Oral sildenafil, 50 mg, or placebo.

Results: At low altitude, acute hypoxia reduced arterial oxygen saturation to 72.0% (95% CI, 66.5% to 77.5%) at rest and 60.8% (CI, 56.0% to 64.5%) at maximum exercise capacity. Systolic pulmonary artery pressure increased from 30.5 mm Hg (CI,

26.0 to 35.0 mm Hg) at rest to 42.9 mm Hg (CI, 35.6 to 53.5 mm Hg) during exercise in participants taking placebo. Sildenafil, 50 mg, significantly increased arterial oxygen saturation during exercise ($P = 0.005$) and reduced systolic pulmonary artery pressure at rest ($P < 0.001$) and during exercise ($P = 0.031$). Of note, sildenafil increased maximum workload (172.5 W [CI, 147.5 to 200.0 W]) vs. 130.6 W [CI, 108.8 to 150.0 W]; $P < 0.001$) and maximum cardiac output ($P < 0.001$) compared with placebo. At high altitude, sildenafil had no effect on arterial oxygen saturation at rest and during exercise compared with placebo. However, sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$) and during exercise ($P = 0.021$) and increased maximum workload ($P = 0.002$) and cardiac output ($P = 0.015$). At high altitude, sildenafil exacerbated existing headache in 2 participants.

Limitations: The study did not examine the effects of sildenafil on normoxic exercise tolerance.

Conclusions: Sildenafil reduces hypoxic pulmonary hypertension at rest and during exercise while maintaining gas exchange and systemic blood pressure. To the authors' knowledge, sildenafil is the first drug shown to increase exercise capacity during severe hypoxia both at sea level and at high altitude.

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Acute and chronic hypoxia are well-characterized causes of pulmonary hypertension (1, 2). Exercise capacity is reduced during severe alveolar hypoxia, regardless of whether the condition is due to environmental factors such as high altitude or to various respiratory diseases. The extent to which hemodynamic constraints related to enhanced right ventricular afterload contribute to limited exercise capacity during hypoxia and pulmonary hypertension remains unknown.

High-altitude pulmonary edema and acute mountain sickness are serious complications that can occur during ascent to high altitudes. Individual susceptibility plays a major role in development of these conditions (3, 4), and the association of high-altitude pulmonary edema with an exaggerated pulmonary hypertensive response to hypoxia and increased vascular leakage is well documented (5, 6). Several factors are thought to cause hypoxia-related exercise limitation. First, alveolar hypoxia leads to systemic hypoxemia, which in itself may cause early fatigue of the peripheral muscles under exercise (mild to moderate hypoxia) or even at rest (severe hypoxia). Second, general hypoxia may cause nonhomogeneous vasoconstriction and compromise

gas exchange. Third, pulmonary hypertension may limit right ventricular performance, resulting in inadequate adaptation of cardiac output to the peripheral demand. Researchers are unsure how much each of these factors contributes to overall exercise limitation in hypoxia.

The selective phosphodiesterase-5 inhibitor sildenafil was originally approved for treatment of erectile dysfunction. Recently, sildenafil was found to reduce pulmonary vascular resistance in different forms of precapillary pulmonary hypertension (7–10) and also mimicked features of a selective pulmonary vasodilator. In a previous study (10), we examined patients with lung fibrosis and pulmonary hypertension who were known to be susceptible to increased gas-exchange disturbances after vasodilator treatment. In these patients, sildenafil reduced pulmonary hypertension, leaving the systemic arterial pressure unchanged, and simultaneously improved gas exchange (10). These effects were probably attributable to preferred vasodilatation in well-ventilated lung areas (intrapulmonary selectivity). Similar results were seen in patients with chronic thromboembolic pulmonary hypertension and ventilation–perfusion mismatch (11).

Context

Alveolar hypoxia causes pulmonary hypertension. Sildenafil causes pulmonary vasodilatation in patients subjected to acute hypoxia at sea level. These observations have generated hypotheses about using sildenafil in acute mountain sickness and for treating pulmonary hypertension in patients with chronic respiratory insufficiency.

Contribution

Sildenafil reduced hypoxic pulmonary hypertension at rest and with exercise and increased maximum exercise capacity and cardiac output in 14 mountain climbers who received sildenafil and placebo in random order at low altitude while breathing hypoxic gas and again at an elevation of 5400 m.

Cautions

The results of this small study are preliminary. Sildenafil's role in the management of acute mountain sickness is unclear.

—The Editors

Sildenafil has also been shown to reduce pulmonary hypertensive response to acute hypoxia in healthy participants at sea level (12). However, its impact on high-altitude pulmonary hypertension and exercise capacity under hypoxic conditions is unknown. We examined the influence of oral sildenafil on pulmonary hemodynamics and exercise tolerance during hypoxia-induced pulmonary hypertension in healthy volunteers who were not susceptible to high-altitude pulmonary edema. We performed the study during acute hypoxic challenge at sea level and during long-term exposure to hypoxia at the base camp on Mount Everest. The study aimed to characterize differences in pulmonary hemodynamics, gas-exchange properties, and exercise limitations during acute hypoxia (without adaptation at low altitude) and after adaptation to prolonged hypoxia (at high altitude).

METHODS**Participants**

Fourteen healthy volunteers (12 men and 2 women) were enrolled in the study. Eight participants were experienced mountaineers who repeatedly performed alpine-style climbing to altitudes higher than 6000 m. The other 6 participants were healthy, well-trained, experienced trekkers who had repeatedly traveled to altitudes above 3500 m. No participants had a history of high-altitude pulmonary edema. The median age, height, and weight of participants were 36.5 years (95% CI, 33.0 to 44 years), 175 cm (CI, 172.5 to 178 cm), and 72.3 kg (CI, 66.0 to 77.0 kg), respectively. Laboratory and clinical testing confirmed the absence of renal, hepatic, or hematologic disorders in all participants. The University Hospital Giessen

Ethics Committee approved the study, and each participant gave written informed consent before inclusion.

Design

All participants underwent electrocardiography, lung function testing, and measurement of peripheral arterial oxygen saturation. Systolic pulmonary artery pressure was measured by using a portable Doppler echocardiography device (ACUSON Cypress, Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania), according to previously evaluated techniques (13, 14). Recordings were stored on a magneto-optical disc and were analyzed by the study investigator and by 2 independent investigators who were unaware of the study procedures.

Cardiac output was assessed noninvasively by using a gas-rebreathing technique and a commercially available device (Innocor, Innovision, Odense, Denmark) (15, 16). The indicator gas mixture contained 1% sulfur hexafluoride, 5% nitrous oxide, and 50% oxygen in nitrogen. After correction for system volume changes using the sulfur hexafluoride, cardiac output was calculated from the rate of uptake of nitrous oxide by using an infrared photoacoustic gas analyzer (AMIS 2001, Innovision). This device allowed reproducible assessments of cardiac output, as reported elsewhere (15, 16). However, the device's measurement of cardiac output at maximum exercise capacity depended strongly on participants' accurate adherence to the required

Figure 1. Flow of participants through the study.

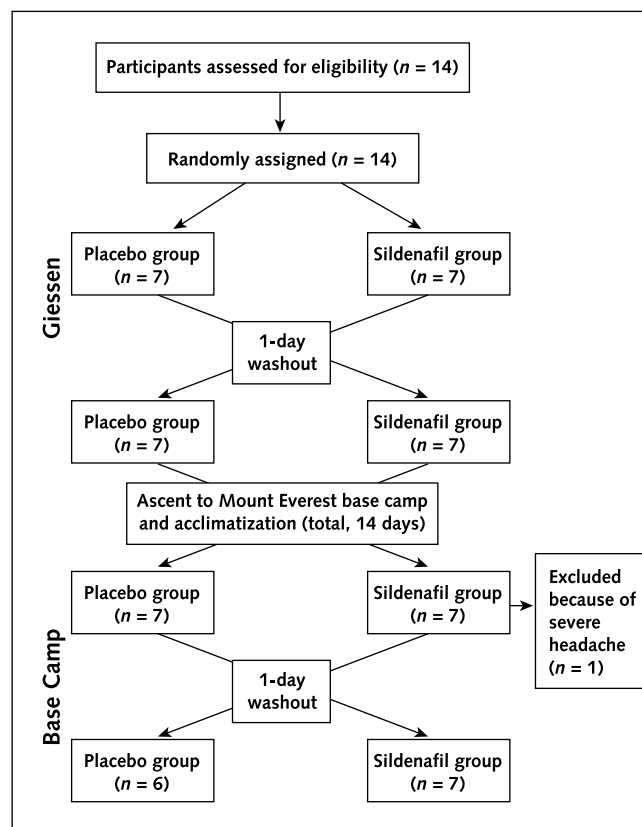


Figure 2. Experimental setting at Mount Everest base camp.



The high-altitude laboratory was equipped with 2 sets of devices for performing exercise testing and assessing pulmonary hemodynamics. The Khumbu Glacier and Mount Nuptse are in the background. A volunteer is seated on the cycle ergometer, and the investigator is performing echocardiography. The device for noninvasive measurement of cardiac output is on the left.

breathing pattern. To determine adherence, we repeatedly trained participants in the use of the device before obtaining study measurements.

Exercise capacity was quantified on a cycle ergometer while participants were in a half-supine position. Exercise was started at 25 W and was increased stepwise every 2 minutes by 25 W until maximum tolerance was reached. Echocardiography was performed at rest and throughout exercise, in parallel with measurements of peripheral oxygen saturation and electrocardiogram readings. Cardiac output was assessed by the rebreathing technique at rest and at maximum exercise capacity.

During the first period of measurements at low altitude in Giessen (171 m above sea level), all participants were examined while breathing room air, at rest and during exercise. After they had fully recovered from the physical effort of the initial exercise session (≥ 6 hours of rest), participants were exposed to a hypoxic gas mixture with 10% fraction of inspired oxygen (corresponding to approximately 70 mm Hg of partial pressure of oxygen in the inspired gas) for 2 hours. The gas mixture was administered through masks that tightly covered participants' noses and mouths throughout the investigation period. The masks were connected to a reservoir to compensate for breathing-related changes in participants' inspiratory flow, especially during effort on the cycle ergometer.

After the first hour, the participants were assigned to receive placebo or sildenafil, 50 mg. Before the study, an

independent pharmacy packed the study medication, which consisted of unlabeled blue diamond-shaped pills, in numbered envelopes that were then administered according to a computerized randomization procedure. The study's crossover design (Figure 1) allowed intraindividual comparison of drug effects. We chose the sildenafil dose on the basis of our experience treating various forms of pulmonary hypertension and after consulting pharmacokinetic and pharmacodynamic data from studies of erectile dysfunction (7, 10, 17, 18). We considered carryover effects to be unlikely because of sildenafil's short half-life and the accordingly chosen washout period of at least 24 hours between investigations.

After 2 hours, while maintaining participants' exposure to the hypoxic atmosphere, we performed echocardiographic assessment at rest. Next, participants again underwent exercise testing, following the previously described protocol. During the next study day, participants repeated the hypoxic challenge following the identical protocol as during the first study day, receiving either placebo or sildenafil in a crossover manner.

The next phase of the study took place on Mount Everest. All participants ascended from Kathmandu, Nepal, to the base camp at Mount Everest in 8 days. The ascent involved a flight from Kathmandu (elevation, 1330 m) to Lukla (elevation, 2880 m) on the first day, with an overnight stay in Phakding (elevation, 2652 m). On the second day, the group ascended to Namche Bazar (elevation,

Table 1. Summary of Hemodynamic and Gas Exchange Variables under Resting Conditions*

Variable	Low Altitude				P Value
	All Participants, Normoxic Rest	Placebo Group, Hypoxic Rest	Sildenafil Group, Hypoxic Rest	Median Difference	
Systolic blood pressure, mm Hg	148.0 (139.5 to 156.5)	142.5 (133.5 to 155.0)	144.0 (134.0 to 155.5)	-1.5 (-12.0 to 9.5)	>0.2
Heart rate, beats/min	76.0 (64.5 to 87.0)	84.8 (74.5 to 95.5)	84.5 (77.0 to 91.5)	1.0 (-7.5 to 7.5)	>0.2
Saturation, %	99.0 (98.0 to 100.0)	72.0 (66.5 to 77.5)	72.8 (68.5 to 78.0)	1.3 (-2.5 to 5.0)†	>0.2
Systolic pulmonary artery pressure, mm Hg	17.5 (15.0 to 20.3)	30.5 (26.0 to 35.0)	22.1 (20.0 to 25.7)	-7.9 (-3.9 to -11.6)	0.001
Cardiac output, L/min	6.0 (5.2 to 6.9)	5.1 (4.7 to 5.5)	5.5 (5.0 to 6.1)	0.5 (0.2 to 0.9)	0.02

* Values are reported as medians (95% CIs). Median differences are Hodges–Lehman estimates of median differences between groups.

† Values are expressed as percentage points.

tion, 3440 m) and stayed for 2 nights. Participants continued the ascent to Tengboche (elevation, 3867 m) on day 4 and to Pheriche (elevation, 4240 m) on day 5. On day 6, the participants reached Lobuche (elevation, 4930 m), then ascended to Gorak Shep (elevation, 5150 m) on day 7 and to the base camp (elevation, 5245 m) on day 8. Although the fraction of inspired oxygen at this altitude is the same as at low altitude (21%), the partial pressure of oxygen was similar to the partial pressure experienced during hypoxic exposure at low altitude because the overall atmospheric pressure was lower (50% of values at sea level).

After 6 days of acclimatization, we obtained baseline high-altitude measurements and tested participants during incremental exercise on a cycle ergometer, as detailed earlier (Figure 2). Again, participants received sildenafil or placebo during 2 consecutive days in a crossover design, allowing intraindividual comparison of the effects of sildenafil on pulmonary hemodynamics, exercise capacity, and gas exchange.

Statistical Analysis

All data are presented as medians with 95% CIs. Hodges–Lehman estimates of point median differences with exact 95% CIs are used to describe treatment effects. The Wilcoxon test was used to assess significant differences between placebo and sildenafil values (StatXact, version 4.0.1, Cytel Software Corp., Cambridge, Massachusetts); *P* values were 2-sided.

Role of the Funding Sources

The funding sources had no influence on the design, conduct, or reporting of the study.

RESULTS

Investigations at Low Altitude

Participants' medical histories, thorough physical examinations, and electrocardiograms showed no evidence of relevant cardiopulmonary disease. Lung function tests excluded substantial ventilatory limitations in all participants. For all participants, FEV₁ was 3.9 L/s (CI, 3.5 to 4.1 L/s), percentage of normal FEV₁ (normalized for age, height, and weight) was 98.0% (CI, 93.0% to 104.5%),

and FEV₁ as a percentage of functional vital capacity was 98.9% (CI, 93.6% to 104.5%) of predicted normal.

Pulmonary Hemodynamics

For all participants, systolic pulmonary artery pressure was 17.5 mm Hg (CI, 15.0 to 20.3 mm Hg) at rest (Table 1) and increased only modestly during exercise under normoxic conditions (Table 2). Cardiac output, which was 6.0 L/min (CI, 5.2 to 6.9 L/min) at normoxic rest, did not significantly change when participants breathed a hypoxic gas mixture for 2 hours under resting conditions (5.1 L/min [CI, 4.7 to 5.5 L/min] with placebo intake and 5.5 L/min [CI, 5.0 to 6.1 L/min] with sildenafil intake). However, systolic pulmonary artery pressure substantially increased under hypoxic conditions in participants taking placebo, both at rest (30.5 mm Hg [CI, 26.0 to 35.0 mm Hg]; *P* < 0.001 vs. normoxic rest) and during exercise (42.9 mm Hg [CI, 35.6 to 53.5 mm Hg]; *P* < 0.001 vs. hypoxic rest). Cardiac output also increased to 11.1 L/min (CI, 9.1 to 13.4 L/min) during hypoxic exercise (*P* < 0.001 vs. hypoxic rest).

After a single oral dose of sildenafil, 50 mg, systolic pulmonary artery pressure at hypoxic rest increased to 22.1 mm Hg (CI, 20.0 to 25.7 mm Hg) (*P* = 0.011 vs. normoxic rest), significantly lower than with placebo (*P* < 0.001). During maximum exercise capacity, systolic pulmonary artery pressure increased to 36.0 mm Hg (CI, 28.3 to 44.0 mm Hg) in participants taking sildenafil, a reduction of 24.1% (CI, -5.3% to -47.0%) compared with placebo (*P* = 0.031). Even when 1 participant with an exaggerated increase in systolic pulmonary artery pressure (88 mm Hg during exercise) was excluded from the analysis, sildenafil was statistically significantly associated with a smaller increase in systolic pulmonary artery pressure during exercise (*P* = 0.048). Also, participants taking sildenafil had significantly better cardiac output at exhaustion (12.9 L/min [CI, 10.8 to 17.6 L/min]; *P* < 0.001).

Exercise Capacity and Peripheral Arterial Oxygenation

The average exercise capacity on the cycle ergometer was 262.5 W (CI, 226.1 to 293.8 W) under normoxic

Table 1—Continued

High Altitude			
Placebo Group, Rest	Sildenafil Group, Rest	Median Difference	P Value
120.0 (112.5 to 125.0)	120.0 (110.0 to 133.0)	0.0 (−26.5 to 10.0)	>0.2
83.5 (72.0 to 93.0)	84.0 (71.5 to 95.0)	1.0 (−9.5 to 9.5)	>0.2
83.0 (80.0 to 86.0)	83.0 (81.0 to 86.0)	1.0 (−1.5 to 3.5)†	>0.2
27.1 (24.1 to 30.0)	22.0 (19.2 to 24.6)	−5.2 (−1.7 to −8.0)	0.005
5.5 (4.7 to 6.1)	5.6 (4.9 to 6.2)	0.0 (−0.6 to 0.9)	>0.2

conditions. Under hypoxic conditions, exercise capacity decreased to 130.6 W (CI, 108.8 to 150.0 W) in participants taking placebo ($P < 0.001$ vs. normoxic exercise). Sildenafil partially restored exercise tolerance to 172.5 W (CI, 147.5 to 200.0 W), an improvement of 20.0% (CI, 9.8% to 31.7%) compared with placebo ($P < 0.001$). In the placebo-first group (that is, the 7 participants who received placebo on day 1 of the investigations and sildenafil on day 2) and the sildenafil-first group (that is, the 7 participants who received sildenafil on day 1 of the investigations and placebo on day 2), the respective results for exercise capacity were as follows: 275.0 W (CI, 158.3 to 325 W) versus 262.5 W (CI, 212.25 to 300.0 W) at normoxic conditions, 130 W (CI, 97.5 to 150 W) versus 187.5 W (CI, 137.5 to 204.7 W) on day 1, and 150 W (CI, 122.5 to 204.0 W) versus 135 W (CI, 104.4 to 160.4 W) on day 2 (Figure 3). The median blood hemoglobin level on day 1 was 14.7 g/L (CI, 13.85 to 15.3 g/L). While peripheral arterial oxygenation consistently ranged above 95% at normoxic rest in all participants, it decreased to 72.0% (CI, 66.5% to 77.5%) under hypoxic conditions in participants taking placebo and 72.8% (CI, 68.5% to 78.0%) in those taking sildenafil. At maximum exercise capacity under hypoxic conditions, oxygen saturation decreased to 60.8% (CI, 56.0% to 64.5%) in participants taking placebo but only to 67.0% (CI, 62.5% to 69.5%) in participants taking sildenafil, despite higher peak exercise levels in the latter group. This corresponds to an increase of 7.9% (CI, 2.4% to 14.4%) in oxygen saturation in the presence of sildenafil ($P = 0.005$). No significant adverse events were observed during sildenafil administration at sea level.

Investigations at High Altitude

Pulmonary Hemodynamics

At the Mount Everest base camp, average systolic pulmonary artery pressure was 27.1 mm Hg (CI, 24.1 to 30.0 mm Hg) at rest and increased to 33.6 mm Hg (CI, 27.1 to 42.5 mm Hg) ($P = 0.003$) during maximum exercise in participants taking placebo. In addition, in these participants, cardiac output was 5.5 L/min (CI, 4.7 to 6.1 L/min) at rest (Table 1) and increased to 12.7 L/min (CI, 9.4 to 15.0 L/min) during exercise (Table 2). In participants taking oral sildenafil, both resting systolic pulmonary artery pressure (22.0 mm Hg [CI, 19.2 to 24.6 mm Hg]; $P = 0.003$) and maximum systolic pulmonary artery pressure

during exercise (27.5 mm Hg [CI, 23.2 to 34.9 mm Hg]) decreased significantly. For the latter variable, the difference versus placebo was −22.7% (CI, −0.5% to −38.4%) ($P = 0.051$). Cardiac output at rest did not change significantly with sildenafil administration (5.6 L/min [CI, 4.9 to 6.2 L/min]). However, at maximum exercise capacity, sildenafil significantly increased cardiac output to 15.1 L/min (CI, 13.0 to 17.1 L/min) compared with placebo ($P = 0.015$).

On day 2, 1 participant presented with a headache. After he took sildenafil, the headache became so severe that he could not undergo exercise testing. No exercise data for this participant were included in the data analysis. Another participant had increased headache after sildenafil intake but was able to exercise. Aside from headache, no significant adverse events were observed after sildenafil intake at high altitude.

Exercise Capacity and Peripheral Arterial Oxygenation

Peripheral arterial oxygen saturation at rest was 83.0% (CI, 80.0% to 86.0%) during placebo intake and 83.0% (CI, 81.0% to 86.0%) during sildenafil intake; median blood hemoglobin level was 16.4 g/L (CI, 15.2 to 17.6 g/L). During placebo intake, exercise capacity was 170.5 W (CI, 139.0 to 190.1 W) and oxygen saturation decreased to 72.5% (CI, 69.5% to 75.5%). After administration of sildenafil, 50 mg, exercise capacity increased significantly to 189.5 W (CI, 161.0 to 210.0 W) ($P = 0.002$). Exercise capacity was 166.0 W (CI, 163.0 to 195.0 W) on day 1 and 184.0 W (CI, 175.0 to 192.0 W) on day 2 in the placebo-first group ($n = 7$) and 220.5 W (CI, 154.8 to 232.8 W) on day 1 and 187.5 W (CI, 119.3 to 207.8 W) on day 2 in the sildenafil-first group ($n = 6$) (Figure 3). Peripheral oxygen saturation decreased to 71.0% (CI, 67.5% to 75.0%) in the sildenafil group during exercise but did not differ significantly compared with placebo.

DISCUSSION

Hypoxic pulmonary vasoconstriction is a fundamental physiologic mechanism, optimizing perfusion–ventilation matching in periods of regional hypoventilation of the lung (19). However, during global alveolar hypoxia, whether due to lung disease or environmental conditions such as

Table 2. Summary of Hemodynamic and Gas Exchange Variables during Exercise*

Variable	Low Altitude				P Value
	All Participants, Normoxic Exercise	Placebo Group, Hypoxic Exercise	Sildenafil Group, Hypoxic Exercise	Median Difference	
Systolic blood pressure, mm Hg	232.0 (215.5 to 249.0)	209.5 (190.0 to 226.5)	214.0 (197.0 to 230.5)	3.5 (−29.0 to 20.0)	>0.2
Heart rate, beats/min	171.0 (160.0 to 181.0)	157.3 (143.5 to 169.5)	157.8 (141.0 to 172.0)	−4.5 (−12.0 to 4.0)	>0.2
Saturation, %	98.0 (97.0 to 99.0)	60.8 (56.0 to 64.5)	67.0 (62.5 to 69.5)	5.5 (1.5 to 10.0)†	0.005
Systolic pulmonary artery pressure, mm Hg	25.1 (20.1 to 31.5)	42.9 (35.6 to 53.5)	36.0 (28.3 to 44.0)	−7.8 (−1.3 to −15.0)	0.03
Cardiac output, L/min	14.4 (12.5 to 16.8)	11.1 (9.1 to 13.4)	12.9 (10.8 to 17.6)	1.3 (0.5 to 2.3)	0.001
Maximum level of exercise, W‡	262.5 (226.1 to 293.8)	130.6 (108.8 to 150.0)	172.5 (147.5 to 200.0)	34.8 (16.8 to 61.3)	0.001

* Values are reported as medians (95% CIs). Median differences are Hodges–Lehman estimates of median differences between groups.

† Values are expressed as percentage points.

‡ Maximum level of exercise performed on the cycle ergometer.

high altitude, this mechanism results in pulmonary hypertension and enhanced right-heart load. These effects were consistently reproduced in the healthy volunteers in our study, who developed substantial pulmonary hypertension both under experimental hypoxia at sea level and at high altitude in the Mount Everest base camp. Moreover, a marked further increase in pulmonary hypertension was noted during hypoxic exercise in participants taking placebo; median systolic pulmonary artery pressure was 42.9 mm Hg at low altitude and 33.6 mm Hg at high altitude. Of note, this pulmonary hypertensive response was observed in persons not previously characterized as sensitive to pulmonary edema at high altitudes. This finding is con-

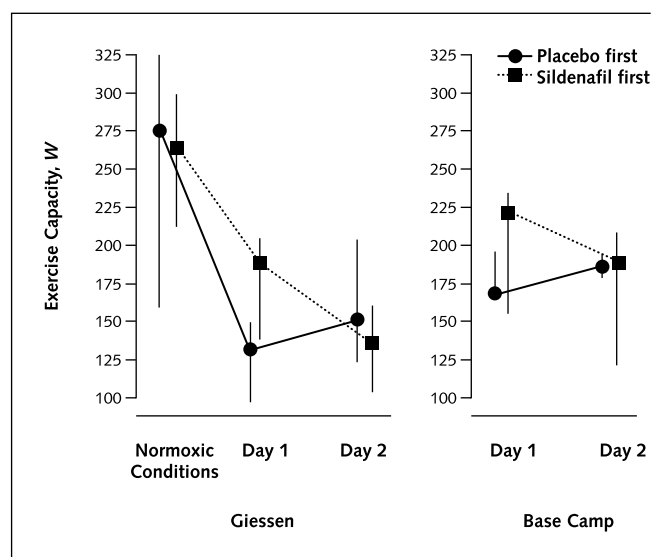
sistent with the notion that exercise enhances even moderate forms of pulmonary hypertension (20). The Doppler echocardiographic technique used to assess systolic pulmonary artery pressure in our study has been extensively evaluated in different types of pulmonary hypertension and is closely correlated with right-heart catheterization in healthy participants (21–23).

We chose Mount Everest as the high-altitude setting for our study for 3 main reasons. First, we wanted to differentiate between the effects of acute hypoxia and long-term hypoxia on pulmonary hemodynamics and limitations of exercise tolerance. Second, changes in pulmonary circulation (for example, pulmonary hypertension and right-heart and vascular remodeling) induced by long-term adaptation to hypoxia can be achieved only after long-term exposure to hypoxic conditions. However, the currently chosen period of hypoxia may have been too short to fully mimic the changes in the pulmonary vasculature and right ventricle of patients with chronic hypoxia caused by ventilatory lung disorders. On the other hand, animal studies have shown that marked morphologic changes can develop both in the lung vasculature and the right ventricle in days to a few weeks (24–26). Third, the resources required to perform such a study at high altitude (that is, material transportation and rescue measures) were available only at Mount Everest.

Phosphodiesterases are a superfamily of enzymes (phosphodiesterase-1 to phosphodiesterase-11) that have wide tissue distribution and substrate specificities that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate (27, 28). Of interest, the major cyclic guanosine monophosphate–degrading phosphodiesterase, phosphodiesterase-5, is abundantly expressed in lung tissue (28), and its inhibition causes pulmonary vasodilatation in experimental models (29, 30). The orally administered selective phosphodiesterase-5 inhibitor sildenafil was recently found to reduce pulmonary vascular resistance in different forms of precapillary pulmonary hypertension (7–10), including short-term exposure to hypoxia at sea level (12).

In line with these previous observations, we found that

Figure 3. Impact of sildenafil on exercise capacity during hypoxic challenge at low and high altitudes.



Maximum exercise levels were assessed at low altitude in Giessen and at the base camp on Mount Everest. At Giessen, participants underwent exercise testing under normoxic conditions at baseline and during hypoxic challenge after receiving placebo or sildenafil in a crossover design on day 1 and day 2. Each group (placebo first and sildenafil first) included 7 participants. Exercise testing was also performed on day 1 and day 2 at the base camp. The placebo-first group had 7 participants, and the sildenafil-first group had 6 participants. Data points represent medians; error bars represent 95% CIs.

Table 2—Continued

High Altitude			
Placebo Group, Exercise	Sildenafil Group, Exercise	Median Difference	P Value
180.0 (160.0 to 195.0)	185.0 (170.0 to 200)	10.0 (−25.00 to 2.5)	0.18
140.0 (130.5 to 150.0)	148.5 (135.0 to 161.5)	6.0 (1.0 to 13.0)	0.02
72.5 (69.5 to 75.5)	71.0 (67.5 to 75.0)	−2.0 (−4.0 to 0.5)†	0.14
33.6 (27.1 to 42.5)	27.5 (23.2 to 34.9)	−7.3 (−0.9 to −11.5)	0.05
12.7 (9.4 to 15.0)	15.1 (13.0 to 17.1)	2.7 (0.3 to 5.6)	0.02
170.5 (139.0 to 190.1)	189.5 (161.0 to 210.0)	16.1 (7.5 to 28.5)	0.002

the customary increase in systolic pulmonary artery pressure after 2-hour exposure to 10% oxygen was substantially reduced after sildenafil administration. A corresponding pulmonary vasodilatory effect of the phosphodiesterase-5 inhibitor was noted at an altitude of 5400 m, without any accompanying decrease in systemic arterial pressure. Of interest, systolic pulmonary artery pressure was somewhat lower at high altitude than after inhalation of 10% oxygen at sea level, despite similar oxygen partial pressures. This finding may reflect acclimatization and the impact of dehydration after several days at a high altitude. The substantial pulmonary vasodilatory effect of sildenafil was also demonstrated under ergometric challenge both at sea level under acute hypoxic conditions and at the Mount Everest base camp, as documented by the significantly lower systolic pulmonary artery pressures at maximum exercise capacity.

Peripheral oxygenation decreased to approximately 72% after short-term exposure to 10% oxygen and further decreased to approximately 61% during exercise. Of interest, oxygenation levels during exercise were consistently and significantly higher (approximately 68%) after pretreatment with sildenafil, even though participants taking sildenafil achieved higher peak exercise levels. Since the ventilatory response was identical with placebo and sildenafil, this observation suggests that a ventilation–perfusion mismatch was provoked during acute hypoxia at low altitude. This effect may have contributed to decreased oxygen saturation, which was attenuated by sildenafil. Of note, these findings are consistent with previous observations in patients with pulmonary hypertension secondary to lung fibrosis (10) and chronic thromboembolism (11), in which sildenafil decreased pulmonary artery pressure while maintaining or even improving gas exchange. In contrast to the measurements obtained at sea level, peripheral oxygen saturation was higher both at rest and during exercise at high altitude and did not increase further after sildenafil administration. Again, this difference between acute hypoxic challenge at sea level and residence at high altitude may be due to acclimatization with optimized ventilation–perfusion matching.

Our most impressive finding is that sildenafil significantly improved exercise capacity under hypoxic condi-

tions. Both at sea level and at high altitude, maximum tolerable workload during ergometric testing was significantly increased and cardiac output values during maximum exercise were considerably higher in participants taking sildenafil. Noninvasive assessment of cardiac output by the gas-rebreathing technique has been shown to be well correlated with both the Fick method and the temperature dilution method (15, 16). The most reasonable explanation for improvement of exercise tolerance with sildenafil is that this agent blunts the pulmonary hypertensive response to hypoxic exercise, thereby reducing right ventricular afterload, which may be a critical factor limiting exercise capacity in hypoxia.

Since the participants in our study did not have chronic pulmonary hypertension, their right ventricular muscle mass and strength are not considered to be adapted to chronic load. Therefore, elevation of systolic pulmonary pressure above the level observed in our study is unlikely (31). Moreover, data from patients with acute pulmonary embolism but no previous episodes of recurrent embolism (that is, without adaptation to high pulmonary resistance) show that right-heart failure begins at pressure levels similar to those measured in our study (32, 33). Thus, the reduction of right ventricular afterload is the most plausible explanation for the increase in cardiac output and exercise capacity in the sildenafil-treated volunteers under conditions of hypoxia. In addition, improved ventilation–perfusion matching may increase the effects of sildenafil on exercise capacity during acute hypoxia, but not at high altitude.

Our study had limitations. Other effects of sildenafil that are unrelated to its impact on the pulmonary circulation may have contributed to our results. Our results cannot be extrapolated directly to patients with chronic pulmonary hypertension, in whom other mechanisms of disease induction and progression may be present. Also, we did not examine sildenafil's effect on normoxic exercise tolerance. However, our results support the possible conception and design of future studies addressing the impact of pharmacologic treatment for pulmonary hypertension, with special emphasis on exercise capacity.

Short-term administration of sildenafil had no serious adverse events, consistent with the excellent safety profile

of this agent (34). However, the drug aggravated symptoms in 2 participants who already had light headaches during their stay at the base camp. Headache is a common feature of acute mountain sickness (35, 36), and a previous study found that high-dose sildenafil (100 mg) increased the incidence of migraine episodes in patients who were prone to them (37). Symptoms of acute mountain sickness and individual susceptibility to migraine episodes combined may have resulted in aggravated headache and acute mountain sickness in participants taking sildenafil at high altitude. However, several studies in patients with pulmonary hypertension reported no increased incidence of headache after long-term intake of up to 150 mg of sildenafil per day (7, 9, 38).

In conclusion, in 2 settings of severe oxygen deprivation—acute hypoxic challenge at sea level and a stay at an altitude of 5400 m—oral sildenafil reduced pulmonary hypertension both at rest and during exercise while maintaining gas exchange and systemic arterial pressure. To our knowledge, this is the first time researchers have demonstrated that a pharmacologic approach increases exercise capacity in healthy volunteers during severe hypoxia, most likely because of reduced right ventricular afterload. Of note, the study participants were not prone to high-altitude pulmonary edema. Therefore, our results are not conclusive for future use of sildenafil as treatment for or prophylaxis of high-altitude pulmonary edema. Further studies are needed to address this particular question. However, our findings may be of interest in treating limitations of exercise tolerance in patients who have lung diseases with severe alveolar hypoxia.

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