Sildenafil improves cardiac output and exercise performance during acute hypoxia, but not normoxia

Andrew R. Hsu, Kimberly E. Barnholt, Nicolas K. Grundmann, Joseph H. Lin, Stewart W. McCallum, and Anne L. Friedlander

Sildenafil improves cardiac output and exercise performance during acute hypoxia, but not normoxia. J Appl Physiol 100: 2031-2040, 2006. First published February 2, 2006; doi:10.1152/japplphysiol.00806.2005.—Sildenafil causes pulmonary vasodilation, thus potentially reducing impairments of hypoxia-induced pulmonary hypertension on exercise performance at altitude. The purpose of this study was to determine the effects of sildenafil during normoxic and hypoxic exercise. We hypothesized that 1) sildenafil would have no significant effects on normoxic exercise, and 2) sildenafil would improve cardiac output, arterial oxygen saturation (SaO₂), and performance during hypoxic exercise. Ten trained men performed one practice and three experimental trials at sea level (SL) and simulated high altitude (HA) of 3,874 m. Each cycling test consisted of a set-work-rate portion (55% work capacity: 1 h SL, 30 min HA) followed immediately by a time trial (10 km SL, 6 km HA). Double-blinded capsules (placebo, 50, or 100 mg) were taken 1 h before exercise in a randomly counterbalanced order. For HA, subjects also began breathing hypoxic gas (12.8% oxygen) 1 h before exercise. At SL, sildenafil had no effects on any cardiovascular or performance measures. At HA, sildenafil increased stroke volume (measured by impedance cardiography), cardiac output, and SaO₂ during set-work-rate exercise. Sildenafil lowered 6-km time-trial time by 15% (P < 0.05). SaO₂ was also higher during the time trial (P < 0.05) in response to sildenafil, despite higher work rates. Post hoc analyses revealed two subject groups, sildenafil responders and nonresponders, who improved time-trial performance by 39% (P < 0.05) and 1.0%, respectively. No dose-response effects were observed. During cycling exercise in acute hypoxia, sildenafil can greatly improve cardiovascular function, SaO₂, and performance for certain individuals.

Address for reprint requests and other correspondence: A. L. Friedlander, Exercise Physiology Laboratory, Clinical Studies Unit, Veterans Affairs Palo Alto Health Care System, GREEC, 182B, MB2, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave., Palo Alto, CA 94304 (e-mail: friedlan@stanford.edu).

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ALTITUDE-INDUCED HYPOXIA CAN cause severe decrements in submaximal and maximal exercise performance during acute and chronic hypoxic exposure (12, 20, 31, 44). These decrements can be attributed primarily to decreased alveolar PO₂ causing reduced oxygen diffusion in the lungs and a subsequent reduction in oxygen transport to working muscles. However, performance impairments at altitude can also be accentuated by hypoxia-induced elevations in pulmonary hypertension and pulmonary arterial pressure (Ppa) resulting in increased right ventricular afterload, decreased right ventricular ejection fraction, and decreased cardiac output (Q) (6, 16, 17, 31). Hypoxia can further exacerbate the reductions in oxygen saturation and delivery by causing heterogeneous, “patchy” vasoconstriction of the pulmonary vasculature leading to a ventilation-perfusion mismatch (43, 44). Therefore, strategies to reduce pulmonary hypertension in hypoxia would be predicted to improve Q and oxygen diffusion, thus increasing arterial oxygen saturation (SaO₂), delivery, and exercise performance.

Sildenafil is a phosphodiesterase-5 inhibitor that has been shown to cause pulmonary vasodilation (1, 35, 45). Phosphodiesterase-5 is a member of a larger group of phosphodiesterase enzymes that degrade the vasodilator cGMP, thus causing vasoconstriction of smooth muscle found in vessel walls (1, 3). Sildenafil has recently gained recognition as a treatment for primary and secondary pulmonary hypertension (15, 28, 32, 47). Because of the documented vasodilatory effects on the pulmonary vasculature, sildenafil could emerge as a potent ergogenic aid during exercise performed under hypoxic conditions.

Thus far, only a few studies have investigated the effects of sildenafil on exercise performance at altitude. Ghofrani et al. (13) found that administration of sildenafil to healthy individuals decreased Ppa and increased Q, and peak exercise capacity during acute hypoxic exposure (10% oxygen) and in the field at Mount Everest base camp (5,245 m) (13). Richalet et al. (32) also observed less of a decrement in maximal exercise performance in subjects treated with sildenafil compared with those taking placebo on days 2–5 at 4,350 m altitude (32), despite no differences in Q between groups. In contrast, a study by Ricart et al. (30) showed a suppression in Ppa with sildenafil during exercise at a simulated altitude of 5,000 m but did not show changes in SaO₂ or ventilatory measures and claimed that the effects of sildenafil on exercise capacity were inconclusive (30).

The previous studies investigating sildenafil at altitude have emphasized the impacts of sildenafil on maximal exercise capacity (13, 32). However, during sojourns at altitude, most exercise is performed for prolonged periods at submaximal intensities perhaps interspersed with short bouts of maximal work. To our knowledge, no studies have yet looked at the performance effects of sildenafil during hypoxic submaximal exercise. Furthermore, previous investigations have used alti-

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tudes above 4,300 m (range: 4,350–5,245 m). Many recre-ational athletes and military personnel spend time at altitudes of lesser extremes and still suffer from altitude-induced decrements in performance. It is unknown whether sildenafil might be of assistance at more moderate altitudes. Finally, there is currently no information on the dose-response effects of sildenafil on exercise performance or information as to the effects of sildenafil on sea level (normoxic) exercise performance. As with high altitude, sildenafil could improve sea-level performance by reducing cardiac afterload, or, more likely, it could impair performance through nonspecific systemic vasodilation resulting in a modest fall in blood pressure.

Therefore, the purpose of this study was to examine the effects of two doses of sildenafil on cardiovascular function during submaximal set-work-rate cycling exercise and time-trial performance during normoxia and acute hypoxia (12.8% oxygen) in healthy, trained men. We hypothesized that 1) sildenafil would provide no benefits during normoxic exercise, and possibly cause a decline in performance due to minor nonspecific peripheral vasodilation, and 2) sildenafil would improve Q, SaO₂, and performance during hypoxic cycling exercise at simulated altitude equivalent to 3,874 m.

METHODS

Subjects

Eleven healthy, nonsmoking, trained male cyclists and triathletes ages 18–35 yr from Palo Alto, Stanford University, and surrounding communities volunteered and were enrolled in this study. One subject withdrew from the study during sea-level testing because of intolerable headaches after testing. The mean age, height, body mass, body fat percent, and peak oxygen consumption (V̇O₂peak) for the remaining 10 subjects were 31 ± 4 yr, 178.2 ± 6.9 cm, 76.83 ± 9.5 kg, 13.5 ± 5.5%, and 59.7 ± 9.5 ml·min⁻¹·kg⁻¹, respectively. Trained cyclists and triathletes were recruited to ensure consistent time-trial performance. As with high altitude, sildenafil could improve sea-level performance by reducing cardiac afterload, or, more likely, it could impair performance through nonspecific systemic vasodilation resulting in a modest fall in blood pressure.

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General Study Design

After screening and two baseline V̇O₂peak tests, subjects performed four sea-level (SL) exercise tests (1 practice, 3 experimental). The experimental trials were performed using placebo, 50 mg, or 100 mg oral sildenafil in a randomized, double-blind, counterbalanced design. Subjects then performed a peak work capacity (Wattspeak) test while breathing hypoxic gas (12.8% oxygen) followed by four exercise tests at simulated high altitude (HA) using a similar design as the SL tests. All exercise tests were spaced at least 3 days apart. Each exercise test at SL and HA included both a set-work-rate portion (55% Wattspeak adjusted for SL or HA Wattspeak) for the determination of metabolic, cardiovascular, and pulmonary changes between trials followed immediately by a time-trial performance test (Fig. 1). The exercise testing protocol was designed to mimic behavior at altitude where prolonged submaximal work output may be interrupted by shorter high-intensity activities.

Screening

Before participating in any physical testing, subjects underwent a screening appointment that included a health history questionnaire, seven-site body fat percent test via skin calipers (Lange skinfold caliper, Cambridge Scientific Industries, Cambridge, MD), vital signs measurement, and resting ECG at the Clinical Studies Unit (CSU) of the Veterans Affairs Palo Alto Health Care System. V̇O₂peak was then determined during a continuous progressive exercise test to volitional exhaustion on an upright electrically braked cycle ergometer (Sensor-Medics 800, VIASYS Healthcare, Yorba Linda, CA). After a 2-min resting period, subjects began cycling at 50 W and the workload was increased by 50-W increments every 2 min until 150 W, after which the workload was increased by 30-W increments until exhaustion was reached and subjects voluntarily stopped exercising. Expired respiratory gases were collected continuously and analyzed by use of an

![Fig. 1. Experimental design and testing protocol. Practice, sea level (SL), and simulated high-altitude (HA) tests were a minimum of 3 days apart. Within SL and HA study portions, experimental trials were randomized, double blind, counterbalanced, and placebo controlled. V̇O₂peak, peak oxygen uptake; Wattspeak, work capacity.](http://jap.physiology.org/DownloadedFrom/10220.33.5.onApril14,2017)
online open-circuit metabolic cart (Parvomedics Truemax 2400, Con- 
sentis Technologies, Sandy, UT). The recorded \( V_{O2 \text{ peak}} \) was the 
highest oxygen uptake (\( V_{O2} \)) value that was sustained for 30 s during 
the test. A 12-lead exercise (ECG; Portrait, Mortara Instrument, 
Milwaukee, WI) was used to monitor heart rate and possible ECG 
signal abnormalities. A second \( V_{O2 \text{ peak}} \) test was performed at least 3 
days later to ensure \( V_{O2 \text{ peak}} \) values and Wattspeak. During the second 
test, heart rate (HR), stroke volume (SV), and Q (calculated as \( SV \times 
HR \)) were recorded every 15 s using the noninvasive impedance 
cardiography device described below.

Cardiovascular Measurements

An impedance cardiography device (Physioflow type PF05L1, 
Manatec Biomedical, Macheren, France) was used in this study to 
determine HR, SV, and Q during rest and exercise. The Physioflow 
uses changes in transthoracic impedance (\( dZ \)) in response to an 
administered electrical current during cardiac ejection to calculate SV. 
The Physioflow emits a high-frequency (75 kHz) and low-amperage 
(3.8 mA peak to peak) alternating electrical current via skin electrodes 
(7). Two pairs of electrodes, one transmitting and the other receiving, 
are applied above one another so as not to overlap at the supraclavicle-
ular fossa at the left base of the neck and at the midpoint of the 
thoracic region of the spine. An additional pair of electrodes is used 
to monitor a single ECG lead (V1/V6 position). The theoretical basis for this device and its validity during rest and 
exercise testing have been previously published (4, 7, 21, 33, 40).

When using the Physioflow device, patient data are first entered 
followed by an initial evaluation of stroke volume index (SVI, ml/m²) 
during an autocalibration procedure based on 30 consecutive heart-
beats recorded in a resting, seated, upright position (SVical) and then 
entry of resting systolic and diastolic blood pressure values. The 
autocalibration stores the largest impedance variation during the 
systole (\( Z_{\text{peak}} - Z_{\text{min}} \)) and the largest rate of variation of the 
impedance signal known as the contractility index (\( dZ/dt_{\text{peak}} \)). SVI 
calculation is dependent on the thoracic flow inversion time (TFIT; 
ms) measured on the first mathematical derivative of the impedance 
signal. TFIT is the time interval between the first zero value after the 
beginning of the cardiac cycle (start of the QRS complex on the ECG) 
and the first nadir after the peak of the ejection velocity (\( dZ/dt_{\text{peak}} \)). 
During data acquisition, the variation in parameters is analyzed and 
compared with those values obtained during calibration. SVI calculation 
(SVIcalc) is calculated according to the following formula: 
\[ SVI_{\text{calc}} = k \times \left( \frac{dZ/dt_{\text{peak}}}{(Z_{\text{peak}} - Z_{\text{min}})} \right) \times W(\text{TFIT}_{\text{calc}}), \]
where \( k \) is an empirically adjusted constant and W is a proprietary correction algorithm. Each 
displayed SV represents the mean over a 15-s artifact-free period (7, 33).

Q calculation by the device is based on the formula \( Q = HR \times SVI \times 
BSA \), where \( Q \) is expressed in liters per minute, HR is based on the 
R-R interval measurement, determined on the ECG first derivative 
(\( dECG/dt \)), which provides a more stable signal than the ECG itself, 
SVI is determined as above, and BSA is the body surface area 
calculated according to the formula of Haycock (BSA = 0.024265 \( \times \) 
BM1.1732 \( \times H^{0.3964} \)), where BM is body mass in kilograms and H is 
height in centimeters.

According to the manufacturers, the novel aspect of the Physioflow 
is that it establishes values of SV independent of baseline impedance 
(Z0). Zo is the variable that causes so many problems in the traditional 
approaches to bi impedance because its value is greatly affected by 
hydration status, distance between electrodes, and resistivity of the 
blood. To avoid this problematic variable, Physioflow uses Zo neither 
during calibration nor after calibration and relies only on \( dZ \) (change 
in impedance). This is important in the present investigation in which 
sildenafil might be expected to change pulmonary capillary blood 
volume. However, the changes in baseline thoracic impedance related 
to fluid expansion in the lungs should not disturb the measurement 
(unless they have a true hemodynamic impact that modifies the pulsatile waveform morphology). Even so, some question the accur-

cacy of impedance cardiography under any conditions, and, because the Physioflow device has not been validated directly during use with 
sildenafil or at simulated altitude, there could be some as-yet-un-
dermined variable related to drug treatment or hypoxia that confounds the SV measurements.

The Physioflow has been previously validated against the direct 
Fick method. Mean differences between Q values obtained by the 
direct Fick method and the Physioflow device (Q_{Fick} - Q_{imp}) are not significant during rest (0.04 l/min) (7), submaximal exercise (0.29 
l/min) (7), or maximal incremental exercise (0.58 l/min) (33). The 
direct Fick method is also highly correlated with the Physioflow 
during rest (r = 0.89, P < 0.001, n = 40) (7), submaximal exercise 
(r = 0.85, P < 0.001, n = 40) (7), and maximal exercise (r = 0.94, 
P < 0.01, n = 50) (33). High correlations in the SV (r = 0.84, P < 0.001) 
and Q values (r = 0.98, P < 0.001) between the direct Fick 
and impedance cardiography method have also been reported during 
maximal cycling exercise in young, fit men (39).

In unpublished data from our laboratory, we found that, in 20 
healthy, fit men (age: 27 ± 4 yr, height: 181.4 ± 4.0 cm, body mass: 
78.52 ± 6.45 kg; body fat: 11.7 ± 3.4%); \( VO2_{\text{peak}} \) = 60.5 ± 8.61 
mL·min⁻¹·kg⁻¹), the coefficient of variations for SV and Q at peak 
exercise using the Physioflow during repeat cycle ergometer \( VO2_{\text{peak}} \) tests spaced at least 2 days apart were 3.6 and 3.4%, respectively.

SL Exercise Testing Protocol

All subjects completed three SL experimental exercise tests spaced 
at least 3 days apart consisting of cycling for 1 h at 55% Wattspeak 
followed immediately by a 10-km cycling time trial in the CSU (7 m 
above sea level) (Fig. 1). Before performing the SL tests, subjects 
completed a practice trial to minimize learning effects of the protocol. 
Subjects were randomly assigned to a counterbalanced dosage order 
for placebo, 50 mg, and 100 mg oral sildenafil. An independent 
pharmacist packed the study prescriptions in dark blue, blinded 
capsules (size 00) that contained sildenafil or granular lactose mono-
hydrate (placebo). The prescriptions were administered in a 
double-blind manner. It was assumed that there were no drug carryover 
effects from one trial to the next because of the short half-life of 
sildenafil (4 h) and the period of at least 3 days between tests.

Subjects arrived at the CSU fully hydrated, having eaten a small, 
self-selected, standardized meal 2 h before the start of exercise that 
simulated their precompetition food intake. For 24 h before testing, 
intake of food and water was standardized and subjects refrained from 
strenuous exercise. Subjects recorded and replicated their food and 
water intake before all trials. Hydration status was estimated using 
preexercise starting body masses. Upon arrival, subjects were given 
their appropriate prescription with 200 ml of water. Subjects then 
rested and sat quietly reading or watching TV in a patient room for 
1 h, allowing optimal sildenafil activation (5, 8, 14, 15).

After the rest-activation period, body mass was taken with subjects 
wearing only cycling shorts. Subjects had equivalent starting body 
masses for all trials. Subjects were then brought into the testing 
laboratory (24 ± 1°C, 29 ± 8% humidity). While sitting quietly on 
the upright electrically braked cycle ergometer, subjects were outfitted 
with exercise ECG electrodes (Ag/AgCl SilverTrace, GE Medical 
Systems) and then connected to the Physioflow device and an 
automated resting blood pressure cuff device (Vital-Check 4200, IVAC, 
San Diego, CA). Patient data were entered, foliased by the calibration 
procedures for the Physioflow. After calibration and entry of resting 
blood pressure data, the resting blood pressure cuff was replaced by an 
automated exercise blood pressure cuff device (Tango, SunTech 
Medical, Morrisville, NC). Subjects wore a mesh, elastic-polyester 
shirt (Spandage 10-02, Medi-Tech, Brooklyn, NY) to minimize elec-

dtrode probe movement and signal instability. Subjects were then 
outfitted with a headset and nose clip, and a T-shape two-way 
norebreathing valve (Hans Rudolph, Kansas City, MO) was inserted 
into their mouths and connected via wide-bore tubing to the metabolic
cart. After a 2-min baseline calorimetry period, subjects began cycling at 50 W and the workload was increased incrementally to 55% Wattspeak (196 ± 23 W) by the end of 5 min of exercise.

VO₂ and respiratory exchange ratio were recorded in 30-s averages during the first 10 min of exercise and for 5-min periods every 15 min thereafter until the end of the 1-h fixed-work-rate portion of the test. HR, SV, and Q were measured continuously with beat-to-beat data smoothed by a 15-s moving averaging algorithm by the Physioflow device, rating of perceived exertion (RPE) was taken every 5 min, systolic blood pressure (BP) was measured every 15 min, and SaO₂ was recorded every 15 min via a pulse oximeter device (Escort II, MDE, Arleta, CA) attached to the left index finger. To avoid occlusion effects on the oxygen saturation reading, subjects were asked to rest their hands lightly on the handlebars of the bike during all sampling time points. Oxygen saturation measurements were only recorded when the heart rate values on the pulse oximeter matched those being measured with the Physioflow device as a marker of adequate flow to the finger. A fan at low intensity was directed at subjects, and subjects were not allowed to consume any water or food during the test. After completion of the 1-h fixed-work-rate exercise, subjects cycled at 100 W for 2 min to facilitate transition from the electrically braked ergometer to the time-trial bike (Velotron, RacerMate, Seattle, WA). Subjects then dismantled the fixed-work-rate bike and were given 200 ml of water while they stretched and prepared for the time trial for 5 min.

Using a gated-style start, subjects remained motionless on the time-trial bike until the test was initiated on the computer monitor directly facing them. For the time trial, subjects were able to change gears as often as desired to simulate actual outdoor racing and complete the 10 km as quickly as possible. Subjects could only see distance completed and bearing on the monitor. All other indicators such as time, watts, and speed were withheld from subjects. Watts, speed, and revolutions per minute were recorded every 5 s by the installed time-trial software (Velotron 3D, RacerMate, Seattle, WA), and HR, SV, and Q were measured every 15 s by the Physioflow. SaO₂ was recorded every 2 min. All other measurements such as VO₂, RER, RPE, and systolic and diastolic BP were omitted during the time trial to minimize interference with subject cycling performance. Verbal motivation was given to subjects every 0.40 km, and the primary performance measure was time to completion. The coefficient of variation for trained male subjects performing this test in our laboratory is ~3.0%.

HA Exercise Testing Protocol

For all HA tests in the CSU, subjects were acutely exposed to a hypoxic gas mixture containing 12.8% oxygen (61.8 Torr PO₂ in the inspired gas) for 1 h before and during exercise. The hypoxic gas was emitted from a commercial hypoxic generator (Hypoxic Hypoxic Generator, Hypoxic, New York, NY) that lowered the oxygen content of room air and administered it to subjects through a HEPA filter and tightly sealed face masks covering the noses and mouths of the subjects. The masks were connected to reservoir bags to compensate for high-intensity exercise-induced increases in subjects’ inspiratory flow rates. Percent oxygen was measured before and after all tests to ensure no drift in oxygen content during exercise.

At least 3 days before experimental HA testing, subjects completed an incremental HA Wattspeak test on the upright electrically braked cycle ergometer that followed the same protocol and workload increases as the screening VO₂peak tests. The only protocol difference was that no VO₂ measurements were taken and the hypoxic generator exercise masks were used in place of the metabolic cart headset, nose clip, and mouthpiece. Wattspeak at HA was determined as the highest workload maintained for 30 s before exhaustion and voluntary termination of exercise. A minimum of 3 days later, subjects completed a HA practice trial consisting of 30 min of cycling at 55% Wattspeak (150 ± 23 W, based on HA Wattspeak) followed immediately by a 6-km cycling time trial. Except for the hypoxic gas and duration of testing, all conditions and measurements were identical to SL testing including diet, exercise, and hydration controls. The experimental exercise tests at HA consisted of 30 min at 55% Wattspeak followed by a 6-km time trial (Fig. 1).

Statistics

Statistics were performed with Stat-View software (SAS Institute, Cary, NC), and data were analyzed by two-way (time × trial) ANOVA tests with repeated measures for the combined subject data. One-way (trial) ANOVA tests with repeated measures were used to analyze differences between trials for rest (0 min) and exercise (10–30 min) within the responder and nonresponder groups at altitude. Tukey-Kramer post hoc significance tests were performed when significant main or interaction effects were found. Paired t-tests were used to evaluate peak exercise values. Statistical significance was set at P < 0.05. All data presented are means ± SD.

RESULTS

Peak Exercise Values

Peak exercise values for normoxia and hypoxia in the nontreated condition are presented in Table 1. SL values for workload capacity and cardiovascular variables were appropriate for the young, trained participants. Wattspeak fell significantly at HA. The fall in peak capacity at HA was accompanied by significant decrements in SaO₂ (26%), Q (15%), and HR (7%) (P < 0.05).

Sildenafil Effects at SL

During the set-work-rate portion of the exercise test at sea level, all values except SaO₂ increased between rest and exercise within each treatment group (Table 2). However, sildenafil at either dose had no effects on any metabolic, cardiovascular, or performance measurements. Systolic BP tended to be lower (~8%) with both doses of sildenafil, and HR tended to be higher (~5.9%) during the later stages of exercise, but neither of these findings was statistically significant. The small differences in HR and systolic BP during the set-work-rate portion of testing did not impact SL performance because time to completion, watts, and cardiovascular values were essentially identical between time trials (Table 2).

Sildenafil Effects at HA

In contrast to SL values, both doses of sildenafil demonstrated significant benefits on oxygenation, cardiovascular, and performance measures at HA (Table 3). Because there was no

<table>
<thead>
<tr>
<th>Variable</th>
<th>SL</th>
<th>HA</th>
<th>% Δ</th>
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<tbody>
<tr>
<td>VO₂peak, ml·min⁻¹·kg⁻¹</td>
<td>59.7 ± 9.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wattspeak, W</td>
<td>354 ± 42</td>
<td>270 ± 35</td>
<td>24%</td>
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<tr>
<td>Qpeak, l/min</td>
<td>28.9 ± 4.9</td>
<td>24.5 ± 4.0*</td>
<td>15%</td>
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<tr>
<td>SVpeak, ml</td>
<td>151.8 ± 27.1</td>
<td>138.6 ± 21.4</td>
<td>9%</td>
</tr>
<tr>
<td>HRpeak, beats/min</td>
<td>191 ± 6</td>
<td>177 ± 11*</td>
<td>7%</td>
</tr>
<tr>
<td>SaO₂ at peak, %</td>
<td>97 ± 1</td>
<td>70 ± 7*</td>
<td>26%</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO₂peak, peak oxygen consumption; SL, sea level; HA, simulated high altitude; Wattspeak, work capacity; Qpeak, peak cardiac output; SVpeak, peak stroke volume; HRpeak, peak heart rate; SaO₂, arterial oxygen saturation. *HA significantly different than SL (P < 0.05).
SILDENAFIL DURING CYCLING EXERCISE

Table 2. Sea-level data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
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<th>100 mg</th>
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<tbody>
<tr>
<td></td>
<td>Rest 30 min</td>
<td>30 min 60 min</td>
<td>Rest 30 min</td>
</tr>
<tr>
<td></td>
<td>Fixed work rate (60 min, ~55% Wattspeak = 196 ± 23 W)</td>
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<tr>
<td>VO₂, l/min</td>
<td>0.38 ± 0.05</td>
<td>2.88 ± 0.31</td>
<td>2.94 ± 0.29</td>
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<tr>
<td>RER</td>
<td>0.88 ± 0.06</td>
<td>0.91 ± 0.02</td>
<td>0.93 ± 0.03</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>5.7 ± 1.3</td>
<td>210 ± 63</td>
<td>22.2 ± 6.2</td>
</tr>
<tr>
<td>SV, ml</td>
<td>99.5 ± 24.2</td>
<td>145.8 ± 44.2</td>
<td>146.4 ± 40.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>58 ± 9</td>
<td>154 ± 14</td>
<td>152 ± 14</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>98 ± 1</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>135 ± 9</td>
<td>191 ± 11</td>
<td>189 ± 19</td>
</tr>
<tr>
<td>RPE</td>
<td>0 ± 0</td>
<td>12 ± 1</td>
<td>13 ± 1</td>
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10-km time trial

<table>
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<tr>
<th></th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
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<tbody>
<tr>
<td></td>
<td>Rest 30 min</td>
<td>30 min 60 min</td>
<td>Rest 30 min</td>
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<td>60 min</td>
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</table>
| Values are means ± SD; n = 10 subjects. Post Hoc Analysis: Sildenafil Responders vs. Nonresponders

Although sildenafil improved mean group time-trial performance by 15%, individual responses varied greatly. At HA, there were two clear sets of subjects, sildenafil responders (n = 4) and nonresponders (n = 6), who improved their time-trial performance by 39% (P < 0.05) and 1.0%, respectively (Fig. 2). In responders, sildenafil also significantly increased Q by 25% at rest (P < 0.05) and 32% during set-work-rate exercise (P < 0.05) compared with the placebo trial, whereas in nonresponders, the drug effects on Q were more modest (9.4% and 14% for rest and exercise, respectively) (Fig. 3). Sildenafil increased SaO₂ at rest and during set-work-rate exercise in both groups, with responders showing slightly larger increases throughout the entirety of exercise (Fig. 4). During the time-trial portion of the test, improvement in SaO₂ was also greater.

Table 3. Simulated high altitude data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 30 min</td>
<td>30 min 60 min</td>
<td>Rest 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 min</td>
</tr>
<tr>
<td></td>
<td>Fixed work rate (12.8% O₂, 30 min, ~55% Wattspeak = 150 ± 23 W)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q, l/min</td>
<td>6.1 ± 1.5</td>
<td>18.4 ± 4.1</td>
<td>7.0 ± 1.4</td>
</tr>
<tr>
<td>SV, ml</td>
<td>89.1 ± 13.2</td>
<td>120.5 ± 21.0</td>
<td>96.3 ± 17.3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68 ± 10</td>
<td>152 ± 11</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>86 ± 4</td>
<td>74 ± 3</td>
<td>90 ± 4*</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>129 ± 10</td>
<td>181 ± 18</td>
<td>126 ± 11</td>
</tr>
<tr>
<td>RPE</td>
<td>0 ± 0</td>
<td>13 ± 2</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

6-km time-trial (12.8% O₂)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 30 min</td>
<td>30 min 60 min</td>
<td>Rest 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 min</td>
</tr>
</tbody>
</table>
| Values are means ± SD; n = 10 subjects. Within each treatment condition, values during exercise were significantly different than those at rest (P < 0.05). *50 mg significantly different than placebo (P < 0.05). †100 mg significantly different than placebo (P < 0.05).
with drug treatment for responders (79 vs. 73% for 50 mg vs. placebo, respectively) than nonresponders (77 vs. 74%). There was no order effect to the benefits seen in response to sildenafil with two responders having the placebo trial first and two responders having the placebo trial last.

Individual performance and SV data are presented in Table 4 for responders and nonresponders. Subjects were considered responders if the improvement in time-trial performance was greater than 1 min. From SL to HA (while on placebo), SV declined by 26% during set-work-rate exercise (P < 0.05) in responders, whereas nonresponders showed mean decrement in SV during exercise of only 2.3%. There was also a strong relationship between higher initial SL exercise SV and the decrement in SV experienced at altitude (r = 0.71, P < 0.03). Finally, a robust association between decrement in SV at altitude and the improvement in time-trial performance with drug was evident (r = 0.93, P < 0.01).

**DISCUSSION**

The main finding of this study was that, during hypoxic exercise, sildenafil significantly increased SV and Q while attenuating the decline in \( \text{SaO}_2 \) during set-work-rate exercise. In addition, sildenafil improved time-trial performance (decreased time to completion) during hypoxia while increasing \( \text{SaO}_2 \). No dose-response relationships were observed between 50 and 100 mg sildenafil. Post hoc analysis revealed that there were two sets of subjects, sildenafil nonresponders and responders, with only the latter deriving benefits in performance with sildenafil treatment. Sildenafil had no significant affect on any metabolic, cardiovascular, or performance measures during normoxic exercise. The present investigation is not the first to show sildenafil-induced improvements in exercise performance during hypoxic exercise. However, it does provide novel information regarding sildenafil use during submaximal exercise performance that is relevant to athletic competition and mountaineering both in more moderate simulated altitude (3,874 m) than previous investigations and in normoxia. It also is the first to describe the distinct individual differences in the hypoxic exercise performance benefits of the drug.

**Sildenafil at HA**

Recent studies have shown that sildenafil can increase peak exercise capacity during acute and chronic hypoxia by lowering Ppa and raising \( \text{SaO}_2 \) (13, 32). Ghofrani et al. (13) observed increases in \( Q, \text{SaO}_2 \), and peak watts with sildenafil during acute hypoxia (10% oxygen) at low altitude (171 m) in unacclimatized subjects and at Mount Everest base camp (5,245 m) in acclimatized subjects. The drug-induced gains in maximal performance of ~20% (acute exposure) and 11% (Mt. Everest base camp) reported by the authors were similar to those observed in our study for time-trial performance (15% decrease...
in completion time). The observation that our performance decrement falls between the 20 and 11% reported by Ghofrani et al. is not surprising, given that the former was at a higher simulated altitude and the latter was in acclimatized subjects. Indeed, the selected simulated altitude in our investigation and the resultant performance improvement with drug treatment were both ~75% of those reported by Ghofrani et al. in unacclimatized subjects (13).

Closer examination of the Ghofrani et al. data (13) indicate that, both during acute hypoxia and at Everest, less benefit was seen in exercise performance in subjects who took sildenafil on day 2 as opposed to day 1. Because the Ghofrani et al. study used a crossover design, smaller effects on day 2 suggest that either 1) subjects were acclimatizing in a way that minimized drug benefits on day 2, or 2) by chance, the subjects who were randomized to take the drug on day 2 were less responsive to the medication. The first explanation is unlikely because the subjects at Everest were already acclimatized, and because a more recent study by Richalet et al. (32) suggests that performance benefits in maximal exercise capacity seen on day 2 at altitude can continue through day 5 with continuous sildenafil treatment. Therefore, as suggested by our data, it is possible that not all subjects were responding equally to sildenafil treatment in the Ghofrani et al. paper as well. Such an interpretation is consistent with the observation that there are certain HAPE-susceptible people who experience greater pulmonary vasoconstriction and exaggerated increases in Ppa when exposed to hypoxia (36). Individual variability may also contribute to the reported inconsistencies between the three existing hypoxic exercise studies in regards to sildenafil’s effects on performance, \(Q\), and \(SaO_2\) (13, 30, 32). Whether increasingly severe hypoxia induces a graded response in pulmonary vasoconstriction or whether there is some threshold above which individuals respond is unclear. However, it is important to consider that, in either case, a nonresponder at one altitude could be a responder at a higher altitude.

**Sildenafil Response at HA**

**Subject differences.** In the present investigation, we were able to identify two sets of subjects based on the sildenafil-induced improvements in time-trial performance (greater or

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**Figure 4.** Arterial oxygen saturation (\(SaO_2\)) during fixed-work-rate exercise at HA for placebo, 50 mg, and 100 mg sildenafil for nonresponders (A) and responders (B). *50 mg significantly different than placebo (\(P < 0.05\)). †100 mg significantly different than placebo (\(P < 0.05\)).

**Table 4.** Individual subject characteristics, altitude-induced decrement in SV, and drug-induced improvements in time-trial performance at HA for responders vs. nonresponders

<table>
<thead>
<tr>
<th>Subject</th>
<th>Weight, kg</th>
<th>SL (V_{O_2})peak, l/m</th>
<th>SL (exercise)</th>
<th>HA (exercise)</th>
<th>(\Delta) in SV during exercise</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
<th>HA 6-km Time-Trial (min)</th>
<th>(\Delta) in Time (Placebo vs. 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>67.0</td>
<td>4.4</td>
<td>162.4</td>
<td>113.2</td>
<td>-49.2</td>
<td>17.2</td>
<td>10.9</td>
<td>11.1</td>
<td>-6.3</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>82.5</td>
<td>5.9</td>
<td>140.7</td>
<td>128.8</td>
<td>-11.9</td>
<td>11.7</td>
<td>10.5</td>
<td>11.4</td>
<td>-1.2</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>98.6</td>
<td>4.2</td>
<td>188.0</td>
<td>153.3</td>
<td>-34.7</td>
<td>16.0</td>
<td>11.5</td>
<td>11.4</td>
<td>-4.5</td>
<td></td>
</tr>
<tr>
<td>R4</td>
<td>78.7</td>
<td>5.3</td>
<td>175.1</td>
<td>108.3</td>
<td>-66.8</td>
<td>15.4</td>
<td>10.3</td>
<td>10.7</td>
<td>-5.1</td>
<td></td>
</tr>
<tr>
<td>Ave.</td>
<td>81.7</td>
<td>5.0</td>
<td>166.5</td>
<td>125.9</td>
<td>-40.6</td>
<td>15.0</td>
<td>10.8</td>
<td>10.9</td>
<td>-4.3</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>13.1</td>
<td>0.8</td>
<td>20.2</td>
<td>21.4</td>
<td>23.2</td>
<td>2.4</td>
<td>0.5</td>
<td>0.4</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td><strong>Nonresponders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NR1</td>
<td>73.7</td>
<td>4.8</td>
<td>111.6</td>
<td>103.5</td>
<td>-8.1</td>
<td>11.1</td>
<td>11.1</td>
<td>10.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NR2</td>
<td>75.6</td>
<td>5.1</td>
<td>137.2</td>
<td>129.6</td>
<td>-7.6</td>
<td>10.4</td>
<td>10.4</td>
<td>10.3</td>
<td>0</td>
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<tr>
<td>NR3</td>
<td>74.2</td>
<td>4.4</td>
<td>139.3</td>
<td>133.9</td>
<td>-5.4</td>
<td>11.4</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>NR4</td>
<td>79.1</td>
<td>4.3</td>
<td>118.8</td>
<td>128.2</td>
<td>9.4</td>
<td>11.1</td>
<td>11.1</td>
<td>11.2</td>
<td>0</td>
<td></td>
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<tr>
<td>NR5</td>
<td>63.3</td>
<td>3.4</td>
<td>84.7</td>
<td>78.6</td>
<td>-6.1</td>
<td>12.1</td>
<td>12.0</td>
<td>11.7</td>
<td>-0.1</td>
<td></td>
</tr>
<tr>
<td>NR6</td>
<td>75.7</td>
<td>3.7</td>
<td>126.7</td>
<td>127.3</td>
<td>0.6</td>
<td>12.1</td>
<td>12.2</td>
<td>12.0</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Ave.</td>
<td>73.6</td>
<td>4.3</td>
<td>119.7</td>
<td>116.9</td>
<td>2.8</td>
<td>11.3</td>
<td>11.3</td>
<td>11.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>5.4</td>
<td>0.6</td>
<td>20.2</td>
<td>21.8</td>
<td>6.8</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Stoke volume (SV) exercise values are averages of minutes 20–30 during set work rate exercise on placebo at SL and HA. Subjects were considered responders if improvement in HA time-trial performance on drug was >1 min.
less than 1 min for responders and nonresponders, respectively). On the basis of that separation, sildenafil responders also demonstrated greater drug-induced increases in \( Q \) and \( SV \) during set-work-rate exercise than the nonresponders. The fact that the impedance cardiography measures of SV response showed significant differences between groups and even tracked individual performance improvements \((r = 0.93, P < 0.01)\) not only supports our hypotheses that sildenafil works through our proposed cardiovascular mechanisms but lends validity to the device’s ability to measure treatment-induced changes. Of the three modulators of SV (preload, contractility, and afterload), it is probable that the exaggerated decrement in SV with hypoxia in responders was caused by a larger pulmonary hypoxic vasoconstriction response with greater increases in pulmonary vascular resistance (PVR) and right ventricular afterload compared with nonresponders. Similarly, decreases in PVR leading to lower right ventricular afterload and improvements in ventilation-perfusion matching are the most likely mechanisms for the observed sildenafil-induced benefits. These possible mechanisms are supported by a number of other studies investigating sildenafil effects during hypoxic exercise (13, 30, 32, 47). However, because \( Ppa \) was not directly measured in this investigation, other explanations for the increase in SV with sildenafil such as changes in left ventricular afterload, cardiac performance, and systemic autonomic or cGMP-mediated effects cannot be eliminated.

It should be noted that \( SaO_2 \) was higher in the treated trials, but only slightly more so for responders compared with nonresponders. The greater increases in \( Q \) in the responders could have reduced pulmonary transit time, thus decreasing oxygen-hemoglobin loading time and preventing some of the gains that would otherwise have been evident from improved ventilatory-perfusion matching. Even if \( SaO_2 \) had not been higher, an increase in \( Q \) would still result in higher oxygen delivery to the tissues because of increased blood flow.

Overall, our data indicate that not everyone will benefit from sildenafil administration during hypoxia. Because there are a number of potentially negative side effects (see Safety and Ergogenic Considerations) associated with sildenafil use, individuals who will not benefit should not take the drug prophylactically. A vital question then arises: Is it possible to predict who will benefit from sildenafil treatment?

Predictors. \( Ppa \) is thought to increase more at altitude in individuals who are susceptible to HAPE (36). The variable response in \( Ppa \) and its hypothesized effects on performance at altitude make it a likely candidate to identify potential responders. Changes in \( Ppa \) have been previously examined through the use of direct heart catheterization (14, 15, 47). Although this technique is well established and provides accurate, reliable \( Ppa \) measurements, it is also highly invasive and requires specifically trained physician investigators to perform the procedure, thus limiting its efficacy as a widespread screening tool (23, 29, 42, 46). \( Ppa \) can also be estimated with the use of echocardiography, as was done in the studies of Ghofrani et al. (13), Richalet et al. (32), and Ricart et al. (30), but it is particularly difficult to perform during exercise, it can be affected by the expertise of the operator, and, with some methods, it may be limited to subjects that experience tricuspid regurgitation (30, 32, 41). As an alternative, \( SV \) may be a more balanced and direct indicator of right ventricular afterload and ejection fraction than \( Ppa \) itself. \( SV \) would be expected to be suppressed to a greater degree in responders at altitude than nonresponders, a hypothesis supported by the data in the present investigation (Table 4). Therefore, use of a noninvasive cardiography device, such as the Physioflow, with and without hypoxic exposure may provide a means of assessing who would be most negatively impacted at altitude and who might benefit most from sildenafil. It is also interesting to note that those subjects who started with the highest \( SV \) (and \( Q \)) in the placebo trial at sea level showed the greatest decrements in \( SV \) in the placebo trials at altitude \((r = 0.71, P < 0.03)\) and the greatest improvements in time-trial performance when on sildenafil at altitude. Responders also tended to have lower \( SaO_2 \) values compared with nonresponders during the set-work-rate placebo trials at HA. Therefore, it appears that the performance advantages elicited by high \( Q \) values at sea level may be minimized at altitude without the use of sildenafil. This observation is consistent with previous studies showing that fit subjects have greater absolute decrements in maximal performance at altitude (11, 20, 25) and that species (such as horses) or individuals with high exercise \( Q \) values are more susceptible to HAPE (38). Whether our finding that responders are associated with larger initial SV is real or simply an artifact of the small sample size in the present study will need to be evaluated in future investigations.

Sildenafil at SL

During normoxic exercise, sildenafil had no significant effects on any of the measurements. The experimental hypothesis for this investigation was that sildenafil would have no effects on normoxic exercise and would possibly cause a decline in performance due to minor nonspecific peripheral vasodilation and blood flow being directed away from exercising muscles. Some (18, 24, 34), but not all (10, 22), previous studies have found modest vasodilatory effects on the peripheral vascular system with sildenafil such as a reduction in systolic BP and systemic vascular resistance and an increase in forearm blood flow. In our study, sildenafil tended to increase HR and decrease systolic BP during fixed-work-rate exercise. Because HR was increased with sildenafil during set-work-rate exercise and essentially the same during the time trial between treatment conditions, it is surprising that performance was not negatively impacted by sildenafil. Nevertheless, the data from the present investigation were consistent with our hypothesis that there are no benefits on exercise performance with sildenafil treatment during normoxic exercise.

Methodological Considerations

The primary limitation of this study was that no direct \( Ppa \) measurements were obtained. However, our observed cardiovascular and \( SaO_2 \) benefits with sildenafil agree with findings of studies that have measured and found significant decreases in \( Ppa \) with sildenafil during acute and chronic hypoxia (13, 30, 32). In addition, sildenafil-induced decrements in \( Ppa \) could be partially masked by increases in \( Q \), so it may not be the optimal measure of drug efficacy. The suppression in SV observed at altitude (with placebo) in our responders suggests that those subjects did experience increases in PVR that were attenuated with sildenafil treatment.

Another limitation to this study was that normobaric hypoxia was used in place of hypobaric hypoxia. Although certain
physiological outcomes of the two methodologies may differ, studies have shown changes in Ppa within 15–20 min of simulated hypoxic exposure and suggest that short-term alterations in lung function are similar between the two conditions (2, 9, 26, 37).

Finally, SV and Q in this investigation were determined by a relatively new technology based on updated principles of impedance cardiography. Impedance cardiography has been shown in the past to be influenced by certain physiological variables such as edema, but the new Physioflow technology attempts to eliminate such confounds (see METHODS). Several studies have validated the Physioflow against the direct Fick method during rest and exercise (7, 33), but no studies have yet used the Physioflow device during set-workload protocols at simulated altitude or with the addition of Sildenafil. Therefore, it is possible that the measurements of SV and Q in this investigation could have been confounded by some as-yet-undetermined factor related to our study design.

Safety and Ergonomic Considerations

Despite the benefits provided to some subjects in the present investigation, our findings are not intended to promote sildenafil as a sports performance-enhancing supplement to be taken without medical consultation or supervision at altitude. Using sildenafil at altitude could be dangerous. For example, exercise at altitude may increase HAPE susceptibility because of an increase in Ppa related to increased Q rather than elevated PVR secondary to pulmonary vasoconstriction (17). Therefore, it is possible that large increases in Q caused by sildenafil during hypoxic exercise could ultimately increase the risk of HAPE by negating its own positive benefits of decreased vasoconstriction. In addition, a few subjects in this investigation reported that sildenafil exacerbated headaches and caused flushed face and blue-colored vision, side effects that have been well documented with sildenafil use in normoxia (5, 19, 27). The headaches were severe enough in one subject to cause withdrawal from the study during normoxic testing. Finally, despite improved performance, several of the study participants reported feeling subjectively worse (more fatigued) and unable to mentally focus during exercise while on active drug treatment at SL and HA.

Interestingly, our data suggest that the active drug returns performance levels in the strong responders to the level of the nonresponders. Meaning, it was the placebo trial that was impaired in the strong responders relative to those with a lesser response, not that their drug trials were better. At sea level, the responders as a group actually had faster 10-km time trials than nonresponders (15.5 vs. 17.2 min). However, at altitude without sildenafil, responders were significantly worse during the 6-km time trial than nonresponders (15.0 vs. 11.3 min) and yet were similar after sildenafil treatment (10.8 vs. 11.2 min). Because our data indicate that sildenafil eliminates a decrement in performance rather than providing additional enhancement above normal (e.g., it partially catches responders back up to nonresponders), sildenafil could be considered a treatment rather than an ergogenic aid per se.

In conclusion, this study shows that certain individuals can benefit from sildenafil use during acute hypoxia, but not normoxia, in terms of Q, \( \Delta O_2 \), and exercise performance under controlled laboratory conditions. Positive sildenafil responders potentially can be identified by decrements in SV upon acute hypoxic exposure, but further research needs to be completed to confirm the possibility. It appears that there is no dose-response relationship for sildenafil during normoxic or hypoxic exercise. What remains to be elucidated are additional predictive measures for positive responders, the threshold altitude for benefits, and the chronic effects of sildenafil use on acute mountain sickness, HAPE, and acclimatization at high altitude.

ACKNOWLEDGMENTS

We are grateful to the subjects for participation as well as to Karen Bratcher, R.N., and the rest of the nursing staff in the CSU at the Veterans Affairs Palo Alto Health Care System for assistance with subject testing. We extend a special thanks to Roger Hoyer, PharmD, for help with drug administration. We thank Jim Gunnerson, Frank Bour, and Jean Bour, M.D., for technical assistance with the Physioflow device. Results from this study in no way constitute endorsement for sildenafil or the Physioflow by the authors or Journal of Applied Physiology.

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SILDENAFIL DURING CYCLING EXERCISE

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