BRIEF REPORT

Sildenafil and Exercise Capacity in the Elderly at Moderate Altitude

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Objective.—Hypobaric hypoxia decreases exercise capacity and causes hypoxic pulmonary vasoconstriction and pulmonary hypertension. The phosphodiesterase-5 inhibitor sildenafil is a pulmonary vasodilator that may improve exercise capacity at altitude. We aimed to determine whether sildenafil improves exercise capacity, measured as maximal oxygen consumption (peak $\dot{V}O_2$), at moderate altitude in adults 60 years or older.

Methods.—The design was a randomized, double-blind, placebo-controlled, crossover study. After baseline cardiopulmonary exercise testing at 1400 m, 12 healthy participants (4 women) aged 60 years or older, who reside permanently at approximately 1400 m and are regularly active in self-propelled mountain recreation above 2000 m, performed maximal cardiopulmonary cycle exercise tests in a hypobaric chamber at a simulated altitude of 2750 m after ingesting sildenafil and after ingesting a placebo.

Results.—After placebo, mean peak $\dot{V}O_2$ was significantly lower at 2750 m than 1400 m: $37.0 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (95% CI, 32.7 to 41.3) vs $39.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (95% CI, 33.5 to 44.7; $P = .020$). After placebo, there was no difference in heart rate (HR) or maximal workload at either altitude ($z = 0.182$; $P = .668$, respectively). There was no difference between sildenafil and placebo at 2750 m in peak $\dot{V}O_2$ ($P = .668$), O_2 pulse ($P = .476$), cardiac index ($P = .143$), stroke volume index ($z = 0.108$), HR ($z = 0.919$), or maximal workload ($P = .773$). Transthoracic echocardiography immediately after peak exercise at 2750 m showed tricuspid annular plane systolic velocity was significantly higher after sildenafil than after placebo ($P = .019$), but showed no difference in tricuspid annular plane systolic excursion ($P = .720$).

Conclusions.—Sildenafil (50 mg) did not improve exercise capacity in adults 60 years or older at moderate altitude in our study. This might be explained by a “dosing effect” or insufficiently high altitude.

Key words: high altitude, exercise, sildenafil, elderly, peak $\dot{V}O_2$

Introduction

In unacclimatized individuals, ascent to high altitude decreases maximal exercise capacity (maximal oxygen

consumption, or peak $\dot{V}O_2$) by about 1% per every 100 m gain in altitude starting at about 1500 m.¹ Decreased maximal exercise capacity at high altitude is primarily caused by arterial hypoxemia. Lower partial pressure of inspired oxygen (P_{iO_2}) leads to a decrease in alveolar and arterial partial pressures of oxygen, which causes hypoxic pulmonary vasoconstriction and increased pulmonary artery systolic pressure.^{1,2} Although hypoxemia at high altitude is a major cause of reduced exercise tolerance, hemodynamic limitations may also play a role.^{3,4} Ascent to high altitude causes hypoxic

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Presented in part at the Wilderness Medical Society annual summer meeting, July 2013, Breckenridge, CO.

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pulmonary vasoconstriction, pulmonary hypertension, and increased right ventricular afterload, and decreased cardiac output, all of which may contribute to reduced peak $\dot{V}O_2$.^{1,5-9} Although the relative influence of right ventricular limitation and hypoxemia on exercise capacity is subject to individual variation, a treatment that reduces altitude-induced pulmonary hypertension may increase exercise capacity at high altitude.

The phosphodiesterase-5 inhibitor sildenafil has been shown to be an effective pulmonary vasodilator for treatment of both hypoxia- and nonhypoxia-associated pulmonary hypertension.^{8,10,11} There is also evidence that, in normal subjects, altitude-induced hypoxemia is attenuated with sildenafil. Previous studies show that sildenafil improves exercise capacity in healthy men and women at high altitudes (4350 m to 5245 m).^{5,9,12} One possible reason for this exercise limitation is increased right ventricular afterload as a result of hypoxic pulmonary vasoconstriction. However, improvement in gas exchange provides the most likely potential mechanism by which sildenafil improves exercise performance at altitude.^{5,6,9}

Previous studies by Ghofrani et al,⁵ Richalet et al,⁹ Faoro et al,¹² and Ricart et al¹³ show that sildenafil improves exercise capacity, decreases pulmonary vascular resistance, and improves arterial oxygenation. However, these studies examined relatively young (mean ages, 29 to 36 years) healthy subjects under hypoxic circumstances at high altitudes of 4350 m to 5245 m. A question remains about the implications of these studies for older adults who participate in mountain recreation at moderate altitude (approximately 2000 to 3000 m).

The population older than 65 years is increasing worldwide, and this age group is expected to make up 19% of the US population by 2030.¹⁴ Although older individuals may, at times, have greater difficulty in acclimatizing to the rigors of travel, persons older than 60 years comprise an increasing proportion of international travelers.¹⁵ Some references suggest between 15% and 30% of international travelers are now older than 60 years.^{15,16} In addition, a study as far back as 1997, which examined 1416 US travelers attending a pretravel clinic, found that a full one third of subjects were older than 60 years.¹⁷ Even healthy, athletic older individuals whose lungs undergo the normal aging process face deterioration in pulmonary function and exercise capacity.¹⁸⁻²³ The potential exercise benefits of sildenafil for this older demographic at a moderate altitude has yet to be elucidated.

The objective of the present study was to investigate whether a 50-mg dose of sildenafil (with dosing based on criteria mentioned in the study design) would increase maximal exercise capacity in persons 60 years or older who reside permanently at approximately 1400 m during

acute exposure to a simulated moderate altitude of 2750 m in a hypobaric chamber. We hypothesized that sildenafil would increase peak oxygen consumption at 2750 m in persons 60 years or older.

Methods

PARTICIPANTS

Twelve healthy male ($n = 8$) and female ($n = 4$) volunteers 60 years or older (mean age, 66.5 years) were enrolled and gave written informed consent to this study. Subjects were recruited from the local Salt Lake City, UT, mountain club (Wasatch Mountain Club) and from the Salt Lake City area (average elevation, 1400 m). All subjects reported being regularly active in self-propelled mountain recreation at moderate altitudes higher than the altitude at which they live. Subject characteristics are shown in Table 1. No subjects had a history of severe chronic obstructive pulmonary disease as defined by American Thoracic Society criteria, left ventricular ejection fraction of less than 45%, severe pulmonary hypertension with New York Heart Association functional class III or IV symptoms, or a requirement for chronic supplemental oxygen.^{24,25} No subjects used sildenafil chronically and none were currently using any drugs known to interact with sildenafil (erythromycin, itraconazole, or ketoconazole CYP3A4 inhibitors). The study was approved by the Intermountain Healthcare institutional review board.

STUDY DESIGN

This study used a randomized (block randomization in blocks of 4), double-blind, placebo-controlled, crossover design to examine the effects of 50 mg of sildenafil vs placebo on parameters of pulmonary circulation, arterial oxygenation, and cardiopulmonary exercise capacity. All subjects performed 3 cardiopulmonary exercise tests: 1 baseline test at 1400 m and 2 study tests at simulated altitude (2750 m). This simulated altitude was the maximum for which our institutional review board would give permission under these study conditions. For the 2 exercise tests at simulated altitude, subjects received initial random assignment to either the placebo group ($n = 6$) or the sildenafil group ($n = 6$) in a double-blind, crossover fashion (Figure 1). All subjects underwent both placebo and sildenafil treatment at 2750 m. There was a minimum 24-hour washout period between study sessions (maximum elapsed time of 9 days between sessions in the case of 1 subject). Based on the study by Ghofrani et al,⁵ 12 subjects would be sufficient to detect a significant change (at 80% power with an alpha of 0.05) in cardiac output (CO) and cycle

Table 1. Subject characteristics

<i>Subject</i>	<i>Sex</i>	<i>Age (y)</i>	<i>Height (cm)</i>	<i>Weight (kg)</i>	<i>Predicted peak $\dot{V}O_2^a$ (mL · kg⁻¹ · min⁻¹)</i>	<i>Peak $\dot{V}O_2$ at 1400 m (mL · kg⁻¹ · min⁻¹)</i>	<i>Peak $\dot{V}O_2$ at 1400 m as percentage of predicted peak $\dot{V}O_2$ (%)</i>
1	M	60	173	66.0	30.5	50.9	167
2	M	62	155	70.5	24.5	53.2	217
3	F	68	160	57.0	20.1	37.0	184
4	M	69	175	69.0	26.4	47.5	180
5	F	64	160	74.0	17.8	28.8	162
6	M	69	175	70.5	27.5	42.9	156
7	M	77	155	61.4	20.9	27.1	129
8	M	65	168	67.0	27.3	51.0	187
9	M	65	170	73.0	26.5	36.1	136
10	F	60	163	54.5	23.5	38.6	164
11	F	66	170	66.8	19.1	28.4	149
12	M	73	155	77.3	19.2	27.6	144
Mean		66.5 (63.6–69.4)	165 (160.5–169.5)	67.2 (63.4–71.0)	23.6 (21.3–25.9)	39.1 (33.5–44.7)	165 (150.9–179.1)

Mean values are reported as mean (95% CI).

^a Values for predicted peak $\dot{V}O_2$ were calculated using Wasserman equations. Male, actual weight equals or exceeds ideal weight: Peak $\dot{V}O_2 = 0.0337 \times \text{Height (cm)} - 0.000165 \times \text{Age} \times \text{Height} - 1.963 + 0.006 \times \text{Weight (actual - ideal)}$. Male, actual weight less than ideal weight: Peak $\dot{V}O_2 = 0.0337 \times \text{Height (cm)} - 0.000165 \times \text{Age} \times \text{Height} - 1.963 + 0.014 \times \text{Weight (actual - ideal)}$. Female: Peak $\dot{V}O_2 = 0.001 \times \text{Height (cm)} \times (14.783 - 0.11 \times \text{Age}) + 0.006 \times \text{Weight (actual - ideal)}$.

Figure 1. Experimental design. Assignment to placebo and sildenafil groups was by a randomized, double-blind, and crossover design.

pedal load in watts of the placebo group exposed to 2750 m simulated altitude.

The Intermountain Medical Center Research Pharmacy prepared the study drugs as 50-mg, single-dose, orally administered, colorless liquid solutions. We determined that liquid was a preferable form to reduce the likelihood that participants would distinguish between the sildenafil and placebo doses. The dose was selected based on previous studies that have examined the effect of sildenafil on exercise capacity, pulmonary vascular resistance, and arterial oxygenation in hypoxic conditions.^{5,12}

EXERCISE TESTING PROTOCOL

Each subject performed a baseline cardiopulmonary exercise test at 1400 m at The Fitness Institute at LDS Hospital in Salt Lake City, UT. The subsequent 2 exercise tests took place inside a hypobaric chamber (Hypobaric and Hyperbaric Chamber, DL-8, Fink Engineering, Warana, Queensland, Australia) at a simulated altitude of 2750 m (544 ± 1.3 mm Hg) at Intermountain Medical Center in Murray, UT. We selected 2750 m as an appropriate moderate altitude in accordance with previous research.^{7,26,27} Echocardiography measurements were taken after the subject had spent approximately 30 minutes at rest in the chamber at 2750 m, and cardiopulmonary exercise testing was initiated immediately after echocardiography. In accordance with previous studies, exercise testing began 60 minutes after ingestion of placebo or sildenafil.^{5,9,28–32}

Exercise tests were completed on a non-breath-by-breath cardiopulmonary exercise testing system, the ParvoMedics TrueOne 2400, with an upright, electrically braked, cycle ergometer and a metabolic cart attached to a personal computer (ParvoMedics, Salt Lake City, UT). The TrueOne 2400 has been shown to be an accurate and

reliable device for the measurement of inspiratory and expiratory gas exchange variables.³³ During exercise, a tight-fitting mask with a nonrebreathing valve connected to a mixing chamber recorded measurements of minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production ($\dot{V}_{CO_2}$).³⁴ The mixing chamber averages expired gas volumes and gas concentrations over a number of breaths. Output signals were used to calculate aerobic threshold and CO. In accordance with published protocol recommendations, subjects exercised using a ramp protocol that started with 2 minutes unloaded pedaling (0 W), then increased the work rate by 25 W/min until symptom-limited maximum was reached over approximately 10 to 12 minutes.^{33,35,36}

Because flattening of the $\dot{V}_{O_2}$ –work relationship is not seen frequently in a maximal exercise test, we defined maximal exercise capacity as peak $\dot{V}_{O_2}$ or the highest $\dot{V}_{O_2}$ achieved during presumed maximal effort.³⁷ In accordance with published guidelines, we defined a maximal test as a respiratory exchange ratio (RER) of 1.1 or greater and a peak $\dot{V}_{O_2}$ of at least 85% of each subject's age- and sex-predicted peak $\dot{V}_{O_2}$.^{28,29,38}

ECHOCARDIOGRAPHY MEASUREMENTS

A limited transthoracic echocardiographic examination was performed at simulated altitude of 2750 m inside the hypobaric chamber, initially at rest 60 minutes after ingestion of the study drug, and again immediately after exercise while still inside the hypobaric chamber, using a Philips CX50 ultrasound system (Philips, Bothell, WA). We recorded images of the right ventricle using a right ventricle-focused apical 4-chamber view, in accordance with published standards.³⁹ We measured 2 indices of right ventricular systolic function, the tricuspid annular plane systolic excursion (TAPSE) from m-mode, and the tricuspid annular plane systolic velocity (RV S'), in accordance with published standards.³⁹ Normal TAPSE is considered greater than 1.6 cm, and normal RV S' is considered greater than 10 cm/s. The interpreting physician was blinded to the patient's treatment arm.

CARDIAC OUTPUT MEASUREMENTS

We used a noninvasive CO monitor (NICOM) to take continuous measurements of stroke volume and cardiac output during all exercise tests at simulated altitude (Cheetah Medical Systems, Newton, MA). This technology, although typically used in a critical care setting, has been validated in 1 study in which results suggest the NICOM provides face validity for measuring cardiac performance during exercise in patients with heart failure.⁴⁰ The NICOM uses bioreactance, or phase shifts in pulsatile flow, to continuously capture hemodynamic

signals. It then uses these data to calculate stroke volume index (SVI) and cardiac index.

STATISTICS

We used a paired Student's *t* test to compare peak $\dot{V}O_2$, oxygen (O_2) pulse, cycle pedal load (W), cardiac index, TAPSE, and RV S' at 2750 m after placebo and after sildenafil because these data showed normal distribution.⁴¹ A paired Student's *t* test was used to compare peak $\dot{V}O_2$, O_2 pulse, and W at 1400 m and at 2750 m after placebo. We used a Mann-Whitney rank sum nonparametric test to compare heart rate (HR) and SVI. Values are presented as mean (95% CI). A probability value .05 or less was considered significant. Statistical analyses were performed using SPSS software (version 21.0; SPSS Inc, Chicago, IL).

Results

A summary of peak exercise values and comparisons of peak $\dot{V}O_2$, O_2 pulse, HR, W, cardiac index, SVI, TAPSE, and RV S' for baseline, placebo, and sildenafil conditions is presented in Table 2. Means for peak V_E and RER are shown in Table 2. All results are reported as mean (95% CI).

PEAK EXERCISE VALUES

All participants met criteria for maximal exercise tests in all 3 study sessions (median RER, 1.2, *n* = 12). Peak $\dot{V}O_2$ after placebo was significantly lower at 2750 m as compared with 1400 m ($P < .05$; Table 2). Peak oxygen consumption at 2750 m was not different after sildenafil treatment as compared with placebo ($P > .05$). A summary of peak $\dot{V}O_2$ for each subject is shown in Figure 2. There was no statistically significant difference in W achieved at 1400 m versus placebo at 2750 m ($P > .05$), or between placebo and sildenafil conditions at 2750 m ($P > .05$).

HEMODYNAMIC MEASUREMENTS

Peak HR, O_2 pulse, cardiac index, and SVI at 2750 m were not different after treatment with sildenafil as compared with placebo ($P > .05$), or between placebo at 2750 m and baseline at 1400 m ($P > .05$; Table 2).

ECHOCARDIOGRAPHY

Echocardiography assessments conducted immediately after exercise in both 2750 m conditions showed no difference in TAPSE ($P > .05$). We observed significantly higher RV S' ($P < .05$) at 2750 m in the sildenafil condition compared with the placebo condition.

Discussion

Altitude-induced hypoxia reduces peak $\dot{V}O_2$. On ingestion of a placebo followed by acute exposure to a simulated altitude of 2750 m, not all participants showed a decrease in peak $\dot{V}O_2$ compared with their exercise capacity at a baseline altitude of their permanent residence at 1400 m. Furthermore, we did not observe any significant differences in performance at 2750 m after ingestion of sildenafil as compared with placebo. The increased HR, decreased pedal load tolerance, and decreased O_2 pulse that, based on previous research, we would expect to see in a normal, healthy person on transition from 1400 m to 2750 m were not statistically significant.^{1,3-5,7-9} Improved right ventricular function, as indicated by an increase in RV S', was the only significant physiologic parameter that increased between the placebo and sildenafil conditions. It is worth noting, however, that 2 recent studies involving trained athletes up to an altitude of 3900 m found little or no improvement in exercise capacity and other physiologic parameters measured after ingestion of sildenafil.^{7,42}

At acute moderate altitude, ingesting sildenafil was not associated with an improvement in exercise capacity as compared with after ingesting a placebo. However, previous studies have shown that sildenafil may improve exercise performance in both acute and chronic hypoxia by indirectly improving gas exchange. Ghofrani et al⁵ observed improved exercise performance after an approximately 1-week acclimatization trek to Everest base camp (5245 m), whereas Richalet et al⁹ found an improvement in exercise capacity over the course of a 6-day stay at 4350 m. In such instances of multiple days of very high altitude exposure, acclimatization starts to become a factor. This may possibly compensate for the decrease in arterial oxygen saturation that occurs on initial ascent.¹²

Sildenafil has also been shown to improve peak $\dot{V}O_2$ during acute hypoxia. Hsu et al⁶ found that sildenafil improves exercise performance during acute hypoxia in subjects breathing a hypoxic gas (approximately 4000 m, 12.8% F_{IO_2}), whereas Faoro et al¹² observed that sildenafil improved maximal $\dot{V}O_2$ and pulmonary gas exchange in acute normobaric hypoxia (approximately 5800 m, 10% F_{IO_2}) but not chronic hypoxia after 2 weeks of acclimatization at 5000 m on Mount Chimborazo (Ecuador). Notably, although Faoro et al¹² observed a greater vasodilating effect in chronic hypoxia, sildenafil only improved peak $\dot{V}O_2$ in acute hypoxia. Our data align with this observation. One possible explanation for the higher RV S' after sildenafil ingestion as compared with placebo is the β -agonist properties of sildenafil. However, although we noted an

Table 2. Peak exercise means and comparisons

Variable	Baseline at 1400 m (n = 12)	Placebo at 2750 m (n = 12)	Sildenafil at 2750 m (n = 12)	Baseline vs placebo		Placebo vs sildenafil	
				t	P value ^a	t	P value ^a
Peak $\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	39.1 (33.5–44.7)	37.0 (32.7–41.3)	36.8 (32.3–41.3)	2.72	0.020	0.44	.668
O ₂ pulse, mL/beat	16.5 (14.0–19.0)	16.0 (14.0–18.0)	16.9 (13.6–20.2)	1.02	.330	-0.74	.476
HR, beats/min	162.3 (157.1–167.5)	163.9 (153.6–174.2)	164.2 (154.3–174.1)	1.34 ^b	.182	-0.10 ^b	.919
Pedal load, W	213.2 (177.7–248.7)	205.1 (171.0–239.2)	204.2 (167.5–240.9)	0.44	.668	0.30	.773
Cardiac index, ^c L · min ⁻¹ · m ⁻²		10.1 (8.6–11.6)	8.7 (7.8–9.6)			1.58	.143
SVI		76.7 (63.4–90.0)	62.8 (52.8–72.8)			1.61 ^b	.108
TAPSE, cm		2.9 (2.7–3.1)	2.9 (2.6–3.2)			-0.37	.720
RV S', cm/s		16.9 (15.1–18.7)	20.0 (17.1–22.9)			-3.02	.019
SpO ₂ , %		88.2 (84.7–91.7)	88.9 (85.8–92.0)				
$\dot{V}_E$, L/min	111.3 (93.8–128.8)	125.2 (107.7–142.7)	122.1 (105.4–138.8)				
RER	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)				

Values are reported as mean (95% CI).

^a Alpha of statistical significance is 0.05.

^b Value represents Wilcoxon signed-rank test z score.

^c Cardiac index is calculated as follows: stroke volume × HR/body surface area.

Peak $\dot{V}O_2$, peak oxygen consumption; O₂ pulse, oxygen consumption per heart beat ($\dot{V}O_2$ /HR); HR, peak heart rate; SVI, stroke volume index (cardiac index/HR); TAPSE, tricuspid annular plane systolic excursion; RV S', right ventricle tissue Doppler peak annular velocity; SpO₂, peripheral capillary oxygen saturation; $\dot{V}_E$, minute ventilation; RER, respiratory quotient.

Figure 2. Peak oxygen consumption ($\dot{V}O_2$) by subject ($n = 12$).

association between ingesting sildenafil and increased RV S' , this potential drug effect did not yield a significantly improved exercise capacity. These observations during acute hypoxia, in combination with the chronic hypoxia studies discussed earlier, suggest that our use of acute hypoxia was not a limitation in this study. Rather, because a likely mechanism for sildenafil-induced benefits is the reduction of right ventricular afterload and improved ventilation-perfusion matching, our subjects simply may not have experienced sufficient altitude stress for hypoxic changes susceptible to sildenafil's effects to occur.

LIMITATIONS

We believe that the primary limitation was that participants did not experience adequate altitude stress. It is possible that there was not enough hypoxia-induced physiologic response between 1400 m and 2750 m for the drug to have been of benefit in healthy subjects. In particular, for those participants in whom we did not see any significant changes in performance measurements, the altitude change may not have been pronounced enough to generate a normal physiologic response to hypoxia (Figure 2; Table 2). Previous research has shown an effect of sildenafil in a much larger altitude difference between baseline and treatment conditions.^{5,9,12} Because subjects in the present study live at approximately 1400 m and exercise regularly at altitudes around 2750 m, they may have already been at least partially acclimatized to the study altitude. This could have contributed to the insignificant associations we observed.

Because our institutional review board required that we always perform the baseline exercise study at 1400 m under the direct supervision of a cardiologist as a first test (for screening and safety purposes), we cannot rule out the possibility that an order or learning effect influenced our results. Such an effect may have allowed

some subjects to push themselves harder on subsequent $\dot{V}O_2$ tests (at 2750 m) after the baseline assessment at 1400 m. Also, the test at 1400 m was not performed in the chamber, nor was there a sildenafil treatment at this altitude.

Another possible limitation of this study is that peak $\dot{V}O_2$ may not be the most appropriate metric for assessing physiologic changes associated with taking sildenafil at high altitude. A recent study by Kressler et al⁷ found no improvement in oxygen delivery and maximal exercise capacity at simulated moderate and high altitudes (2100 m and 3900 m, respectively) in 11 trained athletes ages 18 to 39 years after ingesting sildenafil, whereas Jacobs et al⁴² found that in 20 male and 15 female trained cyclists and triathletes (age range, 18 to 39 years), sildenafil had very little influence on cardiovascular hemodynamics, arterial oxygen saturation, and 6-km time-trial performance at a simulated altitude of 3900 m. Taken together with our observations of changes in RV S' function, it may be possible that sildenafil's influence is dictated by the severity of hypoxemia and by individual physiologic responses to hypoxia. These factors may be associated with changes in performance markers other than $\dot{V}O_2$. The present study's findings merit further investigation into a broader array of metrics in older people who may possibly gain some benefit from taking sildenafil before exercise at moderate altitude.

Finally, we cannot rule out a type II statistical error in this study (accepting the null hypothesis when it is in fact false), given the small number of subjects studied. In addition, heterogeneity in fitness, health, and preacclimatization—owing to varying durations of visits to nearby high altitudes by the subjects—may have affected the results.

Conclusions

The main finding of this study was that, during exercise at simulated moderate altitude, we did not observe an

association between sildenafil and changes in exercise capacity, as measured by peak $\dot{V}O_2$, among people 60 years or older. Whether these study results extrapolate to those living at sea level, then going to and exercising at 2750 m above sea level, is unknown. Further exploration is needed to gain a better understanding of the effects of sildenafil on exercise capacity at moderate elevations among active, elderly people. In particular, based on the results of this study, future studies should investigate a more extreme elevation difference between baseline and altitude conditions.

Acknowledgments

This research was supported by a Wilderness Medical Society Hultgren Award.

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