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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 mL · kg^{-1} · min^{-1} (95% CI, 32.7 to 41.3) vs 39.1 mL · kg^{-1} · 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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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 al[13] 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 CYP34A 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