International Journal of Research in Exercise Physiology

Original Research Article

Effect of Sildenafil on VO_2max in Collegiate Runners Acclimatized to Moderate Altitude

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ABSTRACT

Introduction: There are many factors that contribute to reduced performance at altitude. Some of the physiological responses to hypoxia include a decreased stroke volume, decreased blood oxygen saturation, and an increase in both systemic and pulmonary vasoconstriction. Sildenafil, a potent vasodilator, inhibits phosphodiesterase type 5 which promotes vasodilation via the augmentation of intracellular cGMP. **Methods:** Eight well-trained men (18.5 ± 0.53 yrs), acclimatized to 2348m, were asked to complete three graded exercise tests: A familiarization test, one after taking 50mg orally-ingested sildenafil (SIL) and one with a placebo (PLA). Subjects began the test on the treadmill at a speed of 8mph and a grade of 0%. Speed remained the same and grade was increased 1% each minute until volitional fatigue was reached. Performance was determined by measuring heart rate (HR), blood pressure (BP), time to exhaustion (TTE), blood oxygen saturation (SpO_2), rating of perceived exertion (RPE), and maximal oxygen consumption (VO_2max). HR and VO_2max were continually monitored, while RPE was measured every minute and SpO_2 data was collected every two minutes. BP was measured at rest, at maximal effort (immediately following volitional fatigue), and five minutes post completion. SPSS version 25.0 was used to run a paired-samples t-test for each independent variable and for both groups (PLA vs SIL). **Results:** TTE significantly increased in the SIL group compared to PLA (631.25 ± 52.07 vs. 584.63 ± 51.58, p<.001) as well as average SpO_2 (87.5 ± 2.05% vs. 92.6 ± 1.53%, p<.002). VO_2max decreased in the SIL group compared to PLA (62.38 ± 3.51 vs. 63.43 ± 3.52) though not significantly (p>0.05). Systolic BP at maximal effort decreased in the SIL group compared to PLA (156.88 ± 3.48 vs. 134.38 ± 11.48, p<.001). **Conclusions:** Athletes training or competing at altitude may see an increase in performance with sildenafil. This research is preliminary and further research should include a larger subject pool, a shorter timeframe for data collection, and additional performance measures such as a live race/competition.

KEYWORDS: Vasodilation, Endurance, Performance Enhancement, Hypoxia.

INTRODUCTION

Endurance athletes, competitive and recreational alike, are constantly looking for a means to improve performance. There are certain circumstances where an extreme environment can have a negative impact on performance, such as competing at altitude. Exposure to hypoxia increases systemic and pulmonary vasoconstriction which leads to a reduction in oxygen delivery to working muscles and, consequently, decreases endurance performance[1]. Several interventions have been shown to increase performance at altitude, however few directly address the problem of vasoconstriction. Sildenafil, the main substance in the brand name drug Viagra, was originally proposed to be an antianginal for patients with ischemic heart disease[2]. Many of the physiological responses to sildenafil suggest that it may have practical and clinical applications in the field of exercise science, namely the increase of performance at moderate altitudes.

Interest in sildenafil and the mechanisms through which it may mitigate some of the negative responses to hypoxic exposure has been growing. Results from current literature on what those mechanisms may be are as follows: Significant reduction in pulmonary artery pressure[3], significant increase in oxygen saturation and delivery[3,4], increase in maximum workload and cardiac output, and increased stroke volume[5].

One of the most exciting aspects of this drug is its accessibility and potential for widespread use and application. Much of the research that has been done on this topic has focused on the effects of sildenafil on exercise performance at extreme altitudes compared to sea-level. There is less of an understanding of the effect of sildenafil on exercise performance at residential altitude, as well as its efficacy. The purpose of this study was to examine the effects of the drug sildenafil on VO_2max, oxygen saturation, and blood pressure during exercise at moderate altitude in trained runners acclimatized to 2348m.

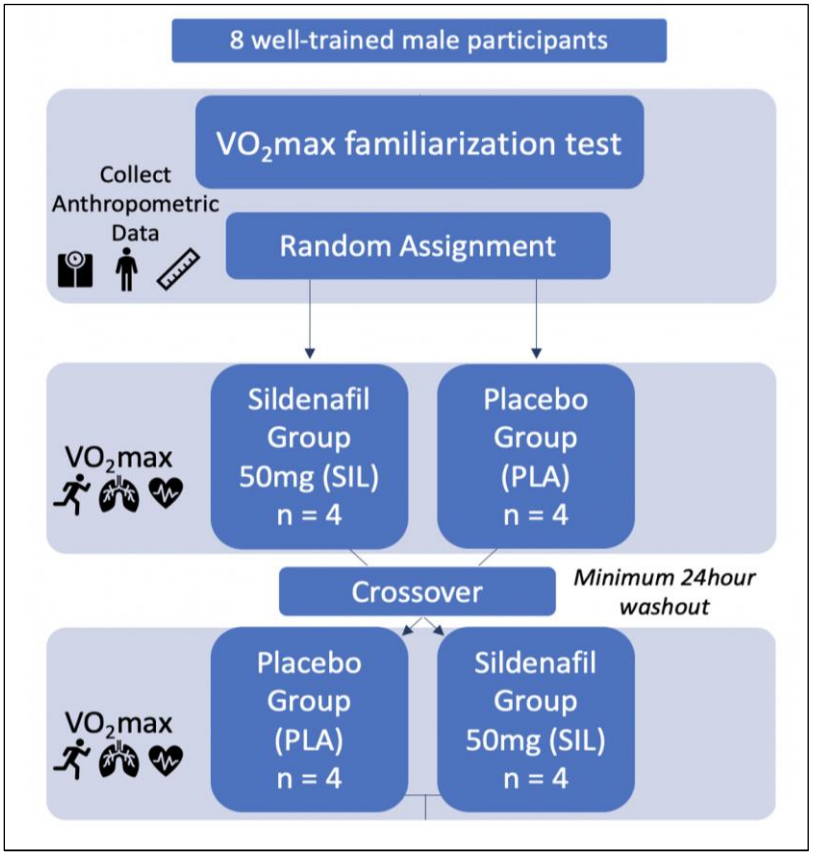
Table 1. Subject Anthropomorphic Data.

Characteristic (n = 8)	Mean ± SD
Age (yrs)	18.5 ± 0.53
Height (cm)	177 ± 7.58
Weight (kg)	63.1 ± 5.01
VO_2max - baseline (mL/kg/min)	65.2 ± 3.23

METHODS

Subjects

Eight well-trained men were recruited via word of mouth and email from the cross-country team at Western Colorado University (WCU). Subject characteristics are presented in Table 1. Inclusion criteria included: being a member of the WCU men's track and field team and low risk according to the American College of Sports Medicine (ACSM) guidelines. Exclusion criteria included: athletes competing outside of the 1500m to 10,000m event range, having an injury that would inhibit the ability to complete two VO_2max tests within a four week timespan, currently taking medication for erectile dysfunction or high blood pressure, or those with a resting blood pressure of less than 100/60 mmHg. All procedures were approved by the University's Human Subjects Institutional Review Board (IRB#: HRC2019-01-03-R76). All subjects signed a written informed consent and were made aware that consent could be withdrawn at any point without penalty. All data was collected in the High Altitude Performance Laboratory on the Western Colorado University Campus (2348m).



Key: = Treadmill test, VO_2max data, and HR = Weight, body comp, and height

Figure 1. Experimental design for the effect of Sildenafil on VO_2max in collegiate runners.

Experimental Design

This randomized, placebo controlled, crossover design evaluated the effects of sildenafil on exercise performance by measuring certain parameters including heart rate (HR), blood pressure (BP), time to exhaustion (TTE), blood oxygen saturation (SpO_2), and maximal oxygen uptake (VO_2max). Subjects were asked to complete a series of three VO_2max tests. The purpose of the first test was to allow subjects to become familiar with the testing protocol and was done without treatment. Results from the familiarization test were recorded but not used in data analysis. Subjects were then randomly placed into one of two groups, sildenafil (SIL) and placebo (PLA). The next test was performed either with treatment (50mg sildenafil) or placebo (sugar pill) and was followed by a third test where subjects crossed over into the opposite group. Experimental design is displayed in Figure 1.

Procedures

Height and weight

Height and weight were obtained using one device that measures both (Tanita Corporation, Tokyo, Japan). Subjects were asked to wear whatever clothing that they would be wearing during the test (including shoes) and to stand tall with their back against the stadiometer and heels together with feet pointing out at an angle of 45degrees. Height (cm) was recorded twice and the average of the two was used as the final measurement. Weight (kg) was also measured twice and the average of the two values was used.

Blood Pressure (BP) and Blood Oxygen Saturation (SpO_2)

BP values were collected manually via sphygmomanometer (Graham-Field Health Products, Atlanta, GA). Subjects were asked to sit down and relax their right arm after the blood pressure cuff was secured. Resting measurements were taken a minimum of two times until systolic and diastolic were within 5 units from the previous measurement. SpO_2 was continually monitored via a pulse oximeter (American Diagnostic Corporation, Hauppauge, NY) which subjects held in their hand while it was attached to their finger for the duration of the test.

Sildenafil and Placebo

The treatment group (SIL) received 50mg of oral sildenafil while the placebo group (PLA) received an inert pill approximately 90 min before warm-up. Subjects were not asked to stay in the lab after ingestion and were allowed to wait the 90 min either in class or in their dorm. Because the sildenafil and placebo tablet were visually identifiable, subjects were asked to ingest the pill (which was given to them in a small clear container) without looking.

VO_2max, Heart Rate (HR) and Time to Exhaustion (TTE)

Subjects were asked to perform a graded exercise test on a treadmill (Trackmaster, Newton, KS). Heart rate was continuously

monitored using a chest strap and paired watch (Polar Electro Model FS1, Woodbury, NY). Using a Parvo Medics metabolic cart (TrueOne, 2400, Parvo Medics, Sandy, UT), gas exchange was continuously monitored and automatically recorded every fifteen seconds. VO_2max was determined by averaging the three highest recorded scores which usually occurred in the last minute of the VO_2max test. The time at which the subject ended the test due to volitional fatigue was considered TTE.

For the warm-up, subjects ran for 10min at a self-selected pace (typically around 7-8mph) on the treadmill. There was a wait period of approximately 3-4 min after completion of warm-up. During this time subjects were fitted with face mask for ventilation data. Once the VO_2max test started, subjects ran at a speed of 8mph and a grade of 0%. Speed remained the same while grade was increased by 1% every minute until volitional fatigue. Heart rate and VO_2 were continually monitored. SpO_2 was measured every 2min. Blood pressure was taken at rest (after 90min wait period post-ingestion) at maximal effort (immediately following point of volitional fatigue) and after 5min of recovery post VO_2max test.

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL, USA) was used to determine the mean and standard deviation (mean $\pm$ SD) for all anthropometric measures. Additionally, this software was used to run a paired-samples t-test for each independent variable (max HR, BP, TTE, etc.) for both groups (PLA vs. SIL). This allowed us to determine whether there was a statistically significant difference in measurements taken under each condition. All statistical tests were run with a confidence interval of 95% ($p<0.05$). For variables that showed statistical significance, Eta squared was calculated to determine the magnitude of the intervention's effect. The formula, as well as guidelines for interpreting this value are as follows:

$$Eta\ squared\ = \frac{t^2}{t^2 + (N-1)}$$

*0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect

RESULTS

Overall, the subjects tolerated the intervention and testing well. Two of the subjects reacted to the sildenafil with mild side effects (flushing and sinus congestion), neither of which affected their ability to complete the test.

VO_2max

There was a non-significant difference in VO_2max between SIL and PLA (62.38 ± 3.51 ml/kg/min, 63.43 ± 3.52 ml/kg/min). See Table 2.

Time to Exhaustion

A paired-samples t-test showed a statistically significant difference in TTE for

PLA vs. SIL (585 ± 52sec, 631 ± 52 sec, t(7) = 9.89, p(two-tailed) < 0.001). On average, athletes who received sildenafil were able to extend their time to exhaustion by 47 seconds with a 95% confidence interval ranging from 35 to 58 seconds. The eta squared statistic (.93) indicated a large effect size. Individual data for TTE is shown in Figure 2.

Table 2. VO_2max Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
VO2max (mL/kg/min) - PLACEBO	62.3750	8	3.50907	1.24064
VO2max (mL/kg/min) - SILDENAFIL	63.4250	8	3.52126	1.24495

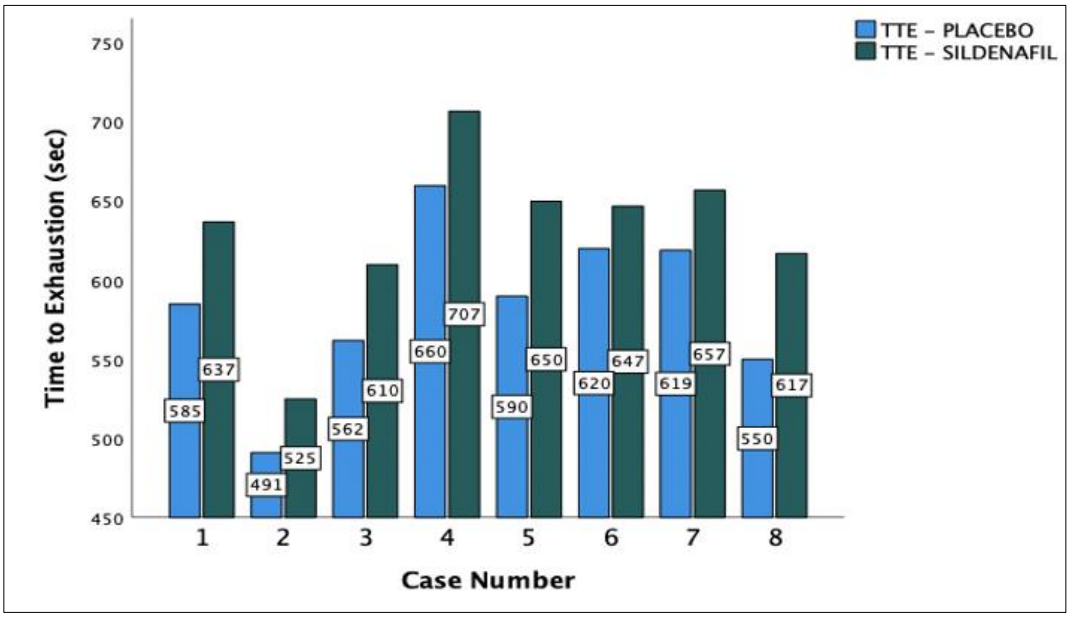


Figure 2. TTE individual case data for PLA and SIL treatments.

Oxygen Saturation

A paired-samples t-test was conducted to evaluate the impact of sildenafil on athletes' average oxygen saturation (% SpO_2) during maximal exercise. There was a statistically significant increase in SpO_2 with SIL when compared to PLA (93 ± 2%, 88 ± 2%, t (7) = 4.86, p(two-tailed) < .002). The mean increase in SpO_2 with sildenafil was 5.06% with a 95% confidence interval ranging from 2.60 to 7.53%. The eta squared statistic (.77) indicated a large effect size.

Resting and Max Blood Pressure (Systolic and Diastolic)

Results from resting BP measurements were like VO_2max in that, while there was a difference between groups, the difference was not statistically significant. It is important to note, however, that resting values for both systolic (SBP) and diastolic blood pressure (DBP) were lower in the SIL vs. PLA group (SBP: 109 ± 7 mmHg vs. 111 ± 6 mmHg, DBP: 59 ± 5 mmHg vs. 60 ± 5 mmHg).

A paired-samples t-test showed that there was a statistically significant decrease in max SBP with SIL when compared to PLA (134 ± 11 mmHg, 157 ± 3 mmHg, t (7) = 5.13, p(two-tailed) < .001). Subjects who took sildenafil saw an average decrease in max systolic blood pressure of 22.5 mmHg with a 95% confidence interval ranging from 12 to 33 mmHg. The eta squared statistic (.79) indicated a large effect size. There was no significant difference in diastolic blood pressure between groups. Individual data for max systolic BP is shown in Figure 3.

Max Heart Rate

A paired-samples t-test showed no significant difference between groups in max heart rate achieved. However, it may be important to note the difference between SIL and PLA groups (188 ± 9 bpm, 185 ± 7 bpm, t (7) = 2.09, p(two-tailed) = .075). The mean increase in max heart rate achieved with sildenafil was 3 beats per minute. The p-value (.075) indicates that, while the differences were not statistically significant using a confidence interval of 95%, they are very close and would likely show greater significance with a larger sample size.

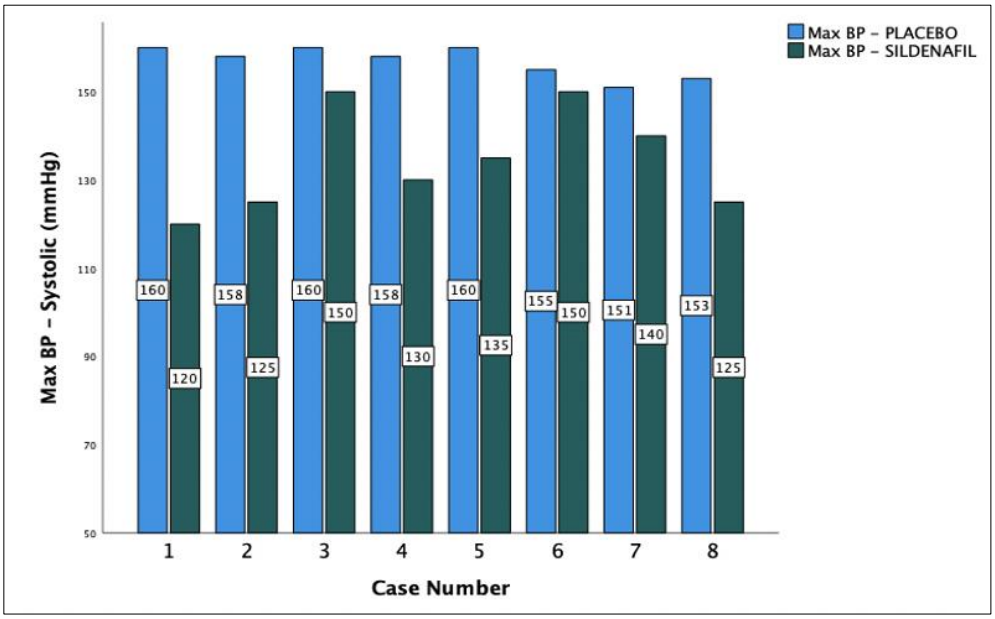


Figure 3. Max BP individual case data for PLA and SIL treatments.

DISCUSSION

The purpose of this study was to examine the effects of sildenafil on VO_2max, oxygen saturation, and blood pressure during exercise at moderate altitude in trained runners acclimatized to 2348m.

VO_2max

It was interesting to see the fluctuations in VO_2max among subjects. While there was a mean increase by approximately 1ml/kg/min, the individual data points tell a different story. Out of the eight subjects tested, five of them saw a reduction in VO_2max with sildenafil. This may be due to the amount of time some subjects had to wait between tests. All subjects for this study were athletes at XXX and tests were conducted during their sport's competitive season. Because of this, several of the subjects were forced to wait three or more weeks between tests (after the conclusion of their season). This is important because, after the conclusion of a season, collegiate athletes often take time off to recover mentally and physically. This could have contributed to the decrease in max VO_2 in four of the subjects who took sildenafil during this scheduled 'break' from normal training. The lack of any statistically significant difference in VO_2max between groups, while TTE was significantly increased, indicates that athletes were able to conserve energy while exercising for a longer period and at a greater intensity.

Even with the results being the opposite of expected for five of the subjects, there was still an overall increase in VO_2max. Literature suggests that typically, it can take high level athletes several months of vigorous training to increase VO_2max by even small margins[6]. The overall results for this measurement, and the fact that three of the subjects saw an average increase of 3.5ml/kg/min, indicate a possible clinical significance, although it is difficult to see statistically significant increases in a group with such a high baseline.

Time to Exhaustion

This was one of the more exciting results from this study. Not only did sildenafil significantly increase subjects' time to exhaustion ($p < .001$), but it did so in a major way. Subjects using sildenafil were able to exercise for an average of 47 seconds longer before reaching volitional fatigue while also reaching a higher stage of intensity (increases in speed and grade were the same for both tests). It is not difficult to see why this would be advantageous for an endurance athlete, especially considering that the average test lasted anywhere from nine to eleven minutes. Increasing the amount of time an individual can perform at maximal effort by approximately 10% would certainly be beneficial for any athlete, especially those participating in competition.

It is well documented that acute exposure to hypoxia leads to a significant reduction in time to exhaustion at a given work rate[7]. Similar improvements in TTE (for well-trained endurance athletes) may require roughly three weeks of intermittent or continuous hypoxic exposure[8]. The fact that the subjects

in this study were already acclimatized to 2348m altitude, but still saw this increase in TTE, indicates that sildenafil may be advantageous to athletes acclimatized to and competing at altitude. This is of particular importance as even acclimatized athletes see a general decrease in aerobic capacity by approximately 15% compared to sea level[9].

Oxygen Saturation

The SIL group's average SpO_2 was five percent higher than the PLA group (93% SIL vs 88% PLA). This confirms the consensus results of previous research which found that, under hypoxic conditions, sildenafil increased SpO_2 during submaximal and maximal efforts[3,5,10] but not at rest[4]. As discussed earlier, SpO_2 is an important factor in determining the cardiovascular state of an athlete at a given point in time with regards to the energy system being used. Typically, a higher SpO_2 would indicate less oxygen extraction, which explains why oxygen saturation numbers are the highest at rest. An average elevated SpO_2 over the course of a VO_2max test suggests an increase in overall oxygen availability which would delay the onset of anaerobic cellular respiration thus potentially improving endurance performance[7]. These findings are also supported by the statistically significant increase seen in TTE with sildenafil.

Resting and Max Blood Pressure (Systolic and Diastolic)

There was no statistically significant difference in resting BP between PLA or SIL groups. This may be, in part, because subjects had a very low baseline average resting blood pressure (112/62 ± 4/3 mmHg). While not statistically significant, resting BP was slightly lower in the SIL group. This result is expected considering the mechanisms through which sildenafil operates, specifically regarding systemic vasodilation. Concerning this measurement, significant results may be more likely in a recreationally active population whose resting measurements are not so low.

Subjects in the SIL group saw a significant decrease in maximal blood pressure ($p < .001$). This implies that an athlete could accomplish a similar or even increased output while reducing the amount of strain on the heart and endothelial tissue. Acutely, increased cardiovascular strain is a normal response to exercise and is typically followed, chronically, by a reduction in resting blood pressure[6, 8]. However, this exercise induced increase in blood pressure may be dangerous for certain populations (cardiovascular disease, kidney disorders, obesity etc.) and could increase risk of experiencing a cardiac event. Consequently, sildenafil may be advantageous for those who (1) have a resting blood pressure above the normal range, (2) have one or more cardiovascular risk factors which may be exacerbated by exercise, (3) wish to reduce the effects of hypoxia-induced hypertension during exercise. Because the effects of sildenafil last approximately three to four hours, it could be especially helpful for non-trained recreational athletes who are visiting an area of altitude for a few

days/weeks and wish to be active (skiing, mountain biking, hiking, etc.).

Max Heart Rate

While the results from this study showed that sildenafil did not have a statistically significant impact on max heart rate, the difference between groups may have clinical significance. Subjects who took sildenafil had a non-significant increase in max heart rate by an average of over three beats per minute ($p = .075$). This non-significant increase in max heart rate was most likely linked to increased TTE, as subjects in the SIL condition ran longer before volitional fatigue. Additionally, from a mechanistic perspective, sildenafil works to increase vasodilation thereby increasing blood flow to working tissue resulting in increased preload on the heart. Increased preload on the heart may therefore result in increased stroke volume and, at the same heart rate, increased cardiac output[5]. Thus, the finding that max heart rate did not increase significantly in the SIL group is not surprising.

CONCLUSIONS

Exposure to hypoxia is met with a number of detriments to physical performance including reduced exercise capacity which is not fully alleviated after acclimatization. Hypoxia induces a number of physiological adaptations to offset reduced oxygen availability, including an increase in erythropoiesis – the production of red blood cells[11]. While this leads to an increase in O_2 carrying capacity which helps offset overall acute detriments to performance, VO_2max stays relatively the same or is suppressed even after acclimatization[12,13]. Additionally, this stimulation of red blood cell production does not increase VO_2max in chronic hypoxia because it is largely offset by a decrease in cardiac output[14,15].

After examining the data from 24 graded exercise tests completed by eight subjects, the statistical analysis concluded that athletes training or competing at altitude may see an increase in performance through the use of sildenafil. This conclusion is supported by previous research involving sildenafil, however this is the first, to our knowledge, to observe its effects on well-trained athletes who are fully acclimatized to moderate altitude. It is also important to note that sildenafil is a prescription drug which is only approved for a small number of medical uses, athletic performance not being included. Future research should include 1) a larger and more diverse subject pool, 2) a shorter timeframe for data collection, and 3) various means of measuring performance such as a time-trial or a real race/competition. Additionally, future research should study the effects of sildenafil in more recreational athletes and over a longer time period. Regardless, our results point to the need for sildenafil to be considered by the medical/exercise science community as a possible means to safely and effectively increase exercise performance under acute or chronic hypoxic conditions.

Utilizing a drug such as sildenafil may therefore confer exercise performance benefits beyond those realized with acclimatization in endurance trained athletes.

ACKNOWLEDGMENTS

Special thanks to the subjects that participated in this study and to Dr. Christina Buchanan for her guidance and support throughout the duration of this project. Also, thanks to my classmate and friend Mr. Jon Specht for his help with organizing this research and data collection.

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