

### ABSTRACT

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Blood pressure typically decreases following exercise, a phenomenon known as post-exercise hypotension (PEH). The cause of PEH is unclear but may include NO dependent mechanism. Men with erectile dysfunction are prescribed PDE-5 inhibitors to prevent the destruction of NO, thus producing a vasodilatory effect. Consumption of PDE-5 inhibitors may increase the effect of PEH by augmenting the effect of NO. This study compared PEH in active middle-aged men following heavy exercise with and without presence of a PDE-5 inhibitor (Sildenafil). Physically active men (mean age  $54 \pm 13$ ) performed 40 minutes of heavy exercise ( $\sim 80\%$  MHR) on two occasions, one hour following ingestion of either 50 mg of Sildenafil or placebo. Blood pressure was measured pre-exercise and immediately post-exercise at 10 minute intervals for 40 minutes. Blood pressure was significantly lower pre-exercise on Sildenafil  $108 \pm 14$  vs.  $116 \pm 15$  and decreased in parallel throughout post-exercise. PDE-5 inhibitors apparently increase the magnitude of reduced blood pressure both before and following heavy exercise. However, there is not an augmented response of PEH on PDE-5 inhibitors.

UNIVERSITY OF WISCONSIN-LA CROSSE

Graduate Studies

THE EFFECT OF PDE-5 INHIBITORS ON POST-EXERCISE BLOOD PRESSURE

A Manuscript Style Thesis Submitted in Partial Fulfillment of the Requirements for the  
Degree of Master of Science

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College of Science and Allied Health  
Clinical Exercise Physiology

December, 2010

# THE EFFECT OF PDE-5 INHIBITORS ON POST-EXERCISE BLOOD PRESSURE

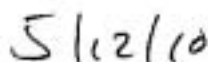
By Jessica Gehrke

We recommend acceptance of this thesis in partial fulfillment of the candidate's requirements for the degree of Master of Science Clinical Exercise Physiology.

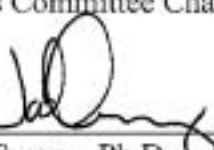
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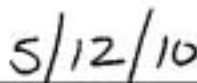
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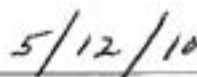
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## INTRODUCTION

Post-exercise hypotension (PEH) can be attributed to a decrease in peripheral vascular resistance (PVR) following exercise caused by both neurohumoral and structural adaptations [1] and can last up to several hours after exercise depending on the intensity [2] and duration [3] of the exercise. Data has suggested an additional factor affecting PEH which was observed very shortly following relatively higher intensity exercise [2], suggesting the potential for nitric oxide (NO) to be a contributor to PEH.

The inability to produce NO and fully dilate the arteries is referred to as endothelial dysfunction and is caused by atherosclerotic damage of the endothelium lining of the arteries. Endothelial dysfunction is the underlying cause for erectile dysfunction. For the millions of men in the U.S. with erectile dysfunction, Phosphodiesterase-5 (PDE-5) inhibitors are prescribed to prevent the destruction of NO, allowing vasodilation and increased blood flow to occur to the areas where PDE-5 sites exist, such as the lungs and the corpora cavernosa in the penis [4]. If a PDE-5 inhibitor is consumed prior to heavy exercise, too much NO could accumulate due to its "modest nitrate-like effect," [5] and may increase the magnitude of PEH, causing dizziness, fainting or other symptoms of hypotension. However, no studies have analyzed the effects of PDE-5 inhibitors on PEH in men.

There are three main PDE-5 inhibitors currently prescribed: Sildenafil (Viagra), Tadalafil (Cialis), and Vardenafil (Levitra). Sildenafil and Vardenafil are short-acting



PDE-5 inhibitors with half-lives of 4-6 hours. Taken daily with other medications, Tadalafil is potentially a more ideal PDE-5 inhibitor due to its long half-life. With Tadalafil the timing of the consumption of the medication is not necessary. The concentration of the PDE-5 inhibitor will be high enough throughout the day so sexual activity need not be scheduled, which is more convenient than timing medication intake an hour prior to effect [6]. Because the future of PDE-5 inhibitors is moving towards the longer-acting, once a day medication Tadalafil (Cialis), and because more of the men being treated for erectile dysfunction may be physically active (including competition), there is a concern about the effects and/or risks of PDE-5 inhibitors on PEH.

To date, no studies have analyzed the effects of PDE-5 inhibitors on PEH after intense exercise. This study was designed to evaluate the effects PDE-5 inhibitors have on PEH following heavy exercise. It was hypothesized that high-intensity exercise in addition to PDE-5 inhibition would significantly lower systolic, diastolic and mean arterial blood pressure compared to high-intensity exercise alone.

## **METHODS**

Ten physically active, apparently healthy males between 41-62 years of age were recruited to participate in this study. Demographic characteristics of subjects are shown in Table 1. The age range of our subject sample approximates PDE-5 inhibitors prescribed for individuals with erectile dysfunction. Subjects recruited for the study had been physically active on a regular basis (at least 3 days/week for 6 months) and were able to complete a strenuous 40 minute exercise bout. The study was approved by the University of Wisconsin-La Crosse Institutional Review Board (IRB) for the Protection

of Human Subjects and subjects provided written informed consent and filled out the American Heart Association Pre-Participation Screening Questionnaire prior to testing [7]. Five total subjects were on cardiac related medications. Two subjects were on a calcium channel blocker, ACE-inhibitor and a statin, one subject was on a calcium channel blocker, and two subjects were taking statins alone. Prescribed drug therapy was continued during the study.

Table 1. Mean Characteristics of Subjects

Age, Y	54 ± 13
Height, cm	177 ± 14
Weight, kg	93 ± 21
VO <sub>2max</sub> , mL/kg/min	34 ± 12
Percent Predicted VO <sub>2max</sub> , %	108 ± 24

### Testing Protocol

A graded exercise test was performed to rule out an underlying heart disease or other contraindications to participation in the study. Subjects were able to select their preferred modality of exercise, either cycle ergometer or treadmill. The exercise test on the cycle ergometer consisted of 2 minute stages starting at 25 watts and increasing 25 watts per stage until the subject was unable to continue. A modified Balke protocol with 2 minute stages was used for subjects who preferred treadmill exercise. During the graded exercise test, subjects were monitored via a 12-lead EKG machine. Blood

pressure, heart rate, RPE and the Talk test were recorded during each of the 2 minute stages. The Category Ratio (1-10) Rating of Perceived Exertion (RPE) Scale was used to rate the subjective intensity of the workload [8].

Ventilatory Threshold was estimated via the Talk Test, in which the subject was asked to recite the "Pledge of Allegiance" to determine if they were able to talk comfortably [7]. The exercise test was used to define the workload for the two experimental exercise trials. The workload chosen for the two exercise trials was the last positive stage of talk test (correlating to an intensity just below ventilatory threshold). A minimum of 48 hours was allotted between the exercise trial to allow for recovery and ensure the "washout" of the active agent.

The subjects completed two exercise bouts at an intensity approximately the ventilatory threshold, one with 50 mg of Sildenafil and one with placebo. Sixty minutes prior to the exercise bout, the subject consumed either a placebo or 50 mg of Sildenafil. Administration was randomly ordered and double blind.

Upon arriving to the lab, the subject sat for 5 minutes prior to the resting blood pressure being measured by the researchers. After acquiring the resting blood pressure, the subject warmed up for five minutes prior to starting the forty minute exercise bout. The subject remained at a constant exercise intensity for the entirety of the workout. After the 40 minute exercise session the subject completed a two minute cool-down. Three minutes after the cool-down a recovery blood pressure was taken with the subject sitting. Blood pressures were obtained every subsequent ten minutes. A physician was readily available during all testing.

Subjects reached a mean heart rate of  $124 \pm 15$  beats per minute (bpm) with placebo and  $125 \pm 17$  bpm with Sildenafil at 40 minutes of exercise, corresponding to  $81.8 \pm 10.5\%$  and  $82.8 \pm 11.3\%$  of their achieved max heart rate, respectively. The rating of perceived exertion (RPE) was  $4.5 \pm 1.8$  and  $4.9 \pm 1.95$  on the placebo and Sildenafil trials, respectively.

### **Statistical Analysis**

Mean values of outcome variables were compared using Repeated Measures of ANOVA. Post Hoc analyses were done using the Tukey test when justified by ANOVA.

## **RESULTS**

### **Systolic Blood Pressure**

Systolic blood pressure increased during exercise and reached a mean systolic blood pressure of  $168 \pm 41.5$  mmHg and  $156 \pm 47$  mmHg for placebo and Sildenafil trials, respectively. Ten minutes post-exercise, systolic blood pressure was  $108 \pm 19.5$  mmHg and  $105 \pm 17$  mmHg for placebo and Sildenafil trials, respectively (see Figure 1). Sildenafil administration created an overall significant reduction in systolic blood pressure compared to the placebo trial ( $p = .002$ ). Systolic blood pressure changed significantly over time during the 40 minute rest period ( $p < .001$ ). Pressure was significantly higher immediately after exercise compared to 10 minutes post-exercise. Although the overall systolic pressure was lower with the PDE-5 inhibitor, PEH was observed in both trials but there was no interaction effect between the exercise trials (placebo vs. Sildenafil) and time.

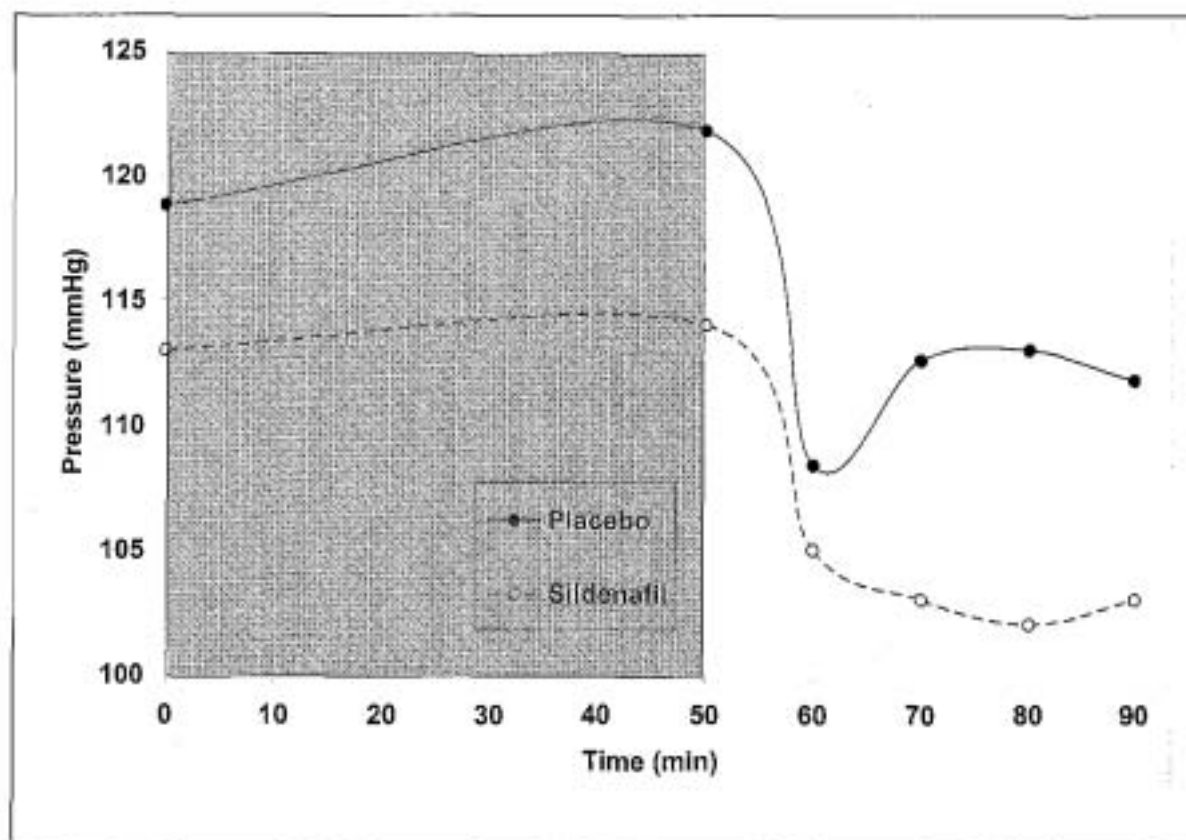


Figure 1. Systolic Pressures for Placebo and Sildenafil. Post-exercise blood pressure were taken 5 min after completion of exercise and every 10 minutes after.

### Diastolic Blood Pressure

Diastolic blood pressure remained constant or decreased slightly throughout the 40 minute intense exercise bout for both the placebo and Sildenafil trials. Diastolic blood pressures at rest were  $74 \pm 11.5$  mmHg and  $72 \pm 15$  mmHg for placebo and Sildenafil groups, respectively. At 40 minutes post-exercise these values decreased significantly ( $p=.033$ ) to  $71 \pm 11.5$  mmHg and  $68 \pm 12.5$  mmHg for placebo and Sildenafil groups (see Figure 2). The overall diastolic blood pressure was lower for the Sildenafil group at rest,

throughout the exercise trial, and stayed lower through the 40 minutes of monitored post-exercise rest. Similar to the systolic blood pressure, there was no interaction effect for diastolic blood pressure in the different exercise trials and time. Although the Sildenafil elicited an overall decrease in diastolic blood pressure compared to the placebo group, the PEH response was not significantly different between the placebo and Sildenafil trials.

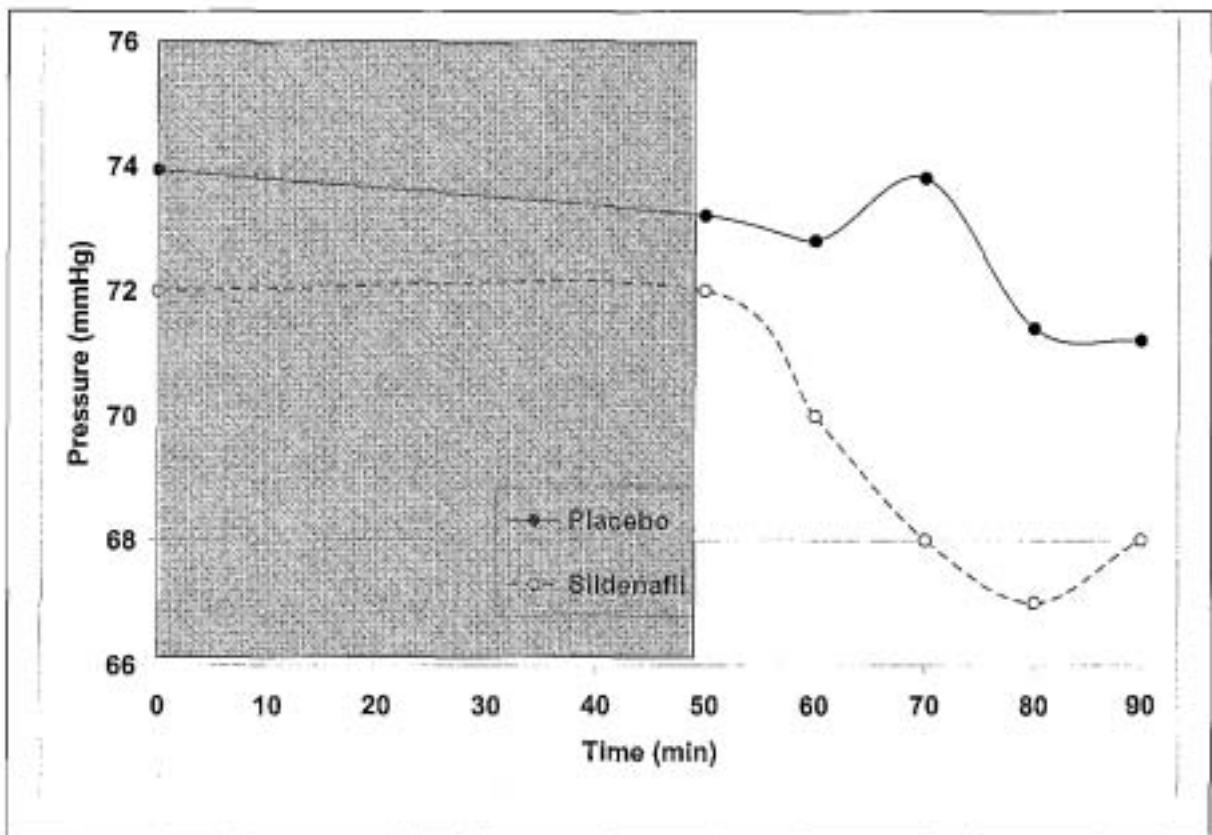


Figure 2. Diastolic Pressures for Placebo and Sildenafil. Post-exercise blood pressure were taken 5 min after completion of exercise and every 10 minutes after.

### Mean Arterial Pressure

Mean Arterial Pressure (MAP) increased during the 40 minute intense exercise bout in both the placebo and Sildenafil exercise trials. Baseline MAP for the control and experimental trials was  $89 \pm 12.4$  mmHg and  $86 \pm 15.5$  mmHg, respectively. At 40 minutes post-exercise, MAP decreased to  $85 \pm 14$  mmHg and  $80 \pm 14.5$  mmHg, for the placebo and Sildenafil exercise trials, respectively (see Figure 3). The MAP values predictably coincided with both the systolic and diastolic blood pressures and were significantly lower throughout the Sildenafil trial compared to the placebo ( $p=.002$ ) and decreased significantly throughout the post-exercise rest period. As with the systolic and diastolic blood pressure, Sildenafil did not create a significant decrease in MAP over time compared to the placebo group.

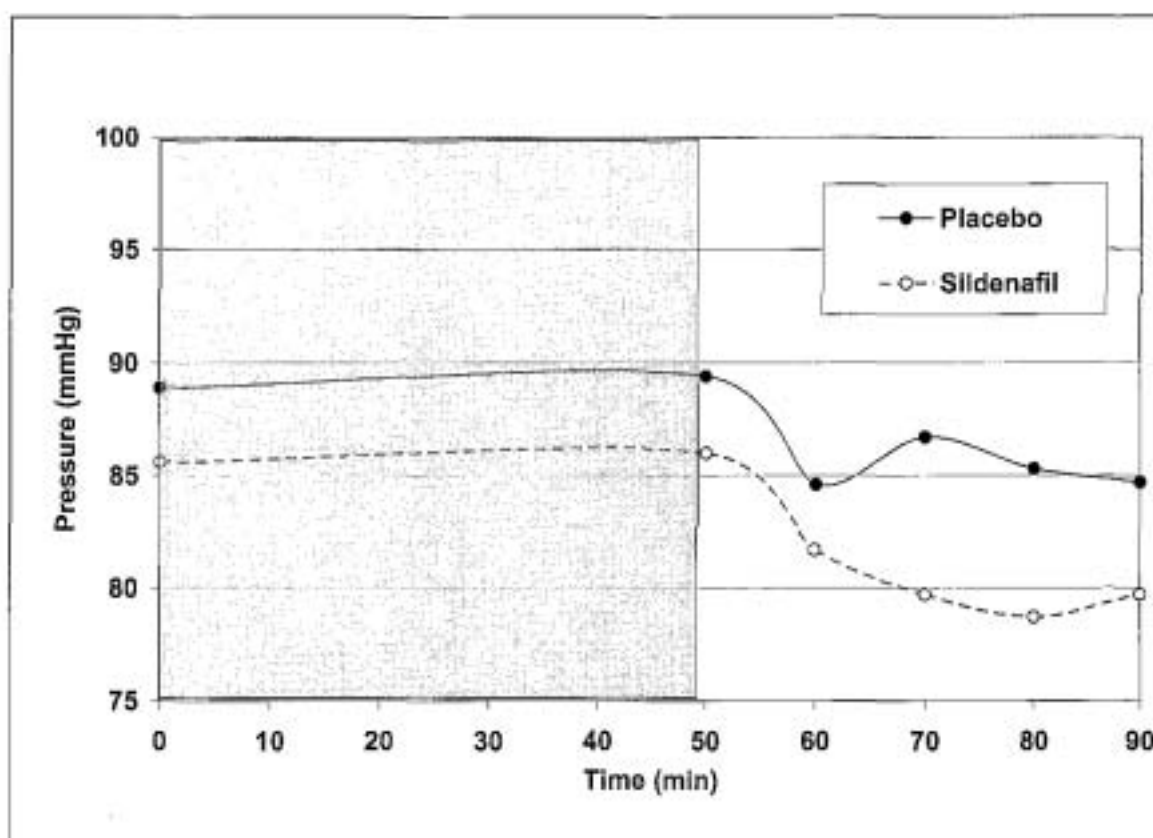


Figure 3. Mean arterial pressure for Placebo and Sildenafil. MAP was calculated by  $DBP + 1/3 PP$  at 5 min post-exercise and at 10 min increments thereafter.

### Heart rate

The heart rate response did not vary significantly between the placebo and Sildenafil exercise trials. Resting heart rate with the Sildenafil trial was higher at baseline,  $70 \pm 14.8$  bpm, compared to  $62 \pm 10.5$  bpm in the placebo trial. At the end of the intense 40 minute exercise bout the average heart rate was  $124 \pm 15$  bpm and  $126 \pm 17$  bpm, corresponding to 82% and 83 % of the achieved max heart rate, for the placebo vs. Sildenafil trials, respectively (see Figure 4). During the 40 minute post-exercise rest period, heart rate was significantly different between placebo and Sildenafil. Heart rate



was elevated immediately following the exercise bout ( $94 \pm 11$  bpm for placebo and  $92 \pm 16$  bpm for Sildenafil) and decreased 10 minutes post-exercise to  $76 \pm 16.5$  bpm and  $81 \pm 13.5$  bpm for placebo and Sildenafil, respectively. Because there was no significant interaction for heart rate between the placebo and Sildenafil exercise trials, heart rate was not significantly affected by Sildenafil ( $p=.453$ ).

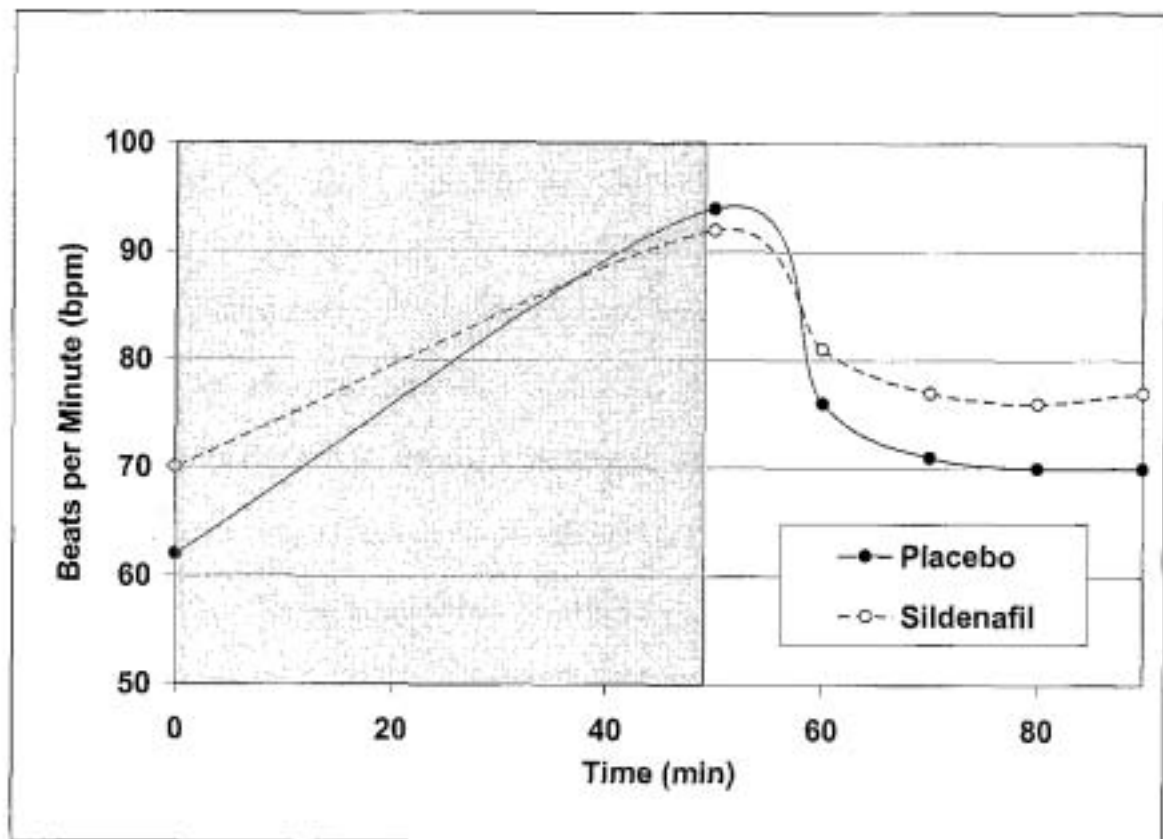


Figure 4. Heart rate trends for Placebo and Sildenafil. Heart rate was recorded 5 min post-exercise and every 10 minutes thereafter.

## DISCUSSION

The objective of this study was to evaluate the effects of a PDE-5 inhibitor (Sildenafil) on post-exercise blood pressure. Overall Sildenafil lowered systolic, diastolic, and mean arterial pressure compared to placebo. However, Sildenafil did not produce a greater magnitude of PEH compared to the placebo trial, but rather produced a parallel decrease in blood pressure in comparison to the placebo, beginning with the pre-exercise measurement.

These findings agree with a study completed using subjects with known coronary artery disease (CAD) who randomly assigned to a placebo or Sildenafil group and performed exercise on a supine bike [10]. Systolic pressure was significantly lower at rest and throughout exercise. Consistent with our findings, the magnitude of PEH was not intensified with Sildenafil compared to placebo. In agreement with our findings, the rest, exercise, and post-exercise heart rate was not significantly different between the Sildenafil and placebo trials.

Several studies have analyzed the effects of exercise on post-exercise blood pressure. Coinciding with the current findings, systolic blood pressure decreased post-exercise after an intense bout of exercise. In 2002, effects of exercise and L-arginine supplementation on post-exercise blood pressure were analyzed. A significant decrease in systolic blood pressure in all groups (exercise, L-arginine supplementation, and exercise and supplementation) was reported; the greatest systolic PEH occurred in the combination group [11]. The present results agree with the findings of a previous study [2] that there is an early and larger decrease in blood pressure post-exercise, consistent with the short acting mechanism (e.g. NO). In 2005, the effect of exercise duration on

PEH was analyzed [3]. Subjects exercised on an average of 68% of maximal heart rate. All exercise trials (10, 20, 40 and 80 min) produced a significant decrease in systolic blood pressure post-exercise in comparison to the control condition. A longer duration and magnitude of PEH with the longer duration (40 and 80 minutes) exercise trials was reported.

Studies that analyzed diastolic pressure post-exercise were not in agreement with findings from this study. No significant decrease in the diastolic pressure was noted at 4 varying intensities in a previous study [2]. Increases in diastolic blood pressure were not observed in a study evaluating the effects of L-arginine, an amino acid that “acts as a precursor to nitric oxide” [11]. Our study found diastolic blood pressure to be significantly lower between the placebo and Sildenafil exercise trials suggesting that PDE-5 inhibitors have a small but measureable effect on the diastolic blood pressure.

The present study subject exercised at  $81.8 \pm 10.5\%$  and  $82.8 \pm 11.3\%$  of their max heart rate in the placebo and Sildenafil trials, respectively. A significantly greater amount of hypotension was observed at 30 minutes post-exercise with an intensity slightly above ventilatory threshold, characteristic of a competitive level exercise, in comparison to the other three intensities [2]. In the present study, two subjects achieved relatively higher intensities during the trials in comparison to the other 8 subjects. These two subjects reached an RPE value of  $7.3 \pm 1.0$  and  $8.3 \pm 1.8$  for the placebo and Sildenafil exercise trials respectively compared to the other subjects who achieved mean RPE values of  $4.0 \pm 0.9$  and  $4.0 \pm 0.7$  for the placebo and Sildenafil trials, respectively.

The two subjects that exercised at a higher intensity defined as “very hard” to “very, very hard” or 8-9 on the RPE scale experienced a larger degree of PEH 40 minutes

post-exercise than the other 8 subjects that exercised in a training intensity representative of a "Moderate" to "Hard" or 3-5 rating on the RPE scale. On average, subjects reached a decrease in systolic pressure of  $8.0 \pm 8.7$  mmHg on placebo and  $7.0 \pm 8.3$  mmHg with Sildenafil 40 minutes post-exercise (see Figure 5). The two subjects that exercised at a competitive intensity experienced a  $4.0 \pm .42$  mmHg decrease in systolic pressure with placebo and  $20.0 \pm 4.2$  mmHg 40 minutes post-exercise with Sildenafil.

Thus, it appears that with higher intensity exercise, at or above ventilatory threshold, the presence of Sildenafil increased the magnitude of PEH [2]. This reasonably would be attributable to higher levels of NO present during harder exercise and preservation of the NO effect by the PDE-5 inhibitor. A follow-up study should be completed analyzing the effect of the PDE-5 inhibitor during training intensity (RPE 3-5) versus competitive intensity (RPE 8-10) exercise to analyze the effect of rapid acting mechanisms of PEH. Ideally, subjects would have familiarization sessions in the lab in order to more accurately estimate workloads for training and competitive intensity exercise trials. Two exercise trials would be completed at both training and competitive intensities, one with placebo and one with 50 mg Sildenafil.

Future studies analyzing the effect of PDE-5 inhibitors and exercise on PEH should perhaps be more carefully controlled for medications that could blunt heart rate, blood pressure and other hemodynamic responses. In the present study, three subjects were on calcium channel blockers. Two of those subjects were taking Angiotensin Converting Enzyme (ACE) inhibitors in addition to the calcium channel blocker to control blood pressure. Medications should either be consistent among subjects or subjects should discontinue medications prior to participating in the study.

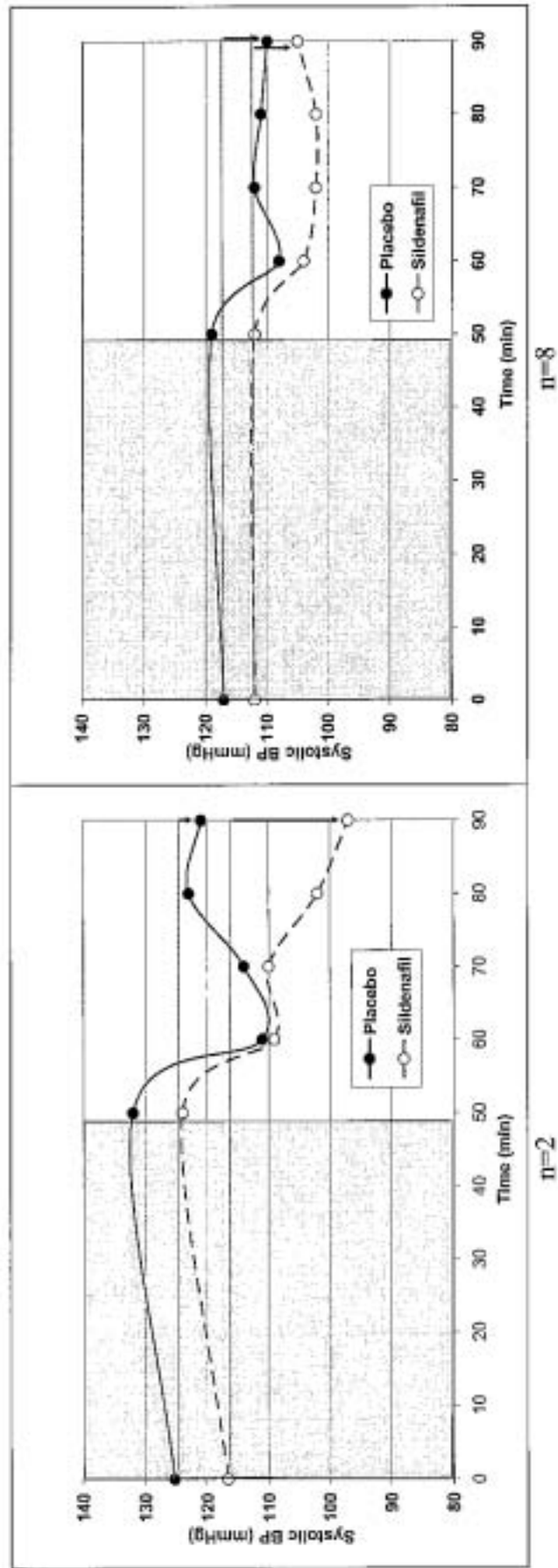


Figure 5. Comparison of Systolic Blood Pressure after competitive intensity (left) and training intensity (right) with Placebo and Sildenafil

The degree of hypotension experienced with long-acting PDE-5 inhibitors, like Tadalafil, has not been evaluated yet. Long-acting PDE-5 inhibitors are more convenient for the treatment of ED due to their long half-life. Unlike Sildenafil and other short-acting PDE-5 inhibitors, Tadalafil does not require correct timing of consumption for it to work effectively. Because Tadalafil is the way of the future for treatment of erectile dysfunction, studies should be performed using these long-acting PDE-5 inhibitors. In the present study, we chose to use a short half life PDE-5 inhibitor in the interest of safety. Given that there was no evidence of untoward events, it would make sense to use the longer acting drugs that are likely to present cause for concern to the exercising public. PDE-5 inhibitors do not produce significantly more PEH than placebo groups with moderate intensity. Men utilizing PDE-5 inhibitors should exercise caution at competitive level intensities as the two subjects who exercised at this intensity did see drastically more PEH than the subjects who exercised at moderate intensity. Further research is needed to analyze long-acting PDE-5 inhibitors and their effect on competitive level intensity exercise.

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## APPENDIX A

### BORG'S RATING OF PERCEIVED EXERTION SCALE



### Borg's Rating of Perceived Exertion Scale

- 0 Rest
- 1
- 2 Easy
- 3 Moderate
- 4 Somewhat Hard
- 5 Hard
- 6
- 7 Very Hard
- 8
- 9
- 10 Maximum

APPENDIX B  
INFORMED CONSENT

**Protocol Title:** Effects of PDE5 Inhibitors (Viagra) on Postexercise Hypotension

**Principle Investigator:** Jenna Shatzer  
3520 Crown Blvd.  
La Crosse, WI 54601  
(608)-788-6584

**Emergency Contact:** Carl Foster  
(608)785-8687

### **Purpose and Procedures**

- The purpose of this study is to examine the effects of Sildenafil (e.g. Viagra) on the blood pressure response following a high-intensity bout of exercise.
- My participation will involve a maximal exercise test and two high-intensity workouts on a cycle or treadmill. Before each high-intensity work bout I will take a tablet, which in one case will be Sildenafil and in the other will be a placebo (non-active agent). The sequence of which tablet I take first will be decided by chance.
- The total time commitment will be seven hours over a two month period.
- Testing will take place in room 3026 of the Health Science Center, UW-L.
- During all tests I will be wearing a heart rate monitor and have my blood pressure monitored every ten minutes.
- I will be asked my rate of perceived exertion every ten minutes.

### **Potential Risks**

- I may experience local muscle fatigue from the workouts.
- I may experience exertional fatigue from the maximal exercise test.
- I may experience a significant drop in blood pressure following a high-intensity exercise bout in conjunction with taking Sildenafil. When I take Sildenafil, I may experience flushing in my face, a stuffed up nose and a mild headache. If, after the study, I am in a sexually stimulating situation I may find that I have a strange reaction. Should an erection lasting longer than 4 hours occur, I should seek medical attention.
- Individuals trained in CPR, Advanced Life Support and First Aid will be in the laboratory, and the test will be terminated if complications occur.
- The risk of serious or life-threatening complications, for healthy individuals, like myself, is near zero.

### **Rights and Confidentiality**

- My participation is voluntary.
- I can withdraw from the study at any time for any reason without penalty.
- The results of this study may be published in scientific literature or presented at professional meetings using grouped data only.
- All information will be kept confidential through the use of number codes. My data will not be linked with personally identifiable information.

**Possible Benefits**

- I will gain a better understanding of the possible effects that Sildenafil can have on post-exercise blood pressure in active individuals.

Questions regarding any procedures in this study can be directed to the primary investigator, Jenna Shatzer (608-788-6584) or overseeing faculty member, Carl Foster, Department of Exercise and Sport Science, UW-L (608-785-8687). Questions regarding the protection of human subjects may be addressed to the UW-La Crosse Institutional Review Board for the Protection of Human Subjects, (608-785-8124 or [irb@uwlax.edu](mailto:irb@uwlax.edu)).

Participant \_\_\_\_\_ Date \_\_\_\_\_

Researcher \_\_\_\_\_ Date \_\_\_\_\_

APPENDIX C  
REVIEW OF LITERATURE

## REVIEW OF LITERATURE

It is widely accepted that physical activity has many health benefits including the reduction of cardiovascular risk factors. The ACSM recommends a minimum of 30 minutes of aerobic activity 5 days of the week to maintain cardiovascular health. Following the ACSM recommendations can reduce the risk factors of cardiovascular disease including diabetes, obesity, hyperlipidemia, and hypertension [1]. High blood pressure is also associated with increased risk of stroke, kidney disease, and premature death. Exercise can be beneficial for the one in four Americans who are currently hypertensive due to the decrease in blood pressure following activity [10].

The decrease in blood pressure post-exercise, a phenomenon known as post-exercise hypotension (PEH), can reduce pressure for up to 13 hours after exercise [10]. PEH can be attributed to a reduction in peripheral vascular resistance (PVR) which could be caused by both neurohumoral and structural adaptations [5]. Exercise causes an increase in sympathetic nerve activity (SNA) causing associated arterial constriction until local metabolites, released by the endothelium, override this effect and dilate the working vessels. The increase of SNA during exercise is thought to have a compensatory effect during resting conditions and lower the overall sympathetic activity in the body resulting in more dilation of vessels; however, this theory remains controversial. The baroreflex control is a more widely accepted attribute to PEH. Baroreceptors located in the aorta and carotid bodies are sensitive to pressure changes and provide feedback to the central nervous system to dilate or constrict to keep arterial pressures controlled. During exercise, baroreceptors detect an increase in pressure and “act to buffer the expected arterial BP change” decreasing blood pressure. These “neurohumoral” responses to

exercise cause immediate and acute reductions in blood pressure that may lead to long-term structural adaptations [5].

In 2002, Schuster-Decker et al, studied the effects of exercise and amino acid L-arginine on lowering blood pressure in hypertensive subjects. L-arginine increases NO production which has a strong vasodilatory effect and helps maintain the vascular tone of blood vessels. The study analyzed outcomes of subjects while supplementing with L-arginine, exercise, or supplementation and exercise. Consistent with previous studies, the exercise group with no L-arginine supplementation had a decrease in blood pressure due to the PEH phenomenon. Schuster-Decker reported that there were significant reductions in systolic blood pressure for all 3 interventions (Heart Bar, Exercise, and Heart Bar + exercise) with significant reductions in the 90 and 120 recovery minutes only in the intervention involving L-arginine supplementation in addition to exercise [12].

In 2004, Smelker et al studied the exercise intensity in relation to PEH. Ten subjects, all with a history of hypertension, performed four, 25 minute exercise bouts on a bicycle ergometer at 70, 80, 90, and 100 percent ventilatory threshold. A significantly greater amount of hypotension was observed 30 minutes post-exercise with an intensity slightly above ventilatory threshold, characteristic of a competitive level exercise, in comparison to the other three intensities. The increase in amount of PEH is attributable to higher levels of NO produced during higher intensity exercise bouts [13].

In 2005, Mach et al studied the effect of exercise duration on the magnitude of PEH. Nine subjects performed four exercise bouts at 80 percent of their ventilatory threshold for 10, 20, 40, and 80 minutes. Mach reported a significant decrease in systolic blood pressure at 30 minutes post-exercise for all four exercise durations; after 90

minutes of recovery systolic blood pressure had returned to the baseline values. Mach's study reported that exercise of any duration will result in PEH; but the extent and magnitude of PEH is greater with longer duration of exercise [9].

Structural adaptations due to exercise (long-term) reduce peripheral vascular resistance. Physically active individuals tend to have larger lumen diameters which increase arterial compliance (stretch) and decrease blood pressure. During exercise, local metabolites, such as nitric oxide (NO), in the endothelial tissue and are released and decrease blood pressure [5]. The inability to produce NO and fully dilate the arteries is referred to as endothelial dysfunction, caused by damage of the blood vessels from hypertension, increased shear stress and atherosclerotic plaque. Endothelial dysfunction is the underlying cause for erectile dysfunction. For the millions of men in the U.S. with erectile dysfunction, PDE-5 inhibitors are prescribed to prevent the destruction of NO, allowing vasodilation and increased blood flow to occur to the selective areas where PDE-5 sites exist, such as the lungs and the corpora cavernosa in the penis [11].

There are three main PDE-5 inhibitors currently prescribed: Sildenafil (Viagra), Tadalafil (Cialis), and Vardenafil (Levitra). Sildenafil and Vardenafil are short-acting PDE-5 inhibitors with half-lives of approximately four hours. Half-life is the time needed for half of the dose of the drug to become "inactive" in the body [4]. Taken daily with other medications, Tadalafil is potentially a more ideal PDE-5 inhibitor; due to its long half-life planning the consumption of the PDE-5 inhibitor is not necessary [Almeri]. Because the future of PDE-5 inhibitors is moving towards the longer-acting, once a day medication, Tadalafil (Cialis), there is a concern about the effects and/or risks of PDE-5 inhibitors on PEH.



PDE-5 inhibitors can be very beneficial to those with underlying diseases such as erectile dysfunction, pulmonary hypertension, and even provide benefit in hypoxic conditions when used as an ergogenic aid. Cardiovascular disease and erectile dysfunction are highly correlated via endothelial dysfunction [11]. However, the safety of PDE-5 inhibitors for those with cardiovascular disease is a great concern for many reasons, one being the combination of nitrates and PDE-5 inhibitors. Patients with heart disease are prescribed nitrates to dilate and increase blood flow to the coronary arteries when the heart is ischemic. Without their prescribing physician's knowledge, these men may be taking PDE-5 inhibitors concurrently with nitrates. Consuming these two medications simultaneously is contraindicated because nitrate, like PDE-5 inhibitors, reduce blood pressure; if both are taken concurrently a "double vasodilator effect" could occur and may cause symptomatic hypotension [7].

In 2000, Ishikura et al conducted a study using healthy male beagles and analyzed the combination Sildenafil and Nitrates on the effects on the heart. Although the study was not conducted on humans, beagles have similar vasculatures as humans. Ishikura concluded that "Sildenafil citrate dilated a normal coronary artery; however, a combined effect with nitrate can result in large and prolonged decreases in systemic blood pressure and coronary blood flow in vessels with critical stenosis. These effects might potentially produce a fatal cardiac outcome." [7].

In 2002, Arruda-Olson et al examined the effects of 50 or 100 mg of Sildenafil (depending on the dosage prescribed by the subject's physician) on exercise blood pressure. The Sildenafil was administered one hour prior to exercise in order for it to take effect in the body. Subjects performed exercise on a supine cycle ergometer starting

at 25 Watts and increased 25 Watts every 2 minutes until they reached maximum workload. One subject who was prescribed 100 mg of Sildenafil became symptomatically hypotensive reaching a blood pressure of 90/60 at peak exercise capacity and his blood pressure continued to fall to 70/50 during recovery (down from 114/70 at rest). The patient was given 500 mL of saline solution to reverse the effects of the hypotension. Although this subject responded negatively to the Sildenafil upon exercising, the mean exercise capacity and heart function was not affected by the Sildenafil for the majority of subjects [3].

In 2002, Schuster-Decker, et al studied the effects of exercise and amino acid L-arginine on lowering blood pressure in hypertensive subjects. L-arginine is a precursor to NO production which has a strong vasodilatory effect and helps maintain the vascular tone of blood vessels. The study analyzed outcomes of subjects while supplementing with L-arginine, exercising, or supplementation and exercise. Consistent with previous studies, the exercise group with no L-arginine supplementation had a decrease in blood pressure due to the PEH phenomenon. Schuster-Decker reported that there were significant reductions in systolic blood pressure for all 3 interventions (Heart Bar, Exercise, and Heart Bar + exercise) with significant reductions in the 90 and 120 recovery minutes only in the intervention involving L-arginine supplementation in addition to exercise [12].

These studies all analyze the PEH phenomenon and other factors that increase the intensity of PEH, such as duration, intensity and utilization of PDE-5 inhibitors. PDE-5 inhibitors, in addition to treating ED, have been tested in patients with heart failure and pulmonary hypertension [10]. As stated early PDE-5 sites are located in the lungs in

addition to the corpus carvermosa. PDE-5 inhibitors have also been tested in hypoxic (high altitude) conditions [6] and with well-trained individuals as an ergogenic aid [4].

In 2006, Hsu et al studied the effects of the PDE-5 inhibitor, Sildenafil, on exercise in hypoxia in healthy trained male cyclists. Hypoxic conditions cause pulmonary hypertension and PDE-5 inhibitors offset the effect of hypoxia by dilating the arteries in the pulmonary tree. Subjects were assigned a random order to complete a six kilometer time trial with 100 mg Sildenafil, 50 mg Sildenafil, and placebo at sea level and hypoxia. Hsu reported that Sildenafil increased peak exercise capacity during acute and chronic hypoxia by lowering pulmonary arterial pressure and raising the oxygen saturation. The administration of Sildenafil also yielded improvements in the time trial performance but had no effect on performance at sea level [6]

Lewis et al studied the effects of Sildenafil taken three times daily (up to 225mg daily as tolerated by subjects) for 12 weeks in individuals with left ventricular systolic dysfunction (LVSD) and pulmonary hypertension. PDE-5 sites are located in the lungs in addition to the corpus carvonosa and induce pulmonary vasodilation which provide benefits to those suffering from pulmonary hypertension. Lewis reported an increase in peak oxygen consumption, six minute walk distance, peak cardiac output and stroke volume when administering Sildenafil to patients with heart failure and pulmonary hypertension [8].

In 2008, Guidetti et al examined the effect of 20 mg Tadalafil on anaerobic performance in healthy well-trained individuals. Individuals were randomly administered either 20 mg of Tadalafil or placebo one day prior to the test. The subjects reported to the lab two times (Tadalafil one time, placebo the other time) to complete a thirty second

Wingate test on a bicycle ergometer with 1 week of rest in between the tests. Guidetti found that the Tadalafil increased blood lactate levels three minutes after a Wingate test, and also reported a decrease in time to peak power by about one second. Despite the increase in blood lactate levels and decrease in time to peak power, 20 mg of Tadalafil did not significantly affect anaerobic performance in well-trained individuals [4].

Because Tadalafil is taken once daily it is the preferred PDE-5 inhibitor and alleviates the problem planning the ingestion of the medication to ensure its proper functioning. There is concern about the safety of PDE-5 inhibitors in combination with exercise, nitrates, or alcohol because it may produce symptomatic hypotension, especially with the longer-acting PDE-5 inhibitor Tadalafil. The effects of PDE-5 inhibitors on PEH need to be investigated to ensure the safety of those using such medications and performing high intensity exercise [2].

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