THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF KINESIOLOGY

EFFECT OF BED REST ON THE RESPONSE OF HUMAN LIMBS TO ADRENERGIC AGONISTS

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FALL 2011

A thesis
submitted in partial fulfillment of the
requirements for a baccalaureate degree in
Kinesiology
with honors in Kinesiology

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Abstract

Previous research by Pawelczyk and Levine identified a heterogeneous distribution of alpha adrenergic receptors between human limbs. The elevated hydrostatic pressure experienced by the legs upon standing is thought to be the main contributor toward this observed difference. This study aimed to determine whether exposure to bed rest deconditioning would ameliorate limb differences in the sensitivity to adrenergic agonists. It was hypothesized that the subsequent decrease in leg hydrostatic pressure, obtained through bed rest, would abolish the difference in α-adrenergic vasoconstriction between limbs. **Methods:** Eleven healthy subjects (10 men, 1 woman, mean age 24 ± 2 years) completed 18 days of bed rest with -6° head down tilt (HDT). Before and after bed rest, phenylephrine (five doses ranging from 0.025-0.8 µg ·100 ml limb volume^{-1} · min^{-1}) and isoproterenol (five doses ranging from 0.75-24.00 ng ·100 ml limb volume^{-1} ·min^{-1}) were infused incrementally into the brachial and femoral arteries. Mean arterial pressure, heart rate, blood flow, vascular resistance and vascular conductance were measured at baseline and after each drug was infused for five minutes. Changes in limb blood flow were recorded using venous occlusion plethysmography. **Results:** Following bed rest, a significant increase in leg resistance was observed at the three highest doses of phenylephrine; however, no difference in the response to phenylephrine or isoproterenol infusion in the arm was noted following bed rest. **Conclusion:** Evidence from this study suggests that 18 days of bed does not normalize the responses of the limbs to infused adrenergic agonists. The increase in leg vasoconstriction post bed rest is likely due to a reduction in NO synthesis or an abnormality in the NO signaling pathway. This demonstrates that, in the short term, the hydrostatic pressure gradient experienced by the legs is not the key mediator of its adrenergic responsiveness.

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Introduction

Exposure to microgravity (spaceflight) or its ground based analog, head down bed rest (HDBR), leads to orthostatic intolerance upon standing [1] [2] [3]. Through post flight stand tests, several studies have examined the severity of orthostatic intolerance in astronauts who have returned from spaceflight [1] [3] [4]. Contributing factors include: hypovolemia [5], structural remodeling of the heart and muscular vasculature [6] [7] and abnormal vasoconstrictor response [2]. Buckey et al. concluded that a decreased vasoconstrictor response was the singular hemodynamic characteristic that separated stand test finishers from non-finishers [3].

Adrenergic vasomotor control plays an essential role in the maintenance of blood pressure and the regulation of blood flow. Neural and humoral stimulation of α- and β-adrenoreceptors leads to the vasoconstriction and vasodilation of the arterioles, respectively. The balance between the activation and deactivation of each is responsible for the sympathetic tone of blood vessels. In order to evaluate sympathetic tone pharmological agents are commonly used to stimulate or block these receptors. Phenylephrine (PE), an agonist selective for post-synaptic α_1-receptors, causes vasoconstriction, leading to higher resistance and decreased blood flow under constant pressure conditions [8]. In contrast, isoproterenol (ISO), a β_2-adrenergic agonist, elicits vasodilation, resulting in decreased resistance and increased blood flow.

Thus, the vascular response to infused agonists provides essential information concerning the regulation of vascular tone [9]. However, when employed systemically this paradigm typically elicits reflex responses that may oppose or mask the local vascular response [9]. To minimize systemic effects, direct intra-arterial infusions of agonists can be used to measure the changes in blood flow and vascular specific to each limb. This approach is well suited to techniques such as venous occlusion plethysmography that estimate arterial inflow by determining the rate of swelling of a limb during a brief period of venous congestion [10].

Using this approach, Pawelczyk and Levine demonstrated a significantly greater response to PE infusion in the legs of humans when compared to their arms. They proposed that a heterogeneous distribution of α_1-adrenergic receptors exists in human limbs [11]. Similarly, Wray et al. suggested a heterogeneous regulation of vasoconstriction, with the prominent site of α_1-adrenergic control found in the distal resistance vasculature of the leg [12].

Pawelczyk and Levine hypothesized that the greater α-adrenergic response in the legs results from the chronic hydrostatic pressure gradient created in the legs of upright humans. As a corollary, we hypothesized that the removal of the pressure gradient will normalize the α_1-adrenergic response. In this study, we used 18 days bed rest with -6° HDT to abolish the hydrostatic gradient between the limbs and subsequently characterized the response of the limbs to infused α- and β– adrenergic receptor agonists.

Methods and Procedures

Subjects

Twelve healthy subjects (11 men, 1 woman) with the following physical characteristics: Mean age 24±2 yr (mean±SE), height 185±23 cm, and weight 79±3 kg, underwent 18 days of bed rest at -6° head down tilt (HDT). Subjects provided a medical history and underwent a physical examination in addition to a resting electrocardiogram and resting echocardiogram. Potential subjects who exhibited any of the following were excluded:

- Smoker
- Recreational drug user
- Chronic medical conditions
- Vascular abnormalities.

Informed consent was provided by each subject and the experiment was approved by The Institutional Review Boards of both the University of Texas Southwestern Medical Center and the Presbyterian Hospital of Dallas [11].

Measurements

The following measurements were made in the same manner described by Pawelczyk and Levine [11]:

Arterial Pressure and Heart Rate. Catheters were placed in the brachial and femoral arteries of the non-dominant arm and leg, respectively. Using a strip chart recorder (AstroMed MT95000), pressure waveforms were transduced, amplified, and displayed. To minimize artifacts from vasospasm at least 1h elapsed between catheter insertion and pressure measurement. Heart rate (HR) was recorded using lead II of the electrocardiogram. Pressures and HR were both stored in beat-to- beat format using a customized data collection system. Mean HR and blood pressure were calculated using time-weighted averages of these values.

Limb Volume. Using anthropometry, the volume of each infused limb was determined. Each limb was modeled as a series of truncated cones, 11 for the leg and 2 for the arm [13].

Limb Blood Flow. Calf and forearm blood flows were obtained both before and during drug infusions by venous occlusion plethysmography. Strain gages, sized to approximate the largest circumference of the calf or forearm, were used to record changes in limb volume. Before measurements at each stage of infusion, ankle or wrist cuffs were inflated to 250 mmHg to arrest blood flow to the foot or hand. Venous occlusion pressures of 50 mmHg were applied proximal to the strain gauge using a cuff on the upper thigh or arm. To facilitate venous drainage between measurements, legs or forearms were elevated 20 cm above the subjects' midaxillary line.

Procedure

HDBR. Initial experiments performed before HDBR are outlined in the previous paper by Pawelczyk and Levine [11]. Following the preliminary series of experiments, subjects were exposed to 18 days of complete bed rest at -6° head down tilt in an attempt to reduce the hydrostatic pressure gradient between the upper and lower body. Subjects were not permitted to rise at any point during the period of bed rest.

The following procedures were conducted in the same fashion described by Pawelczyk and Levine [11].

Arterial infusion. To assess α_1-adrenergic responsiveness Phenylephrine HCl was infused intra-arterially at rates of 0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 $\mu g \cdot 100$ ml tissue volume$^{-1} \cdot$ min^{-1}. Intra-arterial infusions of isoproterenol HCl at rates of 0.075, 1.5, 3, 6, 12, and 24 $ng \cdot 100$ ml tissue volume$^{-1} \cdot$ min^{-1} were used to determine β-adrenergic responsiveness. Both drugs were diluted in a sterile, buffered, isotonic saline solution to a concentration specific for each limb.

Phenylephrine was diluted to 16.7 and 50 µg/ml for arms and legs, respectively, while isoproterenol was set at of 500 and 1,500 ng/ml for arms and legs, respectively. The maximal volume of drug infused was approximately 0.5 ml/min in the arm and 1.6 ml/min in the leg.

Drug infusions were conducted successively from lowest to highest concentration and maintained for a five minute period. A three-min washing period began each stage so that equilibrium could be reached; measurements were made during the concluding two minutes. To determine limb blood flow for each trial, five values were obtained 20 s apart and averaged. To allow recovery the trials were sequenced in the order: isoproterenol arm, isoproterenol leg, phenylephrine arm, and phenylephrine leg. Isoproterenol infusions were preceded by a saline vehicle stage. In this manner, a period of >1 h elapsed between infusions in the arm or the leg.

Maximal Limb Conductance. Published procedures [14] were emulated to determine the maximal conductance of both the forearm and calf on a separate day. Venous occlusion plethysmography was again used to determine maximal flows in the supine position following an exhaustive bout of exercise with total vascular exclusion. Exercises for the arm included: wrist flexion, extension, pronation, and supination. Calf exercises consisted of heel and toe raises. Occlusion pressures of 300 mmHg were delivered using cuffs around the upper arm or leg. Flow values were recorded at 10-s intervals within 6 s of cuff release in the supine position. Blood pressure was determined using an automated auscultatory device at the same time.

Dose Response Curve. Adrenergic responsiveness in the limbs was established by standardizing the infusion responses of the calf and forearm to their respected maximal conductance levels. Dose-response curves were composed based on the averages of these data using a four parameter logistic model. Using these curves, both the maximal response (E_{max}) and the dose producing a half-maximal response (ED_{50}) in each limb were computed.

Statistical analysis. Pre and post bed rest data for heart rate, blood flow, resistance, percent of baseline resistance, conductance, and percent max conductance were analyzed using two-way repeated measures analysis of variance with a post hoc Tukey's test. The maximal conductances of each limb, pre and post bed rest, were compared using a paired t-test.

Results

Pre bed rest data from the original paper by Pawelczyk and Levine [11] were compared to the post bed rest values of the current study. HR was significantly greater post bed rest at all doses of phenylephrine infusion in the leg, in contrast to arm infusions, which showed significantly greater values at BL, 0.025 and 0.2 $\mu g \cdot 100ml^{-1} \cdot min^{-1}$ only. HR was statistically greater post bed rest at all doses of isoproterenol in the arm, whereas it was greater post bed rest at all isoproterenol leg infusion levels, except for .75 and 1.5 $ng \cdot 100ml^{-1} \cdot min^{-1}$ (Figure 1). No significant differences in blood flow were observed at any level of phenylephrine injection in the arm between pre and post bed rest, however, blood flow was significantly lower at BL and .025 $\mu g \cdot 100ml^{-1} \cdot min^{-1}$ during leg phenylephrine infusions after bed rest. Leg resistance following bed rest was greater at the three highest doses of phenylephrine; however, no significant difference occurred in the arm responses to phenylephrine when comparing pre and post bed rest. However, when normalized to baseline resistance, for percent max of baseline resistance, a significant increase was found in the arm at .05 $\mu g \cdot 100ml^{-1} \cdot min^{-1}$ (Figure 3).

Post bed rest, isoproterenol infusion resulted in a significantly greater increase in blood flow compared to pre bed rest levels, at 12 $ng \cdot 100ml^{-1} \cdot min^{-1}$ in the arm only, but no difference in leg blood flow as observed following bed rest. (Figure 2). However, both arm and leg vascular conductance were greater after bed rest at 12 and 24 $ng \cdot 100ml^{-1} \cdot min^{-1}$ and the percent change in maximal conductance of the arm was greater after bed rest at doses of 12 and 24 $ng \cdot 100ml^{-1} \cdot min^{-1}$ (Figure 4).

After bed rest, the maximal conductance of each limb was not statistically significant (Figure 5).

Discussion

A previous study by Pawelczyk and Levine led us to hypothesize that the greater sensitivity of alpha adrenergic receptors in human legs is a result of a hydrostatic pressure gradient [11]. This study determined the change in limb adrenergic responses with the removal of this pressure gradient. The major finding of the present investigation was that for the same concentration of phenylephrine (PE) the resistance of the leg was greater after bed rest. This contradicts the hypothesis that the heterogeneous adrenergic response between limbs would be diminished following bed rest.

The extent of vasoconstriction observed is dependent on the index of measurement used. O'Leary suggests that when measuring the degree of vasoconstrictor response, using resistance as opposed to conductance during low flow states reveals increased vasoconstrictor responses that might not be identifiable as the reciprocal measure approaches its asymptote [15]. Since low flow states are achieved by phenylephrine infusion via arterial constriction, elevated resistance would be expected.

There is much uncertainty as to what effect bed rest and other forms of simulated microgravity have on adrenergic responsiveness. Conflicting findings describe how the resistance of the lower limbs to blood flow changes under these conditions. Several studies propose a decrease in leg vascular reactivity (regional vascular resistance or limb blood flow) [1] [2] [6] [7] [16] [17] [18] while others observe no significant change [19] [20] or an increase [21] [22] [23]. The increase in vascular reactivity to PE present in this study could have resulted from several mechanisms. First, the possible up-regulation of α-adrenergic receptors in the presence of decreased MSNA levels post bed rest [4] [24]. It has been suggested that the number of adrenergic receptors is regulated in part by the volume of agonist to which a tissue receptor population is exposed (Williams, Catt abstract). This line of reasoning is supported by other

studies which show decreases in plasma norepinephrine post head down tilt (HDT) [19] [25] and adrenoreceptor hypersensitivity in patients with dysautonomias in which circulating catecholamines are absent or reduced [26].

The possible up-regulation of α-adrenergic receptor number may lead to an increase in vasoconstrictor reserve in the absence of elevated plasma norepinephrine, similar to what is seen 24 hours after maximal exercise [27]. In contrast to these findings, however, studies examining astronauts after spaceflight, found that upon standing, the ratio in total peripheral resistance to increase in NE was reduced on landing day, suggesting that there was no up-regulation of α_1-adrenoreceptors but a decreased end organ responsiveness to norepinephrine [1] [28].

A second possible contributor to the increased constrictor response seen with infused phenylephrine could be the increased functionality of α_{1D}-receptors which demonstrate higher sensitivity to α_1-adrenergic stimulus and slower decay in contractile tone after stimulus removal in hypertensive rats [29].

Third, increased α_1 and α_2-adrenoreceptor mediated contractile response has been documented in skeletal muscle resistant arteries that have undergone chronic limb ischemia [18]. Their increased response to PE has been associated with a possible increase in alpha receptor density. In a study by Shoemaker et al, 14 days of bed rest resulted in an impaired ability of the forearm to dilate in response to ischemia compared to pre bed rest values [16]. It is possible that the reported decrease in vasodilation after bed rest was the result of an increased density of alpha receptors. Unfortunately, the study did not examine the effect that HDBR had on the lower leg vasculature in response to ischemia.

Perhaps a more likely explanation for the increase in leg vasoconstriction observed is altered production of nitric oxide (NO), which significantly attenuates the vasoconstrictor

responses to α-adrenergic agonists [30] and sympathetic activation [31]. Several studies, specifically those by Sun et al. have shown dilation of isolated arterioles following the infusion of vasoconstrictor agonists [32]. In vitro, decreases in the arteriolar diameter, such as those induced by constrictor agents, led to a significant increase in NO production [32]. In the current study, we suggest that prolonged bed rest causes endothelial dysfunction that decreases the amount of NO released, altering vascular tone in favor of greater vasoconstriction. This hypothesis is favored by Kayima et al. who attributed the increased vasoconstrictor response of the legs post bed rest to an increase in MSNA coupled with a decrease in nitric oxide (NO) [21]. Prior to bed rest, they observed a positive correlation between vasoconstrictor stimuli and NO release. They hypothesize that the disparity between vasoconstrictor stimuli and NO release post HDBR contributes to the elevated peripheral vascular resistance [21]. Similarly, both the disinhibition of NO synthesis and the endothelium caused a significant increase in agonist-induced constriction in the study by Sun and colleagues [32]. This suggests that endothelium-dependent NO-mediated vasodilation plays a significant role in vasoconstrictor response of the vasculature to infused agonists. In comparison to these findings, a suggested down-regulation of the NO-dependent vasodilatory mechanism is thought to lead to the increased myogenic tone present in the cerebral arteries of HU rats [33]. This hypothesis is not supported universally, however. Bleeker et al. was unable to ascertain any difference in endothelial function in the legs of patients after short term (unilateral limb suspension) or chronic (spinal cord injury) physical inactivity [34]. Unfortunately, endothelial function was not assessed pre and post HDBR, therefore a definitive answer toward the role of NO in the vasoconstrictor response cannot be given based on the current study.

With no significant change in arm resistance, an increase in total peripheral resistance (TPR) could have been caused, in part, by greater resistance in the legs. Indeed, several studies have documented an increase in TPR after HDBR as a result of greater cardiopulmonary baroreflex responses [25] [35] [36]. These changes have been attributed to a reduced blood volume, brought upon by a hypovolemic state.

In contrast, other studies propose that microgravity and its ground based analogs have no effect on the responsiveness of leg vasculature to α_1-agonists [5] [19]. Convertino and colleagues found no alteration in blood pressure or vascular resistance in response to PE infusion after 14 days of HDT [19]. Similarly, Pawelczyk and colleagues showed that leg vascular found no difference in the relationship between MSNA and limb resistance [5]. However, these results do not exclude the possibility that vascular tone would be higher in these subjects when they are hypovolemic.

Spinal cord injured (SCI) patients, who experience dramatic atrophy of the lower limbs, retain high leg vascular resistance during head up tilt (HUT). Moreover, tone is retained after the infusion of phentolamine (an α-adrenergic antagonist), suggesting that the increase in leg vasoconstriction experienced by these individuals is unrelated to α-adrenergic responsiveness [37]. Several studies attribute the increase in vasoconstriction to endothelin dysregulation. In contrast to healthy individuals, SCI individuals show a possible up regulation of ET-1_A receptors, suggesting that ET-1 plays a pivotal role in the regulation of vascular tone in these subjects [38]. In the same study, blockade of ET-1_A receptors in the forearm and leg vasculature showed that the effect of these receptors is heterogeneous between limbs.

Similarly, patients with pure autonomic failure (PAF) and dopamine β-hydroxylase deficiency (DBH) experience an increase in leg resistance during HUT, suggesting that the

sympathetic nervous system is not the key mechanism behind their increased leg vasoconstriction during orthostatic challenges [39]. Rather, the drop in systemic vascular resistance experienced by these individuals is contributed to a decrease in the vasoconstrictor ability of other vascular beds, not the leg vasculature which shows an increase in resistance [39].

This hypothesis that orthostatic stress elicits non-adrenergic vasoconstriction in the legs remains controversial. For example, Kooijman et al. observed vasodilation in the upper leg of SCI patients after the infusion of phentolamine, indicating that α-adrenergic vascular tone is preserved in these individuals [40]. Furthermore, Purdy and Delp argue against an effect on α-adrenoreceptor function based on their finding that HU in rats had no effect on vascular sensitivity to norepinephrine [6] [7]. They along with other researchers attribute their reported decreases in vascular tone to the altered ability of the smooth muscle contractile apparatus to generate force [6] [7] [41].

Since several competing factors affect vasomotor tone, it is difficult to propose a definite mechanism for the increase in vasoconstriction observed in the present study. A combination of central and local vasoconstrictor mechanisms likely play a role in the vasoconstriction of smooth muscle [39].

Summary

Results from the current study reveal that, following bed rest deconditioning, an increase in leg, but not arm, vasoconstriction occurred in response to the infusion of phenylephrine. Vasodilation in response to isoproterenol was unaltered by bed rest. This contradicts the original hypothesis stating that the heterogeneity between alpha receptors in the arm and leg would be abolished following 18 days of bed rest at -6° head down tilt. These results imply that the cardiovascular changes that occur during spaceflight and stimulated microgravity may limit in dependent regions such as the legs, exacerbating exercise rather than orthostatic intolerance.

The fact that responses to an α-adrenergic receptor agonist were not normalized after bed rest in the current study leads us to believe that the hydrostatic pressure gradient is not the driving force in determining adrenergic responsiveness. Although several alternative mechanisms are possible, the most likely explanation for the increase in vasoconstriction observed in the current study is endothelial dysfunction causing a decrease in NO production. A comprehensive determination of endothelial function, however, is beyond the scope of this investigation, so a definitive answer toward its role in the vasoconstrictor response cannot be determined by the current study. Future research is needed to determine the impact of the endothelium on the vasoconstrictor response.

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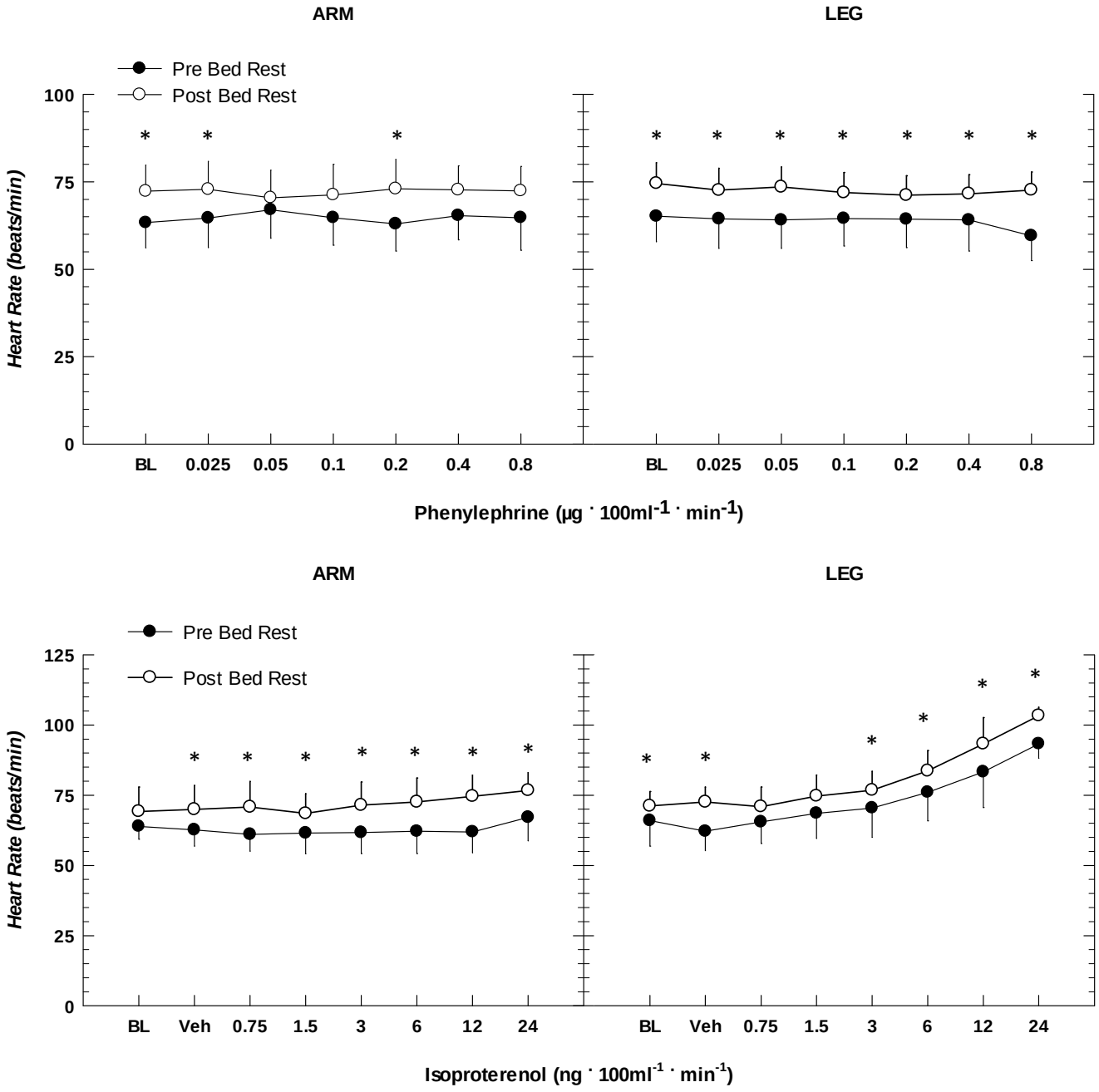
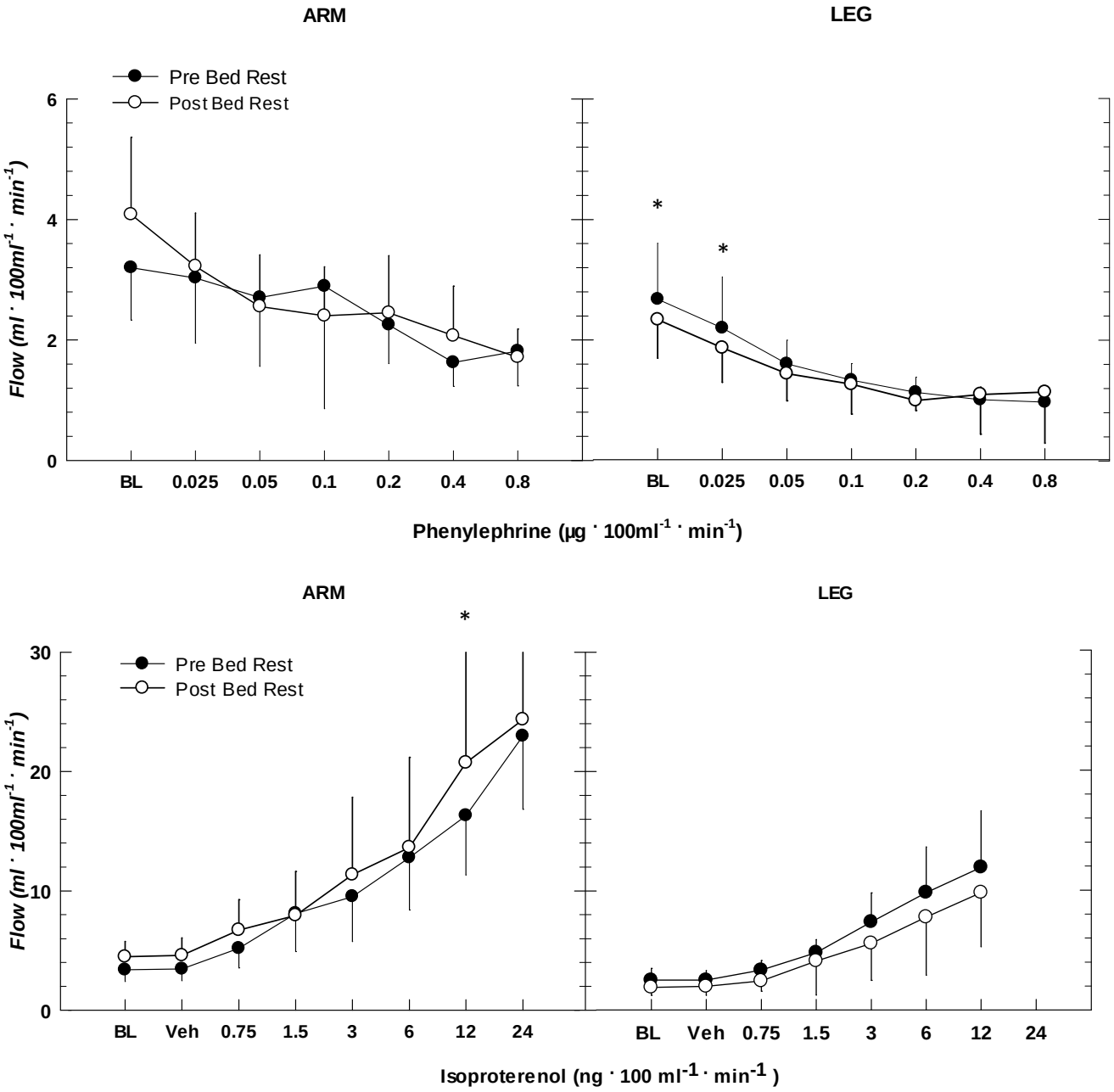


Figure 1. Above: HR response following the infusion of phenylephrine into the arm (left) and leg (right). * indicates a statistical difference from pre bed rest ($p < .05$). Below: HR response following the infusion of isoproterenol into the arm (left) and leg (right). * indicates a statistical difference from pre bed rest ($p < .05$).



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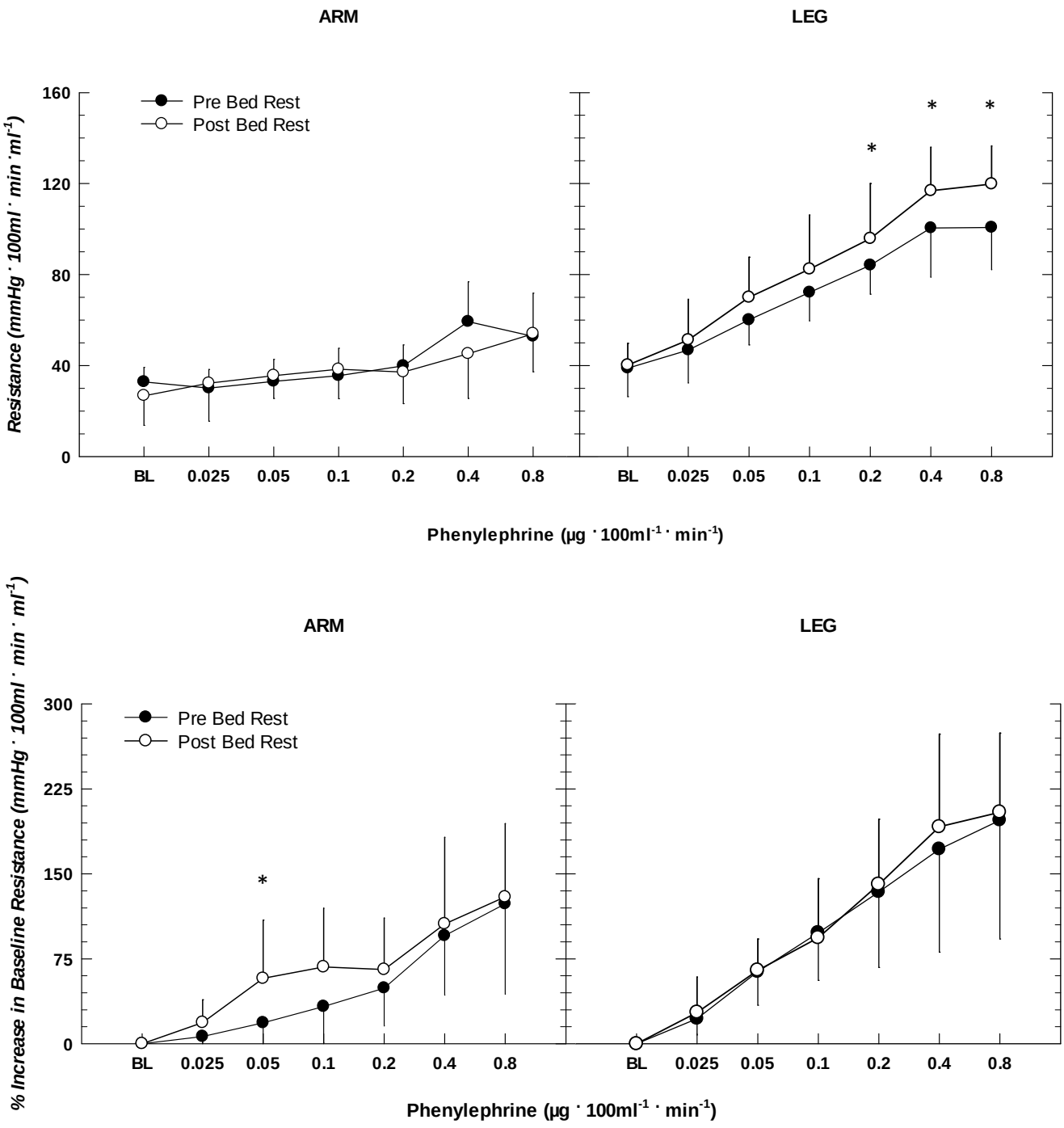

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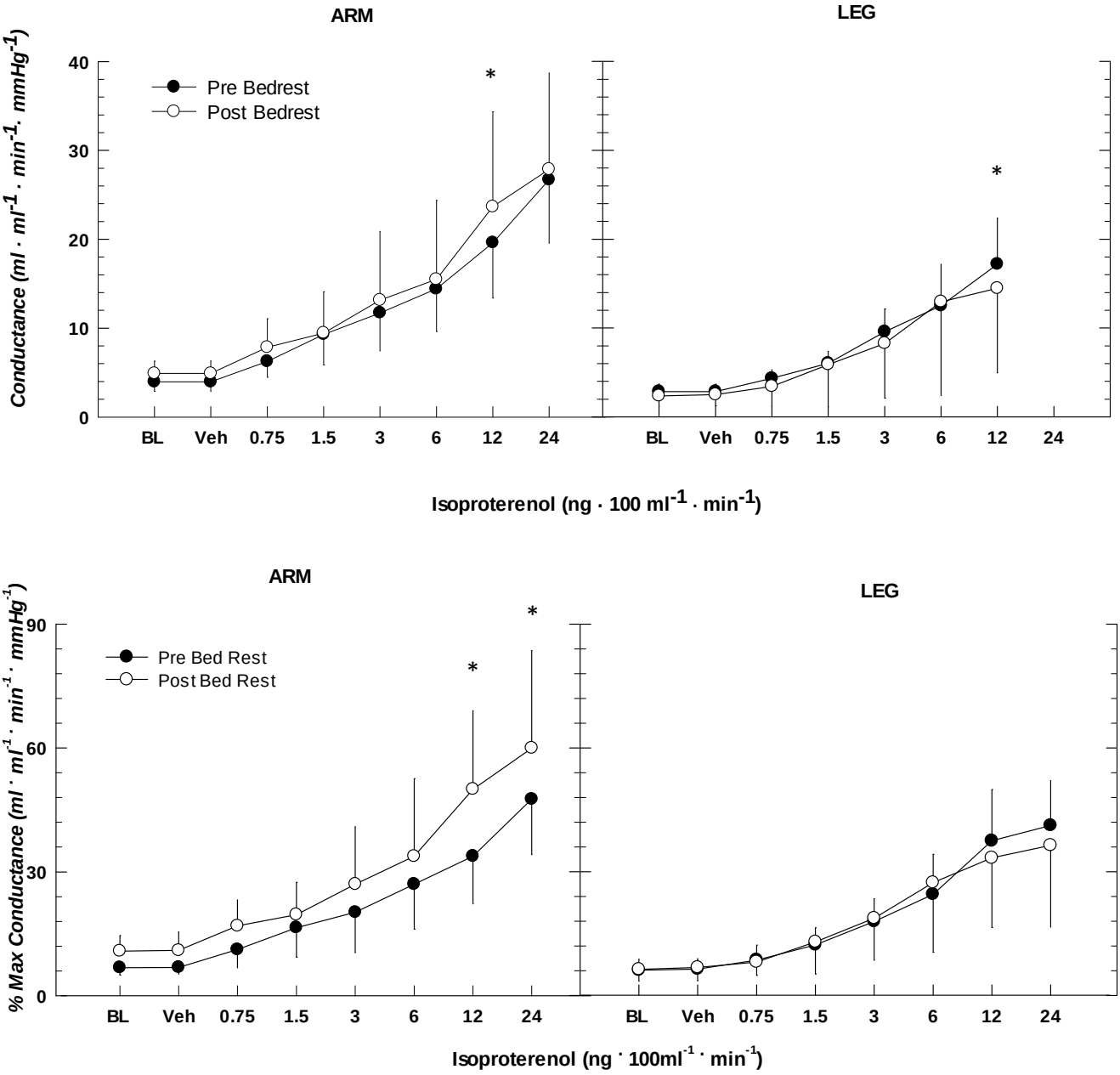

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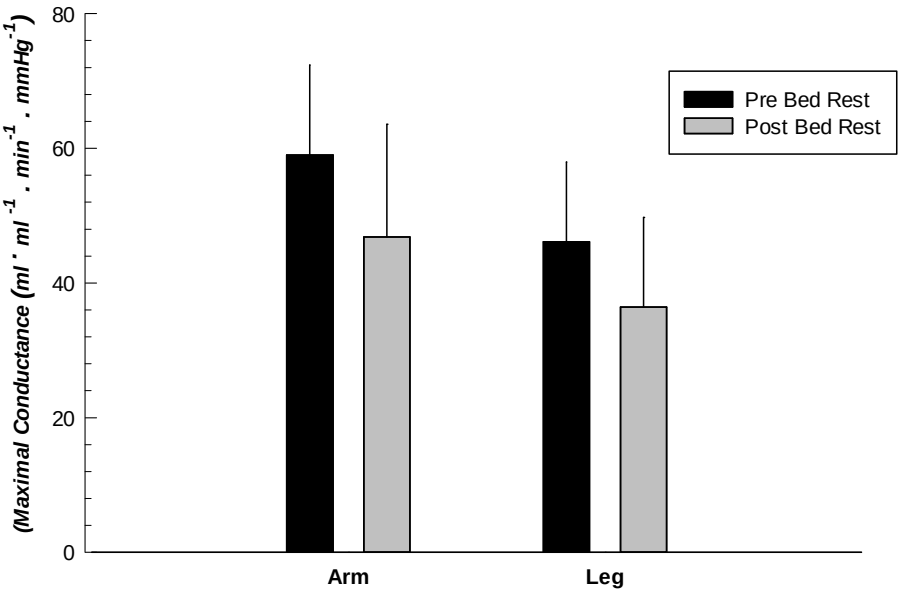

Figure 5. Maximal Conductance of the arm and leg, pre and post bed rest. * indicates a statistical difference from pre bed rest ($p < .05$)

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ACADEMIC VITA OF NATHAN ROBERT REITZ

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EDUCATION

The Pennsylvania State University, University Park, PA
December 2011 Schreyer Honors College
B.S. in Kinesiology – Movement Science Option/Minor: Biology
Dean's List all semesters

WORK EXPERIENCE

Noll Laboratory **University Park, PA**
Autonomic Neurophysiology Lab **Fall 2010 - Present**

- Conduct data analysis, statistical measures, and literature review for thesis aimed to determine the effect of bed rest on the response of human limbs to adrenergic agonists.
- Attend lab meetings to discuss current and past research papers relevant to the field of neurophysiology
- Exposed to various laboratory techniques including Doppler ultrasound, lower body negative pressure, and venous-occlusion plethysmography
- Worked with graduate student in pilot experiments designed to investigate the sensitivity of limbs to the exercise-pressor reflex

Sacred Heart Hospital **Allentown, PA**
Operating Room Volunteer **Summer 2011**

- Observed various operations that were laparoscopic, oncological, orthopedic, plastic or vascular in nature
- Talked with doctors and nurses about several aspects of surgery including types of anesthesia, sterile technique, and the equipment involved in different procedures
- Transported patients from the Short Procedure Unit to the Operating Room once they were cleared by the floor nurses
- Restocked medical supplies and organized patient forms.

Mt. Nittany Hospital **State College, PA**
Emergency Room Volunteer **Fall 2011**

- Transport patients to various locations in the hospital including: CT, MRI, Ultrasound, X-ray and in-patient rooms
- Reassure patients and their loved ones by communicating with them and acquiring assistance from nurses/doctors when needed.
- Gain insight into the life of an Emergency Room employee including the responsibilities and tasks that go along with each position.

Surgical Center Volunteer

- Sanitize and change patient beds post operation.

Whitehall Township Recreation Bureau **Whitehall, PA**
Head Lifeguard/Lifeguard **Summer 2005 – Summer 2011**

- Supervised lifeguards and assessed their abilities through life-saving drills, providing instruction when necessary
- Provided pool managers with feedback for guard evaluations at the end of each season
- Enforced pool rules and provided a safe environment for pool patrons

LEADERSHIP INVOLVEMENT

Sigma Phi Epsilon **State College, PA**

Vice President of Programming **Fall 2008 – Spring 2009**

- Member of the Executive Board responsible for scheduling professional speakers such as Dean Brady of the Schreyer Honors College as well as other activities and community service events.
- Acted as a liaison between the alumni and the undergraduate brotherhood through conferences, retreats and other meetings.

Rush Chair/Brother **Spring 2007 - Present**

- Assist the Vice President of Recruitment in organizing recruitment events and market the fraternity through social activities in order to encourage new members to join and ultimately assume leadership positions
- Participate in a variety of philanthropic events including THON and American Red Cross blood drives
- Met with University President, Graham Spanier, to discuss time management, college lifestyle, and everyday issues facing college students.

HONORS/AWARDS

Phi Kappa Phi Honors Fraternity **2009 - Present**

President's Freshman Award **Spring 2008**