The effect of exercise training on metaboreflex regulation of heart rate and blood pressure

by

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Abstract

The metaboreflex is a cardiovascular reflex which activates the sympathetic nervous system when a mismatch between oxygen delivery and demand occurs during exercise; metabolic by-products accumulate in the interstitium of skeletal muscle tissue and stimulate afferent nerve fibers. This in turn elevates heart rate and blood pressure by increasing cardiac output as well as peripheral vasoconstriction. This thesis investigated the effects of exercise training on metaboreflex regulation of heart rate and blood pressure during dynamic exercise in healthy humans. It was hypothesized that activation of the metaboreflex would produce a smaller increase in heart rate and blood pressure during exercise following aerobic exercise training. Young males (age=24.7±3.9) were assigned to traditional aerobic (n=10) or sprint interval (SPRI n=15) exercise training on a cycle ergometer. The traditional aerobic training group trained five days/week for six weeks at a workload that elicited 75% of maximum heart rate for a flywheel distance of 16 km. The sprint interval training group performed repeats of 30 s bouts of exercise at a resistance equal to 7.5% of the subject's body weight on three days/week for six weeks. Each exercise bout was separated by 4.5 minutes of cycling with minimal resistance to allow for recovery. Young males performed steady-state recumbent cycling exercise at 60% of maximum heart rate in control and partial flow-restricted conditions before and after traditional aerobic and sprint interval exercise training. Once heart rate achieved steady-state, pneumatic leg cuffs were inflated to partially restrict leg blood flow during exercise and stimulate the metaboreflex. Heart rate and blood pressure were measured continuously measured via finger-cuff photo-plethysmography. Traditional aerobic and sprint interval exercise training both improved aerobic fitness (PRE: TRAD-50.3±10.6 mL/kg/min., SPRI-48.7±9.5 kg/mL/min.; POST: TRAD-53.5±8.0 mL/kg/min., SPRI-50.3±8.4 mL/kg/min.) and peak power output (PRE: TRAD-305±35

W., SPRI-289±52 W; POST: TRAD-325±33 W L/min., SPRI-312±52 W). However, neither traditional aerobic nor sprint interval exercise training altered the heart rate and mean arterial pressure response to metaboreflex activation in either the exercise trained legs (ΔHR - PRE: TRAD- 7.7±4.9 bpm, SPRI- 7.4±5.8 bpm; POST: TRAD- 6.9±3.3 bpm, SPRI- 7.2±3.4 bpm)(ΔMAP- PRE: TRAD- 11.1±6.0 mmHg, SPRI- 7.3±5.6 mmHg; POST: TRAD- 12.1±6.7 mmHg, SPRI - 8.9±4.3 mmHg) or the untrained forearm (ΔHR- PRE: TRAD- 0.4±10.7 bpm, SPRI- -2.3±8.4 bpm; POST: TRAD- -3.2±9.7 bpm, SPRI- -2.51±9.8 mmHg)(ΔMAP - PRE: TRAD- 18.3±13.2 mmHg, SPRI- 23.3±10.5 mmHg; POST: TRAD- 15.3±14.0 mmHg, SPRI- 23.5±9.1 mmHg). In conclusion, exercise training did not alter the magnitude of the heart rate and blood pressure response to metaboreflex activation during exercise in healthy young males.

Preface

This thesis is an original work by Chance Reinhart. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board (Health Sciences Panel), under the name “Exercise Training and the Metaboreflex”, No. Pro 00040578, approved June 20, 2013 All participants provided written informed consent.

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List of Abbreviations

BP - blood pressure (mmHg)
ECG - electrocardiogram
HR - heart rate (beats·min^{-1})
HR_{max} - maximum heart rate
IHG - isometric handgrip
MAP - mean arterial pressure (mmHg)
MVC - maximum voluntary contraction (N)
Q - cardiac output (L·min^{-1})
SV - stroke volume (mL·min^{-1})
TPR - total peripheral resistance (mmHg·L-1·min^{-1})
VO_{2max} - maximal oxygen consumption (L·min^{-1}) or (mL·kg-1·min^{-1})
W - watts

Chapter 1: Introduction

Introduction

Cardiovascular disease is the leading cause of death in North America (Public Health Agency of Canada, 2009). Regular physical activity improves cardiovascular function and has been associated with a reduced risk of cardiovascular disease (Blair, Kohl, Paffenbarger, Clark, Cooper & Gibbons, 1989). Surprisingly, ~40% of the reduction in cardiovascular disease risk associated with aerobic exercise-training is not associated with changes in traditional cardiovascular disease risk factor profiles, such as hypertension, elevated plasma LDL cholesterol and blood glucose levels. (Green, O'Driscoll, Joyner, & Cable, 2008). This suggests that changes in the basic physiological mechanisms which regulate cardiovascular function may underlie the physiological and health benefit(s) of aerobic exercise training (Joyner & Green, 2009). Exercise training has been shown to lower resting heart rate and blood pressure (Wilmore & Costill, 2004). During submaximal exercise, the increase in blood pressure is also reduced in aerobically fit compared to unfit individuals (Wilmore & Costill, 2004).

The skeletal muscle metaboreflex is a cardiovascular reflex that contributes to the control of blood pressure and heart rate during exercise (Rowell, 1993). The metaboreflex is activated during exercise in an intensity-dependent manner and the magnitude of metaboreflex response appears to be a function of the degree of mismatch between oxygen demand and oxygen delivery in active muscle. Briefly, when a mismatch between oxygen delivery and demand occurs during exercise, metabolic by-products (lactate, arachidonic acid) accumulate in the interstitium of skeletal muscle tissue and stimulate Type IV chemo-sensitive afferent nerve fibers (Alam & Smirk, 1937; Bull, Davies, Linda & White, 1989; Rotto & Kaufman, 1988). Additionally,

skeletal muscle contraction stimulates mechanically sensitive Type III afferent mechano-receptors (Rotto & Kaufman, 1988). An increase in afferent signaling from Type III and IV afferents is processed in the brain stem and integrated with other afferent signaling. This results in changes in efferent nerve activity including a decrease in parasympathetic nervous activity and an increase in sympathetic nerve activity (Rowell & O'Leary, 1993). The altered efferent nerve traffic leads to an increase in peripheral vasoconstriction and blood pressure (Rowell, 1993), while cardiac output is increased through an increase in heart rate and contractility (Crisafulli et al., 2003; Crisafulli et al., 2011; Spranger et al., 2013). The resulting pressor response maintains blood pressure during exercise despite robust vasodilation in active skeletal muscle that increases tissue blood flow and reduces local accumulation metabolites in active muscle (Rowell & O'Leary, 1990).

A limited number of studies have investigated the effects of exercise training on metaboreflex regulation of heart rate and blood pressure during large muscle mass dynamic exercise in healthy humans. In 1996, Sinoway et al. reported that four weeks of rhythmic handgrip exercise training attenuated the increase in mean arterial pressure, muscle sympathetic nerve activity and norepinephrine spillover during rhythmic handgrip exercise. These results would suggest that rhythmic forearm training also had an effect on efferent nervous activity to the peripheral vasculature, by mediating a decrease in muscle sympathetic nerve activity as well as a decrease in the spillover of the neuro-transmitter norepinephrine (Sinoway et al, 1996). In a subsequent study, it was also shown that four weeks of handgrip training also caused a decrease in lactic acid concentration, increased plasma pH and blunted blood pressure response to ischemic rhythmic handgrip exercise in healthy males, suggesting that exercise training may improve local blood flow and reduce the local accumulation of muscle metabolites and decrease

stimulation of the metaboreflex (Mostoufi-Moab, Widmaier, Cornett, Gray, & Sinoway, 1998). Furthermore, Fisher and White (1999) investigated the effects of six weeks of single-leg calf raise training on the heart rate and blood pressure response to voluntary and electrically-evoked isometric contraction of the triceps surae muscle group followed by post-exercise circulatory occlusion in the exercise trained leg and untrained contra-lateral leg of healthy young men. The blood pressure and heart rate responses were attenuated during voluntary contractions in both the exercise trained and untrained leg following exercise training. Also, a blunted diastolic blood pressure response to electrically-evoked contractions was observed in the trained leg following training, and blood pressure and heart rate responses to electrically evoked contraction of the untrained leg were not altered after training. In addition, exercise training did not alter the response to post-exercise circulatory occlusion in the trained or untrained leg. Taken together these findings suggest that exercise training may attenuate central command during exercise evidenced by the blunted pressor and heart rate response to contraction in both the trained and untrained leg following single-leg exercise training. More recently, exercise training has been shown to attenuate the increase in renal sympathetic nervous activity and blood pressure to exogenous capsaicin stimulation of the Type IV afferent fibers in rats with experimentally induced heart failure, suggesting that exercise training may blunt the responsive of Type IV afferents (Wang et al, 2010; 2012). While these studies have advanced our mechanistic understanding of the effects of exercise training on the metaboreflex and metaboreflex regulation of the cardiovascular system, the investigations utilized isolated small muscle exercise, isometric and ischemic muscle contractions and rat models. Thus, translation of the findings to large muscle mass dynamic exercise in humans is challenging due to the differences in muscle fiber type and recruitment patterns between the upper and lower limb, as well the differences between

metaboreflex activation with pharmacology and isometric or ischemic exercise and post-exercise circulatory occlusion.

In addition to a lack of understanding of the effects exercise training on metaboreflex regulation of heart rate and blood pressure during large muscle mass voluntary exercise in healthy humans, our understanding of the effects of different exercise training modalities and the resulting adaptations in reflex control of the cardiovascular system is also limited. Recent studies have shown that a variety of exercise training paradigms can be used to elicit improvements in exercise performance and cardiovascular function (Gibala et al, 2006; Gibala & Jones, 2013; Rakobowchuk et al, 2008). However, whether different training paradigms differentially impact metaboreflex regulation of the cardiovascular system has not been established. Different intensities and volumes of training may result in different patterns of metaboreflex activation and over the duration of a training program may lead to differential adaptations in the metaboreflex. For example, high-intensity low-volume exercise training causes a large increase in muscle stretch and metabolite accumulation relative to moderate-intensity continuous training and activation of the metaboreflex would be brief and intermittent, but intense. In contrast, traditional continuous training may only be associated with a modest mismatch between oxygen delivery and demand and therefore a modest, but continuous activation of the metaboreflex. Whether these different patterns of metaboreflex activation during training impact metaboreflex regulation of heart rate and blood pressure is unknown. Furthermore, high intensity, low volume sprint interval training appears to produce training adaptations in a number of physiological systems that are similar to those achieved with traditional, continuous training (Gibala & Jones, 2013; Tschakert & Hofmann, 2013). For example, high intensity, low volume and traditional continuous

training have both been shown to cause a similar increase in capillary density in trained skeletal muscle (Laughlin & Roseguini, 2008; Cocks et al, 2013) capillarization following training could improve skeletal muscle blood flow capacity and thereby decrease any mismatch that may occur between oxygen delivery and demand in the active muscle by better distributing blood flow.

Purpose and Hypothesis

With this as a background, the purpose of this study was to: 1) investigate the effects of exercise training on muscle metaboreflex regulation of heart rate and blood pressure during dynamic large muscle-mass exercise in healthy young adults, and; 2) determine the effects of different modalities of exercise training on the metaboreflex regulation of heart rate and blood pressure during exercise. It was hypothesized that both forms of exercise training would attenuate the heart rate and blood pressure to metaboreflex activation during dynamic exercise, with sprint interval training producing a greater attenuation of the metaboreflex than continuous training.

Significance

This study investigated the effect of exercise training on the metaboreflex regulation of heart rate and blood pressure, in addition to assessing the effects of different exercise training modalities on metaboreflex regulation of heart rate and blood pressure. To my knowledge, this is the first study to investigate the effect of exercise training on metaboreflex regulation of heart rate and blood pressure during dynamic voluntary leg exercise. In addition, it is the first to contrast the effects of high volume traditional aerobic training and low-volume, high-intensity sprint-interval training on metaboreflex regulation of heart rate and blood pressure.

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Chapter 2: The Effect of Exercise Training on Metaboreflex Regulation of Heart Rate and Blood Pressure

Introduction

The skeletal muscle metaboreflex is a cardiovascular reflex that contributes to the control of blood pressure and heart rate during exercise (Rowell, 1993). The muscle metaboreflex is activated when a mismatch occurs between oxygen delivery and the oxygen demand of active muscle. This mismatch causes an increase in anaerobic metabolism in active muscle tissue leading to an increase in the concentration of metabolic products such as lactate and arachidonic acid in the interstitium of active muscle tissue (Bull et al, 1989; Rotto & Kaufmann, 1988). The increase in metabolite concentration is sensed by Type IV afferent chemoreceptors and increases afferent nerve activity which is carried to the brainstem where it is integrated with other afferent signals. In addition, the mechanical pressure and stretch resulting from muscle contraction results in stimulation of Type III afferent mechano-receptors (Bell & White, 2005; Fisher, Bell & White, 2005). This results in a change in efferent signaling, specifically a decrease in parasympathetic nervous activity and an increase in sympathetic nervous system activity (Rotto & Kaufman, 1988; Rowell, 1990; Rowell & O'Leary, 1993). The increase in sympatho-excitation causes an increase in peripheral vasoconstriction, as well as an increase in cardiac output via an increase in both heart rate and cardiac contractility. This sustained pressor response causes an increase in blood flow which assists in clearing the metabolite build up in the active muscle tissue and maintain blood pressure during exercise. Therefore, the metaboreflex is composed of an increase in heart rate and blood pressure in response to an increase in the stimulation of Type IV and Type III afferents by an increase in the concentration of metabolic

products as well as an increase in the mechanical compression caused by muscle contraction, respectively.

Chronic endurance exercise training is known to reduce heart rate and blood pressure at rest and during exercise (Wilmore & Costill, 2004). Exercise training has also been shown to improve skeletal muscle blood flow (Delp, 1999; Rowell, 1993). Thus, it is conceivable that an exercise training-mediated improvement in oxygen delivery may attenuate muscle metaboreflex mediated increases in heart rate and blood pressure by either reducing stimulation of the metaboreflex or by altering the reflex regulation of the metaboreflex. Handgrip exercise training has been shown to reduce the magnitude of the heart rate and blood pressure response to metaboreflex activation through a decrease in metabolite build up in response to ischemic handgrip exercise in healthy young men (Moab-Mostoufi et al, 1998) as well as decrease the muscle sympathetic nervous response and norepinephrine spillover during handgrip exercise Sinoway et al, 1996). Aerobic exercise training has also been shown to attenuate the pressor response to metaboreflex activation in rats with experimentally-induced heart failure by reducing the sensitivity of the metaboreflex to stretch (Wang et al, 2010, 2012). In addition, Fisher and White (1999) utilized six weeks of single-leg calf raise training to investigate the effects of training on the heart rate and blood pressure responses to voluntary and electrically-evoked isometric contractions of the triceps surae muscles group followed by post-exercise circulatory occlusion in both the trained limb and contra-lateral untrained limb. The results of that study demonstrated an attenuated heart rate and blood pressure response to voluntary contractions in both the trained and untrained limb following training. As well, they also observed an attenuated diastolic blood pressure response to electrically-evoked contraction in both the trained and untrained limb. However, the blood pressure and heart rate responses to electrically-evoked

contractions of the untrained limb were not altered following training. Exercise training also did not alter the response to post-exercise circulatory occlusion in the trained or untrained limb. Collectively the results of this study suggest that exercise training may attenuate central command during exercise as demonstrated by the blunted heart rate and blood pressure response in both the trained and untrained limb following single-leg calf raise training.

However, previous studies that have investigated the effects of exercise training on metaboreflex regulation of heart rate and blood pressure have typically utilized used isometric exercise followed by post-exercise circulatory occlusion (Fisher & White, 1999; Mostoufi-Moab et al, 1998; Milia et al, 2014). While this approach does allow for the study of the heart rate and blood pressure response to metaboreflex activation, tissue blood flow is altered in a non-physiological manner and may not reflect the normal function of the metaboreflex during dynamic exercise. The present study utilized an approach similar to that of a recent study (Hartwich, D., Dear, W. E., Waterfall, J. L., & Fisher, J. P., 2011) where the metaboreflex was activated by partially occluding blood flow to the legs with pneumatic cuffs during dynamic recumbent cycling exercise. The metaboreflex is therefore, activated during a traditional mode of voluntary exercise that involves a large muscle mass, and requires a considerable hemodynamic response and also activates the metaboreflex by evoking the release of endogenous metabolites in physiological concentrations. The magnitude of the heart rate and blood pressure response to metaboreflex activation appear to be a function of the amount of muscle mass recruited during exercise and the relative cardiac reserve utilized to maintain systemic blood pressure as well as blood flow to active tissue. Therefore, the present experimental approach should produce a robust activation of the metaboreflex. This approach also utilizes the same mode of exercise for

training and experimental data collection which facilitates identification of training adaptations in muscle recruited during exercise training.

This study utilized used both traditional aerobic and sprint interval training paradigms to determine the adaptations in metaboreflex regulation of heart rate and blood pressure in response to different exercise training modalities. Traditional aerobic training represents a high volume, moderate intensity training approach, which would result in moderate sustained metaboreflex activation while low volume high intensity sprint interval training causes a brief intense stimulation of the metaboreflex. Utilization of these training paradigms allows investigation of how different training paradigms may impact metaboreflex regulation of heart rate and blood pressure and will provide novel information related to the adaptations in the metaboreflex to different modalities of exercise training.

Therefore, the purpose of this study was to: 1) investigate the effects of exercise training on muscle metaboreflex regulation of heart rate and blood pressure during dynamic large muscle-mass exercise in healthy young adults, and; 2) determine the effects of different modalities of exercise training on metaboreflex regulation of heart rate and blood pressure by using high volume traditional aerobic and sprint interval training. It was hypothesized that both forms of exercise training would result in an attenuation of the effects of the metaboreflex on heart rate and blood pressure, with sprint interval training producing a greater attenuation of the metaboreflex than continuous training.

Methods

Subjects

Thirty-two healthy, young (24.8±3.9yr) males volunteered to participate in the study and were randomly assigned to either the traditional aerobic or sprint interval exercise training group.

All subjects were non-obese and non-smokers and free from respiratory, cardiovascular, metabolic, neurological or musculoskeletal diseases and were not taking any medications known to alter the cardiovascular response to exercise. Subjects who had an abnormal electrocardiogram (ECG) during maximal exercise testing (n=2) or who could not complete the testing or training sessions were excluded from the study (n=5). Ten subjects completed the traditional aerobic training program, whereas fifteen subjects completed the sprint interval training program.

Experimental Protocol

Subjects reported to the Integrative Human Exercise Physiology Laboratory (IHEP Laboratory; Room 4-246, Van Vliet Complex, University of Alberta) on three different occasions for testing before and after exercise training. Subjects reported to the laboratory approximately two hours after a light meal and after having abstained from alcohol, nicotine, ibuprofen, caffeine and physical activity for at least twenty-four hours.

On the first day of testing, subjects completed an incremental exercise test to volitional exhaustion on an electronically braked cycle ergometer (Ergoselect 200 K, Ergoline, Bitz, Germany) for determination of VO_{2max} and HR_{max}. Subjects breathed through a mouthpiece connected via tubing to a metabolic cart (Vmax® 229d; Viasys™ Healthcare, Palm Springs, CA, USA) and wore a nose clip to prevent breathing through their nose. Testing began with one minute of resting baseline data collection, after which the work rate was progressively incremented in a ramp-like fashion at 30 W/min. to volitional fatigue. Criteria used to establish a maximal test included: a plateau in VO_2 despite an increase in work rate, a respiratory exchange ratio (RER) >1.10, achievement of >90% of age-predicted HR_{max}. VO_{2max} was defined as the highest twenty second average of VO_2 achieved during the test.

On the second day of testing, subjects completed two bouts of constant-load cycle ergometer exercise (Ergoselect 200 K, ergoline GmbH, Bitz, Germany) at a moderate-intensity work rate (~50% VO_{2max}; ~60% HR_{max}) in a semi-recumbent position (DEPO). Prior to exercise, pneumatic cuffs (Hokanson CC17, Bellevue, WA, USA) were attached to the mid-portion of the subject's thigh. To prevent movement of the cuff during exercise the cuffs were secured by adhesive tape. The first bout of exercise was performed with the leg cuffs deflated to establish the work rate that would elicit an exercise heart rate equal to 60% of HR_{max} (TRAD: 60.4±2.7 bpm; SPRI: 59.5±1.9 bpm)and to establish the steady-state heart rate and blood pressure response to exercise under "free-flow" conditions. The protocol began with two minutes of baseline data collection, followed by eleven minutes of recumbent cycling and one minute of recovery. Following approximately twenty-five minutes of recovery and the return of HR and BP to resting levels, a second exercise bout was performed. During the second bout of exercise, subjects exercised at the work rate established in the initial bout and after five minutes of exercise, the leg cuffs were inflated to 90% of the exercising diastolic blood pressure observed in the first exercise bout to transiently decrease leg blood flow and augment muscle metaboreflex stimulation. The cuffs remained inflated for four minutes while the subjects continued to cycle. The cuffs were then deflated and subjects continued to cycle for an additional two minutes, followed by one minute of recovery. Cycling cadence was held constant during cycling trials.

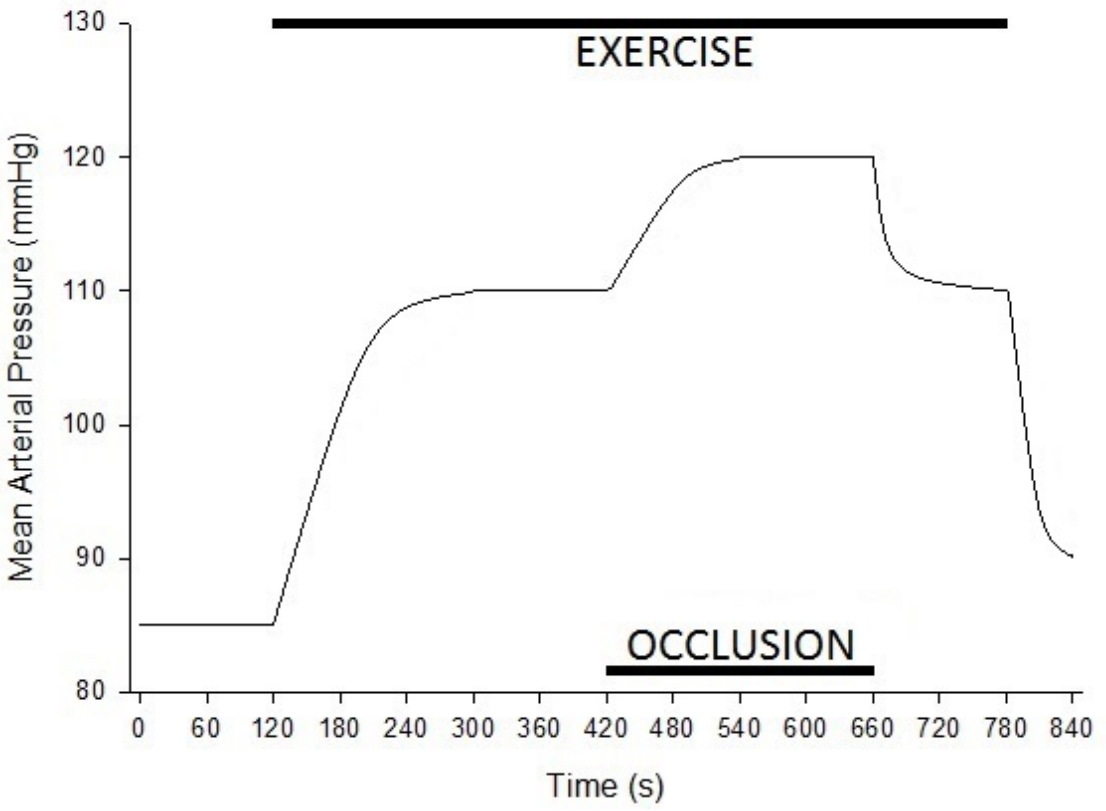

Figure 1: A depiction of the mean arterial blood pressure (MAP) response to dynamic exercise and partial circulatory occlusion of the legs. The top, solid line indicates the onset of exercise. While the lower solid line indicates the application of partial leg occlusion.

On the third day, of testing subjects performed IHG followed by post-exercise circulatory occlusion to investigate the effect of exercise training on the metaboreflex in a vascular bed not activated during cycle exercise training (n=22). A pneumatic cuff (Hokanson SC10D, Bellevue, WA, USA) was placed around the upper portion of the right arm and the subject then performed handgrip exercise at 40% of their maximal voluntary contraction for three minutes which was followed by inflation of the cuff to a supra-systolic pressure (~200 mmHg) for four minutes to occlude blood flow to the arm and activate the metaboreflex. Subjects maintained muscle contraction during the initial ten seconds of the occlusion period then relaxed.

Exercise Training

All exercise training was competed in the IHEP Laboratory and was monitored by trained personnel. Each training session began with a short warm-up period and then resistance on the cycle ergometer was adjusted in order to achieve the subject's target heart rate. The subject's heart rate was continuously monitored during each training session via 3-lead ECG.

Traditional continuous aerobic exercise training

Subjects exercised on a cycle ergometer (Ergomedic 828 E, Monark AB, Vansbro, Sweden) at 75% of HR_{max} for a flywheel distance of 16 km (~25 minutes/training session) five days/week for six weeks.

Sprint interval training

Subjects completed three training sessions/week for six weeks, each training session consisted of four to six exercise intervals. Intervals consisted of 30-s, "all-out" sprints on a manually-braked cycle ergometer (Ergomedic 894 E, Monark AB, Vansbro, Sweden) against a workload resistance equivalent to 0.075 kg/kg body mass. Intervals were separated by 4.5 minutes of active recovery (cycling at ~30W). During the first two weeks of training, subjects

completed four intervals during each training session, five intervals during weeks 3 and 4 of training and six intervals during each training session in weeks 5 and 6.

Measurements

Pulmonary O_2 consumption, CO_2 production and ventilation were measured breath-by-breath using a mass flow sensor and metabolic cart (Vmax® 229d; Viasys™ Healthcare, Palm Springs, CA, USA).

Heart rate was derived from a 3-lead ECG (Power Lab 16/30; AD Instruments, Colorado Springs, CO, USA). The heart rate was determined by counting QRS complexes present on the electrocardiogram.

Beat-by-beat arterial blood pressure was measured via finger-cuff photo-plethysmography (Finometer™, Finapres Medical Systems BV, Arnhem, Netherlands). Cardiac output and stroke volume were derived from the pressure waveform using ModelFlow technology. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac outut.

A grip force transducer (ML T004; AD Instruments, Colorado Springs, CO, USA) connected to a data acquisition system (Power Lab 16/30; AD Instruments, Colorado Springs, CO, USA) was used to measure the subject's maximal voluntary contraction of their right hand. Subjects were given visual feedback on contraction force via a display screen during the post-exercise circulatory occlusion test, allowing subjects to accurately maintain 40% of their maximal voluntary contraction during handgrip exercise.

Statistics and Data Analysis

Data collected during the occlusion trial of the dynamic exercise partial occlusion test was collected beat-by-beat via finger cuff photoplethysmography (Finometer™, Finapres

Medical Systems BV, Arnhem, Netherlands) and recorded and calculated using Beatscope software (Beatscope™, Finapres Medical Systems BV, Arnhem, Netherlands). These data was then sorted into two minute bins. From this data, the two minutes of exercise prior to cuff inflation and the two minutes of exercise prior to cuff deflation were averaged for each variable. The two minute average prior to inflation was considered the steady state average, while the two minute average prior to deflation was considered the occlusion average. The two averages were then compared within the pre-training and post-training tests and the difference between the steady state average and the occlusion average signified the effect of metaboreflex activation (represented by gray area in Fig. 2). Furthermore, the difference between the levels of metaboreflex activation during the pre- and post-training tests was considered to be the training effect on the strength of the metaboreflex reaction in the subjects (Δpre-training, Δpost-training). This data was analyzed as the absolute change from Δpre-training.

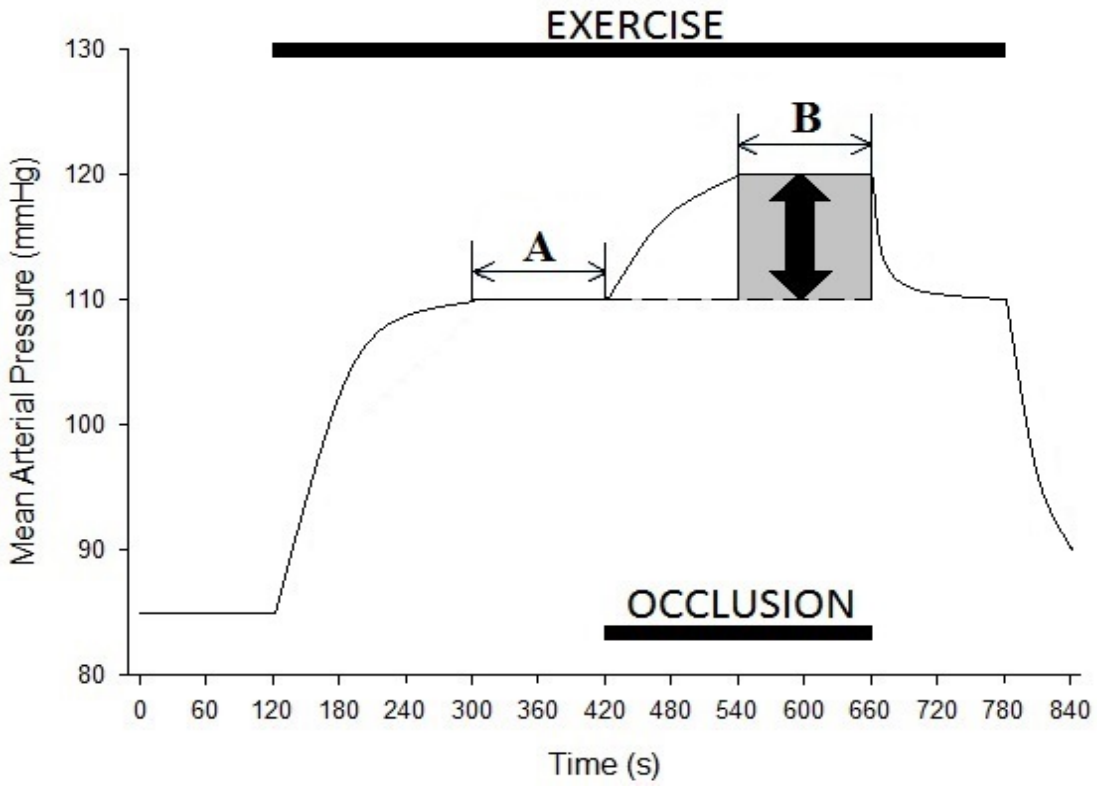

Figure 2: Depiction of a typical response of mean arterial pressure (MAP) to dynamic exercise and partial circulatory occlusion of the legs during exercise and the analysis approach utilized to quantify the magnitude of the blood pressure to activation of the metaboreflex by partial occlusion of the legs. The steady state average (A) equals the mean of the mean arterial pressure during steady state exercise. Occlusion average (B) equals the mean of the mean arterial pressure response to partial leg occlusion during steady-state exercise. The effect of metaboreflex activation was calculated as the difference between the steady state average and occlusion average.

Metaboreflex Activation (Δpre-training, Δpost-training) = (occlusion average (B)) – (steady-state average (A))

Effect of Training on Metaboreflex = Δpost-training - Δpre-training

Data from the post-exercise circulatory occlusion test was averaged into one minute bins. To measure the effect of metaboreflex activation the two minutes of the rest period data, was compared to the third minute of the isometric handgrip exercise and the fourth and final minute of the stationary occlusion period. The difference between the resting and isometric handgrip exercise averages was considered to be the effect of static exercise on the variables measured, while the difference between the resting and final minute occlusion averages was considered to be the effect of metaboreflex activation (Δpre-training, Δpost-training). This data was analyzed as absolute differences from the Δpre-training.

Metaboreflex Activation (Δpre-training, Δpost-training) = final minute of occlusion average – rest average

Effect of Training on Metaboreflex / Static Exercise = Δpost-training - Δpre-training

All data were reported as Mean±SD. Data were analyzed by two-way repeated measures ANOVA. When significant F ratios were found, Student-Newman-Keuls post hoc analysis was performed. Relationships between variables were established by Pearson-Product moment correlation. A p-value <0.05 were considered statistically significant. All statistical analysis was performed using Sigmaplot software (SigmaPlot Version 11.0, Systat Software Inc., San Jose, CA, USA).

RESULTS

Subject Characteristics

Age (Sprint: 25.1±4.2 years, Traditional: 24.3±3.6 years), height (Sprint: 178.9±8.4cm, Traditional: 180.1±7.0cm) weight (Table 1) were not different ($p>0.05$) before or following

training in either exercise training group. Absolute and relative VO_{2max} as well as peak power output were not different ($p>0.05$) between groups prior to training. Exercise training increased VO_{2max} and peak power by a similar magnitude ($p>0.05$) in sprint interval and traditional aerobic groups (Table 1).The conditions of the dynamic exercise partial circulatory occlusion trial including cuff inflation pressure, cadence, target and actual steady state heart rate and power output were kept constant between pre- and post-training trials (Table 2).

Table 1: Subject characteristics for sprint interval (SPRI) and traditional aerobic (TRAD) training groups pre- and post-training.

	SPRI		TRAD	
	PRE	**POST**	**PRE**	**POST**
Weight (kg)	77.5±12.5	77.3±12.5	78.7±10.8	78.8±10.6
Absolute VO_{2max} (L/min.)	3.74±0.84	3.94±0.81*	3.86±0.42	4.14±0.31*
Relative VO_{2max} (mL/kg/min.)	48.7±9.5	50.3±8.4*	50.3±10.7	53.5±8.0*
Peak Power Output (W)	288.7±51.8	312.5±52.4*	305.3±34.8	324.8±32.7*

Values are mean ± SD. * Significant difference from pre-training ($p<0.05$).

Table 2: Subject characteristics for dynamic exercise partial circulatory occlusion trial conditions for sprint interval and traditional aerobic training groups pre- and post-training.

	SPRI		TRAD	
	PRE	**POST**	**PRE**	**POST**
Power Output (W)	76.7±27.7	83.0±27.9	98.5±21.5	98.5±23.1
Percentage of Peak Power Output (%)	26±7	26±7	32±7	30±7
Cuff Inflation Pressure (mmHg)	60.8±9.5	59.3±8.3	64.9±6.8	64.4±7.2
Target Steady-State Heart Rate (bpm)	112.1±4.1	110.7±4.4	107.8±6.9	107.1±6.4
Actual Steady-State Heart Rate (bpm)	111.1±5.9	108.5±5.7	108.6±9.0	107.2±6.6

Values are mean ± SD. * Significant difference from pre-training ($p<0.05$).

Blood Pressure and Heart Rate Response to Metaboreflex Activation during Dynamic Exercise

An original data tracing of the mean arterial pressure and heart rate response to dynamic exercise partial circulatory occlusion from a representative subject is illustrated in Figure 3.

Mean arterial pressure, systolic blood pressure, diastolic blood pressure, heart rate and cardiac output increased in all subjects during cycling exercise and were elevated further as a result of dynamic exercise partial circulatory occlusion.

The work rate required to elicit 60% of HR_{max} during the dynamic exercise partial circulatory occlusion test was not different within groups between pre- (TRAD, 98.5±21.5 W, SPRI, 76.7±27.7 W) and post-training (TRAD, 98.5±23.1 W, SPRI, 83.0±27.9 W) trials. The inflation pressure applied to the legs using the cuffs was not different between groups and was not different pre- (TRAD, 64.9±6.8mmHg, SPRI, 60.8±9.5mmHg) and post-training (TRAD, 64.4±7.2 mmHg, SPRI, 59.3±8.3 mmHg).

The increase in mean arterial pressure (Fig. 4), systolic blood pressure (Fig. 5), diastolic blood pressure (Fig. 6) and heart rate (Fig. 7) during metaboreflex activation was not different between groups ($p>0.05$) pre- or post-training. Following exercise training, the increase in cardiac output (Fig. 8), stroke volume (Fig. 9) was attenuated ($p<0.05$) during metaboreflex activation, whereas the increase in total peripheral resistance (Fig. 10) was increased ($p<0.05$) in the traditional training group, sprint interval training did not alter the blood pressure or heart rate response to activation of the metaboreflex during dynamic exercise.

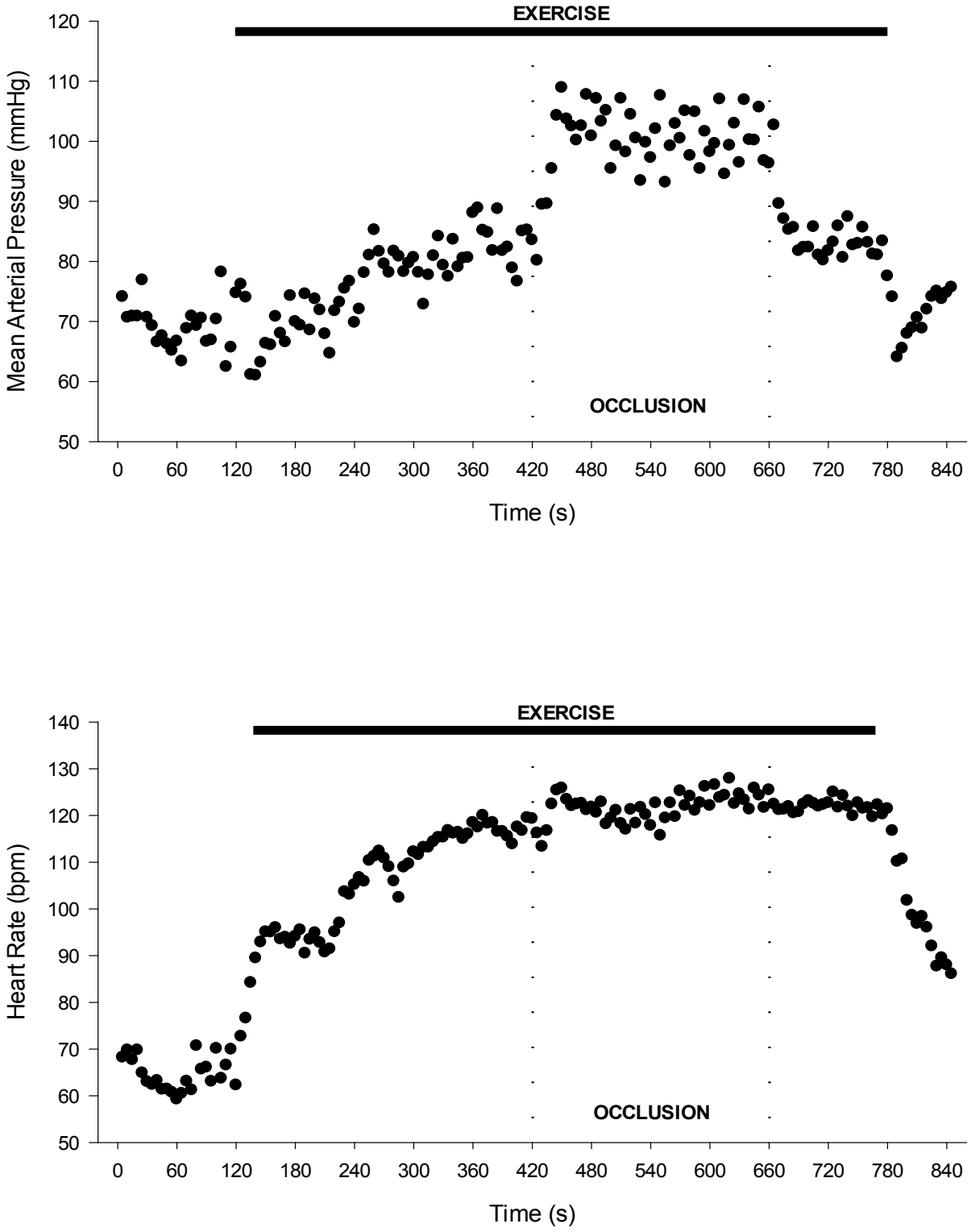

Figure 3: Individual representative tracing of the cardiovascular (heart rate, HR; mean arterial pressure, MAP) response during the dynamic exercise partial circulatory occlusion trial. Exercise was initiated at 120s, followed by partial limb occlusion at 420s. Occlusion was maintained until 660s followed by free flow exercise until 780s, and 60s of recovery. Each data point represents a 5s average.

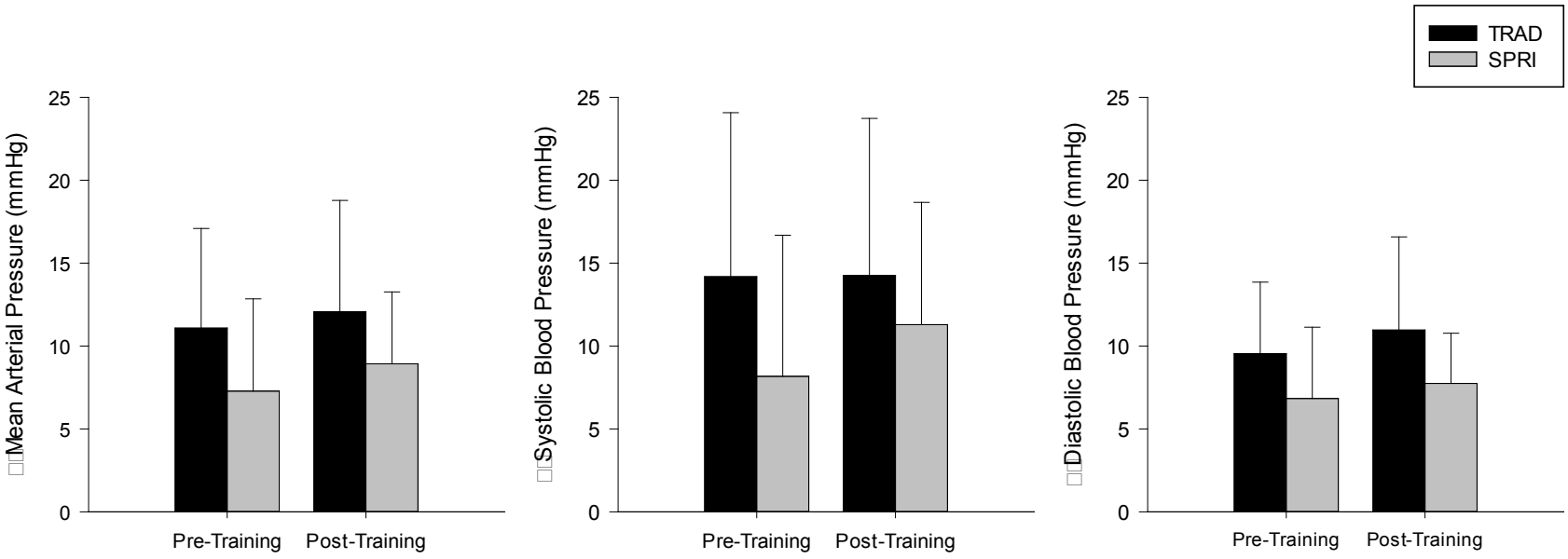

Figure 4: Absolute increase in Mean Arterial Pressure (Panel A; p=0.210), Systolic Blood Pressure (Panel B; p=0.352) and Diastolic Blood Pressure (Panel C; p=0.125) in response to partial circulatory occlusion of the leg during dynamic exercise trial in traditional (TRAD, black bar; n=10) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD.

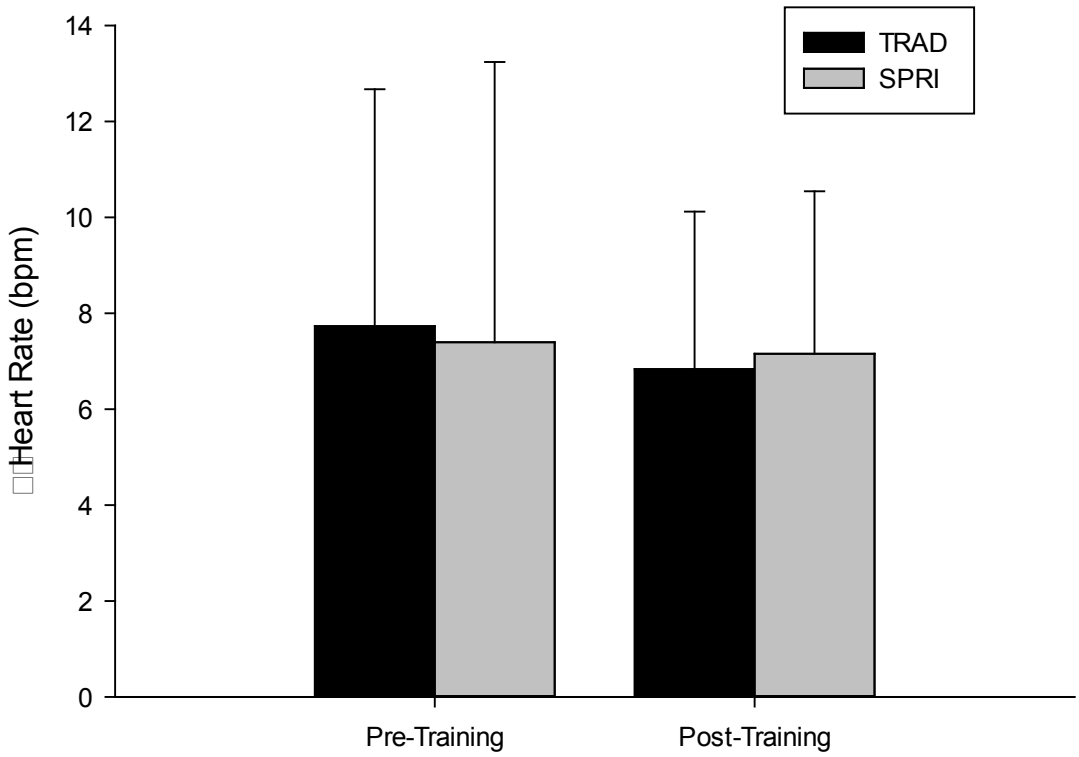

Figure 5: Absolute increase in Heart Rate in response to partial circulatory occlusion of the leg during dynamic exercise trial in traditional (TRAD, black bars; n=10) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD (p=0.523).

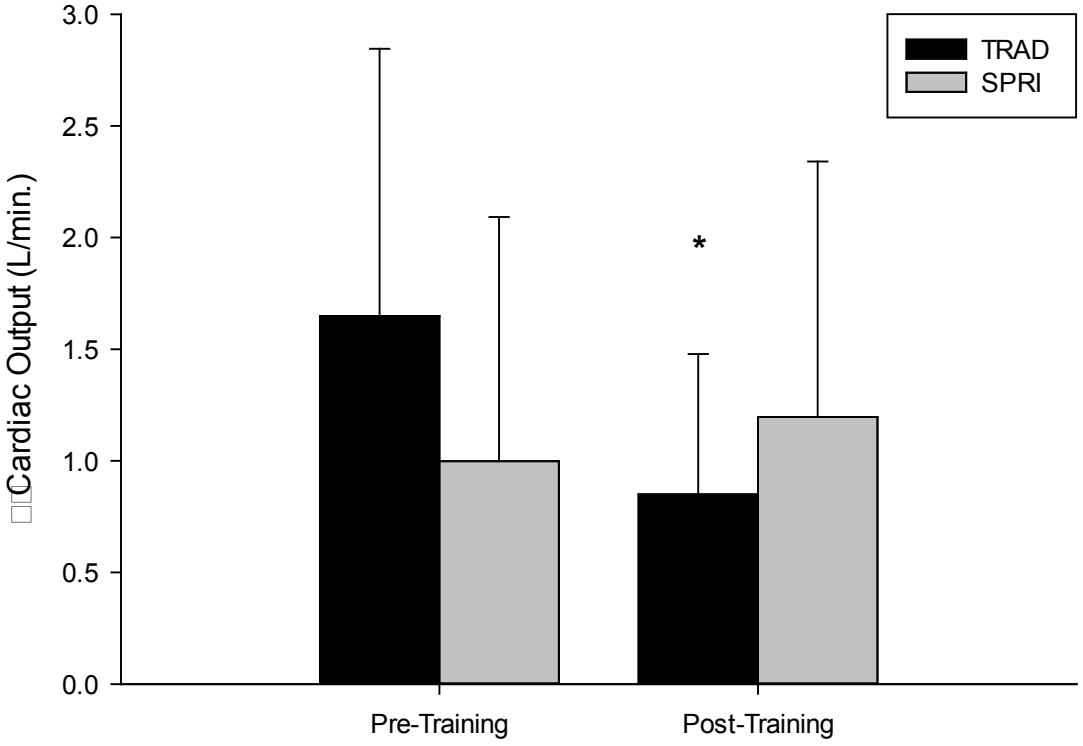

Figure 6: Absolute increase in Cardiac Output in response to partial circulatory occlusion of the leg during dynamic exercise trial in traditional (TRAD, black bars; n=10) and sprint interval training groups (SPRI, gray bars; n=15). Values are Mean±SD. * indicates a significant ($p<0.05$) difference from pre-training ($p=0.027$).

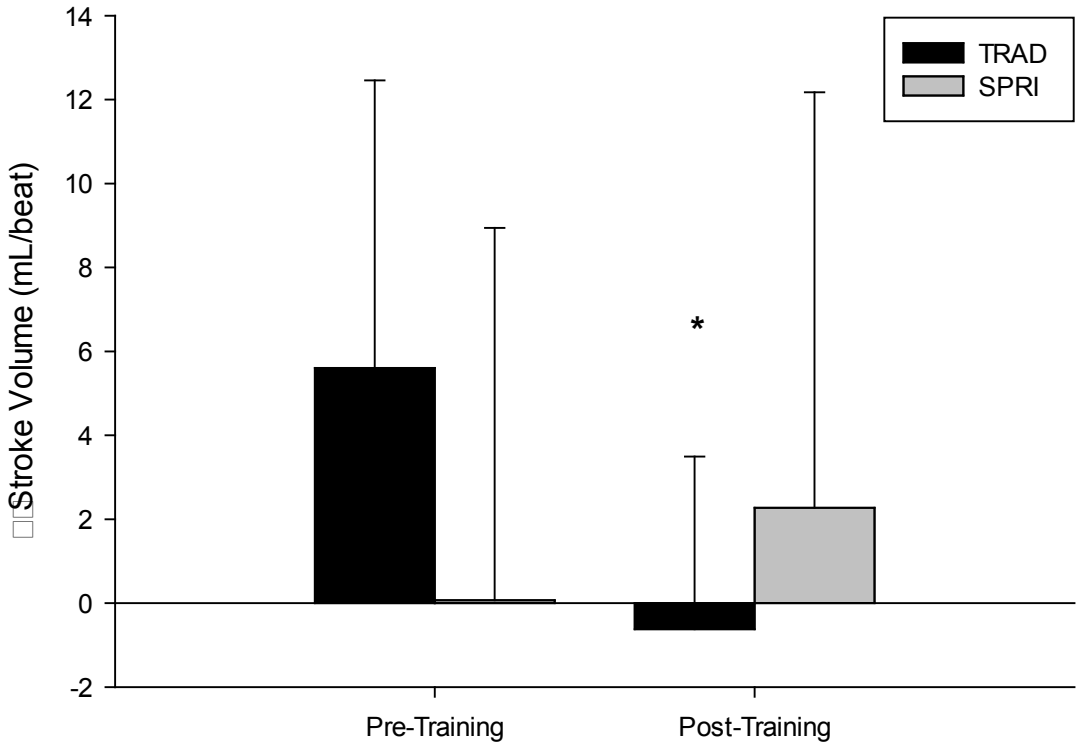

Figure 7: Absolute increase in Stroke Volume in response to partial circulatory occlusion of the leg during dynamic exercise trial in traditional (TRAD, black bars; n=10) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD. * indicates a significant ($p<0.05$) difference from pre-training ($p=0.013$).

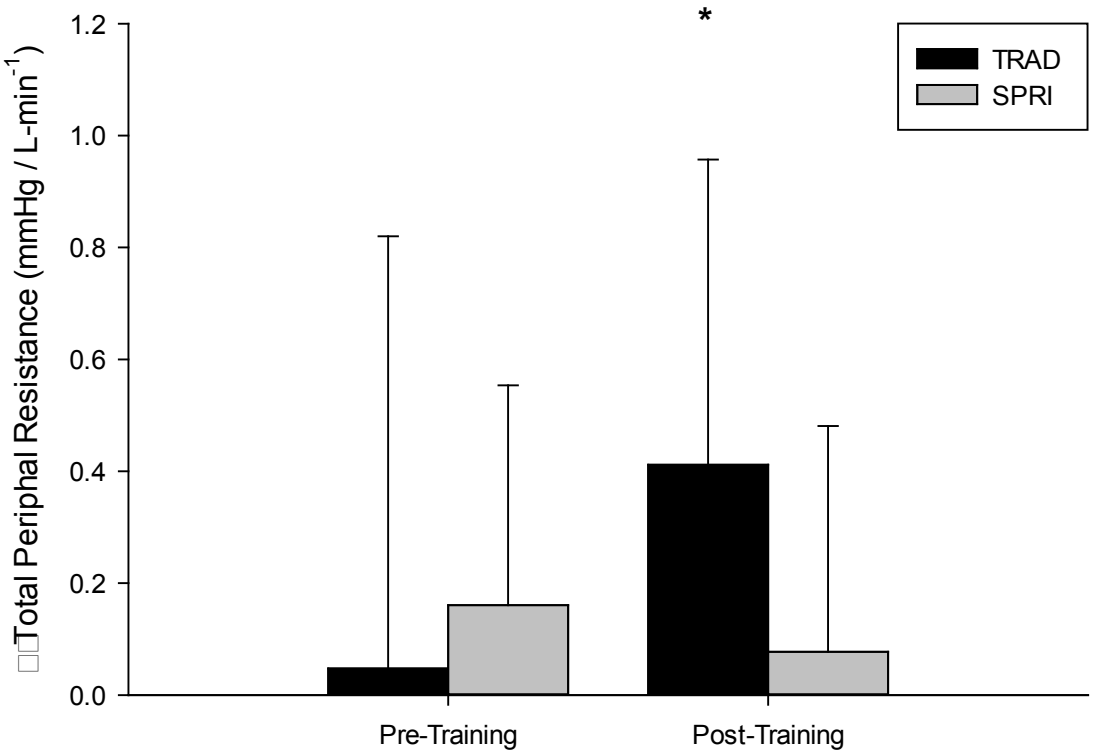

Figure 8: Absolute increase in Total Peripheral Resistance in response to partial circulatory occlusion of the leg during dynamic exercise trial in traditional (TRAD, black bars; n=10) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD. * indicates a significant ($p<0.05$) difference from pre-training ($p=0.011$).

Blood Pressure and Heart Rate Response to Post Exercise Circulatory Occlusion Trial

An original data tracing of the cardiovascular response to isometric hand grip exercise and post-exercise circulatory occlusion from a representative subject is illustrated in Figure 11.

Mean arterial pressure, systolic blood pressure and diastolic blood pressure increased in all subjects as a result of isometric handgrip exercise, and remained elevated during post-exercise circulatory occlusion. Heart rate was increased as a result of isometric handgrip exercise, but decreased to approximately baseline during post-exercise circulatory occlusion.

There was no difference in the mean arterial pressure (Fig. 12), systolic blood pressure (Fig. 13), diastolic blood pressure (Fig. 14), heart rate (Fig. 15), cardiac output (Fig. 16), response during post-exercise circulatory occlusion between pre- and post-training trials ($p>0.05$) in either training group.

Traditional aerobic training resulted in a larger increase in ($p<0.05$) stroke volume (Fig. 17) and total peripheral resistance (Fig. 18) in response to post-exercise circulatory occlusion. In contrast, sprint interval training resulted in no changes in the stroke volume or total peripheral resistance response as compared to pre-training responses.

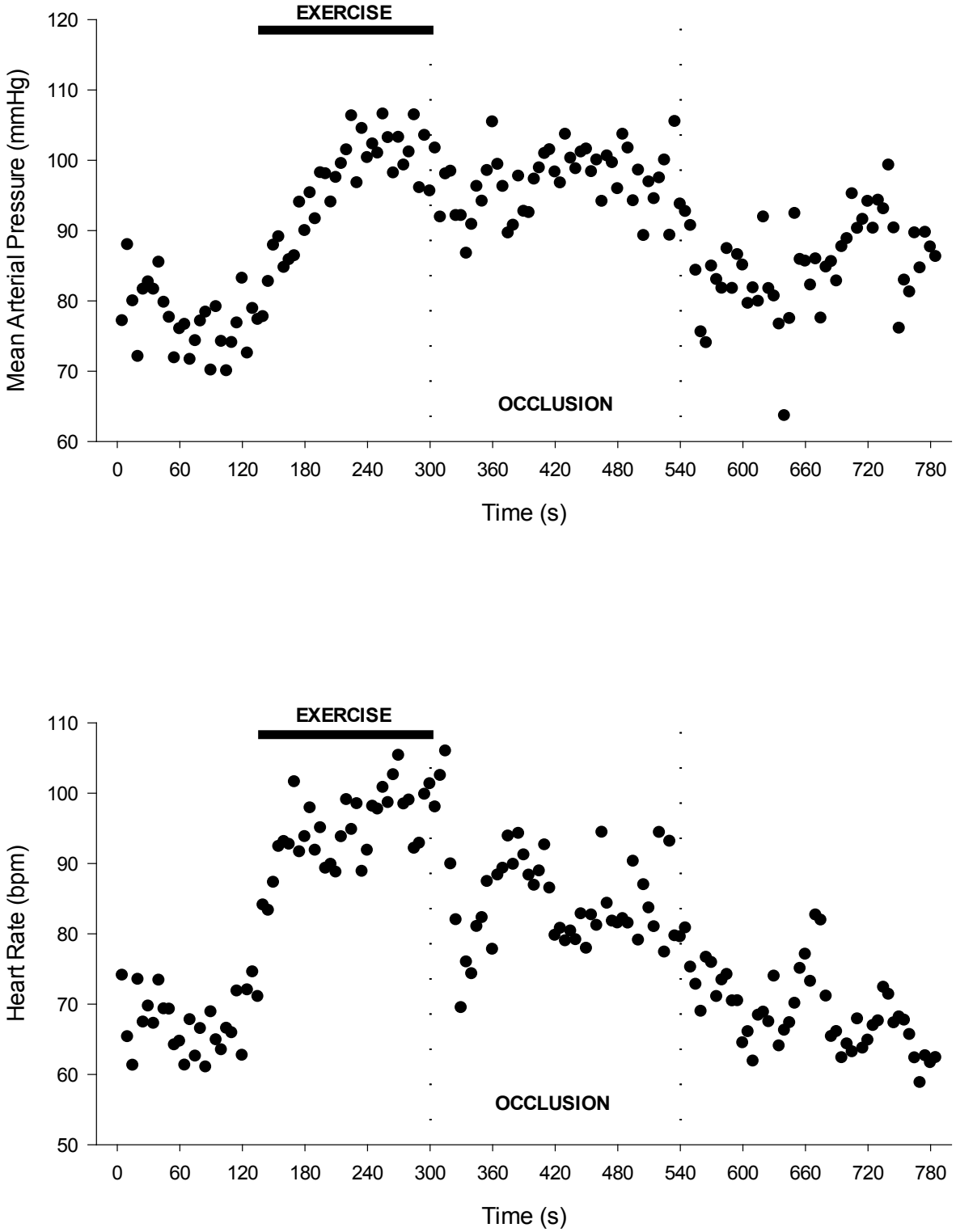

Figure 9: Individual representative tracing of the cardiovascular (heart rate, HR; mean arterial pressure, MAP) response during the post exercise circulatory occlusion trial (PECO). Isometric handgrip was initiated at 120s, and maintained until 310s. Full brachial occlusion occurred at 300s and maintained until 540s. Each data point represents a 5s average.

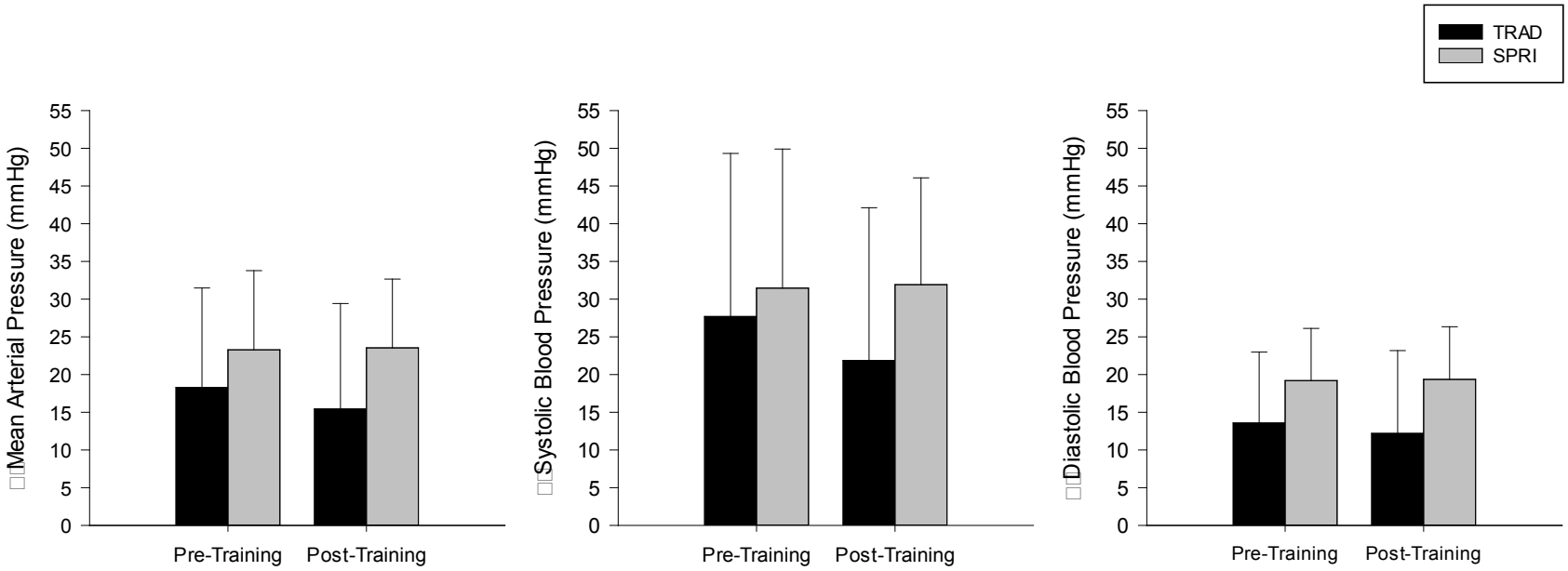

Figure 10: Absolute increase in Mean Arterial Pressure (Panel A; p=0.277), Systolic Blood Pressure (Panel B; p=0.196), Diastolic Blood Pressure (Panel C; p=0.515) during post exercise circulatory occlusion in traditional (TRAD, black bars; n=7) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD.

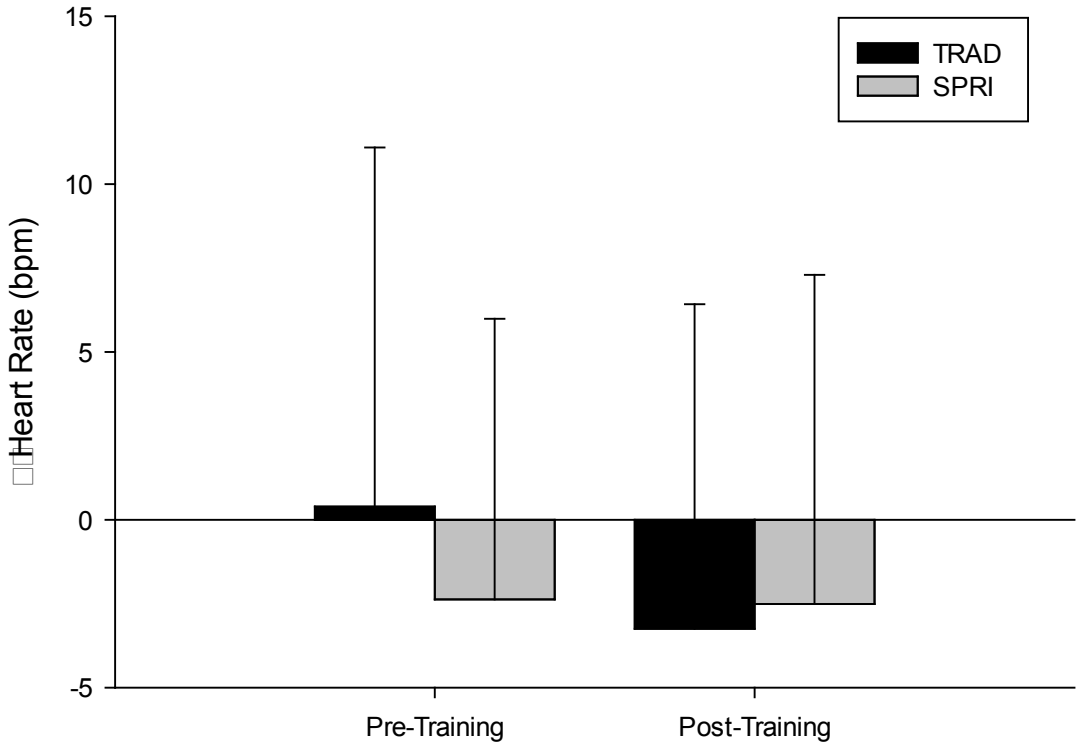

Figure 11: Absolute increase in Heart Rate during post exercise circulatory occlusion in traditional (TRAD, black bars; n=7) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD (p=0.144).

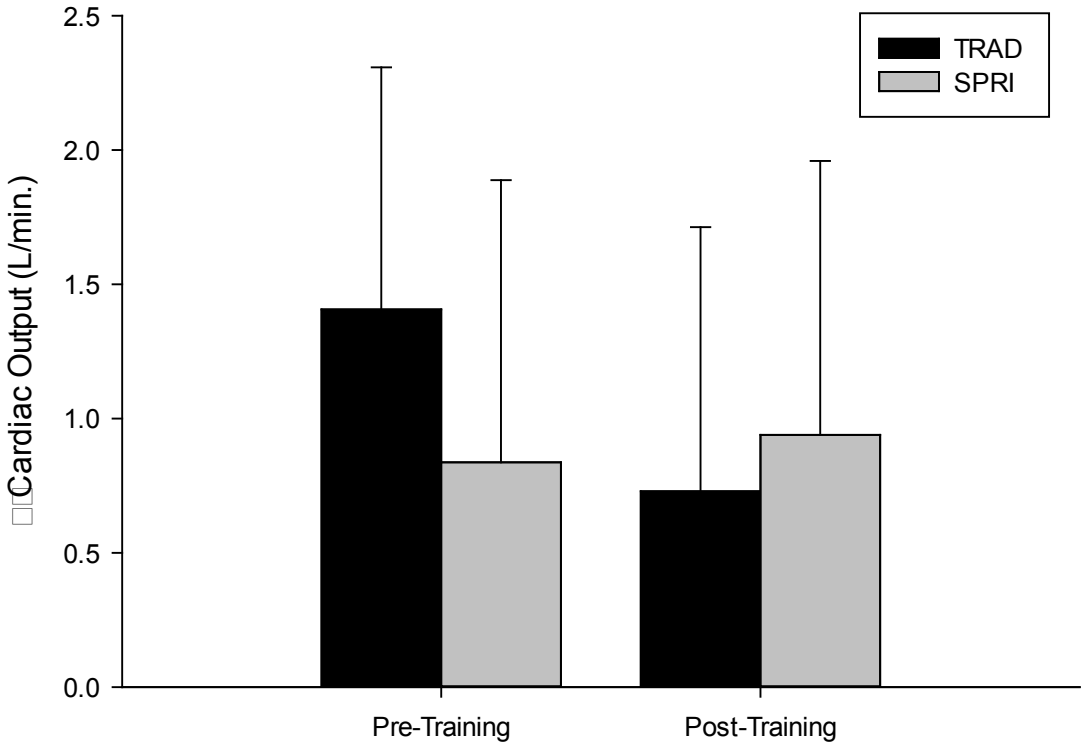

Figure 12: Absolute increase in Cardiac Output during post exercise circulatory occlusion in traditional (TRAD, black bars; n=7) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD (p=0.250).

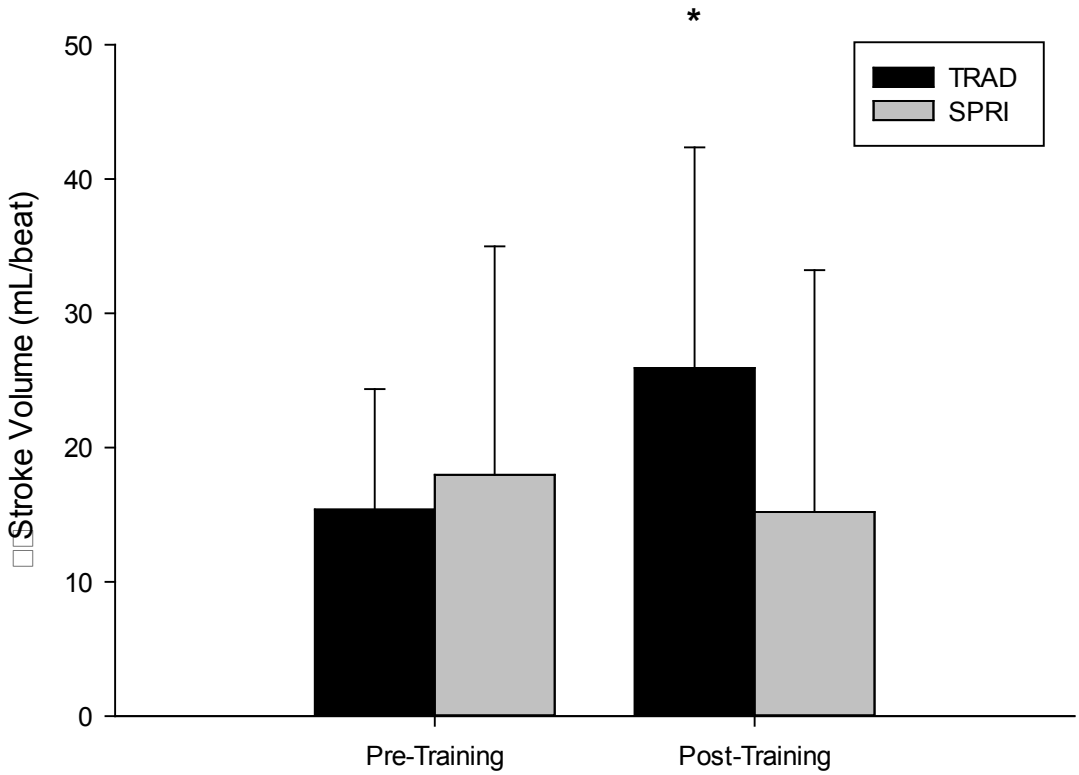

Figure 13: Absolute increase in Stroke Volume during post exercise circulatory occlusion in traditional (TRAD, black bars; n=7) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD. * indicates a significant ($p<0.05$) difference from pre-training ($p=0.034$).

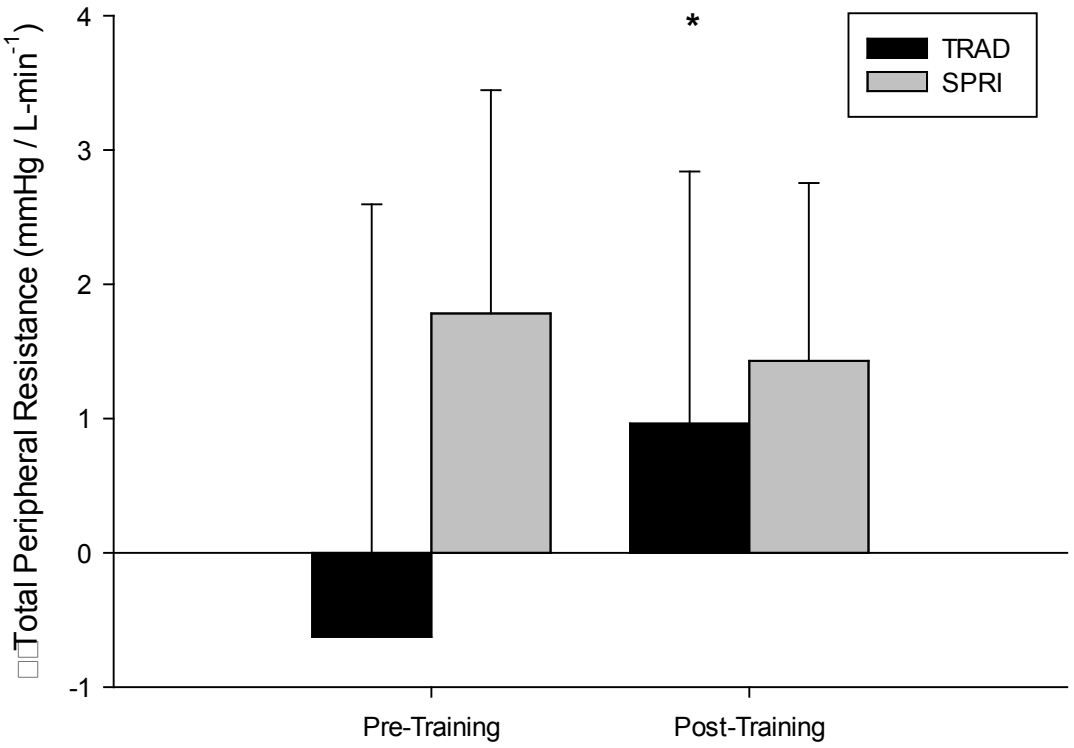

Figure 14: Absolute increase in Total Peripheral Resistance during post exercise circulatory occlusion in traditional (TRAD, black bars; n=7) and sprint interval training groups (SPRI, gray bars; n=15) pre- and post-training. Values are Mean±SD. * indicates a significant ($p<0.05$) difference from pre-training ($p=0.024$)

Relationships between variables

The magnitude of heart rate and blood pressure responses to metaboreflex in the trained legs or untrained arms were not related to VO_{2max} (HR: r=0.262, p=0.206; MAP: r=-0.295, p=0.152) or peak power output (HR: r=0.247, p=0.233; MAP: r=-0.331, p=0.106) before exercise training; post-training trials observed that the increase in heart rate during dynamic exercise partial circulatory occlusion was correlated with absolute (r=0.429; p=0.032) and relative (r=0.578; p=0.003) VO_{2max} and peak power output (r=0.490, p=0.013).

No relationship was observed between the magnitude of training-induced changes in absolute or relative VO_{2max} (aerobic fitness) and the magnitude of the heart rate and blood pressure responses to dynamic exercise partial circulatory occlusion or post-exercise circulatory occlusion.

Discussion

The purpose of this study was to: 1) investigate the effects of exercise training on muscle metaboreflex regulation of heart rate and blood pressure during dynamic large muscle-mass exercise in healthy young adults, and; 2) determine the effects of different types of exercise training modalities and metaboreflex regulation of heart rate and blood pressure by using high volume moderate intensity traditional aerobic and high intensity low volume sprint interval training. It was hypothesized that exercise training would attenuate metaboreflex-mediated increases in heart rate and blood pressure during dynamic exercise and that sprint interval training would result in a greater attenuation of metaboreflex effects on heart rate and blood pressure compared to traditional aerobic training. Consistent with previous studies (Gibala & Jones, 2013; Tschakert & Hofmann, 2013), traditional aerobic and sprint interval training increased aerobic fitness (VO_{2max}) as well as peak power output. In contrast to the hypothesis,

six weeks of traditional aerobic and sprint interval training had no effect on the magnitude of the heart rate and blood pressure response to metaboreflex activation during dynamic exercise in exercise-trained and untrained limbs of young, healthy men. However, the cardiac output and stroke volume response to partial circulatory occlusion during exercise in the trained limbs was blunted compared to the pre-training response, whereas the increase in total peripheral resistance was greater following traditional aerobic training. This would suggest that low-volume; high-intensity training does not have an effect on metaboreflex regulation of heart rate and blood pressure, whereas high-volume moderate-intensity training may alter the contributions of peripheral resistance and stroke volume to the pressor response observed during metaboreflex activation.

Consistent with the effects of exercise training in the trained leg, the magnitude of the heart rate or blood pressure response to post-exercise circulatory occlusion was not altered in the untrained limb following either training paradigm. However, there was an increase in the stroke volume and total peripheral resistance response to metaboreflex activation by post-exercise circulatory occlusion in the untrained limb following traditional training. Sprint interval training resulted in no changes to the metaboreflex response to post-exercise circulatory occlusion in the untrained limb. Collectively, these findings suggest that high volume training such as traditional aerobic training alters the mechanism by which the metaboreflex produces a pressor response in both exercise trained and untrained limbs. The change is characterized by a shift from an increase in cardiac output via an increase in heart rate and stroke volume, to a pressor response produced primarily by an increase in peripheral vasoconstriction, as evidenced by the increase in the total peripheral resistance response following traditional aerobic training. The observation of similar effects in the trained legs and untrained arm suggests that traditional aerobic training did

not cause a local adaptation in the exercise trained limb, but may have altered the distribution of efferent sympathetic nerve activity between the heart and peripheral vasculature or altered skeletal muscle sympathetic vasoconstrictor responsiveness.

Effect of metaboreflex activation

Partial occlusion of the legs during dynamic exercise reduced muscle perfusion and activated the muscle metaboreflex during dynamic cycling exercise; this was evidenced by an increase in heart rate (~10-15 bpm) and mean arterial pressure (~10-25 mmHg). These responses are similar in magnitude to those reported by studies which used a similar approach to activate the metaboreflex (Hartwich et al, 2011; 2013). This allowed for the examination of the effects of the metaboreflex on heart rate and blood pressure during dynamic exercise allowing for the stimulation of the metaboreflex during a traditional mode of aerobic exercise that is associated with a substantial metabolic and cardiac reserve requirement. Previous studies of the effects of exercise training on metaboreflex regulation of the cardiovascular system have typically utilized isometric contractions of small muscle groups followed by post-exercise circulatory occlusion. This has been shown to cause differences in the mechanism and magnitude of the heart rate and blood pressure to metaboreflex activation as compared to dynamic exercise and large muscle groups (Bell & White, 2005; Davies & Starkie, 1985; Hultman & Sjoholm, 1982; McCloskey & Streatfield, 1975).

Effect of exercise training on metaboreflex regulation of heart rate and blood pressure

This study demonstrated that exercise training did not alter the magnitude of the heart rate and blood pressure response to metaboreflex activation during dynamic exercise. This is in contrast with previous studies that demonstrated an attenuation of the pressor response to isometric exercise following rhythmic handgrip training (Sinoway et al, 1996; Mostoufi-Moab et

al, 1998). Sinoway et al. demonstrated that the attenuated pressor response was a result of decreased muscle sympathetic nerve activity and norepinephrine spillover in response to handgrip exercise; while Moab et al. observed a decreased plasma lactate concentration and increased plasma pH during handgrip exercise. These results would suggest that rhythmic handgrip training causes an attenuation of the pressor response to metaboreflex activation through a decrease in efferent sympathetic nerve traffic and an improvement in local muscle blood flow that decreased local metabolite build-up and stimulation of muscle afferents. We did not measure muscle sympathetic nerve activity or norepinephrine spillover in the present study, however the similar heart rate and blood pressure to metaboreflex activation before and after training suggest that the sympathetic response to activation of the metaboreflex during cycling exercise was not altered in the present study. The large muscle mass would require a much larger portion of cardiac reserve to perfuse the active tissue as well maintain blood pressure during exercise. The differences in metaboreflex activation as well as the differences in training stimuli could explain the discrepancies in results of these studies.

The exaggerated exercise pressor reflex observed in heart-failure rats has been demonstrated to be partially attenuated by aerobic exercise training (Wang et al, 2010). The results of that study showed that exercise training attenuated the renal sympathetic nervous response to muscle voluntary contraction and stretch stimulation of mechano-receptors while the blunted response to exogenous capsaicin stimulation of chemo-receptors was significantly prevented. In a subsequent study in heart-failure rats, Wang et al (2012) revealed that the cause for the exaggerated exercise pressor response was due to sensitized mechano-receptors in the contracting muscle tissue and a blunted response to chemo-receptor stimulation in heart-failure mice. This is in agreement with their previous study in that the exaggerated exercise pressor

response was mediated primarily by an exaggerated response to mechanical stimulation while the blunted response to chemical stimulation was partially prevented as a result of training. Both studies by Wang et al. (2010; 2012) utilized a control group of healthy rats that were also exercise trained. These rats displayed no exaggerated exercise pressor response prior to training, and in turn did not see an alteration in the heart rate and blood pressure response to metaboreflex activation following training. Therefore, differences between this study and the present study could be a result of a lack of sensitized mechano-receptors prior to exercise training.

Fisher and White (1999) also demonstrated an attenuation of the heart rate and blood pressure response to voluntary isometric triceps surae exercise in both the trained and untrained limb following six weeks of single-leg calf raise training. However, Fisher and White also stimulated muscle contraction via electrically-evoked contractions. This allowed for the isolation of the mechanoreflex portion of the exercise pressor response as central command was not activated in electrically-evoked contractions. The results of that study revealed that the heart rate and blood pressure response to electrically-evoked contractions were not different following single-leg calf raise training. This would suggest that training altered the manner in which central command responds to isometric exercise. This is in contrast to the present study which did not observe an attenuation of the heart rate and blood pressure response to exercise. In the present study it was observed that exercise training caused an increase in the peripheral resistance and stroke volume response to metaboreflex activation following training in both the trained and untrained limb. This would support the conclusion that traditional training altered central command during exercise and not a local muscle adaptation as evidenced by the changes in the mechanism of the heart rate and blood pressure responses to metaboreflex activation in both the trained and untrained limb. As mentioned above Fisher & White utilized post-exercise

circulatory occlusion following isometric calf exercise after six weeks of single-leg calf raise training. In contrast, this study utilized bilateral recumbent cycling dynamic exercise partial circulatory occlusion to assess the metaboreflex in trained limbs, and forearm post-exercise circulatory occlusion following isometric handgrip exercise in untrained limbs. This approach allowed for the stimulation of the metaboreflex during dynamic exercise and represented a much more authentic activation of the metaboreflex as observed in natural conditions. This is primarily due to the fact that the central command component is present throughout the activation and assist in the mediation of the metaboreflex response in heart rate and blood pressure in conjunction from stimulation via chemo-and mechano-receptors. Also, this method of exercise requires a much larger fraction of available cardiac reserve to properly perfuse active tissue. This is similar to the training stimulus as well exercise typically performed by humans. Therefore, differences between the findings of Fisher & White and the present study could be a result of the manner in which the metaboreflex was activated.

An important distinction to be made regarding the present study is that the metaboreflex was stimulated by partial circulatory occlusion during rhythmic cycling exercise. This pattern of contractile activity is considerably different than isometric and/or ischemic exercise and may lead to different patterns of limb blood flow and therefore metaboreflex activation. Furthermore, the effect of metaboreflex activation on the control of blood pressure and heart rate was investigated during moderate-intensity exercise in the present study. The effects of metaboreflex activation on heart rate and blood pressure have been shown to be exercise-intensity dependant (Augustyniak, Collins, Ansorge, Rossi, O'Leary, 2001) and therefore it is possible that exercise training may have altered metaboreflex regulation during more intense exercise. However,

preliminary testing completed for this project indicated that exercise at a higher intensity with partial flow occlusion was very difficult for subjects to complete.

Difference in effects of sprint interval and traditional training

Both training programs caused a significant increase in absolute and relative VO_{2max} as well as peak power output; however traditional aerobic training caused a significant change in the mechanism of the response to metaboreflex activation. Despite sprint interval training being a more intense stimulus of the metaboreflex it did not result in any alteration in the metaboreflex. This would suggest that the metaboreflex responds more to the volume, rather than the intensity of the training stimulus. This is in contrast with many studies that compared increases in aerobic fitness in response to traditional aerobic and sprint interval training (Gibala & Jones, 2013; Tschakert & Hofmann, 2013) and found similar adaptations to both types of training. The present study has observed a difference in cardiovascular adaptations to traditional aerobic training as opposed to sprint interval training. Therefore, while sprint interval training may have caused a stronger local metabolic stimulus to the metaboreflex than traditional aerobic training, the larger volume of exercise contained within the traditional aerobic training protocol appears to have a stronger effect on the mechanism of the pressor response to stimulation of the metaboreflex action.

In the present study it was observed that traditional exercise training caused an increase in the peripheral resistance and stroke volume response to metaboreflex activation following training in both the trained and untrained limb. This would support the conclusion that traditional exercise training altered central command during exercise and not a local muscle adaptation as evidenced by the changes in the mechanism of the heart rate and blood pressure responses to metaboreflex activation in both the trained and untrained limb. Fisher & White (1999) utilized

six weeks of relatively low volume single-leg calf exercise training, but still demonstrated effects of the heart rate and blood pressure response to metaboreflex activation. This is contrast with the present study which did not observe alterations in the cardiovascular response to metaboreflex activation following low-volume sprint interval training, but did see changes following high-volume traditional aerobic training.

This study did not observe an attenuation of the metaboreflex pressor response, but did demonstrate an alteration in the mechanism by which the metaboreflex causes a pressor response, which was observed in metaboreflex activation in both trained and untrained limbs following traditional aerobic training. Traditional training resulted in an attenuation of the cardiac output and stroke volume response, as well as an increase in total peripheral resistance response to metaboreflex activation. Therefore, while the pressor response was not augmented, it was maintained by an increase in peripheral resistance despite a decrease cardiac output. This would suggest that training altered the mechanism by which the metaboreflex exerted a pressor response by causing increased peripheral resistance, while decreasing cardiac output. Recent studies have indicated that aerobic exercise training augments adrenoreceptor responsiveness in rats (Jendzjowsky & DeLorey, 2013), thereby increasing the ability of the peripheral vasculature to respond to sympathetic activity. Also, recent studies have shown that β2-receptor-mediated vasodilation occurs as a result of muscle metaboreflex activation during mild intensity dynamic exercise (Kaur et al, 2014). This demonstrates that the metaboreflex causes β-mediated vasodilation in peripheral vascular beds; however it is unknown in which tissue this occurs. Skeletal muscle is rich in β-receptors and is a possible candidate for the source of vasodilation seen in response to metaboreflex activation.

Effect of aerobic fitness on metaboreflex regulation

The magnitude of heart rate and blood pressure response to metaboreflex activation was not correlated with aerobic fitness (absolute and relative VO_{2max}). This study also demonstrated that improvements in aerobic fitness were not correlated with changes in the magnitude of the heart rate and pressor response to metaboreflex activation. This would suggest that the changes in the metaboreflex are not related to changes in aerobic fitness nor is the magnitude of the heart rate and blood pressure response related to baseline aerobic fitness. However, these conclusions must be made with caution because the subjects utilized in the present investigation had relatively similar levels of aerobic fitness and improvements in VO2 max following exercise training, thus there was a limited range of aerobic fitness levels over which to observe a relationship between fitness and metaboreflex responses.

Conclusion

In conclusion, sprint interval and traditional aerobic training had no effect on the magnitude of the heart rate and blood pressure response to metaboreflex activation. However, traditional aerobic training altered the mechanism by which the metaboreflex pressor response is mediated, through an attenuation of cardiac output via a decrease in stroke volume and a greater increase in total peripheral resistance in both trained and untrained limbs. These results suggest that the effects of traditional aerobic exercise training were not mediated by a local adaptation in the trained legs. In addition, sprint interval training did not cause any effects on the magnitude of the blood pressure and heart rate response, or alterations in the mechanisms by which the pressor response is caused. This would suggest that the limited volume of sprint interval training may have been insufficient to cause adaptations in the metaboreflex; despite what would presumably be a robust activation of Type IV afferent nerve fiber during the training. These results suggest

that training volume may influence metaboreflex regulation of total peripheral resistance and stroke volume.

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Chapter 3: General Discussion

Main Findings

The purpose of this study was to: 1) investigate the effects of exercise training on muscle metaboreflex regulation of heart rate and blood pressure during dynamic large muscle-mass exercise in healthy young adults, and 2: determining the effect of different exercise training modalities on metaboreflex regulation of heart rate and blood pressure by using high volume traditional aerobic and sprint interval training. This study demonstrated that six weeks of exercise training did not alter the magnitude of metaboreflex action on heart rate and blood pressure. This conclusion remained consistent whether the metaboreflex was activated via partial circulatory occlusion during moderate intensity cycling exercise in a trained limb or post-exercise circulatory occlusion following isometric exercise in an untrained limb. However, this study did demonstrate that high volume, traditional aerobic training did have an effect on the mechanisms by which the metaboreflex pressor response is caused. Specifically, it maintained the pressor response through an increased total peripheral resistance response, while the stroke volume and cardiac output responses were attenuated during metaboreflex activation in trained and untrained limbs. However, in the untrained limb, the stroke volume response was increased due to the decrease heart rate as result of central command withdrawal during the post-exercise circulatory occlusion, as well consistent with the dynamic exercise partial circulatory occlusion the total peripheral resistance response was increased as well. These findings would suggest that high volume training did not have an effect on a local adaptation, but may have had an effect by which central command mediates the mechanism by which the metaboreflex exerts the blood pressure and heart rate response. In addition, low volume sprint interval training had no effect on the magnitude or mechanism of the response to dynamic exercise partial circulatory occlusion or

post-exercise circulatory occlusion metaboreflex activation. This would suggest that the metaboreflex responds to the volume rather than the intensity of exercise training performed.

Experimental Considerations and Limitations

A strength of the present study was the investigation of the effects of exercise training on metaboreflex regulation of heart rate and blood pressure an exercise trained limb and an untrained limb which allowed for the differentiation of local trained muscle and systemic cardiovascular adaptations in metaboreflex function. The dynamic exercise partial circulatory occlusion trial allowed for the determination of the effects of training on the metaboreflex arising from the trained limbs and ultimately the level of afferent signalling that was a result of the metaboreflex. In addition, the post-exercise circulatory occlusion trial tested the effects of metaboreflex activation in the untrained arm. Any differences observed in the magnitude or mechanism of heart rate and blood pressure response to metaboreflex activation in the untrained arm following training would not be a result of a local adaptation governing metaboreflex regulation which would only be observed in the trained limb. Also, a novel aspect of this study was that the dynamic exercise partial circulatory occlusion trial induced a metaboreflex response in a large muscle mass which emulated metaboreflex activation during cycling training, in turn activating the metaboreflex in a similar manner to cycling training. Also, activating the metaboreflex in a large muscle mass utilized a larger portion of cardiac output during exercise than a similar test in a smaller muscle mass, such as the arm, thereby utilizing more of cardiac reserve. This in turn better reflects natural metaboreflex activation during exercise, than a small muscle mass activation.

Also, the dynamic exercise circulatory occlusion test utilized a moderate exercise level with a partial occlusion of the legs at a pressure below that of exercising diastolic blood pressure

(90% of exercising diastolic blood pressure; Sprint: Pre: 60.8±9.5 mmHg, Post: 59.3±8.3 mmHg; Traditional: 64.9±6.8 mmHg, 64.4±7.2 mmHg). This ensured that blood was not prevented from returning to the heart. This, in turn, prevented a decrease in cardiac output due to a lack of venous return of blood to the heart, and therefore any changes in heart rate, stroke volume and cardiac output were a result of metaboreflex activation rather than cuff pressure being exerted on the legs.

Some limitations of the project include the use of exclusively young, male subjects. This was done to prevent any confounding effects of age or sex on the results of the study; it does not allow for the determination of effects in a number of populations, such as females, heart failure patients and the elderly. While Fisher et. al (2013) demonstrated no effect of cyclic estrogen levels on metaboreflex activation using an identical experimental approach; this does not lead to the conclusion that the menstrual cycle has no effect on the metaboreflex as the study did not assess the effect of cyclical progesterone levels on metaboreflex activation. Further studies would be able to explore any differences in the effect of training on the metaboreflex in females and elderly populations as well as the effects on heart failure in humans. In addition, the aerobic fitness of the subject did not lend itself to a large effect of training. Many of the subjects have relative VO_{2max} scores >50 mL/kg/min., which limited their improvement in this in aerobic fitness as a result of exercise training as individuals with high levels of aerobic fitness typically require a stronger training stimulus to elicit the same adaptations in aerobic fitness as compared to individuals with lower aerobic fitness (Wilmore & Costill, 2004). Also, the diet of the subjects was not controlled during the study. The diet of the subject could have affected their physiological reactions and therefore metaboreflex regulation of heart rate and blood pressure during the study. However, intake of alcohol, nicotine, ibuprofen and caffeine were not allowed

within 24 hours of testing. The time of day for pre- and post-training testing was controlled within-subjects, but not between-subjects. This prevented any confounding effects of those substances and the time of day on the results of the metaboreflex activation tests.

Drawbacks of the experimental protocol included the use of pneumatic cuffs to induce metaboreflex activation. For the post-exercise circulatory occlusion and dynamic circulatory occlusion test, the pressure exerted by the cuff on mechanoreceptors in the skeletal muscle likely contributed to the sympathetic response to occlusion. However, since cuff pressure was constant during post-exercise circulatory occlusion or relatively constant such as during dynamic exercise partial circulatory occlusion the effects of cuff pressure on mechanoreceptors should be equal in both pre- and post-training testing trials, effectively controlling for the cuff pressure effects on mechano-receptors. Also, the relative intensity of the exercise during which the metaboreflex was activated may have limited the determination of effects of training on metaboreflex regulation of heart rate and blood pressure. A more intense exercise bout would have activated the metaboreflex more and may have demonstrated some changes in the control of heart rate and blood pressure due to training.

Future Directions

The present study utilized the measurement of heart rate and blood pressure to assess the level of metaboreflex activation. However, the present study did not measure blood flow to the exercising limbs during metaboreflex activation. A subsequent study could include Doppler ultrasound measures of femoral and/or brachial blood flow and calculation of limb vascular conductance during activation of the metaboreflex. Measurement of these variables would allow quantification of the decrement in limb blood flow during partial circulatory occlusion and provide a index of metaboreflex activation. Moreover, the contribution of leg vascular resistance

to changes in total peripheral resistance during partial circulatory occlusion could be calculated to provide insight into the role of vasoconstriction in active skeletal muscle to an increase in total peripheral resistance during metaboreflex activation. However, given the difficulty of performing accurate measurement of femoral blood flow during exercise using Doppler ultrasound, and the complicating factor of a pneumatic cuff being added, such a study would require a large amount of skill in ultrasound blood flow measurement. In addition, it is known that the magnitude of the metaboreflex response is directly related to the intensity of the exercise being performed. Therefore future studies could investigate whether training had an effect on metaboreflex activation at higher and lower intensities of exercise. This would determine whether training alters metaboreflex activation at varying intensities of exercise.

Also, future studies could investigate the mechanism by which exercise training alters the manner in which the metaboreflex exerts a pressor response. Specifically, a follow-up study could measure efferent nervous activity to the active limbs by measuring plasma catecholamines in response to metaboreflex activation, while simultaneously measuring muscle sympathetic nervous activity to the non-active limb. This would measure the efferent response to metaboreflex activation while determining the difference between the sympathetic response in trained active limbs and untrained non-active limbs. These measures would determine the exact mechanism by which training shifts the cause of the pressor response from increased stroke volume to an increase peripheral resistance as well the location of the training adaptation altering the mechanism of the metaboreflex pressor response. Also future studies could utilize a more intense exercise bout during metaboreflex activation, as the metaboreflex is known to be more active at higher intensity exercise (Augsutyniak et al, 2001). This could allow for determination of the effects of training on metaboreflex regulation at an intensity that requires more cardiac

reserve than the present study. However, this may be difficult to perform as the recumbent cycling model is unfamiliar to most human subjects and this limits the intensity of exercise they are able to perform. Therefore, the future directions of this line of study would be into the determination of the effects of training on metaboreflex regulation of blood flow to exercising limbs as well as the mechanism by which training alters the manner in which the metaboreflex exerts a pressor response.

Conclusion

Exercise training resulted in no effects on the magnitude of the heart rate and blood pressure response to metaboreflex activation. However, traditional aerobic training did result in a change in the mechanism by which the metaboreflex exerts the pressor response, specifically a shift from being primarily mediated via an increase in cardiac output to an increase in total peripheral resistance. This was reflected in both the dynamic exercise partial circulatory occlusion in the trained limbs and post-exercise circulatory occlusion in the untrained limb. These results indicated that training adaptations did not result in a change in a local afferent mechanism by which the metaboreflex is activated, as the training resulted in adaptations in both the trained and untrained limbs. These results would suggest that traditional training altered the mechanism by which central command mediates the heart rate and blood pressure response to metaboreflex activation. In addition, it was determined that the adaptations observed in metaboreflex regulation of heart rate and blood pressure following training were more sensitive to the volume of training, rather than the intensity of the training.

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