THE EFFECTS OF STRENUOUS EXERCISE ON CARDIOVASCULAR FUNCTION IN HEALTHY HUMANS

by

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Abstract

RATIONALE: Strenuous exercise has been shown to elicit transient reductions in ventricular systolic and diastolic function, as well as impaired autonomic function. The effects of training status and sex on the development of these acute alterations are not known. The aim of these studies was to examine vascular adjustments, cardiac mechanics and autonomic function as the result of strenuous exercise in healthy, endurance-trained (ET) and normally active (NA), males and females. Statistical significance was set at $p < 0.05$. The ***first investigation*** explored sex differences in the cardiovascular response to an ultra-marathon in 25 runners. Ventricular function was reduced similarly in men and women. Novel associations of life-time ultra-marathons and degree of longitudinal strain were found, demonstrating the absence of cumulative stress on the heart with long-term prolonged strenuous exercise. The ***second investigation*** assessed ventricular function following high-intensity interval exercise (HIT) in 39 men and women. Changes in cardiac mechanics were not differentiated by training status, however, lower baseline arterial stiffness was associated with twist augmentation. Men demonstrated greater reductions in contractility and higher arterial elastance post-exercise than women. The ***third investigation*** assessed autonomic function following HIT and orthostatic stress in 33 men and women. Throughout the intervention, women displayed greater strain, strain rate, and baroreflex sensitivity, but there were no interactions of condition by sex. Autonomic function decreased to a greater degree in ET, but also improved most rapidly in recovery. Thus, it would appear that the cardiac and autonomic stability of ET and women during an orthostatic challenge is not compromised in the face of HIT. The ***fourth investigation*** analyzed post-exercise hypotension (PEH) following HIT in 21

individuals. Hypotension occurred similarly in all individuals however, men experienced greater reductions in stroke volume. These findings suggest men engage a different mechanism of PEH compared to women. The ***fifth investigation*** explored cognitive function in recovery from HIT. Cognition was improved post-exercise and persisted for four hours post-exercise. **SUMMARY:** Together, these studies provide novel findings pertaining to the effects of sex and training status on the cardiovascular responses to strenuous exercise.

Preface

This thesis was written by me, Anita Coté. The research was designed and actualized under the leadership of Dr. Shannon Bredin and Dr. Darren Warburton with significant contributions from Dr. Michael Koehle and Dr. Matthew White. I conducted all data collection with the help of a technician and two research assistants (hired by Drs. Bredin and Warburton), in addition to performing all data analysis and statistical analysis for this dissertation. I received specialized training for these analyses from my supervisors, leading international academic researchers, echocardiography specialists, and representatives from GE Healthcare. Ethical approval was obtained from the University of British Columbia Clinical Research Ethics Board (H08-00607 and H10-00475).

A version of chapter 3 is being prepared for submission (Training Status Differentiates the Cardiovascular Response to a 160-kilometer Ultra-marathon). As part of on-going research in our research group, I defined this specific research question, developed the protocols, and wrote the initial draft of the manuscript. All co-authors provided editorial content and edited the manuscript.

A version of chapters 4, 5 and 6 are being prepared for submission (An Analysis of Sex and Training Status on Left Ventricular Mechanics Following High-Intensity Interval Exercise; Recovery of Baroreflex Function Following Brief Strenuous Exercise: Effect of Training Status; High-intensity Interval Exercise Elicits Marked Post-exercise Hypotension in Healthy Men and Women). My contribution to these studies started from defining the research questions to writing the manuscripts. Darren Warburton and

Shannon Bredin directed and provided input to all aspects of this work. All co-authors have been involved in editing of the manuscripts.

A version of chapter 7 is being prepared for submission (Improved Cognitive Performance Following High-intensity Interval Exercise). This study was designed and implemented under the leadership of Shannon Bredin. I refined the research question, analyzed and the data, and wrote the initial draft of the manuscript. Shannon Bredin edited the manuscript.

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List of Abbreviations

Symbol	*Definition*
BMI	Body Mass Index
BRS	Baroreceptor Sensitivity
BSA	Body Surface Area
CI	Cardiac Index
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic acid
DXA	Dual X-ray Absorptiometry
E:A	Ratio of Early to Atrial Ventricular Filling Velocity
E_A	Arterial Elastance
ECG	Electrocardiogram
EDV	End Diastolic Volume
EF	Ejection Fraction
E_{LV}	Ventricular Elastance
ESP	End Systolic Pressure
ESV	End Systolic Volume
ET	Endurance-trained
FS	Fractional Shortening
HF	High Frequency
HIT	High Intensity Interval Exercise
HRV	Heart Rate Variability

IVRT	Isovolumetric Relaxation Time
LAC	Large Artery Compliance
LBNP	Lower Body Negative Pressure
LF	Low Frequency
LV	Left Ventricle
LVM	Left Ventricular Mass
MAP	Mean Arterial Pressure
MSNA	Muscle Sympathetic Nerve Activity
NA	Normally Active
NADPH	Nicotinamide adenine dinucleotide phosphate-oxidase
PEH	Post-exercise Hypotension
PWV	Pulse-wave Velocity
RMSSD	Root of the Mean of Squared Differences Between Successive RR intervals
RV	Right Ventricle
SAC	Small Artery Compliance
SBP	Systolic Blood Pressure
SVI	Stroke Volume Index
TPR	Total Peripheral Resistance
VO_2	Oxygen Consumption
WS	Wall Stress

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I wish to extend my most heartfelt appreciation to the faculty, staff and students who assisted me during my PhD studies. In particular, I wish to acknowledge the dedication and support I received from my supervisors Dr. Shannon Bredin and Dr. Darren Warburton. I marvel at their accomplishments and am honoured to be able to contribute in a small way to their research programs. Notably, Darren's execution of novel research ideas and Shannon's attention to detail were important contributors to my work. I would like to thank them for all they have taught me during my graduate studies.

Dr. Matthew White was instrumental in the development of my knowledge acquired during my doctoral studies and I thank him for that. In particular he dedicated a great deal of time to advancing my understanding of grant writing and research skills. I am grateful to have been mentored by a leading expert in environmental physiology, an area for which I am passionate about and hope to continue researching in the future.

I am also indebted to the tremendous support I received from Dr. Michael Koehle. His expertise and common sense approach were welcome attributes throughout this dissertation. Michael is a role model both academically and personally and I am fortunate to have his involvement in my work. Future collaborations would be an honour.

In addition to the expertise from my supervisors and committee, PhD candidate Aaron Phillips was an integral part of my PhD efforts. Aaron assisted me with new research techniques and provided me with the additional motivation I needed to accomplish my various research objectives. I am forever grateful for our research partnership and his friendship.

A special acknowledgement is reserved for Dr. Jack Taunton (Chief Medical Officer 2010 Winter Olympic and Paralympic Games) and GE Healthcare for providing me with the specialized equipment and technical assistance required to execute my research.

To all my fellow lab mates and graduate students, I thank them for sharing their experiences and laughter. There are too many to mention here, but each of them served as important role models and friends.

Finally, I am extremely appreciative for the support of my family. They were extremely patient and facilitated my achievements through their understanding and love.

Chapter 1: Introduction

The benefits of regular physical activity on cardiovascular risk have been clearly shown [1]. Furthermore, strong evidence exists revealing a dose-response, in which intensity of activity is positively correlated to health benefits [2]. Thus, physical activity in the form of exercise is an effective means to improve health and cardiovascular risk. Recently, strenuous forms of exercise such as high-intensity interval training and ultra-endurance events have gained popularity particularly in non-athlete populations [3, 4]. Moreover, accumulating evidence supports the use of high-intensity interval exercise as more effective for health and fitness benefits when compared to traditional moderate-intensity aerobic exercise. Protocols typically involve brief (i.e., six seconds to four minutes) near maximal efforts (in excess of 90% maximal capacity) interspersed with low intensity recovery exercise or rest [4]. Chronic adaptations to high-intensity interval training include increased aerobic and anaerobic fitness [5-14], increased skeletal muscle capacity for fatty acid oxidation and glycolytic enzyme content [9, 15, 16], and increased insulin sensitivity [6, 12, 14]. However, the efficacy and safety of this type of exercise has yet to be determined [17].

Prolonged strenuous exercise encompasses exercise bouts from a wide range of endurance durations (i.e., half-marathons and triathlons to multi-day events). Prolonged strenuous events, traditionally dominated by trained athletes, now include a large recreational contingent a population older than in previous years [3]. In a recent analysis of performance trends in 161-km ultra-endurance events, it was revealed that the top performances have remained fairly stable over the last twenty years, however

participation rates increased with more individuals focused on finishing and participating in multiple events [18].

Both prolonged strenuous and high-intensity interval exercise have been linked to altered cardiovascular function such as cardiac fatigue. Exercise-induced cardiac fatigue is characterized by a reduction in left ventricular systolic and diastolic function subsequent to exercise in healthy humans [19]. The literature has demonstrated transient alterations in cardiac dynamics indicative of cardiac fatigue as a result of prolonged strenuous exercise [20]; however, only recently has high-intensity interval exercise also been associated with exercise-induced cardiac fatigue [21]. The clinical significance of cardiac fatigue is uncertain. Post-exercise impairments in right and left ventricular function are thought to be of limited short-term concern clinically; however, the long-term effects of these transient impairments in cardiac function remain unknown.

1.1 STATEMENT OF THE PROBLEM

There is considerable evidence supporting the health benefits of moderate-to-vigorous intensity exercise [1]. However, there is also an acute increase in the risk for cardiac events during and following vigorous intensity activities in comparison to inactive periods in apparently healthy individuals [22] and in those individuals with underlying cardiac anomalies [23]. This transient risk is particularly prevalent in previously inactive individuals who engage in activities that are six metabolic equivalents or greater [24]. Given the popularity of high-intensity interval exercise within the spectrum from athlete to patient populations, as well as the increased participation by recreationally active individuals in ultra-endurance events, the examination of cardiovascular responses to

strenuous work warrants further investigtion. While our understanding of the acute response to high-intensity exercise is advancing, we have yet to discern clearly the effects of chronic training and the subsequent cardiovascular adaptations, known as the athlete's heart [25] on cardiovascular risk. Furthermore, women have been underrepresented in exercise and clinical research. Recently, evidenced-based recommendations were presented advocating for the inclusion of women in clinical cardiovascular trials in equal numbers to that of men [26]. Accordingly, the purpose of this series of five investigations was to examine the effects of sex and training status on the cardiovascular responses to strenuous exercise.

1.2 OVERVIEW

Chapter 2 is a review of the literature pertaining to cardiac function in healthy individuals; the impact of sex and endurance training, as well as potential mechanisms responsible for cardiac fatigue. The first investigation is presented in Chapter 3 where sex differences in cardiovascular function following an ultra-marathon are examined. Chapter 4 presents novel findings of sex differences following an acute bout of high-intensity interval training in men and women of different fitness levels. Chapter 5 investigates baroreceptor sensitivity in men and women during an orthostatic challenge following high-intensity interval exercise. Chapter 6 examines the post-exercise hypotension response to high-intensity interval exercise, and Chapter 7 explores how post-exercise haemodynamics relate to measures of cognitive performance. Finally, Chapter 8 integrates the findings of these investigations, discusses their relevance and impact, and finally provides recommendations for further study.

Chapter 2: Literature Review

Exercise places an increased demand on the cardiovascular system as it works to regulate the metabolic processes called upon to meet greater oxygen needs. The performance of the left ventricle plays an integral role in the effective performance of this system. The optimal performance of the left ventricle depends on a compliant chamber that supports diastolic filling under low atrial pressures, as well as effective ejection of blood (stroke volume) in systole at arterial pressures [27]. In addition, adequate diastolic filling ensures normal stroke volume according to the Frank-Starling mechanism [28].

Exercise-induced cardiac fatigue is a phenomenon shown to occur in the healthy heart as the result of strenuous exercise, and is characterized by a reduction in left ventricular systolic and diastolic function [19]. Systolic dysfunction represents impaired ejection of blood from the left ventricle, often due to a loss of cardiac inotropy (i.e., decreased contractility) [29]. Diastolic dysfunction represents inadequate ventricular filling with abnormal increases in diastolic pressures; alterations in the transmitral pressure gradient produced by changes in elastic recoil (suction), the rate of myocardial relaxation, chamber compliance, and left atrial pressure [27]. To date, the reported post-exercise depressions in ventricular function appear to be transient and small in clinical terms, however, the clinical relevance is not known [30]. Thus, the reliable assessment of ventricular and autonomic function is of key importance for establishing the impact of strenuous exercise on heart function. As such, this narrative review will provide a rationale for the non-invasive autonomic and left-ventricular assessments utilized in this dissertation research, provide a background of what is known pertaining to the impact of

sex and endurance training on these indices of cardiac function, and potential mechanisms underpinning reduced cardiac function with strenuous exercise.

2.1 NON-INVASIVE ASSESSMENT OF CARDIAC FUNCTION

2.1.1 Autonomic Function

The autonomic nervous system plays a key role in cardiovascular control [31]. Increased activity in the sympathetic branch of the autonomic nervous system increases heart rate and constricts blood vessels, whereas an increase in parasympathetic activity opposes these actions [32]. The study of cardiovascular variability provides insight into cardiovascular control mechanisms [33] via analysis of heart rate variability, blood pressure variability, and/ or baroreflex function.

Heart rate variability is a method of quantifying cardiac autonomic modulation through the examination of beat-to-beat fluctuations in heart rate, and is an independent predictor of morbidity and premature mortality (e.g., the incidence of disease and death rates increase in the presence of autonomic imbalance) [34, 35]. Heart rate variability reflects the time intervals between the peaks in the electrocardiogram (ECG) or normal-to-normal (NN or RR) intervals. The variations in heart rate may be evaluated by time domain or frequency domain (spectral) measures. The time domain measures are derived from either direct measurements of the RR intervals or from the differences between RR intervals and spectral measures reflect how power (variance) distributes as a function of frequency [36]. The low frequency band (LF = 0.04 - 0.15 Hz) is suggested to reflect sympathetic control of the heart [37] with the high frequency band (HF = 0.16 - 0.4Hz)

representing respiration-driven vagal modulation of sinus arrhythmia [36]. Typical values in healthy humans are shown in Table 2.1.

Time Domain of Heart Rate Variability

	MeanNN (ms)	SDNN (ms)	rMSSD (ms)	pNN50 (%)
Sedentary	800	70	40	20
Trained	1100	95	70	40

Frequency Domain of Heart Rate Variability

	Total Power (ms^2)	LF (ms^2)	HF (ms^2)
Sedentary	1200-4000	200-900	250-600
Trained	1200-5000	800-1200	500-2500

Baroreflex Sensitivity

	BRS (ms/mmHg)	αLF (ms^2)	αHF (ms^2)
Healthy	6 – 23	7 - 23	8 - 25

Table 2.1 Typical Heart Rate Variability and Baroreceptor Sensitivity Values for Healthy Individuals
MeanNN = Normal to normal interval; SDNN = standard deviation of the RR intervals; rMSSD = square root of the mean squared successive differences between adjacent RR intervals; pNN50 = percentage of successive interval differences larger than 50 ms; LF = low frequency of HRV; HF = high frequency of HRV; αLF = low frequency of spectral BRS; αHF = high frequency of spectral BRS
Table adapted from Aubert [33] and La Rovere [38]

The baroreflexes are neurocardiovascular reflexes that operate in a negative feedback fashion, in an attempt to maintain circulatory homeostasis. The baroreceptors are highly specialized stretch-sensitive nerve endings distributed throughout various regions of the cardiovascular system, which transmit neural impulses associated with their

activation/deactivation to the central nervous system [39]. Arterial (*high pressure)* baroreceptors refer to those located in the aortic arch (monitoring blood pressure to the systemic circuit) and carotid sinuses of the left and right internal carotid arteries (monitoring the blood pressure to the brain) [40]. Cardiopulmonary (*low-pressure)* baroreceptors are found in large systemic veins, pulmonary vessels, in the walls of the right atrium and ventricles of the heart, and are involved with the regulation of blood volume [41]. When an increase in blood pressure is sensed by the baroreceptors, efferent sympathetic outflow is inhibited and parasympathetic outflow is increased. As a result of this efferent response, bradycardia, decreased cardiac contractility, and decreased peripheral resistance and venous return ensues. When blood pressure decreases, an increase in sympathetic activity and vagal inhibition result in tachycardia, increased contractility, increased vascular resistance, and increased venous return [42]. The sympathetic arm of the baroreflex can be measured by changes in sympathetic outflow (i.e., muscle sympathetic nerve activity) in response to changes in baroreceptor input (i.e., a change in BP). The cardiac arm of the baroreflex influences prolongation or shortening of cardiac period in response to changes in baroreceptor input and is referred to as the cardiovagal baroreflex [43].

The cardiovagal baroreflex can be quantitatively assessed by deriving the slope or gain of the relationship between the R-R interval length and systolic arterial blood pressure [38]. Also termed baroreceptor sensitivity, lower levels of this baroreflex gain has been associated with an increased risk of cardiovascular related mortality [44, 45]. Baroreflex function decreases with age and this decline appears to be partially explained by age-related increases in arterial stiffness [46]. The evaluation of baroreflex function by cross-

spectral analysis allows the assessment of the relationship between arterial blood pressure and R-R changes within the same frequency range (LF and HF as described above) and typical values found in Table 2.1.

2.1.2 Left Ventricular Function

A non-invasive means of assessing ventricular function is via echocardiography. Left ventricular (LV) systolic function assessed via echocardiography in earlier research typically included the evaluation of ejection fraction, fractional shortening and velocity of circumferential fibre shortening, all considered indices of global left ventricular contractility [47]. These measures are highly dependent on changes in preload and afterload, thus data should be represented relative to loading. When invasive measures are not available, many studies use end-diastolic volume/diameter as a means to indicate preload, and arterial blood pressure or wall stress as an indicator of afterload [19].

Diastolic function may be assessed via global and regional indices. The ratio of early (E) to late (A) peak diastolic filling velocities is commonly employed as a global measure of diastolic function. With these Doppler derived transmitral filling velocities one can also ascertain the timing of the isovolumetric relaxation period and time of deceleration in early filling from peak velocity to baseline. The detection of altered filling characteristics of the LV can be enhanced by also examining the pulmonary venous flow velocities [48]. However, both mitral and pulmonary flow velocities are problematic as they are load and heart rate dependant [49].

Tissue Doppler imaging (TDI) measures the velocity of a given segment of the myocardium, providing an index of relaxation and contraction [50]. Pulsed-wave TDI for

peak myocardial velocity is typically measured at the mitral valve annulus, and colour TDI provides mean longitudinal myocardial velocities typically from the basal septal segment. The myocardial velocities obtained are reported for early diastole (E') and late diastole (A'), in addition to the E'/A' ratio. The E/ E' ratio has been shown to correlate with pulmonary wedge pressure [50-52]. As with the flow velocities, tissue velocities are also heart rate dependent [53].

More recently, the advent of 2D strain and strain rate analysis via speckle-tracking has provided regional motion analysis of the myocardium in the longitudinal, radial and circumferential planes [54]. Further, assessing rotational strain and strain rate at the base and apical levels of the LV using this technique may be used to determine twist and untwist [55]. LV rotation is an indicator of active diastolic relaxation [56] and shows promise as an early detection tool in various cardiovascular diseases [57].

2.1.3 Arterial-ventricular coupling

While alterations in cardiovascular performance in health or disease may be isolated to the arteries or heart, the effect of this impairment or enhancement will affect the net function of the complete system. Arterial-ventricular coupling allows for the assessment of the interaction of the arterial system and left ventricle. The arterial elastance (E_A) component is calculated from end-systolic pressure / stroke volume (ESP/SV) while ventricular elastance (E_{LV}) is derived from end-systolic pressure / end-systolic volume (ESP/ESV). Through this novel means, the ratio of E_A/E_{LV} provides an index of cardiac energetic efficiency versus cardiac mechanical efficiency [58]. For example, during exercise, E_A/E_{LV} will decrease in order to ensure adequate blood supply to the tissues, but

at the expense of energetic efficiency [59]. Arterial-ventricular coupling can be measured non-invasively; most simply via echocardiography and systolic brachial blood pressure providing mechanistic insights into the pathophysiology of various conditions [58]. A measurement in the range of 0.6 - 1.2 at rest is considered optimal, reflecting an ideal balance between mechanical efficacy and energetic efficiency [28].

2.2 SEX DIFFERENCES IN CARDIOVASCULAR FUNCTION

2.2.1 Autonomic Function

Increased vagal tone, or parasympathetic activity, is considered to be protective against cardiac events, whereas increased sympathetic activity is associated with higher risk of perturbing the heart [60, 61]. Significant sex differences have been identified with respect to autonomic function at rest. Work examining the influence of sex on HRV has revealed women demonstrate greater parasympathetic and less sympathetic control of heart rate than males (i.e., a lower LF/HF power ratio) [62-66] a factor potentially linked to the lower cardiovascular risk and increased longevity in females [64]. It is speculated that hormones may be partially responsible for the sex differences in autonomic function as sex differences in HF cardiac modulation are less apparent after the onset of menopause [67] and hormone-dependent afferent receptor stimulation, central reflex transmission, efferent nervous system, and postsynaptic signaling are dissimilar between the sexes [68].

With respect to blood pressure regulation women have been shown to have similar [69-71] or lower [71-76] cardiovagal baroreflex compared to men. Fluctuations in female hormones throughout the menstrual cycle have not been shown to influence baroreceptor

sensitivity; however oral contraceptive use does appear to affect the response [77, 78]. Of the aforementioned studies, only the work of Beske and colleagues [76] controlled for oral contraceptive use, in addition to other potentially confounding factors such as age, hypertension, smoking, obesity and aerobic fitness. As a result of controlling for these factors, the authors speculate that lower levels of carotid artery distensibility in women may be involved in attenuating the baroreflex response, as these factors were shown to be closely related in earlier work [79]. While the mechanism of this sex-based difference is not known, the age-related decline in baroreflex function appears to occur at similar rates in men and women [75].

2.2.2 Left Ventricular Structure and Function

Males have a greater cardiac size and volumes than females, associated directly with the larger body size of males. However, even after adjusting for body surface area, these differences in cardiac dimensions and volumes remain [80, 81]. Despite lower cardiac volumes in women, improved systolic function with a higher left ventricular ejection fraction for a given end-diastolic volume has been demonstrated [82]. Thus, it appears women have an advantage over men with respect to systolic function. To further support this notion, clinical research has revealed that in the progression to heart failure in older age, women tend to show impaired diastolic function whereas men predominately display systolic heart failure. In a study of healthy volunteers, diastolic function as measured by long-axis tissue velocities was reduced in women compared with men only for the older age group (>60 y) [83]. These sex differences may be related to hormones. LV relaxation falls below that of males around 45-55 years of age, in line with natural menopause [84].

Reasons for this impaired relaxation are speculative. The vasodilatory effect of estrogen on the arterial system is a likely mechanism [85]; however, hormone replacement therapy has not led to improved cardiovascular function post-menopause [86, 87]. Despite this change in cardiac function in aging women, sex does not appear to augment LV rotation and twist across the lifespan [83, 88].

2.3 CHRONIC TRAINING ON CARDIOVASCULAR FUNCTION

2.3.1 Autonomic Function

Athletes typically display higher heart rate variability values than sedentary individuals. Long-term endurance training has been shown to positively influence autonomic nervous system activity via increases in heart rate variability, increased parasympathetic activity, and a decreased sympathetic activity of the heart at rest [62, 89-93]. The mechanism for this reduced sympathetic control of heart rate is thought to result from reduced efferent sympathetic neural outflow to the sinoatrial node with endurance training [92, 94, 95]. Heart rate variability typically declines with age [96, 97]; however, sustained endurance training over many years may attenuate this decline [98, 99]. A comparison of aerobically trained and sedentary individuals is shown in Table 2.1.

More typically used as a clinical indicator of health, these non-invasive autonomic indices have been used to assess the response to a physiological stress such as weightlessness [100], changes in central blood volume through lower body negative pressure [101], and/or exercise [102, 103]. Following exercise, parasympathetic activity is reduced; however, slow parasympathetic recovery may indicate autonomic imbalance [104]. In athletic populations, parasympathetic activity monitoring via heart rate

variability is often being used to reflect the state of recovery. When athletes are over-reaching or over-trained (resulting when both training and non-training stressors overwhelms the body's ability to recover adequately)[105], parasympathetic activity is reduced compared to baseline values [106]. Recently, baseline heart rate variability has been suggested to relate positively to the degree of adaptation in response to a 28-week training program in recreational runners [107]. Thus, the literature supports the use of heart rate variability as a simple, yet powerful method of assessing cardiovascular control.

2.3.2 Left Ventricular Structure and Function

Chronic endurance training may cause an enlargement of the heart in some individuals, known as the athlete's heart [25]. Unlike the pathologically induced ventricular hypertrophy seen in the ailing heart, training induces a physiological adaptation that is thought to be relatively benign [108]. Characteristic adaptations include increased chamber dimensions, increased left ventricular mass, and right ventricular dilatation all in the presence of enhanced systolic and diastolic function [109, 110]. While this eccentric hypertrophy is seen as normal adaptation to chronic endurance training, the similarity to hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia (linked to increased risk of sudden death in athletes) [111] warrants a better understanding of how to differentiate between these two states. Upper normal limits of chamber and wall dimensions (<66 mm and <15 mm, respectively) have been defined according to a meta-analysis [112]. Importantly, not all athlete cohorts present the classic features of the athlete's heart likely due to sport-specific myocardial adaptations [113].

Regular endurance training elicits an improvement in maximal aerobic power (VO_2max) [114] largely due to cardiovascular adaptations. Vascular adaptations with endurance training result in benefits upstream [115] where the trained heart may experience less stress and produce a more efficient ejection [116] potentially reducing the required LV strain and twist observed in endurance athletes at rest [117, 118]. Further, under stress of intense exercise, an enhanced LV untwisting during exercise would be an important means of increasing the rate of LV filling when diastolic time is reduced [119, 120].

2.4 MECHANISMS OF EXERCISE-INDUCED CARDIAC FATIGUE

2.4.1 Myocardial stunning and damage

Exercise-induced cardiac fatigue has been proposed to cause transient ischaemia resulting from myocardial stunning [121] and subsequently causing disruptions in contractile function such as impaired myocyte relaxation [122]. Impaired LV function has been shown to be a transient phenomenon in which normal function is restored within hours following the exercise stress [123]; however to date, exercise-induced cardiac fatigue as the result of myocardial ischemia remains to be corroborated [20].

Myocardial damage has been a topic of much interest in the last decade as increased cellular protein levels have been detected following prolonged exercise. Cardiac troponin T and cardiac troponin I are specific markers of myocardial damage shown to be elevated post myocardial infarction [124]. However, the investigations to date have produced conflicting findings. Studies have either found no evidence of elevated levels of cardiac troponins [125, 126], elevated levels in the occasional participant [127, 128], or elevated

levels in 10-60% of participants [129-133]. Shorter duration high intensity exercise (e.g., 30 minutes of intense running) has also revealed elevated cardiac troponin T [134]. However, analysis of the true incidence of post-exercise myocardial injury is hampered by small sample sizes and methodological variation. Cardiac troponin is released into circulation around 3-4 h post-exercise and peaks at approximately 12-18 h post-exercise [125] thus many investigations may have been unable to detect transient changes in these biomarkers. In a recent meta-analysis, Shave et al. [135] (encompassing 26 investigations) found exercise-induced cardiac troponin T was elevated in half of the participants studied. Further, these occurred in shorter endurance events (such as the marathon). While much remains unknown, given the available data, the validity of elevated troponin levels post-exercise representing myocardial injury has been questioned [136].

2.4.2 β-adrenergic down-regulation

Pharmacological interventions such as isoproterenol and dobutamine have demonstrated a reduced cardiac β-responsiveness following prolonged strenuous exercise [137-141]. This reduced β-adrenergic sensitivity may contribute to the attenuated LV systolic function demonstrated with prolonged strenuous exercise [138] and appears to be affected by sex [139] and age [142]. A prolonged increase in circulating catecholamines may be related to this altered sympathoadrenal response. Catecholamines support the sympathetic system in modifying the circulation during exercise, increasing heart rate, contractile force and cardiac output by stimulation of the adrenergic β-1-receptors in the myocardium [143]. It is thought that elevated circulating catecholamines from strenuous

exercise lead to decreased functional activity of cardiac β_1-adrenergic receptors and thus to marked desensitization of the heart to inotropic β-adrenergic stimulation [144]. Catecholamine levels have been positively associated with exercise intensity [145] and thus parallels findings of greater reductions in β-adrenergic sensitivity with higher exercise intensity in animals [146] and very recently, in humans [141]. However recent work in an animal model of prolonged strenuous exercise found no change in cardiac response to beta-receptor stimulation in isolated rat hearts, but rather found evidence of oxidative stress [147]. These researchers suggest that by using an isolated perfused rat heart model, intrinsic myocardial fatigue can be introduced without potential confounders such as catecholamines and altered loading conditions. Further work is required to ascertain the role of β-adrenergic receptors in the mechanism of cardiac fatigue [148].

2.4.3 Oxidative Stress

Cardiac oxidative stress may impair cardiac function through oxidative damage to cellular proteins and membranes [149, 150]. Chronic increases in oxygen radical production in the mitochondria as seen in myocardial remodelling and heart failure, can lead to a catastrophic cycle of mitochondrial DNA damage as well as functional decline, further oxygen radical generation, and cellular injury [151]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), a source of reactive oxygen species is well known for its role in cardiac dysfunction [152] and is increased in response to tachycardia or exercise [153]. Recently, an increase in oxidative stress was shown in myocardial rat tissue after prolonged strenuous exercise, a response not seen when NADPH oxidase was

inhibited [147]. These authors propose this oxidative stress may initiate the transient vascular and/ or cellular alterations observed in myocardial stunning.

2.4.4 Elevated Free Fatty Acids

Implicated as having a role in exercise-induced cardiac fatigue elevated free fatty acids have been reported to be significantly elevated following prolonged exercise [154] [155]. Through a cascade of metabolic events, free fatty acids are thought to reduce the efficiency of mitochondrial respiration [156]. However, elevations in free fatty acids reported following prolonged strenuous exercise was deemed too low to have had an impact in the exercise-induced cardiac fatigue presented [157]. More recently, elevated free fatty acids were shown to have no effect on LV performance in heart failure patients with Type II diabetes [158], thus the propensity of free fatty acids altering ventricular function in healthy individuals does not appear to be likely.

2.5 CONCLUSIONS

Advances in echocardiography have improved our ability to assess cardiac function in a variety of situations and populations. As recreational exercise evolves to include more extreme pursuits, our ability to monitor the physiological impact of these activities in 'ordinary' individuals becomes more important. The literature herein has provided a brief review of current concepts in acute and chronic responses and adaptations to strenuous exercise in healthy men and women. However, significant gaps persist with respect to the etiology of exercise-induced cardiac fatigue and how various factors impact its development. Further the cardiovascular adaptations occurring during recovery from strenuous exercise remains to be fully elucidated.

Chapter 3: Sex Differences in Cardiac Function Following Prolonged Strenuous Exercise

3.1 INTRODUCTION

Exercise-induced cardiac fatigue is characterized by a reduction in left ventricular systolic and diastolic function subsequent to exercise in healthy humans [19] and becomes evident following bouts of prolonged strenuous exercise [20]. These reductions in left ventricular performance have been found to occur despite the absence of underlying cardiovascular pathologies [154, 159-161], and appear to be transient in nature with normal function restored typically within 48 h [123]. Notwithstanding, given the association of an increased incidence of sudden cardiac events with acute exercise in those at risk [162], the clinical relevance of exercise-induced cardiac fatigue warrants further study [163-165], particularly considering the appreciable increase in ultra-endurance participation over recent years [3]. The average age of winning ultra-marathoners are older than the typical age of winning marathoners [18]. This may be interpreted to suggest that in order to perform well in ultra-endurance events, accumulating greater years of training may be beneficial. However, our understanding of the cumulative effects of chronic ultra-endurance training is limited.

Another emerging trend is the increase in female participants in ultra-endurance events. A recent analysis of the participation trends in ultra-marathons revealed a 20% increase in the percentage of female finishers [166]. Despite this increase in female competitors, the literature to date has yielded limited information regarding the cardiovascular consequences of ultra-endurance exercise in women. Our research group

has found that both men and women experienced a reduction in LV systolic function as a consequence of a half-ironman triathlon, with a greater reduction exhibited in the males [139]. Prolonged strenuous exercise has been shown to significantly increase plasma catecholamines [167] a marker of sympathetic activity. Phenotypical evidence of sex differences in cardiac norepinephrine transporter function [168] suggests that males exhibit differences in cardiac-specific sympathetic activity. As such, greater sympathetic activity in males may be responsible for the greater reductions in cardiac function shown following prolonged-strenuous exercise in males versus females [139]. However, further work is required to substantiate these earlier findings using assessments of regional myocardial function, such as strain and strain rate imaging, that allows for a more thorough analysis of left ventricular function [169]. In addition, sex differences have not been investigated following a longer duration event such as an ultra-marathon. Accordingly, the purpose of this investigation was to evaluate sex differences in cardiac function following an ultra-endurance running race. We hypothesized that following an ultra-marathon men would display evidence of marked exercise-induced cardiac fatigue compared with women.

3.2 METHODS

3.2.1 Participants and Ethical Approval

Thirty-four competitors (43.4 ± 8.2 y; 13 F) participating in a mountain trail running ultra-marathon (Fat Dog 100) volunteered to participate in this research. This field study occurred mid-summer in British Columbia, Canada. Runners were exposed to temperature fluctuations ranging from 6 to 30 degrees Celsius between day and night-

time hours. The terrain was very mountainous with ascents of 600 – 2300 m over two race distances (100 km and 160 km). Prior to testing, all participants completed the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+; Appendix A) and provided written informed consent in exact accordance with the guidelines established by the Clinical Research Ethics Review Board at the University of British Columbia.

3.2.2 Experimental Protocol

Baseline testing occurred one to two days prior to the start of the race in dedicated research space on site. Advance testing at the University of British Columbia was completed in four participants at four days prior to the race. Participants completed a training history questionnaire (Appendix B) for the determination of training volume and race experience. Assessments included basic anthropometrics, arterial compliance, baroreflex function, and echocardiography. At the completion of the race, participants were directed to the research site for repeat assessments, within 30 minutes from crossing the finish line. Runners were to complete a minimum of 50 km to be included in post-race analysis.

3.2.3 Procedures and Analysis

Anthropometrics, Autonomic and Arterial Compliance Assessments. Following the collection of body height and mass, participants were prescribed five minutes of seated rest and were measured for three consecutive measures of seated resting blood pressure (BP-TRU, VSM Medical, Vancouver, BC). Post-race, measures of body mass and blood pressure were conducted at the race finish line prior to transportation to the on-site

research testing facility. Body surface area was calculated as BSA (m^2) = SQR RT ([Height(cm) x Weight(kg)]/ 3600) [170].

At the research testing facility, autonomic function and arterial compliance were evaluated following five minutes of supine rest. Baroreceptor sensitivity (BRS) was determined from the simultaneous assessment of beat-by-beat blood pressure and ECG. Five minutes of continuous blood pressure data was collected using finger photoplethysmography (Finapres, Ohmeda Inc, Englewood, CO), calibrated using an automated blood pressure device (Bp-TRU 100, Coquitlam, Canada) along with three-lead electrocardiography (I, II, III) on Chart software (Version 5.5.6). During this assessment, participants remained supine while wearing industrial strength ear protectors to block-out the ambient noise in the room. BRS analysis occurred off-line after the race at the Cardiovascular Physiology & Rehabilitation Laboratory at UBC. A minimum of 140 s of continuous cardiac cycles were evaluated to determine HRV and BRS. Power spectral evaluations of HRV and BRS were conducted by the same investigator using Nevrokard BRS software (Version 6.1.0, Nevrokard, Kiauta, Slovenia) as described previously [171]. The investigator was blinded to participant testing conditions during this analysis through blinded coding of file names.

Arterial compliance was measured non-invasively via applanation tonometry with the HDI CR-2000 (Hypertension Diagnostics, Eagan, Minnesota) for diastolic pulse contour analysis. After stabilizing the wrist and maximizing signal strength, radial artery tonometry measurements were collected using the right wrist with the automated sphygmomanometer affixed to the upper left arm. Measurements were taken in duplicate with the average used for analysis. The calculations of small and large arterial

compliance are accomplished by the software of the applanation tonometry unit using a paradigm described in detail elsewhere [172] which divides total systemic resistance into individual components using mathematical modeling. This technique has been validated with invasive and non-invasive testing [173, 174].

Echocardiographic Assessments. Two-dimensional transthoracic and pulse-Doppler imaging was used to assess LV function using a commercially available portable ultrasound system (V*ivid i,* GE Medical Systems, Israel) with simultaneous ECG and a 2.5-MHz transducer. Participants were positioned in the left lateral decubitus position for imaging. Cardiac images were acquired by a single clinically certified sonographer according to the American Society of Echocardiography guidelines [175]. Apical two and four-chamber views were acquired for the assessment of stroke volume (SV), LV longitudinal strain (S) and strain rate (SR). Transmitral pulsed Doppler recordings assessed early (E) and late (A) diastolic filling, and pulmonary venous flow velocities were obtained. Myocardial tissue velocities were assessed at the mitral annulus of the LV septal wall (E'septal) and lateral wall (E' lateral), as well as the right ventricular lateral wall (E'RV). Parasternal short axis views obtained at the basal level were obtained to derived circumferential and radial strain and SR data as described in detail elsewhere [176]. Briefly, the basal level was defined as the level of the first appearance of the superior surface of the papillary muscle when imaged down from the mitral valve and imaged at high frame rates (70-90 frames per second).

Ventricular volumes and diameters were analyzed off-line (EchoPAC, GE Healthcare, v. 110.1.1) in accordance with the recommendations of the American Society of Echocardiography [175]. Left ventricular mass was determined using the formula: LV

Mass (g) = 0.8 (1.04 ([LVIDD + PWTD + IVSTD]3- [LVIDD]3))+ 0.6 [177]. End-diastolic volume (EDV) and end-systolic volume (ESV) using Simpson's bi-plane method for which 3 consecutive beats were measured and analyzed. Stroke volume was calculated by EDV-ESV. Cardiac output (CO) was calculated as SV x HR. Ejection fraction (EF) was calculated as a percentage of EDV. Fractional shortening (FS) was calculated from ventricular diameters using the parasternal long axis window and expressed as a percent. Total peripheral resistance (TPR) was derived from dividing CO into MAP. End-systolic meridional wall stress (WS) was determined non-invasively as WS ($g \cdot cm^{-2}$) = 0.334(SBP)(LVESD) /PW(1 + PW) / LVESD, where SBP is systolic blood pressure, LVESD is left ventricular end-systolic diameter, and PW is left ventricular systolic posterior wall thickness [178]. Evaluation of E/E' for both the septal and lateral walls provided an estimate of LV filling pressures.

3.3 STATISTICAL ANALYSIS

Between sex characteristics were analyzed using Student's unpaired *t* tests. A two-way analysis of variance (ANOVA) was used to evaluate the effect of sex on changes in cardiac function with exercise (repeated factor). The change in LV functional measures from pre- to post-race (Δ) was correlated with age, baseline vascular and autonomic indices, in addition to performance and training variables, using Pearson correlation. Linear regression analysis was used to determine the factors responsible for the change in cardiac function. Significance for all tests was set *a priori* at $p<0.05$. All analyses were performed using SPSS software (version 20.0; SPSS IBM, Chicago, IL). Results are reported as mean ± SD.

3.4 RESULTS

3.4.1 Participant Characteristics

Thirty-four participants completed baseline assessments, while 25 individuals (8 F; 32%) returned for follow-up testing (n = 21 of European ethnicity, 3 Asian and 1 Metis). Attrition was due to participants dropping out of the race and decided not to continue with the study. Training volume, race experience, and race practices did not differ between the sexes. Participants trained on average 5 ± 1 d/wk, running 86.0 ± 34.6 km/wk. The group averaged 5.1 ± 3.4 years of competing in ultra-marathons (range 1 to 15 years). Total number of lifetime ultra-marathons averaged 14.2 ± 12.6 (range 0 to 53), with the last reported event occurring 51.5 ± 52.9 days prior to this event. Number of ultra-marathons completed in the year prior to this investigation was 2.5 ± 1.9. Runners reported an average taper of 14.3 ± 11.3 days and 9.7 ± 9.5 days since their last training session. Eighty-four percent of the participants reported ingesting sodium supplements during the race and regularly do so in training. Maximal aerobic power (VO_2max) was assessed in four males and three females (VO_2max = 48.2 $mL \cdot kg^{-1} min^{-1}$; range = 41 - 56 $mL \cdot kg^{-1} min^{-1}$) who volunteered to have this assessed approximately 4 weeks post-race (to allow for adequate recovery). As these seven individuals represented 28% of the participants, this information is presented for information purposes only. Participant characteristics and baseline cardiovascular measures are found in Table 3.1.

3.4.2 Participant Performance

All 25 individuals met the minimum distance criteria, with an average race distance of 134.1 ± 48.8 km completed for the group, over a time course of 27.6 ± 8.9 h (9.0 to 41.9

h). Our sample represented 43% of total race entrants. Our 19 finishers represented 59% of total race finishers placing 1st to 16th for the men (n = 14) and 3rd to 15th for the women (n = 5). As such, our participants represented the upper end of the ultra-endurance athlete continuum. While our sample of women was small relative to the men and consisted of 32% of our total sample, this was in proportion to the total women entered in the race (8 out of 19F; 33%). There were no significant differences between sex for race completion time (29.0 ± 8.6 vs. 25.9 ± 9.7 h), race pace (4.7 ± 1.1 vs. 4.8 ± 0.7 km/h) or race distance completed (141.8 ± 50.4 vs. 121.1 ± 48.4 km) for men and women, respectively.

3.4.3 Physiological and Cardiovascular Outcomes

From pre-race baseline, body weight decreased an average of 1.5 ± 3.1 kg ($p = 0.02$). At the finish line, blood pressure and heart rate responses did not differ by sex. In comparison to baseline, seated blood pressure was not significantly reduced post-race: SBP from 116.2 ± 12.9 to 114.2 ± 14.2 mmHg, respectively; DBP from 76.5 ± 7.2 to 76.1 ± 11.0 mmHg, respectively. The HR assessed at the finish line was significantly higher than observed at pre-race (89.6 ± 13.7 vs. 62.3 ± 8.2 bpm, respectively $p < 0.001$). There were no interactions found for the cardiac variables measured over time (pre-, post-exercise) and sex. Between subject differences were found for baseline cardiac structure and global function where men displayed larger LV diameters and volumes, cardiac output, and lower total peripheral resistance ($p < 0.05$; Table 3.2). Due to the lack of sex-based interactions, the pooled findings (across sexes) are shown in Tables 3.3 and 3.4 to illustrate the effects of exercise on the remaining cardiac variables. No between sex, or sex by time interactions, were found for the $E_AI/E_{LV}I$ ratio (pre-exercise: 0.52 ± 0.14,

post-exercise: 0.58 ± 0.22, $p = 0.245$). Changes in BRS with exercise, is represented in Figure 3.1. Statistically significant bivariate correlations are displayed in Table 3.5. Change in body mass, HR, SBP, ESP/EDV, and E/A were not correlated with any of the cardiovascular outcomes. Change in longitudinal strain was significantly correlated with life-time ultra-marathons (Figure 3.2) and race-pace (Figure 3.3).

Table 3.1 Participant Characteristics and Baseline Cardiovascular Measures

Variable	Men (n = 17)	Women (n = 8)	*p* value
Age, *y*	44.8 ± 6.6	45.9 ± 10.2	0.758
Height, *cm*	177.8 ± 6.3	162.7 ± 5.1	**0.000**
Body Mass, *kg*	77.6 ± 9.3	58.9 ± 3.6	**0.000**
BMI, $kg \cdot m^{2}$	24.5 ± 2.4	22.3 ± 1.4	**0.023**
LVM, *g*	214.7 ± 47.1	160.8 ± 30.7	**0.007**
LVM/BSA, $g \cdot m^{-2}$	109.6 ± 22.5	98.5 ± 18.0	0.235
SBP, *mmHg*	128.4 ± 7.9	120.8 ± 12.5	0.073
DBP, *mmHg*	73.0 ± 7.0	69.3 ± 7.1	0.230
HR, *bpm*	63.5 ± 7.1	59.6 ± 5.2	0.221
CO, $L \cdot min^{-1}$	5.14 ± 1.21	4.00 ± 0.80	**0.026**
LAC, $mL \cdot mmHg \cdot 10$	18.3 ± 6.0	14.0 ± 3.2	0.074
SAC, $mL \cdot mmHg \cdot 100$	9.7 ± 3.1	6.0 ± 2.1	**0.006**
RRI LF/HF	2.25 ± 1.32	0.88 ± 0.92	**0.022**
BRS, $ms \cdot mmHg$	18.5 ± 11.6	25.0 ± 17.6	0.310

Abbreviations: BMI = body mass index; LVM = left ventricular mass; BSA = body surface area; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CO = cardiac output; LAC = large artery compliance; SAC = small artery compliance; RRI = ratio of low frequency to high frequency of RR intervals; BRS = baroreceptor sensitivity
The effect of sex on participant characteristics was analyzed by unadjusted general linear models for continuous variables.
BOLD *p* values denotes statistically significant

Table 3.2 Cardiac Dimensions and Global Systolic Function

Variable	Pre-exercise		Post-exercise	
	Men	*Women*	*Men*	*Women*
LVPWd, *cm*	0.98 ± .18	0.89 ± .25	1.1 ± .27	0.95 ± .18
LVIVSd, *cm*	1.3 ± .20	1.2 ± .16	1.4 ± .30	1.2 ± .13
LVEDD, *cm* ¥	4.81 ± .35	4.41 ± .43	4.44 ± .52	4.21 ± .33
LVPWs, *cm* ¥	1.74 ± .18	1.53 ± .26	1.74 ± .28	1.39 ± .25
LVIVSs, *cm* ¥	1.88 ± .16	1.61 ± .23	1.84 ± .24	1.50 ± .22
LVESD, *cm*	2.86 ± .41	2.54 ± .39	2.91 ± .33	2.75 ± .32
LVEDV, *mL* ¥	138.4 ± 25.1	100.9 ± 7.1	111.5 ± 16.0*	87.8 ± 11.1*
LVESV, *mL* ¥	46.7 ± 13.0	34.0 ± 8.9	40.1 ± 10.2*	30.4 ± 11.2*
SV, *mL* ¥	91.7 16.0	66.9 8.4	71.4 14.7*	57.4 12.0*
SVI, *mL/BSA*	46.9 ± 7.8	41.2 ± 6.3	36.9 ± 8.9*	35.2 ± 7.1*
EF, *%*	66.4 5.2	66.4 8.3	63.8 7.8	65.5 11.6
CO, $L \cdot min^{-1}$ ¥	5.19 ± 1.19	4.01 ± 0.80	5.16 ± 1.31	4.24 ± 1.09
CI, $L \cdot min^{-1}/BSA$	2.65 ± 0.55	2.47 ± 0.55	2.65 ± 0.68	2.60 ± 0.66
FS, *%*	40.9 ± 6.4	42.5 ± 6.5	34.1 ± 7.6*	34.6 ± 7.9*
SBP/ESV ¥	2.91 ± 0.69	3.89 ± 1.60	3.17 ± 0.72*	4.40 ± 2.09*
TPR, $mmHg \cdot L \cdot min^{-1}$ ¥	18.6 ± 5.0	22.6 ± 6.3	17.7 ± 5.2	20.2 ± 4.7
Wall Stress, $x10^3\ dyn \cdot cm^2$	67.7 ± 4.0	67.3 ± 7.0	64.0 ± 5.9	67.0 ± 4.8

Abbreviations: LV = left ventricular; PWd = posterior wall in diastole; IVSd = intraventricular septum in diastole; EDD = end-diastolic diameter; PWs = posterior wall in systole; IVSs = intraventricular septum in systole; ESD = end-systolic diameter; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; SVI = stroke volume index; EF = ejection fraction; CO = cardiac output; CI = cardiac index; FS = fractional shortening; SBP = systolic blood pressure; TPR = total peripheral resistance

Effect of exercise obtained using general linear models adjusted for sex.
* $p<0.05$ from baseline; ¥ $P<0.05$ between men and women

Table 3.3 Doppler Flow Velocities

	Pre-exercise		Post-exercise		*p* value		
Variable	*Men*	*Women*	*Men*	*Women*	*	#	€
E, *m/s*	0.81 ± 0.20	0.84 ± 0.18	0.68 ± 0.13	0.84 ± 0.08	0.096	0.108	**0.039**
A, *m/s*	0.53 ± 0.10	0.57 ± 0.13	0.55 ± 0.11	0.67 ± 0.12	0.093	0.248	0.153
E/A	1.28 ± 0.68	1.55 ± 0.51	1.26 ± 0.33	1.30 ± 0.27	0.299	0. 379	0.433
DecT, *ms*	216.9 ± 40.4	206.0 ± 35.7	206.4 ± 38.7	189.9 ± 22.2	0.092	0.713	0.091
IVRT, *ms*	84.4 ± 14.9	89.8 ± 11.7	83.1 ± 10.4	73.5 ± 19.4	**0.045**	0.082	0.129
S, *m/s*	0.56 ± 0.12	0.52 ± 0.08	0.51 ± 0.17	0.50 ± 0.15	0.433	0.723	0.341
D, *m/s*	0.50 ± 0.13	0.47 ± 0.11	0.43 ± 0.07	0.47 ± 0.08	0.343	0.310	0.191
S/D	1.02 ± 0.46	1.13 ± 0.13	1.17 ± 0.28	1.05 ± 0.21	0.602	0.151	0.277
Ar, *m/s*	0.24 ± 0.03	0.25 ± 0.04	0.24 ± 0.05	0.26 ± 0.04	0.995	0.604	0.871
Ar Duration, *ms*	142.8 ± 34.5	133.4 ± 25.9	123.5 ± 29.3	119.6 ± 12.0	**0.030**	0.678	**0.015**

Abbreviations: E = peak early transmitral flow velocity; A = peak late flow velocity; DecT = E wave deceleration time; IVRT = isovolumetric relaxation time; S = peak systolic pulmonary venous flow velocity; D = peak diastolic pulmonary venous flow velocity; Ar = peak atrial reverse pulmonary artery flow velocity

BOLD *p* values denotes statistically significant
Effect of exercise obtained using general linear models adjusted for sex.
* from pre-exercise; # sex by time interaction; € from pre-exercise (pooled data – all subjects)

Table 3.4 Tissue Doppler Imaging and Strain

	Pre-exercise		Post-exercise		*p* value		
Variable	*Men*	*Women*	*Men*	*Women*	*	#	€
Tissue Velocities							
E' septal, *m/s*	0.13 ± 0.03	0.12 ± 0.03	0.11 ± 0.02	0.11 ± 0.02	**0.008**	0.946	**0.005**
E/E' septal	5.10 ± 3.25	7.24 ± 1.81	5.96 ± 1.03	8.24 ± 2.02	0.121	0.899	0.100
E' lateral, *m/s*	0.17 ± 0.03	0.16 ± 0.04	0.15 ± 0.04	0.15 ± 0.04	**0.021**	0.156	**0.004**
E/E' lateral	3.91 ± 2.10	5.63 ± 1.98	4.64 ± 0.89	5.67 ± 1.27	0.331	0.391	0.172
E' RV, *m/s*	0.15 ± 0.03	0.15 ± 0.03	0.15 ± 0.03	0.14 ± 0.03	0.390	0.729	0.420
Strain / Strain Rate							
Longitudinal S, *%*	-21.02 ± 1.98	-20.28 ± 1.90	-18.44 ± 1.87	-18.44 ± 2.34	**0.001**	0.518	**0.000**
Longitudinal SRsys, s^{-1}	-1.05 ± 0.13	-1.00 ± 0.11	-1.08 ± 0.18	-1.02 ± 0.22	0.606	0.920	0.546
Longitudinal SRdia, s^{-1}	1.37 ± 0.24	1.47 ± 0.24	1.29 ± 0.30	1.52 ± 0.31	0.854	0.329	0.565
Circumferential S, *%*	-17.64 ± 5.02	-18.39 ± 5.24	-17.69 ± 4.95	-18.49 ± 4.59	0.933	0.976	0.937
Circumferential SRsys, s^{-1}	-1.06 ± 0.31	-1.04 ± 0.32	-1.25 ± 0.33	-1.10 ± 0.25	0.112	0.404	**0.036**
Circumferential SRdia, s^{-1}	1.16 ± 0.49	1.32 ± 0.58	1.15 ± 0.43	1.44 ± 0.56	0.639	0.544	0.810
Radial S, *%*	-1.87 ± 1.15	-4.06 ± 4.02	-4.57 ± 4.95	-2.10 ± 1.52	0.751	0.058	0.603
Radial SRsys, s^{-1}	1.77 ± 0.44	1.61 ± 0.46	1.94 ± 0.46	1.84 ± 0.51	0.125	0.798	0.109
Radial SRdia, s^{-1}	-2.04 ± 0.50	-1.88 ± 0.72	-2.06 ± 0.67	-2.38 ± 0.50	0.198	0.238	0.381

Abbreviations: E' = myocardial tissue velocity; E = peak early transmitral flow velocity; RV = right ventricle; S = strain; SR = strain rate; sys = systolic; dia = diastolic

Effect of exercise obtained using general linear models adjusted for sex.

BOLD *p* values denotes statistically significant

* from pre-exercise; # sex by time interaction; € from pre-exercise (pooled data- all subjects)

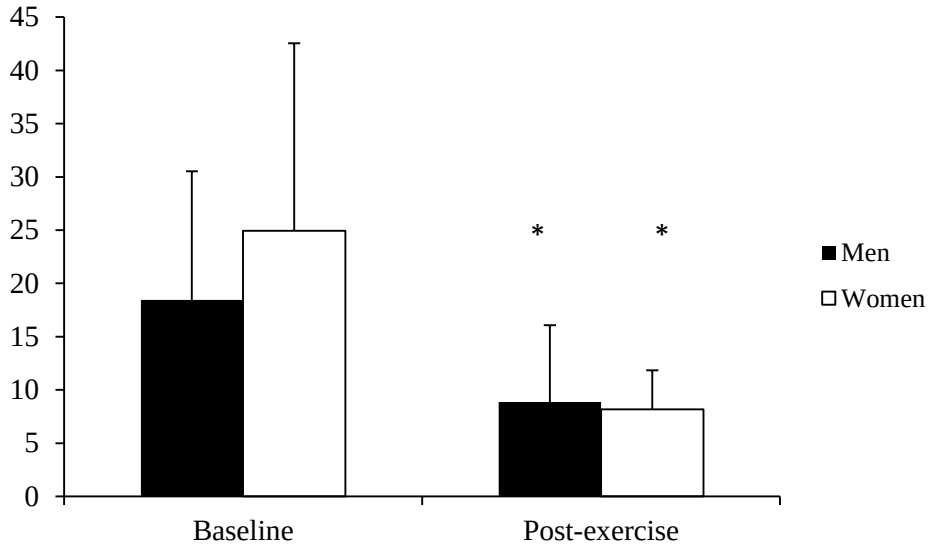

Figure 3.1 Change in Baroreceptor Sensitivity with Prolonged Exercise

* $p<0.05$ between rest and exercise

Table 3.5 Significant Correlations

Associated Variables	Pearson r	*p* value
Age, Δ Longitudinal Strain	-0.40	0.048
Race Pace, Δ Longitudinal Strain	0.49	0.012
LAC, Δ Longitudinal Strain	0.59	0.002
Total Ultras, Δ Longitudinal Strain	0.42	0.035
Δ HR, Δ Fractional Shortening	0.69	0.000
preLF/HF, Δ Longitudinal Strain	-0.41	0.049
LAC, Lifetime Ultras	0.47	0.017

Abbreviations: Δ = change; LAC = large artery compliance; HR = heart rate; BRS = baroreceptor sensitivity; SR = strain rate; dia = diastolic; sys = systolic; LF = low frequency; HF = high frequency
Data obtained from Pearson's Correlation analysis

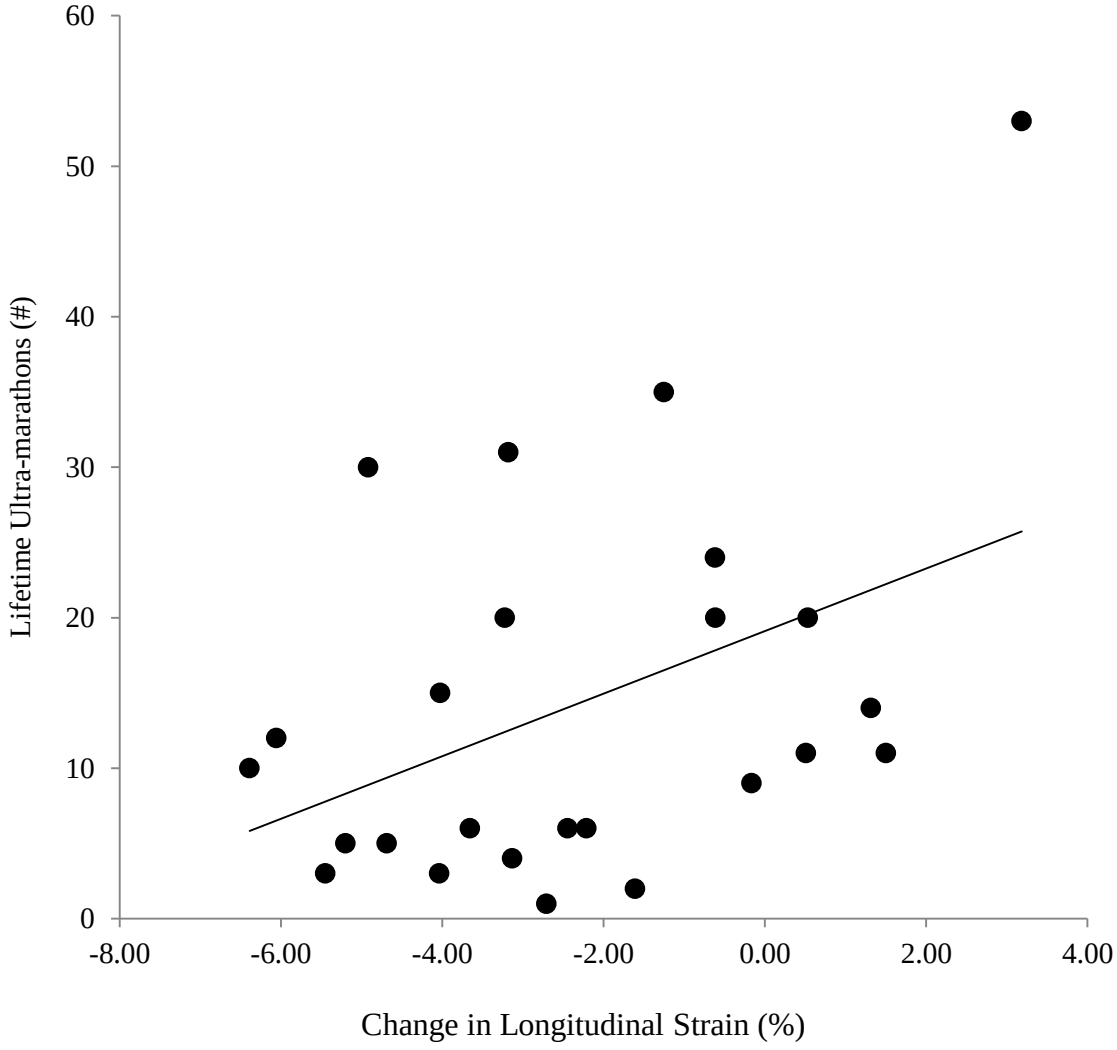

Figure 3.2 Association of Lifetime Ultra-marathons to Longitudinal Strain

Pearson r=0.423, *p*=0.035
Linear Regression r^2=0.21, Std Beta=0.438 (adjusted for sex) *p*=0.031

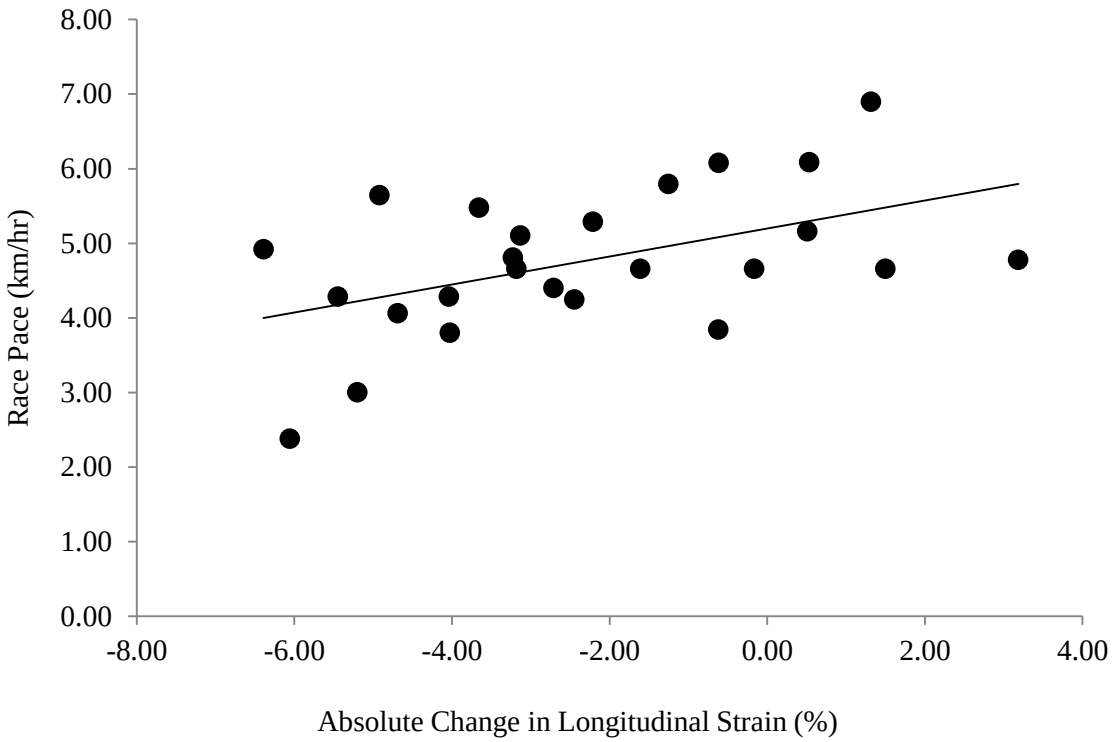

Figure 3.3 Association of Race-Pace to Longitudinal Strain

Pearson r=0.493, *p*=0.012

3.5 DISCUSSION

We aimed to compare the cardiovascular response to prolonged strenuous exercise between men and women. The major findings of this investigation are that 1) men and women displayed similar indications of exercise-induced cardiac fatigue following an ultra-marathon, and 2) more experienced runners displayed less exercise-induced cardiac fatigue. This paper represents the first comparison of the cardiovascular response to an ultra-marathon between men and women.

Following an ultra-marathon, we showed evidence of systolic and diastolic impairment, confirming previous findings in ultra-marathons [157, 176, 179] and other forms of prolonged exercise [180-182]. Other than fractional shortening, decrements in systolic function as indicated by post-exercise reductions of longitudinal strain, and myocardial wall velocities, were unrelated to a change in loading conditions (HR, and indirect measures of preload and afterload). Furthermore, the reductions in peak early transmitral flow velocity and pulmonary vein atrial reverse flow duration in the current investigation, is evidence of impaired LV relaxation [182].

Contrary to our hypothesis, we did not find sex to influence the response to an ultra-marathon. Early diastolic filling appears to have reduced to a greater extent in the men but may not have reached statistical significance due to our small sample size. The issue of sample size is addressed further in the limitations section. To our knowledge, only an earlier investigation from our laboratory had the objective of comparing sex differences in the acute response to ultra-endurance exercise in triathletes [139]. In this prior work, contractility was found to differ among men and women. However, in the present

investigation, we did not find a sex difference with our indicators of contractility. La Gerche et al. [180] studied a similar sample of men and women to that of our previous work; however, they did not report any sex differentiation other than pre-race characteristics. Other than sample size considerations, the discrepant findings between our current and past work may be explained by differences in the exercise stimulus employed involving different exercise intensity (estimated from running pace to be 80 vs. 50% of maximum capacity), and duration (6 vs.29 h) for the half-ironman triathlon and ultra-marathon, respectively. The combined impact of intensity and duration on exercise-induced cardiac fatigue is unclear. The varied intensities and competitive situations within the literature make isolating any dose-response difficult [19]; however we speculate that exercise-induced cardiac fatigue may present differently in response to varied exercise intensities and durations.

Despite the lack of interactions between exercise-induced cardiac fatigue and sex, we did find a number of between group sex differences. As expected, men had greater LV mass, greater cardiac dimensions and volumes, with most differences disappearing when indexed for body surface area. Men also showed greater resting small artery compliance and a trend of higher large artery compliance. Arterial compliance has been shown to relate to artery diameter [183] and possibly explains the sex difference. Another commonly used indicator of cardiovascular health is that of RRI LF/HF. Women typically demonstrate greater parasympathetic and less sympathetic control of heart rate than males (i.e., a lower LF/HF power ratio) [62-66] a factor potentially linked to the lower cardiovascular risk and increased longevity in females [64]. Our results are in

agreement with this; however, the relevance of the positive association between this ratio and baseline radial systolic strain rate is unclear.

The lack of marked exercise-induced cardiac impairment was unexpected considering the significant duration and volume of exercise engaged in by our participants. This is particularly salient as exercise duration has previously been shown to be associated with exercise-induced cardiac fatigue [161, 184] most notably in exercise sessions longer than 6 h [160]. In particular, only longitudinal strain was reduced significantly from baseline. Similar investigations have found reductions in radial, circumferential and longitudinal strain, in addition to reductions in *strain rates* [176, 181]. Our findings of reduced LV tissue velocities are in agreement with these findings; however, the lack of altered strain rate was unexpected.

We propose two possible explanations for the lower degree of exercise-induced cardiac fatigue in our results: temperature and intensity. While our race was similar in duration to the ultra-marathon of the Western States Endurance Race, the California racers would have had much higher thermal strain to contend with than our temperate mountain race. Heat stress translocates blood volume from the centre to the periphery for which the demand for skin blood flow is met in part by an increase in cardiac output [185]. Severe heat stress during whole body exercise pushes the cardiovascular system to its regulatory limit, where cardiac output and blood flow to exercising limb muscles and skin cannot be maintained for a longer duration. It has been postulated that a small attenuation in the myocardial perfusion-to-work relationship may occur, leading to impaired myocardial function, as oxygen (extraction) reserve is too small to compensate

for a significant blunting in oxygen supply [186]. Thus, we cannot rule out the effects of thermal strain field measures of cardiac function.

Another consideration relative to the magnitude of cardiac fatigue is the extreme mountainous terrain of the Fat Dog 100 where four major ascents /descents may have induced considerable neuromuscular fatigue [187] and as a result lowered exercise intensity enough to spare cardiovascular fatigue. Mattsson and colleagues [188] recently showed that when exercise duration exceeds 24 h, cardiac work (stroke work x heart rate) and myocardial oxygen consumption decrease, likely as a physiological adaptation to maintain cardiac output when total energy expenditure demands are high.

A novel finding in our work is that runners who have run more ultra-marathons in their lifetime demonstrated less evidence of exercise-induced cardiac fatigue in this ultra-marathon. This correlation is intriguing considering the efficacy and potential risks of long-term ultra-endurance training are not yet understood clearly [165]. It has been hypothesized that repetitive strenuous exercise could lead to fibrous replacement of the myocardium potentially propagating arrhythmias [189]. We hypothesize that this finding is related to fitness, as we also found the degree of EICF correlated strongly with race pace. Thus, the individuals capable of running faster actually experienced less cardiac fatigue. This initially appears to contradict our intensity hypothesis; yet if we consider the terrain of the race course, it is possible that the cardiovascular strain of this race was not as severe for highly trained as compared to less trained individuals. Cardiac output and perfusion pressure are compromised in untrained individuals when both the metabolic and thermoregulatory demands are high [186]. Further, in a meta-analysis reviewing LV function with ultra-endurance exercise, one of the factors influencing a decline in systolic

function was poor training status [123]. In an analysis of performance trends in ultra-marathons, Hoffman et al. found an increase in recreational pursuits with the goal of finishing [18]. The small sample of individuals from our cohort who participated in VO_2max testing possessed low aerobic capacity relative to athletic norms [190]. Longitudinal studies are warranted to determine the nature of cardiac fatigue and training status.

3.6 LIMITATIONS

The following limitations must be considered in this investigation. First, the smaller sample size representing our female subjects increases the probability of making a Type II error. Recruitment of participants in field studies is limited to those runners who wish to participate. As ultra-endurance competitors are typically only 20% female [166] it becomes increasingly difficult to study females when there are so few available. After attrition, females represented 32% of our cohort. However, this is in proportion to the female racers participating in the event. In concert with the same recruitment issues, it is also not possible to recruit based on fitness. Our sample included the first place finisher completing the race in 28 h with our last finisher coming in at 41 h. As logistical issues limited the assessment of each participant's aerobic capacity, we are unable to determine if the men and women were equal with respect to relative VO_2max. As such cannot rule out the possible effect of fitness in the sex response to prolonged strenuous exercise [165].

Another consideration pertains to sodium. Sodium supplementation was quite prevalent in our sample of ultra-marathoners. In this field research we were unable to

control for the form, quantity, and frequency of sodium ingested. Sodium loading has been shown to increase plasma volume at rest and reduce physiological strain in warm conditions, significantly improving exercise capacity [191]. How sodium effects exercise-induced cardiac fatigue is not known and should be the focus of future investigations exploring exercise-induced cardiac fatigue.

3.7 CONCLUSIONS

The results of this investigation demonstrate that in response to an acute bout of prolonged strenuous exercise, adjustments in cardiac function are similar in men and women. Our results support the idea that cardiac fatigue occurs after prolonged strenuous exercise and advances our knowledge by showing that increased experience in ultra-endurance events may induce a cardioprotective effect. However, further research is required to assess the impact of duration and intensity of exercise on exercise-induced cardiac fatigue in both men and women.

Chapter 4: Effects of Sex and Training Status on the Cardiovascular Responses to an Acute Bout of High Intensity Interval Exercise

4.1 INTRODUCTION

The nature of exercise-induced cardiac fatigue following high-intensity interval exercise has yet to be determined. The transient impairments in ventricular function that are characteristic of exercise-induced cardiac fatigue [19] have been shown to result from various forms of prolonged exercise [139, 154, 159, 182, 192-198], the magnitude of which has been suggested to be duration dependant [161]. Recently, Scott and colleagues [21] reported reduced ventricular function following an acute bout of high intensity interval exercise in endurance-trained males, a phenomenon not shown in normally active men, supporting the role of exercise intensity in the development of exercise-induced cardiac fatigue.

High-intensity interval exercise has been shown to be an effective alternate to traditional endurance training, enhancing physiological, health and performance-related components [199]. Chronic adaptations to high-intensity interval training include increased aerobic and anaerobic fitness [7, 8], increased skeletal muscle capacity for fatty acid oxidation and glycolytic enzyme content [9, 15, 16], and increased insulin sensitivity [6, 12, 14]. Despite these numerous benefits, the safety of this strenuous form of exercise has yet to be determined [17]. Compared with inactive periods, there is an transient increased risk of sudden cardiac death during and immediately after vigorous exertion in apparently healthy individuals [22] and athletes [200]. Supramaximal exercise shifts sympathovagal balance more toward sympathetic dominance as compared to less intense

forms of exercise [201]. Furthermore, myocardial damage and cardiac fibrosis have been identified in marathon runners [202, 203] which may be a substrate for an increased susceptibility to arrhythmias in response to increased exercise-related catecholamine levels [162]. However, it should be highlighted that the risk of sudden cardiac death following high intensity exercise is markedly lower in individuals that engage in routine physical activity and exercise [24].

Catecholamines are elevated significantly in trained versus untrained males following intense exercise [204-207]. This is thought to be due to a greater oxygen demand and substrate degradation, stimulating higher sympathoadrenal activation in trained individuals [207]. Thus, differences in sympathetic activity between endurance-trained and normally active men following high-intensity exercise may be responsible for the presence of exercise-induced cardiac fatigue shown in those endurance-trained only [21]. However, there has been no evidence of a training effect on catecholamine response in women [208-211]. As such, it is unclear how high-intensity interval exercise would impact left ventricular function in females, endurance-trained and untrained. Accordingly, the purpose of this investigation was to evaluate the effects of high-intensity interval exercise on cardiac mechanics and plasma catecholamines in endurance-trained and normally active males and females. We hypothesized that endurance-trained males would be most susceptible to an acute bout of high-intensity interval exercise as evidence by greater alterations in left ventricular strain and twist mechanics, and higher catecholamine levels.

4.2 METHODS

4.2.1 Participants and Ethical Approval

We recruited 39 healthy, non-smoking men and women between the ages of 20 – 45 y (21 males, 18 females). 'Normally active' participants were considered active at anticipated population-based levels, but were not engaged in any formal endurance training program. Endurance-trained athletes required a VO_2max >55mL·kg·min^{-1} and participated in endurance training ≥ 10 hours/week for a minimum of two years. Maximal aerobic capacity was evaluated in our laboratory and training volume was determined through a questionnaire. Individuals were also pre-screened via the PAR-Q+ (Appendix A). Approval for this research was obtained via the Clinical Research Ethics Board at the University of British Columbia and conformed to the standards set by the latest revision of the Declaration of Helsinki.

4.2.2 Experimental Protocol

Participants visited the laboratory on two separate occasions. The first testing day involved the acquisition of baseline vascular measures (height, body mass, arterial compliance, and pulse wave velocity) and the determination of maximal aerobic power (VO_2max). The second testing day consisted of the exercise protocol. Cardiac function was assessed prior to and immediately following a high-intensity interval session. A minimum of 1 week separated the two test sessions. All participants were instructed to abstain from caffeine, exercise, and alcohol for 24 hours prior to testing.

4.2.3 Procedures and Analysis

***Anthropometrics, Pulse Wave Velocity, and Arterial Compliance*.** Height and body mass were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body surface area was calculated as BSA (m^2) = SQR RT ([Height(cm) x Weight(kg)]/ 3600) [170]. Baseline vascular measures were assessed following 10 minutes of supine rest. Participants were instrumented with an ECG and finger plethysmography secured to the middle finger, using a beat-by-beat blood pressure device (Finapres; Ohmeda Inc, Englewood, CO). Automated blood pressure measurements were obtained by brachial occlusion (BpTRU 100, Coquitlam, Canada) for calibration and collected in duplicate. In addition, pulse wave contours were collected at the carotid and femoral arteries using infrared photoelectric sensors (ADInstruments, Colorado Springs, CO). Continuous recordings were sent to a data acquisition system (PowerLab/16SP ML 795, ADInstruments, Colorado Springs, CO) and displayed using Chart (version 7.0, ADInstruments, Colorado Springs, CO). Pulse wave velocity was determined via post-collection analysis as previously described [212]. Briefly, a minimum of 30 consecutive cardiac cycles were averaged to calculate the foot-to-foot pulse transit time between the carotid artery and femoral artery. The shortest distances between the sites of pulse contour collection were measured to the nearest 0.5 cm using a standard measuring tape and this distance was divided by the corresponding pulse transit time in order to calculate pulse wave velocity.

Arterial compliance was measured non-invasively via applanation tonometry with the HDI CR-2000 (Hypertension Diagnostics, Eagan, Minnesota) for diastolic pulse contour analysis. This method of vascular assessment using waveform shape analysis is

considered optimal for measuring systemic compliance [213] and is based on a modified Windkessel model which allows for estimation of large (capacitive) artery and small (oscillatory) artery compliance. After stabilizing the wrist and maximizing signal strength, radial artery tonometry measurements were collected using the right wrist with the automated sphygmomanometer affixed to the upper left arm. Measurements were taken in duplicate with the average used for analysis.

VO_2max. An incremental bike test to exhaustion (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA) was used for the assessment of VO_2max. The protocol began at a workload of 80-100 watts and increased 25 watts every 2 minutes until volitional fatigue. Participants donned a face mask (Oro-nasal 7400 Vmask with Headgear, Hans Rudolph, Kansas, USA) for the collection of expired gases analyzed by metabolic cart (Medisoft Ergocard, Sorinnes, Belgium). In addition, heart rate and arterial haemoglobin saturation were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to the participant's right index finger.

Echocardiography. Echocardiographic assessments were performed by a trained clinical sonographer using a portable ultrasound unit *(Vivid i,* GE Medical Systems, Israel) with simultaneous ECG and a 2.5-MHz transducer. Participants were positioned in the left lateral decubitus position for imaging. Apical two- and four-chamber views were acquired for the assessment of left ventricular (LV) volumes, LV longitudinal strain and strain rate, in addition to transmitral pulsed Doppler flow velocities and tissue Doppler mitral annular velocities. Optimal parasternal short axis views obtained at the base (mitral valve) and apex (before apical obliteration) were acquired for the assessment of left ventricular rotation, rotation rate, twist, circumferential and radial strain, and strain

rate. All strain imaging was acquired at high frame rates (80-90 frames per second). Ventricular volumes and diameters were analyzed offline (EchoPAC, GE Healthcare, v. 110.1.1) in accordance with the recommendations of the American Society of Echocardiography [175]. Left ventricular mass was determined using the formula: LV Mass (g) = 0.8 (1.04 ([LVIDD + PWTD + IVSTD]3- [LVIDD]3))+ 0.6 [177]. End-diastolic volume (EDV) and end-systolic volume (ESV) using Simpson's bi-plane method for which 3 consecutive beats were measured and analyzed. Stroke volume (SV) was calculated by EDV-ESV. Cardiac output (CO) was calculated as SV x HR. Ejection fraction (EF) was calculated as a percentage of EDV. Fractional shortening (FS) was calculated from ventricular diameters using the parasternal long axis window and expressed as a percent. Total peripheral resistance (TPR) was derived from dividing CO into MAP. LV wall stress was determined non-invasively as calculated as 0.133 x P x R/2T x (1 + T/2R), where P is systolic blood pressure, R is left ventricular end-systolic diameter, and T is left ventricular systolic posterior wall thickness [178]. Speckle tracking echocardiography was used to assess all of the LV strain, rotation and twist parameters using EchoPAC. Twist and twist velocity were obtained by subtracting apical from basal rotation and rotation rates [214]. Arterial elastance was calculated as E_A = ESP/SV where ESP = 0.9 x SBP. Ventricular elastance was calculated via the formula E_{LV} = ESP/ESV. Arterial-ventricular coupling was then determined as the ratio of arterial and ventricular elastance (E_A/E_{LV}).

High Intensity Interval Exercise. An incremental bike test to exhaustion (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA) was used for the assessment of VO_2max. The protocol began at a workload of 80-100 watts and increased 25 watts every 2 minutes

until volitional fatigue. Participants donned a face mask (Oro-nasal 7400 Vmask with Headgear, Hans Rudolph, Kansas, USA) for the collection of expired gases analyzed by metabolic cart (Medisoft Ergocard, Sorinnes, Belgium). In addition, heart rate and arterial haemoglobin saturation were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to the participant's right index finger.

Hydration Assessment. A urine sample was collected prior to the interval session. A drop of urine was analyzed for urine specific gravity (Atago Pocket Refractometer, PAL-10S, Japan), which has been shown to be a valid means of assessing hydration status [215]. A result <1.02 served as the threshold of hydration status acceptable to commence testing [216, 217]. Once adequate hydration was verified, a measure of body mass was recorded to the nearest 0.1 kg using a digital scale (Seca, Birmingham, UK) and measured again post-exercise.

Blood Sampling. Pre- and post-exercise blood samples (6 mL each) were drawn from a medial cubital vein using a needle (23-gauge butterfly) and Vacutainer system to EDTA tube. The blood was centrifuged and to remove plasma. Serum samples were stored at -80°C until analysis. Epinephrine and norepinephrine concentrations were derived from immunoassay (TriCat Elisa RE59395, IBL Diagnostics, Hamburg, Germany).

4.3 STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation. Baseline characteristics between sex and training status were assessed using a 2-way ANOVA. The effect of exercise on dependent variables were analyzed using a mixed-model ANOVA with between (sex; training status) and repeated (condition) factors. Pearson's correlation analysis was used

to find associations between significant factors. Significance for all tests was set *a priori* at $p<0.05$. All analyses were performed using SPSS software (version 20.0; SPSS IBM, Chicago, IL). Results are reported as mean ± SD.

4.4 RESULTS

4.4.1 Participant Characteristics

The endurance-trained (ET) group represented 20 category 1 and 2 competitive cyclists (9 F) who reported an average training frequency and volume of 5.2 ± 1.0 days and 231.0 ± 129.3 km of training per week. The normally active (NA) group consisted of 19 individuals (9 F) who reported moderate levels of physical activity (i.e., yoga, resistance training, recreational level soccer) 3.9 ± 1.5 d/wk. Participant characteristics including vascular assessments are presented in Table 4.1. Sex differences ($p<0.05$) were found for height, body mass, arterial compliance, left ventricular mass (LVM), stroke volume, and cardiac output (indexed for body size). Endurance-trained differed from NA participants for VO_2max, heart rate, large artery compliance, left ventricular mass, stroke volume, and cardiac output ($p<0.05$).

4.4.2 Hydration, Catecholamines and Haemodynamic Parameters

Prior to the interval session, urine specific gravity was within the range considered to represent adequate hydration [215] averaging 1.012 ± 0.01. Body mass decreased 0.27 ± 0.47 kg following exercise and this response was unaffected by sex or training status. Epinephrine baseline values were not different by group (0.74 ± 0.18 $nmol \cdot l^{-1}$); but increased to a greater extent in ET than NA (3.38 ± 0.57 $nmol \cdot l^{-1}$ and 2.87 ± 0.54, respectively; $p=0.016$). Norepinephrine increased from 2.56 ± 0.50 to 22.90 ± 4.43

$nmol \cdot l^{-1}$ ($p<0.001$) and was not different between groups. Heart rate was significantly increased post-exercise (57.0 ± 9.0 to 76.7 ± 10.5 bpm; $p<0.001$) as was cardiac index (CI; 2.65 ± 0.75 to 2.91 ± 0.66 $L \cdot min^{-1}/m^2$; $p=0.031$). The ET displayed greater reductions in absolute stroke volume (-17.9 ± 15.2%) compared to NA (-14.6 ± 19.4%; $p=0.031$) as well as stroke volume indexed to body size (SVI; ET, -16.6 ± 12.9; NA, -15.3 ± 19.9, $p=0.024$). There was also an effect of sex for SVI as men experienced greater reductions post-exercise than women (Men: 51.3±12.9 to 39.7±9.0 mL/m^2; Women: 41.8±9.2 to 36.6±7.1 mL/m^2, $p=0.028$).

4.4.3 Cardiac Function and Arterial-Ventricular Coupling

Indices of systolic and diastolic function were reduced post-exercise (Table 4.2). An interaction was only present for early diastolic filling (E), whereby NA began with higher baseline E but post-exercise, displayed lower early diastolic filling than ET. Longitudinal, circumferential, and radial strain and strain rate, in addition to rotation and twist parameters (Table 4.3) were similar regardless of sex or training status, except for longitudinal diastolic strain rate. Diastolic longitudinal strain rate was reduced to a greater extent post-exercise in men compared with women ($p=0.011$; Figure 4.1). Time to peak twist and time to peak untwisting rate were delayed post-exercise ($p<0.001$ and $p=0.002$, respectively; Figure 4.2). A significant association was found for baseline pulse wave velocity and alterations in cardiac twist with exercise (Figure 4.3). Individuals with higher pulse wave velocity (greater arterial stiffness) were less likely to increase twist following exercise. No correlations were found for changes in heart rate, strain rate,

diastolic filling, pressures, or volumes. In addition, changes in catecholamines were not associated with the any cardiac parameters.

Ventricular-vascular coupling results showed endurance-trained individuals displayed lower E_A and E_{LV} than NA, and women had higher E_{LV} than men (Figure 4.4). An interaction was revealed between sex and time for E_A (p=0.034) where arterial elastance increased in men post-exercise and plateaued in women. A strong correlation was observed for the change in arterial elastance and the change in stroke volume index (r=0.875, p<0.001) indicating the greater the decrease in stroke volume, the greater the increase in arterial elastance.

Table 4.1 Participant Characteristics and Baseline Cardiovascular Measures

	Males		Females		*p* value	
	NA *n=10*	ET *n=11*	NA *n=9*	ET *n=9*	sex	group
Age, *y*	28.50 ± 5.90	33.00 ± 5.60	29.40 ± 4.60	29.10 ± 4.30	0.468	0.170
Height, *cm*	179.80 ± 6.50	178.50 ± 8.00	164.10 ± 8.60	167.90 ± 4.20	**0.001**	0.569
Body Mass, *kg*	77.00 ± 7.40	74.50 ± 8.50	62.30 ± 13.30	59.30 ± 5.70	**0.001**	0.355
VO_2max, $ml \cdot kg \cdot min^{-1}$	46.90 ± 5.30	59.60 ± 4.10	44.80 ± 4.50	56.40 ± 3.90	0.081	**0.001**
SBP, *mmHg*	112.60 ± 6.60	109.20 ± 10.40	106.00 ± 4.50	108.90 ± 4.30	0.136	0.907
DBP, *mmHg*	66.20 ± 5.60	66.70 ± 7.40	64.70 ± 4.60	66.40 ± 6.20	0.648	0.562
HR, *bpm*	56.50 ± 4.70	50.90 ± 6.50	58.00 ± 7.90	53.30 ± 7.40	0.383	**0.023**
PWV, *cm/s*	557.50 ± 49.50	567.00 ± 156.10	629.30 ± 145.30	557.60 ± 136.10	0.584	0.430
LAC, $ml \cdot mmHg^{\cdot 10}$	18.50 ± 3.10	23.60 ± 7.10	17.90 ± 3.60	20.00 ± 4.20	**0.028**	**0.028**
SAC, $ml \cdot mmHg^{\cdot 10}$	9.90 ± 2.30	12.20 ± 5.00	8.90 ± 3.10	8.40 ± 2.00	**0.036**	0.400
LVM/BSA, g/m^2	101.20 ± 15.20	122.10 ± 20.90	78.40 ± 11.10	105.80 ± 11.80	**0.001**	**0.001**
SVI, mL/m^2	43.40 ± 12.10	58.50 ± 9.00	37.30 ± 8.60	46.30 ± 7.90	**0.006**	**0.001**
CI, $L \cdot min^{-1}/m^2$	2.60 ± 0.83	3.20 ± 0.57	2.10 ± 0.53	2.60 ± 0.71	**0.019**	**0.019**

Abbreviations: NA=normally active; ET=endurance-trained; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; PWV=pulse wave velocity; LAC=large artery compliance; SAC=small artery compliance; LVM=left ventricular mass; BSA=body surface area; SVI=stroke volume index; CI=cardiac index
The effects of sex and training status on participant characteristics were analyzed by unadjusted general linear models.
BOLD *p* values denotes statistically significant

Table 4.2 Effects of Exercise on Systolic and Diastolic Function

	Males				Females			
	NA		ET		NA		ET	
Systolic	Baseline	Post-Exercise	Baseline	Post-Exercise	Baseline	Post-Exercise	Baseline	Post-Exercise
EF, %	59.0 ± 7.6	55.0 ± 4.5	65.4 ± 9.7	61.6 ± 7.7	62.6 ± 9.2	63.3 ± 4.1	61.2 ± 7.7	60.3 ± 6.4
FS, % *	39.1 ± 6.3	36.3 ± 7.2	37.3 ± 8.2	33.7 ± 8.9	34.8 ± 5.7	36.4 ± 5.0	36.5 ± 4.8	30.9 ± 6.2
Wall Stress *	136.2 ± 19.9	117.9 ± 28.9	136.5 ± 55.2	116.9 ± 47.1	76.3 ± 23.0	60.3 ± 15.8	99.6 ± 24.9	99.3 ± 32.7
SBP/ESV	2.08 ± 0.64	2.14 ± 0.56	2.08 ± 0.81	1.98 ± 0.73	2.91 ± 1.08	3.28 ± 0.99	2.31 ± 0.88	2.31 ± 0.65
EF/EDV *	0.43 ± 0.10	0.48 ± 0.10	0.45 ± 0.12	0.49 ± 0.17	0.65 ± 0.20	0.78 ± 0.20	0.51 ± 0.15	0.54 ± 0.10
E' septal, *m/s**	0.14 ± 0.02	0.11 ± 0.02	0.12 ± 0.02	0.11 ± 0.02	0.13 ± 0.02	0.12 ± 0.02	0.13 ± 0.02	0.13 ± 0.01
E' lateral, *m/s**	0.19 ± 0.02	0.16 ± 0.04	0.17 ± 0.03	0.15 ± 0.03	0.18 ± 0.03	0.18 ± 0.02	0.17 ± 0.02	0.15 ± 0.02
E' RV, *m/s*	0.17 ± 0.02	0.15 ± 0.03	0.15 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	0.15 ± 0.06
Diastolic								
E, *m/s* ¥	0.83 ± 0.13	0.70 ± 0.09	0.81 ± 0.12	0.72 ± 0.12	0.87 ± 0.16	0.75 ± 0.14	0.82 ± 0.14	0.77 ± 0.11
DecT, *ms*	242.2 ± 57.3	227.7 ± 22.7	219.4 ± 58.9	220.1 ± 46.4	210.9 ± 23.1	200.9 ± 33.5	208.7 ± 47.2	205.5 ± 27.3
IVRT, *ms* *	76.7 ± 7.9	67.8 ± 10.6	77.9 ± 10.6	63.5 ± 8.0	67.8 ± 9.8	59.6 ± 10.4	73.9 ± 11.0	65.1 ± 8.8
E/E' septal	6.05 ± 1.20	6.42 ± 1.08	6.85 ± 1.34	6.91 ± 1.71	6.80 ± 1.42	6.27 ± 0.86	6.24 ± 1.39	6.14 ± 0.90
E/E' lateral	4.44 ± 0.80	4.47 ± 1.09	4.80 ± 0.97	4.81 ± 1.08	4.89 ± 1.10	4.32 ± 0.85	4.82 ± 0.83	5.12 ± 0.95

Abbreviations: EF=ejection fraction; FS=fractional shortening; SBP=systolic blood pressure; ESV=end-systolic volume; EDV=end diastolic volume; E=early diastolic filling; DecT=deceleration time; IVRT=isovolumetric relaxation time; E'=mitral annular tissue velocity; RV=right ventricle

Effect of exercise obtained using general linear models adjusted for sex and training status.

* $p<0.05$ from baseline; ¥ training status by time interaction

Table 4.3 Peak Left Ventricular Mechanics and Rest and During Exercise

	Males				Females			
	NA		ET		NA		ET	
	Rest	Post-Exercise	Rest	Post-Exercise	Rest	Post-Exercise	Rest	Post-Exercise
Peak (systole)								
Basal Rotation (°)	-11.71 ± 21.27	-5.85 ± 2.20	-5.76 ± 1.68	-6.12 ± 2.71	-6.75 ± 3.21	-7.11 ± 2.71	5.21 ± 2.69	-6.11 ± 2.09
Apical Rotation (°)	12.94 ± 5.16	15.01 ± 2.79	12.20 ± 3.93	11.69 ± 4.55	11.80 ± 5.91	12.63 ± 5.64	11.45 ± 4.86	12.21 ± 5.32
Twist (°)	17.79 ± 6.15	19.82 ± 3.26	17.36 ± 4.94	16.65 ± 7.13	17.77 ± 8.06	18.74 ± 6.85	15.88 ± 6.27	16.94 ± 6.29
Time to Peak Twist (% sys) *	94.30 ± 9.39	109.83 ± 11.23	89.30 ± 5.72	97.01 ± 9.95	94.27 ± 14.24	105.71 ± 13.79	98.14 ± 26.26	103.28 ± 13.02
Longitudinal Strain (%) *	-18.95 ± 2.90	-16.79 ± 2.41	-18.51 ± 2.06	-16.47 ± 1.79	-20.13 ± 2.84	-18.80 ± 1.61	-18.85 ± 2.14	-17.77 ± 2.15
Radial Strain (%)								
Basal Level	40.95 ± 10.33	28.74 ± 12.60	56.82 ± 13.71	43.10 ± 19.25	45.70 ± 35.32	38.66 ± 11.47	31.97 ± 20.13	29.99 ± 11.08
Apical Level	10.37 ± 8.96	13.69 ± 9.98	10.96 ± 11.90	15.20 ± 9.52	17.91 ±18.40	16.95 ± 17.99	11.41 ± 8.26	13.01 ± 8.98
Circumferential Strain (%)								
Basal Level	-16.33 ± 5.29	-13.63 ± 3.21	-16.60 ± 4.25	-16.06 ± 4.40	-13.72 ± 3.55	-14.03 ± 3.02	-13.29 ± 2.86	-14.33 ± 1.40
Apical Level	-26.39 ± 10.23	-23.05 ± 10.39	-25.92 ± 10.72	-26.59 ± 6.83	-26.94 ± 6.37	-25.64 ± 7.02	-28.82 ± 3.62	-26.58 ± 6.32
Basal Rot. Velocity ($°\cdot s^{-1}$)	-68.54 ± 11.81	-65.83 ± 27.68	-53.43 ± 21.72	-62.75 ± 21.67	-64.34 ± 19.63	-71.60 ± 22.12	-54.80 ± 16.89	-63.14 ± 12.76
Apical Rot. Velocity ($°\cdot s^{-1}$)*	72.06 ± 17.85	94.52 ± 27.33	54.79 ± 16.43	68.02 ± 19.68	63.90 ± 23.34	75.10 ± 18.45	74.51 ± 32.95	78.18 ± 43.25
Twist Velocity ($°\cdot s^{-1}$)	111.13 ± 31.88	121.77 ± 26.42	101.63 ± 21.39	101.23 ± 45.50	119.81 ± 36.78	128.70 ± 32.98	96.89 ± 26.30	102.90 ± 36.07
Strain Rate (s^{-1})								
Longitudinal	-1.01 ± 0.17	-0.96 ± 0.16	-0.89 ± 0.11	-0.89 ± 0.10	-1.08 ± 0.18	-1.05 ± 0.12	-0.92 ± 0.08	-0.91 ± 0.09
Radial Basal	1.90 ± 0.84	1.93 ± 1.25	1.53 ± 0.20	1.58 ± 0.26	1.66 ± 0.63	1.49 ± 0.30	1.70 ± 0.82	1.54 ± 0.27
Radial Apical*	1.03 ± 0.46	1.40 ± 0.65	1.10 ± 0.57	1.30 ± 0.46	1.07 ± 0.52	1.36 ± 0.60	0.82 ± 0.23	1.01 ± 0.45
Circumferential Basal	-1.04 ± 0.31	-1.01 ± 0.23	-0.98 ± 0.17	-1.00 ± 0.23	-0.86 ± 0.17	-0.98 ± 0.19	-0.81 ± 0.18	-0.97 ± 0.11
Circumferential Apical	-2.02 ± 0.51	-1.77 ± 0.57	-1.78 ± 0.54	-1.82 ± 0.68	-1.67 ± 0.53	-1.90 ± 0.68	-1.72 ± 0.34	-1.71 ± 0.60

	MALES				FEMALES			
	NA		ET		NA		ET	
	Rest	Post-Exercise	Rest	Post-Exercise	Rest	Post-Exercise	Rest	Post-Exercise
Peak (diastole)								
Basal Rot. Velocity ($°\cdot s^{-1}$)	65.02 ± 22.61	66.18 ± 12.60	56.82 ± 17.57	72.74 ± 21.89	71.41 ± 19.48	76.14 ± 17.32	67.04 ± 30.63	75.13 ± 18.69
Apical Rot. Velocity ($°\cdot s^{-1}$)*	-85.57 ± 30.71	-108.57± 30.40	-70.56 ± 25.23	-89.39 ± 23.81	-79.92 ± 47.44	-106.38± 49.76	-75.03 ± 20.46	-84.71 ± 40.54
Untwisting Velocity ($°\cdot s^{-1}$)	-139.86± 44.45	-128.05± 23.09	-108.71± 32.99	-120.22± 41.61	-112.19± 44.75	-135.61± 57.85	-123.98± 41.94	-130.12± 62.00
Strain Rate (s^{-1})								
Longitudinal ǂ	1.58 ± 0.14	1.32 ± 0.29	1.36 ± 0.17	1.24 ± 0.17	1.69 ± 0.28	1.67 ± 0.28	1.56 ± 0.21	1.59 ± 0.25
Radial Basal	-1.58 ± 0.39	-1.66 ± 0.51	-1.48 ± 0.44	-1.65 ± 0.41	-1.55 ± 0.57	-1.59 ± 0.64	-1.50 ± 0.35	-1.62 ± 0.66
Radial Apical	-1.36 ± 0.70	-1.96 ± 1.34	-1.24 ± 0.53	-1.73 ± 1.09	-1.83 ± 1.12	-1.77 ± 0.70	-1.75 ± 1.09	-1.64 ± 0.81
Circumferential Basal *	1.16 ± 0.53	1.08 ± 0.35	1.11 ± 0.29	1.42 ± 0.35	1.11 ± 0.39	1.38 ± 0.35	1.05 ± 0.26	1.24 ± 0.19
Circumferential Apical	2.72 ± 0.96	2.32 ± 1.40	2.94 ± 1.08	3.15 ± 1.3	2.80 ± 0.77	3.27 ± 1.27	3.11 ± 0.84	3.15 ± 0.85

Effect of exercise obtained using general linear models adjusted for sex and training status.
* $p<0.05$ from baseline; ǂ $p<0.05$ sex by time interaction

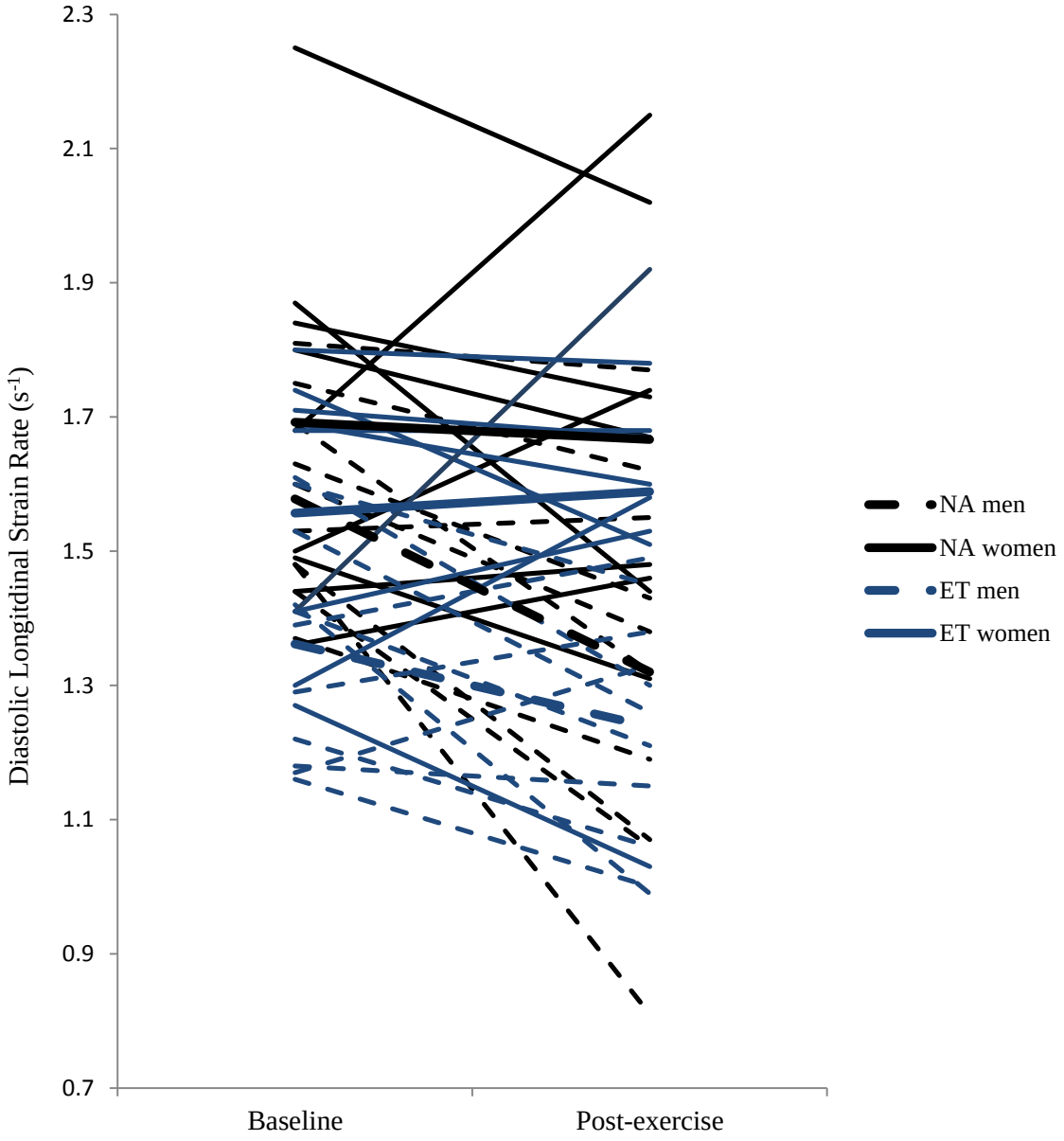

Figure 4.1 Effect of Exercise on Diastolic Longitudinal Strain Rate.

Diastolic longitudinal strain rate was reduced post-exercise in men, but not women (p=0.011) regardless of training status.

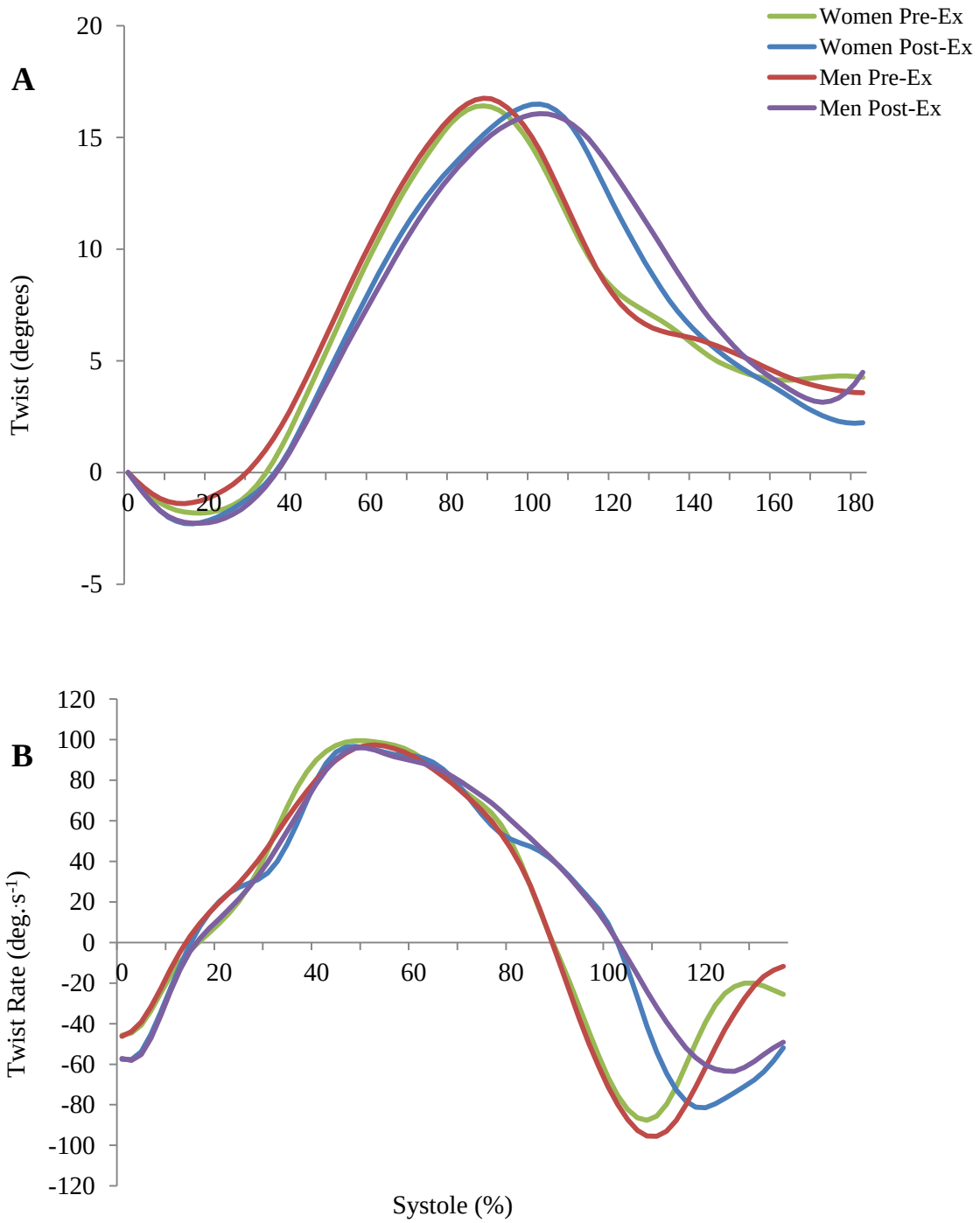

Figure 4.2 Time Course of Left Ventricular Twist and Twist Rates.

Time to peak twist (A) was delayed post-exercise ($p<0.001$) and was not different based on sex or training status. Time to peak twist rate (B) was not significantly different from baseline, however, time to peak untwist rate (B) was significantly delayed ($p=0.002$) but not this response was not different among groups.

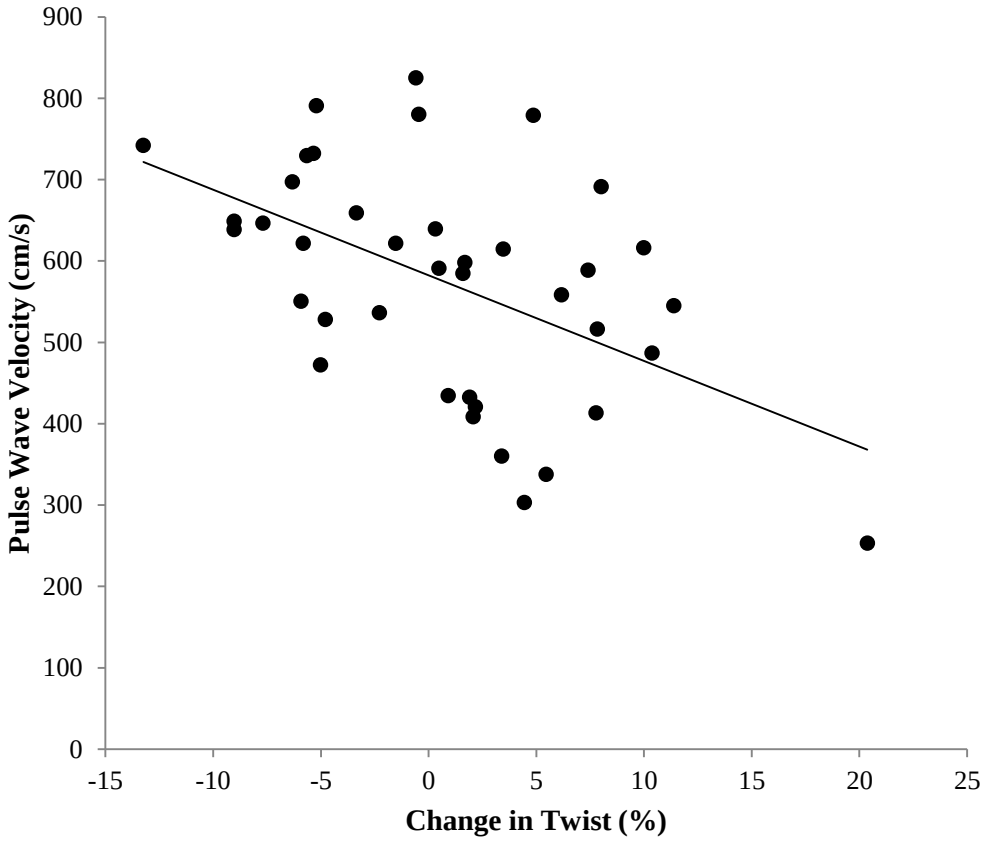

Figure 4.3 Relationship of Baseline Pulse Wave Velocity to Exercise-Induced Change in Left Ventricular Twist

Individuals with higher pulse wave velocity (greater arterial stiffness) were less likely to increase twist following exercise.
Pearson r=-0.51, p=0.001

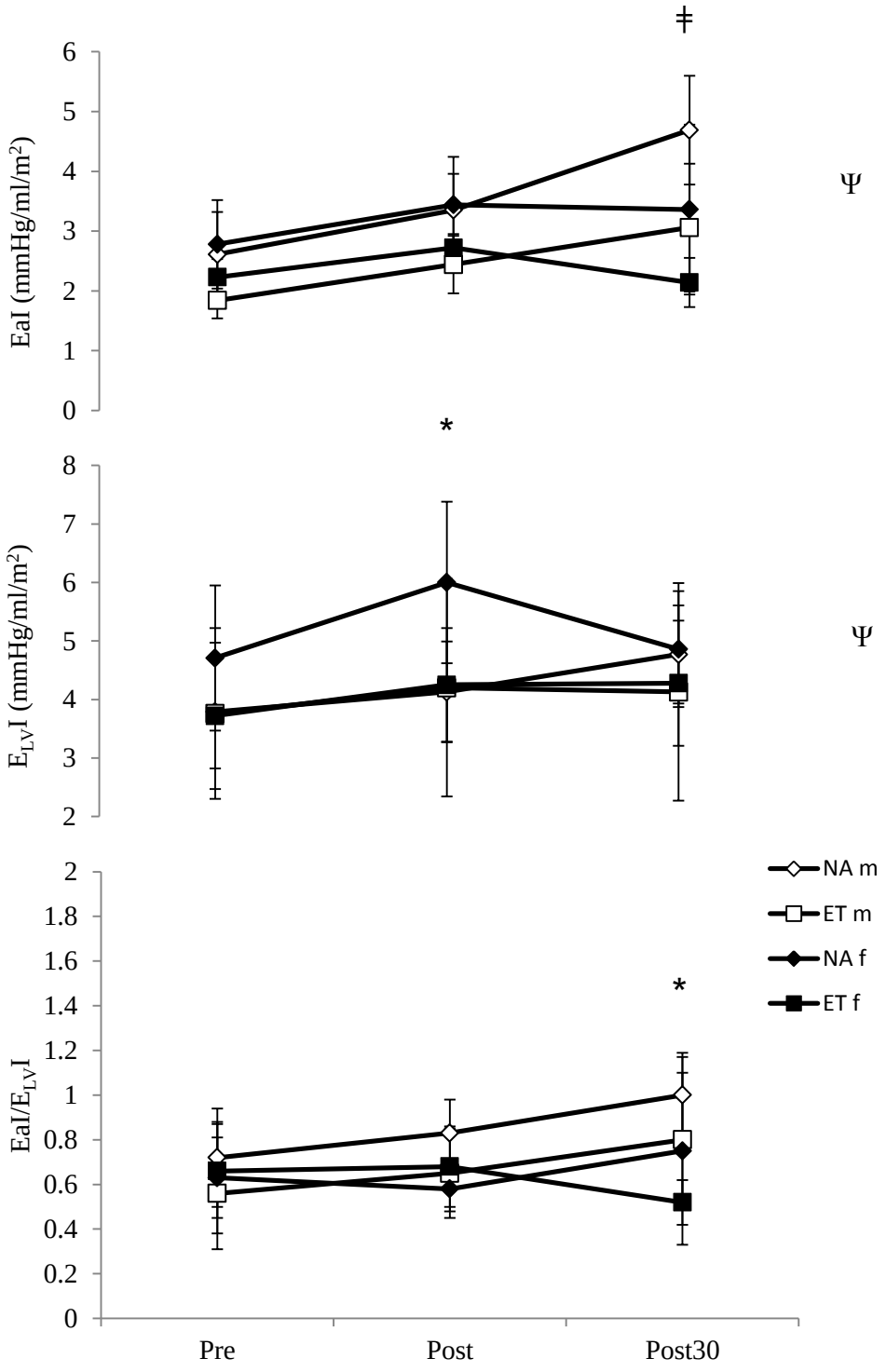

Figure 4.4 Arterial Ventricular Coupling Indexed to Body Surface Area

Abbreviations: Pre = baseline; Post=immediately post-exercise; Post30=30 min post-exercise

ǂ $p<0.05$ condition by sex; * $p<0.05$ from baseline; $p<0.05$ Ψ between group

4.4 DISCUSSION

The aim of this investigation was to evaluate the effects of sex and training status on cardiovascular function following high-intensity interval exercise. Our results show that exercise-induced cardiac fatigue is not limited to prolonged exercise, as both systolic and diastolic function were depressed following acute high-intensity interval exercise. Cardiac mechanics were similar between all four groups with the exception of altered diastolic longitudinal strain rate and ventricular-vascular coupling in males compared with females. Aside from significantly different haemodynamics, only early diastolic filling, differentiated training status.

Alterations in systolic and diastolic parameters illustrate the impact of high-intensity interval exercise on the heart. Prior work assessing very short duration, supra-maximal efforts such as the Wingate [218], and strenuous exercise of six to eight minutes failed to show any LV functional decline [194, 219]. It is plausible that some intensity-duration threshold is required to alter cardiac dynamics to which previous work did not meet.

Similar to other forms of strenuous exercise [123], we found reduced function in traditional systolic indices such as fractional shortening and wall stress, in addition to novel strain and twist mechanics. Specifically, we showed reductions in peak longitudinal strain and peak systolic tissue velocities, which are indicative of altered myocardial contractility [220, 221]. Furthermore, the delayed twist mechanics occurring during a shortened isolvolumetric relaxation phase, likely impacted diastolic suction [181] as evidenced by reduced early diastolic filling. These reductions in strain, tissue velocities and delayed twist may reflect altered intrinsic myocardial relaxation properties as a result of fatigue-induced impaired metabolism within cardiomyocytes [181, 182]. Thus, our data clearly shows that high-intensity interval exercise is a

sufficient stimulus to cause impairment of both relaxation and contraction of the left ventricle, as shown in clinical diastolic dysfunction [50].

We found a novel association of baseline arterial stiffness and change in twist mechanics with high-intensity exercise. Pulse wave velocity is established as the gold standard for estimating vascular stiffness [213]. An elastic vascular system reduces cardiac demand [222]. As such, this relationship infers that those individuals with lower arterial stiffness were better able to augment cardiac twist in the face of increased demands. An inability to increase twist during exercise has been shown in several clinical populations to also be related to increased arterial stiffness [223]. Our study, using a diverse yet healthy population, is the first to show this relationship directly, and supports the emerging literature showing that ventricular-vascular interactions are a crucial mediator of cardiac function [224].

Arterial-ventricular coupling is a common technique for relating the LV and arterial system, and is expressed as a ratio of arterial and ventricular elastance (E_A/E_{LV}). At rest, normal values representing optimal function range from 0.7 to 1.0 [225]. Following exercise, E_A/E_{LV} increased similarly in all groups, resulting from a reduction in ventricular elastance in combination with a rise in arterial elastance, while remaining in the optimal range. Furthermore, an interaction of sex and arterial elastance was found. In recovery from exercise, the men in our study demonstrated an increase in E_A that was not observed in the women. The arterial component of this coupling is said to parallel increases in arterial stiffness [226, 227] and is derived by the ratio of end-systolic pressure to stroke volume. As end-systolic pressure did not differ between men and women, the change in stroke volume was the mediator of this effect. A greater sympathetic vasoconstrictor outflow opposing peripheral vasodilatation in men may be responsible as cardiac output was maintained in both groups despite significantly larger decrements in stroke volume in the men

[228]. Sympathetically mediated increases in arterial elastance could raise myocardial oxygen consumption for a given stroke volume [229].

With respect to the ventricular component, women across all ages have been shown to have a higher E_{LV} than age-matched males [230] suggesting this higher LV contractility may allow women to tolerate cardiovascular stress better than men [82]. Our women not only displayed higher E_{LV}, they also showed less alteration in this component over the intervention. Given the women also presented a higher EF for a given EDV, together these findings are indicative of enhanced systolic function.

This investigation is the first to assess sex differences in cardiac mechanics with high-intensity interval exercise. Only longitudinal diastolic strain rate differed between men and women, with reductions post-exercise experienced by the males whereas females did not change from baseline. Ventricular dysfunction has been suggested to begin in the longitudinal plane while circumferential and radial compensations remain to preserve ejection fraction in individuals with cardiovascular risk factors [231]. Thus, while this parameter provides an indication that males could exhibit cardiac mechanical limitations compared with women in response to strenuous exercise, further evidence is required in order to ascertain its validity.

With respect to training status, we found endurance-trained participants displayed greater alterations in haemodynamics than untrained, typical of chronic endurance training. Early diastolic filling was reduced to a lesser degree in endurance-trained individuals following exercise, likely a reflection of superior diastolic suction to that of their normally active counterparts [30]. The greater elevations in epinephrine following exercise in endurance-trained participants support previous work reporting higher catecholamine concentrations in trained individuals following high-intensity exercise [145]. However, these changes were not associated

with any cardiac function measures. By contrast to the findings of Scott et al. [21] we did not find ventricular responses between the groups to differ between training groups, with the aforementioned greater reduction in early diastolic filling. Both investigations employed a similar protocol and population, thus the nature of the discrepant findings are unclear. Certain parameters of cardiac mechanics may be quite variable between individuals and this may be a factor worth consideration.

4.5 LIMITATIONS

In this study our objective was to assess cardiac function as close to the cessation of exercise, as possible. We did not attempt to image the heart during exercise as obtaining quality images at such high work rates are exceptionally difficult. While we accomplished our objective in this regard we did not include a follow-up assessment (with the exception of ventricular-vascular coupling) by which the persistence of altered ventricular function could be determined. Recently, Goodman et al. [232] demonstrated a preserved left ventricular function during prolonged strenuous exercise that became significantly reduced in the recovery period. Thus, it is possible that further ventricular alterations may have occurred given a longer recovery time. The work of Scott et al. [21] included two post-exercise cardiac assessments and found ventricular dysfunction to persist for certain measures at the second assessment (approximately 38 minutes post-exercise) however, the authors did not detect any further depressions. Thus, we do not expect further evidence of cardiac fatigue would have been realized with follow-up assessments in our study.

4.6 CONCLUSIONS

Our results show that high-intensity interval exercise can provoke cardiac fatigue in healthy individuals. Our findings showing an association of arterial stiffness and twist mechanics, and the sex differences in arterial-ventricular coupling are novel and deserve further study to ascertain their role in the development of cardiovascular disease risk, exercise tolerance, and performance. In addition, future research pertaining to cardiac function and strenuous exercise should involve sex comparisons to delineate the findings thus far.

Chapter 5: Cardiac and Autonomic Function in Recovery from High-Intensity Interval Exercise

5.1 INTRODUCTION

The use of non-invasive autonomic indices such as heart rate variability and baroreflex sensitivity have been shown to be strong prognostic indicators for the development of cardiovascular disease [233-235] and risk of ventricular fibrillation and cardiac events [38, 236]. Endurance training and female sex have both been shown to affect positively resting cardiac autonomic modulation as evidenced by greater cardiac parasympathetic activity at rest, a trait associated with a reduced risk of sudden cardiac death [62-66, 237, 238]. These factors positively influence blood pressure in females, mediated by changes in baroreflex sensitivity [239]. Acute exercise results in transient reductions in autonomic function, to which exercise intensity exacerbates the response [240]. Reductions in cardiac vagal tone with strenuous exercise have been proposed to be associated with the pathogenesis of ventricular arrhythmias and sudden cardiac death [22, 241]. However, the improved autonomic profile in females does not appear to mitigate the acute exercise response. Athletes have demonstrated higher sympathoadrenal activation with intense exercise when compared with untrained individuals [242] and it has also been shown recently that following a single bout of supramaximal exercise, women experienced greater shifts to sympathetic dominance than men despite a more favourable initial resting profile [66]. Exercise presents a significant orthostatic stressor due to venous pooling in the legs [243] and persistent vasodilatation related to altered sympathetic outflow and transduction of sympathetic activity to vascular resistance [244]. Thus, it is plausible that following strenuous exercise, an increased cardiac sympathetic drive is required to maintain

blood pressure in these individuals. Notably, females and endurance trained individuals have demonstrated reduced tolerance to an orthostatic challenge [171, 245-247].

Lower body negative pressure (LBNP) is a gravitational stress that alters loading conditions to the heart [248] and provides a unique stimulus whereby sympathetic vasomotor tone is drastically increased [249]. Cardiac baroreflex sensitivity is reduced as lower body negative pressure unloads the baroreceptors [250, 251]. Additionally, baroreflex sensitivity is markedly reduced during dynamic exercise due to resetting of the baroreceptors allowing the baroreflex function to move to a new operational point [252, 253]. Thus, when combining exercise with a gravitational challenge the onset of orthostatic intolerance can be expedited [254] and as such, greater autonomic compensation maybe required [255]. Endurance trained individuals demonstrate accelerated heart rate recovery post-exercise than untrained [256-259] indicating a more rapid reversal of sympathetic activation. To investigate this, we sought to evaluate the effects of training and sex on the autonomic responses to combined strenuous exercise and LBNP. We hypothesized that as a result of high intensity interval exercise: 1) greater reductions in autonomic function would occur in endurance-trained individuals following exercise, yet they would display superior recovery during post-exercise lower body negative pressure, and 2) women would display greater baseline autonomic function, greater post-exercise reductions, and a more rapid recovery to baseline than men.

5.2 METHODS

5.2.1 Participants and Ethical Approval

We recruited thirty-three (13 F) healthy individuals, normally active or endurance-trained, between the ages of 20 and 45 y. Normally active participants were considered physically active

but were not engaged in any formal endurance training program. Endurance-trained athletes required a VO_2max >55mL·kg·min^{-1} and participated in endurance training ≥ 10 hours/week for a minimum of two years. All were screened using the new Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) to determine eligibility to participate: free from chronic disease and no contraindications to exercise. Ethical approval was obtained through the University of British Columbia Clinical Ethics Board in exact accordance with the *Declaration of Helsinki*, and all participants provided written informed consent.

5.2.2 Experimental Protocol

Participants participated in two days of testing. On the first day participants were assessed for height, body mass and aerobic capacity (VO_2max). On the second day of testing (occurring a minimum of one week later) the following assessments were conducted: 1) baseline cardiovascular assessments, 2) pre-exercise autonomic and cardiac assessments during graded LBNP, 3) high-intensity interval exercise on a cycle ergometer, and 4) post-exercise autonomic and cardiac assessments during LBNP. Following baseline assessments, the LBNP challenge was initiated at -20 mmHg below atmospheric pressure for five minutes. Subsequent five-minute stages were performed at -40 and -60 mm Hg. The negative pressure was terminated if the participant encountered symptoms of presyncope (drop in systolic blood pressure of 15 mmHg, and a drop in heart rate of 15 beats per minute, dizzy, lightheaded, or nauseous) or at participant request. Beat-by-beat blood pressure, ECG, and echocardiographic assessments were established during each stage. Individual responses to LBNP, including heart rate variability responses, have been shown to be highly reproducible within the same individual [237, 238]. A 30-minute

washout period preceded the high-intensity interval session and repeat LBNP pressure was subsequently performed. A schematic of the protocol can be found in Appendix C.

5.2.3 Procedures

VO_2max. Height and body mass was measured to the nearest 0.1 cm and 0.1 kg, respectively. An incremental bike test to exhaustion (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA) was used for the assessment of maximal aerobic power (VO_2max). The protocol began at a workload of 80-100 watts and increased 25 watts every 2 minutes until volitional fatigue. Participants donned a face mask (Oro-nasal 7400 Vmask with Headgear, Hans Rudolph, Kansas, USA) for the collection of expired gases analyzed by a metabolic cart (Medisoft Ergocard, Sorinnes, Belgium). In addition, HR and arterial oxyhaemoglobin saturation were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to the participant's right index finger.

Hydration Assessment. A urine sample was collected prior to the interval session. A drop of urine was analyzed for urine specific gravity (Atago Pocket Refractometer, PAL-10S, Japan) which has been shown to be a valid means of assessing hydration status [215]. A result <1.02 served as the threshold of hydration status acceptable to commence testing [216, 217]. Once adequate hydration was verified, a measure of body mass was recorded to the nearest 0.1 kg using a digital scale (Seca, Birmingham, UK) and measured again post-exercise.

Baroreflex Sensitivity. Baseline autonomic measures were assessed following ten minutes of supine rest. Participants were instrumented with an ECG and finger plethysmography secured to the middle finger, using a beat-by-beat blood pressure device (Finapres; Ohmeda Inc, Englewood, CO). Automated blood pressure measurements were obtained by brachial occlusion

(BpTRU 100, Coquitlam, Canada) for calibration and collected in duplicate. Continuous recordings were sent to a data acquisition system (PowerLab/16SP ML 795, ADInstruments, Colorado Springs, CO) and displayed using Chart (version 7.0, ADInstruments, Colorado Springs, CO).

Echocardiography. Echocardiographic assessments were performed by a trained clinical sonographer using a portable ultrasound unit *(Vivid i,* GE Medical Systems, USA) with simultaneous ECG and a 2.5-MHz transducer. Participants were positioned in the left lateral decubitus position for imaging. Apical two- and four-chamber views were acquired for the assessment of left ventricular (LV) volumes, LV longitudinal strain and strain rate, in addition to transmitral pulsed Doppler flow velocities and tissue Doppler mitral annular velocities. All strain imaging was acquired at high frame rates (80-90 frames per second). End-diastolic volume (EDV) and end-systolic volume (ESV) using Simpson's bi-plane method for which three consecutive beats were measured and analyzed. Ventricular volumes, diameters, and strain analyses were performed offline (EchoPAC, GE Healthcare, v. 110.1.1) in accordance with the recommendations of the American Society of Echocardiography [175].

High Intensity Interval Exercise. Pre- and post-exercise blood pressure was measured in the seated position (BpTRU 100, Coquitlam, Canada) after five minutes of quiet sitting. The test began after five minutes of warm up followed by two minutes of inactive rest while seated on the bike. The interval exercise involved fifteen one-minute maximal work bouts interspersed with two-minute recovery periods on a stationary cycle ergometer (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA). The workload was assigned in watts equivalent to the final power output obtained during the VO_2max test. The recovery periods were active rest at 50 W. Participants

were allowed to drink water ad libitum. The test ended with one minute of active recovery totalling 44 minutes of exercise.

5.2.4 Data Analysis

Body surface area was calculated as BSA (m^2) = SQR RT ([Height(cm) x Weight(kg)]/ 3600) [170]. Mean arterial pressure (MAP) was calculated as DBP + 1/3 (SBP – DBP). All two-dimensional and Doppler data were analyzed off-line by taking an average of three consecutive beats. Left ventricular mass was determined using the formula: LV Mass (g) = 0.8 (1.04 ([LVIDD + PWTD + IVSTD]3- [LVIDD]3))+ 0.6 [177]. Stroke volume was calculated as EDV-ESV, and cardiac output was calculated as stroke volume x heart rate. Ejection fraction (EF) was calculated as stroke volume as a percentage of EDV. Total peripheral resistance (TPR) was derived from dividing cardiac output into MAP. An index of left ventricular filling pattern was assessed by calculating the ratio of early (E) to late (A) diastolic filling (E/A). The ratio of transmitral flow to transmitral tissue velocity (E´; E/E´), provides an estimation of LV filling pressures.

Baroreceptor sensitivity was analyzed by selecting a clean five-minute segment of the Chart file via specialized programmed to exclude ectopic beats (Nevrokard NKFP 8.7.0 and BRS 5.7.0, Nevrokard, Izola, Slovenia). The sequence method was derived from the calculation of the slope between changes in R-R interval (RRI) and changes in systolic blood pressure, and the alpha coefficient in the low frequency (LF) or high frequency (HF) bands represented the cross-spectral method of baroreflex sensitivity analysis [38]. For the sequence method, inclusion criteria was set as: a RR interval variation of greater than 5 ms, blood pressure changes greater than 0.5 mmHg, minimum sequence duration of four beats, sequence correlation coefficient

greater than 0.85, and a one beat delay between SBP and RR interval. For the spectral method, the fast Fourier transformation was used to power spectral density of blood pressure and RR interval. The spectral gain of oscillations was set to fixed signal bandwidths of low frequency (0.04 – 0.15 Hz, LF) and high frequency (0.15 – 0.45 Hz, HF) as per current recommendations [38]. In the data analysis the sequence method values were labeled BRS, and the spectral components αLF and αHF. The ratio of LF to HF of the RRI as a measure of heart rate variability was labeled RRI LF/HF. Finally, the LF of blood pressure variability was labeled SBP LF was expressed as a percent of total power.

5.3 STATISTICAL ANALYSIS

A four-way mixed model ANOVA was used to compare differences in haemodynamic measures between sex (male, female) and group (NA=normally active, ET=endurance trained) over time (stage of LBNP) by condition (pre-exercise, post-exercise) with Bonferroni adjustment for multiple comparisons (SPSS v20, IBM). Pearson's correlation analysis was used to find associations between significant factors. Significance for all tests was set *a priori* at $p<0.05$. All analyses were performed using SPSS software (version 20.0; SPSS IBM, Chicago, IL). Results are reported as mean ± SD.

5.4 RESULTS

5.4.1 Participant Characteristics

All 33 recruited participants completed this study with no exercise-related adverse events. Participant characteristics are found in Table 5.1. Endurance-trained individuals reported engaging in aerobic training four to six d/week and consisted of 12 cyclists, four tri-athletes, two cross-country skiers, and one runner. The ET participants had higher LV mass and stroke volume

at baseline. Men displayed higher EDV and ESV than women. When indexed for body surface area, volumes remained greater in athletes (EDVI, p=0.005; ESVI, p=0.047; SVI, p=0.002) with sex differences only remaining for ESVI (p=0.036).

5.4.2 Cardiovascular Responses to Exercise and Lower Body Negative Pressure

Stroke volume was reduced post-exercise compared to baseline. Throughout lower body negative pressure, stroke volume was reduced to a greater extent before exercise than with LBNP post-exercise, and this effect was greater in males. Stroke volume and cardiac output (indexed for body surface area) began at higher values but decreased to a greater degree in ET compared with NA (Figure 5.1). An interaction of condition by LBNP by sex was also found for stroke volume index. Mean arterial pressure did not change with LBNP however, women displayed lower MAP post-exercise compared to men (Figure 5.2). Total peripheral resistance significantly increased with LBNP (p<0.001) and was lower post-exercise (p=0.023; Figure 5.2). Diastolic filling determined from Doppler flow is shown in Figure 5.3. Early diastolic filling decreased with LBNP but more so post-exercise. There were no significant alterations in late diastolic filling. An interaction was revealed for the E/A ratio in which normally active females maintained a higher E/A ratio, particularly during early post-exercise LBNP. Heart rate was altered less during LBNP post-exercise than occurred pre-exercise and was not different by sex or group (Figure 5.4). Main effects were found for ejection fraction and LBNP (p=0.003) and ejection fraction by condition (p<0.001), with higher values in women versus men (Figure 5.5).

As one group, the cardiac responses to LBNP pre and post-exercise are reported in Table 5.2. Of these variables, only myocardial tissue velocity of the septal segment (E septal) presented an interaction (Figure 5.6). Normally active females had higher tissue velocity, with endurance-

trained females suffering a greater reduction post-exercise from baseline values. A surrogate for filling pressure, E/E' was not affected by lower body negative pressure, but there was an interaction of sex and group pre and post-exercise (Figure 5.6). Endurance-trained females appeared to reduce filling pressures post-exercise compared to before exercise, whereas, endurance-trained males did not. Finally, LV strain and diastolic strain rate were reduced with exercise (p=0.001) and LBNP (p<0.001) but there were no interactions (Figure 5.7). Women displayed higher strain and strain rates than men throughout the intervention.

5.4.3 Baroreflex Function with Exercise and Lower Body Negative Pressure

Baroreflex function revealed training status differences with an interaction of condition by LBNP by group (Figure 5.8). Pre-exercise, ET show greater reductions in αLF with lower body negative pressure compared to normally active, whereas post-exercise, αLF was reduced similarly in all groups. Furthermore, alterations as demonstrated throughout LBNP pre-exercise were attenuated post-exercise. The LF/HF of heart rate variability was altered with LBNP and with exercise but there was no interaction with sex or group. Pearson correlation analysis revealed significant correlations for absolute VO_2max and post-exercise baroreflex sensitivity (r=-0.38, p=0.04) and post-exercise αLF (r=-0.50, p=0.004), as well as for relative VO_2max and post-exercise αLF (r=-0.41, p=0.023). Between sex differences were evident for all measures with women possessing higher sequence baroreflex sensitivity (p=0.014), higher αLF (p=0.016) lower RRI LF/HF (p=0.049) and lower absolute SBP LF (p=0.048) than men. When expressed as percent of total spectral power, a three-way interaction was displayed where after exercise women showed a drop in SBP LF (%) at the most severe lower body negative pressure stage where before exercise this had increased at that time point, similar to the men (Figure 5.9).

Table 5.1 Participant Characteristics

	Males		Females	
	NA *n* = 8	ET *n* = 12	NA *n* = 6	ET *n* = 7
Age, *y*	29.50 ± 4.6	29.9 ± 5.7	29.7 ± 5.7	29.9 ± 5.8
Height, *cm* ¥	182.1 ± 4.8	178.2 ± 5.5	162.1 ± 4.1	168.5 ± 4.7
Body Mass, *kg* ¥	79.8 ± 4.9	73.6 ± 6.8	58.5 ± 5.4	58.4 ± 6.3
VO_2max, $mL \cdot kg^{-1} \cdot min^{-1}$ ǂ	46.8 ± 5.4	58.5 ± 4.0	45.0 ± 4.2	56.4 ± 4.4
SBP, *mmHg*	111.6 ± 6.9	107.3 ± 10.6	104.2 ± 5.9	104.3 ± 4.4
DBP, *mmHg*	66.4 ± 5.3	63.7 ± 5.9	65.3 ± 5.2	65.4 ± 4.4
LV Mass, *kg* ¥ ǂ	200.4 ± 25.9	215.5 ± 43.0	122.6 ± 17.5	175.7 ± 26.2
EDV, *mL* ¥	145.4 ± 32.4	164.0 ± 31.6	97.5 ± 25.3	114.9 ± 17.8
ESV, *mL* ¥	60.5 ± 8.4	60.0 ± 23.1	37.8 ± 13.5	43.9 ± 14.8
SV, *mL* ǂ	84.9 ± 28.6	104.0 ± 17.7	59.7 ± 18.2	71.0 ± 9.9

Abbreviations: SBP=systolic blood pressure; DBP=diastolic blood pressure; LV=left ventricle; EDV=end diastolic volume; ESV=end-systolic volume; SV=stroke volume
The effects of sex and training status on participant characteristics were obtained via unadjusted linear models.
¥ $p<0.01$ between sex; ǂ $p<0.01$ between group

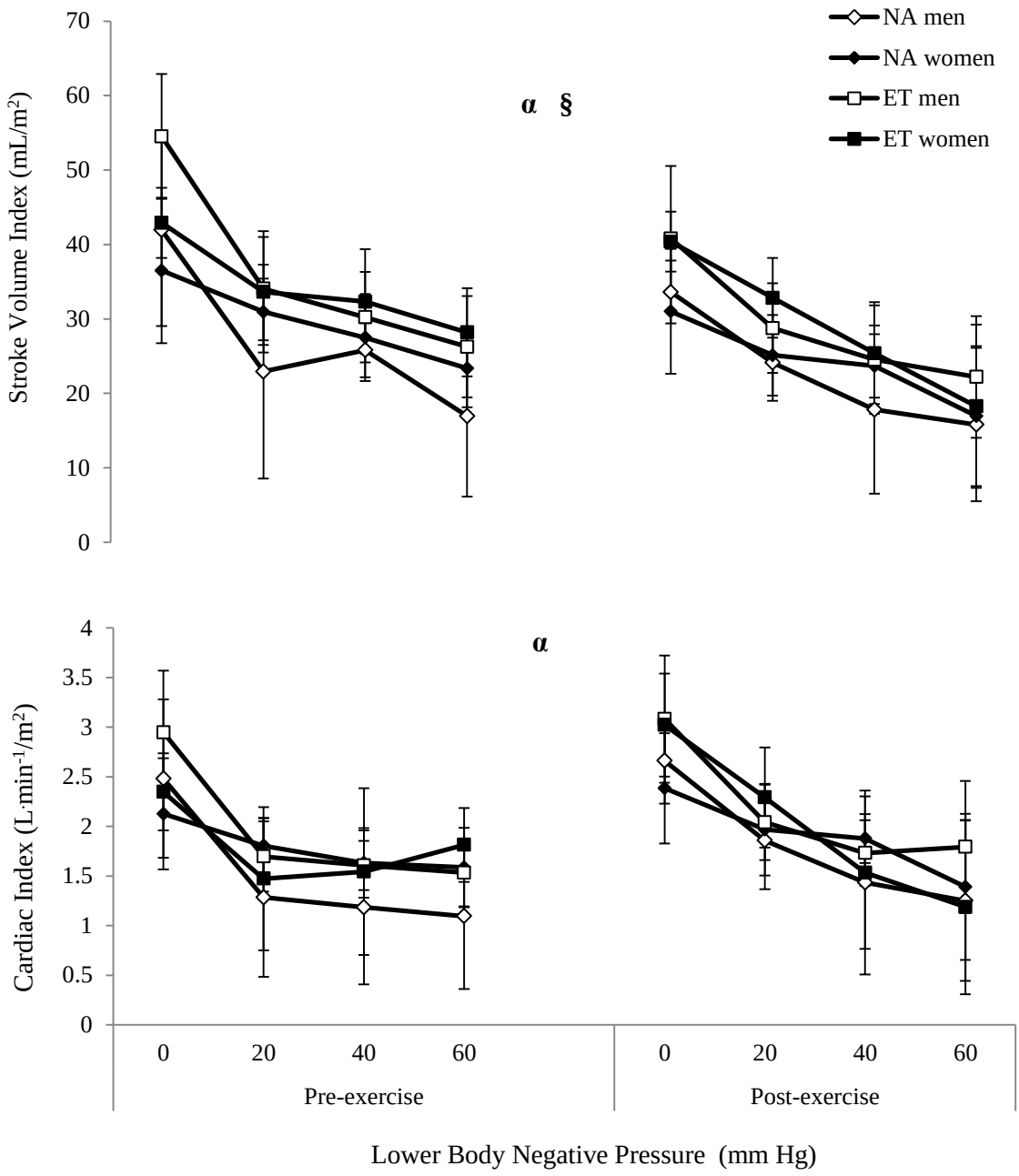

Figure 5.1 Stroke Volume and Cardiac Ouput Responses

§ $p<0.05$ condition x LBNP x sex; α $p<0.05$ LBNP x group

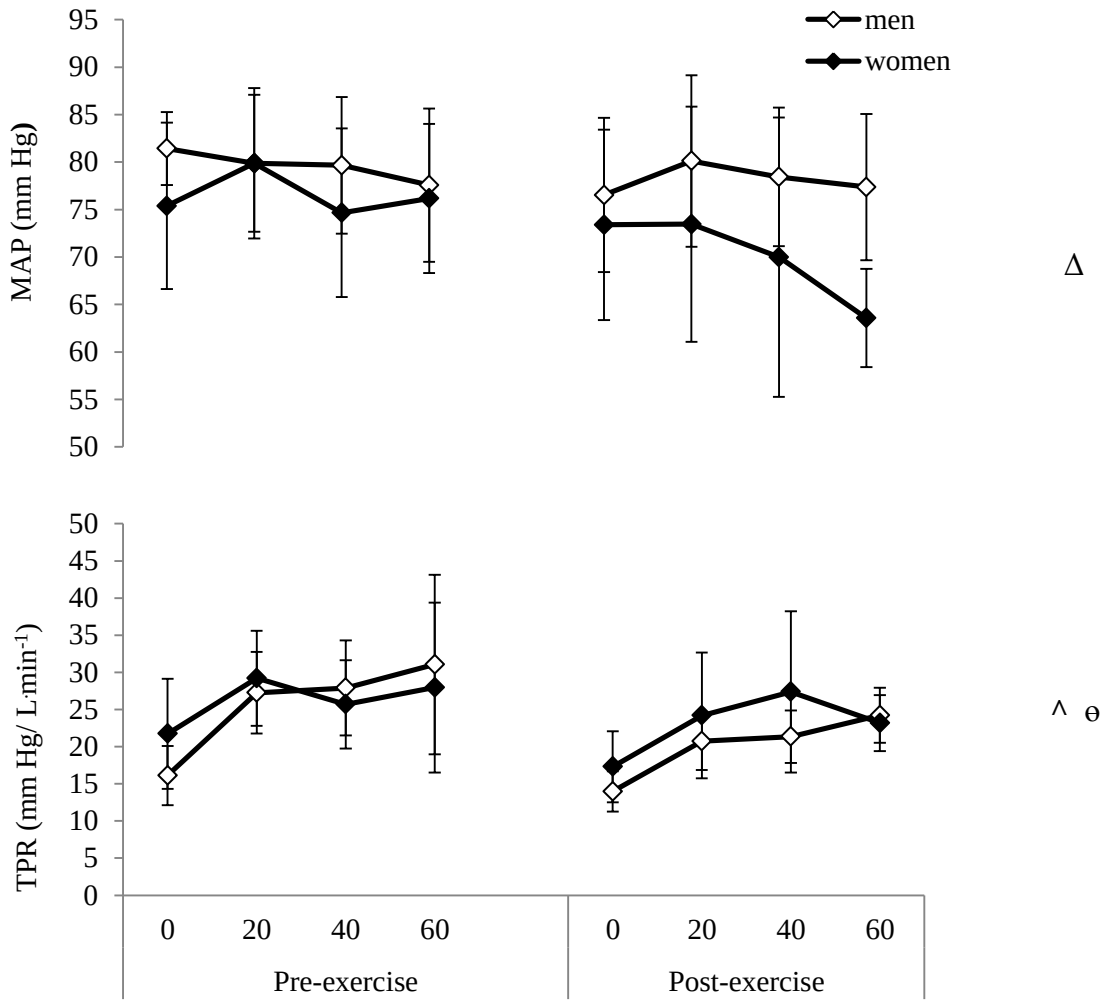

Figure 5.2 Sex Differences in Haemodynamic Response to Lower Body Negative Pressure and Exercise

Δ $p<0.05$ condition x sex; ^ $p<0.05$ condition; ɵ $p<0.05$ LBNP
MAP=mean arterial pressure; TPR=total peripheral resistance

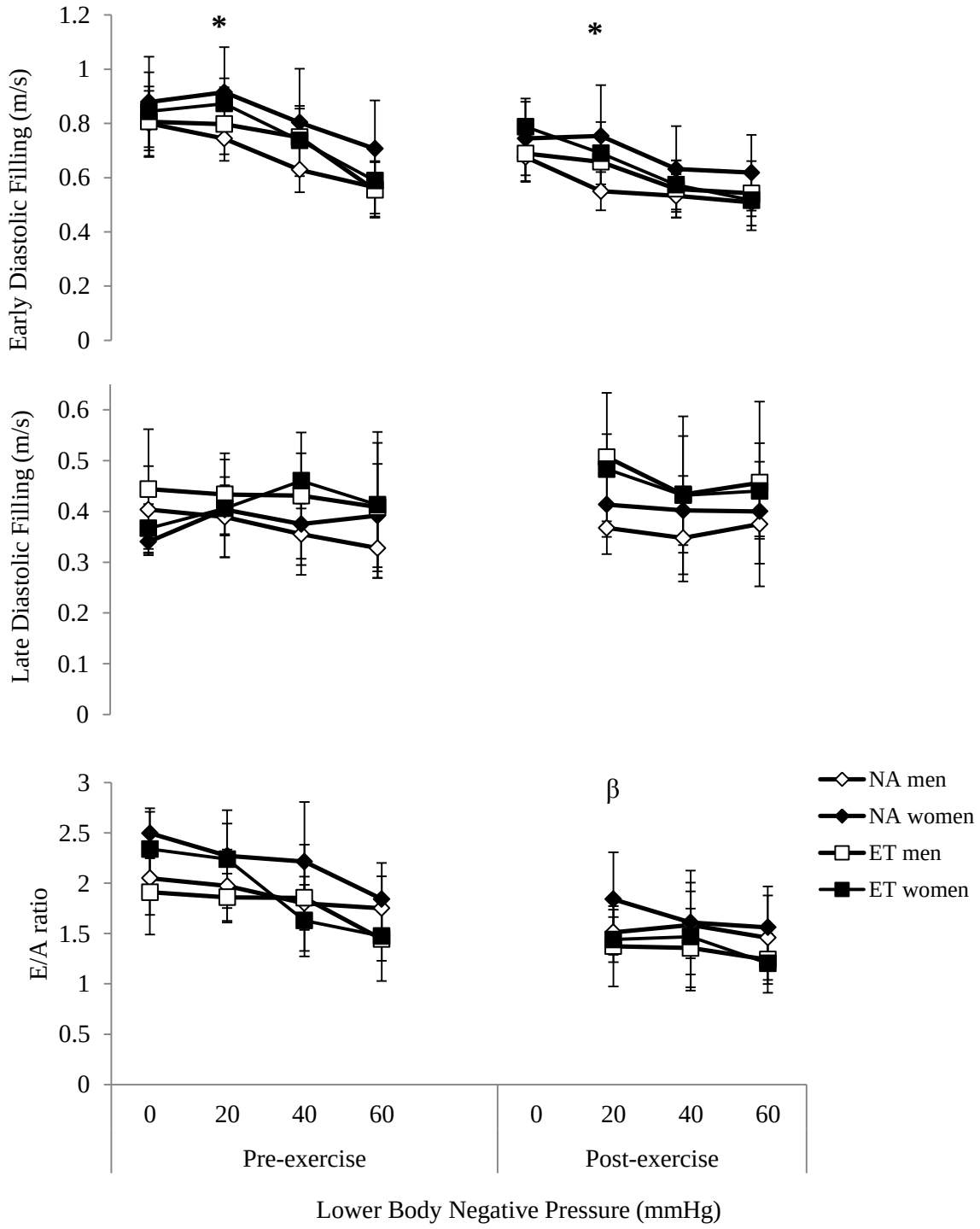

Figure 5.3 Diastolic Filling Across Lower Body Negative Pressure Before and After Exercise

* p=0.002 condition x LBNP; β p=0.014 condition x LBNP x sex x group

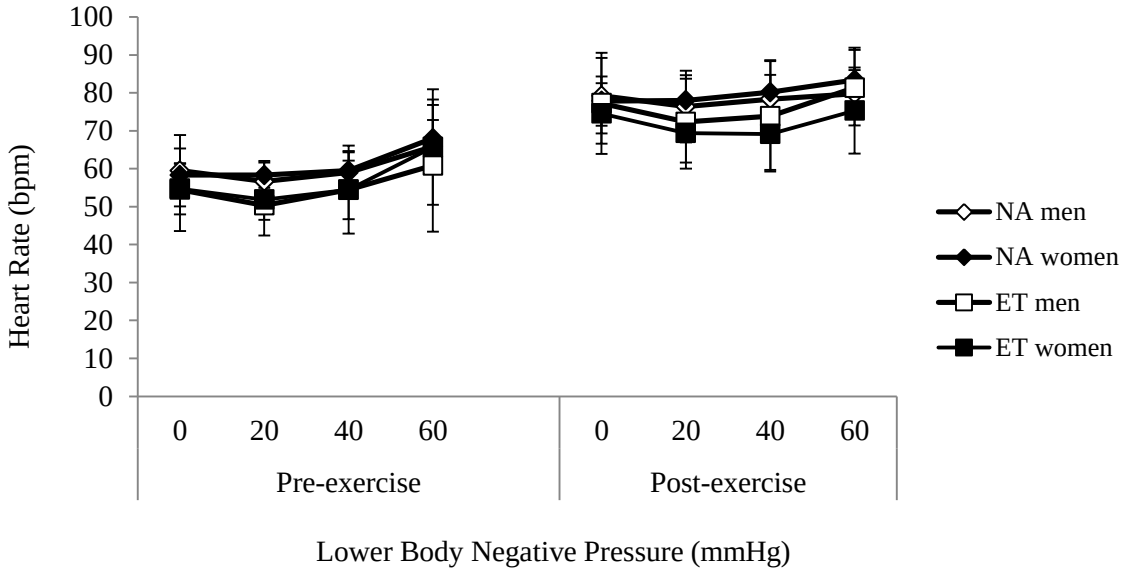

Figure 5.4 Heart Rate Across Lower Body Negative Pressure Before and After Exercise
p=0.008 condition x LBNP

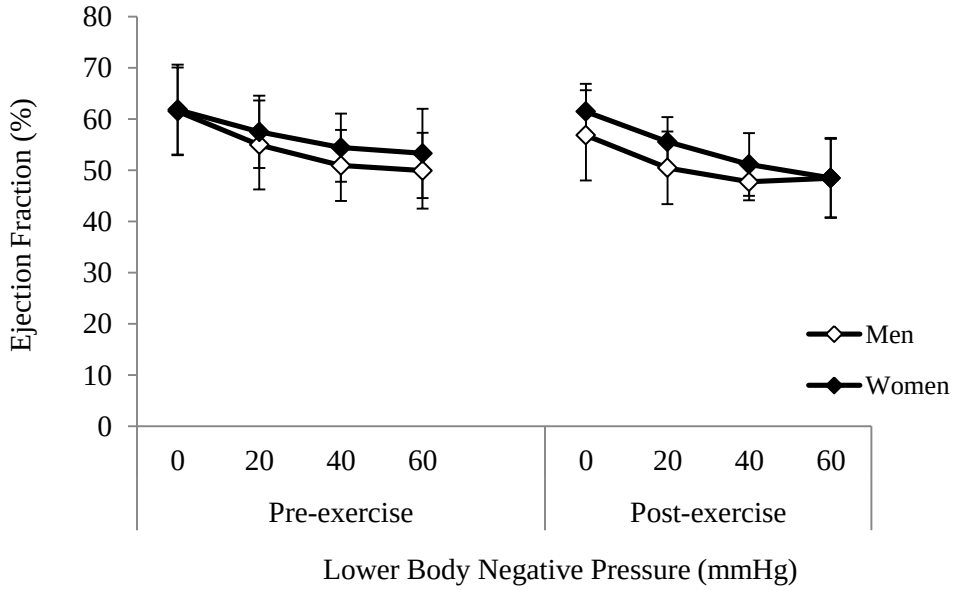

Figure 5.5 Ejection Fraction Across Lower Body Negative Pressure Before and After Exercise

p=0.003 condition; *p*=0.000 LBNP; *p*=0.006 between sex

Table 5.2 Indices of Left Ventricular Systolic and Diastolic Function

	Pre-Exercise				Post-Exercise			
	0 mmHg	*-20 mmHg*	*-40 mmHg*	*-60 mmHg*	*0 mmHg*	*-20 mmHg*	*-40 mmHg*	*-60 mmHg*
EDVI, *mL/m²* ^ɵ	74.36 ± 16.45	55.23 ± 17.95	56.19 ± 11.26	45.56 ± 14.81	63.76 ± 12.80	53.16 ± 10.31	46.45 ± 15.79	39.00 ± 18.61
ESVI, *mL/m²* ^ɵ	28.63 ± 9.40	24.62 ± 10.40	26.97 ± 7.45	22.67 ± 8.24	25.57 ± 8.18	25.32 ± 6.67	23.59 ± 8.13	20.11 ± 10.19
EF, *%* ^ ɵ	61.65 ± 8.50	55.97 ± 8.04	52.33 ± 6.93	51.35 ± 8.02	58.66 ± 7.90	52.48 ± 6.69	49.10 ± 4.97	48.48 ± 7.58
E' sep, *cm/s* ǂ	11.8 ± 2.3	11.6 ± 2.3	11.0 ± 2.6	10.0 ± 2.6	11.7 ± 1.8	11.2 ± 2.0	9.4 ± 2.3	8.8 ± 1.9
E' lat, *cm/s* ^ɵ	17.5 ± 2.9	15.4 ± 2.5	14.9 ± 3.2	14.0 ± 3.8	15.3 ± 3.0	15.2 ± 2.0	13.8 ± 3.2	11.9 ± 3.8
E' RV, *cm/s* *	14.7 ± 2.8	13.3 ± 2.4	13.2 ± 3.0	12.6 ± 2.6	13.4 ± 2.4	11.4 ± 2.1	11.2 ± 2.7	10.4 ± 2.4
E/E' septal €	6.05 ± 1.46	5.61 ± 1.29	5.32 ± 1.57	5.64 ± 1.67	6.31 ± 1.17	6.17 ± 1.39	5.94 ± 1.62	6.27 ± 1.40
E/E' lateral *	4.14 ± 1.03	4.13 ± 1.00	4.17 ± 1.16	4.38 ± 1.95	4.83 ± 1.01	4.46 ± 0.79	4.02 ± 1.50	4.92 ± 1.90
LV Strain, *%* ^ɵ	-17.41 ± 2.27	-14.67 ± 2.70	-13.20 ± 2.10	-13.01 ± 3.46	-16.50 ± 2.40	-14.56 ± 2.24	-13.78 ± 2.78	-12.64 ± 2.83
LV sSR, s^{-1}	-1.01 ± 0.14	-1.34 ± 0.15	-0.88 ± 1.62	-0.87 ± 1.70	-0.87 ± 0.16	-0.81 ± 1.04	-0.80 ± 0.17	-0.80 ± 0.15
LV dSR, s^{-1} ^ ɵ	1.44 ± 0.23	1.18 ± 0.33	1.07 ± 0.23	1.00 ± 0.24	1.35 ± 0.28	1.17 ± 0.28	1.03 ± 0.30	0.97 ± 0.22

Abbreviations: EDVI=end-diastolic volume index; ESVI=end-systolic volume index; EF=ejection fraction; E'=mitral annular tissue velocity; sep=septal wall of left ventricle; lat=lateral wall of left ventricle; RV=right ventricle; E=early diastolic filling; LV=left ventricle; sSR=systolic strain rate; dSR=diastolic strain rate

Effect of exercise obtained using general linear models adjusted for sex and training status.
* $p<0.05$ condition x LBNP; ^ $p<0.05$ condition; ɵ $p<0.05$ LBNP

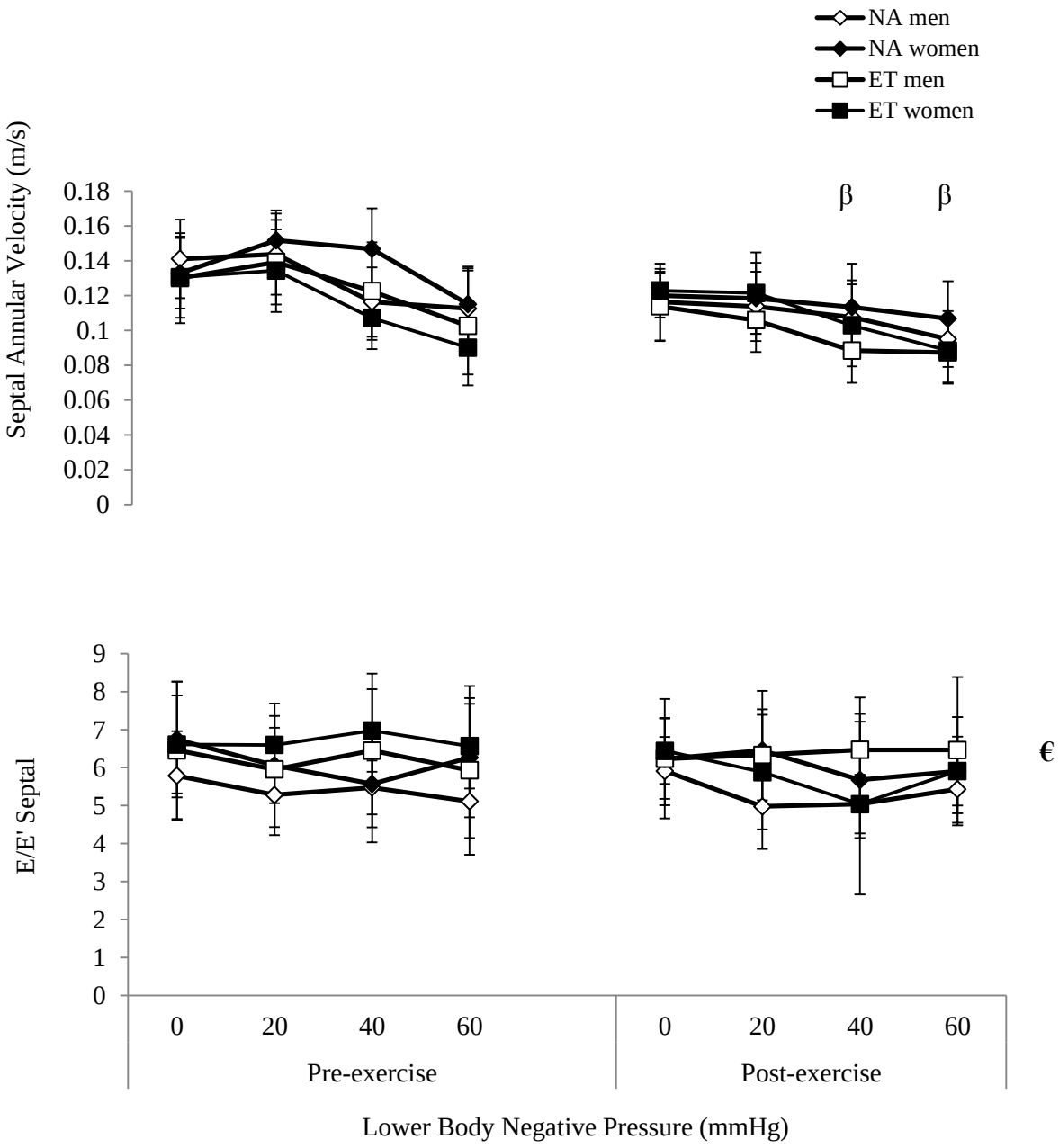

Figure 5.6 Septal Wall Tissue Velocity and Filling Pressures

β p=0.022 condition x LBNP x sex x group; € p=0.016 condition x sex x group

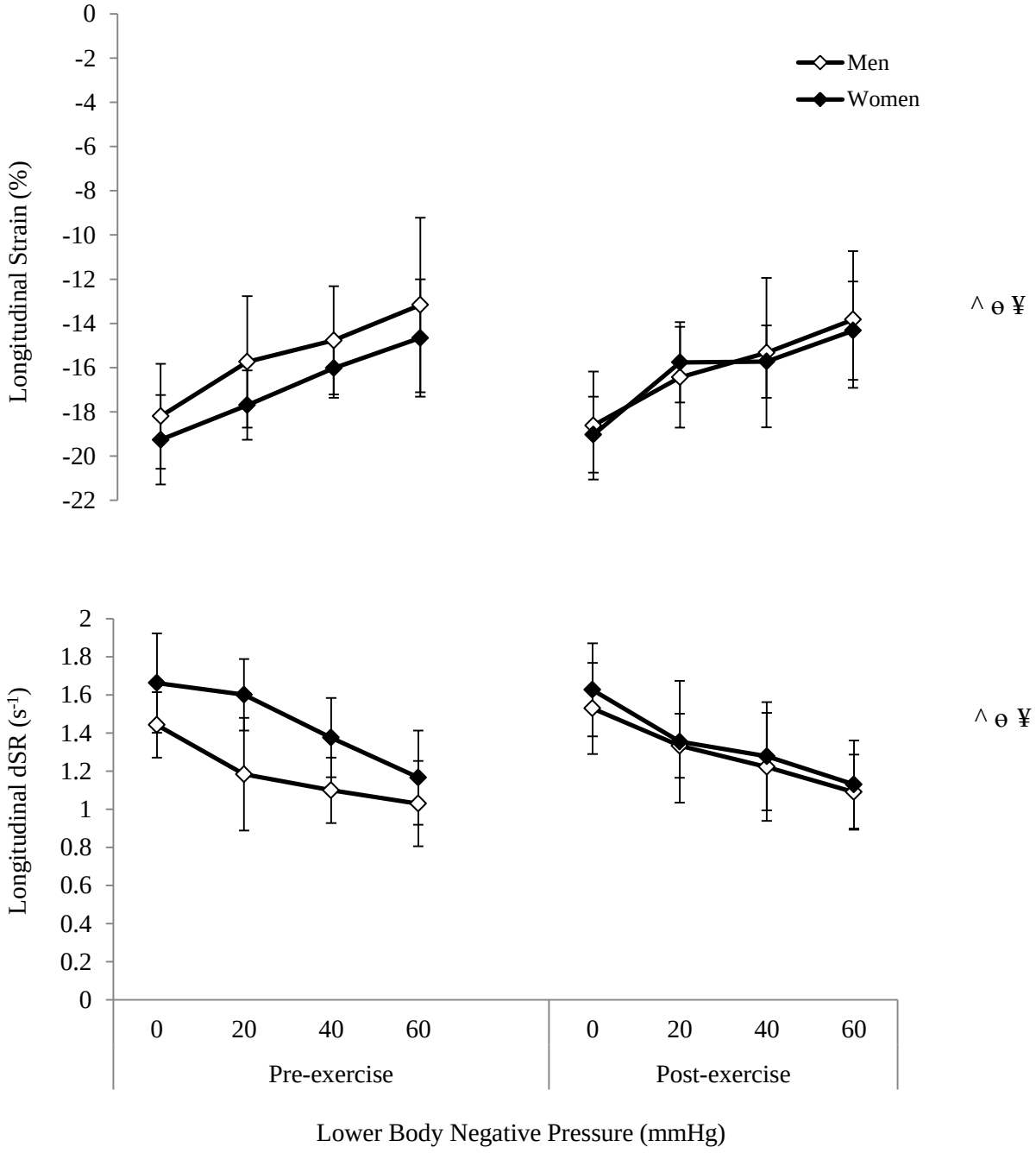

Figure 5.7 Longitudinal Strain and Diastolic Strain Rate

^ $p<0.05$ condition; ɵ $p<0.05$ LBNP; ¥ $p<0.05$ between sex; dSR = diastolic strain rate

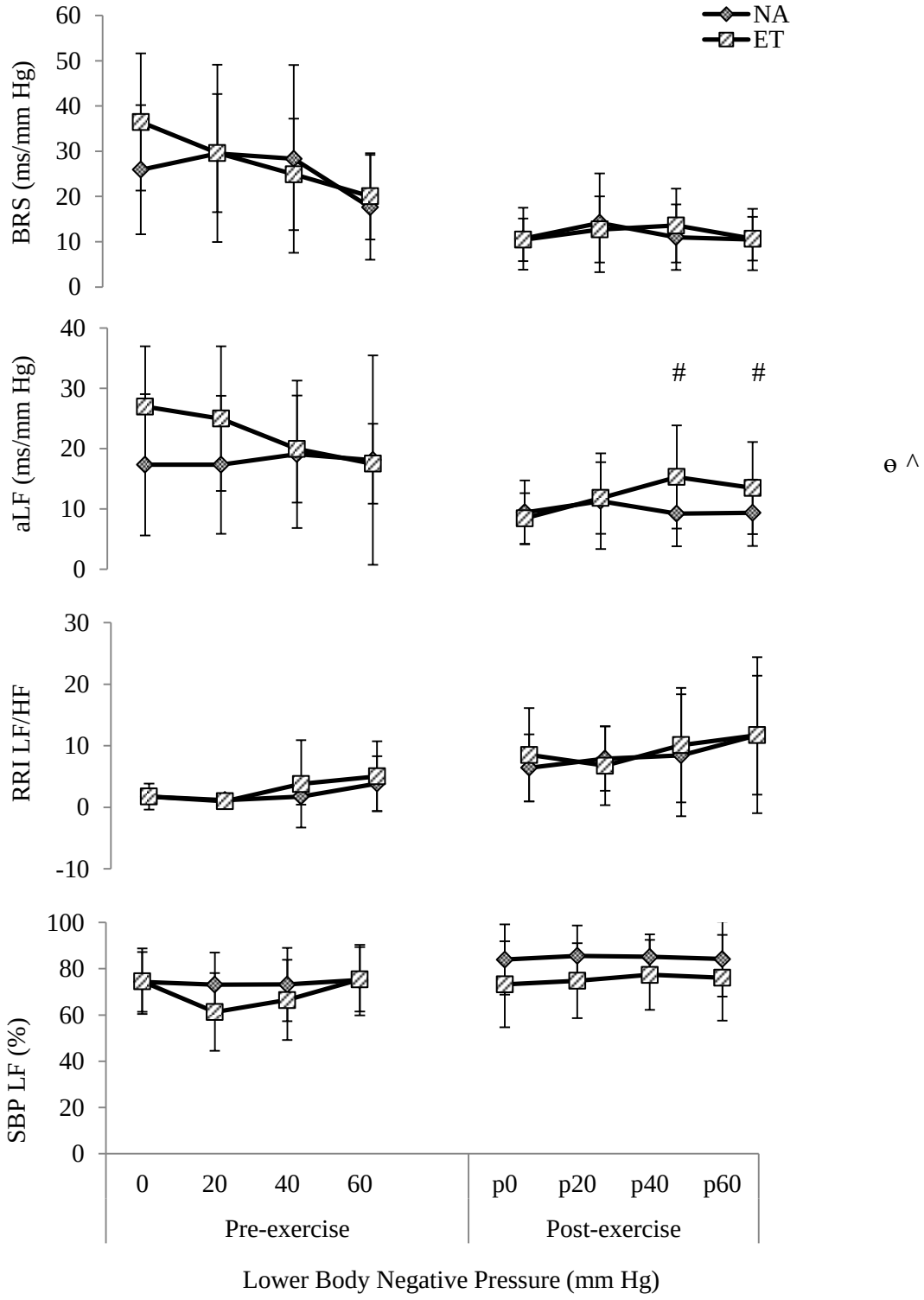

Figure 5.8 Training Group Differences in Autonomic Indices
# $p<0.05$ condition x LBNP x group; ɵ $p<0.05$ LBNP; ^ condition

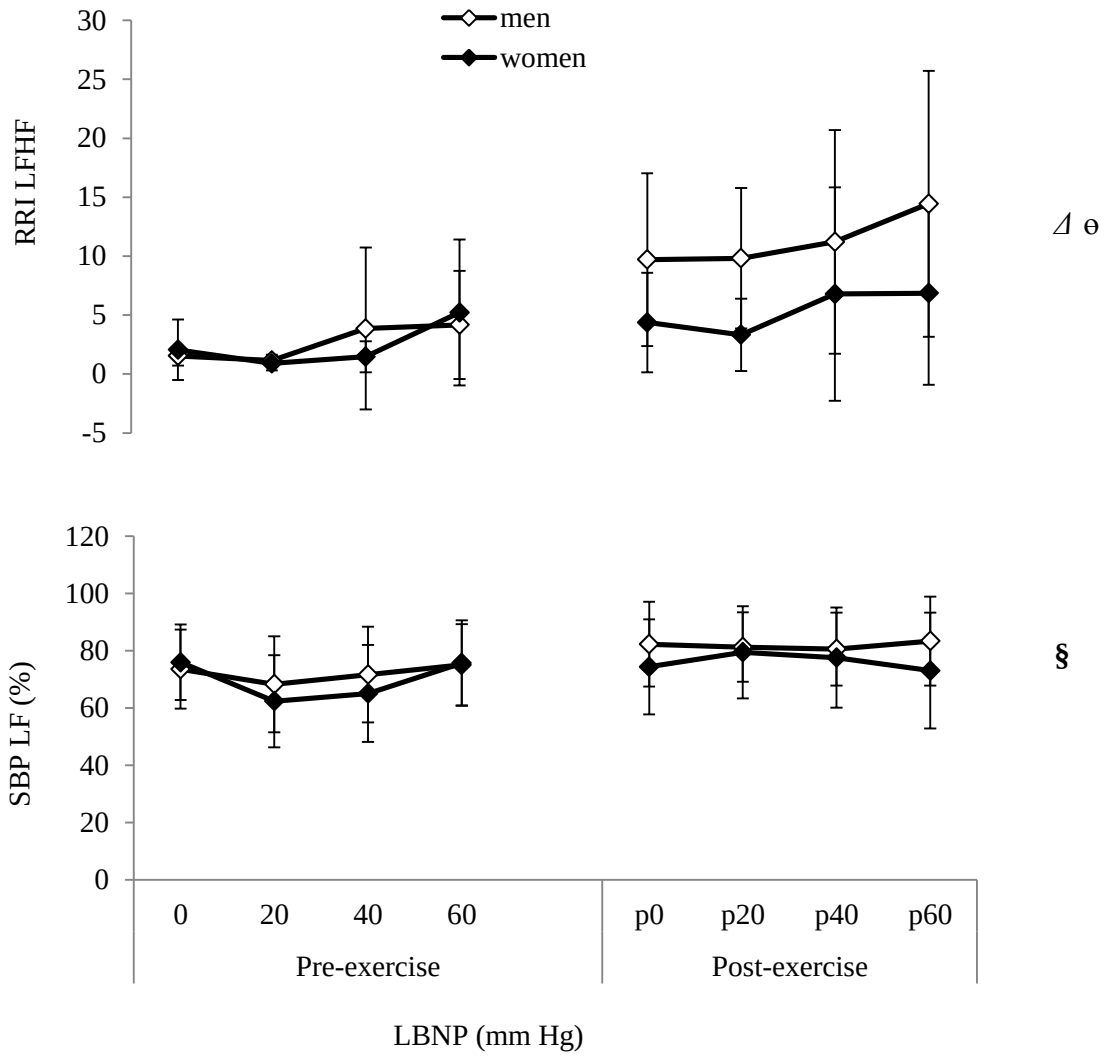

Figure 5.9 Sex Differences in Autonomic Indices

§ $p<0.05$ condition x LBNP x sex*; Δ* $p<0.05$ condition x sex; **ɵ** $p<0.05$ LBNP

5.5 DISCUSSION

This investigation aimed to determine the effects of endurance training and sex on cardiac and autonomic responses to high intensity interval exercise. We observed significant independent effects of sex and training status on the response to exercise and lower body negative pressure. The main findings of this investigation are that 1) women exhibit altered autonomic and cardiac function at rest compared to men and maintained this throughout the intervention; 2) endurance-trained individuals presented enhanced cardiac and autonomic function at rest however at intense levels of lower body negative pressure (> -40 mmHg) showed significant reductions compared with normally active individuals; and 3) endurance-trained individuals demonstrated a more rapid recovery in autonomic indices post-exercise despite greater reductions in left ventricular function than normally active participants. Our investigation supports previous work showing enhanced resting autonomic function in women [260] and endurance-trained individuals [62, 89-93], as well as their susceptibility to an orthostatic challenge [73, 247, 261, 262]. Our work is novel wherein it shows that under an aggregate physiological stress, those with improved training status have increased capacity to rebound (i.e., improve back to baseline) autonomic control more quickly, despite undergoing more significant reductions in cardiac function.

Before exercise, endurance-trained individuals demonstrated the traditional response to lower body negative pressure where measures of cardiac and baroreflex function reduced drastically with intense lower body negative pressure. Sex affected this response as endurance-trained women held diastolic function until the later stages of lower body negative pressure, where ET women fell to values similar to ET males. Also, throughout

lower body negative pressure, ET displayed lower heart rates but at -60 lower body negative pressure, mean heart rate in ET females increased sharply to the heart rates of the untrained individuals. Post-exercise, NA females showed the least reductions from baseline of left ventricular function, heart rate variability and baroreflex sensitivity and maintained their values better than the other groups. Thus, we show an interaction of sex and training status in our intervention, where normally active females represented the best tolerance to lower body negative pressure and exercise, and endurance trained males faired the poorest. Finally, despite ET males showing greater depressions in E/A ratio, ejection fraction, tissue velocities and higher filling pressures, they demonstrated a significantly improved recovery of baroreflex function over the other groups as shown by their improved αLF in severe lower body negative pressure post-exercise.

5.5.1 The Sex Factor

Potential mechanisms previously associated with sex differences to orthostasis include greater venous compliance [73], lower blood volume, impaired baroreflex function [75] and lower resting SV [263] in women. However, the women we examined tolerated the orthostatic stress quite well particularly due to the resiliency of the normally active women. Further, this ability to tolerate orthostatic stress persisted into the post-exercise lower body negative pressure intervention. This was unexpected as the compensation required to maintain blood pressure after exercise is considerably more than what is needed to an orthostatic challenge independently [264]. Exercise-induced reductions in blood volume [265], and blood pooling in the extremities with the cessation of the skeletal muscle pump [244] are exacerbated with lower body negative pressure. Our

observations reveal that women did not experience any greater reductions in venous return than the men based on stroke volume and cardiac output. In fact, our endurance trained men experienced the greatest reductions in stroke volume in either lower body negative pressure condition, which supports our previous findings in women [171] that suggests that the rate of change in stroke volume is a more valid indication of orthostatic intolerance than absolute stroke volume. Thus, considering the women in this study did not experience greater orthostatic intolerance than the men, it is plausible to assume autonomic function was not challenged beyond capacity.

Previous work indicates that the sympathovagal balance of women may be more vulnerable to the effects of strenuous exercise than men [66, 266]. Certainly autonomic indices were markedly reduced (baroreflex sensitivity and αLF) or elevated (RRI LF/HF and SBP LF) post-exercise, however this did not occur to a greater extent in women. Only one sex-response was evident (higher RRI LF/HF ratio) for the men, thus opposing this previous work. In support of our findings, other work has demonstrated females to be more resilient to exercise induced alterations in cardiac autonomic modulation [267, 268]. The inclusion of highly trained participants is likely responsible for our findings as training status has been shown to further protect against cardiac autonomic modulations [267].

The low frequency component of systolic blood pressure (SBP LF) did not change markedly with lower body negative pressure and less so following exercise. The SBP LF measure is considered a broad index of the vascular sympathetic modulation; one of the multiple, non-invasive autonomic indices that might be useful in the clinical management of conditions characterized by disturbed autonomic regulation such as hypertension or

diabetes [269]. We observed higher SBP LF values in men, indicating greater systemic sympathetic vascular tone [270] during post-exercise LBNP, likely in response to the greater post-exercise fall in cardiac output. Kimmerly et al. [271] found men had greater heart rate and sympathetic responses during 35mmHg LBNP. This was associated with greater changes in forebrain activity, leading to the postulation that forebrain regions may be involved with the generation of sex-specific differences in baroreflex-mediated sympathetic and cardiovascular responses to LBNP.

5.5.2 The Training Factor

Our study revealed greater haemodynamic and baroreflex alterations in endurance-trained subjects. In addition, both load dependent (Doppler transmitral flow velocities) and less load-dependent measures of cardiac function (tissue Doppler and strain indices) [196] revealed an effect of training status on response to lower body negative pressure to which there was an interaction with sex. Similar to previous work from our laboratory, peak early transmitral filling and diastolic strain rate were reduced with LBNP in the endurance trained individuals suggesting greater reductions in left atrial pressure [272] impacting right ventricular stroke volume and subsequently LV stroke volume via the Frank Starling relationship. While shown to influence orthostatic tolerance [171] these drastic reductions in stroke volume will require sufficient vasoconstrictor capacity to maintain arterial blood pressure. Thus, as discussed above, the endurance-trained males appeared to rely on greater sympathetic outflow to defend blood pressure in the post-exercise condition. As total peripheral resistance was not affected by sex or training status in our study, we can safely assume that the mechanisms of vasoconstriction

employed by the endurance trained males, was adequate. In a recent investigation, vasoconstriction was not found to be impacted by training status at rest, nor was it limb specific [273]. However, when the participants in that study exercised, sympathetic vasoconstriction was blunted in both arms and legs but less so in the arms of the cyclists versus controls. These researchers infer this to reflect an increase in α-adrenergic sensitivity in the arms as part of the adaptations to chronic exercise demands, which is necessary to ensure optimal blood flow to the exercising legs and to avoid over-perfusion of the arm. Other recent work has illustrated the impact of endurance training on reducing sympathetic outflow to the renal vasculature and diminished renal vasoconstriction during head-up tilt [274]. This further supports the notion that regional alterations in vasoconstriction may be a compensatory mechanism under heavy demand. It has been said that humans have limited, individual and restricted vasoconstrictor reserve to which fitness may be one important factor [275]. While our data is unable to validate these mechanisms as active in our endurance-trained cohort, our indirect evidence suggests vasoconstrictor activity may play a role.

5.5.3 Other Considerations

In the present investigation we intentionally measured exercise-related changes in baroreflex control in conjunction with lower body negative pressure to assess the effects of sex and training status on the ability to influence potential indicators of cardiovascular risk [276]. However, other factors may impact the observed responses: peripheral arterial structure and function [277]; leg venous compliance and function [278]; and morphological adaptions of the LV [279]. It must also be considered that factors more

commonly found in women versus men, or endurance-trained individuals have influenced our findings and may not be limited to the groups to which they have been identified. For example, baroreflex sensitivity declines with age [280]. Compelling evidence suggests that exercise-related maintenance of arterial compliance is associated with the attenuated decline in baroreflex sensitivity with healthy aging [46, 281]. The impact of a healthy diet on arterial compliance [282] cannot be ignored and is not limited to athletes or a particular sex.

5.5.4 Cardiovascular Risk

We have shown that endurance-trained individuals displayed remarkable recovery in autonomic function following our strenuous intervention. In clinical work, heart rate recovery after exercise has been shown to be a powerful independent predictor of mortality in healthy subjects and those recovering from myocardial infarction [104, 283]. While the immediate post-exercise period harbours higher risk than without strenuous exercise even in healthy individuals [22] the clinical relevance of these transient large shifts in sympathovagal balance are unclear, particularly in light of an improved autonomic profile as a chronic training adaptation.

5.6 LIMITATIONS

Participants were asked to refrain from exhaustive exercise for 24 hours prior to testing. In endurance trained individuals, particularly cyclists, being in an over-reaching or over-trained state cannot be ruled out. After very intensive training, cardiovagal baroreflex sensitivity has been shown to shift from parasympathetic toward sympathetic dominance [284]. In a study by Middleton and De Vito [285] endurance-trained females

were found to have significantly lower baroreflex sensitivity than untrained females (7.95 vs. 13 ms mmHg, respectively), a finding the authors concede may be due to the intense training schedule the women were engaged in at the time of testing. Our resting values were similar to the normative data presented by Iellamo and colleagues [284] during the rested phase of their training cycle. This along with subjective observations in the participants tested, we do not feel overtraining was likely in our group.

Another consideration is that we compared active men and women as opposed to a sedentary cohort. This was by design as we wanted to assess the impact of training on cardiovascular function without the confounding factors that are associated with a sedentary lifestyle. Both groups had individuals who engaged in strength training. Strength training has been shown to affect the blood pressure response to head-up tilt differently than endurance training [279]. Although none of the participants were involved in high volume strength training and likely did not do enough to appreciable affect blood pressure regulation, this remains a factor that could be considered in future work.

Finally the sample size was too small to assess confidently the sex and training interactions (i.e., condition x LBNP x sex x group). However, we identified that sex and training status independently have an impact on the haemodynamic and baroreflex responses to exercise and lower body negative pressure. Thus, future work should aim to assess this intervention with larger numbers in order to explore the interaction of these factors more effectively.

5.7 CONCLUSIONS

This investigation showed that female sex was particularly resilient under a severe orthostatic stress. In particular, normally active women demonstrated the most tolerance based on cardiovascular and autonomic indicators. Endurance-trained males were presented with the greatest haemodynamic challenges and demonstrated greater sympathetic activity as evidenced by spectral measures of blood pressure variability. Endurance-trained individuals displayed a significantly more rapid baroreflex recovery than untrained. These findings highlight the impact of sex and training status on the recovery from strenuous exercise; yet the interplay between the paradoxical training and sex-related cardioprotection seen at rest and the acute exercise-induced cardiac impairments require further exploration.

Chapter 6: Post-exercise Hypotension in Men and Women Following High-Intensity Interval Exercise

6.1 INTRODUCTION

An acute reduction in blood pressure can be observed after a single bout of exercise, termed post-exercise hypotension [286]. Post-exercise hypotension is thought to occur as a result of a mismatch between the drop in systemic vascular resistance and increase in cardiac output [287, 288]. There may be an intensity dependent relationship between exercise and acute reductions in blood pressure [289-291]. Typically thought to occur following moderate intensity aerobic exercise [292, 293], post-exercise hypotension has also been shown after prolonged endurance [232], brief maximal exercise [243, 294], and high intensity interval exercise [254, 295]. As the metabolic and cardiovascular benefits of high-intensity interval exercise have become more apparent recently [10, 296], the use of this type of exercise as an effective blood pressure–lowering strategy for at-risk populations is appealing and warrants further investigation.

The limited research to date measuring changes in blood pressure resulting from high-intensity exercise, would suggest that the magnitude of the blood pressure reduction is similar when compared to steady-state exercise [254, 295, 297] or between sexes [228, 295]. While the magnitude may be similar, the mechanisms behind the post-exercise hypotension response are unclear [228, 254, 295]. Autonomic, vascular, and cardiac mechanisms have been implicated in post-exercise hypotension [288, 298]. It has been suggested that differences in baroreflex function may be involved [299] but this has yet to be determined. As baroreflex, autonomic, and cardiac function are highly influenced by

sex and training status, their impact on the post-exercise hypotension response to strenuous interval exercise would benefit our understanding of this important physiological response.

The purpose of this investigation was to explore the mechanisms of the post-exercise hypotension response following a strenuous bout of interval exercise in normotensive, endurance-trained and untrained men and women. It was hypothesized that the magnitude of post-exercise hypotension (i.e., blood pressure change) would be similar for all individuals but the mechanism of this response would differ by training status.

6.2 METHODS

6.2.1 Participants and Ethical Approval

Participants in this investigation were healthy, young, normotensive individuals. A total of 40 individuals (18 F) volunteered to partake in this research. Individuals were classified as endurance-trained if they participated in a minimum of ten hours of endurance training per week, in addition to a VO_2max greater than 55mL·kg·min^{-1}. All were screened using the new Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) to determine eligibility to participate: free from chronic disease and no contraindications to exercise. Participants were non-smokers and were not taking any medications other than oral contraceptives. Volunteers provided written informed consent, and this research was approved by the Clinical Research Ethics Board at the University of British Columbia.

6.2.2 Experimental Protocol

All individuals participated in three separate testing sessions with a minimum of 48 hours between sessions. The first session involved a maximal aerobic power assessment (VO_2max), followed by a second session where volunteers were assessed for body composition via a Dual-energy X-ray absorptiometry (DXA) scan. The third session involved the high-intensity interval session and was completed at least one week after the VO_2max test. Cardiovascular variables were measured before exercise (pre) and 30-minutes following the cessation of exercise (post).

6.2.3 Procedures and Analysis

Anthropometrics and DXA. Body mass and stature were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body surface area was calculated as BSA (m^2) = SQR RT ([Height(cm) x Weight(kg)]/ 3600) [170]. Whole body and sub-regional composition analysis was performed using dual energy x-ray absorptiometry on a 2006 Hologic Discovery Wi running the Apex 3.0 software suite. Participants were scanned in metal free clothing in standard anatomical position, with the toes restrained using a small section of paper tape. Sub-regional and whole body values for lean, fat and bone mineral content were produced.

VO_2max Assessment. Baseline automated blood pressure and heart rate was obtained at the start of this session (BMP-100 VSM Medtech, Coquitlam, Canada). Participants then completed a structured warm up, which included a five-minute rest period prior to starting an incremental bike test to exhaustion (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA). The protocol began at a workload of 80-100 watts and increased 25 watts

every two minutes until 1) the respiratory exchange ratio reached 1.0, and 2) the participant rated themselves a 6 or greater on the Ratings of Perceived Exertion scale. At this point, the test continued with workload increments every minute until volitional fatigue. Participants donned a face mask (Oro-nasal 7400 Vmask with Headgear, Hans Rudolph, Kansas, USA) for the collection of expired gases analyzed by metabolic cart (Medisoft Ergocard, Sorinnes, Belgium). In addition, HR and arterial hemoglobin saturation were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to the participant's left ear lobe.

Cardiovascular Variables. Baseline cardiovascular measures were measured following ten minutes of supine rest. Participants were instrumented with an ECG and finger plethysmography secured to the middle finger, using a beat-by-beat blood pressure device (Model-1 Pro: Finapres Medical Systems BV, The Netherlands). Continuous recordings were sent to a data acquisition system (PowerLab/16SP ML 795, ADInstruments, Colorado Springs, CO) and displayed using Chart (version 7.0, ADInstruments, Colorado Springs, CO). Automated blood pressure measurements obtained by brachial occlusion (BMP-100 VSM Medtech, Coquitlam, Canada) in the seated position were also collected in duplicate. Pulse pressure was calculated from systolic blood pressure (SBP) – diastolic blood pressure (DBP), and mean arterial pressure (MAP) was calculated as DBP + 1/3 pulse pressure.

Echocardiographic assessments were performed by a trained clinical sonographer using a portable ultrasound unit *(Vivid i,* GE Medical Systems, Israel) with simultaneous ECG and a 2.5-MHz transducer. Participants were positioned in the semi-left lateral decubitus position for imaging. Ventricular volumes and diameters were analyzed off-

line using EchoPAC software (GE Healthcare, v. 110.1.1) in accordance with the recommendations of the American Society of Echocardiography [175]. Left ventricular mass was determined using the formula: LV Mass (g) = 0.8 (1.04 ([LVIDD + PWTD + IVSTD]3- [LVIDD]3))+ 0.6 [177]. Apical four-chamber views were acquired for the assessment of end-diastolic volume (EDV) and end-systolic volume (ESV) using Simpson's bi-plane method for which three consecutive beats were measured and analyzed. Stroke volume (SV) was calculated by EDV-ESV. Cardiac output (CO) was calculated as SV x heart rate. Ejection fraction (EF) was calculated as a percentage of EDV. Fractional shortening (FS) was calculated from left ventricular diameters, using the parasternal long axis window, and expressed as a percent. Total peripheral resistance (TPR) was derived from MAP/CO. All cardiac dimensions, volumes and flow parameters, as well as total peripheral resistance were expressed relative to body size by indexing to body surface area (BSA) and presented as EDVI, ESVI, SVI, CI, and TPRI.

Hydration Assessment. A urine sample was collected prior to the interval session. A drop of urine was analyzed for urine specific gravity (Atago Pocket Refractometer, PAL-10S, Japan) which has been shown to be a valid means of assessing hydration status [215]. A result <1.02 served as the threshold of hydration status acceptable to commence testing [216, 217]. Once adequate hydration was verified, a measure of body mass was recorded to the nearest 0.1 kg using a digital scale (Seca, Birmingham, UK) and measured again post-exercise.

High Intensity Interval Exercise. For the high-intensity interval session, participants performed 15 one-minute maximal workbouts interspersed with two-minute recovery periods on a stationary cycle ergometer (Velotron Dynafit Pro, RacerMate Inc, Seattle,

USA). The workload was assigned in watts equivalent to the final power output obtained during the VO_2max test. The recovery periods were active rest at 50 W. The test began after five minutes of warm up followed by two minutes of inactive rest while seated on the bike. Participants were allowed to drink water ad libitum. The test ended with one minute of active recovery totalling 44 minutes of exercise. Seated blood pressure and body mass was measured before and immediately after the high-intensity interval session.

Baroreceptor Sensitivity Analysis. Baroreceptor sensitivity was analyzed by selecting a five minute segment of the Chart file via specialized software (Nevrokard NKFP 8.7.0 and BRS 5.7.0, Nevrokard, Izola, Slovenia). The sequence method was derived from the calculation of the slope between changes in R-R interval (RRI) and changes in systolic blood pressure, and the alpha coefficient in the low frequency (LF) or high frequency (HF) bands represented the cross-spectral method of BRS analysis [38]. For the sequence method, inclusion criteria was set as: a RR interval variation of greater than 5 ms, blood pressure changes greater than 0.5 mmHg, minimum sequence duration of four beats, sequence correlation coefficient greater than 0.85, and a one beat delay between SBP and RR interval. For the spectral method, the fast Fourier transformation was used to power spectral density of blood pressure and RR interval. The spectral gain of oscillations was set to fixed signal bandwidths of low frequency (0.04 – 0.15 Hz, LF) and high frequency (0.15 – 0.45 Hz, HF) as per current recommendations [38]. In the data analysis the sequence method values were labeled baroreceptor sensitivity, and the spectral components αLF and αHF. The ratio of LF to HF of the RRI as a measure of heart rate variability was labeled RRI LF/HF. Finally, the LF of blood pressure variability was labeled SBP LF.

6.3 STATISTICAL ANALYSIS

A mixed-model ANOVA was used to assess differences in haemodynamic and autonomic variables between pre- and post-exercise (time) by the factors sex (male, female) and training (NA, ET). Haemodynamic variables were related to VO_2max, muscle mass, percent body fat, baseline blood pressure and baroreceptor sensitivity, and magnitude of change in baroreceptor sensitivity using Pearson's correlation analysis. Linear regression analysis was used to determine the factors responsible for the change in cardiac function. Significance for all tests was set *a priori* at $p<0.05$. All analyses were performed using SPSS software (version 20.0; SPSS IBM, Chicago, IL). Results are reported as mean ± SD.

6.4 RESULTS

The participant characteristics are shown in Table 6.1. Sex differences at baseline were present as expected with men displaying greater height, body mass, lean body mass, aerobic capacity, peak power, and lower body fat ($p<0.01$). Endurance-trained individuals had greater aerobic capacity, peak power, and lower body fat than normally active individuals ($p<0.05$).

Prior to the interval session, urine specific gravity was within the range considered to represent adequate hydration [215] averaging 1.01 ± 0.01. Unaffected by sex or training status, body mass decreased 0.27 ± 0.47 kg following exercise. The peak heart rate response to the interval exercise bout was 94.7 ± 3.1 and 92.2 ± 3.8 % of maximum heart rate for NA and ET, respectively ($p=0.037$). There was no sex difference in this exercise heart rate response. All cardiovascular and autonomic variables displayed a main time

effect, or interaction of time and group (p<0.05), except ESVI, EF and SBP LF (Table 6.2; Table 6.3). Systolic blood pressure, DBP and MAP decreased from pre-exercise values by 6.2, 5.1, and 5.5%, respectively. Total peripheral resistance index decreased an average of 6% and was highly variable, while stroke volume index decreased 15% (9 – 22%) with an interaction of training status (p=0.026; Figure 6.2). Fractional shortening was significantly different from baseline and a trend was revealed by group (p=0.076; Figure 6.3). Among the autonomic variables, a time by training interaction was found for αLF (p=0.037) and αHF (p=0.002; Figure 6.4). Between subject effects (sex, training status) are also shown in Table 6.2 and 6.3. Men displayed greater SBP, EDVI, SVI, and CI than women, whereas women displayed higher BRS, αLF and αHF values than men. Endurance-trained individuals had greater EDVI, SVI, αLF and αHF and lower TPRI, RRI LF/HF and SBP LF than the normal active participants. Select correlations are listed in Table 6.4. Relationships of absolute stroke volume and VO_2max and LV mass are shown in Figures 6.5 and 6.6, respectively. Lastly, the change in SVI as it relates to baseline SVI is shown in Figure 6.7.

Table 6.1 Participant Characteristics

	Men		Women		*p* value		
	NA	**ET**	**NA**	**ET**	#	∞	^
n	*10*	*12*	*9*	*9*			
Age, *y*	28.0 ± 5.9	34.5 ± 5.6	29.4 ± 4.6	29.1 ± 5.9	0.209	0.045	**0.046**
Height, *cm*	179.8 ± 6.5	179.5 ± 6.9	164.1 ± 8.6	167.9 ± 4.2	**0.000**	0.467	0.339
Mass, *kg*	77.0 ± 7.4	76.2 ± 7.0	62.3 ± 13.3	59.3 ± 5.8	**0.000**	0.528	0.694
BMI, kg/m^2	23.8 ± 1.4	23.7 ± 1.7	22.9 ± 2.2	21.7 ± 2.0	**0.019**	0.269	0.369
VO_2max, $L \cdot min^{-1}$	3.61 ± 0.54	4.54 ± 0.53	2.81 ± 0.83	3.35 ± 0.49	**0.000**	**0.001**	0.328
VO_2max, $ml \cdot kg \cdot min^{-1}$	46.9 ± 5.3	59.7 ± 4.0	44.0 ± 4.0	56.4 ± 3.9	0.069	**0.000**	0.659
LVM, *g*	197.9 ± 29.4	242.0 ± 49.5	131.1 ± 19.2	176.2 ± 25.0	**<0.001**	**<0.001**	0.963
LVM/BSA, g/m^2	179.8 ± 6.5	179.5 ± 6.9	164.1 ± 8.6	167.9 ± 4.2	**<0.001**	**<0.001**	0.614
LBM, *kg*	58.9 ± 6.0	58.6 ± 7.0	41.5 ± 6.5	42.9 ± 5.3	**0.000**	0.785	0.670
LBM/BSA, kg/m^2	30.0 ± 1.4	27.6 ± 8.9	24.6 ± 1.1	23.0 ± 8.8	**0.021**	0.329	0.853
Fat, *%*	20.6 ± 3.9	18.8 ± 4.9	28.6 ± 3.6	22.5 ± 3.9	**0.000**	**0.004**	0.106
Peak Power, *W*	225 ± 45.6	300.0 ± 41.3	182.2 ± 44.5	235.0 ± 24.5	**0.000**	**0.000**	0.542

Abbreviations: LVM=left ventricular mass; LBM=lean body mass; BSA=body surface area
The effects of sex and training status on participant characteristics were analyzed by unadjusted general linear models.
BOLD *p* values denotes statistically significant; # between sex, ∞between group, ^ between sex by group.

Table 6.2 Baseline and Post-Exercise Haemodynamics

		Men		Women	
		NA	**ET**	**NA**	**ET**
SBP, *mm Hg* * #	Pre	113.4 ± 6.1	111.6 ± 10.3	101.0 ± 6.9	104.0 ± 8.8
	Post	110.1 ±	99.3 ± 11.8	95.4 ± 8.2	98.7 ± 12.8
DBP, *mm Hg* *	Pre	64.7 ± 3.7	66.6 ± 3.9	63.7 ± 6.2	67.0 ± 7.1
	Post	60.8 ± 8.6	63.2 ± 7.4	61.4 ± 8.4	62.8 ± 13.3
MAP, *mm Hg* *	Pre	80.9 ± 3.7	81.6 ± 5.0	76.1 ± 5.7	79.1 ± 6.8
	Post	77.2 ± 9.2	75.2 ± 7.4	72.8 ± 8.0	74.7 ± 12.8
HR, *bpm* *	Pre	57.9 ± 5.2	52.3 ± 7.6	56.3 ± 10.1	59.0 ± 8.5
	Post	78.3 ± 8.2	72.8 ± 12.3	74.9 ± 8.8	74.1 ± 9.6
EDVI, *mL/ m* ^{2} ¥#	Pre	72.8 ± 14.7	85.9 ± 15.7	59.7 ± 10.4	77.0 ± 17.9
	Post	60.9 ± 9.5	71.9 ± 14.9	50.8 ± 10.2	67.9 ± 5.2
ESVI, *mL/ m* ^{2}	Pre	29.4± 6.0	31.1 ± 10.9	22.4 ± 6.4	30.7 ± 11.9
	Post	27.5± 5.3	28.4 ± 7.8	18.5 ± 3.9	27.1 ± 5.8
SVI, *mL/ m* ^{2} ¥# ∞	Pre	26.4±8.2	33.2 ± 7.4	23.3 ± 5.9	27.4 ± 5.5
	Post	20.3±3.6	26.3 ± 5.5	20.2 ± 4.7	24.1 ± 2.5
EF, *%* ^	Pre	59.1±7.6	64.0 ± 9.3	62.5 ± 9.1	61.2 ± 7.5
	Post	55.0±4.3	60.8 ± 5.9	63.4 ± 4.1	60.3 ± 6.5
FS, *%* *	Pre	39.1±6.1	38.6 ± 7.3	34.9 ± 5.7	36.4 ± 4.7
	Post	36.2±7.4	33.3 ± 9.8	36.5 ± 5.0	30.9 ± 6.3
CI, $L \cdot min^{-1}/m^2$ * #	Pre	2.5 ± 0.6	2.8 ± 0.6	2.1 ± 0.6	2.8 ± 0.7
	Post	2.7 ± 0.5	3.1 ± 0.5	2.5 ± 0.6	3.2 ± 0.7
TPRI, *mm Hg/* $L \cdot min^{-1}/m^2$ * # ∞	Pre	9.0 ± 2.5	8.0 ± 2.3	14.7 ± 6.5	11.1 ± 3.1
	Post	7.8 ± 2.2	6.6 ± 1.4	11.5 ± 4.0	8.8 ± 2.4

Abbreviations: SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; HR=heart rate; EDV=end-diastolic volume; ESV=end-systolic volume; SV=stroke volume; EF=ejection fraction; FS=fractional shortening; CO=cardiac output; TPR=total peripheral resistance

* $p<0.05$ time, ¥ $p<0.05$ time by group # $p<0.05$ between sex, ∞ $p<0.05$ between group, ^ $p<0.05$ between sex by group.

Table 6.3 Baseline and Post-Exercise Autonomic Parameters

		Men		Women	
		NA	**ET**	**NA**	**ET**
BRS, *ms.mm Hg* * #	Pre	23.3±10.3	28.3±8.7	38.8±14.2	30.0±18.0
	Post	7.4±2.8	11.4±6.1	17.3±13.5	13.3±7.3
αLF, *mm Hg* ¥ #	Pre	13.5±6.6	20.3±8.7	22.0±14.0	28.5±8.2
	Post	7.0±3.2	10.1±6.0	14.1±9.6	9.3±4.3
αHF, *mm Hg* ¥ #	Pre	21.1±9.6	34.9±18.	37.0±27.0	56.9±16.9
	Post	7.2±4.5	10.7±5.6	25.1±16.3	15.0±7.8
RRI LFHF * ∞	Pre	2.1±1.2	1.2±0.6	1.5±0.8	1.1±0.7
	Post	8.4±5.9	8.4±7.4	3.4±3.1	5.0±5.0
SBP LF, *mm Hg* ∞	Pre	12.2±8.0	4.4±4.3	13.0±17.6	2.5±0.8
	Post	19.1±15.1	9.2±9.4	4.9±2.4	10.0±8.5

Abbreviations: BRS=baroreceptor sensitivity; αLF=alpha coefficient of low frequency spectral power; αHF=alpha coefficient of high frequency spectral power; RRI LFHF=low frequency to high frequency ratio of RR interval; SBP LF=low frequency power of systolic blood pressure variability

The effects of exercise on cardiovascular haemodynamics were analyzed by general linear models adjusted for sex and training status.

* $p<0.05$ time effect, ¥ $p<0.05$ time by group, # $p<0.05$ between sex, ∞ $p<0.05$ between group

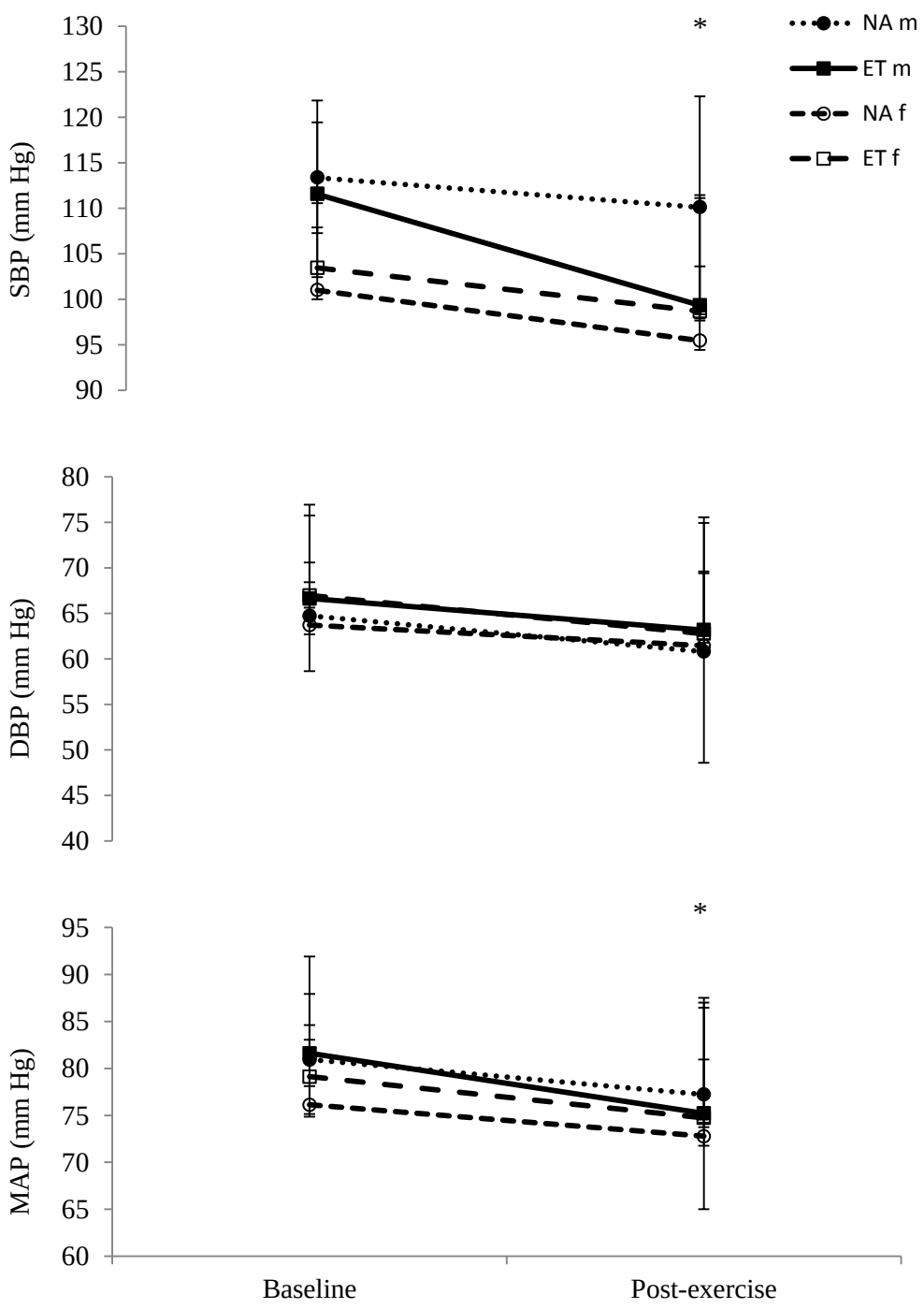

Figure 6.1 Effect of Exercise on Blood Pressure
* $p<0.05$ from baseline

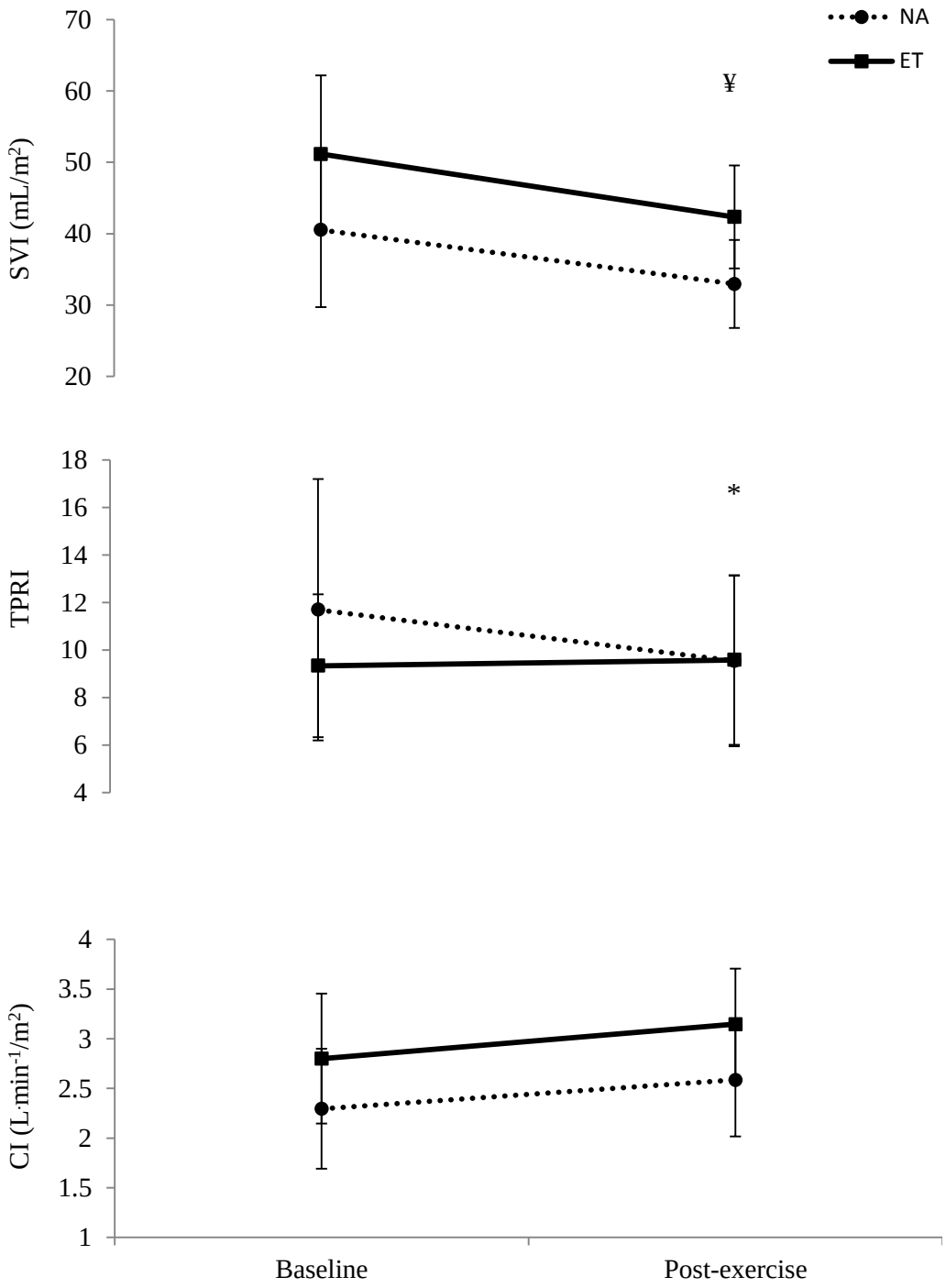

Figure 6.2 Exercise Haemodynamics

* $p<0.01$ from baseline; ¥ $p=0.026$ time by group

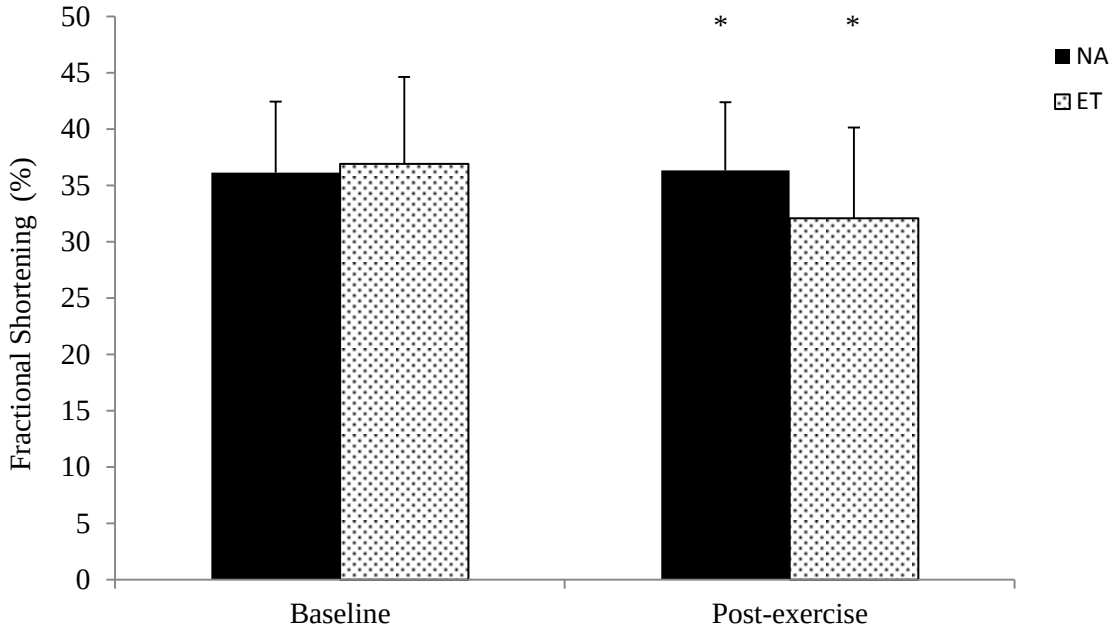

Figure 6.3 Effects of Exercise on Fractional Shortening

* p=0.026 from baseline

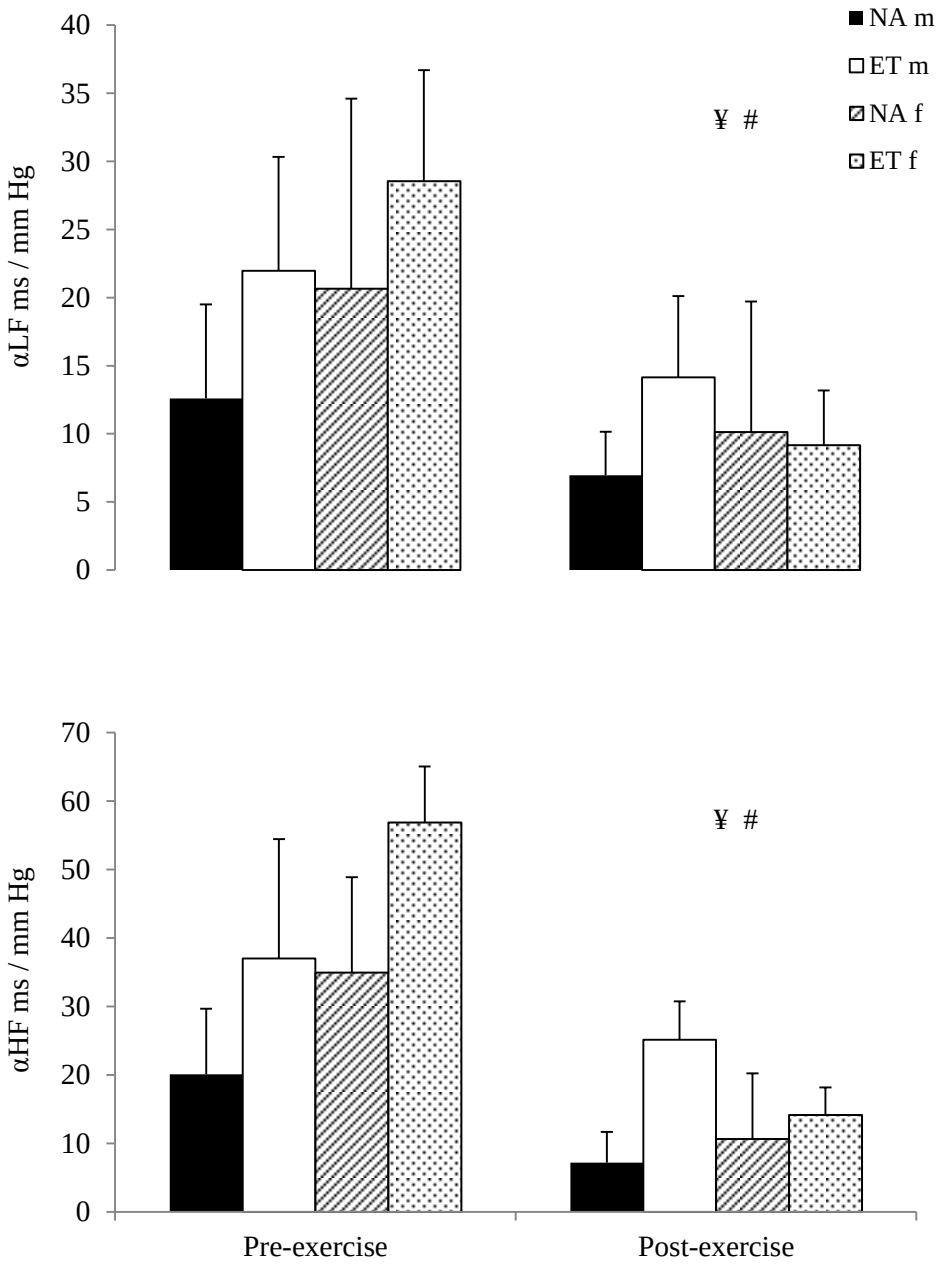

Figure 6.4 Effect of High-Intensity Interval Exercise on Indices of Baroreceptor Sensitivity

¥ $p<0.05$ time by group; # between sex

Table 6.4 Select Correlations

	Δ SBP	Δ EDVI	Δ SVI	Δ aLF	Δ aHF
Pre SBP	**r = -0.314**	r = 0.205	r = -0.214	r = 0.044	r = -0.027
	***P* = 0.048**	*P* = 0.204	*P* = 0.186	*P* = 0.787	*P* = 0.868
Pre EDVI	**r = -0.365**	**r = 0.653**	**r = -0.623**	r = 0.244	r = 0.157
	***P* = 0.021**	***P* = 0.000**	***P* = 0.000**	*P* = 0.129	*P* = 0.332
Pre SVI	r = -0.290	**r = 0.388**	**r = -0.755**	r = 0.102	r = 0.209
	P = 0.069	***P* = 0.013**	***P* = 0.000**	*P* = 0.529	*P* = 0.196
Pre TPRI	r = 0.082	r = -0.288	**r = 0.547**	r = -0.193	r = -0.208
	P = 0.615	*P* = 0.071	***P* = 0.000**	*P* = 0.232	*P* = 0.198
Pre BRS	r = 0.227	r = -0.104	r = -0.003	**r = 0.389**	**r = 0.433**
	P = 0.158	*P* = 0.523	*P* = 0.988	***P* = 0.013**	***P* = 0.005**
RRI LF/HF	r = -0.041	r = 0.053	r = 0.081	r = -0.137	**r = -0.344**
	P = 0.807	*P* = 0.754	*P* = 0.629	*P* = 0.413	***P* = 0.035**
VO_2max	r = -0.285	r = 0.107	**r = -0.373**	r = 0.045	r = 0.097
$L \cdot min^{-1}$	*P* = 0.075	*P* = 0.510	***P* = 0.018**	*P* = 0.782	*P* = 0.550
VO2max	**r = -0.365**	r = 0.097	r = -0.215	r = 0.198	r = 0.275
$mL \cdot kg \cdot min^{-1}$	***P* = 0.021**	*P* = 0.550	*P* = 0.183	*P* = 0.221	*P* = 0.086
LBM	r = 0.038	r = -0.106	r = -0.024	r = -0.097	r = -0.068
	P = 0.817	*P* = 0.515	*P* = 0.885	*P* = 0.554	*P* = 0.677
LBM/BSA	r = -0.056	r = 0.129	**r = -0.369**	r = -0.050	r = -0.050
	P = 0.739	*P* = 0.439	***P* = 0.023**	*P* = 0.764	*P* = 0.764
LVM	r = -0.191	r = 0.093	**r = -0.364**	r = -0.032	r = 0.019
	P = 0.254	*P* = 0.577	***P* = 0.025**	*P* = 0.850	*P* = 0.910
LVM /BSA	r = -0.189	r = 0.065	r = -0.264	r = -0.042	r = 0.061
	P = 0.255	*P* = 0.699	*P* = 0.109	*P* = 0.801	*P* = 0.718

Abbreviations: SBP=systolic blood pressure; EDVI=end-diastolic volume index; SVI=stroke volume index; TPRI=total peripheral resistance index; BRS=baroreceptor sensitivity; αLF=alpha coefficient of low frequency spectral power; αHF=alpha coefficient of high frequency spectral power; RRI LFHF=low frequency to high frequency ratio of RR interval; LBM=lean body mass; BSA=body surface area; LVM=left ventricular mass
BOLD *p* values denotes statistical significance ($p<0.05$)

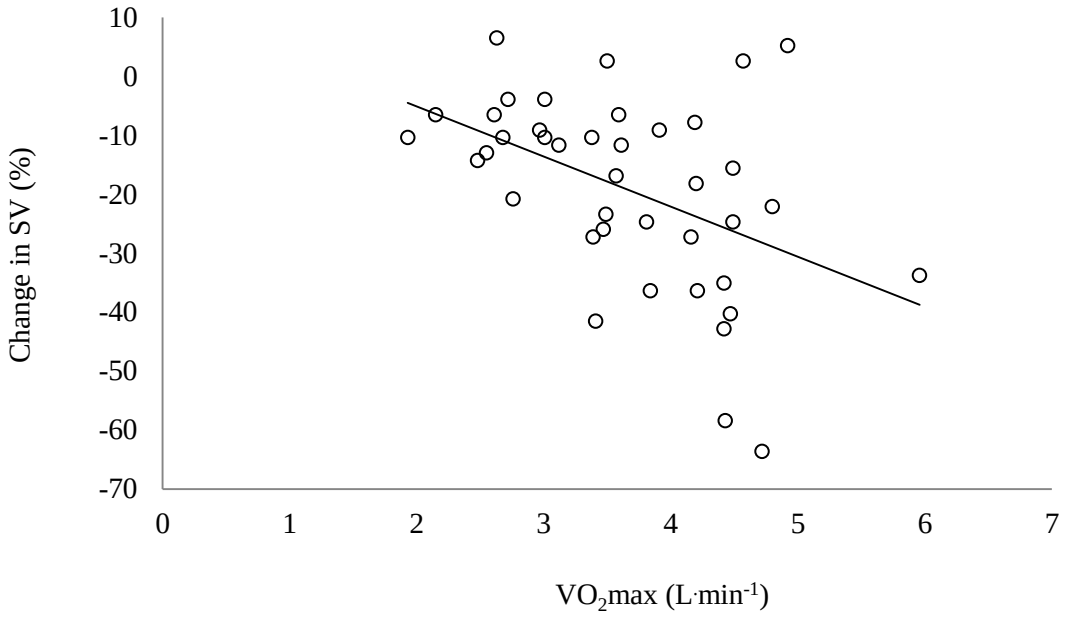

Figure 6.5 Relationship of Aerobic Capacity to Percent Change in Stroke Volume

Pearson r=-0.49, p=0.007; Linear Regression: r^2=0.24, Std. Beta=-0.548 (adjusted for group), p=0.002

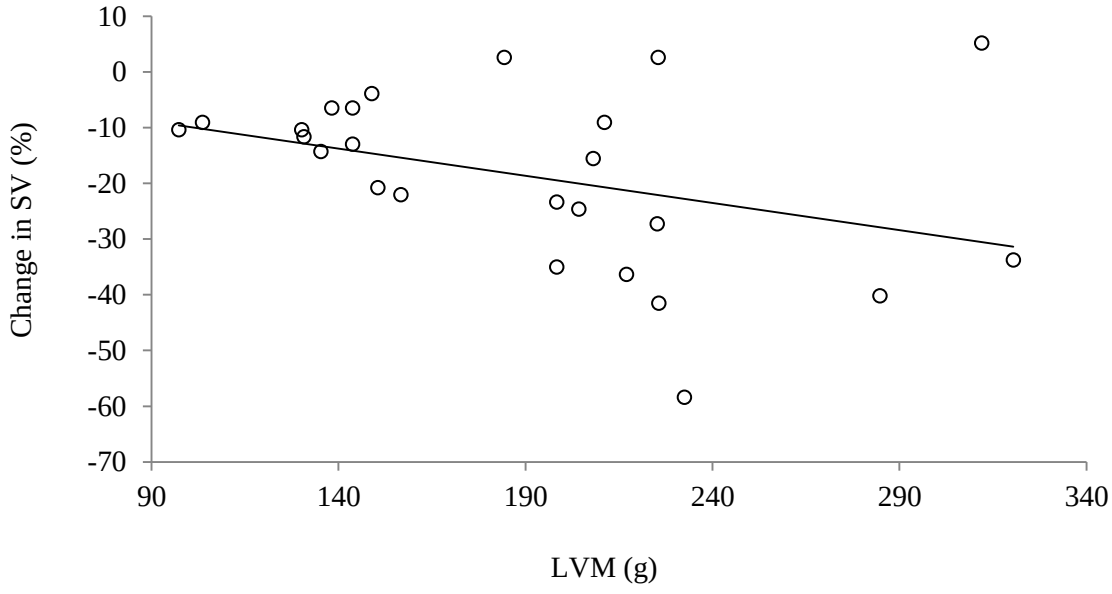

Figure 6.6 Association of Left Ventricular Mass to Change in Stroke Volume

Pearson r=-0.47, p = 0.011; Linear Regression: r^2=0.22, Std. Beta=-0.515 (adjusted for group), p=0.004

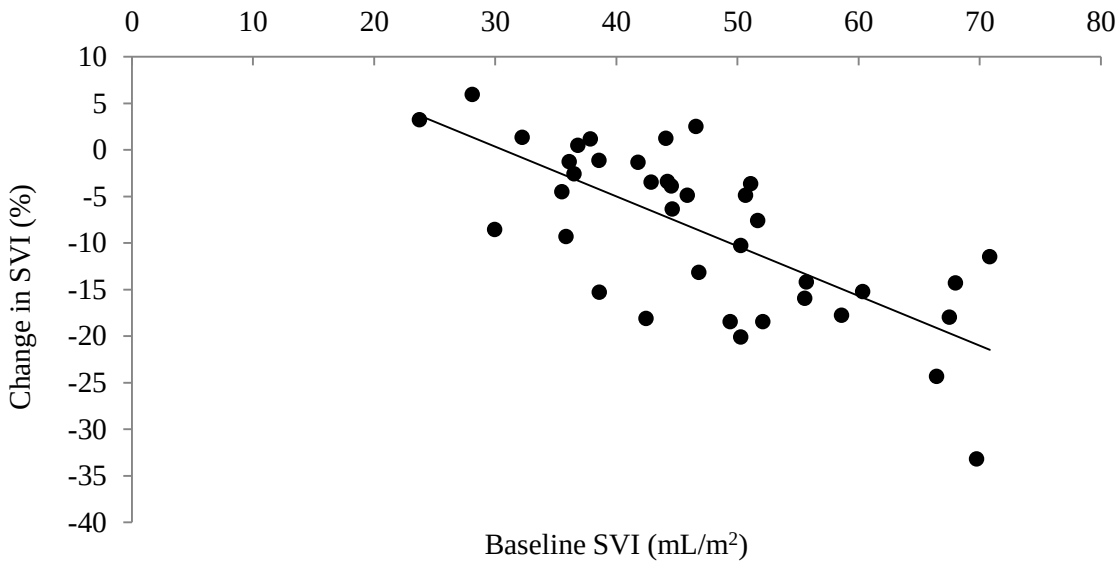

Figure 6.7 Association of Change in Stroke Volume to Baseline Stroke Volume

Pearson r=-0.750, $p<0.001$; Linear Regression: r^2=-0.63, Std. Beta=-0.851 (adjusted for group), $p<0.001$

6.5 DISCUSSION

The aim of this investigation was to assess post-exercise hypotension following a strenuous bout of interval exercise in normotensive, endurance-trained and untrained men and women. The primary findings of this investigation are that 1) the magnitude of post-exercise hypotension following high intensity interval exercise was similar regardless of sex or training status, and 2) endurance-trained individuals displayed more marked reductions in stroke volume than normally active individuals, and 3) greater reductions in baroreceptor sensitivity occurred in the trained group. To our knowledge this the first study to investigate post-exercise hypotension following high-intensity interval exercise incorporating both sex and training status into the design. Our study suggests that high intensity interval exercise elicits a similar acute blood pressure response in healthy individuals but that training status differentiates the mechanism of this response.

Earlier work investigating post-exercise hypotension in healthy men and women found a sex and training interaction where endurance trained men presented a different mechanism of post-exercise hypotension compared with endurance-trained women, however in untrained individuals this sex difference did not exist [228]. These authors reported that untrained men experienced a fall in cardiac output with no change in total peripheral resistance whereas the other groups maintained cardiac output with significant reductions in peripheral resistance, an indication of more active vasodilation. Furthermore, these authors propose that a greater fall in central venous pressure and thus cardiac preload was responsible. Our work supports these findings, and extends this mechanism to include endurance-trained women, however differs from the work of Senitko and colleagues in a few ways. First they utilized a submaximal protocol at an

intensity of 60% VO_2max. While exercise intensity appears to have little effect on the magnitude of post-exercise hypotension, higher intensity exercise alters hemodynamics to a greater extent than submaximal exercise [254, 295]. Second, the reported VO_2max values of the endurance-trained individuals in the former study were similar to that of our normally active participants, subsequently making it difficult to compare with our competitive cyclists. By contrast, Rossow and colleagues [295] found endurance-trained males and females to have a similar mechanism of post-exercise hypotension following high intensity interval exercise, in agreement with our results: a decrease in SVI, an increase in CI, and a decrease in TPRI for both men and women.

Contrary to our hypothesis, we did not find sex differences in the post-exercise hypotension response. We speculated that the larger cardiac size of males due to sex-related differences coupled with the chronic training adaptations would create an acute exercise response unique to the four groups [300]. Further it has been shown that women experience higher peripheral resistance during endurance exercise [301] thus we expected normally active women to represent the other end of the spectrum. Indeed it has been suggested that men may experience post-exercise hypotension without vasodilation [302], however, a number of studies are in disagreement. Scott et al. [254] reported total peripheral resistance significantly reduced in endurance-trained males following both high-intensity interval exercise, and steady-state exercise. Moreover, vasodilation was found to occur in normally active males [228] and endurance-trained males following steady-state exercise [295].

There is a general consensus that post-exercise hypotension typically occurs as a result of a mismatch between the drop in systemic vascular resistance and increase in cardiac

output [288]. While this was reflected in our sample as a whole, the endurance-trained individuals exhibited greater reductions in stroke volume. Possible factors affecting stroke volume are preload, afterload, and myocardial contractility. Using systolic blood pressure as a surrogate of afterload, and cardiac indicators of contractility (end-systolic volume and fractional shortening), we did not find any differences in these responses among groups. Granted, a slight trend was observed for a greater reduction in fractional shortening for endurance trained subjects however this was not statistically significant. Thus, we cannot support the notion of differences in contractility between the groups, however we acknowledge this is a possibility. We did not measure central venous pressure in this investigation however, we found a prominent interaction of group by time for EDVI which would indicate differences in preload in endurance-trained versus normally active individuals. Possible explanations include alterations in baroreflex function, or the redistribution of cardiac output from less compliant to more compliant vascular beds, and are discussed below.

Differences in baroreflex function may play a role. Following exercise, the baroreflex sets to a lower pressure [252] and sympathetic vasoconstrictor influence is reduced [292]. In the presence of reduced afterload, reduced vasoconstrictive capacity could alter cardiac filling. Earlier research showed that blocking the cardiac afferents and efferent fibers with intrapericardial procainamide prevented post-exercise hypotension, while blocking the cardiac efferent alone elicited no effect [303]. Chandler et al demonstrated in rats that by removal of the arterial baroreflex afferents via sinoaortic denervation, post-exercise hypotension was prevented [304]. Hence, these investigations showed the importance of a functioning baroreflex for the expression of post-exercise hypotension. In our study

using non-invasive cardiovagal measurements of baroreflex function, we found evidence of greater reductions in αLF and αHF components in the endurance-trained individuals. However, we did not find any association of these changes to the magnitude of post-exercise hypotension or haemodynamic alterations. Lacombe et al. [297] compared the haemodynamic and BRS responses following high intensity interval exercise to that of steady state exercise in pre-hypertensive older (50 – 65y) men. They found similar post-exercise hypotension responses between the two protocols but reductions in baroreceptor sensitivity for the high intensity exercise only. As in our study, the change in baroreceptor sensitivity did not evoke any differences in the post-exercise hypotension response. It has been suggested that a combination of central and peripheral mechanisms regulating blood pressure are likely responsible for post-exercise hypotension [286] and may explain why a direct link is not shown.

The reduced venous return after exercise may be a result of the redistribution of cardiac output from less compliant to more compliant vascular beds such as the splanchnic organs and the skin [305]. Recently shown to be unrelated to post-exercise hypotension, new evidence suggests that vasoconstriction in other areas, perhaps the splanchnic or renal vascular beds, may offset the vasodilation in skeletal muscle in endurance-trained individuals [306] and would explain why they typically do not exhibit the post-exercise augmentation of systemic vascular conductance [302]. Recent work using pharmacological blockade has highlighted histaminergic mechanisms responsible for the post-exercise hyperemia in endurance-trained men and women [302]. Further, ventricular compliance is known to be greater in endurance-trained athletes and may potentially result in larger reductions in stroke volume for a given cardiac filling pressure

[263]. While a more compliant ventricle allows for greater cardiac efficiency during exercise, in concert with hyperemia in the lower limbs after exercise, may exaggerate the reduction in stroke volume for a given reduction in LV filling pressure [245].

6.6 LIMITATIONS

The potential decreased in plasma volume due to sweat loss in the endurance-trained subjects must be considered as possible factor affecting preload in our study. While we did not measure plasma volume, we did assess weight loss following the exercise; the small decrease was not different between groups. Also, participants were encouraged to drink throughout, thus we do not anticipate decreases in plasma volume were responsible for our results. Finally, while our sample size was determined to be adequately powered to detect the expected physiological changes *a priori*, the division of four groups lowered the observed power significantly for certain variables. This needs to be considered when interpreting the interaction of sex and training status on post-exercise hypotension.

6.7 CONCLUSIONS

We determined that high intensity interval exercise induced post-exercise hypotension in normotensive men and women of different training status. We also demonstrated that following high intensity interval exercise training status, but not sex, differentiated the mechanisms of post-exercise hypotension where endurance-trained individuals presented post-exercise hypotension via a decrease in stroke volume whereas normally active did not. This work has implications for the use of interval exercise as an effective means of acute blood pressure modifications, and may be an alternate form of exercise that could be used in interventions aimed at prevention of hypertension.

Chapter 7: The Effects of High Intensity Exercise on Cognitive Function in Healthy Young Adults

7.1 INTRODUCTION

Cognition broadly defined pertains to knowledge processing (i.e., attention, memory, learning, reasoning, problem solving, and decision making) mediated by a centralised nervous system [307]. Physical activity and exercise positively influence cognition. Regular physical activity has been associated with a reduction in the decline in cognitive function that is typically associated with aging [308-313], and this cognitive decline may be due to age-related brain atrophy [314]. There have also been reports that aerobic exercise in childhood may increase cerebral resilience to age-related decline, whereby improved cognition is shown in those who exercised more [315]. This suggests that there are lasting effects of exercise on cognitive function. Furthermore, a recent study has shown cognitive function was higher in physically active compared with inactive individuals, with cognition correlated to VO_2max [316]. Fit individuals were also shown to have greater cerebrovascular conductance and increased cerebrovascular reserve. Both acute and chronic effects of exercise such as alterations in neurotransmitters, neurotrophins, and vasculature changes, and their association with cognitive function have been of recent mechanistic interest [317]. Hence a large gap remains in how exercise mediates cognitive benefits.

Dopamine, a key neurotransmitter in the brain, has been shown to be involved in learning [318-321] and may mediate improvements in memory [322]. However investigations exploring the plasma dopamine response to physical exercise have

produced conflicting results as not all investigations report an increase in dopamine with exercise [323]. Intensity of exercise may be a key factor in stimulating dopamine release whereby a certain degree of acidosis is required [324]. In this regard, high-intensity exercise may be an effective means of stimulating dopamine and accentuating circulation, resulting in a substantial impact on cognition. Currently the research involving high intensity exercise and cognition is limited. It has been suggested that cognitive performance decrements would occur with strenuous exercise due to substantial physiological fatigue [325] or diminished attention [326]. Reaction time, the time taken to complete a task, may also be affected when under a fatigued state as increased reaction times (decreased cognitive performance) were reported after high-intensity exercise [327, 328]. However, improved cognitive function (i.e., working memory, reaction time, vocabulary learning) may occur during the recovery period [328-330]. Collectively, the findings of these investigations suggest that enhanced cognitive performance may occur during recovery from exercise, when attentional resources become available while an increase in systemic circulation persists.

High-intensity interval exercise is increasing in popularity, in part due to the greater physiological and metabolic gains that have been reported over traditional aerobic exercise in various populations [17]. Therefore, the assessment of cognition following high-intensity interval exercise may reveal further health benefits for this type of exercise. The small body of work investigating cognition in relation to high-intensity exercise has predominately involved very brief exercise bouts, such as the 30-second Wingate. The repeated nature of high-intensity interval exercise produces a substantial physiological stimulus and would be expected to impact cognition differently to that of a

30-second sprint. Accordingly we investigated the impact of maximal high-intensity interval exercise on cognitive function (reaction time and working memory) following one and four hours of recovery. As haemodynamic indicators of recovery have been shown to return towards baseline very rapidly following high-intensity exercise in healthy young adults [331], it was hypothesized that increased reaction time and working memory would be enhanced from baseline values following one hour of recovery but return to baseline at four hours.

7.2 METHODS

7.2.1 Participants and Ethical Approval

Twelve healthy, physically active individuals (2 F) with a mean age 28 ± 3.7 y volunteered for this study. All participants answered pre-screening questionnaires indicating they were free of chronic disease, with no history of concussion. All individuals were non-smokers and not taking any medications other than oral contraceptives. Volunteers provided informed consent and this research was approved by, and executed in exact accordance with the guidelines set out by the Clinical Research Ethics Board at the University of British Columbia.

7.2.2 Experimental Protocol

Participants were engaged in two days of testing. On day 1, participants were assessed for basic anthropometrics, baseline cardiovascular and cognitive function, as well as maximal aerobic capacity (VO_2max). After one to two weeks, individuals returned to the laboratory and completed two more baseline assessments of cognition (Pre), the last of which was considered true baseline. Following 44 minutes of exercise, basic

haemodynamic variables were assessed at three time points: immediately post-exercise (Post), one hour post-exercise (Rec 1), and four hours post-exercise (Rec 2). Cognitive assessments after exercise were conducted at one hour post-exercise (Rec 1), and four hours post-exercise (Rec 2). Blood samples were taken before exercise and immediately post-exercise. A schematic of the protocol can be found in Appendix C.

7.2.3 Procedures

Basic Anthropometrics. Anthropometrics and Cardiovascular Variables. Height and body mass were measured to the nearest 0.1 cm and 0.1 kg, respectively. Baseline cardiovascular measures of heart rate, blood pressure, arterial compliance and pulse wave velocity were assessed on day 1 following 10 minutes of supine rest. Participants were instrumented with an ECG and finger plethysmography secured to the middle finger, using a beat-by-beat blood pressure device (Model-1 Pro: Finapres Medical Systems BV, The Netherlands). Automated blood pressure measurements obtained by brachial occlusion (BMP-100 VSM Medtech, Coquitlam, Canada) were used to verify and correct readings obtained from the Finometer. At the femoral and carotid arteries, infared photoelectric sensors (MLT1020PPG Plethysmograph, AD Instruments) recorded changes in pulsatile blood flow by recording changes in blood volume as the arterial pulse expands and contracts the microvasculature. These instruments plug directly into a bridge amp to the PowerLab (Bridge Amp/ML221; Powerlab/16SP ML 795: ADInstruments, Colorado Springs, CO). Pulse wave velocity was determined via post-collection analysis as previously described [212]. Briefly, a minimum of 30 consecutive cardiac cycles were averaged to calculate the foot-to-foot pulse transit time between the

carotid artery and femoral artery. The shortest distances between the sites of pulse contour collection were measured to the nearest 0.5 cm using a standard measuring tape and this distance was divided by the corresponding pulse transit time in order to calculate pulse wave velocity.

Baseline arterial compliance was obtained as a measure of vascular health, and was assessed non-invasively using an applanation tonometer (CR-3000, HDI Hypertension Diagnostics). This technique, based on a modified Windkessel model that allows for the calculation of large (capacitive) artery and small (oscillatory) artery compliance, has been validated with invasive testing [173]. The radial arterial waveform acquisition of the right arm was obtained in conjunction with automated blood pressure on the left arm inflated to 20-30 mmHg below radial pulsatory pressure. For the exercise sessions, blood pressure was measured before and after exercise, with heart rate measured every minute throughout.

VO_2max. Following the acquisition of seated automated blood pressure and heart rate (HR; BMP-100 VSM Medtech, Coquitlam, Canada), participants completed a structured warm up, which included a 5 minute rest period prior to starting the incremental bike test to exhaustion (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA). The protocol began at a workload of 80-100 watts and increased 25 watts every 2 minutes until 1) the respiratory exchange ratio reached 1.0, and 2) the participant rated themselves a 6 or greater on the Ratings of Perceived Exertion scale. At this point, the test continued with 25 watt increments every minute until volitional fatigue, and the criteria for maximal testing were met. Participants donned a face mask (Oro-nasal 7400 Vmask with Headgear, Hans Rudolph, Kansas, USA) for the collection of expired gases analyzed by

metabolic cart (Medisoft Ergocard, Sorinnes, Belgium). In addition, heart rate and arterial hemoglobin saturation were measured continuously using a pulse oximeter (Masimo Radical, Irvine, CA, USA) attached to the participant's left ear lobe.

High-Intensity Interval Exercise. For the high intensity interval session participants performed fifteen 1-minute maximal work intervals interspersed with two-minute recovery periods on a stationary cycle ergometer (Velotron Dynafit Pro, RacerMate Inc, Seattle, USA). The workload was 100% of the power output obtained during the VO_2max test, and the recovery periods were active rest (50-100 watts). Participants completed a warm up at a self-selected intensity followed by two minutes of inactive rest while seated on the bike with the final set ending after one minute of active rest for total session duration of 44 minutes. Participants were allowed to drink water ad libitum.

Blood Sampling and Dopamine Analysis. Pre- and post-exercise blood samples (6 ml each) were drawn from a medial cubital vein using a needle and vacutainer system. The blood was centrifuged and frozen at -80°C until analysis. Dopamine was analyzed by immunoassay using ELISA kit RE59395 (IBL International, Hamburg, Germany) with an analytical sensitivity of 4 pg.mL-1 and cross-reactivity <0.5%. The intra-assay and inter-assay coefficient of variation were <10.9% and 16%, respectively.

Cognitive Test Battery. Cognitive testing was performed using computerized assessment to measure simple reaction time, choice reaction time, working memory task time, and working memory task accuracy (CogState Ltd, Carlton, VIC, Australia). This computerized assessment is easy to administer and shown to be sensitive to mild cognitive impairment from various causes [332-337]. Each testing situation started with

three to five warm-up stimuli (specific practice for each task). The chosen tests are briefly described below:

Detection Task (Simple Reaction Time): In front of a monitor displaying a green background and a deck of cards (face down), the participant was instructed to hit the space bar as rapidly as possible after the card displayed on the monitor turned face up. The next card was then displayed, and the participant repeated the task until 35 stimuli were presented. Reaction time was recorded in milliseconds (ms).

Identification Task (Choice Reaction Time): Similar to the Detection Task, the participant answered the question "Is the card red?" by clicking the yes or no assigned keys as rapidly as possible after the card displayed on the monitor turned face up. The next card was then displayed, and the participant repeated the task until 30 stimuli were presented. Choice reaction time was measured in ms.

CPAL Task (Visual Learning and Memory): This task was divided into two stages. In Stage 1, one ball was presented in the middle of the computer monitor, around which seven other balls were displayed. The participant was required to click on the peripheral balls to reveal a hidden picture. The participant was asked to memorize the pictures hidden under each of the balls, and their respective locations. In Stage 2, the participant was asked to answer the question "In what locations do these pictures belong?". The ball in the middle displays a picture, and the participant clicked on the peripheral ball hiding the same picture. Seven rounds of eight stimuli were presented to the participant, for a total of 56 stimuli. Time to complete the total task in milliseconds, and total number of errors were assessed.

7.3 STATISTICS

Cognitive and corresponding cardiovascular variables were assessed using repeated-measures ANOVA with Bonferroni adjustment for multiple comparisons. Simple and choice reaction time and working memory were correlated with baseline vascular measures, VO_2max, change in heart rate and blood pressure, and change in dopamine, using Pearson's r. Linear regression analysis was used to determine the factors responsible for the change in cardiac function. Significance for all tests was set *a priori* at $p<0.05$. All analyses were performed using SPSS software (version 20.0; SPSS IBM, Chicago, IL). Results are reported as mean ± SD.

7.4 RESULTS

All 12 recruited individuals completed the testing protocol and were included for analysis. Participant characteristics, baseline cardiovascular measures, and maximal aerobic capacity are found in Table 7.1. Mean group heart rate during exercise increased from 147.2 ± 12.1 bpm after the first interval to a mean heart rate of 174.5 ± 7.4 bpm following the last work bout. Figure 7.1 presents pre-exercise and recovery heart rates. At the first recovery measurement (Post), mean heart rate decreased to 100.5 ± 10.9 bpm compared to the last exercise bout. Participants post body mass was 74.6 ±10.1 from 74.9 ± 10.1 kg ($p<0.001$), all significantly different from baseline and each other. Resting heart rate was negatively correlated with VO_2max ($r=-0.81$, $p=0.001$).

Table 7.1 Participant Characteristics

Variable	*n = 12 (2F)*
Age, y	28.0 ± 3.7
Height, cm	176.7 ± 8.5
Body Mass, kg	74.5 ± 10.0
BMI, $kg.m^2$	23.7 ± 1.5
SBP, mm Hg	115.5 ± 10.8
DBP, mm Hg	61.1 ± 6.7
LAC, $ml \cdot mmHg \cdot 10$	19.6 ± 3.8
SAC, $ml \cdot mmHg \cdot 100$	10.5 ± 1.8
PWVc, cm/s	624.2 ± 211.2
PWVu, cm/s	547.3 ± 348.4
VO_2max, $mL \cdot kg.min^{-1}$	48.9 ± 8.1

Abbreviations: BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; LAC=large artery compliance; SAC=small artery compliance; PWVc=central pulse wave velocity; PWVu=upper segment of pulse wave velocity

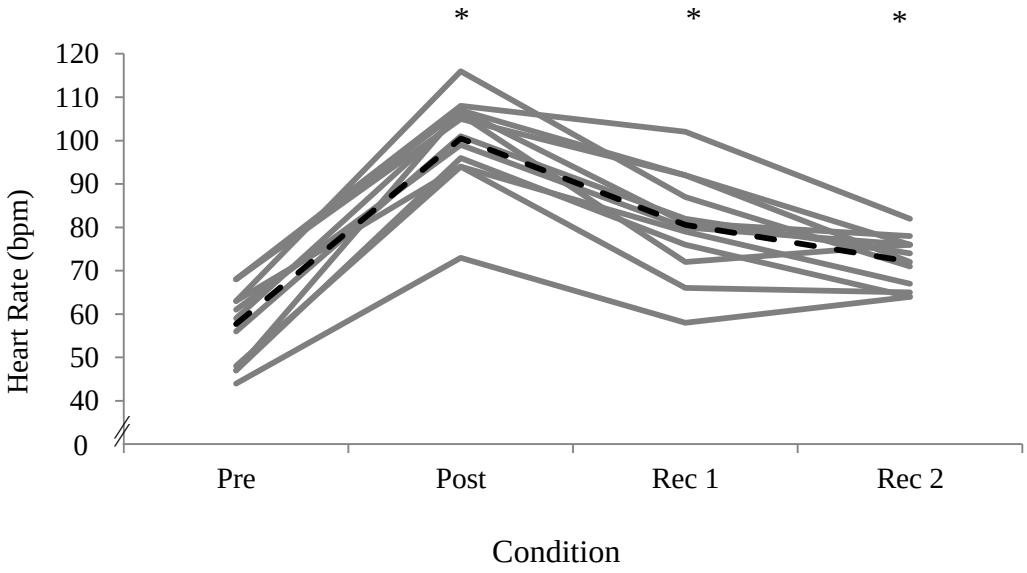

Figure 7.1 Individual Results for Change in Heart Rate

Baseline (Pre), immediately post-exercise (Post), 1 hour post-exercise (Rec 1) and 4 hours post-exercise (Rec 2). The mean is represented by the dashed (- - -) line.
* different from baseline $p<0.001$.

Simple reaction time decreased from baseline (Figure 7.2, p=0.001) with both Rec 1 and Rec 2 different from baseline (p=0.008 and p=0.028, respectively) and not different from each other (p=0.546). Choice reaction time decreased over time (Figure 7.3, p=0.001), also with both Rec 1 and Rec 2 different from baseline (p=0.024 and p=0.016, respectively) and not different from each other (p=0.863). The participants performed better on the CPAL test from baseline (Figure 7.4, p<0.001) for Rec 1 (p<0.001) and Rec 2 (p=0.003), with no difference between the recovery measurements (p=0.212). Errors on the other hand were not significantly impacted differently over time (p=0.325). Dopamine was significantly elevated post-exercise (Figure 7.5). Moderate correlations were found for post-exercise dopamine and the change in CPAL scores from pre-exercise to Rec 1 (r=0.572, p=0.08) and baseline dopamine and large artery compliance (r=0.601, p=0.07) but these did not reach the statistical significance threshold established for this research (Figures 7.6 and 7.7, respectively). A significant correlation was found for baseline blood pressure and CPAL duration indicating those with higher baseline blood pressure took longer to complete the CPAL test (Figure 7.8).

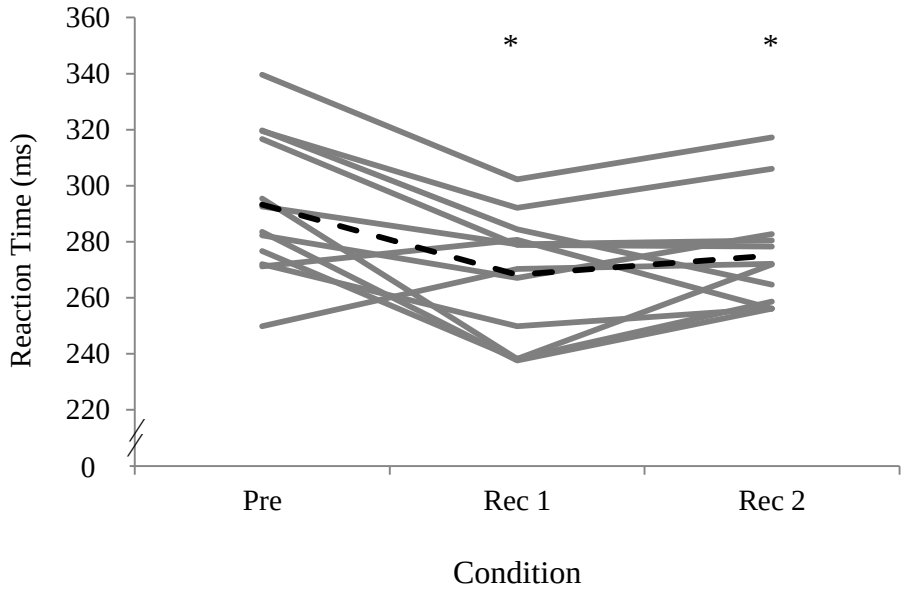

Figure 7.2 Individual Results for the Comparison of Simple Reaction Time

Baseline (Pre), 1 hour post-exercise (Rec 1) and 4 hours post-exercise (Rec 2). The mean is represented by the dashed (- - -) line. * different from baseline $p<0.05$.

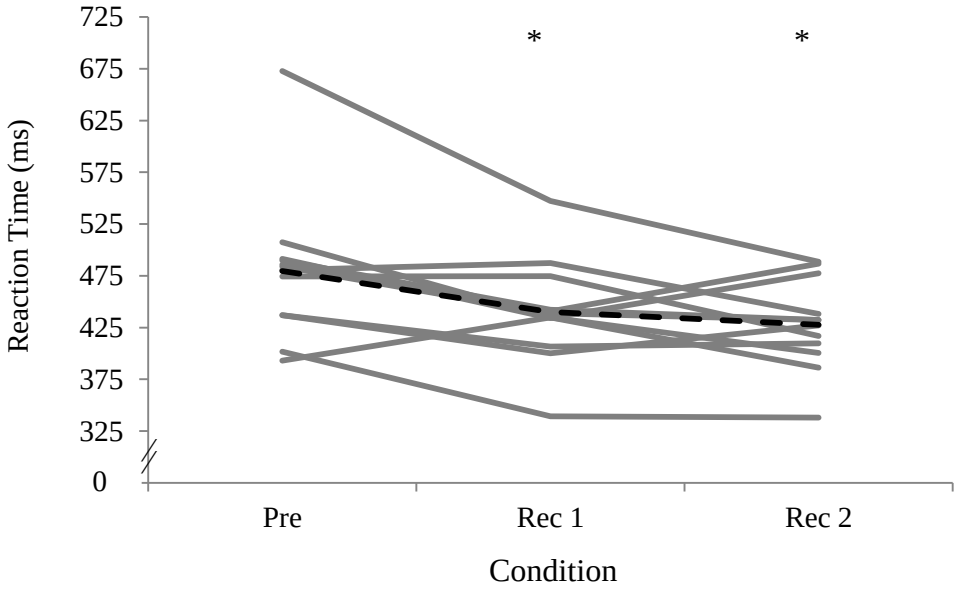

Figure 7.3 Individual Results for the Comparison of Choice Reaction Time

Baseline (Pre), 1 hour post-exercise (Rec 1) and 4 hours post-exercise (Rec 2). The mean is represented by the dashed (- - -) line. * Significant from baseline $p<0.05$.

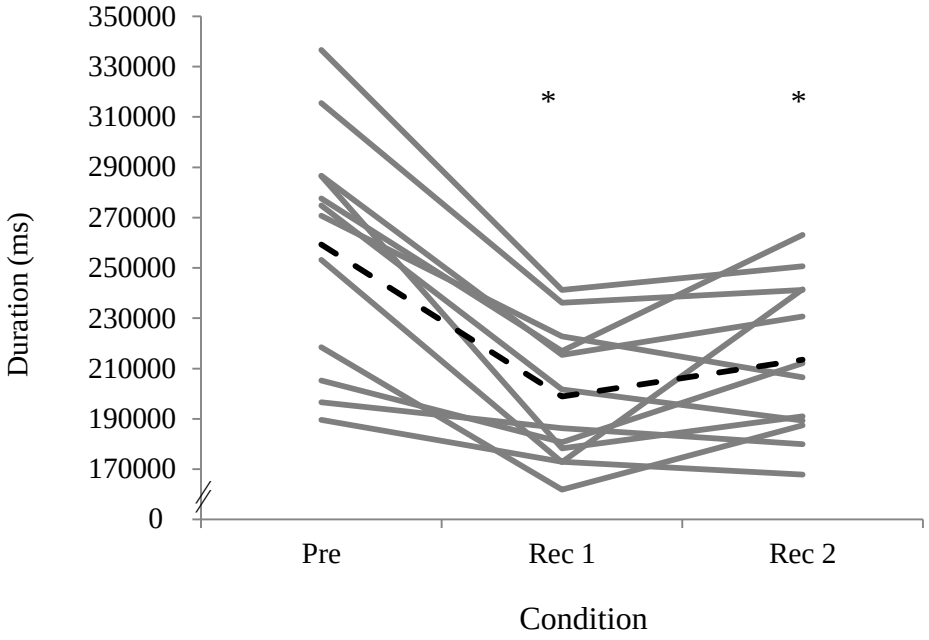

Figure 7.4 Individual Results for Working Memory Duration

Baseline (Pre), 1 hour post-exercise (Rec 1) and 4 hours post-exercise (Rec 2). The mean is represented by the dashed (- - -) line. * Significant from baseline $p<0.05$.

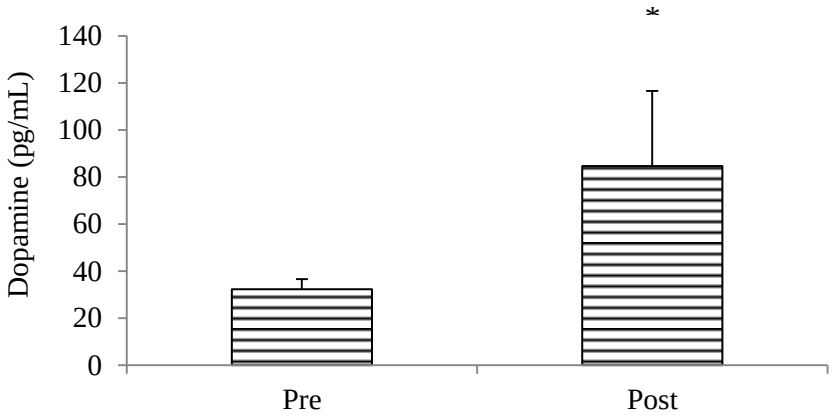

Figure 7.5 Change in Dopamine with Exercise

Values at baseline (Pre), and immediately post-exercise (Post).
* Significant from baseline $p=0.001$

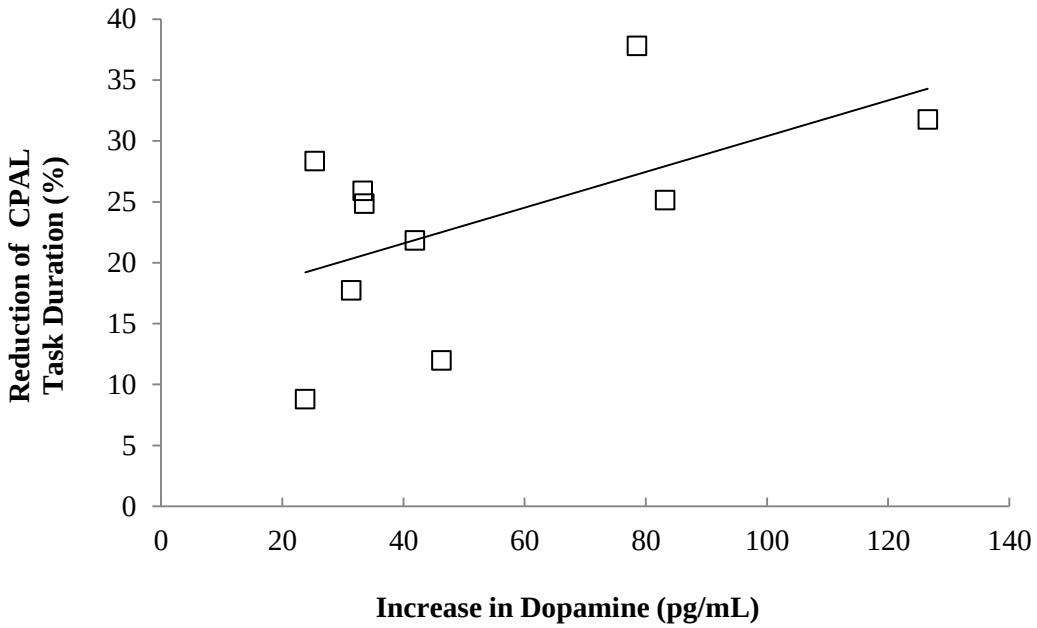

Figure 7.6 Relationship of the Change in Dopamine to the Change in Working Memory Duration
Pearson r =0.56, *p*=0.09

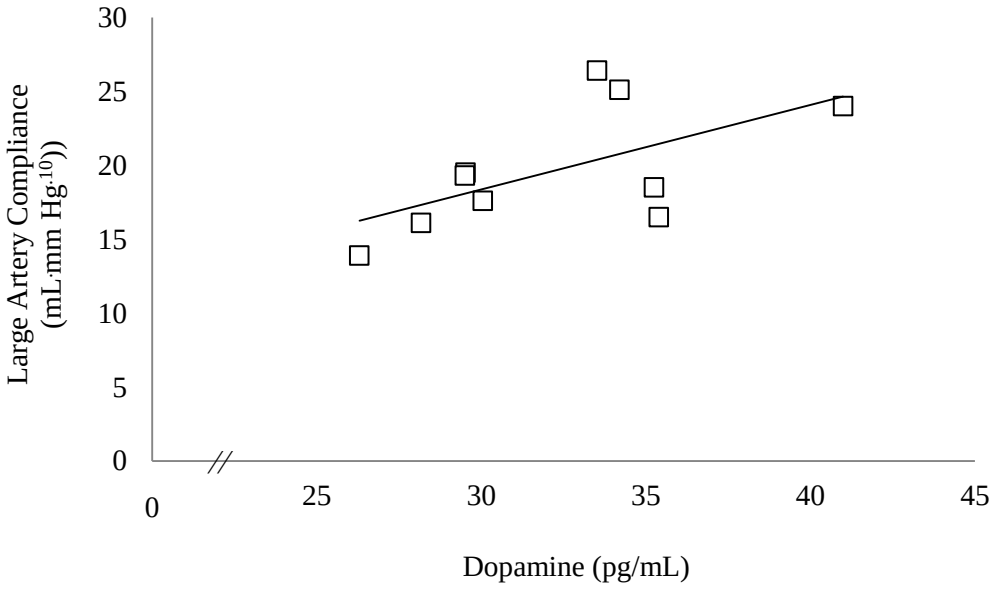

Figure 7.7 Relationship of Baseline Dopamine Values to Large Artery Compliance
Pearson r = 0.60, *p*=0.07

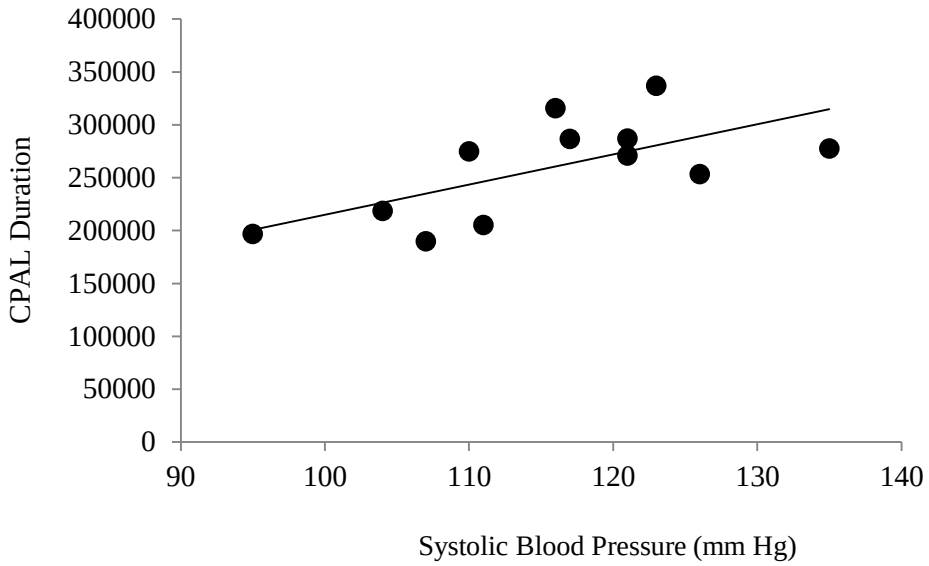

Figure 7.8 Relationship of Baseline Working Memory Duration to Systolic Blood Pressure

Pearson r =0.65, *p*=0.022

7.5 DISCUSSION

The main findings of this investigation are that vigorous exercise in the form of intervals has a positive effect on cognitive performance early in the recovery period and that these effects were still prominent four hours after the cessation of exercise. Participants displayed improved reaction time and choice reaction time, as well as completed the working memory task more quickly. Our work supports other findings shwoing improvements in cognition following intense exercise [328, 330] and adds to the literature by showing lasting effects in cognitive performance.

An earlier meta-analysis from the literature revealed moderate intensity exercise has positive effects on acute cognitive performance including selective attention, planning,

organizing, multitasking, inhibition, and working memory [338]. These positive effects may be affected by the intensity and duration of exercise [338]. Maximal exercise has been studied minimally in comparison to lower intensity exercise (i.e., aerobic exercise). In a narrative review by Tomporowski [339] it was proposed that minor decrements in cognitive performance may occur with maximal exercise, although there were very few studies to draw conclusions from. The author further speculated that submaximal aerobic exercise leading to dehydration may be the most detrimental, as shown in tests examining information processing and memory. As shown in the heart rate response, the exercise protocol elicited near maximal heart rates and the protocol involved 30 minutes of strenuous work. However, participants were allowed to drink water ad libitum and experienced very little weight loss as a result of the exercise. Thus, it is possible that through the maintenance of hydration status, we mitigated this supposed negative influence on cognition. However, this only explains why our protocol may have avoided large decrements in performance. The more important question is how did this strenuous interval exercise and the other recent studies showing the benefits of intense exercise [330] [328] elicit improvements in cognitive function?

One aspect to consider is fitness. Fitness level has been identified as a factor in the cognitive response to exercise, where higher cognitive function was found in those who exercised versus inactive individuals [316]. It has been speculated that the relative stress of the exercise will be different depending on how accustomed one is to such stress. Our participants were recreational exercisers with three individuals engaging in regular aerobic training for cycling and cross-country skiing. The range in VO_2max verified that

this was a diverse group yet fitness was not correlated to any of our cognitive measures. This may suggest that cognitive benefits of physical activity are not limited to aerobic exercise [309]. Indeed in a cohort of elderly individuals, any history of physical activity was associated with better episodic memory and decreased likelihood of developing dementia [340]. Furthermore, the effects of a healthy lifestyle in already cognitively high functioning subjects cannot be overlooked as an additional factor [308].

Importantly we showed that working memory was improved following high-intensity interval exercise. We also showed a significant improvement in simple reaction time and choice reaction time. Our findings are in agreement with prior work involving intense exercise. In one investigation, two three-minute bouts of intense running improved retention in a verbal fluency task at one week post-exercise and this improved memory was associated with immediate post-exercise dopamine levels [330]. Another investigation reported improved working memory at 30 minutes post-aerobic exercise to exhaustion [328]. By contrast, Lemmink et al. found that following an eight-minute bout of interval exercise (40:20 second work:rest ratio) choice reaction time was no different from that of the control group who rested (seated) [341]. To our knowledge we are the first to investigate the time course of acute exercise on cognitive function so far into the controlled recovery period following intense exercise. Other work involving lower intensity exercise shows similar trends. Cognition in the form of speed and accuracy of mathematical problem solving was shown to remain heightened 15 minutes following sub-maximal exercise [342] and choice reaction time peaked at eight minutes post-exercise after which the performance began to return to baseline [343]. Recently, an

investigation analyzing the lasting effects of sub-maximal exercise on response execution and response inhibition using a stop-signal task observed improved performances up to 52 minutes post-exercise [344]. Our findings of improved working memory evident four hours post-exercise is intriguing, particularly considering the CPAL duration was not yet close to returning to baseline. The investigation by Winter et al. [330] which reported enhanced retention at one week post-exercise, is limited by the potential effects of other influences on their participants during the week between assessments. Our work brings us closer to understanding if cognition may truly be enhanced when assessed at such lengths post-exercise. Taken together, our work and that of others, suggests that cognitive benefits of exercise could extend further than the day of exercise.

Regular aerobic exercise increases endothelial function, reduces arterial stiffness, and increases arterial compliance [345-348]. These vascular adaptations benefit cerebral circulation as individuals with higher cardiorespiratory fitness exhibit higher brain blood flow [349], greater cerebral vascular conductance at rest, and greater cerebrovascular reserve [350]. Furthermore, vascular adaptations as the result of exercise may be involved in neurogenesis [351]. Dopamine is a modulator of sympatho-adrenal activity and serves as an important hormone involved in altering the inotrophic and chronotrophic response of the myocardium and vascular system to exercise [352]. It may also indirectly regulate blood pressure by increasing angiotensin II [353]. Given enhanced cognition is associated with lower blood pressure [354], dopamine is an important regulator of blood pressure [355] and recent findings linking higher dopamine levels with better retention of verbal fluency [330], dopamine was an appropriate target catecholamine for our research. Our

findings are in agreement with this prior work. First, we found a significant correlation between SBP and CPAL duration demonstrating that higher SBP was associated with longer time to complete the working memory task. Second, we found a trend of greater resting dopamine and higher large artery compliance, a measure of vascular health. With respect to the change in dopamine, we also found a trend for faster working memory in the presence of a greater increase in dopamine. Our investigation was adequately and highly powered to detect the cognitive, cardiovascular and catecholamine changes (average statistical power 0.976) however, future investigations involving more participants will help determine the nature of this relationship.

7.6 LIMITATIONS

In this investigation we did not collect plasma samples during the recovery period. In this way our investigation is limited to associating post-exercise dopamine to cognition measured at different time points. However, catecholamines have a very short half-life (~ 2 minutes) and thus we expected detectable elevations to disappear by these later time periods. This is shown in other investigations involving a much shorter interval (i.e., 10 x 6s sprints or one 2-min sprint) where post-exercise plasma dopamine concentrations were not statistically different from baseline [323, 356]. Another consideration with respect to dopamine is that peripheral dopamine levels are not necessarily reflective of brain dopamine levels [357], thus conclusions should be drawn with caution. Finally, our investigation did not include serial assessments of cognition in the recovery phase. This was by design to avoid any confounding learning effects, although the CogState test battery has not displayed any learning effects after the second assessment in studies of

serial assessment [358, 359]. Our participants completed 3 baseline assessments of which we considered trial 3 to be our true baseline. Future investigations should include an immediate post-exercise time point to see if detriments in cogntition occurred which would strenthen the interpretation of cognition in recovery. In addition, a comparison of high-intensity interval exercise in comparison to other forms of exercise, and the inclusion of more women, would provide greater insight into the effects of strenuous exercise on cognitive function.

7.7 CONCLUSIONS

In this investigation we showed that substantial improvements in reaction time and learning were evident following an intense bout of interval exercise. Additionally, we showed that the enhanced cognition persisted for a period of four hours. These results provide further support of the benefits of exercise. Future work should involve a more systematic exploration of the recovery period over multiple days to gain further insight into how the acute and chronic adaptations of exercise may impact cognition.

Chapter 8: General Summary and Conclusions

8.1 INTEGRATION AND INTERPRETATION OF MAJOR FINDINGS

Research has demonstrated that strenuous forms of acute exercise have the ability to reduce ventricular function [123], particularly high volume exercise [161, 184]. Recent evidence suggests that cardiac fatigue is not limited to extreme duration but rather can be provoked with brief, but maximal exercise [21]. Our understanding of the implications of acute bouts of strenuous exercise on short term cardiovascular risk remains limited, particularly in athletes [189] and women [26].

In this dissertation, Chapter 2 provides a narrative review of the literature pertaining to effects of endurance training and sex on cardiovascular responses at rest and with exercise. The literature suggests that women demonstrate enhanced autonomic [62-66] and cardiac function [82] at rest, however with strenuous exercise, women may show greater vulnerabilities than men [66]. Similarly, athletes typically display an improved autonomic profile over untrained individuals [62, 89-93], structural adaptations (eccentric hypertrophy), and enhanced systolic and diastolic function [109, 110]. These adaptations increase the efficiency of the cardiovascular system to do more work under less stress [115-118]. However, while eccentric hypertrophy is seen as a normal adaptation to chronic endurance training, the similarity to hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia (linked to increased risk of sudden death in athletes) [111] questions the actual risks associated with strenuous exercise. Consequently, the series of studies contained in this dissertation examined the

cardiovascular consequences of strenuous exercise in healthy men and women, representing diverse physical training backgrounds.

In Chapter 3, our investigation of ultra-marathoners provided unique findings pertaining to exercise-induced cardiac fatigue in women. Results show similar responses to an ultra-marathon between the sexes. Females have been rarely studied in previous work and we provide unique insight in to how women respond to strenuous exercise. From this work, an interesting novel finding was that more experienced ultra-marathoners presented less evidence of cardiac fatigue. The association with race pace and ventricular strain also demonstrates that the faster runners (and presumably the fittest) may experience less relative physiological strain. We provide for the first time an association of lifetime involvement in ultra-endurance training and cardiac fatigue which recently has come into question [165]. It is also unknown what impact cardiac fatigue has on performance. This work is limited in the echocardiographic measures collected and could have been strengthened by more advanced techniques of strain imaging [30].

The work presented in Chapter 4 addresses the effects of brief, strenuous exercise on cardiac function. Gaps in the cardiac fatigue literature have included insufficient exercise intensity, variability in protocols, and the need for more research using high-level female athletes [145]. Our work addressed these concerns by assessing both sexes, trained and untrained. In addition, we employed the same protocol as Scott et al. [21] so that our findings could be compared to this ground-breaking work. In support of this work, our findings revealed significant cardiac fatigue following high-intensity interval work. By contrast, endurance athletes did not experience greater cardiac fatigue than normally active individuals. Some novel aspects of this work include the assessment arterial-

ventricular coupling following high-intensity interval exercise. We found men displayed greater cardiac efficiency in the recovery from strenuous exercise, driven by higher arterial elastance. These findings would indicate a greater sensitivity to volume change [58]. Limitations of this study are the lack of exercise or follow up cardiac assessments. Currently, the use of echocardiography during exercise is limited and would not have been possible at the high intensities in our protocol. However, future work should include additional assessments in the recovery period, which may provide more insight into the manifestation of chronic adaptations [232].

To build upon our understanding of the response to very high intensity exercise, the investigation presented in Chapter 5 focused on autonomic responses to LBNP and high-intensity interval exercise. We expected this protocol could highlight group differences not identified following exercise alone, as we have previously shown exercise and LBNP to represent a substantial stressor [272]. Indeed our findings did feature sex differences in autonomic and ventricular function. Under cumulative physiological stress, we discovered females experienced less disruption from baseline values compared with men. We also found evidence of greater reductions in baroreflex function in endurance-trained individuals. Insight into the post-exercise response is of particular interest as reduced cardiovagal baroreflex function is associated with impaired regulation of arterial blood pressure and in the presence of myocardial ischemia, with increased risk of ventricular tachyarrhythmias and sudden cardiac death [45]. While our work is not able to ascertain the full meaning of the post-exercise autonomic responses on cardiovascular risk, we can infer from the faster recovery in endurance trained individuals that this potential susceptibility occurs within a shorter timeframe than untrained individuals undergoing

strenuous exercise. A major limitation surrounding this work is the sample size is too small to assess the three-way interactions involving training and sex over lower body negative pressure and within condition (rest vs. exercise). Hence, improvements to this investigation would involve recruiting more participants for each group.

Chapter 6 investigated the impact of training status and sex on post-exercise hypotension. The literature shows clearly the benefits of acute exercise on lowering blood pressure in hypertensives [288] but in healthy individuals, alterations to blood pressure are less clear. We used our 4 group model (training x sex) to assess post-exercise hypotension, which has yet to be explored with high-intensity interval exercise. Clinically, there is a lot of interest in understanding the risks versus benefits of high-intensity interval exercise as it is being used increasingly in various rehabilitation programs [4, 17]. We found that healthy individuals experience significant blood pressure reductions following high intensity exercise, especially endurance trained athletes. Our work and others [295] demonstrates that post-exercise hypotension is apparent when utilizing very strenuous aerobic work, and perhaps intensity is responsible for the lack of hypotension in earlier work. We also found an association of baseline systolic blood pressure and the drop in post-exercise systolic blood pressure that has previously been shown in pre-hypertensives [297]. These researchers also showed greater autonomic alterations following high-intensity interval exercise compared with steady state exercise. Taken together with our findings, we have further evidence to support that high-intensity exercise has a significant acute effect on blood pressure. In endurance trained athletes however, it would appear that a more substantial stress need be applied in order to

recognize this acute response. This study was limited in not measuring plasma volume to show the degree of loss which occurred with this strenuous exercise.

In Chapter 7 we present the findings of our final investigation. Here our aim was to explore cognitive performance following high intensity interval exercise. Known as an effective means to improve aerobic capacity [7, 9] we hypothesized that this form of exercise could improve cognitive performance as well. As in Chapter 6, we were attempting to establish a link between acute cardiovascular responses and enhanced cognitive function. Habitual exercisers have demonstrated improved cognition [338] into old age compared to those who do not exercise. Considering high-intensity interval exercise has been shown to improve metabolic parameters which lead to better health outcomes [15, 16], and compromised glucoregulation and cardiovascular health has been associated with an increased risk of developing cognitive impairment and Alzheimer disease [360], our work suggests that high-intensity interval exercise is an appropriate stimulus for affecting cardiovascular *and* cognitive improvements. Our association of systolic blood pressure to working memory duration, and our trends independently linking dopamine to vascular function and cognitive performance, are promising indications that the acute exercise response leading to fitness adaptations are also capable of influencing positively, cognitive function. This work could be improved by incorporating more physiological measures in the recovery period, such as measures of blood pressure regulation, arterial stiffness, brain blood flow and other blood markers (i.e., brain-derived neurotrophic factor). This would allow for better insight into the mechanisms of this adaptation. Further, the addition of other cognitive assessments

would be useful in confirming the impact of exercise on this aspect of human performance.

8.2 FUTURE STUDIES

Interval Exercise: Collectively, this body of work comprehensively illustrates the effects of strenuous exercise in healthy humans. The exercise protocols used in this body of work consists of very high intensity exercise that is typical in training programs of elite athletes. However, interval exercise typically performed in recreational settings (i.e., spin classes), and in rehabilitation programs for those with chronic disease, offer very different forms of physical stress. While to the healthy person they represent a gradation of exercise intensity, to an individual with heart failure, assessing the degree of relative intensity becomes more complex. As such, future work should assess the cardiovascular impact of various forms of interval exercise performed by appropriate populations. In this way, we will gain a better understanding of the true efficacy of this type of exercise.

Cognitive Performance: The integration of the cardiovascular responses to strenuous exercise and effects on cognition are an emerging area of research. In addition to addressing the limitations listed above, future work should investigate the progression of cardiovascular adaptations in conjunction with cognitive assessment, and over longer serial time points.

Chronic Endurance Training: The structural adaptations present in endurance athletes remains of clinical concern [361, 362]. Longitudinal studies are needed in which cardiovascular adaptations to endurance training can be tracked. From this work,

researchers and clinicians may better understand the risks versus benefits from life-long endurance participation.

Prolonged strenuous exercise: The impact of strenuous long duration exercise and its role in the development of cardiac fatigue has been a popular area of study in the last thirty years [19, 123]. However we remain limited in our understanding of training and sex effects. With greater numbers of older athletes participating each year, as well as more women [3, 18], further study in these populations are required.

In summary, strenuous exercise has significant reductions in acute measures of cardiovascular function. Despite the benefits of chronic exercise, the risks of long-term participation, remains uncertain. As strenuous exercise increases in popularity, further work is warranted to ascertain the true costs versus benefits specific to various populations, so that individualized exercise recommendations may be specific and relevant.

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Appendices

A: PHYSICAL ACTIVITY READINESS QUESTIONNAIRE FOR EVERYONE (PAR-Q+)

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your **doctor OR a qualified exercise professional before becoming more physically active.**

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition **OR** high blood pressure?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition?	☐	☐
6) Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer **NO** if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Go to Page 4 to sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow Canada's Physical Activity Guidelines for your age (www.csep.ca/guidelines).
- **You may take part in a health and fitness appraisal.**
- **If you have any further questions, contact a qualified exercise professional** such as a Canadian Society **for Exercise Physiology - Certified Exercise Physiologist® (CSEP-CEP) or a CSEP Certified Personal Trainer®** (CSEP-CPT).
- If you are over the age of 45 yr and **NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional (CSEP-CEP) before engaging in this intensity of** activity.

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better
- **You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional,** and/or complete the **ePARmed-X+ at www.eparmedx.com** before becoming more physically active
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or **qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity program.**

OSHF

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PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have Heart Disease or Cardiovascular Disease? *This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm*

If the above condition(s) is/are present, answer questions 3a-3e — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐
3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have any Metabolic Conditions? *This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes*

If the above condition(s) is/are present, answer questions 4a-4c — If **NO** ☐ go to question 5

4a.	Is your blood sugar often above 13.0 mmol/L? (Answer **YES** if you are not sure)	YES ☐ NO ☐
4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	YES ☐ NO ☐
4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	YES ☐ NO ☐

5. Do you have any Mental Health Problems or Learning Difficulties? *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)*

If the above condition(s) is/are present, answer questions 5a-5b — If **NO** ☐ go to question 6

5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
5b.	Do you **ALSO** have back problems affecting nerves or muscles?	YES ☐ NO ☐

PAR-Q+

6. Do you have a Respiratory Disease? *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*

If the above condition(s) is/are present, answer questions 6a-6d — If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

7. Do you have a Spinal Cord Injury? *This includes Tetraplegia and Paraplegia*

If the above condition(s) is/are present, answer questions 7a-7c — If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

8. Have you had a Stroke? *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*

If the above condition(s) is/are present, answer questions 8a-8c — If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

9. Do you have any other medical condition not listed above or do you have two or more medical conditions?

If you have other medical conditions, answer questions 9a-9c — If **NO** ☐ read the Page 4 recommendations

9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
9c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20-60 min of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional (CSEP-CEP) before engaging in this intensity of activity.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional (CSEP-CEP) to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the **ePARmed-X+ at www.eparmedx.com** before becoming more physically active
- Your health changes - talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- Please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact

www.eparmedx.com
Email: eparmedx@gmail.com

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06-01-2012

B: FAT DOG 100 ULTRA-MARATHON QUESTIONNAIRE

Participant #:_____

QUESTIONNAIRE

1. Lifestyle and Demographics

1.0 What is your gender and current age?

Gender (circle one): M F Date of Birth (dd/mm/yr):_____

1.1 How would you classify your family ethnically? Please check the appropriate box

- ☐ Caucasian
- ☐ First Nations/Inuit/Métis
- ☐ Latin (Hispanic)
- ☐ West Asian (e.g. Iranian, Afghan, etc)
- ☐ Southeast Asian (e.g. Vietnamese, Cambodian, etc)
- ☐ South Asian (e.g. East Indian, Sri Lankan, Pakistani, Punjabi, etc)
- ☐ Other, if other please define: _____
- ☐ Korean
- ☐ African
- ☐ Japanese
- ☐ Chinese
- ☐ Arab

1.2 What is your current postal code/zip code? _____

2. Competition

2.0 What distance will you be running? _____ km *or* miles (please circle)

2.1 Do you plan to ingest salt supplementation during the race? _____

2.1 Do you train with salt supplementation? _____

2.2 Do you plan to recover with salt supplementation? _____

2.3 What do you plan to eat/drink during the race? (please list)

_____

_____

_____

3. Physical Activity

3.0 What is your resting heart rate? _____ bpm

3.1 When was your last ultra endurance event as a participant? _____

3.2 How far was your last ultra endurance race? _____

3.3 When was your last ultra endurance event as a pacer? _____

Participant #:_____

3.4 When was your last race of any distance? _____

3.5 What distance was your last race? _____

3.6 How many ultra endurance events have you completed in total? _____

3.7 How many ultra endurance events have you attempted in total? _____

3.8 How many ultra endurance events have you completed this year? _____

3.9 How many ultra endurance events have you attempted this year? _____

3.10 For how many years have you been competing in ultra endurance events? _____

3.11 How would you describe your foot strike? Ball *or* Mid-foot *or* Heel (please circle)

3.12 When did you last do a training session? _____

3.13 How many days prior to the Race did/will you taper? _____

3.14 In your normal training schedule:

i/ How many days per week do you train? _____

ii/ How far do you run in a week? _____ km *or* miles (please circle)

iii/ How far do you run in a month? _____ km *or* miles (please circle)

iv/ Do you run shorter back to back runs or do you run long runs? _____

_____

v/ Do you do hill training? How much? How often? _____

_____

vi/ Do you do interval or speed training? How much? How often? _____

_____

vii/ What other training do you do? (please list) How often?

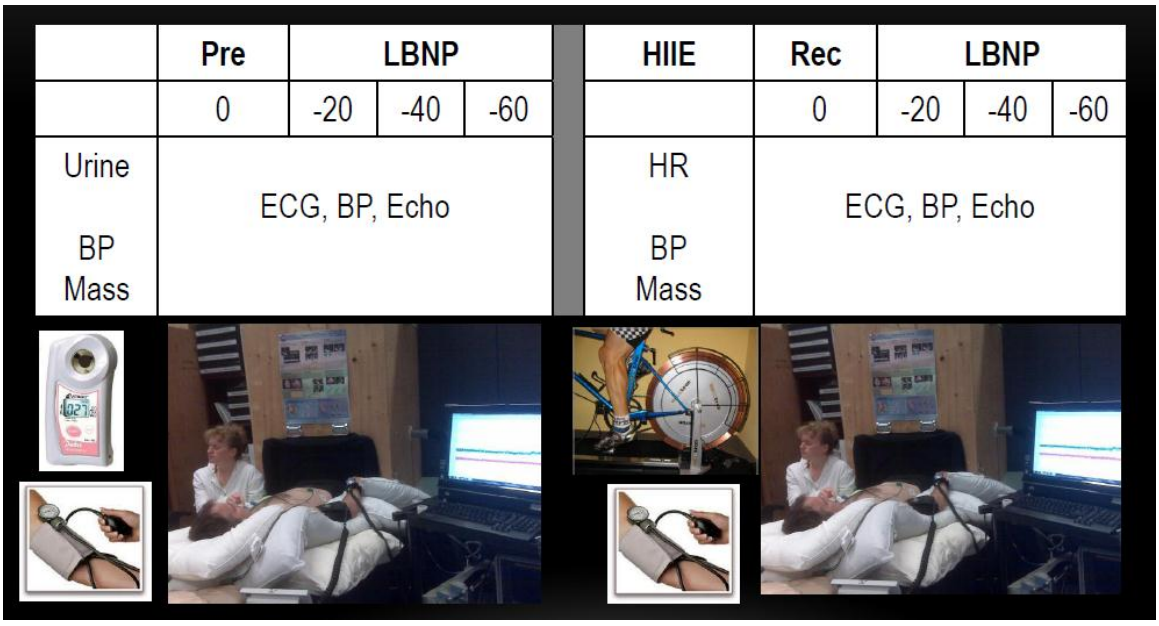
_____

_____

_____

C: SCHEMATIC OF PROTOCOLS

Protocol Chapter 5



Protocol Chapter 7