

EFFECTS OF LOW INTENSITY EXERCISE TRAINING ON CIRCULATORY AND
AUTONOMIC MEASURES IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

BY

INGRID KAREN MARIA BRENNER

A thesis submitted to the Graduate Program in Nursing
in conformity with the requirements for the
Degree of Doctor of Philosophy

Queen's University
Kingston, Ontario, Canada

February, 2017

Copyright © Ingrid Karen Maria Brenner, 2017

Abstract

The purpose of this study was to examine the effects of a progressive, low-intensity walking intervention on circulatory and autonomic adaptations in patients with peripheral arterial disease after controlling for potential confounders such as age, sex, β -blockers and smoking. Secondary objectives were 1) to determine the effect of the intervention on walking performance and self-report measures and 2) to determine if there were any sex-specific differences that might exist at rest or in response to training. Forty-eight participants (aged 67.81 ± 8.13 years, mean \pm standard deviation) with intermittent claudication (ankle-brachial index 0.54 ± 0.18) were randomly assigned to either a walking group ($n = 27$) who performed a structured walking program, 5 days per week for 12 weeks, or a comparison group ($n = 21$) who performed usual activities. Thirty-three (69%) participants (15 comparison group members and 18 walking group members) completed the study. Circulatory measures (ankle-brachial index, heart rate, blood pressure, mean arterial pressure and rate pressure product), autonomic measures (heart rate variability, low frequency power, high frequency power, total power, parasympathetic nervous system indicator and sympathetic nervous system indicator), tests of walking performance (pain-free, functional and maximal walking distance as well as the 6 minute walk test) and self-report measures (the Walking Impairment Questionnaire and Quality of Life Questionnaire were obtained at the beginning (Week 1) and end (Week 12) of the study. Autonomic function (heart rate variability) improved and overall walking performance increased in members of the walking group. Men and women responded similarly to the training program. These findings suggest that a structured, low-intensity, high frequency walking program is effective in improving HRV, increasing walking performance and daily walking distance.

Acknowledgements

I would first like to thank the participants of this study for volunteering. Without them this study would not have been possible. I am very grateful to Dr. Peter Brown and Dr. David Zelt who provided access to the participants as well as financial support for conducting the study. Additional support for this study was provided by the Frieda Paltiel Award of the School of Nursing at Queen's University. I also would like to acknowledge the contributions and hard work of Dr. Ann Brown, my thesis supervisor; Dr. Sylvia Hains and Dr. Barbara Kisilevsky for their statistical advice; Dr. Joan Tranmer, a member of my thesis advisory committee and Dr. Dana Edge, Queen's School of Nursing for their support and guidance. Lastly, I would like to thank my parents (Otto and Jeannette Brenner) and my daughter (Katherine Petrasek) for their patience and support.

Table of Contents

Abstract	ii
Acknowledgements	iii
List of Tables	viii
List of Figures	ix
List of Abbreviations	x
Chapter 1 - Introduction	1
Chapter 2 – Literature Review	4
Circulatory and Autonomic Effects of Peripheral Artery Disease	4
Heart rate variability (HRV).....	5
Factors influencing HRV.....	8
Arterial baroreceptors	8
Atherosclerosis.....	8
Respiration	9
Age.....	10
Sex.....	10
Orthostatic stress.....	11
Acute exercise.....	12
Pharmacological agents	13
Smoking	13
HRV and peripheral arterial disease	15
Exercise Therapy.....	19
Exercise Compliance.....	27

Previous Relevant Work	28
Summary and Conclusions	30
Statement of the Problem	31
Rationale for the Study	32
Purpose	33
Hypothesis	33
Chapter 3 – Method	35
Participants	35
Apparatus/Instruments	40
Procedures	45
Data Reduction	50
Statistical Analysis	51
Chapter 4 – Results	53
Analysis of Walking and Comparison Groups over Time	56
Circulatory Measures	58
Heart rate variability measures.	62
Walking performance measures	66
Self-report measures	68
Chapter 5 – Discussion	71
Limitations	81
Implications for Nursing	82
Conclusion	84
References	85

Appendices.....	109
Appendix A – Ethics Approval	110
Appendix B – Informed Consent.....	115
Appendix C – Exercise Protocol	120
Appendix D - Measuring Your Heart Rate	121
Appendix E – Borg’s Perceived Exertion Scale.....	122
Appendix F - Borg’s Pain Scale.....	124
Appendix G - Exercise Log OF Walking Group	125
Appendix H - Activity Log Comparison Group	126
Appendix I - Participant Demographic Form	127
Appendix J – Walking Impairment Questionnaire	131
Appendix K – Quality of Life Questionnaire	133
Appendix L - Editing HRV Data	135
Appendix M – Disease Severity	136
Appendix N – Medication Use	137
Appendix O – Body Composition.....	138
Appendix P – Chi Square Summary Tables at Entry	139
Appendix Q - ANOVA Summary Tables at Entry	145

Appendix R - ANOVA Summary Tables over Time	155
Appendix S - Data Reduction.....	193

List of Tables

Table 1. Studies examining HRV in patients with PAD.....	16
Table 2. Studies on the effect of low-intensity exercise on PAD outcome measures.....	24
Table 3. Resting circulatory measures at entry into the study.....	53
Table 4. Resting HRV measures (raw values) at entry into the study.....	54
Table 5. Walking performance measures at entry into the study.....	55
Table 6. Self-report measures at entry into the study.....	56
Table 7. Baseline characteristics of participants who completed the study (n = 33).....	57
Table 8. Summary of study variables that were influenced by covariates.....	58
Table 9. Means (SD) for circulatory measures over time.....	59
Table 10. Means (SD) for HRV measures (raw values) over time.....	63
Table 11. Means (SD) of performance measures over time.....	67
Table 12. Means (SD) of walking impairment questionnaire data over time.....	69
Table 13. Means (SD) of quality of life scores (SF-36) over time.....	70

List of Figures

Figure 1. One of the possible roles of exercise in the treatment of PAD.	22
Figure 2. Participant flow chart for recruitment for the study.	36
Figure 3. Time by group interaction for Log ABI values, Week 12 vs Week 1.	60
Figure 4. Time by group interaction for systolic blood pressure (SBP), Week 12 vs Week 1.	61
Figure 5. Time by group interaction for Log transformed PNS indicator, Week 12 vs Week 1. .	64
Figure 6. Time by group interaction for Log transformed SNS indicator, Week 12 vs Week 1. .	65
Figure 7. Change in walking distance over time.....	68

List of Abbreviations

ABI	Ankle-Brachial Index
6MWT	Six-minute walk test
BMI	Body mass index
BP	Blood pressure
BRS	Baroreflex sensitivity
ECG	Electrocardiogram
FCD	Functional claudication distance
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
LF	Low frequency
MWD	Maximal walking distance
PFWD	Pain-free walking distance
PNS	Parasympathetic nervous system
SNS	Sympathetic nervous system
SF-36RL	SF-36, Quality of Life Questionnaire- Role limitations
SF-36PF	SF-36, Quality of Life Questionnaire- Physical function
TP	Total Power
WIQ	Walking Impairment Questionnaire

Chapter 1 - Introduction

Cardiovascular disease is a leading cause of morbidity and mortality around the world and includes disorders of the heart and blood vessels and diagnoses of coronary artery disease, stroke, hypertension, peripheral artery disease, rheumatic heart disease, heart failure and congenital heart disease (W.H.O., 2009). Atherosclerosis is a major mechanism contributing towards the development of cardiovascular circulatory disorders (Frostegard, 2013). The most common sites of atherosclerosis are first the coronary arteries (contributing to coronary artery disease), second the carotid arteries (leading to ischemic stroke) and third the arteries of the lower extremities (leading to peripheral artery disease [PAD]) (Fowkes et al., 2013). Between 10 to 20% of the population over age 55 will develop PAD, with prevalence increasing with age: over 30% of older adults have PAD (Aronow, 2009; Oka, 2006; Vavra & Kibbe, 2009). The majority (approximately 50%) of patients are asymptomatic, 30% of patients experience atypical leg symptoms (tingling or numbness), 15% experience leg pain (also known as intermittent claudication, IC) and a very small minority (1-2%) suffer from critical limb ischemia (Carman & Fernandez, 2006; Hiatt, 2001). Approximately 800,000 Canadians and more than 202 million people worldwide (Hirsch & Duval, 2013) are affected by PAD. However, only 36% of the Canadian population are aware of this chronic condition making it an underdiagnosed and undertreated disease (Lovell et al., 2009).

Intermittent claudication (IC) is defined as pain, weakness and/or fatigue that occurs in the muscles of the lower extremities (buttocks, thighs or calves) during physical activity and is relieved by rest (Carman & Fernandez, 2006; Marsico et al., 2013). In contrast to patients with CAD, whereby fifty-percent of patients present with angina (Ohman, 2016), as few as 2.5 % of women and 5% of men with PAD, over the age of 60 years present with intermittent claudication

(Shammas, 2007). Intermittent claudication is attributed to nociceptive pain that is associated with ischemia (Schorr & Treat-Jacobson, 2013) as well as lactic acidosis that occurs due to increased reliance on anaerobic metabolism (Hiatt, Armstrong, Larson, & Brass, 2015) similar to that felt by athletes during strenuous sports (Parr, Noakes, & Derman, 2008).

Patients with PAD have a partial or complete blockage in the blood vessels that deliver oxygen to the muscles of the lower extremities, affecting the ability to walk, thereby contributing to a sedentary lifestyle, reduced productivity and a poor quality of life (Shammas, 2007). Typically, metabolically-mediated vasodilation occurs in exercising muscles in response to the local need for increased oxygen (Taylor, Li, Yang, Laughlin, & Terjung, 2008). However, Goernig et al. (2008) found altered autonomic function in patients with PAD, specifically, decreased heart rate variability (HRV) and higher sympathetic versus parasympathetic modulation. Patients with a reduced HRV are more likely to suffer a cardiac event as well as subsequent death due to sudden onset of malignant ventricular arrhythmias (Fowkes et al., 2013; Lovell et al., 2009; Rosenwinkel, Bloomfield, Arwady, & Goldsmith, 2001). In addition, the combination of arterial narrowing or obstruction and sympathetically mediated vasoconstriction may negate the exercise-induced vasodilatory response that occurs in exercising muscles, leading to ischemia and pain. Goernig et al. also suggest that a change in autonomic control in patients with PAD is a compensatory mechanism for reduced vasodilatory capacity.

In other groups with CVD (e.g., those with coronary artery disease, hypertension) a regimen of regular physical activity has been shown to increase HRV (Goldie, Brown, Hains, Parlow, & Birtwhistle, 2013; Hua, Brown, Hains, Godwin, & Parlow, 2009) as well as to decrease blood pressure (BP), heart rate (HR), and rate pressure product (RPP) which is an indirect measure of myocardial oxygen consumption (Gobel, Nordstrom, Nelson, Jorgensen, &

Wang, 1978). A large epidemiological study involving 29,972 participants was conducted world-wide to investigate the prevalence of 9 risk factors associated with cardiovascular disease (Yusuf et al., 2004). Factors such as participation in regular physical activity, daily consumption of fruits and vegetables and minimal alcohol consumption were protective against development of a myocardial infarction, whereas the ratio of ApoB to ApoA, history of hypertension, cigarette smoking, diabetes, abdominal obesity and psychosocial factors were significant risk factors related to the development of an acute myocardial infarction. Bronas, Treat-Jacobson and Leon (2011) have also demonstrated that participation in regular physical activity improves cardiorespiratory function in PAD patients but did not include HRV analysis in their measures. The main purpose of this study was to examine the circulatory and autonomic effects of a progressive, 12-week home-based, low-intensity (walking) exercise program in patients with PAD after controlling for potential confounders such as age, sex, β -blockers and smoking. Secondary objectives were to determine the effect of the intervention on (1) walking performance and self-report measures such as the walking impairment questionnaire and health related quality of life and (2) to determine if there were any sex-specific differences that might exist at rest or in response to training.

This thesis is organized as follows: Chapter 2 is a literature review discussing the circulatory and autonomic effects of peripheral artery disease, the effects of exercise programs on autonomic function in patients with PAD and the role of exercise therapy for patients with PAD. Chapter 3 outlines the materials and methods used to conduct this study and the results of the study obtained are presented in Chapter 4. Lastly, Chapter 5 discusses the findings of this study.

Chapter 2 – Literature Review

The purpose of this literature review is to discuss the circulatory and autonomic effects of peripheral artery disease (PAD); including a description of heart rate variability (HRV), a brief summary of factors that can influence HRV and a discussion on the relationship between HRV and PAD at rest and following exercise training. Following this, an analysis of the current scientific evidence regarding the effects of exercise therapy in patients with PAD will be done. Lastly, the literature review ends with an in-depth examination of previous work on HRV that has been conducted in this laboratory.

Circulatory and Autonomic Effects of Peripheral Artery Disease

Peripheral artery disease (PAD) results from atherosclerotic lesions in the large peripheral arteries supplying blood flow to the pelvis and legs (Hiatt, 2001). The arterial lumen of these vessels become progressively occluded with atherosclerotic plaque, increasing arterial stiffness and partially or completely blocking blood flow to skeletal muscle of the legs (Hiatt et al., 2015). The extent of occlusion is reflected by the ratio of the blood pressure in the foot relative to that of the arms, known as ankle-brachial index. A ratio greater than 1.00 is normal, with ratios of 0.7 to 0.9, 0.5 to 0.69 and < 0.5 as mild, moderate and severe disease classifications (Shammas, 2007). Patients with PAD also may exhibit autonomic dysfunction (as reflected by a decrease in heart rate variability [HRV]) as observed in patients with other cardiovascular conditions (Thayer, Yamamoto, & Brosschot, 2009). These patients are more likely to suffer a cardiac event as well as subsequent death due to sudden onset of malignant ventricular arrhythmias (Fowkes et al., 2013; Lovell et al., 2009; Rosenwinkel et al., 2001). In fact, the presence of PAD has been classified as a coronary artery disease risk equivalent (Hiatt et al., 2015; Shammas, 2007), whereby patients with PAD have more than a 20% risk of

suffering from a coronary event in 10 years. Moreover, individuals with coronary artery disease (CAD) and comorbid PAD are at greater risk of cardiovascular events than those with CAD alone (Grenon et al., 2013). Further, compared to asymptomatic patients, symptomatic patients with PAD have a 70% higher risk of suffering a cardiovascular event and an 80% higher risk of death.

Heart rate variability (HRV). The beat-to-beat variability in heart rate, as measured by the duration of consecutive R-R intervals and referred to as heart rate variability (HRV), is a sensitive, non-invasive tool to study autonomic neural control (Akselrod et al., 1985; Akselrod et al., 1981; Bernardi et al., 2011; Pagani et al., 1986). Analysis of HRV is one of the most sensitive and specific way of measuring autonomic control of HR and BP (Bernardi et al., 2011). The control of heart rate is regulated through the autonomic nervous system (ANS) which is comprised of the sympathetic and parasympathetic divisions (Gibbins, 2013). These two divisions of the ANS operate in a highly integrative manner to ensure that cardiac output (the product of heart rate and stroke volume) is sufficient to meet the metabolic needs of various organs and tissues of the body (Akselrod et al., 1985; Akselrod et al., 1981).

Both the parasympathetic and sympathetic nervous systems operate through efferent neural pathways that run from the brainstem to the heart and blood vessels to regulate heart rate, contractility, venous capacitance and systemic vascular resistance (Malik & Camm, 1995). In the heart, the parasympathetic (vagus) nerve innervates the sinoatrial (SA) node, atrial tissue and the atrioventricular (AV) node, whereas sympathetic fibers innervate the SA node, the AV node and the ventricular myocardium (Amiya, Watanabe, & Komuro, 2014; Malik & Camm, 1995). The PNS slows the heart rate by inhibiting activity at the SA node (via binding of acetylcholine to cardiac muscarinic receptors) whereas the SNS stimulates the SA node (via the release of nor-

epinephrine acting on β -adrenergic receptors) and increases HR, blood pressure (BP), mean arterial pressure (MAP, the average blood pressure in the arteries during a single cardiac cycle) and rate pressure product (RPP, an index of the workload of the heart) (Gobel et al., 1978). The PNS alters HR within 400 ms allowing beat-by-beat control of HR whereas the SNS takes 3 to 5 seconds to induce a change in HR. Sympathetic neurons also are located in the muscular layer of blood vessel walls, whereas cholinergic (i.e., parasympathetic) neurons are found in both the muscular and endothelial layers. At any specific time, the physical demands that are placed upon an individual and their emotional state (such as anger, anxiety, fear etc.) will determine which component of the autonomic nervous system predominates (Lewis, 2005).

In healthy adults who are at rest in the supine position, both systems are active, but parasympathetic activity predominates (Pomeranz et al., 1985). At the onset of acute exercise, vagal activity decreases and at approximately 50% of maximal aerobic activity or above sympathetic activity increases (Goldsmith, Bloomfield, & Rosenwinkel, 2000). Adjustments in autonomic nerve activity occurs through various feedback mechanisms including information coming from the cerebral cortex of the brain (central command), arterial baroreceptor reflexes (Blaber, Yamamoto, & Hughson, 1995), and exercise pressor reflexes (EPR) (Murphy, Mizuno, Mitchell, & Smith, 2011).

Cardiac autonomic modulation can be assessed by analyzing time domain and /or frequency domain parameters of heart rate variability at rest and in response to various physical and mental challenges. In time domain analyses of HRV, the time interval between adjacent R-R intervals are recorded for anywhere from 5 min and up to 48 hours (Kleiger, Stein, & Bigger, 2005). Various statistical variables are derived from this measure both directly and indirectly. One of the most commonly used time domain measures of HRV is the standard deviation of all

normal R-R intervals (SDNN). However, at least 18-hours of data are required to calculate this variable properly (Lewis, 2005; Malik & Camm, 1995).

The frequency domain parameters can be derived through spectral analysis (via Fast-Fourier transformation or auto-regressive techniques) of R-R intervals. Spectral analysis can be used to quantify the cyclic fluctuations in R-R intervals that occur over time (Kleiger et al., 2005). Using this method of analysis of the heart rate power spectrum reveals three frequency components: a high frequency (HF) peak (between 0.15 and 0.40 Hz), a low frequency (LF) peak (between 0.04 and 0.15 Hz) as well as very-low frequency (< 0.04 Hz) which are expressed in absolute values of power (ms^2) (Bernardi et al., 2011; Kleiger et al., 2005; Yamamoto & Hughson, 1991). The HF power reflects the influence of respiration on the cardiac vagal nerve (respiratory sinus arrhythmia) or parasympathetic activity whereas the LF power is a reflection of both sympathetic and parasympathetic nerve activity. Parasympathetic nervous system (PNS) modulation can be inferred from the parasympathetic indicator (a ratio of the high frequency to total power), whereas, sympathetic (SNS) modulation can be inferred from the sympathetic indicator (a ratio of low to high frequency power).

Additional information on autonomic control of the heart can be gleaned from analysis of the spontaneous baroreflex sensitivity (BRS) which is also a marker of vagal reflexes (De Ferrari et al., 1995). This requires collecting data on beat-by-beat changes in systolic blood pressure (SBP) and corresponding R-R intervals, with the understanding that changes in blood pressure produce linear changes in the R-R interval. Analysis of spontaneous baroreflex sequences can be defined as 3 or more beats in which both the SBP and R-R interval change in the same direction (Blaber et al., 1995).

Factors influencing HRV. Numerous factors can influence cardiac autonomic function in patients with PAD including physiological factors (arterial baroreceptors, atherosclerosis, respiration, age, sex), physical challenges (orthostatic stress, acute exercise and exercise training) and pharmacological agents (beta-blockers, alcohol and nicotine intake through smoking cigarette tobacco).

Arterial baroreceptors. Arterial baroreceptors are pressure receptors located in the adventitia of the endothelium of the aortic arch and carotid sinus (Tortora and Grabowski, 2003). The receptors respond to increases or decreases in blood pressure exerted on the blood vessel wall. The aortic baroreceptors send afferent information via the vagus nerve and the carotid sinus sends information via the glossopharyngeal nerve to the cardiac control center, which is located in the medulla oblongata of the brain stem. It has a homeostatic set point for blood pressure. If blood pressure increases or decreases beyond this set point, a correction signal is sent from the brain to the heart to alter heart rate and blood pressure. If blood pressure rises, the carotid and aortic baroreceptors detect this and increase vagal input to the cardiac control center and decrease SNS stimulation. An efferent signal is then sent via the vagus nerve to the SA node (which releases acetylcholine and slows the heart rate). If blood pressure decreases, there is a withdrawal of PNS influence to the SA node and an efferent signal is sent via sympathetic fibers located in the cardiac nerves to the SA node to release norepinephrine and increase heart rate, blood pressure and total peripheral resistance.

Atherosclerosis. Patients with atherosclerotic cardiovascular disease (defined as coronary artery disease, cerebrovascular disease, or peripheral vascular disease) have a lower HRV compared to a healthy population (Fowkes et al., 2013; Lovell et al., 2009; Rosenwinkel et al., 2001). Systemic inflammation, enhanced coagulation, platelet activation and increased

macrophage-LDL cholesterol oxidation promote atherosclerosis and this can lead to an imbalance in cardiac autonomic activity (Franchini & Mannucci, 2011). Hayano et al. (1991) examined HRV in 80 patients who were having coronary angiograms performed on them. They found a significant negative correlation between HRV (as assessed by the size of the HF component) and the degree of coronary atheromatosis (process of accumulation of lipid containing plaques) ($r = -.43, p < 0.001$) and severity of coronary stenosis ($r = -0.30, p = .007$). Both the Framingham Heart Study (Tsuji et al., 1996) and the Atherosclerosis Risk in Communities Study (ARIC) (Liao et al., 1997) have reported that low HRV may be predictive of incident coronary heart disease (hospitalized myocardial infarction, fatal CHD or the need for cardiac revascularization procedures) over 3 years.

Respiration. An individual's pattern of breathing can alter heart rate (and the R-R interval). During inspiration, heart rate increases and during expiration, heart rate decreases (Lewis, 2005). This phenomenon is referred to as respiratory sinus arrhythmia (Haggenmiller, Baumert, Adt, & Frey, 1996) and is mediated through parasympathetic nerve activity. Tidal volume, or the amount of air exchanged with one inspiration or expiration cycle, can also influence the variability of the R-R interval. Since respiration can influence heart rate variability in the high frequency region of the HRV spectrum, some researchers have suggested that respiratory rate (Grossman, 1992; Hayano et al., 1994; Ori, Monir, Weiss, Sayhouni, & Singer, 1992) be controlled (through paced breathing) when conducting studies involving HRV analysis. However, paced breathing can impose additional stress upon an individual by reducing the high frequency component and increasing the low frequency component (Patwardhan, Vallurupalli, Evans, Bruce, & Knapp, 1995). Subsequent studies comparing the effects of spontaneous breathing (14.4 breaths per minute) with controlled breathing (15, 18 and 21 breaths

per min) at rest (Patwardhan, Evans, Bruce, & Knapp, 2001; Patwardhan et al., 1995; Pinna, Maestri, La Rovere, Gobbi, & Fanfulla, 2006) on HRV have demonstrated no differences.

Age. As individuals age, structural and functional changes occur within the cardiovascular system which leads to a deterioration in the function of the heart and blood vessels. Maximal heart rate, ejection fraction and cardiac output all decrease with increasing age (Davis, 2014). Increasing age has been shown to decrease HRV in both healthy individuals (Liao et al., 1995; Lipsitz, Mietus, Moody, & Goldberger, 1990) and patients with cardiovascular disease. Part of this is attributed to central autonomic dysregulation (Piccirillo et al., 2001), a reduction in cardiac M₂ muscarinic receptor density and function (Broddie et al., 1998) and a decrease in arterial compliance (Kardos et al., 2001). Blood pressure increases with increasing age due to stiffening of the large elastic arteries, endothelial dysfunction (Seals, 2014) and a reduction in baroreceptor sensitivity (defined as a BRS < 3 ms/mmHg) (Laitinen et al., 1998; Piccirillo et al., 2001).

Sex. Any sex-related differences in HRV measures can be attributed to sex-related differences in hormones. Receptors for estrogen, progesterone and testosterone are located in areas of the brain regulating cardiovascular function (Dart, Du, & Kingwell, 2002). In the periphery, the synthesis and release of acetylcholine (ACh) is also modulated by sex hormones. At rest, premenopausal women and age-matched men exhibit significant sex-related differences in HRV parameters (Abdel-Rahman, Merrill, & Wooles, 1994; Bigger et al., 1995; Gregoire, Tuck, Yamamoto, & Hughson, 1996; Liao et al., 1995). Women tend to have a greater HRV (as reflected by a higher total spectral power and/or greater SDNN measures, a lower LF power, a lower SNS indicator and a greater PNS indicator) compared to men. After menopause, HRV in healthy middle-aged and elderly women is similar to healthy, age-matched men (Arai et al.,

1989). Post-menopausal women on hormonal replacement therapy (HRT) have a greater baroreflex sensitivity to the valsalva manoeuvre (described as a forceful expiration against a closed epiglottis) compared to those not on HRT (Huikuri et al., 1996). Thus, sex-related difference in hormones such as estrogen contribute to a reduction in sympathetic activity and enhances vagal activity.

Orthostatic stress. The sympathetic nervous system plays an important role in regulating blood flow to the legs during postural change from the supine position to upright tilt and the standing position (Delis, Nicolaidis, & Wolfe, 2001). It involves both central neural control via the baroreceptors and peripheral sympathetic auto regulation. In healthy, young individuals (9 men, 1 woman) postural change from the supine position to standing (i.e., orthostatic stress) was shown to shift blood volume from the chest to the lower extremities and reduce venous return to the heart, thereby decreasing central venous pressure and stroke volume (Westerhof et al., 2006). This leads to a decrease in blood pressure that is sensed by the baroreceptors and a message is sent to the cardiorespiratory center via the vagus nerve and glossopharyngeal nerves. Adjustments are made in the vasomotor center of the medulla to activate sympathetic activity and decrease vagal activity. This results in an increase in heart rate and peripheral vasoconstriction. Simultaneously, a reflexive contraction of the arteriolar and pre-capillary sphincters also occurs in order to reduce blood flow to the legs. This sympathetically-mediated reflex (known as the venoarteriolar reflex) is one of the body's homeostatic mechanisms to prevent edema from developing in the lower extremities with postural change to standing or sitting (Delis, Lennox, Nicolaidis, & Wolfe, 2001). An increased pressure in the venules is sensed which induces contraction of the arteriolar and pre-capillary sphincters, decreasing blood flow into the calf muscle. Studies that have been done using laser Doppler flowmetry to

examine skin blood flow in foot compared to the standing position have demonstrated that the venoarteriolar reflex is impaired in patients with intermittent claudication (Belcaro, Vasdekis, Rulo, & Nicolaides, 1989; Delis, Lennox, et al., 2001).

Studies that have examined the effects of postural change on measures of cardiac autonomic control in patients with cardiovascular disease (e.g., coronary artery disease patients who have undergone coronary artery bypass graft (CABG) surgery have consistently shown a reduction in PNS activity and an increase in SNS activity with orthostatic stress (Brown, Wolfe, Hains, Ropchan, & Parlow, 2003; Chenier-Hogan, Brown, Hains, & Parlow, 2012). In healthy patients, standing and head-up tilt is also associated with an increase in LF power (Kamath, Fallen, & McKelvie, 1991; Pomeranz et al., 1985) and a decrease in HF power (Fei, Anderson, Statters, Malik, & Camm, 1995; Pomeranz et al., 1985). Studies that have compared the effects of orthostatic stress in men versus women, have demonstrated a differential effect between the two sexes. In patients with cardiovascular disease, men tend to have a greater PNS withdrawal and SNS increase in response to standing compared to women (Chenier-Hogan et al., 2012). The reduction in baroreceptor sensitivity that occurs with standing in healthy adults (Westerhof et al., 2006) is greater in men after cardiac surgery (Brown et al., 2003).

Acute exercise. Acute exercise can be defined as physical activity that is performed in a single session (da Pureza et al., 2012). The effect of acute aerobic exercise on HRV measures is dependent upon body posture and the intensity of exercise (Kamath et al., 1991; Perini et al., 1993; Yamamoto, Hughson, & Peterson, 1991). Overall, total spectral power decreases exponentially as a function of exercise intensity, irrespective of posture (Perini et al., 1993). In the upright position, the exercise induced increase in heart rate, stroke volume and myocardial contractility can be attributed to a gradual withdrawal of PNS activity until exercise intensity

approaches approximately 60% of peak oxygen intake at which time SNS activity and the release of epinephrine and norepinephrine as measured by high-performance liquid chromatography (HPLC) begin to rise (Nakamura, Yamamoto, & Muraoka, 1993).

Pharmacological agents. Pharmacologic agents such as anti-thrombotic medications and/or cholesterol lowering agents as well as anti-hypertensive medications are commonly prescribed for patients with PAD (Dobesh, Stacy, & Persson, 2009). One class of anti-hypertensive medications, known as β -blockers (β -adrenergic antagonists) has been shown to influence the HRV power spectrum. β -blockers decrease sympathetic activity and increase parasympathetic activity at rest (Pagani et al., 1986). The use of β -blockers lead to a reduction in heart rate, blood pressure, mean arterial pressure and an increase in spontaneous baroreceptor sensitivity (BRS, which is a marker of vagal activity) (Blaber et al., 1995) at rest and in response to exercise (Bangalore, Sawhney, & Messerli, 2008; Goldie et al., 2013). Goldie et al. (2013) found that in women with hypertension, the use of β -blockers in combination with low-intensity exercise training has a synergistic effect (greater reductions in heart rate and rate pressure product were observed). The proposed mechanism for this adaptation is not completely understood, but may be related to an improvement in PNS modulation. This effect occurs in hypertensive patients and thus would be expected in patients with PAD.

Smoking. Findings from the INTERHEART study indicate that cigarette smoking is the most important risk factor for an acute myocardial infarction (Yusuf et al., 2004). Cigarette smoking is also a strong risk factor for the development of PAD (Conene et al., 2011; Willigendael et al., 2004), especially if smoking begins early in life (for example, at 16 years of age or earlier) (Planas et al., 2002). Thus, many patients with PAD are either smokers or were previous smokers. Cigarette smoking has acute, transient effects as well as long-term effects on

cardiac autonomic function. Immediately following cigarette smoking, resting heart rate, vascular resistance and blood pressure rise (Cryer, Haymond, Santiago, & Shah, 1976; Gropelli, Giorgi, Omboni, Parati, & Mancia, 1992). Within 3 minutes of smoking a cigarette, the HF spectral component of the HRV power spectrum representing respiratory sinus arrhythmia (0.25Hz) is reduced (Hayano et al., 1990) and within 10 – 17 minutes the LF spectral region (0.04 – 0.15 Hz, representing Mayer wave sinus arrhythmia which includes sympathetically-mediated activity) is increased. These effects last for approximately 30 minutes (Manzano, Vanderlei, Ramos, & Ramos, 2011). This occurs due to the effects of nicotine and other smoking by-products on the neuroendocrine system. Nicotine and tobacco smoke increase sympathetic activity (Kotamaki, 1995; Narkiewicz et al., 1998), impair baroreceptor sensitivity (Erdem et al., 2015) and stimulate the release of epinephrine and norepinephrine from the adrenal medulla and sympathetic nerve terminals, respectively (Grassi et al., 1994). It has also been shown that acute cigarette smoking alters the autonomic response to acute exercise in young, healthy volunteers. Following smoking, HR is increased at rest and in response to submaximal exercise. Although the raw high and low frequency powers were reduced following smoking, the SNS indicator (i.e., the low to high frequency ratio) was increased both at rest and during submaximal exercise (Mendonca, Pereira, & Fernhall, 2011). Long-term habitual cigarette smokers have lower HRV and elevated sympathetic nervous system activity (as reflected by higher LF/HF power ratios) (Harte & Meston, 2014; Mendonca et al., 2011), placing them at risk for increased mortality due to arrhythmias (Harte & Meston, 2014).

In summary, the measurement of HRV is a sensitive and non-invasive way to assess autonomic control of the heart. In using this measure, it is important to consider the various factors which can influence HRV. For this study, factors such as age, sex, smoking status and

use of β -blockers are known to influence the HRV in patients with PAD and were included as potential confounders in any statistical analyses that were initially done.

HRV and peripheral arterial disease. Vascular changes (such as metabolic alterations and vascular remodeling) that accompany the atherosclerotic process leads to an increase in arterial stiffness (Bruno, Ghiadoni, Seravalle, Dell'Oro, & Taddei, 2012; Fowkes et al., 2013). Part of this is due to a reduction in endothelial function (due to reduced nitric oxide release, production of free-radicals (reactive oxygen species), increased production of endothelin-1 and angiotensin-II) as well as an increase in sympathetic outflow at the central and peripheral levels. Arterial stiffness subsequently impairs baroreflex sensitivity (BRS) thus increasing SNS activity (Bruno et al., 2012).

To date, only 4 studies have examined HRV in patients with PAD either at rest or following aerobic training (Table 1). Two of these examined HRV at rest (Goernig et al., 2008; Jelinek et al., 2013) and two examined the influence of moderate to high intensity exercise training on resting HRV (Leicht, Crowther, & Golledge, 2011; Sandercock, Hodges, Das, & Brodie, 2007). Goernig et al. (2008) reported on a descriptive study designed to explore HRV in men with or without PAD. They examined HRV in 53 men (67 ± 11 years) recruited from a cardiovascular unit; 27 cardiac patients had PAD ($ABI < 0.9$) and 26 cardiac patients did not have PAD ($ABI > 0.9$). Fourteen men from another rehabilitation unit in the hospital who did not have a history of cardiovascular disease were included as a reference group. HRV data were recorded for 30 minutes at rest, however the position in which the recordings were made was not

Table 1

Studies examining HRV in patients with PAD.

Authors/ Study Design	Participants	HRV analyses	Intervention	Results
Goernig et al. 2008/ X-sectional	n = 53 CAD pts (27 PAD; 26 without PAD)	Time & frequency domain	None	LF and HF indices increased in CAD patients with PAD, with LF increased to a greater extent
Jelinek et al. 2013/X-sectional	n = 235 diabetics	Time & frequency domain,	None	HRV reduced below an ABI of 1.1 and higher than an ABI of 1.2
Leicht et al. 2011/ Longitudinal	n = 25 PAD pts n = 24 controls	Time & frequency domain	<u>Training</u> : 3 x/wk to max pain on TM, 25-40 min	PAD patients similar to controls. No change in HRV parameters. Increased maximal walking time
Sandercocock et al. 2007/ Longitudinal	n = 44 PAD pts SU = 13 (10 M, 4 F) HB = 15 (12 M, 3 F) CT = 15 (10 M, 5 F)	Frequency domain	<u>Training</u> : 3 x/wk, 75% peak VO ₂ , 30 min, 12 wk HB= 3x/wk RPE 12 – 14, 30 min, 12 wk	Supervised exercise (SU) - increase in maximal walking time - No change in HRV measures - No change in peak aerobic capacity Home-based exercise: no change in HRV measures

Legend: ABI = ankle-brachial index; CAD = coronary artery disease; CT = control; HB = home-based; HF= high frequency, HRV = heart rate variability; LF = low frequency; Pts = patients; RPE = Ratings of perceived exertion; SU = supervised exercise training.

reported. Linear time-domain, frequency-domain and other non-linear dynamics (measures related to entropy or disorder) were determined, but the program used to do these analyses was not indicated. They found that patients with PAD demonstrated higher spectral power measures for LF and HF components compared to cardiac patients and the reference controls without PAD. The LF component was seven times elevated and the HF component was 4 times elevated, indicating higher sympathetic to parasympathetic activation in the cardiac patients with PAD compared to the cardiac patients without PAD. The LF/HF ratios were not presented by the authors but could be calculated as 1.51 for healthy reference controls, 1.38 for cardiac patients and 1.88 for cardiac patients with PAD. Time domain measures such as the standard deviation of the R-R interval (SDNN) and the square root of the mean squared differences of successive beat-to-beat intervals (RMSSD) were significantly higher in the patients with PAD (ABI < 0.9) indicating greater vagal activation (corresponding to the four-fold elevation in the HF component that was observed).

In a descriptive study, Jelinek et al. (2013) investigated the relationship between ABI and HRV in 235 diabetic participants (aged 57 ± 14 years) with and without a diagnosis of PAD who attended a rural diabetic screening clinic between 2002 and 2012. Based upon ABI measures, participants were divided into three groups: ABI < 1.1 (low values); ABI 1.1-1.2 and ABI > 1.2 (high values). High ABI values in diabetics may indicate severe disease with non-compressible vessels. Electrocardiograph (ECG) recordings were made for 20 minutes and HRV was determined in the resting state using time and frequency domain analysis. A direct relationship between disease severity (ABI) and HRV (as determined by linear and non-linear measures) was found. HRV measures were lower in participants who had ABI values outside the range of 1.1 to 1.2.

Only two studies have examined the effects of high intensity, low frequency aerobic exercise conditioning (i.e., walking) on autonomic function in patients with PAD (Leicht et al., 2011; Sandercock et al., 2007). Sandercock et al. (2007) randomly assigned 44 patients with PAD to one of the following three groups: a supervised walking group (n = 14; 10 men and 4 women) involving exercise twice per week performed for 30 min at 75% peak oxygen uptake over 12-weeks; a home-based walking group (n = 15; 12 men and 3 women) whereby participants walked twice per week for 30 min over 12 weeks or no exercise (n = 15; 10 men, 5 women). It was hypothesized that improvements in walking performance in the exercise groups would be due to an increase in global and vagal measures of HRV. Five min, 12 lead ECG recordings were obtained from the participants while they rested in a semi-recumbent position at entry into the study and after 12-weeks of training. HRV acquisition and analysis were performed using a Cardio Perfect ST 2001 system, which includes an ECG recorder and management system that provided frequency-domain information. No significant changes occurred in peak oxygen consumption or HRV measures over time indicating a lack of central cardiorespiratory or neural adaptations. However, maximal walking time significantly increased in the participants who were involved in the supervised training program. A limitation of the study was the small sample size for each group. The authors did acknowledge this and indicated that their power analysis and sample size determination was based upon changes in walking performance and likely lacked power to demonstrate a significant effect for HRV measures.

In follow-up to this study, Leicht et al. (2011) examined the effects of a 1-year exercise intervention in patients with PAD. Twenty-five participants with either PAD (n= 13) or healthy, aged matched individuals (n = 12) were randomly assigned to either a conservative medical group or a supervised walking program that included medical treatment. The method of

randomization was not indicated. Nine (69%) participants in the conservative treatment group and eight (67%) participants in the exercise group completed the study at one year. Participants in the walking program were required to perform supervised exercise on a treadmill 3 days per week, near maximal claudication pain. Each exercise session lasted 25 to 40 min per session. Five-min ECG recordings were obtained at rest at entry into the study and after 1 year. Time- and frequency-domain measures as well as non-linear HRV measures were obtained from these recordings and analyzed using the Kubios HRV analysis software program (Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2014; Tarvainen, Ranta-aho, & Karjalainen, 2002). Patients with PAD demonstrated similar resting HRV measures as the healthy participants. Twelve months of training did not alter HRV in either the PAD patients or in the healthy comparison group. In concurrence with the findings of Sandercock et al. (2007), exercise training induced a significant 183% increase in walking capacity compared to a 57% increase in the comparison group.

The lack of any notable change in HRV following training in both of these studies may be a function of the type of walking intervention implemented. These 2 studies had patients walk at 75% peak aerobic capacity or to maximum pain intensity, 2-3 days per week. Thus, aerobic exercise training in patients with PAD to maximum pain intensity, but low frequency does not alter autonomic function in these patients, probably due to the low frequency. To date, no one has examined the effects of a low-intensity, high frequency exercise (walking) program on cardiac autonomic function patients with PAD.

Exercise Therapy

Exercise has been used as therapy for patients with intermittent claudication for more than 40 years (Conte et al., 2015). Patients with PAD are limited in their physical function and

exercise tolerance (Hamburg & Balady, 2015); they walk more slowly, have poor endurance, frequently lose their balance and have less confidence in their walking ability than healthy individuals (McDermott, 2013). Severe claudication is associated with a reduction in mobility (Brach et al., 2008), increased difficulty in performing activities of daily living (ADL) (Brach et al., 2008) and consequently a poorer quality of life (Gardner et al., 2008). As the disease progresses, functional ability worsens and individuals with PAD may eventually experience leg pain at rest. Based upon the findings of a review paper by Hamburg and Balady (2015), the primary goal of exercise therapy for patients with cardiovascular disease including PAD is to reduce the risk of cardiovascular events, decrease disease progression, reduce disability and to improve physical function preventing an increase in blood flow to the exercising muscles.

Current clinical guidelines of the Society for Vascular Surgery (Conte et al., 2015) and the American Heart Association (Anderson et al., 2013) recommend supervised, hospital or clinic-based exercise for patients with PAD and rate it as a Grade 1A intervention (indicating a general agreement on the effectiveness of treatment) for patients with PAD. According to their guidelines, supervised walking, three times per week for 30-60 min/session should be performed. The American College of Sports Medicine (2014) recommend that patients with PAD perform weight-bearing exercise 3 to 5 days per week at a moderate intensity (40 to 60% of the heart rate reserve (HRR; 64-76% HR_{max} ; ratings of perceived exertion of 12 to 13 or to a pain score of 3 out of 4). If necessary, patients can perform the exercise in bouts of 10-15 min.

Supervised exercise programs are safe with an all-cause incident rate of one injury in 10,340 patient hours of exercise (Ritti-Dias et al., 2011). However, few programs are available in North America and of those that are available, they tend to be hospital-based and resource intensive for patients and health-care providers (Makris, Lattimer, Lavidia, & Geroulakos, 2012).

Only 30.4% of patients have access to supervised exercise programs world-wide, with the majority of programs being offered in Europe. The prescription of regular exercise now is usually encouraged as “go-home-and walk”. Unfortunately, such unstructured home-based interventions have limited efficacy (Cunningham, Swanson, O'Carroll, & Holdsworth, 2012). Thus, home-based, unsupervised exercise programs are rated as a Grade 1B (indicating conflicting or insufficient evidence for its efficacy) (Anderson et al., 2013). The published exercise guidelines described above are based upon past research and do not address the role and possible mechanisms of action of a structured, low-intensity (pain-free) home exercise program in the treatment of patients with PAD.

Figure 1 illustrates the possible roles which exercise can have in the treatment of PAD. Regular physical activity can block the effects of a sedentary life style and lead to an improvement in physical function, walking and associated self-report measures such as the walking impairment questionnaire and quality of life measures. One mechanism whereby regular low-intensity exercise may work is by improving autonomic function.

Brenner, Parry and Brown (2012) performed a literature review on exercise interventions for patients with PAD. In general, it was found that exercise programs could be divided into 2 categories: (1) protocols that encourage participants to exercise to maximum pain tolerance or (2) protocols whereby participants exercise up to the onset of pain. Walking tended to be the predominant activity, however, alternative exercise training programs such as pole-striding exercise (Collins et al., 2005; Langbein et al., 2002), cycle ergometer exercise (Sanderson et al., 2006) or upper extremity exercise (Treat-Jacobson, Bronas, & Leon, 2009) or a combination of upper and lower body exercise were utilized (Treat-Jacobson et al., 2009; Zwierska et al., 2005). Exercise to maximum pain tolerance has consistently improved walking performance (pain-free

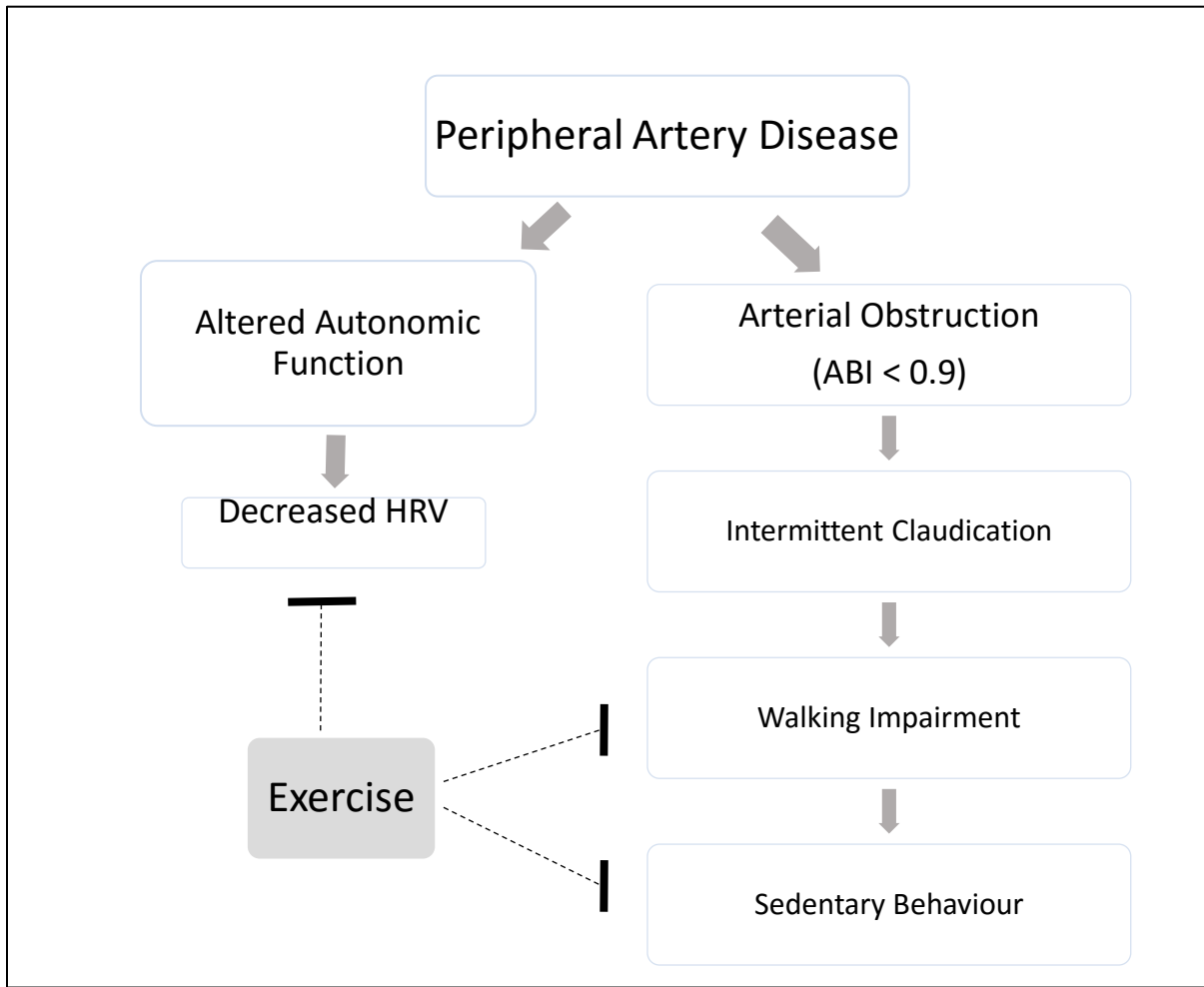


Figure 1. One of the possible roles of exercise in the treatment of PAD.

walking distance [PFWD]; maximal walking distance [MWD) as well as self-report measures such as the extent of walking impairment and quality of life (increasing walking performance and reducing bodily pain) (Nicolai, Teijink, & Prins, 2010). In addition, training to maximum pain tolerance can increase peak aerobic capacity (Gardner, 2002; Hiatt, Regensteiner, Hargarten, Wolfel, & Brass, 1990; Zwierska et al., 2005) and promote the development of collateral circulation (Alpert, Larsen, & Lassen, 1969) as well as increase calf blood flow (Gardner, Montgomery, Flinn, & Katzel, 2005). One study reported a 3 percent increase in ABI following high-intensity exercise training (Izquierdo-Porrera, Gardner, Powell, & Katzel, 2000). A recent Cochrane review (Lane, Ellis, Watson, & Leng, 2014) of thirty randomized controlled-studies concluded that the ABI does not change following high-intensity exercise training. They reported a mean difference of 0.05 for ABI following participation in an exercise program when compared to pre-exercise baseline data.

The INTERHEART Study confirmed previous reports that heavy or vigorous exertion may trigger a cardiovascular event (such as a myocardial infarction) and that emotional upset or anger at the time of exertion can have an additive effect (Smyth et al., 2016). One drawback to exercise to maximum pain tolerance is that patients with PAD exhibit an exaggerated blood pressure response to continuous treadmill exercise, with peak increases in blood pressure occurring when patients walk near their maximal pain tolerance level (Bakke, Hisdal, Jorgensen, Kroese, & Strandén, 2007). Furthermore, the rise in HR that occurs with exercise is initially due to PNS withdrawal and at 50% of the maximum aerobic capacity SNS activation further increases HR and BP to meet metabolic demands (Goldsmith et al., 2000). This could further contribute to the abnormal cardiovascular response that is observed in patients with PAD who exercise.

Table 2

Studies on the effect of low-intensity exercise on PAD outcome measures.

Authors	N	Length (wks)	Training			Min	Outcome
			Frequency	Intensity	Type		
Barak et al. (2009)	10 5W/5M	6	2x/wk	Pain free	Treadmill	45	- No change in HR, BP - Increase in MWD
Boyd et al. (1984)	8 2W/6M	12	3/wk	Pain free	Treadmill, Bike, Track	25-40	- No change in ABI. Increase in PFWD; MWD
Carter et al. (1989)	56 15W/41M	24	2x/wk	Mild pain	Track	60	- Increase in brachial-ankle difference. - Increase in MWD. Increase in 6mwt
Gardner et al. (2005)	31 27M/4F	24	3x/wk	40% max	Treadmill	15-40	- No change in ABI; Increase in PFWD; MWD; WIQ-distance; SF36-PF
Mannarino et al. (1989)	8EG 8CG	24	7x/wk	Pain onset	Ground	20-60	- No change in ABI. Increase in PFWD; MWD. No change in lipids
Martinez et al. (2009)	84 28/30/26 per group	Up to 94	2x/wk	Pain free	Treadmill	30-50	-Increase in MWD
Mika et al. (2005)	80 41EG/39CG	12	3x/wk	Pain free	Treadmill		- Increase in PFWD - No change in WBC
Tsai et al. (2002)	27EG 26CG	12	3x/wk	Mild pain	Treadmill	30	-Increase in PFWD, MWD, 6MWT -Increase in WIQ; SF36-PF and RL

Legend: 6mwt = six-minute walk test; ABI = ankle-brachial index; BP = blood pressure; CG = Comparison group; EG = exercise group; HR = heart rate; MWD= maximum walking distance; PF = physical function; PFWD = pain-free walking distance; RL = role limitation; T = time; TM = treadmill; WBC = white blood cells; WIQ= walking impairment questionnaire; wk = week.

Several studies have examined the influence of either pain-free walking interventions in patients with PAD on cardiovascular, performance and/or self-report measures. These studies are summarized in Table 2. Pain-free exercise has several advantages over exercise programs that encourage participants to walk to maximal pain. First, participants are more likely to engage in exercise that is pain-free or with a pain level that they are willing to accept (Rejeski, Tian, Liao, & McDermott, 2008). Second, low-intensity exercise conditioning trains the aerobic energy systems without the development of claudication pain (Martinez, Carmeli, Barak, & Stopka, 2009). Third, it is less likely to induce any inflammatory response due to ischemia (Martinez et al., 2009; Mika, Spodaryk, Cencora, Unnithan, & Mika, 2005). Lastly, pain-free exercise minimizes involvement of the sympathetic nervous system (Goldsmith et al., 2000), thereby limiting the increase in heart rate, blood pressure and the workload of the heart which makes it an ideal exercise intervention to study autonomic adaptations in patients with PAD.

Programs that require patients to walk to minimal pain can also lead to an increase in pain-free walking distance (PFWD) (Mika et al., 2005) and/or maximal walking distance (Gardner et al., 2005; Mannarino, Pasqualini, Menna, Maragoni, & Orlandi, 1989; Martinez et al., 2009; Tsai et al., 2002). Moreover, the physical function component (Gardner et al., 2005; Tsai et al., 2002) and role limitation component (Tsai et al., 2002) of the SF-36 Quality of Life Questionnaire improve following training. Although Carter et al. (1989) found that 24 weeks of walking twice a week on a track lead to an increase in the difference between the arm and ankle blood pressures (indicating a possible reduction in ABI), most studies show that ABI also does not change with exercise training, especially over the short term (Boyd et al., 1984; Gardner et al., 2005; Mannarino et al., 1989).

There is little information on the influence of pain-free exercise on other cardiovascular parameters and to the best of our knowledge, no studies that have investigated autonomic responses. Barak et al. (2009) examined the effects of regular 45 min bouts of treadmill walking to mild/moderate intensity exercise on walking performance measures and resting hemodynamic measures in a very small sample of patients with PAD (5 men and 5 women) over 6 weeks. The primary outcome measures included walking performance variables (e.g., walking distance, duration and speed). Secondary outcome measures included ergometric calculation variables (e.g., estimated relative oxygen consumption, metabolic equivalents and estimated total as well as rate of energy expenditure) and tertiary outcome measures include hemodynamic variables (resting HR and BP). Participants attended a local fitness center for their training sessions and were encouraged to walk as fast as possible without pain on the treadmill for two days per week. Maximal walking distance and time increased 104% and 56%, respectively following training, however resting heart rate and blood pressure did not change demonstrating that cardiovascular adaptations may not have occurred. This is the first and only study to have compared walking performance measures to training in men with PAD with that of women with PAD and found that men respond similarly as women to the exercise intervention. Unfortunately, sex-specific data on ergonomic and hemodynamic measures were not presented.

Weaknesses of many of the studies outlined in Table 2 are that they include small sample sizes of mostly men and do not have a comparison group. In addition, the studies describe improvements in either PFWD and/or MWD and none measured the functional claudication distance. Many of the studies also do not investigate the possible mechanisms that may have contributed to the observed improvements in performance and self-report measures.

The mechanisms that may contribute towards the training-induced adaptations in walking ability that occur in patients with PAD are multifactorial and not clearly understood. Studies involving pain-free exercise have demonstrated that the ABI remains the same following training (Carter et al., 1989; Mannarino et al., 1989). This could indicate that exercise training delays the progression of arterial narrowing, disease or disability. However, there may be other adaptations such as changes in autonomic function that could contribute to the observed functional improvements. Regular low-intensity exercise training alters autonomic balance in favor of PNS activity at rest and during submaximal exercise (Goldie et al., 2013; Hua et al., 2009).

Exercise Compliance

In order for an exercise program to be effective, patients must comply with their exercise prescription. The extent to which the behaviour of an individual complies with the advice given by a health care provider is referred to as compliance (Haynes, McDonald, & Garg, 2002). Factors that have been shown to affect compliance can be categorized as patient-centered factors, therapy-related factors, social and economic factors, and disease factors (Jin, Sklar, Oh & Li, 2008). Exercise compliance rates for patients with peripheral artery disease, who are enrolled in a home-based walking intervention, will vary depending on the type of walking intervention and whether or not patient follow-up is provided. One study reported a 41% compliance rate, in which patients walked 1 hour each day, for 5 days per week over 12 weeks, to maximal claudication pain, with weekly telephone follow-up calls (Tan et al., 2000). Another study involving fewer exercise sessions (i.e., 3 days per week to maximal pain tolerance) with feedback provided through use of a step-activity monitor had an 80% compliance rate (Gardner et al., 2011). High compliance rates (i.e., 80%) to both home-based and supervised walking programs have been reported when patients are monitored and have feedback provided to them

(Gardner et al., 2011). Wullink, Stoffers and Kuipers (2001) found that use of a counseling technique (i.e., the Health Counseling Model) as well as walking diaries could be used to promote adherence to a walking exercise program.

Previous Relevant Work

Previous research performed in this laboratory has led to the development of a model to study short-term autonomic control of heart rate in healthy individuals and in individuals with cardiovascular disease. This model involves testing participants in various physiological conditions (resting supine, standing, exercise) and collecting short-terminal R-R interval and beat-by beat arterial blood pressure data over 10 to 15 min in accordance with recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [TFESCNASPE] (1996). Autonomic modulation of heart rate can be determined through spectral analysis of heart rate variability (HRV) and sequence analysis of spontaneous baroreflex sensitivity (BRS) in the different conditions.

Myslivecek, Brown and Wolfe (2002) compared HRV and BRS in 16 pre-menopausal women with 16 post-menopausal women before and after a 12- week, home-based low-intensity exercise (walking) training program. Participants in each menopausal state were randomly assigned to either an exercise group or a control group. Participants in the exercise group walked 3 days per week, at an intensity corresponding to an RPE of 13 (somewhat hard), beginning at 0.6 km/day and gradually increasing to 4 km/day by the end of the study (week 12). Reproductive state did not influence HRV measures (R-R interval, SBP, SBR slope, TP, SNS and PNS indicators). Postural change (from left lateral decubitus or sitting to standing) induced an increase in SNS indicator and SBP in all groups. Acute moderate-intensity exercise induced changes in HRV measures indicating vagal withdrawal and increased SNS activation. Lastly,

physical conditioning resulted in an increased R-R interval and BRS in both the sitting and standing positions, decreased SNS activity in the standing posture and decreased SNS modulation and an increase PNS (vagal) modulation (increased PNS indicator, BRS and R-R interval) during steady-state exercise of low-moderate intensity.

Hua, Brown, Hains, Godwin and Parlow (2009) examined the effects of a 12-week, home-based, low-intensity exercise program on cardiac autonomic function and blood pressure in men and women with mild hypertension. Forty participants were randomly assigned, based upon their sex, to either a walking exercise program or a comparison group. Participants in the exercise group walked 4 days per week, at an intensity corresponding to an RPE of 11-13 (fairly light to somewhat hard; target HR 35% - 40% HR reserve), beginning at 0.8 km/day (0.5 mile/day) for the first 2 weeks and gradually increasing walking distance to 4.8 km/day by the end of the study (week 12). Hua et al. found that the 12-week walking intervention induced a significant increase in PNS activity (R-R interval and BRS measures) and a decrease in blood pressure in both the sitting and standing positions.

In a recent study by Goldie, Brown, Hains, Parlow and Birtwhistle (2012), the findings of the studies by both Myslivecek et al. (2002) and Hua et al. (2009) were further extended. Goldie et al. examined the effects of a similar low-intensity walking program but increased the frequency to 5 days per week (4 days per week in the previous study) on blood pressure, heart rate, rate pressure product (RPP) and cardiac autonomic function in 40 women with hypertension. Women were assigned randomly to either an exercise group (n = 20) or a comparison group (n = 20). Significant reductions in SBP, DBP and RPP were observed in all 3 conditions (supine, standing and exercise) with training. These responses were further augmented in the women who took β -

blockers to treat hypertension. However, the women in the exercise group who were on β -blockers showed significant improvements in HRV measures over time.

No one has investigated the effects of a home-based, progressive, low-intensity, high frequency exercise program on autonomic balance in patients with PAD. A change in autonomic balance towards an increase in PNS activity and a decrease in SNS activity could potentially lead to vasodilation and an increase in blood flow to the extremities. Previous work in this lab has recommended that the frequency of the exercise sessions be maintained at 5 days per week in order to achieve autonomic adaptations. This was observed in HRV measures for women taking β -blockers and who participated in the walking program (Goldie et al., 2012). However, as a result of the symptoms of intermittent claudication associated with PAD, walking ability is limited in these patients. Thus, the low-intensity exercise program established by Brown et al. (1994) was used in this study of patients with PAD.

Summary and Conclusions

In summary, minimal research has examined HRV in patients with PAD. Thus far, it has been shown that HRV at rest is reduced and that sympathetic activity is enhanced in patients with PAD. High intensity, low frequency training interventions have not demonstrated any changes in autonomic function in patients with PAD following training. However, studies from this lab have demonstrated that low-intensity, high frequency exercise training can alter autonomic balance to increase HRV in favor of an enhanced parasympathetic activity and a reduced sympathetic activity in patients with cardiovascular disease (hypertension and CAD). Low-intensity (pain-free) exercise in patients with PAD has recently been the focus of research as it encourages adherence, reduces the risk of inflammation and ischemia of the lower extremities, decreases the risk of a CV event from occurring. The studies performed to date have demonstrated that

physical function is improved following participation in a low-intensity exercise program, although very few studies have examined the cardiovascular response to such a training program. Moreover, many of the studies performed to date on the effects of low-intensity exercise programs for patients with PAD are poorly designed, have small sample sizes and do not include a comparison group.

Statement of the Problem

The hemodynamic severity of PAD is related to the extent to which the ABI is below 0.90. An ABI less than 0.50 is associated with a shorter walking distance and a slower walking speed (Brach et al., 2008). A lower ABI is also associated with a lower ADL/IADL (Widener, 2011), a poorer health-related quality of life (Widener, 2011) and altered autonomic function (Jelinek et al., 2013). This loss of mobility and functional decline that occurs in patients with PAD results in the individual subsequently adopting a sedentary lifestyle (McDermott et al., 2004). Physical activity (i.e., regular exercise) can slow or reverse these physiological changes that occur and slow the progression towards disability (Hamburg & Balady, 2015).

Autonomic dysfunction (as reflected by a decrease in HRV) in patients with PAD is a serious risk for death and morbidity due to CV events as well as decreased physical function. In addition, low-intensity, high frequency exercise protocols have been effective in patients with CVD in improving autonomic function in favor of increased PNS activity and decreased SNS activity. In patients with PAD, this type of adaptation could reduce CV risk, increase CV function and increase walking ability. Thus, the main purpose of this study was to examine circulatory and autonomic effects of a progressive, 12-week home-based, low-intensity (walking) exercise program in patients with PAD after controlling for potential confounders such as age, sex, β -blockers and smoking. Secondary objectives were to determine the effect of the

intervention on 1) walking performance and self-report measures such as the walking impairment questionnaire and health-related quality of life and 2) to determine if there were any sex-specific differences that might exist at rest or in response to training.

Rationale for the Study

Cardiovascular disease, attributed primarily to atherosclerosis, is the leading cause of morbidity and mortality around the world. Peripheral artery disease affects approximately 10-20% of the population over the age of 55 years and can have a significant impact on walking ability and an individual's quality of life (Regensteiner & Hiatt, 1998). The presence of PAD is clinically significant in that 40 to 60% of patients with PAD will also have underlying coronary artery disease.

Lifestyle intervention, including exercise, is one approach to the treatment of PAD (Dobesh et al., 2009). The majority of exercise interventions have focused on having patients with PAD perform low-frequency exercise to maximal pain threshold. A few researchers have examined the effects of exercise below the pain threshold on individuals with PAD and have documented improvements in physical function, circulatory measures and quality of life. None has shown an improvement in autonomic function. Moreover, the mechanisms behind these improvements need clarification.

One possible adaptation may be an increase in parasympathetic activity and a reduction in sympathetic activity following training. Autonomic dysfunction has been associated with atherosclerotic disorders including PAD (Thayer et al., 2009). Several studies have demonstrated that patients with cardiovascular disease (i.e., hypertension, CAD) who participate in a 12-week low-intensity walking program alter their autonomic balance in favor of an increased parasympathetic modulation, decreased sympathetic activity and increased

spontaneous baroreceptor sensitivity (Goldie et al., 2013; Hua et al., 2009). In patients with PAD, these adaptations in autonomic function could improve cardiac function and decrease the risk of morbidity and mortality due to sympathetically mediated CV events. However, to date, no one has examined the effects of a low-intensity exercise program on cardiac autonomic function in patients with PAD. Finally, since there is minimal information on sex differences in patients with PAD and how they respond to an exercise intervention, this study will examine the responses between the two sexes.

Purpose

The main purpose of this study was to examine the circulatory and autonomic effects of a structured progressive, 12-week home-based, low intensity (walking) exercise program in patients with PAD after controlling for potential confounders such as age, sex, β -blockers and smoking. Secondary objectives were 1) to determine the effect of the intervention on walking function and self-report measures such as the walking impairment questionnaire and health-related quality of life and 2) to determine if there are any sex-specific differences that might exist at rest or in response to training. The dependent variables included circulatory (ABI, HR, BP, MAP, RPP) and autonomic measures (HRV: SNS and PNS activity), walking performance measures (PFWD, FCD, MCD, 6MWT) and self-report measures (WIQ, SF-36). The independent variable is defined as the walking intervention. The intervening variables age, sex, β -blockers and smoking were statistically controlled in the study.

Hypothesis

It was hypothesized that participation of men and women with PAD in a progressive 12-week, home-based, low-intensity, high frequency exercise (walking) program would improve circulatory (HR, BP, RPP, MAP) and autonomic (increase PNS and decrease SNS activity)

measures. Secondly, walking performance measures (pain-free walking distance [PFWD], functional claudication distance [FCD] and maximal walking distance [MWD]) and self-report measures (the WIQ and SF-36) would improve.

Chapter 3 – Method

This was an experimental study that used a pretest-posttest comparison group design (Neutens & Rubinson, 2010). Participants were randomly allocated to their group assignment. Approval for this study was obtained from Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Appendix A). Written, informed consent was obtained from all participants prior to enrolment in the study (Appendix B).

Participants

Patients 18 years of age or older, diagnosed with stable PAD (Zwierska et al., 2005), symptoms of intermittent claudication (IC), and an ankle-brachial index [ABI] ≤ 0.9 were included in the study. Participants ranged in age between 49 and 88 years and were excluded from the study if they: were unable to read or write English; resided in a nursing home; were involved in an exercise program; were wheel-chair dependent; had co-morbid conditions that limited participation in exercise (angina, congestive heart failure, chronic obstructive pulmonary disease, severe arthritis, or limb amputation); had non-compressible arteries (ABI > 1.2) (Amini, Gordon, Wilson, & Williams, 2013); or were cognitively impaired (i.e., presence of dementia or Alzheimer's disease).

Participants were recruited from an ongoing cohort study (designed to determine factors associated with functional performance in PAD patients), held at a vascular clinic in an acute care hospital located in South Eastern, Ontario over a two-year period. The participant recruitment process is described in Figure 2 as outlined by Moher et al. (2010). A total of 436 patients who attended the vascular clinic between 2011 and 2013 were assessed for eligibility to participate in the on-going cohort study. Of these patients, 174 were excluded for not meeting

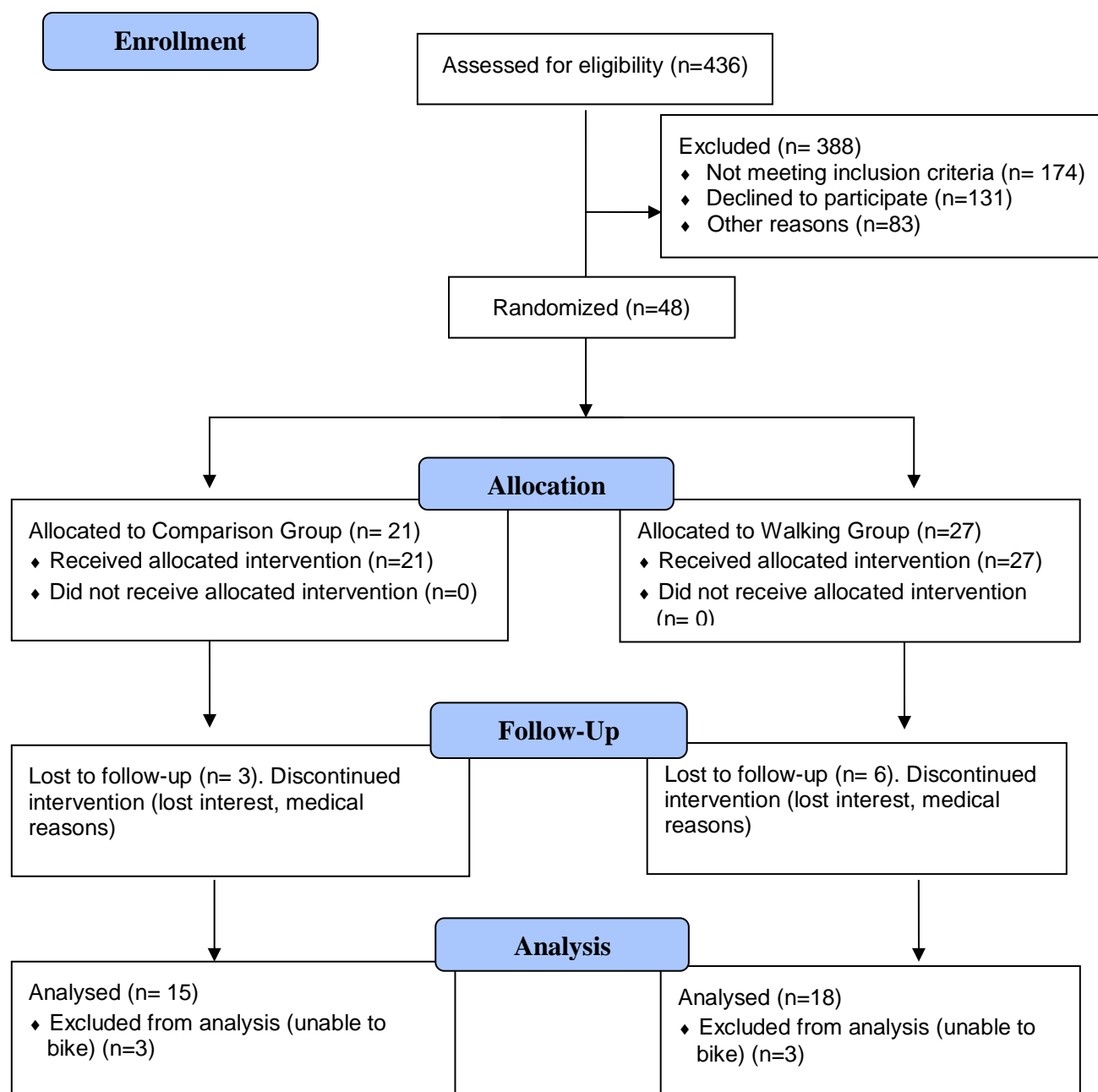


Figure 2. Participant flow chart for recruitment for the study.

the inclusion criterion of the cohort study and 75 patients were not interested in participating. Thus, 187 patients were recruited into the initial cohort study. Participants of this cohort study were asked to indicate (on their consent forms) if they were interested in being contacted for recruitment for participation in further studies. Ten participants did not want further contact. Patients (n = 177) who agreed to be contacted for participation in future studies (by checking a “yes” box on their consent form) were then approached to see if they would be interested in participating in a study examining the effects of a low-intensity walking program on patients with peripheral artery disease. Forty-five patients could not be contacted by telephone; 46 patients were not interested in participating and 38 patients could not travel regularly to the clinic (primarily due to distance from clinic or family obligations).

At the time of the design of this study, there were no studies that examined HRV in patients with PAD. As a result of this, walking distance was used to determine sample size. The estimated sample size for this study was based upon the results of a meta-analysis of 21 studies involving patients with IC (Gardner & Poehlman, 1995). Sample size was determined from the noted change in claudication pain distance scores that occurred in these studies. Only studies (n = 15) that used the onset of pain as the end point during the training session were included. Distance to the onset of pain was increased by 104.7 m ± 91.2 m following training. The formula that was used to calculate sample size was:

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(\sigma)^2\} / (\mu_1 - \mu_2)^2] \text{ (Sakpal, 2010)}$$

Where:

n = sample size required in each group,

$\mu_1 - \mu_2$ = change in walking distance (104.7),

σ = standard deviation (91.2 m),

$Z_{\alpha/2}$ = 5% level of significance (= 1.96)

Z_{β} = power 80% (= 0.84)

Based upon the above formula, the calculated sample size required per group was 12. However, the sample size was adjusted to account for potential drop-outs using the following formula:

$$N1 = n/1-d \text{ (Sakpal, 2010)}$$

Where:

n = sample size required as per formula (12),

d = drop-out rate (.50).

The drop-out rate was determined based on the results of other studies. Other studies examining the effects of a walking interventions on patients with PAD have reported that between 34% (Mouser, Zlabek, Ford, & Mathiason, 2009) to 77% (Wullink, Stoffers, & Kuipers, 2001) of participants complete their study. Considering a drop-out rate of 50%, which averages between the results obtained on these other studies, the total sample size that was required for this study is 48 (24 participants per group).

Forty-eight patients (28 men and 20 women) who met eligibility criteria volunteered to participate in the study. Thirty-three out of the initial 48 participants completed the study. Participants were randomly assigned to their groups by having each participant select a piece of paper from an envelope that was for men or women. The piece of paper was labeled as either exercise group or comparison group. Overall, there were two main differences between the participants who remained in the study compared to those who dropped out from the study, with two exceptions. Participants who remained in the study tended to be more active (140 ± 199 vs 19 ± 30 min/week, $M \pm SD$), $t(40) = 2.091$, $p < 0.05$ and scored significantly higher on the

physical function component of the SF-36 questionnaire, $t(39) = 2.958$, $p < 0.01$ at entry into the study. Patients did not alter their medications during the course of the study.

Participants recruited into the study ranged in age between 49 and 88 years (67.81 ± 8.13 years) and had an ABI ranging from 0.26 to 0.96, averaging at 0.54 (0.18). The majority (85%) of participants in the study had a disease severity of either moderate (ABI of 0.50 to 0.69) or severe (ABI < 0.50). Most patients (75%) experienced claudication symptoms in their calves, with the remaining experiencing claudication symptoms in the thigh, buttocks or other location (most commonly the foot) (Appendix M). There was a significant difference between men and women at entry in several measures: hip circumference (men: $101.28 \text{ cm} \pm 7.06 \text{ cm}$ vs women: $107.84 \text{ cm} \pm 11.73 \text{ cm}$); $F(1, 44) = 5.655$, $p = 0.022$; waist to hip ratio (W:H ratio) (men: 0.97 ± 0.06 vs women: 0.89 ± 0.07 , $M \pm SD$); $F(1, 44) = 15.911$, $p = .000$ and percent body fat for men ($27.76 \pm 7.58 \%$, $M \pm SD$) and women ($39.95 \pm 6.57\%$); $F(1, 44) = 35.097$, $p = .000$. Men had a narrower hip circumference, a greater waist-to-hip ratio and less percent body fat when compared to women. In addition, compared to women, men reported drinking more alcoholic beverages on a weekly basis (i.e., drinking more than 5 drinks per week), $X^2(1, N = 48) = 4.114$, $p < .05$). Significantly more women (i.e. 35% of women) self-reported having a history of high cholesterol levels, $X^2(1, N = 48) = 11.473$, $p < .01$.

Medication use by volunteers, those lost to attrition and remaining participants is presented in Appendix N. The most common medications prescribed for these patients were blood lipid medications (Statins and Ezetrol), anti-clotting medications (acetylsalicylic acid [ASA] and Warfarin), followed by various anti-hypertensive medications. A chi-square test of independence indicated that there were no significant differences in the medication use between

men and women. However, significantly more members of the walking group at entry received Clopidogrel (an anti-platelet drug) $X^2(1, N = 48) = 7.467, p = .006$.

Following testing at Week 1, participants were randomly assigned to their respective group by selecting their assignment from a sex specific envelop. Fifteen patients dropped out of the study prior to the second test session due to: lack of interest ($n = 3$), hip fractures ($n = 2$), fibromyalgia ($n = 2$), anxiety disorder ($n = 1$), renal failure ($n = 1$), or they could not perform the bike test at either Week 1 or Week 12 ($n = 6$). Data obtained on those lost to attrition and those that remained in the study are presented in the Appendix (Appendices M through O). Fifteen participants of the comparison group and eighteen participants of the walking group completed the study. All participants were provided with self-report diaries whereby they were asked to record their daily activity (See Appendix G and H).

Apparatus/Instruments

Cardiac monitoring was performed using three standard surface electrodes placed in the Lead II configuration and connected to a Spacelab 514T cardiac monitor with a QRS detector (Squibb Vitatek Inc., Hillsboro, OR, USA). Analogue R-R interval output from the ECG was transferred from the cardiac monitor to a research computer (PC - Packard Bell Force 203 with Acer 6772 Monitor) via a cable attached to the monitor's output port. An analog input board DAS-16 (Metrabyte Corp., Multitest electronics, Scarborough, ON, Canada), which had been previously added to the PC, digitized the data. Using a sampling rate of 1000 Hz (which provides an R-R interval accuracy of 1 ms), this analogue-digital converter digitized the analog data obtained from the cardiac monitor. Data were stored on a dedicated PC for later spectral analysis. A computer software program designed by Yamamoto and Hughson (1991) was used

for data acquisition and spectral analysis of heart rate variability (HRV) in order to determine autonomic balance (sympathetic and parasympathetic nervous system activity).

A bi-directional Doppler device (ES-100VX minidop, Koven Technologies Canada, Winnipeg, Manitoba) was used to assess the systolic blood pressure in the ankle and brachium to allow for determination of the ankle-brachial index (ABI). Blood pressure (BP) and heart rate (HR) were measured using an automated, non-invasive BP monitor (BpTRU) (Model BPM-300, VSM Medtech Ltd., Coquitlam, BC). The BpTRU takes six measures of BP and HR, eliminates the first measure and provides the average of the remaining five measurements. This non-invasive device is an accurate means to measure BP in individuals ranging in age between 3 and 83 years (Mattu, Heran, & Wright, 2004).

Body mass (kilogram [kg]) and height (meters [m]) were obtained using a Health-O-Meter scale (Health-O-Meter Corporation, Bedford Heights, Ohio). A soft, plastic measuring tape was used to measure waist and hip circumferences, which allowed for the calculation of the waist-to-hip ratio. Body composition (% body fat) was determined from skinfold measures that were obtained using a Harpenden Skinfold Caliper and Body Assessment Software Package (Baty International, West Sussex, UK).

Treadmill testing was conducted using the TRUE Performance treadmill (PS300, St. Louis, Missouri). This treadmill is suitable for users of all fitness levels. It has a shock-absorbing (orthopedic belt), can run at a speed of 0.5 – 12.0 miles per hour (mph) (i.e., 0.8 – 19.3 km/h) and achieve an incline between the range of 0 and 15%. Use of a treadmill is an objective, reliable and valid method to assess a patient's walking ability and response to an intervention (Brass, Jiao, & Hiatt, 2007; Regensteiner, Gardner, & Hiatt, 1996).

The six-minute walk test (6MWT) measures an individual's ability to walk a predefined track or course (commonly set-up in a corridor) for 6 minutes. Montgomery and Gardner (1998) have demonstrated that the 6MWT has a high reliability coefficient ($R = 0.90$) and low coefficient of variation (11.7%). The test correlates well with the treadmill data obtained values for pain-free walking distance ($r = 0.346$, $P = 0.007$), with maximal walking distance ($r = 0.525$, $P < 0.001$) and the ABI ($r = 0.552$, $P < 0.001$).

Steady state exercise was tested using a Monark cycle ergometer (Monark Ergonomic 828E, Fitsystems, Calgary Alberta). This cycle ergometer has an electronic instrument keyboard that indicates exercise watts.

The SF-36 is a global, reliable and valid instrument for measuring an individual's perceived health-related quality of life and the emotional and physical components associated with it (McHorney, Ware, & Raczek, 1993). The questionnaire has two subscales that are useful to assess a patient's physical function; the physical function (PF) and role limitations (RL) subscales. The PF sub-scale consists of 10 items that assess limitation in physical function such as walking ability and the ability to climb stairs. The RL component consists of 4 items that determine the effect of a patient's physical condition on the ability to perform work or other daily activities.

Within the Canadian population, normative values for the PF and RP subscales are: 85.8 and 82.1, respectively, whereas patients with PAD have been shown to have lower values (PF = 52.4 and RP = 51) (Nicolai et al., 2010). These lower values for patients with PAD would indicate that they experience some limitation in their physical function as a result of their disease. Exercise therapy can improve functional scores obtained on the SF-36 (i.e. physical function, physical role and physical summary score) (Nicolai et al., 2010).

The WIQ is a self-administered, disease-specific questionnaire consisting of 14-items with 3 subscales designed to assess the presence of PAD as well as the effect the disease has on self-reported walking limitations (i.e., walking distance, walking speed and stair climbing ability) (Nicolai et al., 2009). In assessing walking distance, patients are asked to report the degree of physical difficulty they experience when they walk on level ground without stopping to rest for a specified distance (e.g., 50 to 1500 feet). For walking speed, the WIQ requires patients to report how difficult it is for them to walk one city block on level ground at various speeds without using specific aids. Stair climbing ability is assessed by having patients report on the degree of difficulty they experience when they climb stairs without stopping to rest. There are also questions contained on the WIQ that are designed to rule out PAD as the cause of impairment (i.e., pain, stiffness or aching in joint; chest pain, shortness of breath or heart palpitations).

Responses are scored on a Likert scale from 0 to 3 (0 = unable to do, 1 = much difficulty, 2 = some difficulty and 3 = no difficulty). Several WIQ subscales scores can be obtained by multiplying a pre-defined number to represent distance (feet), speed ($\text{mile}\cdot\text{hr}^{-1}$) or stairs climbed (steps) by the degree of difficulty. A number is then obtained for each of the three subscales (distance, speed and stair-climbing ability). A total score can be calculated from these measures. The numbers obtained are divided by a total possible score and then multiplied by 100 to give a number that represents a percentage. Based upon this percentage scale, a score of 100 represents no difficulty walking long distances, walking fast or climbing 3 flights of stairs and a score of 0 represents extreme limitation in a measure.

The WIQ is a reliable and valid instrument with a Chronbach α of 0.97 for the total score and 0.96, 0.87 and 0.94 for the sub-scales of distance, speed and stair climbing ability,

respectively (Collins, O'Connell, Jelinek, Miskevics, & Budiman-Mak, 2008). All of the subscales have high intra-class correlation coefficients (ICC) (distance subscale ICC = 0.87, $p < 0.001$; speed subscale ICC = 0.86, $p < 0.001$; stair climbing ICC = 0.87, $p < 0.001$). The WIQ distance subscale has been correlated with results on the 6-minute walk test (Spearman rank $r = 0.557$, $p < 0.001$ for PAD and $r = 0.484$, $p < 0.001$ for patients without PAD (McDermott et al., 1998).

The Ratings of Perceived Exertion (RPE) scale (Borg, 1982) is an accepted tool used to assess and prescribe exercise intensity (Appendix E). Ratings are based on the physical sensations that are experienced by an individual during exercise (for example, increases in HR, respiration and muscle fatigue). The original scale developed by Borg is a 6-20 point ordinal scale where 6 represents, "no exertion at all" and 20 represents "maximal exertion" (Borg, 1982). The greater level of exertion felt by the participant, the greater the number reported on the scale. Borg's Rating of Perceived Exertion, 6-20 scale, has been shown to provide reliable and valid measures of exercise intensity (Buckley, Eston, & Sim, 2000). Although the reliability improved with repeated administration of the RPE scale, the intraclass correlation coefficient (ICC) for RPE values between 9 and 13 obtained at a percentage of the maximal heart rate ranged between 0.80 and 0.83. In addition, the RPE levels of 9, 11 and 13 were found to correspond to mean values of 47%, 53% and 65% VO_2max , indicating good criterion validity.

Borg's CR-10 scale is a general intensity category ratio scale that can be used to assess pain intensity (Borg, 1998) (Appendix F). For the purpose of this study, the CR10 scale was used to quantify the degree of pain associated with intermittent claudication experienced during the treadmill exercise test. The CR-10 test is a reliable and valid test to use to assess pain. Test-retest reliability coefficients for the CR10 have been reported to be around 0.90 and the test has

been validated with the visual analogue scale (VAS). The scale ranges from 0 to 10, with 0 equivalent to no pain to 10 representing extremely strong or maximum pain. The treadmill test was stopped when pain was about 8/10 or when the patient asked to stop.

Procedures

Upon arrival at the Exercise laboratory associated with the Vascular Clinic at Kingston General Hospital, eligible participants were given an explanation of the study, provided an opportunity to have their questions answered (if any) and gave their written informed consent to testing. After screening, participants were invited to return to the Exercise laboratory associated with the Vascular Clinic at Kingston General Hospital for baseline testing.

At the exercise laboratory, relevant demographic and medical information (including age, gender, education, marital status, occupation, comorbidities, and medication use) was obtained from the participants (Appendix I) followed by completion of the walking impairment questionnaire (WIQ) (Appendix J) and the physical component of the quality of life questionnaire (SF-36) (Appendix K). Anthropometric measures (height, weight, waist circumference and skinfold measures), resting blood pressure and heart rate were obtained prior to the performance of the treadmill test and the 6-minute walk test. Body mass index (BMI) (kg/m^2) was determined from the height and weight measures obtained. Skinfolds were also measured at 4 locations: triceps, biceps, subscapular and supriliac crest.

Following a 10-min rest period in the supine position on a couch located in the exercise laboratory, the right and left brachial and crural pulses (dorsal pedis artery and posterior tibial artery) were measured using a Doppler probe. The ABI for each leg was calculated using the mean of the ankle systolic pressures on each foot divided by the average pressure in both arms, except when there was a 10 mmHg or more difference, in which case, the higher pressure was

used (Klein & Hage, 2006). The lower of the ABI readings (i.e., the ABI of the more diseased extremity) are reported and were used for analyses. ABI results can vary depending on numerous factors such as patient position during measurement, width and level of the sphygmomanometer cuffs used to perform the measurements and the BP values used to determine the ABI and inconsistent methods of measuring (Al-Qaisi, Nott, King, & Kaddoura, 2009). ABI measures were obtained by the same investigator (with BP cuffs being placed in the same location on each patient) and calculated using one equation as suggested by McDermott et al. (2000) was used to determine ABI measures. Inter-observer data was assessed on 65% of the participants and indicated a correlation of .81.

Participants then moved to a treadmill located adjacent to the couch whereby they performed a progressive, symptom-limited treadmill exercise test using the Gardner-Skinner protocol (Gardner, Skinner, Cantwell, & Smith, 1991). Briefly, to warm-up, participants began walking on the treadmill at 1.1 miles per hour (mph), 0% gradient with a 0.1 mph increase in speed until 2 mph was reached (equivalent to 3.22 km/h). After 1.5 minutes of warm-up on the treadmill, the speed was held constant at 2 mph (3.22 km/h) and the gradient was increased every 2 min by 2% until maximal claudication pain, exhaustion or 30 min had elapsed. Participants were asked to indicate when they initially experienced pain (pain-free walking [PFWD]), when they normally would stop walking (functional claudication distance [FCD]) as well as when the pain was so severe that they had to stop (maximal walking distance [MWD]) (i.e., a score of 8 out of 10 on the Borg Pain Scale). Functional claudication distance (FCD) is defined as the distance covered when a patient would prefer to stop walking as a result of their claudication pain, as most people do not stop initially when they first experience pain (Kruidenier et al., 2009). Functional claudication distance has been shown to be both a reliable and valid measure

for assessing physical function in patients with PAD (Kruidenier et al., 2009). It is also thought to be a better reflection of how limited the patient feels about their walking ability. The duration walked on the treadmill was recorded and the distance was calculated based upon walking speed of the treadmill and how long the patient walked at that speed.

Lastly, participants rested until their leg pain resolved following the treadmill test and then performed the 6-minute walk test (6MWT). For this test, they walked up and down a hospital corridor around a marker set at a specific distance (27.4 m [90.0 ft.]) for 6 minutes. Participants were allowed to stop if they needed to do so due to pain /discomfort in their lower extremities. The distance walked in 6 min was measured and recorded.

Autonomic function testing was performed in the Exercise Physiology Laboratory at Hotel Dieu Hospital. Cardiac autonomic function (heart rate variability) was assessed under three conditions: 1) at rest in the supine position, 2) standing, and 3) during steady-state exercise. For the supine rest condition, participants rested comfortably, in the supine position, on an examination table located in a quiet, light attenuated room. Participants lay quietly and refrained from speaking for 15 min to allow for the recording of R-R intervals and BpTRU data. Beat-by beat R-R intervals were recorded continuously for a minimum of 512 beats using an ECG Lead II configuration. Beat-by beat R-R intervals were then recorded with the participant standing in an upright position with the same ECG electrode configuration as in the rest condition. Participants remained in the freestanding position without support for an adaptation period of 3 minutes followed by 10 minutes (or 512 heart cycles) of beat-by beat data recording. Participants were reminded to relax, remain as still as possible, avoid talking and refrain from leaning backwards on the examination table that was located behind them.

With data acquisition temporarily stopped and the ECG electrodes remaining in place, the participants then moved to the stationary cycle ergometer that was situated parallel to the examination table. Once the participant was seated on the cycle ergometer, care was taken to ensure that the seat height, handles and foot straps of the ergometer were adjusted to allow the participant to sit upright comfortably. The participant's target exercise HR (40% of the HRR) was calculated according to the Karvonen formula ($\text{Target HR} = (0.40) (\text{HR max} - \text{HR rest}) + \text{HR rest}$ with maximal heart rate calculated as $\text{HR max} = 220 - \text{age in years}$).

For the cycle exercise test, participants performed a 4-min warm-up at 20 watts followed by ramp increase in work rate within 30 s to a work rate equivalent to 40% of the maximal HR reserve. Participants maintained this low-intensity exercise for up to approximately 10 min and maintained their cycling rate between 50 to 60 revolutions per min (rpm) during the test. After a 2 - 3 min adjustment to steady state (defined as a plateau in the HR response), beat-by beat R-R interval was recorded for 512 beats.

Members of each sex were then assigned randomly to either a 12-week walking intervention program (walking group, men; walking group, women) or to a non-walking comparison group (comparison group, men; comparison group, women) resulting in the creation of 4 groups. Participants selected their group assignment from a sex-specific envelop, which had slips of paper labeled as either "comparison group" or "exercise group". For each dropout (those who did not complete test 2), a new participant was recruited from a list of participants until no more participants could be recruited. Replacement was not provided for those participants who did not complete the cycle ergometer portion of the study.

Participants in the walking group were provided with verbal as well as written instructions for a structured 12-week, progressive, low intensity walking program, an exercise

log, Borg's RPE scale and Borg's CR-10 pain scale. They were asked to walk 5 days per week, at a rating of perceived exertion (RPE) ranging between 11 (fairly light) to 13 (somewhat hard) and a pain score of less than or equal to 2 (light) on Borg's pain scale. The exercise program required participants to begin walking at $0.4 \text{ km}\cdot\text{day}^{-1}$, with a gradual progression every two weeks to $3.2 \text{ km}\cdot\text{day}^{-1}$ at the end of 12 weeks (see Appendix C, for the rate of progression) (Brown, 1990; Brown et al., 1994). All participants were provided with verbal and written instructions on how to measure their heart rate at their radial pulse (Appendix D) and were required to demonstrate proficiency in this skill prior to leaving the laboratory. Members of the walking group were instructed on how to record a summary of their walking sessions on to the log including: time, distance, heart rate, ratings of perceived exertion, and pain score (Appendix G).

Members of the comparison group were also provided with an activity log and were given instructions on how to record the type and amount of physical activity that they performed during the week, the duration of activity, heart rate, as well as type and amount of physical activity (Appendix H). Members of both groups were contacted by phone every two weeks to monitor their progress and to answer any additional questions.

Follow-up phone calls were made to each participant (in both groups) after the first week of the intervention and then at regular two-week intervals, to address any questions or concerns regarding the exercise intervention or log-book and to ensure compliance with the exercise prescription. Approximately 93% of the participants completed all entries into their log books. Compliance rates both groups were determined by averaging the number of walking sessions completed per week.

Data Reduction

To understand the relationship between and to decrease the number of variables that were to be used in the statistical analyses and data interpretation, data reduction was performed. HRV measures were performed to obtain a measure of SNS and PNS activity. Heart rate and blood pressure measures were obtained to determine mean arterial pressure (MAP) and rate pressure product (RPP). Rate pressure product, also referred to as the double product, was determined from the product of heart rate and systolic blood pressure. Mean arterial pressure was determined using systolic and diastolic blood pressures obtained with the BpTRU instrument in the different conditions and was calculated using the following formula: $MAP = 1/3 (SBP-DBP) + DBP$. It is the average blood pressure in a person's arteries during one cardiac cycle and is considered a better indicator of organ perfusion than systolic blood pressure. For variables that had multiple entries on the same measure, bivariate correlational analyses were performed to reduce the number of variables in statistical analyses. This was performed for performance measures, self-report measures and compliance measures.

The R-R interval time series was screened for any movement artifact or interference. Artifact was removed from the time series before the data underwent analysis by power spectrum. The methods used for editing can be found in the Appendix and were based upon the methods described by Dougherty (1999) and Swansburg (2005). Spectral analysis of HRV involved converting digitized R-R interval data via fast Fourier transformation into a frequency spectrum that separates signals into low frequency (LF) (0.04 - 0.15 Hz) power, high frequency (0.15 - 0.5 Hz) (power) and total power [TFESCNASPE], 1996) and has shown intra-individual reproducibility over time (Amara & Wolfe, 1998). The low frequency power reflects both parasympathetic and sympathetic activity whereas the HF power reflects primarily

parasympathetic (vagal) modulation (Akselrod et al., 1981; TFESCNASPE, 1996). Thus, autonomic control of the heart could be inferred from the LF to HF ratio (which reflects SNS activity), and the HF to TP ratio that reflects PNS activity. All HRV measures were positively skewed and as a result were converted into Log 10 values for analysis.

Statistical Analysis

All data analyses were performed using the IBM Statistical Package for Social Sciences version 24 (IBM SPSS, Chicago, IL). Descriptive statistics were used to determine the relevant means and standard deviation or the frequencies and percentages for participant characteristics, demographic characteristics, physiological data, physical function parameters and self-report measures. All data was initially assessed for outliers (by determining the z score) and normality (by applying the Shapiro-Wilktest). Data that were not normally distributed were either log transformed (e.g., ABI, HRV measures and performance measures at entry) or converted to delta values (treadmill performance measures) for further analyses. Comparisons between the data obtained at entry into the study for men and women were performed using either the General Linear Model Univariate Measures Analyses of Variance (ANOVA) or a Chi-Square analysis for categorical data.

The cardiac autonomic measures that were obtained in the three different conditions over time were analyzed using the General Linear Model, Repeated measures analyses of variance (ANOVA). Preliminary analyses were first performed on heart rate (HR), blood pressure (BP), MAP, RPP and HRV variables using covariates known to affect circulatory parameters (age, sex, smoking and use of beta blockers). An alpha threshold of 0.1 was used for initial covariate selection. Significant covariates were then entered into an ANOVA with one between-group factor (Group - walking, comparison) and two within factors (Time - week 1, week 2; Condition

– Rest, Standing, Exercise). An alpha threshold of 0.05 was used to determine statistical significance. The rest of the variables were also analyzed using repeated measures ANOVA with one between-group factor (Group - walking, comparison) and one within-group factor (Time- week 1, week 12). Univariate analysis was performed on the delta values obtained for the walking performance measures obtained on the treadmill. Compliance rates were determined by dividing the number of walking sessions that were completed by the number of walking sessions that were prescribed for each week (Cox, Burke, Gorely, Beilin, & Puddey, 2003). The same comparison was done to assess compliance with the prescribed walking distance and walking duration.

Chapter 4 – Results

Resting circulatory measures at entry into the study are presented in Table 3. Resting diastolic blood pressure was significantly higher in men compared to women, $F(1, 44) = 7.263$, $p = .010$. At rest, there were no significant differences in men versus women or between comparison and walking groups for the ankle-brachial index (ABI), heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP) and rate pressure product (RPP).

Table 3

Resting circulatory measures at entry into the study.

Variable	Group		p value
	Comparison (n = 21)	Walking (n = 27)	
ABI	0.49 (0.16)	0.57 (0.18)	.116
HR (bpm)	68.37 (12.56)	60.97 (10.80)	.058
SBP (mmHg)	129.33 (24.95)	130.92 (21.54)	.656
DBP (mmHg)	69.14 (11.52)	69.09 (10.65)	.775
MAP (mmHg)	88.64 (14.15)	89.54 (13.49)	.629
RPP (bpm x mmHg)	8745.38 (2484.47)	7949.67 (1865.10)	.322

Legend: Values are means (\pm SD). ABI = ankle-brachial index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.

There were no significant differences in the HRV measures in men compared to women nor between the comparison and walking groups at entry into the study. The raw values of the HRV measures are presented in Table 4.

Table 4

Resting HRV measures (raw values) at entry into the study.

Variable	Group		p value
	Comparison (n = 21)	Walking (n = 27)	
LF (ms ² /Hz)	101.44 (167.84)	190.90 (292.22)	.199
HF (ms ² /Hz)	373.48 (1198.67)	209.84 (313.69)	.322
TP (ms ² /Hz)	793.41 (1476.88)	1055.79 (965.10)	.570
PNS indicator (HF/TP)	0.27 (0.21)	0.18 (0.17)	.106
SNS indicator (LF/HF)	0.98 (0.93)	1.60 (1.26)	.085

Legend: Values are means (\pm SD). LF = low frequency power; HF = high frequency power; TP = total power; PNS = parasympathetic nervous system; SNS = sympathetic nervous system.

Walking performance measures of the comparison and walking groups at entry into the study are presented in Table 5. One participant was removed from the analysis of the treadmill data as she did not meet criteria for test termination. There were no significant differences in pain-free, functional and maximal walking measures (as expressed as distance) on the treadmill as well as for the 6MWT between men and women and between members of either group at entry into the study.

Table 5

Walking performance measures at entry into the study.

GROUP			
Measures	Comparison (n = 21)	Walking (n = 27)	p value
PFWD (m)	116.18 (101.85)	154.17 (99.55)	.377
FCD (m)	191.55 (141.14)	259.15 (156.09)	.198
MWD (m)	231.20 (172.71)	330.44 (182.82)	.121
6MWT (m)	310.21 (100.56)	314.99 (98.90)	.981

Legend: Values are means (SD). PFWD = pain free walking distance; FCD = functional claudication distance; MWD = maximal walking distance; 6MWT = 6-minute walk test. Note: for the 6MWT data on 28 (vs 27) participants in the walking group is provided.

Self-report measures (obtained on the Walking Impairment Questionnaire and components of the SF-36) obtained from the walking and comparison groups at entry into the study are presented in Table 6. The SF-36 physical function measure, was significantly higher in men, 55.38 ± 20.54 , $M \pm SD$, compared to women, 41.63 ± 19.82 , $M \pm SD$; $F(1, 43) = 5.061$, $p = .030$. There were no significant differences between the comparison and walking groups on the self-report measures.

Table 6

Self-report measures at entry into the study.

Variable	GROUP		
	Comparison (n = 20)	Walking (n = 27)	p value
WIQ - Distance Score	37.82 (24.91)	42.18 (31.44)	.814
WIQ - Speed Score	43.78 (28.23)	43.78 (25.28)	.889
WIQ - Stair Climbing Ability Score	44.44 (28.54)	50.77 (27.44)	.453
WIQ - Overall Score	42.02 (21.84)	45.59 (24.04)	.733
SF-36 Physical Function	46.02 (18.59)	52.63 (22.82)	.249
SF-36 Role limitations	34.19 (39.18)	55.56 (45.29)	.052

Legend: Values are means (\pm standard deviation). WIQ = walking impairment questionnaire. Note: for physical function and role limitations, the n for the comparison group = 20. One participant did not complete the SF-36 form.

Analysis of Walking and Comparison Groups over Time

Thirty-three of the initial 48 participants completed the 12-week study, 15 of whom were assigned to the comparison group and 18 to the walking group. The frequency of activity performed by members of the Walking Group (5.2 ± 1.6 sessions per week, $M \pm SD$) was significantly greater than the Comparison Group (3.3 ± 2.4 sessions per week, $M \pm SD$), $F(1, 30) = 7.246$, $p = .012$. Members of the walking group were compliant to the prescribed exercise regimen frequency (averaging 4.3 ± 2.1 days/week; $97 \pm 37\%$ compliance), duration (averaging 33.7 min/session; $95 \pm 11\%$ compliance) and walking distance (averaging 2.65 ± 2.10 km/session; $74 \pm 9\%$).

Baseline characteristics for the comparison (n = 15) and walking (n = 18) groups are presented in Table 7. The means (\pm SD) for body composition measures (body mass index BMI], waist circumference, waist to hip ratio, percent body fat) obtained at the time of testing at Week 1 are shown in the Appendix O. BMI did not change over time in either group. There was no difference in medication use for either group.

Table 7

Baseline characteristics of participants who completed the study (n = 33).

Variable	GROUP		p value
	Comparison (n = 15)	Walking (n = 18)	
Age (years) (M \pm SD)	63.67 (8.47)	68.56 (6.87)	.077
PAD (years) (M \pm SD)	7.08 (4.73)	8.02 (9.23)	.741
BMI (kg/m ²) (M \pm SD)	26.44 (5.23)	27.64 (5.20)	.516
MWD (m) (M \pm SD)	252.10 (198.91)	364.03 (172.59)	.097
WIQ overall score (M \pm SD)	38.50 (18.41)	52.35 (21.49)	.058
SF-36 physical function (M \pm SD)	51.08 (15.71)	61.69 (18.84)	.100
Sex (men, n, %)	9 (60)	12 (67)	.692
Smokers (n, %)	8 (53)	8 (44)	.611
β -Blockers (n, %)	4 (27)	6 (33)	.678

Legend: BMI = body mass index; MWD = maximal walking distance; PAD = peripheral artery disease; WIQ = walking impairment questionnaire. Values are means (SD) and n (%).

Additional data comparing those participants who dropped out from the study with those remaining participants is presented in appendix M through O. Any covariates (age, sex, β -

blockers and smoking) that could influence each parameter were initially included in the analyses. Those variables that did not significantly influence the parameter in question were removed from the final analysis. A summary of those that did is provided below (Table 8).

Table 8

Summary of study variables that were influenced by covariates.

Variable	Age	Sex	β-Blocker	Smoking
HR			√	
SBP	√			
RPP			√	
HF power	√			
Log SNS indicator	√			√

Circulatory Measures. The mean (\pm SD) for circulatory measures over time including ankle brachial index (ABI), heart rate (HR), blood pressure (SBP, DBP) and their derivatives (including mean arterial pressure (MAP) and rate-pressure product [RPP]) at Week 12 and Week 1 for the comparison and walking groups are shown in Table 9. ABI measures were skewed and not normally distributed so these values were transformed into a logarithm to the base of 10 in order to do parametric analyses. The means and standard deviation (\pm SD) of the original data are shown in Table 9. Comparison of resting Log ABI measures at Week 12 with Week 1 indicated a time by group interaction, $F(1, 31) = 4.073$, $p = .052$, ns, whereby ABI decreased in the Comparison group and increased in the Walking group after 12 weeks (Figure 3). There were no other main effects or interactions for ABI measures.

Table 9

Means (SD) for circulatory measures over time.

		Week 1		Week 12	
	Condition	Comparison Group (n = 15)	Walking Group (n = 18)	Comparison Group (n = 15)	Walking Group (n = 18)
ABI	Rest	0.48 (0.17)	0.56 (0.20)	0.44 (0.12)	0.62 (0.21)
HR ^{ABE} (bpm)	Rest	66 (13)	63 (12)	66 (11)	63 (12)
	Stand	72 (17)	73 (17)	74 (14)	71 (16)
	Exercise	96 (28)	88 (24)	86 (20)	79 (15)
SBP ^{CF} (mmHg)	Rest	129 (17)	124 (15)	119 (20)	122 (16)
	Stand	131 (18)	121 (15)	119 (21)	117 (16)
	Exercise	163 (30)	162 (38)	142 (30)	149 (28)
DBP (mmHg)	Rest	69 (11)	67 (8)	68 (11)	68 (6)
	Stand	76 (15)	75 (7)	74 (12)	71 (8)
	Exercise	84 (17)	77 (12)	78 (13)	76 (15)
MAP ^{AB} (mmHg)	Rest	89 (10)	86 (10)	85 (12)	87 (8)
	Stand	94 (13)	90 (8)	89 (13)	87 (9)
	Exercise	110 (13)	105 (16)	99 (16)	100 (15)
RPP ^{ABDE} (bpm· mmHg ⁻¹)	Rest	8409 (1884)	7876 (2091)	7851 (1873)	7730 (2177)
	Stand	9379 (2707)	8693 (2466)	8930 (2234)	8275 (2107)
	Exercise	15585 (5384)	14584 (6340)	11913 (2517)	11629 (3769)

Legend: ABI = ankle brachial index; ^A = Significant main effect of Time; ^B = Significant main effect of Condition; ^C = Significant Time by Group Interaction, ^D = Significant Time by Condition interaction; ^E = Significant Time by β -blocker interaction; ^F = Significant Time by Age interaction; $p < 0.05$.

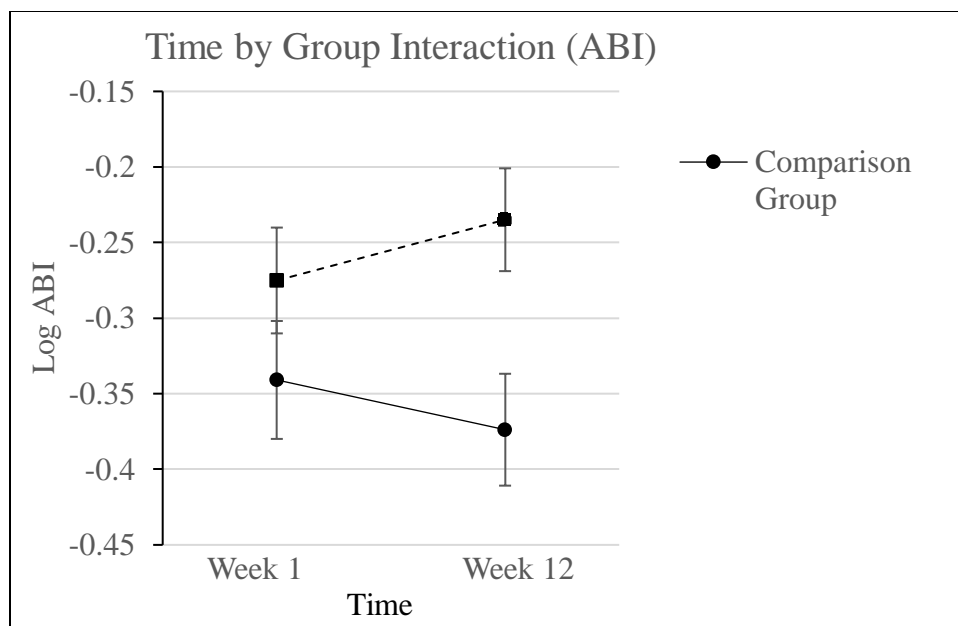


Figure 3. Time by group interaction for Log ABI values, Week 12 vs Week 1.

For HR, there were significant main effects of Time, $F(1, 30) = 6.012$, $p = .020$, such that HR decreased over time, and Condition, $F(2, 60) = 70.963$, $p = .000$, whereby HR significantly increased in response to Standing, $F(1, 30) = 32.896$, $p = .000$, and in response to Exercise, $F(1, 30) = 130.841$, $p = .000$. There also was a Time by Condition interaction for Exercise vs. Rest, $F(1, 30) = 5.747$, $p = .023$, whereby HR was lower during exercise at Week 12. The main effect of Time was further qualified by a significant Time by β -Blocker interaction, $F(1, 30) = 4.627$, $p = 0.040$. HR was significantly lower at Time 1 in those participants who were on β -blockers.

The analysis of SBP data indicated a Time by Group interaction, $F(1, 30) = 4.503$, $p = .042$, with SBP decreasing significantly in the Comparison Group compared to the Walking Group (Figure 4). There also was a Time by Age interaction, $F(1, 30) = 5.442$, $p = .027$. Simple effects analysis for the Comparison group indicated that SBP was significantly reduced at

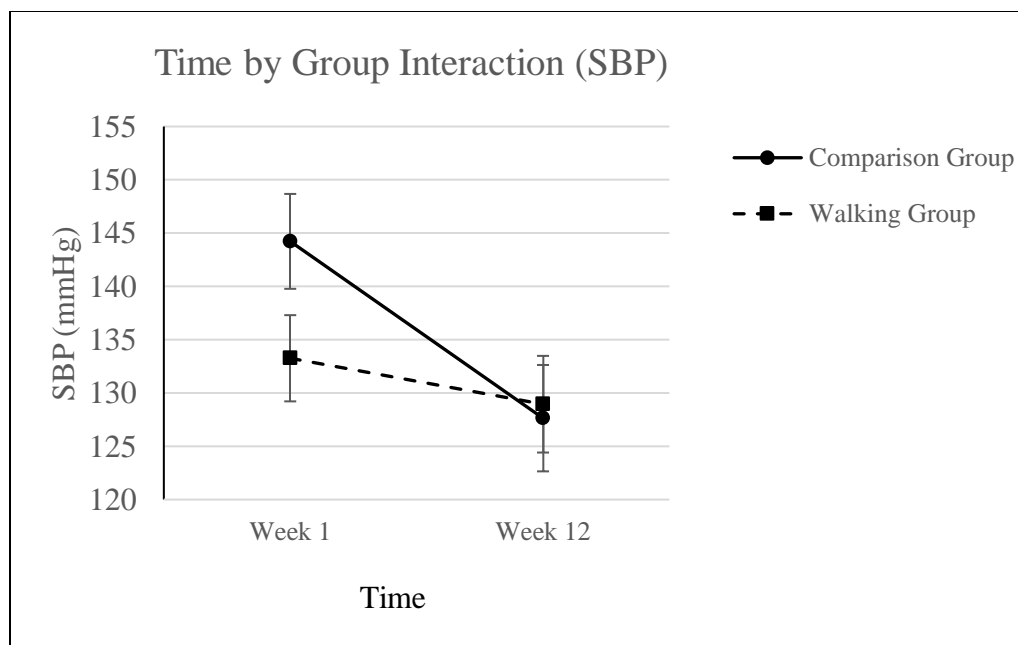


Figure 4. Time by group interaction for systolic blood pressure (SBP), Week 12 vs Week 1.

Week 12 in the older (> 66 years) participants, Time by Age interaction, $F(1, 13) = 7.443$, $p = .017$.

There were no main effects of Time nor Time by Group interaction for DBP measures. However, there was a main effect of condition $F(2, 62) = 18.175$, $p = .000$. Compared to rest, DBP significantly increased in response to standing, $F(1, 31) = 21.832$, $p = .000$, and in response to exercise, $F(1, 31) = 28.718$, $p = .000$.

For MAP, there were significant main effects of Time, $F(1, 31) = 8.623$, $p = .006$ such that MAP decreased over time, and Condition, $F(2, 62) = 52.221$, $p = .000$. Compared to rest, MAP significantly increased in response to standing, $F(1, 31) = 5.612$, $p = .024$, and in response to exercise, $F(1, 31) = 80.365$, $p = .028$.

For RPP, there was a significant main effect of Time, $F(1, 30) = 17.008$, $p = .000$, such that RPP decreased over time. There also was a main effect of Condition, $F(2, 60) = 69.188$, $p =$

.000, whereby RPP increased during standing vs rest, $F(1, 30) = 14.367$, $p = .001$, and increased during exercise vs rest, $F(1, 30) = 89.232$, $p = .000$. These effects were further qualified by a Time by Condition interaction, $F(2, 60) = 10.832$, $p = .000$, whereby RPP was significantly lower during exercise at Week 12, $F(1, 30) = 11.185$, $p = .002$. Furthermore, there was a significant Time by β -Blocker interaction, $F(1, 30) = 4.718$, $p = .038$, whereby RPP decreased over time in participants who were not on β -Blockers.

Heart rate variability measures. Heart rate variability measures were skewed and not normally distributed so these values were transformed into a logarithm to the base of 10 in order to do parametric analyses. The means and standard deviation (\pm SD) of the original data for the heart rate variability measures of participants in the Comparison and Walking groups are shown in Table 10.

There were no main effects of Time, Condition or Time by Group interactions in the main analysis of low frequency power.

Similarly, no main effects of Time or Time by Group interactions were observed in the analyses performed on high frequency power. There was a significant main effect of Condition $F(2, 60) = 5.188$, $p = 0.008$, whereby (compared to rest) HF power decreased in response to standing, $F(1, 30) = 9.552$, $p = .004$, and in response to exercise, $F(1, 30) = 5.114$, $p = .031$. In addition, there was a significant Condition by Age interaction, $F(2, 60) = 3.715$, $p = 0.030$, whereby the younger participants (< 66 years) had a greater reduction in HF power in response to Standing compared to Rest, $F(1, 30) = 6.888$, $p = .014$, compared to the older participants (> 66 years).

Table 10

Means (SD) for HRV measures (raw values) over time.

Variable	Condition	Week 1		Week 12	
		Comparison (n=15)	Walking (n = 18)	Comparison (n=15)	Walking (n = 18)
LF (ms ² /Hz)	Rest	88 (111)	189 (305)	150 (341)	129 (159)
	Stand	76 (999)	159 (296)	148 (262)	102 (124)
	Exercise	280 (647)	118 (255)	198 (305)	321 (963)
HF ^B (ms ² /Hz)	Rest	486 (1414)	243 (366)	437 (1347)	118 (94)
	Stand	183 (463)	356 (1100)	527 (1363)	91 (234)
	Exercise	619 (1504)	273 (765)	497 (957)	555 (1667)
Total (ms ² /Hz)	Rest	833 (1595)	965 (987)	1001 (2533)	1681 (4238)
	Stand	1205 (3184)	1039 (1480)	1141 (2171)	649 (760)
	Exercise	1684 (2963)	905 (1542)	1233 (1948)	1525 (3337)
PNS ^{BC} (HF/TP)	Rest	0.28 (0.20)	0.21 (0.19)	0.25 (0.14)	0.22 (0.17)
	Stand	0.21 (0.18)	0.13 (0.19)	0.16 (0.20)	0.11 (0.13)
	Exercise	0.23 (0.21)	0.11 (0.17)	0.20 (0.18)	0.16 (0.14)
SNS ^{BC} (LF/HF)	Rest	0.90 (0.88)	1.64 (1.40)	1.24 (1.43)	1.39 (1.03)
	Stand	2.10 (2.14)	3.33 (2.66)	2.93 (3.48)	3.10 (2.39)
	Exercise	1.51 (1.43)	2.44 (2.28)	2.16 (2.45)	1.82 (2.15)

Legend: LF = low frequency; HF = High frequency, Total = total power; ^B = Significant main effect of Condition; ^C = Significant Time by Group Interaction; p ≤ 0.05

No main effects or interactions were observed in the analyses for total spectral power.

For the main analysis of the PNS indicator, no main effects of time were observed. There was a main effect of Condition $F(2, 62) = 12.348, p = .000$, whereby compared to rest, the PNS indicator decreased in response to standing, $F(1, 31) = 29.531, p = .000$, and decreased in response to exercise, $F(1, 31) = 10.387, P = .003$. A significant Time by Group interaction was also observed $F(1, 31) = 5.927, p = .021$ (Figure 5). A simple effect analysis performed on data obtained from members of the walking group only indicated a main effect of time, $F(1, 17) = 7.645, p = .013$, whereby participants in the walking group had a significant increase in the PNS indicator at Week 12 versus Week 1. Simple effects analysis performed on data obtained from the comparison group did not indicate any main effects. There also was a main effect of condition $F(2, 34) = 9.144, p = .001$, whereby compared to rest, the PNS indicator decreased in

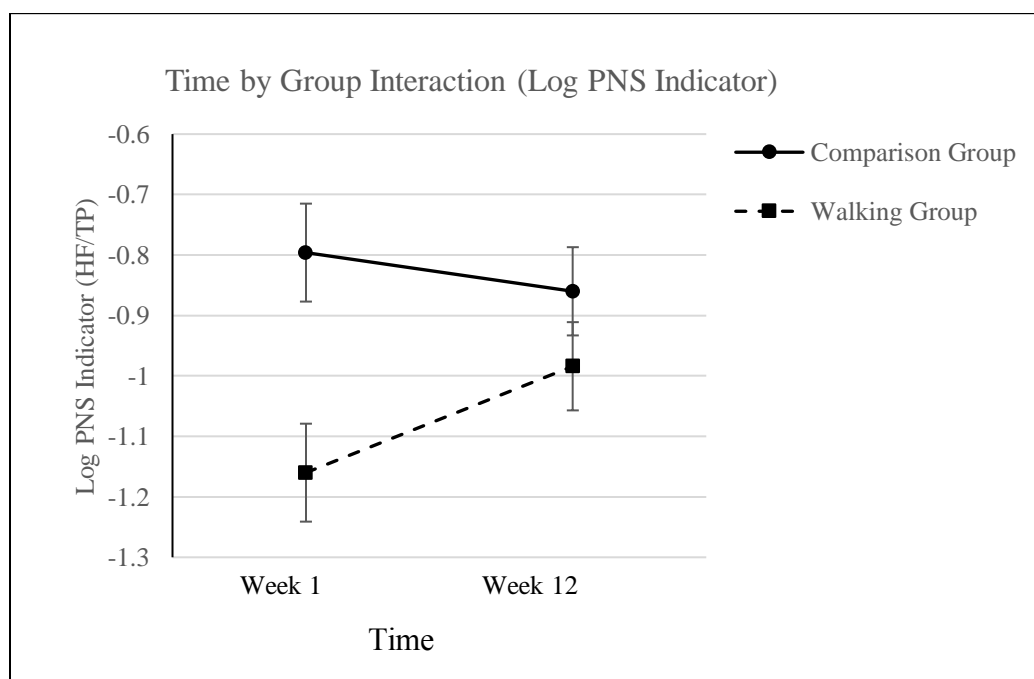


Figure 5. Time by group interaction for Log transformed PNS indicator, Week 12 vs Week 1.

response to standing, $F(1, 17) = 14.108$, $p = .002$, and decreased in response to exercise, $F(1, 17) = 8.206$, $p = .011$. Simple effect analysis performed on data obtained from members of the comparison group only indicated a main effect of condition, $F(2, 28) = 4.088$, $p = .028$, whereby the PNS indicator was significantly lower in the standing condition compared to rest, $F(1, 14) = 4.088$, $p = .028$.

For the SNS indicator, there was no main effect of Time, but a significant main effect of Condition, $F(2, 58) = 7.302$, $p = .001$, whereby compared to rest, the SNS indicator significantly increased in response to standing, $F(1, 29) = 7.909$, $p = .009$. For interactions, there was a significant Time by Group interaction (Figure 6), $F(1, 29) = 6.805$, $p = .014$, whereby the SNS

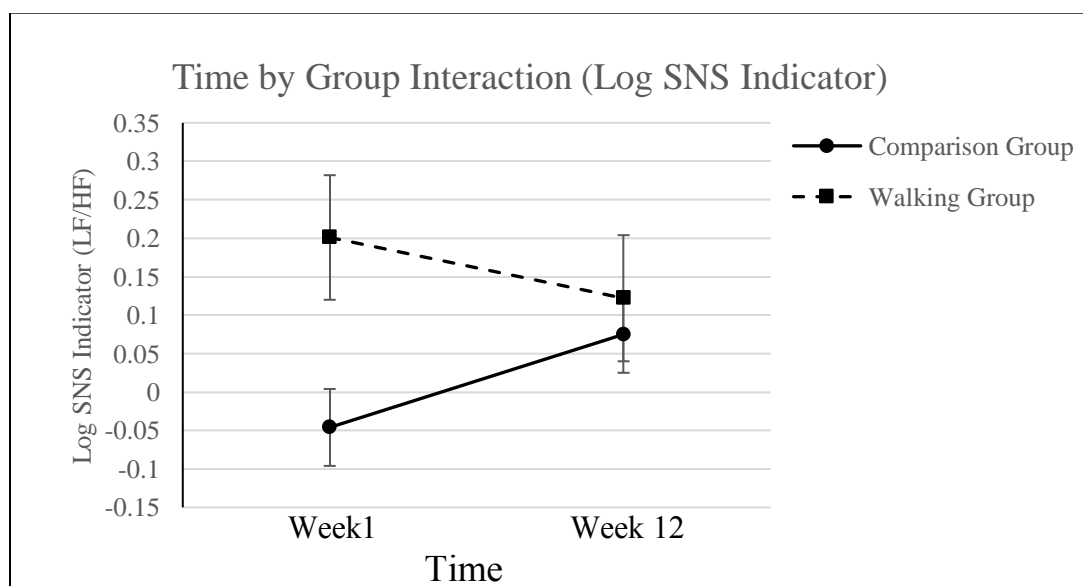


Figure 6. Time by group interaction for Log transformed SNS indicator, Week 12 vs Week 1.

indicator increased over time in the comparison group and decreased over time in the walking group. There was a Time by Smoking interaction $F(1, 29) = 11.553$, $p = .002$ in which the SNS

indicator increased over time in the smokers. Simple effects analysis for both groups did not indicate any main effect of Time. A significant Condition by Age interaction was observed, $F(2,58) = 5.851$, $p = 0.005$, and indicated a significant difference in Standing vs Rest, $F(1, 29) = 8.318$, $p = .007$, as well as in Exercise vs Rest, $F(1, 29) = 6.286$, $p = .018$ in the younger participants (< 66 years) who had had a greater increase in the SNS indicator in these conditions compared to the older participant (≥ 66 years). Smoking interacted with condition, as indicated by the Condition by Smoking interaction in the exercise condition Exercise vs Rest, $F(1, 29) = 4.319$, $p = 0.47$.

Simple effects analysis of the SNS indicator for members of the comparison group indicated a significant main effect of Condition, $F(2, 24) = 5.371$, $p = .012$, and a Condition by Age interaction, $F(4.277) = .026$. There also was a significant Time by Smoking interaction, $F(1, 12) = 6.258$, $p = .028$ as well as a Time by Condition by Smoking interaction $F(1, 12) = 5.371$, $p = .039$. Simple effects analysis for the walking group indicated a main effect of Condition, $F(2, 30) = 3.343$, $p = 0.049$, a Time by Smoking interaction, $F(1,15)=6.053$, $p = .027$.

Walking performance measures. Raw data (means \pm SD) obtained on the walking performance measures on the treadmill and six-minute walk test are included in Table 11. Data obtained on the treadmill test was not normally distributed. Also, participants differed on their performance measures at Week 1. Logarithmic values to the base 10 were calculated for PFWD, FCD and MWD and repeated measures ANOVA were performed on these data. Main effects of time were observed on the logarithmic transformed values for PFWD, $F(1, 30) = 10.134$, $p = .000$, FCD, $F(1, 30) = 10.556$, $p = .003$, and MWD, $F(1, 30) = 86.971$, $p = .000$. Further, the change over time values (or delta values) were calculated for PFWD, FCD and MWD. These values were found to be normally distributed and univariate analyses of variance were performed

for each variable obtained in the treadmill test. Univariate analysis on the change in performance measure over time indicated a significant main group effect for FCD $F(1, 30) = 7.038, p = .013$ and MWD $F(1, 30) = 6.778, p = .014$ (Figure 7).

Table 11

Means (SD) of performance measures over time.

Time:	Week 1		Week 12	
Group:	Comparison (n = 15)	Walking (n = 17)	Comparison (n = 15)	Walking (n = 17)
PFWD (m) ^A	118.58 (115.96)	168.27 (90.77)	144.60 (104.71)	233.07 (115.27)
FCD (m) ^A	203.30 (163.31)	284.65 (137.77)	226.80 (144.14)	418.82 (196.51)
MWD (m) ^A	252.10 (198.91)	364.53 (172.59)	278.09 (176.68)	488.50 (209.54)
6MWT (m)	332.86 (98.17)	335.53 (87.29)	338.46 (66.65)	347.61 (91.99)
Δ PFWD			26.02 (63.74)	64.80 (95.87)
Δ FCD*			23.50 (119.68)	134.17 (116.04)
Δ MWD*			26.00 (94.01)	123.97 (115.88)

Legend: Values are means (\pm standard deviation), FCD = Functional claudication distance; MWD = Maximal walking distance; PFWD = Pain-free walking distance; 6MWT = six-minute walk test; Δ = change from time 1; * = significant difference between group, $p \leq 0.05$. Note for treadmill performance measures, one participant was removed from the analyses as test termination criteria were not met. Data presented for the 6MWT is based upon a Comparison group of 15 members and a Walking group of 18 members. ^A = Significant main effect of time, $p \leq 0.05$

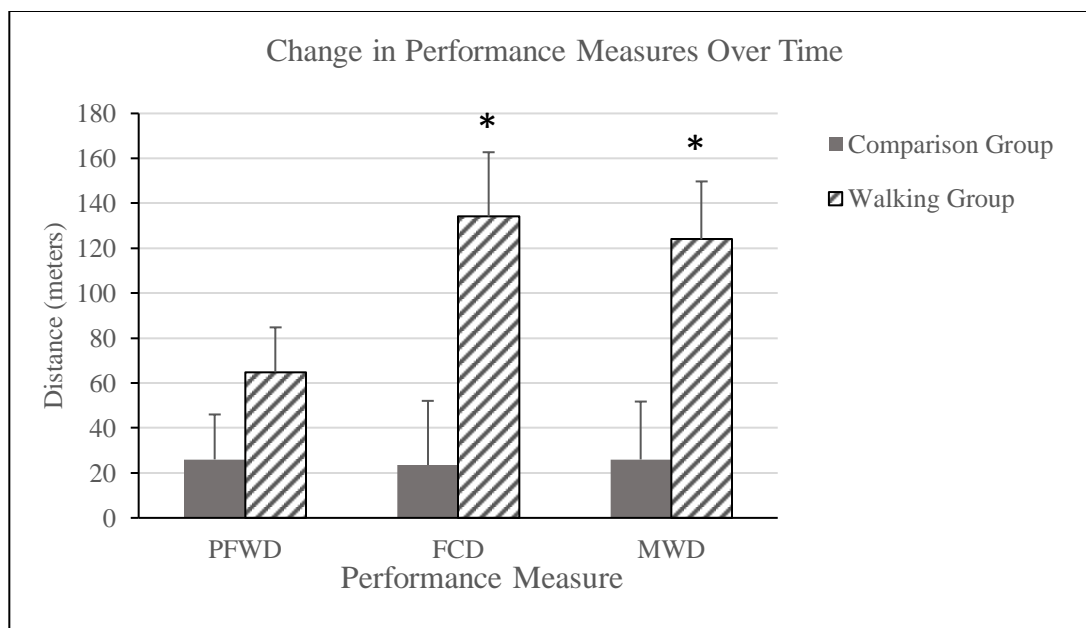


Figure 7. Change in walking distance over time.

Legend: * = significant difference between walking and comparison groups, $p < 0.05$.

There were no significant main effects or interactions for performance on the six-minute walk test, by members of comparison and walking groups.

Self-report measures. Self-report measures (means, [\pm SD]) for the Walking Impairment Questionnaire (WIQ) and Quality of Life Questionnaire (SF-36) are displayed in Tables 12 and 13, respectively. Main effects of Time were observed for the Walking Impairment Distance Score, $F(1, 31) = 7.740$, $p = 0.009$, the Stair Climbing Ability Score, $F(1, 29) = 5.042$, $p = 0.033$ and overall WIQ score, $F(1, 29) = 8.305$, $p = 0.007$, with each of these scores increasing at Week 12 (Table 12). For the WIQ distance score, there was a Time by Sex interaction, $F(1, 29) = 5.779$, $p = 0.023$, with men scoring higher at Week 12.

Table 12

Means (SD) of walking impairment questionnaire data over time.

Time	Week 1		Week 12	
Group	Comparison (n = 15)	Walking (n = 18)	Comparison (n = 15)	Walking (n = 18)
Distance ^A	36.32 (23.77)	51.95 (30.51)	58.61 (31.13)	62.62 (29.83)
Speed	40.00 (25.55)	48.37 (24.17)	43.91 (21.08)	57.61 (22.79)
Stairs ^A	39.17 (21.87)	56.71 (25.68)	45.28 (19.15)	66.44 (26.48)
Overall ^A	38.49 (18.41)	52.35 (21.49)	49.27 (17.54)	62.22 (22.47)

Legend: ^A = Significant main effect of time.

For the SF-36 Physical Function scores, a significant main effect of Time was observed, $F(1, 30) = 10.645$, $p = .003$, with Physical Function scores increasing at Week 12 (Table 13). However, no significant Time effects were observed for the Role Limitation component of the SF-36. Moreover, there were no Time by Group interactions for either physical function scores or for role limitation scores.

Table 13

Means (SD) of quality of life scores (SF-36) over time.

Time	Week 1		Week 12	
Group	Comparison (n = 14)	Walking (n = 18)	Comparison (n = 14)	Walking (n = 18)
Physical Function ^A	51.08 (15.71)	61.69 (18.84)	56.79 (17.82)	70.83 (14.78)
Role Limitations	39.32 (39.02)	61.11 (41.62)	57.14 (31.84)	66.20 (41.96)

^A = Significant main effect of time; $p < 0.05$.

Chapter 5 – Discussion

The main purpose of this study was to examine the circulatory and autonomic effects of a progressive, 12-week home-based, low-intensity (walking) exercise program in patients with PAD after controlling for potential confounders such as age, sex, β -blockers and smoking. Secondary objectives were 1) to determine the effect of the intervention on walking performance and self-report measures such as the walking impairment questionnaire and health related quality of life and 2) to determine if there were any sex-specific differences that might exist at rest or in response to training. The main findings of this study were that autonomic function (HRV) improved and overall walking performance increased. These findings suggest that the structured, low-intensity, high frequency walking protocol was effective in 1) reducing cardiovascular risks associated with low HRV and 2) increasing functional claudication and daily walking distance. This appears to be the first study on the effects of low-intensity, high frequency, pain-free exercise conditioning on cardiac autonomic measures in patients with PAD. The data support the hypothesis that participation in this program would improve autonomic function (increase PNS and decrease SNS activity) and increase walking performance.

The most significant finding of this study was that HRV improved in the walking group which is important since low HRV has been associated with > 20% increased risk of coronary event within 10 years (Hiatt et al., 2015; Shamma, 2007). Moreover, individuals with coronary artery disease (CAD) and comorbid PAD are at greater risk of cardiovascular events than those with CAD alone (Grenon et al., 2013). Further, symptomatic PAD events are associated with a 70% higher risk of cardiovascular events and an 80% risk of death than asymptomatic PAD (Grenon et al., 2013).

This is the first study to document improvement in HRV in patients with PAD following a progressive low-intensity, high frequency walking program. In the walking group, the PNS indicator increased and the SNS indicator decreased over time. It has been reported that patients with PAD can have an impairment in peripheral sympathetic regulation, which controls blood flow to the extremities (Delis, Nicolaidis, et al., 2001), thus, this adaptation (i.e., the decrease in the SNS indicator) to training may improve sympathetic regulation. In this study, exercise-training changed the sympathovagal balance to favor an increase in vagal activity and a decrease in sympathetic activity which could in-turn lead to a reduction in vasoconstriction in the lower extremities (Goldsmith et al., 2000). Thus, the improvement in autonomic function following exercise training may improve blood flow to the lower extremities, enhance physical walking performance, and decrease the risk of future CV events. Interestingly, Boyd et al. (1984) showed an increase in muscle blood flow after training after eliminating one person for low attendance.

Studies from this laboratory using a similar protocol have demonstrated that regular low-intensity, high frequency exercise training increases HRV in patients with hypertension (Goldie et al., 2013; Hua et al., 2009) and has a training effect on HR, BP and RPP during the early weeks after coronary artery bypass graft surgery (Brown et al., 1994). However, other researchers who examined the influence of a 3-month (Sandercock et al., 2007) or a 12-month walking program (Leicht et al., 2011) on patients with PAD did not find any change in HRV parameters. This discrepancy may be explained by differences in the types of exercise program implemented (high intensity, low frequency vs low intensity, high frequency as in this study), the conditions under which the participants were tested as well as the quality of each study design.

Sandercock et al. (2007) had their participants walk twice weekly at 75% peak oxygen uptake (Supervised Exercise Group) or at an RPE of 12-14 (Home-Based Exercise Group) for 12

weeks and found that resting HRV was not altered by either exercise intervention. The exercise intensity (75% peak oxygen intake/RPE of 12-14) in the study of Sandercock et al. was sufficient to induce an increase in SNS modulation during and after exercise (Kamath et al., 1991). Leitch et al. (2011) had patients exercise regularly (3 times per week) over a year, for 25 to 40 min on a treadmill (in a supervised setting) to maximum leg pain. Supervised treadmill training did not influence either the time or frequency domain components of HRV. The frequency of training (2-3 days per week) used in both of these studies may have been insufficient to induce any physiological adaptations. In the current study, participants performed at a lower intensity, but higher frequency of exercise (i.e., exercise 5 days per week as opposed to 2-3 times per week) which minimized involvement of the sympathetic nervous system and induced a change in autonomic regulation at rest.

Preliminary analyses of cardiovascular measures indicated that β -blockers and age influenced one or more cardiovascular measures. In this study, participants who were on β -blockers had lower HR and RPP than those who were not on β -blockers. It is well known that HR is lowered through the use of β -blockers (Bangalore et al., 2008) by blocking the effect of norepinephrine on the heart (Gorre & Vandekerckhove, 2010). At week 1 (entry into the study) participants who were on β -blockers had a lower heart rate and rate pressure product than those who were not on β -blockers. However, the HR responses and the RPP between those on β -blockers and those not on β -blockers were similar at week 12 in the walking group only. This indicates that the HR was reduced (most likely by an increase in PNS activity) after 12 weeks of training in participants who were not on β -blockers.

An unexpected finding of this study was that SBP decreased to a greater extent in the comparison group versus the walking group. Members of the walking group had a reduction of 2

mmHg compared to the 10 mm Hg reduction in SBP that was observed in members of the comparison group. These findings were unexpected since others from this laboratory have reported a decrease in SBP following participation in a structured, low-intensity walking intervention (Goldie et al., 2013; Hua et al., 2009). Hua et al. (2009) demonstrated that hypertensive men and women who participated in a similar exercise program, reduced their SBP by 11 mmHg compared to 6 mmHg in the comparison group. Further, Goldie et al. (2013) found a decrease of 6 mmHg SBP in hypertensive pre-and post-menopausal women following a walking intervention compared to a 1.5 mmHg reduction in the comparison group. This is in keeping with the results of a meta-analysis performed by Fagard (2001). A review of 44 randomized controlled studies, involving 2674 participants, on the effects of exercise training on resting blood pressure determined that on average, systolic and diastolic blood pressures are reduced by 3.4 and 2.4 mmHg, respectively with exercise training. However, blood pressure decreases to a greater extent following exercise training in hypertensive individuals (-7.4/5.8 mmHg) compared to normotensive individuals (-2.6/1.8 mmHg). Interestingly, Fagard did not find any relationship between frequency, intensity, type of exercise or duration of activity and the BP response.

Two reasons may explain our unexpected findings of a greater reduction in systolic blood pressure in the comparison group (compared to the walking group) as reported above. First, systolic blood pressure was measured at only one point in time and these results may be spurious and could account for these findings. Secondly, more participants in the comparison group entered into the study with a high systolic blood pressure compared to members of the walking group. This was supported by the responses obtained on the participant demographic form of a diagnosis of hypertension in 26.7% of members of the comparison group compared to 22.2% of

members of the walking group. In addition, during the study members of the comparison group became involved in some form of physical activity, 3 days per week. Participants in comparison group in the study by Goldie et al. (2013) only walked 0.6 (\pm SD 1.1) sessions/week. Thus, the greater reduction in SBP in the comparison group may be attributed to more participants with hypertension becoming regularly active (albeit in an unstructured way).

Furthermore, in this study, the older participants (>66 years) had a higher SBP compared to the participants who were younger than 66 years of age. The PNS and SNS activity measured by HRV analysis were also influenced by the age of the participants such that greater changes in PNS and SNS activity occurred in the younger participants (< 66 years) in response to standing. Aging is known to contribute to an increase in blood pressure due to several factors: an increase in sympathetic nerve activity that occurs with age, age-related changes in the distribution of vascular β -adrenergic receptors (most notably in women), an increase in arterial stiffness and atherosclerosis (Hart & Charkoudian, 2014).

The lack of a significant change in the other cardiovascular parameters (HR, DBP, RPP and MAP) examined is similar to that reported by Barak et al. (2000). They reported no change in resting HR or BP in 10 participants (5 men and 5 women) following treadmill training (45 min per session to mild claudication pain, 2 times per week over 6 weeks). Despite the lack of cardiovascular adaptations in the study by Barak et al. (2009), participants in that program were still able to increase their maximal walking distance (148%) and maximal walking time (94%) similar to the findings here. The training frequency (2 days per week), intensity (to minimal pain), and duration of study (6 weeks) may not have been frequent, intense and/or long enough to induce any central cardiovascular adaptations.

In this study, participants in the walking group walked 5 days per week and members of the comparison group adopted some form of activity (performed on average 3 days per week) during the study, albeit a different mode (e.g., swimming, cycling, weight training or dog walking) and as a result may have incurred some adaptations to their training stimulus since there was a main effect of time for HR, MAP and RPP such that each variable was lower at Week 12 for both the comparison and walking groups. In addition, there was a time by condition interaction whereby HR, MAP and RPP were all lower by week 12 when comparing the exercise *vs* rest condition (i.e., HR, MAP and RPP). This would indicate that members of the comparison group had performed some form of regular physical activity during the study and through this gained some cardiovascular adaptations.

In order to induce additional cardiovascular adaptations in patients with PAD, it appears that additional or alternative muscle groups might need to be used or integrated into the exercise program. Collins et al. (2005) demonstrated that a cardiovascular training effect (decreased HR, BP and RPP, overtime) can occur in patients with PAD, following 24 weeks of pole-striding (walking with poles that resemble ski-poles). Their participants performed supervised, intermittent pole-striding exercise for 40 to 60 minutes per session at 60 to 70% of peak oxygen uptake, 3 days per week. Other studies examining the effects of arm- or leg-ergometry have indicated that use of additional or alternative muscle groups can induce improvements in central cardiorespiratory function that subsequently could contribute towards an improvement in walking performance (i.e., a cross-transfer effect) (Langbein et al., 2002; Treat-Jacobson et al., 2009; Zwierska et al., 2005). However, a concern of use of exercises involving arm muscles in this population is that BP could rise placing them at risk of a cardiovascular event (Fletcher et al., 1992).

The second important finding of this study is the improvement in walking performance that occurred following the 12-week walking intervention. An increase in walking performance may lead to an improvement in functional independence and may allow the patient to carry out more activities of daily living. Following 12-weeks of intervention, participants in the walking group significantly improved their functional claudication distance 147% and maximal walking distance 134% compared to 112 and 110%, respectively in the comparison group. The results of this study are consistent with reports on the effects of low-intensity, pain-free exercise on walking ability in patients with PAD. Martinez et al. (2009) reported a 156% increase in walking duration following training. Other studies have demonstrated that low-intensity exercise or training to the onset of claudication pain can increase pain-free walking distance (Carter et al., 1989; Mannarino et al., 1989) and maximal walking distance (Mannarino et al., 1989; Martinez et al., 2009; Zetterquist, 1970), none of these examined functional claudication distance nor the mechanisms that could be involved.

Additionally, this study demonstrated that the presence of peripheral artery disease did not alter the circulatory response to either orthostatic stress (standing) or acute exercise. At both the beginning and end of the study, HR, SBP, MAP and RPP increased in the walking and comparison groups in response to orthostatic stress (standing) and acute exercise at each testing time. This pattern of response is comparable to what has been reported in previous studies examining orthostatic stress and acute exercise in healthy individuals (Jagoda, Myers, Kaminsky, & Whaley, 2014; Westerhof et al., 2006) and in patients early after coronary artery bypass graft surgery (Brown, Wolfe, Hains, Ropchan, & Parlow, 2004; Chenier-Hogan et al., 2012).

The rise in HR and BP that occurred in response to standing and acute exercise can be attributed to a withdrawal of PNS activity and an increase in SNS activity that was more

pronounced in the younger group of participants (< 66 years of age). For standing, this occurs due to a decrease in blood pressure that is detected by the baroreceptors which in-turn initiates a series of events to increase blood pressure (Delis, Lennox, et al., 2001). For acute exercise, central command and metaboreceptors increase HR by increasing SNS input to the heart (Fisher, 2013). The reduction in HRV that occurs with increasing age has been attributed to an impairment in central autonomic function (Piccirillo et al., 2001), a reduction in cardiac M₂ muscarinic receptor density and function (Brodie et al., 1998) and an age- as well as disease-related reduction in arterial compliance (Kardos et al., 2001).

The 12-week low-intensity walking intervention was effective in maintaining the ABI. These findings suggest that the disease did not progress further in participants in the walking group during the twelve weeks of the study. Although, most studies show that ABI also does not change with exercise training, especially over the short term (Boyd et al., 1984; Gardner et al., 2005; Mannarino et al., 1989), one study reported a 3 percent increase in ABI following exercise training to maximum pain tolerance (Izquierdo-Porrera et al., 2000). The subsequent consequence of a reduced ABI value is that it is associated with a functional decline in performance (McDermott et al., 2004). The change in autonomic function that was observed over time in this study may have contributed towards changes observed in the ABI and SBP.

Because this study used a low-intensity exercise protocol, an exaggerated BP response to steady-state exercise was not observed. Blood pressure was measured at the immediate end of each exercise bout and the response was typical to what would be expected. In other studies whereby BP is continuously monitored throughout an exercise bout (lasting approximately 10 minutes on a treadmill) to maximal claudication pain, patients with PAD exhibit an exaggerated,

continuous BP response to steady-state exercise (Baccelli et al., 1999; Bakke et al., 2007; Ritti-Dias et al., 2011).

Members of both groups improved on their self-report measures by week 12. There was no difference between the exercise group and the comparison group for distance, stairs and overall scores on the WIQ. There was no change in the speed score, indicating that patients with PAD did not walk faster following this type of progressive, low-intensity walking intervention and this is supported by the data obtained on the six-minute walk test (6MWT) which also did not change over time. In addition, physical function scores on the SF-36 were increased in both groups at week 12. Thus, there were no changes attributable specifically to the exercise intervention. This may be explained by the fact that participants in the comparison group began exercising while they were in the study even though they were asked to continue their usual activity. Improvements in self-report measures following a low-intensity exercise training program have been reported by Gardner et al (2005) and Tsai et al. (2002). Izquierdo-Porrera et al. (2005) reported that self-reported disease specific (WIQ) and generic quality of life measures (SF-36 PF and RL) were correlated with objective measures of physical function.

Lastly, although this study was designed to examine the circulatory and autonomic effects of a walking intervention on patients with PAD, a secondary focus was to determine if there were any sex-specific differences that might exist at rest or in response to training. Only a few studies have compared men and women with PAD (Aronow, 2009; Gardner, 2002; Maksimovic et al., 2010; Vavra & Kibbe, 2009) and none examined HRV. The results of this study suggest that there are minimal differences between men and women with peripheral artery disease and that both sexes respond similarly to exercise training. At entry to the study, men and women with PAD were similar in their educational level, employment status, co-morbidity

(diabetes, hypertension and coronary artery disease) and medication use. Similar to the findings of Maksimovic et al. (2010), women with PAD had significantly more body fat, a smaller waist girth and a lower waist-to-hip ratio than men. At rest, women also had significantly lower diastolic blood pressures compared to men which might be attributed to differences in the use of β -blockers. Thirty-five percent (7/20) of the women in this study were on β -blockers, whereas only 29% (8/28) of the men reported use. There were no differences in walking performance measures (PFWD, FCD, MWD, 6MWT) between men and women at entry into the study, although men reported a significantly higher level of physical functioning. Gardner et al. (2002) reported shorter walking distance scores for PFWD, MWD and 6MWT as well as lower self-perceived ability to climb stairs measures for women compared to men. The discrepancy between the findings of this study and those of Gardner et al (2002) may be attributed to the differences in sample size and disease severity as reflected by ABI measures.

Sixty-nine percent of participants completed the study. Other studies examining the effects of a walking interventions on patients with PAD have reported that 34% (Mouser et al., 2009) to 77% (Wullink et al., 2001) of participants complete their study. Differences in length of the study (12 weeks vs 24 weeks), type of walking intervention (i.e., walking to pain onset or maximal pain) and the extent of feedback received and/or support provided by the investigators contribute to the variations in the attrition rate (Gardner, Parker, Montgomery, Scott, & Blevins, 2011). Participants were asked to record their daily walking activities and any additional physical activity they performed.

Walking diaries are an effective means for patients with PAD to keep track of their walking activity and to provide feedback (Gardner et al., 2011; Tan et al., 2000; Wullink et al., 2001) and in this study walking diaries were used to record their activity levels. Approximately

91% of participants completed all entries for all weeks on their log. They also had bi-weekly phone calls to assess progress and to address any questions they may have. Of those participants who completed the study, members of the walking group demonstrated a compliance rate of 92%. Compliance rates greater than 67% are considered high (Anton et al., 2005). Other studies performed in this laboratory reported similar compliance rates (81 to 95%) with this type of exercise protocol (Goldie et al., 2013; Hua et al., 2009). Members of the walking group participated in an average of 5 walking sessions per week. This confirms that they exercised according to the study requirements and suggests that the written, structured, progressive low-intensity high frequency is an effective intervention in improving autonomic function and walking ability in patients with PAD. Although participants in the comparison group, who were supposed to continue the same level of activity during the study, became involved in physical activity (i.e., walking, swimming, aqua-fitness classes) on their own 3 sessions per week, they did not show an improvement in autonomic function nor did they increase their walking performance significantly. This is consistent with the observation that unstructured home-based interventions have limited efficacy (Cunningham et al., 2012).

Limitations

A major limitation of this study was that participants of the comparison group did not maintain their usual lifestyle, even though they were instructed to do so. However, the finding that participants in the comparison group increased their activity when involved in such a study is not unusual and has been reported by others (Mika et al., 2005). Several participants increased their activity level because they were participating in an “exercise study”, received biweekly phone calls and completed an activity log. In addition, the participants reported that they tried to guess what the exercise group was doing and began increasing their activity. Some participants

purchased a dog to walk, other participants began walking more, participated in aqua-fit classes or became involved in a resistance training program. This may have reduced the likelihood of finding significant time-by-group findings. This study also included a disproportionate number of men (64%) compared to women (36%), although the ratio of men to women in the study is comparable to what would be found in the clinical setting. Another limitation of this study was that the sample size for this study was determined based upon desired improvements in walking distance. At the time that this study was designed there were no effect sizes available for HRV measures for patients with PAD, as there had been no studies published. Finally, this study could have been strengthened through use of an accelerometer to quantify the actual amount of activity that the participants performed.

Implications for Nursing

Despite the established use of HRV assessment in the clinical setting to determine CV risk, very few Schools of Nursing in Canada teach HRV to their students. In the United States, The University of California, San Francisco School of Nursing (UCSF) has conducted research on HRV (Harris, Stein, Fung, & Drew, 2013) for decades. Other US University Schools of Nursing (Burr et al., 2006) and Nursing Schools in Korea (Lim & Kim, 2014) have been doing this as well. In Canada, Queen's University, School of Nursing is the only School of Nursing that studies HRV. Nursing education programs in Canada should include education on HRV, which is a more sophisticated and sensitive way of measuring HR and BP (Akselrod et al., 1981; Bernardi et al., 2011). These programs should provide instruction on data collection and interpretation. With a greater understanding of HRV and the implications of a low HRV, more research can be done to enhance HRV in patients with cardiovascular disease.

The results of this study are a first step towards providing support for the efficacy of a structured, progressive, low intensity home exercise program for patients with peripheral artery disease. Further research is required to support the efficacy of this structured, low-intensity exercise program. Various modifications of the current study protocol could be done to enhance the research design in future studies. This includes use of fitness trackers (i.e., cell phones, smart watches, all day trackers and accelerometers) to monitor exercise intensity as opposed to use of log books. HRV testing could be performed on a treadmill as opposed to a stationary cycle ergometer to better reflect what physiological adaptations may be occurring when a participant is actually walking. Lastly, the walking intervention program could be modified to include a shorter walking distance. Most participants had difficulty with attaining the recommended distance of 3.2 km per session and only attained 2.65 km by the end of the study. Further study should also be directed towards determining what adaptations are occurring in the peripheral circulation. For example, in order to determine whether an increase in blood volume in the legs was due to increased vasodilation or increased collateral circulation, techniques such as flow-mediated vasodilation measured by ultrasound or magnetic resonance angiography (MRA)-assessment of collateral vessels, respectively, could be performed. Another study that could be conducted would be longitudinal study examining HRV in PAD patients with a follow-up on their medical history to see if any adverse cardiovascular events occur over time.

Based upon the review of literature and the results of this study, nurses who work with patients with PAD should encourage their patients to exercise regularly. Following physician clearance, participation in a structured walking program with regular follow-up visits or phone calls could be beneficial to the patient.

Conclusion

Patients with PAD are limited in their walking performance, may have limb symptoms (such as IC) and are at an increased CV risk. Besides the finding that this 12-week, structured, low-intensity exercise (walking) program, performed 5 days per week improved walking performance (FCD and MWD), this is the first study to show that HRV increases following this type of training. Analysis of HRV is one of the most sensitive and specific tools used to investigating cardiac autonomic function (Bernardi et al., 2011). Patients with a reduced HRV are more likely to suffer a cardiac event as well as subsequent death due to sudden onset of malignant ventricular arrhythmias. This study demonstrated that low intensity, high frequency exercise-training in patients with PAD can change the sympathovagal balance to favor an increase in vagal activity, a decrease in sympathetic activity and an increase in HRV. A reduction in sympathetic activity could lead to a reduction in vasoconstriction in the lower extremities. Thus, this adaptation to training may improve sympathetic regulation of blood flow to the lower extremities during exercise. The increase in HRV also lowers the patient's risk of experiencing further CV events. Finally, what makes this exercise intervention unique was that it was home-based, low-intensity and pain free.

References

- Abdel-Rahman, A. R. A., Merrill, R. H., & Wooles, W. R. (1994). Gender-related differences in the baroreceptor reflex control of heart rate in normotensive humans. *Journal of Applied Physiology*, 77(2), 606-613.
- Akselrod, S., Gordon, D., Madweg, J. B., Snidman, N. C., Shannon, D. C., & Cohen, R. J. (1985). Hemodynamic regulation: Investigation by spectral analysis. *American Journal of Physiology*, 249(4), H867-H875.
- Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Barger, A. C., & Cohen, R. J. (1981). Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*, 213, 220-221.
- Al-Qaisi, M., Nott, D. M., King, D. H., & Kaddoura, S. (2009). Ankle brachial pressure index (ABPI): an update for practitioners. *Vascular health and risk management*, 5, 833-841.
- Alpert, J. S., Larsen, O. A., & Lassen, N. A. (1969). Exercise and intermittent claudication. Blood flow in the calf muscle during walking studied by Xenon-133 clearance method. *Circulation*, 39(3), 353-359.
- Amara, C. E., & Wolfe, L. A. (1998). Reliability of non-invasive methods to measure cardiac autonomic function. *Canadian Journal of Applied Physiology*, 23(4), 396-408.
- Amini, A., Gordon, I., Wilson, S., & Williams, R. A. (2013). Noncompressible arteries correlate with increased cardiovascular mortality at 2 years. *Annals of Vascular Surgery*, 27(7), 918-923.
- Amiya, E., Watanabe, M., & Komuro, I. (2014). The relationship between vascular function and the autonomic nervous system. *Annals of Vascular Diseases*, 7(2), 109-119.

- Anderson, J. L., Halperin, J. L., Albert, N. M., Bozcurt, B., Brindis, R. G., Curtis, L. H., . . . Shen, W. (2013). Management of patients with peripheral artery disease. Compilation of 2005 and 2011 ACCF/AHA guideline recommendation. *Journal of Vascular Surgery*, *52*, 348-355.
- Anton, S. D., Perri, M. G., Riley, J., Kanasky, W. F. J., Rodrigue, J. R., Sears, S. F., & Martin, A. D. (2005). Differential predictors of adherence in exercise programs with moderate versus higher levels of intensity and frequency. *Journal of Sport and Exercise Psychology*, *27*, 171-197.
- Arai, Y., Saul, J. P., Albrecht, P., Hartley, L. H., Lilly, L. S., Cohen, R. J., & Colucci, W. S. (1989). Modulation of cardiac autonomic activity during and immediately after exercise. *American Journal of Physiology*, *256*, H132-H141.
- Aronow, W. S. (2009). Peripheral arterial disease in women. *Maturitas*, *64*(4), 204-211.
doi:10.1016/j.maturitas.2009.10.001; 10.1016/j.maturitas.2009.10.001
- Baccelli, G., Reggiani, P., Mattioli, A., Corbellini, E., Garducci, S., & Catalano, M. (1999). The exercise pressor reflex and changes in radial arterial pressure and heart rate during walking in patients with arteriosclerosis obliterans. *Angiology*, *50*(5), 361-374.
- Bakke, E. F., Hisdal, J., Jorgensen, J. J., Kroese, A. J., & Strandén, E. (2007). Blood pressure in patients with intermittent claudication increases continuously during walking. . *European Journal of Vascular and Endovascular Surgery*, *33*, 20-25.
- Bangalore, S., Sawhney, S., & Messerli, F. H. (2008). Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *Journal of the American College of Cardiology*, *1482-1489*.

- Belcaro, G., Vasdekis, S., Rulo, A., & Nicolaides, A. N. (1989). Evaluation of skin blood flow and venoarteriolar response in patients with diabetes and peripheral vascular disease by laser Doppler flowmetry. *Angiology*, *40*(11), 953-957.
- Bernardi, L., Spallone, V., Stevens, M., Hilsted, J., Frontoni, S., Pop-Busui, R., . . . Valenci, P. (2011). Methods of investigation for cardiac autonomic dysfunction in human research studies. *Diabetes/Metabolism Research and Reviews*, *27*, 654-664.
- Bigger, J. T. J., Fleiss, J. L., Steinman, A. B., Rolnitzky, L. M., Schneider, W. J., & Stein, P. K. (1995). RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation*, *91*, 1936-1943.
- Blaber, A. P., Yamamoto, Y., & Hughson, R. L. (1995). Methodology of spontaneous baroreflex relationship assessed by surrogate data analysis. *American Journal of Physiology*, *268*(4), H1682-H1687.
- Borg, G. A. (1982). Psychophysical basis of perceived exertion. *Medicine and Science in Sports and Exercise*, *14*(5), 377-378.
- Borg, G. A. (1998). *Borg's Perceived Exertion and Pain Scales*. Windsor, ON: Human Kinetics.
- Boyd, C. E., Bird, P. J., Teates, C. D., Wellons, H. A., MacDougall, M. A., & Wolfe, L. A. (1984). Pain free physical training in intermittent claudication. *Journal of Sports Medicine & Physical Fitness*, *24*(2), 112-122.
- Brach, J. S., Solomon, C., Naydeck, B. L., Sutton-Tyrrell, K., Enright, P. L. L., Jenny, N. S., . . . Newman, A. B. (2008). Incident physical disability in people with lower extremity peripheral arterial disease: the role of cardiovascular disease. *Journal of the American Geriatric Society*, *56*, 1037-1044.

- Brass, E. P., Jiao, J., & Hiatt, W. R. (2007). Optimal assessment of baseline treadmill walking performance in claudication clinical trials. *Vascular Medicine, 12*, 97-104.
- Brenner, I., Parry, M., & Brown, C. A. (2012). Exercise interventions for patients with peripheral arterial disease: a review of the literature. *The Physician and sportsmedicine, 40*(2), 41-55. doi:10.3810/psm.2012.05.1964; 10.3810/psm.2012.05.1964
- Broddie, O.-E., Korschak, U., Becker, K., Ruter, F., Poller, U., KJakubetz, J., . . . Zerkowski, H.-R. (1998). Cardiac muscarinic receptors decrease with age. In vitro and in vivo studies. *Journal of Clinical Investigation, 101*, 471-478.
- Bronas, U. G., Treat-Jacobson, D., & Leon, A. S. (2011). Comparison of the effect of upper body-ergometry aerobic training vs treadmill training on central cardiorespiratory improvement and walking distance in patients with claudication. *Journal of Vascular Surgery, 53*(6), 1557-1564.
doi:<http://dx.doi.org.proxy.queensu.ca/10.1016/j.jvs.2011.01.077>
- Brown, C. A. (1990). *Cardiovascular adaptations to low intensity exercise conditioning early after coronary artery bypass graft surgery*. (M.Sc.), Queen's University, Kingston, Ontario.
- Brown, C. A., Wolfe, L. A., Hains, S., Pym, J., & Parker, J. O. (1994). Early low intensity home exercise after coronary artery bypass graft surgery. *Journal of Cardiopulmonary Rehabilitation, 14*, 238-245.
- Brown, C. A., Wolfe, L. A., Hains, S., Ropchan, G., & Parlow, J. (2003). Spontaneous baroreflex sensitivity after coronary artery bypass graft surgery as a function of gender and age. *Canadian journal of physiology and pharmacology, 81*(9), 894-902. doi:10.1139/y03-087

- Brown, C. A., Wolfe, L. A., Hains, S., Ropchan, G., & Parlow, J. (2004). Heart rate variability following coronary artery bypass graft surgery as a function of recovery time, posture, and exercise. *Canadian journal of physiology and pharmacology*, 82(7), 457-464.
doi:10.1139/y04-076
- Bruno, R. M., Ghiadoni, L., Seravalle, G., Dell'Oro, R., & Taddei, S. G. G. (2012). Sympathetic regulation of vascular function in health and disease. *Frontiers in Physiology*, 3, 1-15.
- Buckley, J. P., Eston, R. G., & Sim, J. (2000). Rating of perceived exertion in Braille: validity and reliability in production mode. *British Journal of Sports Medicine*, 34, 297-302.
- Burr, R. L., Motzer, S. A., Chen, W., Cowan, M. J., Shulman, R. J., & Heitkemper, M. M. (2006). Heart rate variability and 24-hour minimum heart rate. *Biological Research for Nursing*, 7(4), 256-267.
- Carman, T. L., & Fernandez, B. B. (2006). Contemporary management of peripheral artery disease: improving walking distance and quality of life. *Cleveland Clinic Journal of Medicine*, 73(4), S38-S44.
- Carter, S. A., Hamel, E. R., Paterson, J. M., Snow, C. J., & Mymin, D. (1989). Walking ability and ankle systolic pressures: Observations in patients with intermittent claudication in a short-term walking exercise program. *Journal of Vascular Surgery*, 10, 642-649.
- Chenier-Hogan, N., Brown, C. A., Hains, S. M., & Parlow, J. L. (2012). Heart rate variability response to standing in men and women receiving d,l-sotalol following coronary artery bypass graft surgery. *Biological research for nursing*, 14(1), 38-47.
- Collins, E. G., Langbein, W. E., Orebaugh, C., Bammert, C., Hanson, K., Reda, D., . . . Littooy, F. N. (2005). Cardiovascular training effect associated with polestriding exercise in

- patients with peripheral arterial disease. *Journal of Cardiovascular Nursing*, 20(3), 177-185.
- Collins, E. G., O'Connell, S., Jelinek, C., Miskevics, S., & Budiman-Mak, M. (2008). Evaluation of psychometric properties of Walking Impairment Questionnaire in overweight patients with osteoarthritis of the knee. *Journal of Rehabilitation Research and Development*, 45(4), 559-566.
- Conene, D., Everett, B. M., Kurth, T., Creager, M. A., Buring, J. E., Ridker, P. M., & Pradhan, A. D. (2011). Smoking, smoking cessation, and risk for symptomatic peripheral artery disease in women: a cohort study. *Annals of Internal Medicine*, 154(11), 719-726.
- Conte, M. S., Pomposelli, F. B., Clair, D. G., Geraghty, P. J., McKinsey, J. F., Mills, J. L., . . . Sidawy, A. N. (2015). Society for vascular surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *Journal of Vascular Surgery*, 61(3S), 2S-41S.
- Cox, K. L., Burke, V., Gorely, T. J., Beilin, L. J., & Puddey, I. B. (2003). Controlled Comparison of Retention and Adherence in Home- vs Center-Initiated Exercise Interventions in Women Ages 40–65 Years: The S.W.E.A.T. Study (Sedentary Women Exercise Adherence Trial). *Preventive medicine*, 36(1), 17-29. doi:10.1006/pmed.2002.1134
- Cryer, P. E., Haymond, M. W., Santiago, J. V., & Shah, S. D. (1976). Nor-epinephrine and epinephrine release and adrenergic mediation of smoking associated hemodynamic and metabolic events. *New England Journal of Medicine*, 295, 573-577.
- Cunningham, M. A., Swanson, V., O'Carroll, R. E., & Holdsworth, R. J. (2012). Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *British Journal of Surgery*, 99(1), 49-56.

- da Pureza, D. Y., Jorge, L., Sanches, I. C., Irigoyen, M., de Souza, R. R., & de AnGelis, K. (2012). Acute exercise adjustments of cardiovascular autonomic control in diabetic rats. *Muscle Nerve*, *46*, 96-101.
- Dart, A. M., Du, X. J., & Kingwell, B. A. (2002). Gender, sex hormones and autonomic nervous control of the cardiovascular system. *Cardiovascular Research*, *53*, 678-687.
- Davis, L. L. (2014). Cardiovascular issues in older adults. *Critical Care Nursing Clinics of North America*, *26*, 61-889.
- De Ferrari, G. M., Landolina, M., Mantica, M., Manfredini, R., Schwartz, P. J., & Lotto, A. (1995). Baroreflex sensitivity, but not heart rate variability, is reduced in patients with life threatening ventricular arrhythmias long after myocardial infarction. *American Heart Journal*, *130*(3), 473-480.
- Delis, K. T., Lennox, A. F., Nicolaidis, A. N., & Wolfe, J. H. (2001). Sympathetic autoregulation in peripheral vascular disease. *British Journal of Surgery*, *88*(4), 523-528.
- Delis, K. T., Nicolaidis, A. N., & Wolfe, J. H. N. (2001). Peripheral Sympathetic Autoregulation in Arterial Calf Inflow Enhancement with Intermittent Pneumatic Compression. *European Journal of Vascular and Endovascular Surgery*, *22*(4), 317-325.
doi:10.1053/ejvs.2001.1466
- Dobesh, P. D., Stacy, Z. A., & Persson, E. L. (2009). Pharmacologic therapy for intermitten claudication. *Pharmacotherapy*, *29*(5), 526-533.
- Dougherty, J. M. (1999). *The autonomic modulation of heart rate in healthy middle-aged adults*. (M.Sc.), Queen's University, Kingston, Ontario, Canada.

- Erdem, A., Ayhan, S. S., Ozturk, S., Ozlu, M. F., Alcelik, A., Sahn, S., . . . Yazici, M. (2015). Cardiac autonomic function in healthy young smokers. *Toxicology and Industrial Health, 31*(1), 67-72.
- Fagard, R. H. (2001). Exercise characteristics and the blood pressure response to dynamic physical training. *Medicine & Science in Sports & Exercise, 33*(6).
- Fei, L., Anderson, M. H., Statters, D. J., Malik, M., & Camm, A. J. (1995). Effects of passive tilt and submaximal exercise on spectral heart rate variability in ventricular fibrillation patients without significant structural heart disease. *American Heart Journal, 129*(2), 285-290.
- Fisher, J. P. (2013). Autonomic control of the heart during exercise in humans: role of skeletal muscle afferents. *Experimental Physiology, 99*(2), 300-305.
- Fletcher, G. F., Blair, S. N., Blumenthal, J., Caspersen, C., Chaitman, B., Epstein, S., . . . Pina, I. L. (1992). Statement on Exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation, 86*(1), 340-344.
- Fowkes, F. G. R., Rudan, D., Rudan, I., Aboyans, V., Denenberg, J. O., McDermott, M. M., . . . Criqui, M. H. (2013). Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet, 382*, 1329-1340.
- Franchini, M., & Mannucci, P. M. (2011). Thrombogenicity and cardiovascular effects of ambient air pollution. *Blood pressure, 118*(9), 2405-2412.

- Frostegard, J. (2013). Immunity, atherosclerosis and cardiovascular disease. *Biomed Central Journal*, 11, 171-130.
- Gardner, A. W. (2002). Sex differences in claudication pain in subjects with peripheral arterial disease. *Medicine and Science in Sports and Exercise*, 34(11), 1695-1698.
doi:10.1249/01.MSS.0000035043.05178.58
- Gardner, A. W., Montgomery, P. S., Flinn, W. R., & Katzell, L. I. (2005). The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. *Journal of Vascular Surgery*, 42(4), 702-709.
- Gardner, A. W., Montgomery, P. S., Scott, K. J., Blevins, S. M., Afaq, A., & Nael, R. (2008). Association between daily ambulatory activity patterns and exercise performance in patients with intermittent claudication. *Journal of Vascular Surgery*, 48(5), 1238-1244.
- Gardner, A. W., Parker, D. E., Montgomery, P. S., Scott, K. J., & Blevins, S. M. (2011). Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication. *Journal of Vascular Surgery*, 48(5), 1238-1244.
- Gardner, A. W., & Poehlman, E. T. (1995). Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA*, 274(12), 975-980.
- Gardner, A. W., Skinner, J. S., Cantwell, B. W., & Smith, L. K. (1991). Progressive vs single-stage treadmill tests for evaluation of claudication. *Medicine and Science in Sports and Exercise*, 23, 402-408.
- Gibbins, I. (2013). Functional organization of autonomic pathways. *Organogenesis*, 9(3), 169-175.

- Gobel, F. L., Nordstrom, L. A., Nelson, R. R., Jorgensen, C. R., & Wang, Y. (1978). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation*, *57*(3), 549-556.
- Goernig, M., Schroeder, R., Roth, T., Truebner, S., Palutke, I., Figulla, H. R., . . . Voss, A. (2008). Peripheral arterial disease alters heart rate variability in cardiovascular patients. *Pacing and clinical electrophysiology*, *31*(7), 858-862. doi:10.1111/j.1540-8159.2008.01100.x; 10.1111/j.1540-8159.2008.01100.x
- Goldie, C. L., Brown, C. A., Hains, S. M., Parlow, J. L., & Birtwhistle, R. (2013). Synergistic Effects of Low-Intensity Exercise Conditioning and beta-Blockade on Cardiovascular and Autonomic Adaptation in Pre- and Postmenopausal Women With Hypertension. *Biological research for nursing*, *15*(4), 433-442. doi:10.1177/1099800412461562; 10.1177/1099800412461562
- Goldsmith, R. L., Bloomfield, D. M., & Rosenwinkel, E. T. (2000). Exercise and Autonomic function. *Coronary Artery Disease*, *11*, 129-135.
- Gorre, F., & Vandekerckhove, H. (2010). Beta-blockers: Focus on mechanism of action. Which beta-blocker, when and why? *Acta Cardiologica*, *65*(5), 565-570.
- Grassi, G., Seravalle, G., Calhoun, D. A., Bolla, G. B., Giannattasio, C., Marabini, M., . . . Mancia, G. (1994). Mechanisms responsible for sympathetic activation by cigarette smoking in humans. *Circulation*, *90*, 248-253.
- Gregoire, J., Tuck, S., Yamamoto, Y., & Hughson, R. L. (1996). Heart rate variability at rest and exercise: influence of age, gender, and physical training. *Canadian journal of applied physiology = Revue canadienne de physiologie appliquee*, *21*(6), 455-470.

- Grenon, S. M., Vittinghoff, E., Owens, C. D., Conte, M. S., Whooley, M., & Cohen, B. E. (2013). Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: Insights from the Herra and Soul Study. *Vascular Medicine*, *18*(4), 176-184.
- Gropelli, A., Giorgi, D., Omboni, S., Parati, G., & Mancia, G. (1992). Persistent blood pressure increase induced by heavy smoking. *Journal Hypertension*, *10*, 495-499.
- Grossman, P. (1992). Respiratory and cardiac rhythms as windows to central and autonomic bio-behavioural regulation: selection of window frames, keeping the panes clean and viewing the neural topography. *Biological Psychology*, *34*, 131-161.
- Haggenmiller, C., Baumert, J. H., Adt, M., & Frey, A. W. (1996). Modulation of respiratory science arrhythmia by breathing pattern. *Clinical Science*, *91*, s1.
- Hamburg, N. M., & Balady, G. J. (2015). Exercise rehabilitation in peripheral artery disease. Functional impact and mechanisms of benefits. *Circulation*, *123*, 87-97.
- Harris, P. R. E., Stein, P. K., Fung, G. L., & Drew, B. J. (2013). Prognostic value of heart rate turbulence for risk assessment in patients with unstable angina and non-ST elevation myocardial infarction. *Vascular health and risk management*, *9*, 465-473.
- Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: influences of sex and aging. *Physiology*, *29*(1), 8-15.
- Harte, C. B., & Meston, C. M. (2014). Effects of smoking cessation on heart rate variability among long-term male smokers. *International Journal of Behavioural Medicine*, *21*, 302-309.

- Hayano, J., Mukai, S., Sakakibara, M., Okada, A., Takata, K., & Fujinami, T. (1994). Effects of respiratory interval on vagal modulation of heart rate. *American Journal of Physiology*, 267, H33-H40.
- Hayano, J., Yamada, A., Mukai, S., Sakakibara, M., Yamada, M., Nobuyuki, O., . . . Takata, K. (1991). Severity of coronary atherosclerosis correlates with the respiratory component of heart rate variability. *American Heart Journal*, 4(1), 1070-1079.
- Hayano, J., Yamada, M., Sakakibara, Y., Fujinami, T., Yokoyama, K., Watanabe, Y., & Takata, K. (1990). Short- and long-term effects of cigarette smoking on heart rate variability. *American Journal of Cardiology*, 65, 1990.
- Haynes, R. B., McDonald, H. P., & Garg, A. X. (2002). Helping patients follow prescribed treatment: clinical applications. *JAMA*, 288(22), 2880-2883.
- Hiatt, W. R. (2001). Medical treatment of peripheral arterial disease and claudication. *New England Journal of Medicine*, 344(21), 1608-1621.
- Hiatt, W. R., Armstrong, E. J., Larson, C. J., & Brass, E. P. (2015). Pathogenesis of the limb manifestations and exercise limitations in peripheral artery disease. *Circulation Research*, 116, 1527-1539.
- Hiatt, W. R., Regensteiner, J. G., Hargarten, M. E., Wolfel, E. E., & Brass, E. P. (1990). Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*, 81, 602-609.
- Hirsch, A. T., & Duval, S. (2013). The global pandemic of peripheral artery disease. *Lancet*, 382, 1312-1314.
- Hua, L. P., Brown, C. A., Hains, S. J., Godwin, M., & Parlow, J. L. (2009). Effects of low-intensity exercise conditioning on blood pressure, heart rate, and autonomic modulation

- of heart rate in men and women with hypertension. *Biological research for nursing*, 11(2), 129-143. doi:10.1177/1099800408324853; 10.1177/1099800408324853
- Huikuri, H. V., Pikkujamsa, S. M., Airaksinen, K. E., Ikaheimo, M. J., Rantala, A. O., Kauma, H., . . . Kesaniemi, Y. A. (1996). Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. *Circulation*, 94(2), 122-125.
- Izquierdo-Porrera, A. M., Gardner, A. W., Bradham, D. D., Montgomery, M. S., Sorkin, J. D., Powel, C. C., & Katzel, L. I. (2005). Relationship between objective measures of peripheral artery disease severity to self-reported quality of life in older adults with intermittent claudication. *Journal of Vascular Surgery*, 41(4), 625-630.
- Izquierdo-Porrera, A. M., Gardner, A. W., Powell, C. C., & Katzel, L. I. (2000). Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *Journal of Vascular Surgery*, 31, 670-677.
- Jagoda, A., Myers, J. N., Kaminsky, L. A., & Whaley, M. H. (2014). Heart rate response at the onset of exercise in an apparently healthy cohort. *European Journal of Applied Physiology*, 114, 1367-1375.
- Jelinek, H. F., De Silva, D., Bursyein, F. S., A., Khalaf, K., Khandoker, A., & Al-Aubaidy, H. (2013). Association of ankle brachial index with heart rate variability in a rural screening clinic. *Computing in Cardiology*, 40, 755-758.
- Kamath, M. V., & Fallen, E. L. (1995). *Heart Rate Variability* (M. Malik & A. J. Camm Eds.). New York: Futura Publishing Company.
- Kamath, M. V., Fallen, E. L., & McKelvie, R. (1991). Effects of steady state exercise on the power spectrum of heart rate variability. *Medicine and Science in Sports and Exercise*, 23, 428-434.

- Kardos, A., Watterich, G., de Menezes, R., Csanady, M., Casadei, B., & Rudas, L. (2001). Determinants of spontaneous baroreflex sensitivity in healthy subjects. *Journal of Applied Physiology*, *84*(2), 576-583.
- Kleiger, R. E., Stein, P. K., & Bigger, J. T. J. (2005). Heart rate variability: Measurement and clinical utility. *A. N. E.*, *10*(1), 88-101.
- Klein, S., & Hage, J. J. (2006). Measurement, calculation, and normal range of the ankle-arm Index: A bibliometric analysis and recommendation for standardization. *Annals of Vascular Surgery*, *20*, 282-292.
- Kotamaki, M. (1995). Smoking induced differences in autonomic responses in military pilot candidates. *Clinical Autonomic Research*, *5*, 31-36.
- Kruidenier, L. M., Nicolai, S. P., Willigendael, E. M., de Bie, R. A., Prins, M. H., & Teijink, J. A. W. (2009). Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC cardiovascular disorders*, *9*:9.
- Laitinen, T., Hartikainen, J., Vanninen, E., Niskanen, L., Geelen, G., & Lansimies, E. (1998). Age and gender dependency of baroreflex sensitivity in healthy subjects. *Journal of applied physiology (Bethesda, Md.: 1985)*, *84*(2), 576-583.
- Langbein, W. E., Collins, E. G., Orebaugh, C., Maloney, C., Williams, K. J., Littooy, F. N., & Edwards, L. C. (2002). Increasing exercise tolerance of persons limited by claudication pain. *Journal of Vascular Surgery*, *35*, 887-893.
- Leicht, A. S., Crowther, R. G., & Golledge, J. (2011). Influence of peripheral arterial disease and supervised walking on heart rate variability. *Journal of Vascular Surgery*, *54*(5), 1352-1359.

- Lewis, M. J. (2005). Heart rate variability analysis: a tool to assess cardiac autonomic function. *CIN: Computers, Informatics, Nursing*, 23(6), 335-341.
- Liao, D., Barnes, R. W., Chambless, L. E., Simpson, R. J., Jr., Sorlie, P., & Heiss, G. (1995). Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability--the ARIC study. Atherosclerosis Risk in Communities. *The American Journal of Cardiology*, 76(12), 906-912.
- Liao, D., Cai, J., Rosamond, W. D., Barnes, R. W., Hutchinson, R. G., Whitsel, E. A., . . . Heiss, G. (1997). Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC study. Atherosclerosis risk in communities study. *American Journal of Epidemiology*, 145, 696-706.
- Lim, S.-J., & Kim, C. (2014). Effects of autogenic training on stress response and heart rate variability in nursing students. *Asian Nursing Research*, 8, 286-292.
- Lipsitz, L. A., Mietus, J., Moody, G. B., & Goldberger, A. L. (1990). Spectral characteristics of heart rate variability before and during postural tilt. *Circulation*, 81, 1803-1810.
- Lovell, M., Harris, K., Forbes, T., Twillman, G., Abramson, B., Criqui, M. H., . . . Peripheral Arterial Disease, C. (2009). Peripheral arterial disease: lack of awareness in Canada. *The Canadian journal of cardiology*, 25(1), 39-45.
- Makris, G. C., Lattimer, C. R., Lavidia, A., & Geroulakos, G. (2012). Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. *European Journal of Vascular and Endovascular Surgery*, 44(6), 569-575.
- Maksimovic, M., Vlajinac, H., Radak, D., Marinkovic, J., Djuriscic, N., & Jorga, J. (2010). Relationship between sociodemographic, anthropometric and biochemical characteristics

- and degree of peripheral artery disease. *Srpski Arhiv za Celokupno Lekarstvo*, 138(9-10), 584-589.
- Malik, M., & Camm, A. J. (1995). *Heart rate variability*. Armonk, NY: Futura Publishing Company.
- Mannarino, E., Pasqualini, L., Menna, M., Maragoni, G., & Orlandi, U. (1989). Effects of physical training on peripheral vascular disease: A controlled study. *Angiology*, 40(1), 5-10.
- Manzano, B. M., Vanderlei, L. C. M., Ramos, E. M., & Ramos, D. (2011). Acute effects of smoking on autonomic modulation: Analysis by Poincare Plot. *Arquivos Brasileiros de Cardiologia*, 96(2), 154-160.
- Marsico, F., Ruggiero, D., Parent, A., Pirozzi, E., Musella, F., Iudice, F. L., . . . Perrone-Filardi, P. (2013). Prevalence and severity of asymptomatic coronary and carotid artery disease in patients with lower-limbs arterial disease. *Atherosclerosis*, 228, 386-389.
- Martinez, C. A., Carmeli, E., Barak, S., & Stopka, C. B. (2009). Changes in pain-free walking based on time in accommodating pain-free exercise therapy for peripheral arterial disease. *Journal of Vascular Nursing*, 27(1), 2-7.
- Mattu, G. S., Heran, B. S., & Wright, J. M. (2004). Overall accuracy of the BpTRU--an automated electronic blood pressure device. *Blood pressure monitoring*, 9(1), 47-52.
- McDermott, M. M. (2013). Functional impairment in peripheral artery disease and how to improve it in 2013. *Current Cardiology Reports*, 15, 347-354.
- McDermott, M. M., Criqui, M. H., Lui, K., Guralnik, J. M., Greenland, P., Martin, G. J., & Pearce, W. (2000). Lower ankle/brachial index, as calculated by averaging the dorsal

- pedis and posterior tibial artery pressures, and association with leg functioning in peripheral artery disease. *Journal of Vascular Surgery*, 32, 1164-1171.
- McDermott, M. M., Liu, K., Greenland, P., Guralnik, J. M., Criqui, M. H., Chan, C., . . . Clark, E. (2004). Functional decline in peripheral arterial disease. Associations with the ankle-brachial index and leg-symptoms. *JAMA*, 292(453-462).
- McDermott, M. M., Liu, K., Guralnik, J. M., Martin, G. J., Criqui, M. H., & Greenland, P. (1998). Measurement of walking endurance and walking velocity with questionnaire: validation of the walking impairment questionnaire in men and women with peripheral arterial disease. *Journal of Vascular Surgery*, 28, 1072-1081.
- McHorney, C. A., Ware, J. E., & Raczek, A. E. (1993). The MOS 36-Item Short-Form Health Survey (SF-36):II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care*, 31(3), 247-263.
- Mendonca, G. V., Pereira, F. D., & Fernhall, B. (2011). Effects of cigarette smoking on cardiac autonomic function during dynamic exercise. . *Journal of Sports Sciences*, 29(9), 879-886.
- Mika, P., Spodaryk, K., Cencora, A., Unnithan, V. B., & Mika, A. (2005). Experimental model of pain-free treadmill training in patients with claudication. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*, 84(10), 756-762.
- Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., . . . Altman, D. G. (2010). CONSORT 2010 Explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal*. doi:BMJ2010;340:c869doi:10.1136/bmj.c869

- Montgomery, P. S., & Gardner, A. W. (1998). The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *Journal of the American Geriatric Society*, *46*, 706-711.
- Mouser, M. J., Zlabek, J. A., Ford, C. L., & Mathiason, M. A. (2009). Community trial of home based exercise therapy for intermittent claudication. *Vascular Medicine*, *14*, 103-107.
- Murphy, M. N., Mizuno, M., Mitchell, J. H., & Smith, S. A. (2011). Cardiovascular regulation by skeletal muscle reflexes in health and disease. *American Journal of Physiology - Heart Circulation Physiology*, *301*, H1191-H1204.
- Nakamura, Y., Yamamoto, Y., & Muraoka, I. (1993). Autonomic control of HR during physical exercise and fractal dimension of HR variability. *Journal of Applied Physiology*, *74*, 875-881.
- Narkiewicz, K., van de Borne, P. J. H., Hausberg, M., Cooley, R. L., Winniford, M. D., Davison, D. E., & Somers, V. K. (1998). Cigarette smoking increases sympathetic outflow in humans. *Circulation*, *98*, 528-534.
- Neutens, J. J., & Rubinson, L. (2010). *Research techniques for the health sciences*. San Francisco: Benjamin Cummings.
- Nicolai, S. P., Kruidenier, L. M., Rouwet, E. V., Graffius, K., Prins, M. H., & Tejjink, J. A. W. (2009). The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. *Journal of Vascular Surgery*, *50*(1), 89-94.
- Nicolai, S. P., Tejjink, J. A. W., & Prins, M. H. (2010). Multi-center randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *Journal of Vascular Surgery*, *52*, 348-355.

- Ohman, A. M. (2016). Chronic stable angina. *New England Journal of Medicine*, 375, 1167-1176.
- Oka, R. K. (2006). Peripheral arterial disease in older adults: management of cardiovascular disease risk factors. *The Journal of cardiovascular nursing*, 21(5 Suppl 1), S15-20.
- Ori, Z., Monir, J., Weiss, J., Sayhouni, X., & Singer, D. (1992). Heart rate variability: frequency domain analysis. *Cardiology clinics*, 10, 499-537.
- Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., . . . Piccaluga, E. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulation Research*, 59(2), 178-193.
- Parr, B., Noakes, T. D., & Derman, E. W. (2008). Factors predicting walking intolerance in patients with peripheral arterial disease and intermittent claudication. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*, 98(12), 958-962.
- Patwardhan, A. R., Evans, J., Bruce, E., & Knapp, C. (2001). Heart rate variability during sympatho-excitatory challenges: comparison between spontaneous and metronomic breathing. *Integrative Physiological and Behavioural Science*, 36(2), 109-120.
- Patwardhan, A. R., Vallurupalli, S., Evans, J. M., Bruce, E. N., & Knapp, C. F. (1995). Override of the spontaneous respiratory pattern generator reduces cardiac parasympathetic influence. *Journal of Applied Physiology*, 79, 1048-1054.
- Perini, R., Orizio, C., Milesi, S., Biancardi, L., Baselli, G., & Veicsteinas, A. (1993). Body position affects the power spectrum of heart rate variability during dynamic exercise. *European Journal of Applied Physiology*, 66, 207-213.

- Pescatello, L. S., Arena, R., Riebe, D., & Thompson, P. D. (2014). *ACSM's Guidelines for Exercise Testing and Prescription. 9th Ed.* (Eighth ed.).
- Piccirillo, G., Cacciafesta, M., Viola, E., Santagada, E., Nocco, M., Lionetti, M., . . . Marigliano, V. (2001). Influence of aging on cardiac baroreflex sensitivity determined non-invasively by power spectral analysis. *Clinical Science, 2001*, 267-274.
- Pinna, G. D., Maestri, R., La Rovere, M. T., Gobbi, E., & Fanfulla, F. (2006). Effect of paced breathing on ventilatory and cardiovascular variability parameters during short-term investigations of autonomic function. *American Journal of Physiology - Heart and Circulatory Physiology, 290*.
- Planas, A., Clara, A., Marrugat, J., Pou, J. M., Gasol, A., de Moner, A., . . . Vidal-Barraquer, F. (2002). Age at onset of smoking is an independent risk factor in peripheral artery disease development. *Journal of Vascular Surgery, 35*(3), 506-509.
- Pomeranz, B., Macaulay, R. J. B., Caudill, M. A., Kutz, I., Adam, D., Gordon, D., . . . Benson, H. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *American Journal of Physiology, 248*, H151-H153.
- Regensteiner, J. G., Gardner, A., & Hiatt, W. R. (1996). Exercise testing and exercise rehabilitation for patients with peripheral arterial disease: status in 1997. *Vascular Medicine, 2*(2), 147-155.
- Regensteiner, J. G., & Hiatt, W. R. (1998). Exercise in the management of peripheral arterial disease. In J. L. Roitman (Ed.), *ACSM's resource manual for guidelines for exercise testing and prescription* (pp. 281-287; 233). Baltimore: Williams & Wilkins.

- Rejeski, W. J., Tian, L., Liao, Y., & McDermott, M. M. (2008). Social cognitive constructs and the promotion of physical activity on patients with peripheral artery disease. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 28, 65-72.
- Ritti-Dias, R. M., Meneses, A. L., Parker, D. E., Montgomery, P. S., Khurana, A., & Gardner, A. W. (2011). Cardiovascular responses to walking in patients with peripheral artery disease. *Medicine & Science in Sports & Exercise*, 43(11), 2017-2023.
- Rosenwinkel, E. T., Bloomfield, D. M., Arwady, M. A., & Goldsmith, R. L. (2001). Exercise and autonomic function in health and cardiovascular disease. *Cardiology clinics*, 19(3), 369-387.
- Sakpal, T. V. (2010). Sample size estimation in clinical trial. *Perspectives in Clinical Research*, 1(2), 67 - 69.
- Sandercock, G. R. H., Hodges, L. D., Das, S. K., & Brodie, D. A. (2007). The impact of short term supervised and home-based walking programmes on heart rate variability in patients with peripheral arterial disease. *Journal of Sports Sciences and Medicine*, 6, 471-476.
- Sanderson, B., Askew, C., Stewart, I., Walker, P., Gibbs, H., & Green, S. (2006). Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *Journal of Vascular Surgery*, 44(1), 119-127.
- Schorr, E. N., & Treat-Jacobson, D. (2013). Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: A review. *Vascular Medicine*, 95-111.
- Seals, D. R. (2014). Edward F. Adolph Distinguished Lecture: The remarkable anti-aging effects of aerobic exercise on systemic arteries. *Journal of Applied Physiology*, 117, 425-439.

- Shammas, N. W. (2007). Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vascular health and risk management*, 3(2), 229-234.
- Smyth, A., O'Donnell, M., Lamelas, P., Teo, K., Rangarajan, S., & Yusuf, S. (2016). Physical activity and anger or emotional upset as triggers of acute myocardial infarction. *Circulation*, 134, 1059-1067.
- Swansburg, M. L. (2005). *Maternal cardiac autonomic function and fetal behaviour in preeclamptic and normotensive pregnancies*. (M.Sc.), Queen's University, Kingston, Ontario, Canada.
- Tan, K. H., Cotterrell, D., Sykes, K., Sissons, G. R. J., de Cossart, L., & Edwards, P. R. (2000). Exercise training for claudicants: Changes in blood flow, cardiorespiratory status, metabolic functions, blood rheology and lipid profile. *European Journal of Vascular and Endovascular Surgery*, 20, 72-78.
- Tarvainen, M. P., Niskanen, J., Lipponen, J. A., Ranta-aho, P. O., & Karjalainen, P. A. (2014). Kubios HRV - Heart rate variability analysis software. *Computer Methods and Programs in Biomedicine*, 113, 210-220.
- Tarvainen, M. P., Ranta-aho, P. O., & Karjalainen, P. A. (2002). An advanced detrending method with application to HRV analysis. *IEEE Transactions on Biomedical Engineering*, 49, 172-175.
- Taylor, J. C., Li, Z., Yang, H. T., Laughlin, M. H., & Terjung, R. L. (2008). Alpha-adrenergic inhibition increases collateral circuit conductance in rats following acute occlusion of the femoral artery. *Journal of Physiology*, 586(6), 1649-1667.
- TFESCNASPE. (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the

- North American Society of Pacing and Electrophysiology. *European heart journal*, 17(3), 354-381.
- Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2009). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, 141, 122-131.
- Treat-Jacobson, D., Bronas, U. G., & Leon, A. S. (2009). Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vascular Medicine*, 2009(14), 203-213.
- Tsai, J. C., Chan, P., Wang, C. H., Jeng, C., Hsieh, M. H., Kao, P. F., . . . Liu, J. C. (2002). The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. *Journal of Internal Medicine*, 252(5), 448-455.
- Tsuji, H., Larson, M. G., Venditti, F. J. J., Manders, E. S., Evans, J. C., Feldman, C. L., & Levy, D. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation*, 94, 2850-2855.
- Vavra, A. K., & Kibbe, M. R. (2009). Women and peripheral arterial disease. *Women's health (London, England)*, 5(6), 669-683. doi:10.2217/whe.09.60; 10.2217/whe.09.60
- W.H.O. (2009). *Cardiovascular diseases* (Vol. 2010): World Health Organization.
- Westerhof, B. E., Gisolf, J., Karemaker, J. M., Wesseling, K. H., Secher, N. H., & van Lieshout, J. J. (2006). Time course analysis of baroreflex sensitivity during postural stress. *American Journal of Physiology-Heart and Circulatory Physiology*, 291, H2864-H2874.
- Widener, J. M. (2011). Peripheral arterial disease and disability from NHANES 2001-2004 data. *Journal of Vascular Nursing*, 29, 104-112.

- Willigendael, E. M., Teijink, J. A., Bartelink, M. L., Kuiken, B. W., Boiten, J., Moll, F. L., . . . Prins, M. H. (2004). Influence of smoking on incidence and prevalence of peripheral artery disease. *Journal of Vascular Surgery*, *40*(6), 1158-1165.
- Wullink, M., Stoffers, H. E., & Kuipers, H. (2001). A primary care walking exercise program for patients with intermittent claudication. *Medicine and Science in Sports and Exercise*, *33*, 1629-1634.
- Yamamoto, Y., & Hughson, R. L. (1991). Coarse-graining spectral analysis: new method for studying heart rate variability. *Journal of Applied Physiology*, *71*(3), 1143-1150.
- Yamamoto, Y., Hughson, R. L., & Peterson, J. C. (1991). Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. *Journal of Applied Physiology*, *71*(3), 1136-1142.
- Yusuf, S., Hawkin, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*, *364*, 937-952.
- Zetterquist, S. (1970). The effect of active training on the nutritive blood flow in exercising ischemic legs. *Scandinavian Journal of Clinical and Laboratory Investigation*, *25*, 101-111.
- Zwierska, I., Walker, R. D., Choksy, S. A., Male, J. S., Pockley, A. G., & Saxton, J. M. (2005). Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. *Journal of Vascular Surgery*, *42*(6), 1122-1130. doi:10.1016/j.jvs.2005.08.021

Appendices

Appendix A – Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING
HOSPITALS RESEARCH ETHICS BOARD

March 2, 2011

This Ethics Application was subject to:

- Full Board Review
Meeting Date:
 Expedited Review

Ms. Ingrid Brenner
School of Nursing
Cataraqui Building
92 Barrie Street
Queen's University

Dear Ms. Brenner,

Study Title: Effect of low-intensity exercise training on individuals with peripheral artery disease
Co-Investigators: Dr. A. Brown and Dr. P. Brown

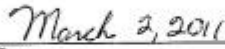
I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol, Participant Instructions and Activity Log (Exercise Group), Participant Instructions and Activity Log (Comparison Group), SF-36 Health Survey, Walking Impairment Questionnaire (WIQ), Human Activity Profile, Borg's Rating of Perceived Exertion, Borg's CR10 Scale, Physical Activity Readiness Questionnaire (PAR-Q), the consent form for the exercise group and the consent form for the comparison group for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- **Reporting of Amendments:** If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see <http://www.queensu.ca/vpr/reb.htm>).
- **Reporting of Serious Adverse Events:** Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.
- **Reporting of Complaints:** Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. **Note:** All documents supplied to participants must have the contact information for the Research Ethics Board.
- **Annual Renewal:** Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,



Chair, Research Ethics Board



Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL - BINDER COPY - FILE COPY

Study Code: NURS-268-11

- Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined by the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number : #FWA00004184
#IRB00001173

**Current 2011 membership of the Queen's University Health Sciences
& Affiliated Teaching Hospitals Research Ethics Board**

Dr. A.F. Clark	Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)
Dr. H. Abdollah	Professor, Department of Medicine, Queen's University
Dr. R. Brison	Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans	Community Member
Dr. S. Horgan	Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services Assistant Professor, Department of Psychiatry
Ms. D. Morales	Community Member
Dr. W. Racz	Emeritus Professor, Department of Pharmacology & Toxicology, Queen's
Dr. B. Simchison	Assistant Professor, Department of Anesthesiology, Queen's University
Dr. A.N. Singh	WHO Professor in Psychosomatic Medicine and Psychopharmacology Professor of Psychiatry and Pharmacology Chair and Head, Division of Psychopharmacology, Queen's University Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital
Dr. E. Tsai	Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University
Rev. J. Warren	Community Member
Ms. K. Weisbaum	LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)



Amendment Acknowledgment/Approval Letter

February 14, 2012

Ms. Ingrid Brenner
School of Nursing
Queen's University

File #: 6005832 NURS-268-11 Effect of Low-Intensity Exercise Training on Individuals With Peripheral Artery Disease

Dear Ms. Brenner

I am writing to acknowledge receipt of the following:

- Request to compensate participants for their time and travel expenses
- Notification that all blood testing will take place at Hotel Dieu Hospital
- Provision of a copy of the revised consent form

I have reviewed these materials and hereby give my approval. Receipt of these amendments will be reported to the Health Sciences Research Ethics Board.

Yours sincerely,

Albert F. Clark

Albert Clark, Ph.D.
Chair
Research Ethics Board



QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement, 1998" prepared by the Medical Research Council, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. M. Evans, Community Member

Dr. S. Horgan, Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services Assistant Professor, Department of Psychiatry

Ms. J. Hudacin, Community Member

Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital

Dr. W. Racz, Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. B. Simchison, Assistant Professor, Department of Anaesthesiology and Perioperative Medicine, Queen's University

Dr. A.N. Singh, WHO Professor in Psychosomatic Medicine and Psychopharmacology Professor of Psychiatry and Pharmacology Chair and Head, Division of Psychopharmacology, Queen's University Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital

Dr. E. Tsai, Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University

Dr. E. VanDenKerkhof, Professor, School of Nursing and Department of Anaesthesiology and Perioperative Medicine, Queen's University

has reviewed the request for renewal of Research Ethics Board approval for the project **Effect of Low-Intensity Exercise Training on Individuals With Peripheral Artery Disease** as proposed by **Ms. Ingrid Brenner** of the **School of Nursing**, at Queen's University. The approval is renewed for one year, effective **March 02, 2012**. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert F. Clark

Date: February 29, 2012

Chair, Research Ethics Board

Renewal 1 Renewal 2 Extension Code# NURS-268-11 Romeo file# 6005832



QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement, 1998" prepared by the Medical Research Council, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

- Dr. A.F. Clark**, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)
- Dr. H. Abdollah**, Professor, Department of Medicine, Queen's University
- Dr. C. Cline**, Assistant Professor, Department of Medicine, Director, Office of Bioethics, Queen's University, Clinical Ethicist, Kingston General Hospital
- Dr. R. Brison**, Professor, Department of Emergency Medicine, Queen's University
- Dr. M. Evans**, Community Member
- Ms. J. Hudacin**, Community Member
- Dr. J. MacKenzie**, Pediatric Geneticist, Department of Paediatrics, Queen's University
- Mr. D. McNaughton**, Community Member
- Ms. P. Newman**, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital
- Ms. S. Rohland**, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
- Dr. B. Simchison**, Assistant Professor, Department of Anaesthesiology and Perioperative Medicine, Queen's University
- Dr. A. Singh**, Professor, Department of Psychiatry, Queen's University
- Dr. J. Tang**, Medical Resident, Department of Emergency Medicine, Queen's University
- Ms. K. Weisbaum**, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

has reviewed the request for renewal of Research Ethics Board approval for the project **Effect of Low-Intensity Exercise Training on Individuals With Peripheral Artery Disease** as proposed by **Ms. Ingrid Brenner** of the **School of Nursing, at Queen's University**. The approval is renewed for one year, effective **March 02, 2013**. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert F. Clark

_____, Date: February 19, 2013

Chair, Research Ethics Board

Renewal 1[] Renewal 2 [X] Extension [] Code# NURS-268-11 Romeo file# 6005832

Appendix B – Informed Consent



QUEEN'S UNIVERSITY SCHOOL OF NURSING RESEARCH INFORMATION SHEET AND CONSENT FORM

TITLE OF RESEARCH PROJECT: Effects of low-intensity exercise training on individuals with peripheral artery disease.

BACKGROUND INFORMATION:

You are being invited to participate in a research study being conducted by Ingrid Brenner, R.N., Ph.D. (Doctoral student in Nursing). This study is designed to evaluate the effects of a 12-week walking program on peripheral artery disease and is part of a larger study directed by Dr. Peter Brown M.D. to determine optimum conservative management of patients with severe peripheral artery disease. Ingrid Brenner will read through this consent form with you, describe the procedures in detail and answer any questions you may have. This study has been approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Aim of the study:

The purpose of this study is to determine the extent to which participation in a low-intensity exercise program improves your circulation and reduces any symptoms (such as leg pain) that you may have due to your condition known as peripheral artery disease.

You will be considered for the study if you are at least 18 years of age, have an ankle to arm blood pressure ratio of 0.9 or less, have medical clearance to participate in an exercise program and are not currently involved in another exercise program.

Visits and tests to be performed as part of the study:

This study will require 2 visits over the next 12 weeks, to a research laboratory located at Hotel Dieu Hospital. Each visit will be a total of approximately 3 hours in length. You will be asked to refrain from making any changes in your normal diet or in your exercise routine that may differ from the study guidelines over your 12-week involvement in the study.

At each visit you will be asked to complete 2 questionnaires. A quality of life questionnaire (i.e., SF-36) is being used to assess your physical function and any limitations imposed by your condition. It consists of 4 questions (with subsections). The Walking Impairment Questionnaire (WIQ) also consists of 14 questions, but these are designed to determine how much your peripheral artery disease affects your walking. Each questionnaire will take about 10 minutes to complete.

You will have your height, weight, waist and hip circumference and skin-fold measurements made at five different locations on your body (front of arm, back of arm, upper back, hip region

and calf). The skin-fold measurement will involve a brief pinching of the skin and application of measuring device known as a skin-fold caliper.

You are advised to avoid eating a large meal two hours in advance and to refrain from strenuous physical activity for 24 hours prior to testing. Please refrain from consuming alcohol or caffeine 12 hours before coming to the exercise laboratory at Hotel Dieu Hospital. We will measure your heart rate and blood pressure while you lay quietly on a cot, while you stand and during light exercise on a stationary bike. For this, we will attach electrodes to your arms and one leg to record your heart rate. We will take blood pressure measurements in your arm, leg and finger by using blood pressure measuring devices. This will take about 15 minutes in each position and up to 10 minutes during light exercise on an exercise bike.

You will walk on a treadmill at a slow speed (beginning at 1.1 miles per hour and gradually increasing to 2 mph) starting on a flat surface (0% incline) for 1.5 minutes followed by a gradual rise in the surface every 2 minutes thereafter. You will continue walking until you feel too tired to walk any more or have too much pain in your legs. You will be asked to tell us when you first feel pain, when you have pain that would cause you to stop walking normally and when you have maximum pain (when you need to stop walking). HR and BP will be monitored at regular intervals for 10 min following the treadmill exercise test.

In order to assess your ability to walk, a 6 minute-walk test will be performed. For this test you will walk up and down a hospital corridor (approximately 89.5 ft in length) and the distance that you walk will be recorded.

You will be asked to have a fasting blood sample taken, by a qualified laboratory technician at a recognized medical laboratory, at the beginning and end of the study.

Intervention:

At the end of the first test session, you will be randomly assigned to either an experimental group or a comparison group. You will be asked to refrain from making dietary changes during the 12-week study period. If you are in the low-intensity exercise group, you will be given verbal and written instructions for a 12-week progressive walking program, an exercise log, a perception of exertion scale and a pain scale. You will walk at a prescribed heart rate and a perceived effort corresponding to fairly light to somewhat hard. You will keep any leg pain to a minimum (≤ 2 on a 0-10 pain scale). You will be asked to walk 5 days-week⁻¹, beginning at 0.4 km-day⁻¹ for two weeks, with a gradual progression every week to 3.2 km-day⁻¹ by the end of 12-weeks. You also will be taught to monitor your HR response to exercise by palpation of your radial artery.

If you are assigned to the comparison group, you will be given verbal and written instructions to record daily physical activities and you will be asked to continue the same level of activity as you have done prior to your involvement in the study. At the end of 12 weeks, you will be provided with an explanation of what the program involves, written instructions and materials for the low-intensity walking program should you wish to do the program that the other group did.

You will be receiving follow-up phone calls, after the first week of the intervention and then at regular 2-week intervals, to address any questions or concerns you may have regarding the exercise intervention or log book and to ensure that you are complying with the study guidelines.

Personal health information:

In order for the researchers to gain a better understanding of your health status and any physical conditions that you may have (that could affect your ability to perform in this study), or would benefit the researchers in determining the results of the study, you agree to grant access to your KGH medical records.

Special research techniques to be used (randomization):

As a study participant, you will participate in either a 12-week low-intensity walking program OR a comparison group which does not participate in the exercise program. Assignment to the comparison group will help us document the effects (or lack of effects) of physical inactivity on your condition.

Alternative therapies:

At this time, your attending physician has recommended lifestyle change and/or medications as a means of reducing the effect of peripheral artery disease. Exercise is one of the first lifestyle changes that physicians may recommend. Other lifestyle changes include smoking cessation and diet interventions. You may choose other treatments rather than enter the study.

Risks/Side-effects:

Although there are minimal risks associated with the low-intensity walking program and the treadmill exercise test, patients with peripheral artery disease have an increased risk of experiencing leg pain, chest pain (angina) or, in the worst-case scenario, a heart attack (cardiac arrest) during exertion. For individuals who are not used to exercising, there is the risk of experiencing muscle soreness 24-48 hours following the exercise test or exercise session (for members of the exercise group). You will have your heart rate and blood pressure monitored continuously during the exercise test and will be taught to take your own heart rate during the exercise session. There also is the slight risk of bruising, infection and discomfort at the site of the blood sample. In addition, you may experience some discomfort or slight bruising (if you are on blood thinning medication) at the site of each skin-fold measurement as a result of the pressure applied by application of the calipers.

Emergency contact persons: If you experience any untoward symptoms during or immediately after following the walking program, please contact your family physician or local emergency department. After contacting your physician or an emergency room, please notify the study investigators (Dr. Peter Brown, Kingston General Hospital, (613)-548-3232 ext. 4964, Dr. Ann Brown, School of Nursing, 613-533-6000, ext. 74763, Ingrid Brenner, 613-533-6000 ext. 74744, Dr. Jennifer Medves, School of Nursing, 613-533-6000, ext. 2668 of your symptoms or Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board).

Benefits:

While you may not benefit directly from this study, results from this study may improve the understanding of peripheral artery disease and may benefit patients in the future. If you are in the exercise group you may experience a decrease in symptoms associated with peripheral arterial disease, an improvement in walking ability and physical condition. If you are in either the exercise group or the control group, you will get the benefit of regular monitoring of your disease status.

Exclusions:

You will not be considered for this study if you are unable to read or write English; reside in a nursing home; are currently involved in an exercise program; are wheel-chair dependant; have other medical conditions (for example, angina, congestive heart failure, chronic obstructive pulmonary disease, severe arthritis or limb amputation) that could limit your participation in an exercise program or exercising testing; have non-compressible arteries preventing measurement of leg blood pressure; are cognitively impaired (for example have dementia or Alzheimer's disease). You may be removed from the study if there is a change in the type of medication or dose of medication that you were on between Time 1 and Time 2.

Confidentiality:

All information obtained during the course of this study is strictly confidential and will be protected at all times. You will be identified by a code known only to the research team. Data will be stored in locked files and access will be available only to the investigators of the study. You will not be identified in any publication or reports.

Voluntary nature of study/Freedom to withdraw or participate:

Your participation in this study is voluntary. You may withdraw from this study at any time for any reason and your withdrawal will not affect your future medical treatment or care with your physician or at this hospital.

Withdrawal of subject by principle investigator:

The study investigators reserve the right to withdraw you from the study if your attending physician wishes to change your medical treatment (including medication dose or type) or if you experience any symptoms (aside from leg pain) during the exercise test or training sessions.

Liability:

In the event of any injury that may be incurred as a result of study procedures, medical care will be provided to you until the medical problem is stabilized or resolved. By signing this consent form, you will not waive your legal right(s) nor release the investigators and sponsors from their professional and legal responsibilities.

Payment:

You will receive \$20.00 per test session as compensation for your time and to cover parking expenses. Travel expenses will also be provided at 40 cents a kilometer.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had purposes, procedures and technical language of the study explained to me. I have been given sufficient time to consider the above information and seek advice if I chose to do so. I have had the opportunity to ask questions and have had all of my questions answered to my satisfaction. I am voluntarily signing this form. I will receive a copy of this consent form for my information.

If at any time I have further questions, problems or adverse event, I can contact:

Principal Investigator: Dr. Peter Brown at 613-548-3232 ext. 4964.

Co-Investigator: Dr. Ann Brown at 613-533-6000 ext. 74763.

Ph.D. Student: Ingrid Brenner 613-533-6000 ext. 74744.

Director, Queen's School of Nursing: Dr. Jennifer Medves, R.N., Ph.D., at 613-533-6000 ext. 2668.

If I have questions regarding my rights as a research subject I can contact:
Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals
 Research Ethics Board at 613-533-6081.

 Signature of Participant

 Date

 Signature of Witness

 Date

STATEMENT OF INVESTIGATOR:

I have carefully explained to the participant, the nature of the above research study. I certify that to the best of my knowledge, the participant clearly understands the nature of the study and demands, benefits, and risks involved to participants in the study.

 Signature of Investigator

 Date

Appendix C – Exercise Protocol

Low Intensity Exercise Conditioning (Walking) Protocol © C. A .Brown

Week	Distance (km/day)	Distance (mile/day)	Total daily duration (min)	RPE	CR10 Pain Scale
1	0.4 km/day	.25 mile/day	20-30	13	≤ 2
2	0.4 km/day	.25 mile/day	15-30	13	≤ 2
3	0.8 km/day	.50 mile/day	30-40	13	≤ 2
4	0.8 km/day	.50 mile/day	20-30	13	≤ 2
5	1.2 km/day	.75 mile/day	45-60	13	≤ 2
6	1.2 km/day	.75 mile/day	35-50	13	≤ 2
7	1.6 km/day	1.0 mile/day	55-65	13	≤ 2
8	1.6 km/day	1.0 mile/day	45-60	13	≤ 2
9	2.4 km/day	1.5 mile/day	60-75	13	≤ 2
10	2.4 km/day	1.5 mile/day	50-60	13	≤ 2
11	3.22 km/day	2.0 mile/day	60-75	13	≤ 2
12	3.22 km/day	2.0 mile/day	50-60	13	≤ 2

(Brown, 1990; Brown et al., 1994)

Please do not exercise within 2 hours of eating a large meal or after consumption of alcohol or caffeine. It is advisable to do a 10-minute warm-up before and 10-minute cool-down after each walking session, to drink adequate liquids, to contact your family physician if you experience symptoms such as shortness of breath, chest pain or any injuries and illnesses.

NB. Total daily exercise should be performed without symptoms (i.e., no shortness of breath, chest pain or leg pain). Initially, begin walking 5 min, 4 times per day.

Maximum Target Heart Rate: _____

Frequency of Exercise: 5 days per week

Target Rating of Perceived Exertion: 11-13 (fairly light to somewhat hard)

Target Rating of Pain: ≤ 2

Appendix D - Measuring Your Heart Rate



<http://extension.missouri.edu/publications/DisplayPub.aspx?P=GH1900>

What is your heart rate (or pulse)?

Your heart rate (or pulse) is the number of times your heart beats in one minute. It can be felt in your neck (at the carotid artery) and in your wrist (at the radial artery). Heart rates will vary between different individuals. It will be lower at rest and will increase with exercise.

How to take your heart rate (pulse)

1. It is recommended that you measure your heart rate at your wrist, not in your neck. This is because applying too much pressure to the carotid artery in the neck can slow your heart rate, causing you to feel faint as well as to miscalculate your actual heart rate.
2. When measuring your heart rate, use two fingers - your index and middle - not your thumb. The thumb has a pulse of its own and this can interfere with your calculation of your heart rate.
3. When assessing your heart rate, it is recommended that you use a watch or clock that has a second hand.
4. Count the number of beats that you feel for ten seconds and multiply that number by six to get your heart rate (pulse).
Number of beats in 10 seconds: _____ x 6 = _____ heart rate (pulse)
5. Practice finding your pulse so you can begin counting immediately after stopping exercise. Your heart rate will have significantly slowed down if it takes you 20 to 30 seconds to find your pulse after you stop exercising.

Adopted from: [How to Measure Your Pulse by Hand When Exercising | eHow.com](http://www.ehow.com/how_9127_measure-pulse-hand.html#ixzz1A6eZjvk9C)
http://www.ehow.com/how_9127_measure-pulse-hand.html#ixzz1A6eZjvk9C

Appendix E – Borg’s Perceived Exertion Scale

Borg’s RPE Scale Instructions: While exercising we want you to rate your perception of exertion, i.e., how heavy and strenuous the exercise feels for you. The perception of exertion depends mainly on the strain and fatigue in your muscles and on your feeling of breathlessness or aches in the chest.

Look at this rating scale; we want you to use this scale from 6 to 20, where 6 means “no exertion at all” and 20 means “maximal exertion”.

9	Corresponds to very light exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes.
13	On the scale is “somewhat hard” exercise, but it still feels OK to continue.
17	“very hard” is very strenuous. A healthy person can still go on, but he or she really has to push him or herself. It feels very heavy and the person is very tired.
19	On the scale is an extremely strenuous exercise level. For most people, this is the most strenuous exercise they have ever experienced.

To appraise your feeling of exertion as honestly as possible, without thinking about what the actual load is. Don't underestimate it, but don't overestimate it either. It's your own feeling of effort and exertion that's important, not how it compares to other people's. What other people think is not important either. Look at the scale below and the expressions and then give a number.

6	No exertion at all
7	
	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix F - Borg's Pain Scale

Basic Instruction: Use the scale below to rate the leg pain (if any) experienced during exercise. 10, "Extremely strong – Max P," is the main anchor. It is the strongest perception (P) that you have ever experienced. It may be possible, however, to experience or to imagine something even stronger. Therefore, "Absolute maximum" is placed somewhat further down the scale without a fixed number and marked with a "*". If you perceive an intensity stronger than 10, you may use a higher number.

Start with a *verbal expression* and then choose a *number*. If your perception is "Very weak," say 1; if "Moderate," say 3; and so on. You are welcome to use half values (such as 1.5, or 3.5 or decimals, for example, 0.3, 0.8, or 2.3). It is very important that you answer what you perceive and not what you believe you ought to answer. Be as honest as possible and try not to overestimate or underestimate the intensities.

Scaling Pain: What are your worst experiences of pain? If you use 10 as the strongest pain you have ever experienced or can think of, how strong would you say that your three worst pain experiences have been?

10 = "Extremely strong-max P" is your main point of reference. It is anchored in your previously experienced worst pain, which you just described, the "Max P".

* = Your worst pain experienced, the "Max P," may not be the highest possible level. There may be pain that is still worse. If that feeling is somewhat stronger, you will say 11 or 12. If it is much stronger, 1.5 times "Max P", you will say 15!

0	Nothing at all	No "P"
0.3		
0.5	Extremely weak	Just noticeable
1	Very Weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Max P"
11		
*	Absolute maximum	Highest possible

Appendix H - Activity Log Comparison Group

Week _____

ID: _____

Date(s): _____

Please indicate on the table below, any physical activity that you participated in during the week.

<u>Day</u>	Type of Physical Activity (describe)	Duration (min)	Heart Rate (Pulse)	Borg's Perceived Exertion #
<u>Mon</u>				
<u>Tues</u>				
<u>Wed</u>				
<u>Thurs</u>				
<u>Fri</u>				
<u>Sat</u>				
<u>Sun</u>				

Appendix I - Participant Demographic Form

Date ____/____/____ (day/month/year)

Participant ID: _____

What is your sex? (check one) Male Female

Home Address:

Contact phone number:

What is your email address?

What is your date of birth? _____

Age: _____ (years)

What is your living arrangement (check one)?

- Living alone
- Living with spouse or significant other
- Living with other family members

What is your highest level of education completed? (check one):

- Grade 8 or less
- Grade 9-13 without diploma
- High school diploma
- Trade or professional school certificate / diploma
- Some university

University degree

Post-graduate degree

What is your occupational status (check one)?

Looking for work

Working

Retired/Not working

Occupation: _____

Are you a smoker (check one)?

No

Yes If yes, number of years smoking: _____

Average # of cigarettes per day? _____ OR # packages per day? _____

What is your alcohol consumption?

None

Less than 5 drinks per week

More than or equal to 5 drinks per week

Do you exercise regularly (more than twice a week for at least 20 minutes)?

No

Yes

If yes, please list the type(s) of exercise performed?

Medical Information

Family Physician: _____, Phone # _____

Primary Diagnosis: _____

How long have you had peripheral artery disease? _____

What part of your body does it affect?

- Calf (below the knee)
- Thigh or buttocks area
- Other (please specify _____)

Where is it located?

- Right side of body
- Left side
- Both sides

Menopausal Status (women only) (please check one box):

- Premenopausal
- Peri-menopausal (presently going through menopause)
- Post-menopausal
- Not sure

Please list any other medical conditions that you may have:

Appendix J – Walking Impairment Questionnaire

Participant ID: _____

Walking impairment: These questions ask about the reasons why you have difficulty walking. We would like to know how much difficulty you had walking during the past week. By difficulty, we mean how hard it was or how much physical effort it took to walk because of each of these. Please circle your response below.

PAD SPECIFIC QUESTIONS	DEGREE OF DIFFICULTY				
	None	Slight	Some	Much	Very
Pain, aching or cramps in your calves (or buttocks)?					
RIGHT LEG	4	3	2	1	0
LEFT LEG	4	3	2	1	0
BOTH LEGS	4	3	2	1	0

DIFFERENTIAL DIAGNOSIS	DEGREE OF DIFFICULTY				
	None	Slight	Some	Much	Very
1. Pain, stiffness or aching in your joints (ankles, knees or hips)?	4	3	2	1	0
2. Weakness in one or both of your legs?	4	3	2	1	0
3. Pain or discomfort in your chest?	4	3	2	1	0
4. Shortness of breath?	4	3	2	1	0
5. Heart palpitations?	4	3	2	1	0
6. Other problems? (please list)	4	3	2	1	0

Walking distance: Report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

DISTANCE	DEGREE OF DIFFICULTY				
	None	Slight	Some	Much	Unable
1. Walking indoors such as around your home?	4	3	2	1	0
2. Walking 50 feet?	4	3	2	1	0
3. Walking 150 feet (1/2 block)?	4	3	2	1	0
4. Walking 300 feet (1 block)?	4	3	2	1	0
5. Walking 600 feet (2 blocks)?	4	3	2	1	0
6. Walking 900 feet (3 blocks)?	4	3	2	1	0
7. Walking 1500 feet (5 blocks)?	4	3	2	1	0

Walking speed: Report the degree of difficulty that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week:

SPEED	DEGREE OF DIFFICULTY				
	None	Slight	Some	Much	Unable
1. Walking one block slowly?	4	3	2	1	0
2. Walking one block at an average speed?	4	3	2	1	0
3. Walking one block quickly?	4	3	2	1	0
4. Walking or jogging one block?	4	3	2	1	0

Stair climbing: For each of these questions, report the degree of physical difficulty that best describes how hard it was for you to climb stairs without stopping to rest during the past week:

STAIRS	DEGREE OF DIFFICULTY				
	None	Slight	Some	Much	Unable
1. Climbing one flight of stairs?	4	3	2	1	0
2. Climbing two flights of stairs?	4	3	2	1	0
3. Climbing three flights of stairs?	4	3	2	1	0

Appendix K – Quality of Life Questionnaire

SF-36 HEALTH SURVEY (Physical Component)

Participant ID: _____

Date when completing form: _____

INSTRUCTIONS: This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

When complete, please return the questionnaire in the envelope provided.

1. In general, would you say your health is:

		(Circle one)
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

		(Circle one)
Much better than 1 year ago	1
Somewhat better than 1-year ago	2
About the same as one year ago	3
Somewhat worse than 1 year ago	4
Much worse than 1-year ago	5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (circle one number on each line)

Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling or stooping	1	2	3
Walking more than a mile	1	2	3
Walking half a mile	1	2	3
Walking one hundred yards	1	2	3
Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the kind of work or other activities	1	2

Appendix L - Editing HRV Data

The original (raw) data file that was obtained for each participant in each test condition contained beat-by-beat heart rate measures. Using the general spectral analysis program computer program developed by Yamamoto and Hughson, the data was converted into R-R interval data and saved under a different file extension (.rr). This file was then run through the GSA040 program, designed by Hughson and Yamamoto, using the command line: gsa040 filename.rr start time end time filename.gsa. This produced an R-R interval time series graph with time on the X-axis and R-R interval data on the Y-axis, in milliseconds, which could be edited.

The editing procedure was used to remove motion artifact and obvious outliers from the time series data set. A toggle (red mark) located at the zero-time mark was moved across the time points using the arrow key. Any point that was greater than 30% from the previous data point was considered an outlier (Kamath & Fallen, 1995), marked and deleted from the graph. The deletion of the series of data points that made up the artifact (or outlier) was accomplished by marking each point. By pressing the “enter” key while the toggle was positioned on the point, the part to be deleted was marked. When all points within a series were marked, the “delete” key was pressed and the outlier was removed.

Once the editing was completed, the computer program generated a second-time series plot, which could no longer be edited. This data was converted into a frequency distribution using fast Fourier transformation.

Appendix M – Disease Severity

Disease severity and location of claudication symptoms of participants and dropouts in the study
(values are numbers, (%)).

	All volunteers (n = 48)	Drop-outs (n = 15)	Remaining (n = 33)
Disease Severity			
0 (borderline > 0.90- 1.00)	2 (4)	0 (0)	2 (6)
1 (mild = 0.70 – 0.90)	5 (10)	3 (20)	2 (6)
2 (moderate, 0.50 – 0.69)	20 (42)	6 (40)	14 (42)
3 (severe, < 0.50)	21 (44)	6 (40)	15 (46)
Disease Location			
Calf	36 (74)	10 (67)	26 (79)
Thigh or buttocks	6 (13)	2 (13)	4 (12)
Other	6 (13)	3 (20)	3 (9)

Appendix N – Medication Use

Medication use by volunteers, dropouts and remaining participants.

Medication	All Participants (n = 48)	Drop Outs (n = 15)	Remaining (n = 33)
Antihypertensive medications			
Alpha-1 antagonists	2 (4)	6 (40)	2 (6)
ACE-inhibitors	19 (40)	3 (20)	16 (49)
Angiotensin II receptor-antagonist	7 (15)	3 (20)	4 (12)
Beta-blockers	15 (31)	5 (33)	10 (30)
Calcium channel blockers	12 (25)	5 (33)	7 (21)
Diuretics	15 (31)	5 (33)	10 (30)
Cholesterol-lowering agents			
Statins	37 (77)	10 (67)	27 (82)
Ezetrol	4 (8)	1 (7)	3 (9)
Platelet/clot formation inhibitors			
ASA	24 (50)	6 (40)	18 (55)
Clopidogrel	12 (25)	8 (53)	4 (12)
Warfarin	6 (13)	2 (13)	4 (12)
Diabetic medications			
Metformin	12 (25)	4 (26)	9 (27)
Insulin	3 (6)	1 (7)	2 (6)

Appendix O – Body Composition

Body composition at entry into the study (Week 1).

Measure	All volunteers	Dropouts	Remaining
	(n = 48)	(n = 15)	(n = 33)
Body composition			
BMI	26.9 (4.9)	26.4 (4.3)	27.1 (5.2)
Waist (cm)	97.2 (11.9)	96.1 (11.7)	97.7 (12.2)
W:H ratio	0.93 (0.08)	0.93 (0.08)	0.93 (0.08)
% Body fat	32.8 (9.3)	33.2 (8.7)	32.7 (9.7)

Appendix P – Chi Square Summary Tables at Entry

Chi-Squared Summary Tables of Participant Demographic Characteristics and Medication Use at Entry

Participant Smoking Status at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.470	1	.493
Likelihood Ratio	.472	1	.695
Linear-by-linear Association	.460	1	.498
N of valid cases	48		

Participant Smoking Status at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.048	1	.827
Likelihood Ratio	.048	1	.827
Linear-by-linear Association	.047	1	.828
N of valid cases	48		

Participant Drinking Status at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	4.114	1	.043
Likelihood Ratio	4.482	1	.034
Linear-by-linear Association	4.029	1	.045
N of valid cases	48		

Participant Drinking Status at Entry (Comparison Group vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.028	1	.867
Likelihood Ratio	.028	1	.866
Linear-by-linear Association	.028	1	.868
N of valid cases	48		

Participant Self-Reported Diabetes Status at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	3.017	1	.082
Likelihood Ratio	3.002	1	.083
Linear-by-linear Association	2.954	1	.086
N of valid cases	48		

Participant Self-Reported Diabetes Status at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	2.341	1	.126
Likelihood Ratio	2.338	1	.126
Linear-by-linear Association	2.292	1	.130
N of valid cases	48		

Participant Self-Reported Hyperlipidemia Status at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	11.473	1	.001
Likelihood Ratio	13.982	1	.003
Linear-by-linear Association	11.234	1	.000
N of valid cases	48		

Participant Self-Reported Hyperlipidemia Status at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.767	1	.381
Likelihood Ratio	.796	1	.372
Linear-by-linear Association	.751	1	.386
N of valid cases	48		

Participant Self-Reported Hypertension Status at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.148	1	.701
Likelihood Ratio	.147	1	.702
Linear-by-linear Association	.145	1	.704
N of valid cases	48		

Participant Self-Reported Hypertension Status at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.738	1	.390
Likelihood Ratio	.735	1	.391
Linear-by-linear Association	.723	1	.395
N of valid cases	48		

Participant Status Selective Alpha-1 agonist use at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	2.971	1	.085
Likelihood Ratio	3.667	1	.056
Linear-by-linear Association	2.907	1	.088
N of valid cases	46		

Participant Selective Alpha 1 agonist use at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.036	1	.849
Likelihood Ratio	.036	1	.850
Linear-by-linear Association	.035	1	.851
N of valid cases	46		

Participant use of ACE inhibitors at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.266	1	.606
Likelihood Ratio	.267	1	.605

Linear-by-linear Association	.260	1	.610
N of valid cases	46		

Participant use of ACE inhibitors at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.025	1	.875
Likelihood Ratio	.025	1	.875
Linear-by-linear Association	.024	1	.876
N of valid cases	46		

Participant use of angiotensin II receptor antagonist at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.008	1	.928
Likelihood Ratio	.008	1	.928
Linear-by-linear Association	.008	1	.929
N of valid cases	46		

Participant use of angiotensin II receptor antagonist at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	2.863	1	.091
Likelihood Ratio	3.203	1	.073
Linear-by-linear Association	2.801	1	.094
N of valid cases	46		

Participant use of β -Blockers at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.224	1	.636
Likelihood Ratio	.223	1	.637
Linear-by-linear Association	.220	1	.639
N of valid cases	48		

Participant use of β -Blockers at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.962	1	.327
Likelihood Ratio	.445	1	.505
Linear-by-linear Association	.942	1	.332
N of valid cases	48		

Participant use of calcium channel blockers at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.457	1	.499
Likelihood Ratio	.465	1	.495
Linear-by-linear Association	.448	1	.503
N of valid cases	48		

Participant use of calcium channel blockers at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	2.286	1	.131
Likelihood Ratio	2.388	1	.122
Linear-by-linear Association	2.238	1	.135
N of valid cases	48		

Participant use of diuretics at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.025	1	.875
Likelihood Ratio	.025	1	.874
Linear-by-linear Association	.024	1	.876
N of valid cases	48		

Participant use of diuretics at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.814	1	.367
Likelihood Ratio	.811	1	.368
Linear-by-linear Association	.797	1	.372
N of valid cases	48		

Participant use of statins at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	1.216	1	.270
Likelihood Ratio	1.262	1	.261
Linear-by-linear Association	1.191	1	.275
N of valid cases	48		

Participant use of statins at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	2.293	1	.130
Likelihood Ratio	2.288	1	.130
Linear-by-linear Association	2.245	1	.134
N of valid cases	48		

Participant use of Ezetrol at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.480	1	.488
Likelihood Ratio	.508	1	.476
Linear-by-linear Association	.470	1	.493
N of valid cases	46		

Participant use of Ezetrol at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
------------------	-------	----	-------------

Pearson Chi-Square	.609	1	.435
Likelihood Ratio	.643	1	.423
Linear-by-linear Association	.595	1	.440
N of valid cases	46		

Participant use of ASA at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.300	1	.584
Likelihood Ratio	.300	1	.584
Linear-by-linear Association	.293	1	.588
N of valid cases	46		

Participant use of ASA Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.067	1	.796
Likelihood Ratio	.067	1	.796
Linear-by-linear Association	.066	1	.798
N of valid cases	46		

Participant use of Clopidogrel at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.069	1	.793
Likelihood Ratio	.069	1	.793
Linear-by-linear Association	.067	1	.796
N of valid cases	31		

Participant use of Clopidogrel at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	7.467	1	.006
Likelihood Ratio	10.438	1	.001
Linear-by-linear Association	7.311	1	.007
N of valid cases	48		

Participant use of Warfarin at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	1.728	1	.189
Likelihood Ratio	1.913	1	.167
Linear-by-linear Association	1.690	1	.194
N of valid cases	48		

Participant use of Warfarin at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.119	1	.730
Likelihood Ratio	.119	1	.731
Linear-by-linear Association	.117	1	.733
N of valid cases	46		

Participant use metformin of at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.506	1	.477
Likelihood Ratio	.502	1	.479
Linear-by-linear Association	.495	1	.482
	46		

Participant use of metformin at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	1.458	1	.227
Likelihood Ratio	1.450	1	.229
Linear-by-linear Association	1.426	1	.232
N of valid cases	46		

Participant use of Insulin at Entry (Men vs Women)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.852	1	.356
Likelihood Ratio	.839	1	.360
Linear-by-linear Association	.833	1	.361

Participant use of Insulin at Entry (Comparison vs Walking Group)

Chi-Square Tests	Value	Df	Asymp. Sig.
Pearson Chi-Square	.134	1	.714
Likelihood Ratio	.138	1	.711
Linear-by-linear Association	.131	1	.717
N of valid cases	46		

Appendix Q - ANOVA Summary Tables at Entry

Anthropometric Measures

Between-Subjects Factors – Hip Circumference

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		20

Between Subjects Effects- Hip Circumference

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	657.335	3	219.112	2.536	.069
Intercept	495511.305	1	495511.305	5734.518	.000
Group (G)	108.564	1	108.564	1.256	.268
Sex (S)	488.650	1	488.650	5.655	.022
G X S	22.628	1	2.650	.262	.611
Error	3801.976	44	22.628		
Total	523777.082	48	86.409		
Corrected total	4459.311	47			

Between-Subjects Factors – Waist to Hip ratio

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		20

Between Subjects Effects - Waist to Hip Ratio

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	.072	3	.024	5.311	.003
Intercept	39.024	1	39.024	8637.365	.000
Group (G)	.001	1	.001	.257	.615
Sex (S)	.072	1	.072	15.911	.000
G X S	.002	1	.002	.369	.547
Error	.199	44	.005		
Total	42.142	48			
Corrected total	.271	47			

Between-Subjects Factors – Percent Body Fat

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		20

Between Subjects Effects – Percent Body Fat

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	1927.310	3	.642.437	12.981	.000

Intercept	51806.658	1	51806.658	1046.779	.000
Group (G)	83.296	1	83.296	1.683	.201
Sex (S)	1736.992	1	1736.992	35.097	.000
G X S	75.782	1	75.782	1.531	.222
Error	2177.627	44	49.492		
Total	55876.540	48			
Corrected total	4104.937	47			

Resting Circulatory Measures at Entry (Week 1)

Between-Subjects Factors – Log Ankle Brachial Index at Week 1

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		20

Between Subjects Effects – Log Ankle Brachial Index at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	.103	3	.034	1.707	.179
Intercept	3.925	1	3.925	194.379	.000
Group (G)	.050	1	.050	2.495	.121
Sex (S)	.044	1	.044	2.159	.149
G X S	.001	1	.001	.036	.851
Error	.889	44	.020		
Total	5.160	48			
Corrected total	.992	47			

Between-Subjects Factors – Resting Heart Rate at Week 1

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		20

Between Subjects Effects – Resting Heart Rate at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	756.480	3	252.160	1.825	.156
Intercept	188663.627	1	188663.627	1365.595	.000
Group (G)	524.727	1	524.727	3.798	.058
Sex (S)	40.797	1	40.797	.295	.590
G X S	85.097	1	85.097	.616	.437
Error	6078.817	44	85.097		
Total	204725.380	48	138.155		
Corrected total	6835.297	47			

Between-Subjects Factors – Resting Systolic Blood Pressure at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Resting Systolic Blood Pressure at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	881.943	3	293.981	.547	.653
Intercept	760365.042	1	760365.042	1413.644	.000
Group (G)	108.372	1	108.372	.201	.656
Sex (S)	566.878	1	566.878	1.054	.310
G X S	408.569	1	408.569	.760	.388
Error	23666.536	44	537.876		
Total	838611.000	48			
Corrected total	24548.479	47			

Between-Subjects Factors – Resting Diastolic Blood Pressure at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Resting Diastolic Blood Pressure at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	806.981	3	268.994	2.468	.074
Intercept	212147.518	1	212147.518	1946.826	.000
Group (G)	8.978	1	8.978	.082	.775
Sex (S)	791.440	1	791.440	7.263	.010
G X S	64.719	1	64.719	.594	.445
Error	4794.724	44	108.971		
Total	234861.690	48			
Corrected total	5601.705	47			

Between-Subjects Factors – Resting Mean Arterial Pressure at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Resting Mean Arterial Pressure at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	713.974	3	237.991	1.304	.285
Intercept	354713.535	1	354713.535	1943.734	.000
Group (G)	43.215	1	43.215	.237	.629
Sex (S)	651.382	1	651.382	3.569	.065

G X S	120.247	1	120.247	.659	.421
Error	8029.596	44	182.491		
Total	390228.901	48			
Corrected total	8743.570	47			

Between-Subjects Factors – Resting Mean Rate Pressure Product (RPP) at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Resting Mean Rate Pressure Product (RPP) at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	15755784	3	5251927.98	1.124	.350
Intercept	3.110E+9	1	3.110E+9	665.437	.000
Group (G)	4689117.58	1	4689117.58	1.003	.322
Sex (S)	4812690.98	1	4812690.98	1.030	.316
G X S	4684859.94	1	4684859.94	1.003	.322
Error	205619334	44	4673166.68		
Total	3.526E+9	48			
Corrected total	221375118	47			

Resting HRV Measures at Entry

Between-Subjects Factors – Log LF power at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Log LF Power at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	1.794	3	.598	1.784	.164
Intercept	144.705	1	144.705	431.772	.000
Group (G)	1.307	1	1.307	3.899	.055
Sex (S)	.347	1	.347	1.035	.315
G X S	.037	1	.037	.112	.740
Error	14.746	44	.335		
Total	170.660	48			
Corrected total	16.540	47			

Between-Subjects Factors – Log HF power at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Log HF power at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	1.330	3	.443	.932	.433
Intercept	161.135	1	161.135	338.789	.000
Group (G)	.061	1	.061	.129	.722
Sex (S)	1.193	1	1.193	2.508	.120
G X S	.001	1	.001	.001	.970
Error	20.927	44	.476		
Total	188.382	48			
Corrected total	22.257	47			

Between-Subjects Factors – Log Total power at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Log Total power at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	2.081	3	.694	2.531	.069
Intercept	322.158	1	322.158	1175.277	.000
Group (G)	1.256	1	1.256	4.581	.038
Sex (S)	.575	1	.575	2.099	.154
G X S	.035	1	.035	.128	.723
Error	12.061	44	.274		
Total	354.488	48			
Corrected total	14.142	47			

Between-Subjects Factors – Log PNS Indicator at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Log PNS Indicator at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	.781	3	.260	1.618	.199
Intercept	29.044	1	29.044	180.507	.000
Group (G)	.546	1	.546	3.392	.072

Sex (S)	.210	1	.210	1.306	.259
G X S	.088	1	.008	.048	.827
Error	7.080	44	.161		
Total	40.432	48			
Corrected total	7.861	47			

Between-Subjects Factors – Log SNS Indicator at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subject Effects – Log SNS Indicator at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	.986	3	.329	1.614	.200
Intercept	.442	1	.442	2.168	.148
Group (G)	.802	1	.802	3.939	.053
Sex (S)	.253	1	.253	1.244	.271
G X S	.028	1	.028	.138	.712
Error	8.963	44	.204		
Total	10.174	48			
Corrected total	9.949	47			

Performance Measures at Entry

Between-Subjects Factors – Log Pain Free Walking Distance (PFWD) at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	26
Men or Women	0.00	Men	28
	1.00	Women	19

Between Subjects Effects – Log Pain Free Walking Distance (PFWD) at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	.478	3	.159	1.955	.135
Intercept	185.264	1	185.264	2275.120	.000
Group (G)	.073	1	.073	.899	.348
Sex (S)	.018	1	.018	.218	.643
G X S	3.17	1	.317	3.898	.055
Error	3.502	43	.081		
Total	199.373	47			
Corrected total	3.979	46			

Between-Subjects Factors – Log Functional Claudication Distance (FCD) at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	26
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Functional Claudication Distance (FCD) at Week 1

Source	Type III SS	df	Mean Square	F	Sig.
Corrected model	.269	3	.090	1.223	.313
Intercept	228.893	1	228.893	3126.041	.000
Group (G)	.121	1	.121	1.659	.205
Sex (S)	.011	1	.011	.145	.705
G X S	.082	1	.082	1.119	.296
Error	3.149	43	.073		
Total	246.759	47			
Corrected total	3.417	46			

Between-Subjects Factors – Log Maximal Walking Distance (MWD) at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	26
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – Log Maximal Walking Distance (MWD) at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	.591	3	.197	3.174	.034
Intercept	248.593	1	248.593	4007.911	.000
Group (G)	.227	1	.227	3.659	.062
Sex (S)	.055	1	.055	.881	.353
G X S	.189	1	.189	3.046	.088
Error	2.667	43	.062		
Total	268.657	47			
Corrected total	3.258	46			

Between-Subjects Factors – Six Min Walk Test at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	26
Men or Women	0.00	Men	27
	1.00	Women	20

Between Subjects Effects – Six Minute Walk Test at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	175108.43	3	58369.476	.541	.657

Intercept	47252387.7	1	47252387.7	438.227	.000
Group (G)	59.829	1	59.829	.001	.981
Sex (S)	23308.731	1	23308.731	.216	.644
G X S	131303.020	1	131303.020	1.218	.276
Error	4636533.88	43	107826.369		
Total	54327128.5	47			
Corrected total	4811642.31	46			

WIQ Scores at Entry

Between-Subjects Factors – WIQ Distance Score at Week 1

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women

Between Subjects Effects – WIQ Distance Score at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	1905.346	3	635.115	.767	.519
Intercept	76306.624	1	76306.624	92.180	.000
Group (G)	46.338	1	46.338	.056	.814
Sex (S)	580.218	1	580.218	.701	.407
G X S	1322.871	1	1322.871	1.598	.213
Error	36423.348	44	827.803		
Total	116184.699	48			
Corrected total	38328.694	47			

Between-Subjects Factors – WIQ Speed Score at Week 1

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women

Between Subjects Effects – WIQ Speed Score at Week

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	517.696	3	172.565	.237	.870
Intercept	87914.820	1	87914.820	120.737	.000
Group (G)	14.265	1	14.265	.020	.889
Sex (S)	1.154	1	1.154	.002	.968
G X S	498.195	1	498.195	.684	.413
Error	32038.741	44	728.153		
Total	124610.024	48			
Corrected total	32556.437	47			

Between-Subjects Factors – WIQ Stair Climbing Score at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – WIQ Stair Climbing Score at Week 1

Source	Type III SS	Df		F	Sig.
Corrected model	2716.868	3	905.623	1.185	.326
Intercept	99196.399	1	99196.399	129.799	.000
Group (G)	437.136	1	437.136	.572	.453
Sex (S)	1682.158	1	1682.158	2.201	.145
G X S	302.228	1	302.228	.395	.533
Error	33626.101	44	764.230		
Total	146954.169	48			
Corrected total	36342.968	47			

Between-Subjects Factors – WIQ Overall Score at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	20

Between Subjects Effects – WIQ Overall Score at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	890.844	3	296.948	.548	.652
Intercept	87563.944	1	87563.944	161.683	.000
Group (G)	63.666	1	63.666	.118	.733
Sex (S)	35.997	1	35.997	.066	.798
G X S	643.481	1	643.481	1.188	.282
Error	23829.365	44	541.576		
Total	117756.041	48			
Corrected total	24720.210	47			

SF-36 Scores at EntryBetween-Subjects Factors – SF-36 Physical Function Score at Week 1

		Value label	N
Group	0.00	Comparison	21
	1.00	Walking	27
Men or Women	0.00	Men	28
	1.00	Women	19

Between Subjects Effects – SF-36 Physical Function Score at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	2999.617	3	999.872	2.442	.077
Intercept	99989.543	1	99989.543	244.222	.000
Group (G)	559.470	1	559.470	1.366	.249
Sex (S)	2071.920	1	2071.920	5.061	.030*
G X S	135.959	1	135.959	.332	.567
Error	17605.056	43	409.420		
Total	137256.210	47			
Corrected total	20604.673	46			

Between-Subjects Factors – SF-36 Role Limitation Score at Week 1

	Value label	N
Group	0.00	Comparison
	1.00	Walking
Men or Women	0.00	Men
	1.00	Women
		21
		27
		28
		19

Between Subjects Effects – SF-36 Role Limitation Score at Week 1

Source	Type III SS	Df	Mean Square	F	Sig.
Corrected model	9191.560	3	3063.853	1.677	.186
Intercept	80515.390	1	80515.390	44.073	.000
Group (G)	7283.173	1	7283.173	3.987	.052
Sex (S)	768.050	1	768.050	.420	.520
G X S	3672.559	1	3672.559	2.010	.163
Error	78555.786	43	1826.879		
Total	189216.917	47			
Corrected total	87747.347	46			

Appendix R - ANOVA Summary Tables over Time

Circulatory Measures over Time

Ankle-Brachial Index (ABI)

Descriptive Statistics (ABI)

Variable	Group	Mean	Std. Deviation
ABIWeek1	Comparison	.4793	.17052
	Walking	.5639	.19563
	Total	.5255	.18662
ABIWeek12	Comparison	.4387	.12432
	Walking	.6178	.20989
	Total	.5364	.19588

Between-Subjects Factors (Log ABI)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (Log ABI)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
Time	.001	1	.001	.102	.752
Time X Group	.037	1	.037	5.197	.030
Error (Time)	.218	31	.007		
<u>Between subjects</u>					
Intercept	18.035	1	18.035	310.081	.000
Group	.284	1	.284	4.890	.035
Error	1.803	31	.058		

Descriptive Statistics (Log ABI)

Variable	Group	Mean	Std. Deviation
Log ABIWeek1	Comparison	-.3409	.13668
	Walking	-.2751	.15932
	Total	-.3050	.15088
Log ABIWeek12	Comparison	-.3738	.12107
	Walking	-.2349	.15893
	Total	-.2980	.15736

Between-Subjects Factors (Log ABI)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (Log ABI)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
Time	.000	1	.000	.041	.841
Time X Group	.022	1	.022	4.073	.052
Error (Time)	.166	31	.005		
<u>Between subjects</u>					
Intercept	6.136	1	6.136	163.787	.000
Group	.171	1	.171	4.575	.040
Error	1.161	31	.037		

BpTRU Heart Rate (HR)Descriptive Statistics (HR)

Variable	Group	Mean	Std. Deviation
HRrest1	Comparison	65.5133	13.43699
	Walking	62.9056	12.00179
	Total	64.0909	12.54007
HRstand1	Comparison	71.6667	16.49531
	Walking	73.1667	16.82872
	Total	72.4848	16.43381
HRsex1	Comparison	95.7333	27.62366
	Walking	87.8889	24.19015
	Total	91.4545	25.69909
HRrest12	Comparison	65.9333	11.37332
	Walking	62.8333	12.01592
	Total	64.2424	11.65126
HRstand12	Comparison	74.1333	13.94820
	Walking	70.6667	16.42810
	Total	72.2424	15.21724
HRex12	Comparison	85.8667	19.71173
	Walking	79.0556	14.69483
	Total	85.1212	17.22121

Between-Subjects Factors (HR)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (HR)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
Time	1191.978	1	1191.978	6.012	.020*
Time X Beta-blockers	917.378	1	917.378	4.627	.040*
Time X Group	53.908	1	53.908	.272	.606
Error(time)	5947.991	30	198.266		
Condition	13482.243	2	6741.121	70.963	.000*
Condition X Beta-Blockers	89.405	2	44.702	.471	.627
Condition X Group	324.598	2	162.299	1.709	.190
Error(Condition)	5699.694	60	94.995		
Time X Condition	604.769	2	302.384	4.894	.011*
Time X Condition X Beta-Blockers	39.117	2	19.559	.317	.730
Time X Condition X Group	87.165	2	43.583	.705	.498
Error (Time X Condition)	3706.967	60	61.783		
<u>Between subjects</u>					
Intercept	270057.629	1	270057.629	664.819	.000
Beta-blockers	653.066	1	653.066		.215
Group	173.440	1	173.440		.518
Error	12186.369	30	406.212		

Tests of Within-Subject Contrasts (HR)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		397.326	1	397.326	6.012	.020*
T X BB		305.793	1	305.793	4.627	.040*
T X G		17.696	1	17.696	.272	.606
Error (Time)		1982.664	30	66.089		
C	S vs R	3219.186	1	3219.186	32.896	.000
	E vs R	26185.456	1	26185.456	130.841	.000
C X BB	S vs R	10.350	1	.106	.106	.747
	E vs R	165.094	1	.825	.825	.371
C X G	S vs R	60.519	1	60.519	.618	.438
	E vs R	293.177	1	293.177	1.465	.236
Error (C)	S vs R	2935.823	30	97.861		
	E vs R	6003.939	30	200.131		
T X C	S vs R	23.110	1	23.110	.720	.403
	E vs R	1038.998	1	1038.998	5.747	.023*
T X C X BB	S vs R	58.083	1	58.083	1.809	.189
	E vs R	.006	1	.006	.000	
T X C X G	S vs R	91.716	1	91.716	2.856	.101
	E vs R	9.505	1	9.505	.053	.820
Error (Time X Condition)	S vs R	963.243	30	32.108		
	E vs R	5423.254	30	180.775		

Systolic Blood Pressure (SBP)Descriptive Statistics (SBP)

Variable	Group	Mean	Std. Deviation
SBPrest1	Comparison	129.333	16.70187
	Walking	124.3889	15.46206
	Total	126.6364	15.97815
SBPstand1	Comparison	131.000	17.70391
	Walking	120.5556	15.16273
	Total	125.3030	16.94566
SBPex1	Comparison	163.0667	30.14599
	Walking	162.5556	38.14249
	Total	162.7879	34.21326
SBPrest12	Comparison	119.4000	19.70787
	Walking	122.3389	15.95372
	Total	121.0030	17.53134
SBPstand12	Comparison	118.8667	20.96891
	Walking	117.5372	15.54908
	Total	118.1415	17.92375
SBPex12	Comparison	142.2667	29.76687
	Walking	148.9444	28.40976
	Total	145.9091	28.77213

Between-Subjects Factors (SBP)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (SBP)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	1340.531	1	1340.531	3.615	.067
T X Age (A)	2018.126	1	2018.126	5.442	.027*
T X G	1670.055	1	1670.055	4.503	.042*
Error (T)	11125.151	30	370.838		
C	375.025	2	187.512	.563	.572
C X A	1826.057	2	913.029	2.742	.073
C X G	217.727	2	108.863	.327	.722
Error(C)	19980.057	60	333.001		
T X C	17.433	2	8.716	.040	.961
T X C X A	61.662	2	30.831	.140	.870
T X C X G	1.987	2	.994	.005	.996
Error (T X C)	13236.626	60	220.610		
<u>Between subjects</u>					
Intercept	5932.701	1	5932.701	11.638	.002
Beta-blockers	1916.651	1	1916.651	3.760	.062

Group	344.245	1	344.245	.675	.418
Error	15293.342	30	509.778		

Tests of Within-Subject Contrasts (SBP)

Source	Condition	SS	Df	MS	F	P
<u>Within subjects</u>						
T		893.697	1	893.697	3.615	.067
T X A		1345.417	1	1345.417	5.442	.027*
T X G		1113.370	1	1113.370	4.503	.042
Error(T)		7416.767	30	247.226		
C	S vs R	.004	1	.004	.000	.995
	E vs R	282.374	1	282.374	.690	.413
C X A	S vs R	1.299	1	1.299	.012	.912
	E vs R	1326.732	1	1326.732	3.243	.082
C X G	S vs R	166.801	1	166.801	1.581	.281
	E vs R	.077	1	.077	.000	.989
Error(C)	S vs R	3165.649	30	105.522		
	E vs R	12273.667	30	409.122		
T X C	S vs R	9.100	1	9.100	.041	.842
	E vs R	27.45	1	27.405	.026	.873
T X C X A	S vs R	4.068	1	4.068	.018	.894
	E vs R	155.749	1	155.749	.147	.704
T X C X G	S vs R	7.380	1	7.380	.033	.857
	E vs R	4.049	1	4.049	.004	.951
Error (T X C)	S vs R	6719.931	30	223.998		
	E vs R	31809.247	30	1060.308		
<u>Between subjects</u>						
Intercept		2966.351	1	2966.351	11.638	.002
Age		958.326	1	958.326	3.760	.062
Group		172.122	1	172.122	.675	.418
Error		7646.671	30	254.889		

BpTRU Systolic Blood Pressure (SBP) for the Control Group

Source		SS	Df	MS	F	P
<u>Within subjects</u>						
Time		244.427	1	244.427	4.207	.061
Time X Age		432.420	1	432.420	7.443	.017*
Error (Time)		755.232	13	58.095		
Condition	S vs R	1.335	1	1.335	.012	.915
	E vs R	24.605	1	24.605	.029	.867
Condition X Age	S vs R	.584	1	.586	.005	.944
	E vs R	621.647	1	621.647	.732	.408
Error (Condition)	S vs R	1470.280	13	113.098		
	E vs R	11035.153	13	848.858		
Time X Condition	S vs R	.874	1	.874	.008	.931
	E vs R	311.762	1	311.762	.471	.505
Time X Condition X Age	S vs R	2.949	1	2.949	.026	.874
	E vs R	195.314	1	195.314	.295	.596

Error (Time X Condition)	S vs R	1455.251	13	111.942		
	E vs R	8602.553	13	661.735		
<u>Between subjects</u>						
Intercept		6112.611	1	6112.611	9.144	.010
Age		241.539	1	241.539	.361	.558
Error		8690.069	13	1381.093		

BpTRU Systolic Blood Pressure (SBP) for the Exercise Group

Source		SS	Df	MS	F	P
<u>Within subjects</u>						
Time		189.599	1	189.599	1.029	.326
Time X Age		245.045	1	245.045	1.330	.266
Error (Time)		2948.396	16	184.275		
Condition	S vs R	.915	1	.915	.003	.957
	E vs R	920.536	1	920.536	1.124	.305
Condition X Age	S vs R	2.440	1	2.440	.008	.930
	E vs R	2441.251	1	2441.251	2.981	.103
Error (Condition)	S vs R	4860.589	16			
	E vs R	13102.747	16			
Time X Condition	S vs R	18.706	1	18.706	.159	.696
	E vs R	644.656	1	644.656	1.624	.221
Time X Condition X Age	S vs R	16.505	1	16.505	.140	.713
	E vs R	834.524	1	834.524	2.103	.166
Error (Time X Condition)	S vs R	1887.294	16	117.956		
	E vs R	6350.108	16	396.882		
<u>Between subjects</u>						
Intercept		847.007	1	847.007	2.280	.151
Age		2334.350	1	2334.350	6.284	.023
Error		5944.036	16	371.502		

Diastolic Blood Pressure (DBP)

Descriptive Statistics (DBP)

Variable	Group	Mean	Std. Deviation
DBPrest1	Comparison	68.5333	11.36955
	Exercise	67.4611	7.89886
	Total	67.9485	9.48561
DBPstand1	Comparison	75.8000	14.61017
	Exercise	74.7222	7.03609
	Total	75.2121	10.95376
DBPex1	Comparison	84.2667	17.26461
	Exercise	76.6667	12.22822
	Total	80.1212	14.98699
DBPrest12	Comparison	68.1533	10.82965
	Exercise	68.4611	6.01499
	Total	68.3212	8.39973
DBPstand12	Comparison	73.7733	12.46478
	Exercise	71.4261	7.53354

	Total	72.4930	9.97667
DBPex12	Comparison	77.5333	13.29268
	Exercise	75.6111	13.82507
	Total	76.4848	14.57693

Between-Subjects Factors (DBP)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (DBP)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	212.784	1	212.784	1.983	.169
T X G	45.688	1	45.688	.426	.519
Error (T)	3326.740	31	107.314		
C	3532.931	2	1766.465	18.175	.000*
C X G	164.936	2	82.468	.848	.433
Error (C)	6025.964	62	97.193		
T X C	152.874	2	76.437	1.251	.293
T X C X G	100.574	2	50.287	.823	.444
Error (T X C)	3789.361	60	61.119		
<u>Between subjects</u>					
Intercept	353929.303	1	353929.303	2799.812	.000
Group	85.459	1	85.459	.676	.417
Error	3918.766	30	126.412		

Tests of within-subject contrasts (DBP)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		70.928	1	70.928	1.983	.169
T X G		15.229	1	15.229	.426	.519
Error (T)		1108.913	31	35.771		
C	S vs R	2185.366	1	2185.366	21.832	.000*
	E vs R	7035.009	1	7035.009	28.718	.000*
C X G	S vs R	28.958	1	28.958	.289	.595
	E vs R	313.767	1	313.767	1.281	.266
Error (C)	S vs R	3103.052	31	100.098		
	E vs R	7594.101	31	244.971		
T X C	S vs R	144.477	1	144.477	3.859	.059
	E vs R	289.266	1	289.266	1.795	.190
T X C X G	S vs R	28.716	1	28.716	.767	.388
	E vs R	75.563	1	75.563	.469	.499
Error (Time X Condition)	S vs R	1160.703	31	37.422		
	E vs R	4996.571	31	161.181		

Mean Arterial Pressure (MAP)Descriptive Statistics (MAP)

Variable	Group	Mean	Std. Deviation
MAPrest1	Comparison	88.7000	10.29037
	Walking	86.2794	9.68828
	Total	87.3797	9.88384
MAPstand1	Comparison	94.0827	13.20715
	Walking	89.9067	8.36311
	Total	91.8048	10.85946
MAPex1	Comparison	110.3713	13.35927
	Walking	105.0878	15.85996
	Total	107.4894	14.79352
MAPrest12	Comparison	85.0887	11.76281
	Walking	86.9472	7.80346
	Total	86.1024	9.68335
MAPstand12	Comparison	88.6940	13.05047
	Walking	86.6828	9.24538
	Total	87.5970	10.99803
MAPex12	Comparison	98.9159	15.56055
	Walking	100.1094	15.01726
	Total	99.5669	15.03672

Between-Subjects Factors (MAP)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (MAP)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	1068.316	1	1068.316	8.623	.006*
T X G	227.661	1	227.661	1.837	.185
Error(T)	3840.854	31	123.899		
C	10558.178	2	5279.089	52.221	.000*
C X G	66.121	2	33.060	.327	.722
Error(C)	6267.717	62	101.092		
T X C	375.400	2	187.700	3.113	.051
T X C X G	38.042	2	19.021	.315	.731
Error (T X C)	3738.204	62	60.294		
<u>Between subjects</u>					
Intercept	571063.837	1	571063.837	3884.913	.000
Group	53.404	1	53.404	.363	.551
Error	4556.854	30	146.995		

Tests of Within-Subject Contrasts (MAP)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		356.105	1	356.105	8.623	.006*
T X G		75.887	1	75.887	1.837	.185
Error (T)		1280.285	31	41.300		
C	S vs R	624.034	1	624.034	5.612	.024*
	E vs R	18622.174	1	18622.174	80.365	.000*
C X G	S vs R	129.449	1	129.449	1.164	.289
	E vs R	50.920	1	50.920	.220	.643
Error (C)	S vs R	3446.888	31	111.190		
	E vs R	7183.282	31	231.719		
T X C	S vs R	131.472	1	131.472	3.115	.087
	E vs R	744.484	1	744.484	5.309	.028*
T X C X G	S vs R	18.288	1	18.288	.433	.515
	E vs R	19.763	1	19.763	.141	.710
Error (T X C)	S vs R	1308.453	31			
	E vs R	4346.990	31			

Rate Pressure Product (RPP)Descriptive Statistics (RPP)

Variable	Group	Mean	Std. Deviation
RPPrest1	Comparison	8409.8667	1884.23686
	Walking	7875.5556	2090.86763
	Total	8118.4242	1987.14667
RPPstand1	Comparison	9378.8667	2706.78504
	Walking	8693.5556	2465.76322
	Total	9005.0606	2560.37104
RPPex1	Comparison	15585.4000	5384.39621
	Walking	14584.0556	6340.34637
	Total	15039.2121	5856.32087
RPPrest12	Comparison	7851.000	1873.12836
	Walking	7729.5944	2176.78589
	Total	7784.7788	2013.96591
RPPstand12	Comparison	8930.0467	2233.54194
	Walking	8274.5500	2106.58609
	Total	8572.5030	2156.37462
RPPex12	Comparison	11912.8000	2517.11627
	Walking	11628.6667	3769.12870
	Total	11757.8182	3215.54040

Between-Subjects Factors (RPP)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (RPP)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
Time (T)	126813293	1	126813293	17.008	.000*
Time X β -Blockers (BB)	35175803.06	1	35175803.06	4.718	.038*
Time X Group (G)	851136.017	1	851136.017	.114	.738
Error (time)	223681873	30	7456062.43		
Condition (C)	800953792	2	400476896	69.188	.000*
C X BB	144123.089	2	72061.544	.012	.988
C X G	1120630.86	2	560315.431	.097	.908
Error (C)	347296669	60	5788277.82		
T X C	84809496.3	2	42404748.2	10.832	.000*
T X C X BB	4342438.80	2	2171219.40	.555	.577
T X C X G	777117.510	2	388558.755	.099	.906
Error (T X C)	234883119	60	3914718.65		
<u>Between subjects</u>					
Intercept	4.962E+9	1	4.962E+9	394.917	.000
BB	15992996.1	1	15992996.1	1.273	.268
G	3679041.50	1	3679041.50	.293	.592
Error	376968226	30	12565607.5		

Tests of Within-Subject Contrasts (RPP)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		42271097.5	1	42271097.5	17.008	.000*
T X BB		11725267.9	1	11725267.9	4.718	.038*
T X G		283712.006	1	283712.006	.114	.738
Error (Time)		74560624.3	30	2485354.14		
C	S vs R	36276934.8	1	36276934.8	14.376	.001*
	E vs R	1.390E+9	1	1.390E+9	89.232	.000*
C X BB	S vs R	198462.661	1	198462.661	.079	.781
	E vs R	232556.100	1	232556.100	.015	.904
C X G	S vs R	1822140.84	1	1822140.84	.722	.402
	E vs R	1526693.53	1	1526693.53	.098	.756
Error (C)	S vs R	75702817.2	30	2523427.24		
	E vs R	467214416	30	15573813.9		
T X C	S vs R	329161.993	1	329161.993	.183	.672
	E vs R	133514401	1	133514401	11.185	.002*
T X C X BB	S vs R	296910.984	1	296910.984	.165	.687
	E vs R	7731899.30	1	7731899.30	.648	.427

T X C X G	S vs R	659627.542	1	659627.542	.367	.549
	E vs R	170595.030	1	170595.030	.014	.906
Error (Time X Condition)	S vs R	53991511.4	30	1799717.05		
	E vs R	358118149	30	11937271.6		

HRV Measures Over Time (Raw Data)

Low frequency power (LF power)

Descriptive Statistics (LF power)

Variable	Group	Mean	Std. Deviation
LFpowerrest1	Comparison	88.8824	110.49903
	Walking	188.6854	305.25217
	Total	143.3204	239.56195
LFpowerstand1	Comparison	76.4045	98.50011
	Walking	158.7806	295.75080
	Total	121.3369	229.01401
LFpowerex1	Comparison	280.2510	646.86560
	Walking	117.5197	254.77783
	Total	191.4885	473.62491
LFpowerrest12	Comparison	150.4132	340.86914
	Walking	128.6652	158.82317
	Total	138.5507	253.68387
LFpowerstand12	Comparison	148.4740	262.04262
	Walking	102.1342	123.83412
	Total	123.1977	196.81775
LFpowerex12	Comparison	198.2224	304.84770
	Walking	320.5152	963.27264
	Total	264.9276	733.09307

Between-Subjects Factors (LF power)

	Value Label	N
Group	.00 Comparison	15
	1.00 Walking	18

Test of Within-Subject Effects (LF power)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	25931.676	1	25931.676	.173	.681
T X G	1647.361	1	1647.361	.011	.917
Error (T)	4655638.72	31	150181.894		
C	436413.238	2	218206.619	1.171	.317
C X G	29529.049	2	14764.524	.079	.924
Error (C)	11551211.3	62	186309.860		
T X C	34912.963	2	17456.481	.172	.843
T X C X G	458912.068	2	229456.034	2.257	.113
Error (T X C)	6303287.81	62	101665.932		

<u>Between subjects</u>					
Intercept	1744307.55	1	1744307.55	19.826	.000
G	2465.797	1	2465.797	.028	.868
Error	2727336.83	31	87978.607		

High frequency power (HF power)

Descriptive Statistics (HF power)

Variable	Group	Mean	Std. Deviation
HFpowerrest1	Comparison	485.6643	1414.62308
	Walking	242.6773	365.89203
	Total	353.1259	980.67585
HFpowerstand1	Comparison	183.2555	463.80627
	Walking	356.3157	1099.62161
	Total	277.6520	862.63626
HFpowerex1	Comparison	619.2987	1503.99389
	Walking	272.9101	764.51394
	Total	430.3595	1153.60643
HFpowerrest12	Comparison	437.1346	1347.40448
	Walking	521.0401	1702.87476
	Total	482.9012	1528.59092
HFpowerstand12	Comparison	526.6084	1363.06642
	Walking	91.3437	233.54249
	Total	289.1913	943.54064
HFpowerex12	Comparison	496.5418	957.35622
	Walking	554.9608	1666.63685
	Total	528.4067	1370.21769

Between-Subjects Factors (HF Power)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within-group Effects (HF Power)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	13780.849	1	13780.849	.009	.923
T X A	32222.011	1	32222.011	.022	.883
T X G	6524.678	1	6524.678	.004	.947
Error (T)	43873909.5	30	1462463.65		
C	3687899.10	2	1843949.55	1.441	.245
C X A	3402667.93	2	17901333.97	1.330	.272
C X G	527418.421	2	263709.210	.206	.814
Error (C)	76763477.1	60	1279391.28		
T X C	945614.294	2	472807.147	.505	.606
T X C X A	935998.203	2	476999.102	.510	.603
T X C X G	2979899.27	2	1489949.63	1.592	.212
Error (T X C)	56159106.1	60	935985.103		

<u>Between subjects</u>					
Intercept	1408187.62	1	1408187.62	1.845	.185
Age	2424330.81	1	2424330.81	3.176	.085
Group	884935.884	1	884935.884	1.159	.209
Error	22903050.9	30	763435.030		

Total PowerDescriptive Statistics (Total power)

Variable	Group	Mean	Std. Deviation
Totalpowerrest1	Comparison	832.6282	1594.61185
	Walking	965.4276	986.55136
	Total	905.0643	1278.29391
Totalpowerstand1	Comparison	1204.5259	3184.41090
	Walking	1038.9028	1480.23682
	Total	1114.1861	2368.01454
Totalpowerex1	Comparison	1683.7531	2962.59932
	Walking	905.0141	1542.28828
	Total	1258.9864	2293.17442
Totalpowerrest12	Comparison	1000.7176	2533.01218
	Walking	1660.3839	4243.48313
	Total	1360.5356	3533.35907
Totalpowerstand12	Comparison	1141.0059	2170.63248
	Walking	649.1355	759.76069
	Total	872.7129	1558.80094
Totalpowerex12	Comparison	1233.2225	1948.28756
	Walking	1525.2327	3337.47389
	Total	1392.5008	2756.79643

Between-Subjects Factors (Total power)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-group Effects (Total power)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	457851.847	1	457851.847	.073	.788
T X G	2204152.87	1	2204152.87	.354	.556
Error (T)	193169485	31	6231273.71		
C	3675635.97	2	1837817.99	.355	.703
C X G	5138018.70	2	2569009.35	.496	.611
Error (C)	320925768	62	5176222.06		
T X C	3547602.97	2	1773801.48	.387	.680
T X C X G	4057105.42	2	2028552.71	.443	.644
Error (Time X Condition)	283829272	62	4577891.49		
<u>Between subjects</u>					

Intercept	87065551.2	1	87065551.2	26.038	.000
Group	56242.132	1	56242.132	.017	.898
Error	103658121	31	3343810.35		

Parasympathetic Nervous System Indicator (PNSI)

Descriptive Statistics (PNSI)

Variable	Group	Mean	Std. Deviation
PNSIrest1	Comparison	.2772	.20315
	Walking	.2094	.18644
	Total	.2403	.19416
PNSIstand1	Comparison	.1663	.11527
	Walking	.1260	.18887
	Total	.1443	.15868
PNSIex1	Comparison	.2275	.20531
	Walking	.1099	.17131
	Total	.1633	.19383
PNSIrest12	Comparison	.2456	.13884
	Walking	.2176	.16938
	Total	.2303	.15452
PNSIstand12	Comparison	.1602	.19627
	Walking	.1076	.13119
	Total	.1315	.16342
PNSIex12	Comparison	.1999	.17973
	Walking	.1558	.13953
	Total	.1759	.15803

Between-Subjects Factors (PNSI)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (PNSI)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	.001	1	.001	.070	.793
T X G	.014	1	.014	.825	.371
Error (T)	.522	31	.017		
C	.321	2	.161	6.508	.003*
C X G	.012	2	.006	.251	.779
Error (C)	1.530	62	.025		
T X C	.005	2	.002	.213	.809
T X C X G	.015	2	.008	.665	.518
Error (T X C)	.714	62	.012		
<u>Between subjects</u>					
Intercept	1744307.55	1	1744307.55	19.826	.000
G	2465.797	1	2465.797	.028	.868
Error	2727336.83	31	87978.607		

Tests of Within-Subject Contrasts (PNSI)

Source	Condition	SS	Df	MS	F	P
<u>Within subjects</u>						
T		.000	1	.000	.070	.793
T X G		.005	1	.005	.825	.371
Error (T)		.174	31	.006		
C	S vs R	.622	1	.622	11.171	.002
	E vs R	.270	1	.270	4.138	.051
C X G	S vs R	3.618E-5	1	3.618E-5	.001	.980
	E vs R	.018	1	.018	.272	.606
Error (C)	S vs R	1.725	31	.056		
	E vs R	2.020	31	.065		
T X C	S vs R	3.383E-6	1	3.383E-6	.000	.989
	E vs R	.007	1	.007	.265	.611
T X C X G	S vs R	.011	1	.011	.654	.425
	E vs R	.005	1	.005	.172	.682
Error (T X C)	S vs R	.526	31	.017		
	E vs R	.843	31	.027		
<u>Between subjects</u>						
Intercept		2.206	1	2.206	77.220	.000
Group		.056	1	.056	1.954	.172
Error		.886	31	.029		

Sympathetic Nervous System Indicator (SNSI)Descriptive Statistics (SNSI)

Variable	Group	Mean	Std. Deviation
SNSIrest1	Comparison	0.9007	.88085
	Walking	1.6405	1.40408
	Total	1.3042	1.23561
SNSIstand1	Comparison	2.1016	2.13541
	Walking	3.3282	2.65574
	Total	2.7706	2.47519
SNSIexer1	Comparison	1.5117	1.43447
	Walking	2.4447	2.27662
	Total	2.0206	1.96883
SNSIrest12	Comparison	1.2417	1.43463
	Walking	1.3924	1.03074
	Total	1.3239	1.21271
SNSIstand12	Comparison	2.9306	3.48392
	Walking	3.1019	2.39434
	Total	3.0240	2.89194
SNSIexer12	Comparison	2.1636	2.45312
	Walking	1.8201	2.15089
	Total	1.9762	2.26289

Between-Subjects Factors (SNSI)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (SNSI)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	.216	1	.216	.219	.643
T X A	.591	1	.591	.601	.445
T X Sm	12.313	1	12.313	12.508	.001*
T X G	7.268	1	7.268	7.383	.011*
Error (T)	28.547	29	.984		
C	29.106	2	14.553	3.786	.028*
C X A	25.901	2	12.951	3.369	.041*
C X Sm	23.019	2	11.509	2.994	.058
C X G	6.616	2	3.308	.861	.428
Error (C)	222.932	58	3.844		
T X C	3.297	2	1.649	.861	.428
T X C X A	3.551	2	1.775	.928	.401
T X C X Sm	.506	2	.253	.132	.876
T X C X G	1.534	2	.767	.401	.672
Error (T X C)	111.006	58	1.914		
<u>Between subjects</u>					
Intercept	27.415	1	27.415	7.560	.010
A	14.477	1	14.477	3.992	.055
Sm	6.129	1	6.129	1.690	.204
G	10.574	1	10.574	2.916	.098
Error	105.168	29	3.626		

Tests of Within-Subject Contrasts (SNSI)

Source	Condition	SS	df	MS	F	P
T		.072	1	.072	.219	.643
T X A		.197	1	.197	.601	.445
T X Sm		4.104	1	4.104	12.508	.001*
T X G		2.423	1	2.423	7.383	.011*
Error (T)		9.516	29	.328		
C	S vs. R	49.886	1	49.886	6.198	.019*
	E vs. R	36.366	1	36.366	5.968	.021*
C X A	S vs. R	43.203	1	43.203	5.368	.028*
	E vs. R	33.943	1	33.943	5.570	.025*
C X Sm	S vs. R	44.651	1	44.651	5.548	.025*
	E vs. R	5.388	1	5.388	.884	.355
C X G	S vs. R	13.068	1	13.068	1.624	.213
	E vs. R	2.121	1	2.121	.348	.560
Error (C)	S vs. R	233.398	29	8.048		
	E vs. R	176.719	29	6.094		

T X C	S vs. R	5.843	1	5.843	2.857	.102
	E vs. R	.210	1	.210	.047	.829
T X C X A	S vs. R	6.195	1	6.195	3.029	.092
	E vs. R	.176	1	.176	.040	.843
T X C X Sm	S vs. R	.974	1	.974	.476	.496
	E vs. R	.105	1	.105	.024	.879
T X C X G	S vs. R	2.545	1	2.545	1.244	.274
	E vs. R	2.028	1	2.028	.547	.504
Error (T X C)	S vs. R	59.306	29	2.045		
	E vs. R	128.632	29	4.436		

SNS Indicator (SNSI) Comparison Group

Tests of Within-Subjects Effects – Comparison Group (SNSI)

Source	SS	Df	MS	F	P
T	2.395	1	2.395	2.654	.129
T X A	2.950	1	2.950	3.269	.096
T x Sm	11.638	1	11.638	12.895	.004*
Error(T)	10.830	12	.902		
C	13.438	2	6.719	1.311	.288
C X A	11.870	2	5.935	1.158	
C X Sm	9.638	2	4.819	.940	.404
Error (C)	122.990	24	5.125		
T X C	.014	2	.007	.003	.997
T X C X A	.268	2	.134	.056	.945
T X C X Sm	9.077	2	4.538	1.904	.171
Error (T X C)	57.198	24	2.383		

Tests of Within-Subjects Contrasts - Comparison Group (SNSI)

Source	Condition	SS	Df	MS	F	P
T		.789	1	.789	2.654	.129
T X A		.983	1	.983	3.269	.096
T X Sm		3.879	1	3.879	12.895	.004*
Error(T)		3.610	12	.301		
C	S vs. R	26.791	1	12.791	2.686	.127
	E vs. R	8.070	1	8.070	1.431	.255
C X A	S vs. R	23.730	1	23.730	2.379	.149
	E vs. R	5.521	1	5.521	.979	.342
C X Sm	S vs. R	12.097	1	12.097	1.213	.292
	E vs. R	.338	1	.338	.060	.811
Error(C)	S vs. R	119.705	12	9.975		
	E vs. R	67.677	12	5.640		
T X C	S vs. R	.010	1	.010	.003	.956
	E vs. R	.004	1	.004	.001	.979
T X C X A	S vs. R	.051	1	.051	.016	.901
	E vs. R	.241	1	.241	.040	.844
T X C X Sm	S vs. R	.123	1	.123	.039	.847
	E vs. R	14.843	1	14.843	2.490	.141
Error (T X C)	S vs. R	37.932	12	3.161		
	E vs. R	71.537	12	5.961		

Tests of Between-Subjects Effects - Comparison Group (SNSI)

Source	SS	Df	MS	F	P
Intercept	18.398	1	18.398	7.002	.021
Age	11.632	1	11.632	4.427	.057
Smoking	1.967	1	1.967	.749	.404
Error	31.533	12	2.628		

SNS Indicator - Walking Group (SNSI)

Test of With-in Subject Effects

Source	SS	Df	MS	F	P
T	1.474	1	1.474	1.961	.182
T X A	.836	1	.836	1.112	.308
T x Sm	2.404	1	2.404	3.198	.094
Error(T)	11.275	15	.752		
C	21.968	2	10.984	3.770	.035*
C X A	21.558	2	10.779	3.699	.037*
C X Sm	17.7523	2	8.876	3.046	.062
Error ©	87.412	30	2.914		
T X C	6.064	2	3.032	2.797	.077
T X C X A	5.962	2	2.981	2.750	.080
T X C X Sm	9.061	2	4.531	4.180	.025*
Error (T X C)	32.517	30	1.084		

Tests of Within-Subjects Contrasts - Walking Group (SNSI)

Source	Condition	SS	Df	MS	F	P
T		.491	1	.491	1.961	.182
T X A		.279	1	.279	1.112	.308
T X Sm		.801	1	.801	3.198	.094
Error (T)		3.758	15	.251		
C	S vs. R	24.181	1	24.181	3.245	.092
	E vs. R	39.788	1	39.788	6.850	.019*
C X A	S vs. R	20.436	1	20.436	2.743	.118
	E vs. R	40.764	1	40.764	7.018	.018*
C X Sm	S vs. R	34.471	1	34.471	4.626	.048*
	E vs. R	14.565	1	14.565	2.508	.134
Error(C)	S vs. R	111.773	15			
	E vs. R	87.125	15			
T X C	S vs. R	12.025	1	12.025	11.581	.004*
	E vs. R	2.120	1	2.120	1.164	.298
T X C X A	S vs. R	11.915	1	11.915	11.474	.004*
	E vs. R	2.705	1	2.705	1.485	.242
T X C X Sm	S vs. R	.819	1	.819	.789	.388
	E vs. R	9.922	1	9.922	5.449	.034*
Error (T X C)	S vs. R	15.576	15	1.038		
	E vs. R	27.314	15	1.821		

Tests of Between-Subjects Effects - Walking Group (SNSI)

Source	SS	Df	MS	F	P
Intercept	9.092	1	9.092	1.872	.191
Age	3.647	1	3.647	.751	.400
Smokers	4.121	1	4.121	.849	.372
Error	72.831	15	4.855		

Log low frequency power (Log LF power)

Descriptive Statistics (Log LF power)

Variable	Group	Mean	Std. Deviation
LogLFpowerrest1	Comparison	1.6999	.45903
	Walking	1.9071	.58091
	Total	1.8129	.53145
LogLFpowerstand1	Comparison	1.6232	.48422
	Walking	1.7548	.61100
	Total	1.6950	.55258
LogLFpowerex1	Comparison	1.6926	.81290
	Walking	1.4063	.77726
	Total	1.5364	.79436
LogLFpowerrest12	Comparison	1.7999	.46764
	Walking	1.8260	.54624
	Total	1.8141	.50435
LogLFpowerstand12	Comparison	1.7336	.61641
	Walking	1.7049	.55504
	Total	1.7180	.57455
LogLFpowerex12	Comparison	1.8247	.67824
	Walking	1.5827	.86174
	Total	1.6927	.78194

Between-Subjects Factors (Log LF power)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Test of Within-Subject Effects (Log LF power)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	.205	1	.205	.580	.452
T X G	.120	1	.120	.341	.564
Error(T)	10.961	31	.354		
C	1.088	2	.554	2.162	.124
C X G	1.357	2	.679	2.698	.075
Error (C)	15.596	62	.252		
T X C	.201	2	.100	.695	.503
T X C X G	.127	2	.064	.440	.646

Error (T X C)	8.955	62	.144		
<u>Between subjects</u>					
Intercept	192.061	1	192.061	445.652	.000
G	.017	1	.017	.039	.845
Error	13.360	31	.431		

High frequency power (Log HF power)

Descriptive Statistics (Log HF power)

Variable	Group	Mean	Std. Deviation
LogHFpowerrest1	Comparison	1.9336	.70180
	Walking	1.8844	.74793
	Total	1.9067	.71643
LogHFpowerstand1	Comparison	1.5330	.72926
	Walking	1.4113	.95189
	Total	1.4666	.84724
LogHFpowerex1	Comparison	1.6300	1.02631
	Walking	1.1701	.95320
	Total	1.3791	.99880
LogHFpowerrest12	Comparison	1.8884	.66330
	Walking	1.8504	.56203
	Total	1.8677	.60056
LogHFpowerstand12	Comparison	1.5269	.91731
	Walking	1.3783	.67783
	Total	1.4458	.78604
LogHFpowerex12	Comparison	1.7182	.95296
	Walking	1.5193	1.02349
	Total	1.6097	.98179

Between-Subjects Factors (Log HF Power)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within-Group Effects (Log HF Power)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	.126	1	.126	.296	.590
T X A	.159	1	.159	.375	.545
T X G	.022	1	.022	.051	.822
Error (T)	12.717	30	.424		
C	3.525	2	1.763	5.188	.008*
C X A	2.524	2	1.262	3.715	.030*
C X G	1.374	2	.687	2.022	.141
Error (C)	20.386	60	.340		
T X C	.291	2	.145	.549	.581
T X C X A	.241	2	.121	.456	.636

T X C X G	.245	2	.123	.463	.631
Error (T X C)	15.888	60	.265		
<u>Between subjects</u>					
Intercept	.011	1	.011	.014	.908
Age	1.871	1	1.871	2.289	.141
Group	1.162	1	1.162	1.422	.242
Error	24.520	30	.817		

Test of With-in Subject Contrasts (Log HF power)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		.042	1	.042	.296	.590
T X A		.053	1	.053	.375	.545
T X G		.007	1	.007	.051	.822
Error (T)		4.239	30	.141		
C	S vs R	6.102	1	6.120	9.552	.004*
	E vs R	4.320	1	4.320	5.114	.031*
C X A	S vs R	4.400	1	4.400	6.888	.014*
	E vs R	3.049	1	3.049	3.609	.067
C X G	S vs R	1.014	1	1.014	1.587	.217
	E vs R	2.702	1	2.702	3.198	.084
Error (C)	S vs R	19.164	30	.639		
	E vs R	25.344	30	.845		
T X C	S vs R	.400	1	.400	2.188	.150
	E vs R	.469	1	.469	.593	.447
T X C X A	S vs R	.394	1	.394	2.153	.153
	E vs R	.327	1	.327	.413	.525
T X C X G	S vs R	.015	1	.015	.083	.776
	E vs R	.434	1	.434	.549	.465
Error (T X C)	S vs R	5.490	30	.183		
	E vs R	23.729	30	.791		

Log Total Power (Log total power)

Descriptive Statistics (Log total power)

Variable	Group	Mean	Std. Deviation
LogTotalpowerrest1	Comparison	2.5167	.54148
	Walking	2.7432	.51170
	Total	2.6403	.52961
LogTotalpowerstand1	Comparison	2.4735	.60004
	Walking	2.6802	.58112
	Total	2.5862	.58978
LogTotalpowerex1	Comparison	2.5441	.84760
	Walking	2.5175	.60051
	Total	2.5296	.71139
LogTotalpowerrest12	Comparison	2.5778	.46100
	Walking	2.7673	.56737
	Total	2.6812	.52266

LogTotalpowerstand12	Comparison	2.5646	.59852
	Walking	2.5496	.50258
	Total	2.5564	.53941
LogTotalpowerex12	Comparison	2.5718	.72261
	Walking	2.4415	.84476
	Total	2.5007	.78224

Between-Subjects Factors (Log total power)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-group Effects (Log total power)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	8.773E-6	1	8.773E-6	.000	.996
T X G	.179	1	.179	.596	.446
Error (T)	9.309	31	.300		
C	.589	2	.295	1.255	.292
C X G	.682	2	.341	1.451	.242
Error (C)	14.558	62	.235		
T X C	.046	2	.023	.105	.901
T X C X G	.072	2	.036	.164	.849
Error (Time X Condition)	13.503	62	.218		
<u>Between subjects</u>					
Intercept	435.348	1	435.348	1145.149	.000
Group	.092	1	.092	.243	.626
Error	11.785	31	.380		

Log Parasympathetic Nervous System Indicator (LogPNSI)

Descriptive Statistics (Log PNSI)

Variable	Group	Mean	Std. Deviation
LogPNSIrest1	Comparison	-.6513	.30066
	Walking	-.8588	.42948
	Total	-.7645	.38541
LogPNSIstand1	Comparison	-.8127	.35703
	Walking	-1.2692	.57099
	Total	-1.0617	.53129
LogPNSIex1	Comparison	-.8563	.4886
	Walking	-1.3504	.62062
	Total	-1.1258	.60953
LogPNSIrest12	Comparison	-.6894	.29476
	Walking	-.8058	.37936
	Total	-.7529	.34341
LogPNSIstand12	Comparison	-1.0377	.50305
	Walking	-1.1712	.40721
	Total	-1.1105	.45096

LogPNSIex12	Comparison	-8529	.38477
	Walking	-.9751	.41812
	Total	-.9196	.40182

Between-Subjects Factors (Log PNSI)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (LogPNSI)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	.151	1	.151	1.272	.268
T X G	.706	1	.706	5.927	.021
Error (T)	3.691	31	.119		
C	4.080	2	2.040	12.348	.000
C X G	.183	2	.091	.553	.578
Error (C)	10.241	62	.165		
T X C	.451	2	.226	2.350	
T X C X G	.163	2	.082	.849	.433
Error (T X C)	5.951	62	.096		
<u>Between subjects</u>					
Intercept	59.048	1	59.048	334.955	.000
G	.974	1	.974	5.524	.025
Error	5.465	31	.176		

Tests of Within-Subject Contrasts (LogPNSI)

Source	Condition	SS	df	MS	F	P
<u>Within subjects</u>						
T		.050	1	.050	1.272	.268
T X G		.235	1	.235	5.927	.021*
Error (T)		1.230	31	.040		
C	S vs R	7.478	1	7.478	29.531	.000*
	E vs R	4.334	1	4.334	10.387	.003*
C X G	S vs R	.163	1	.163	.643	.429
	E vs R	.350	1	.350	.839	.367
Error (C)	S vs R	7.850	31	.253		
	E vs R	12.935	31	.417		
T X C	S vs R	.023	1	.023	.224	.640
	E vs R	.541	1	.541	2.591	.118
T X C X G	S vs R	.112	1	.112	1.080	.307
	E vs R	.323	1	.323	1.544	.223
Error (T X C)	S vs R	3.206	31	.103		
	E vs R	6.478	31	.209		

Test of With-in Subject Effects - Comparison Group (LogPNSI)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	.093	1	.093	.708	.414
Error(T)	1.843	14	.132		
C	1.277	2	.639	4.088	.028*
Error (C)	4.375	28	.156		
T X C	.106	2	.053	.782	.391
Error (T X C)	1.894	28			

Test of With-in Subject Contrasts – Comparison Group (LogPNSI)

Source	Condition	SS	Df	MS	F	P
<u>Within subjects</u>						
T		.031	1	.031	.708	.414
Error(T)		.614	14	.044		
C	S vs R	2.490	1	2.490	26.361	.000*
	E vs R	1.018	1	1.018	2.974	.107
Error(C)	S vs R	1.323	14	.094		
	E vs R	4.792	14	.342		
T X C	S vs R	.108	1	.108	1.127	.306
	E vs R	.013	1	.013	.118	.737
Error (T X C)	S vs R	1.347	14	.096		
	E vs R	1.535	14	.110		

Test of With-in Subject Effects – Walking Group (LogPNSI)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	.831	1	.831	7.645	.013
Error(T)	1.848	17	.109	.109	
C	3.156	2	1.578	9.144	.001*
Error (C)	5.867	34	.173		
T X C	.548	2	.274	2.298	.116
Error (T X C)	4.057	34	.119		

Test of With-in Subject Contrasts – Walking Group (LogPNSI)

Source	Condition	SS	Df	MS	F	P
<u>Within subjects</u>						
T		.277	1	.277	7.645	.013*
Error(T)		.616	17	.036		
C	S vs R	5.417	1	5.417	14.108	.002*
	E vs R	3.931	1	3.931	8.206	.011*

Error(C)	S vs R	6.528	17	.384		
	E vs R	8.144	17	.479		
T X C	S vs R	.018	1	.018	.167	.688
	E vs R	.935	1	.935	3.216	.091
Error (T X C)	S vs R	1.859	17	.109		
	E vs R	4.942	17	.291		

Log Transformed Sympathetic Nervous System Indicator (LogSNSI)

Descriptive Statistics (LogSNSI)

Variable	Group	Mean	Std. Deviation
LogSNSIrest1	Comparison	-.2337	.46266
	Walking	.0228	.47431
	Total	-.0938	.47956
LogSNSIstand1	Comparison	.0902	.49989
	Walking	.3431	.47082
	Total	.2281	.49340
LogSNSIexer1	Comparison	.0048	.42663
	Walking	.2363	.38850
	Total	.1311	.41655
LogSNSIrest12	Comparison	-.0885	.38248
	Walking	-.0244	.44681
	Total	-.0535	.41365
LogSNSIstand12	Comparison	.2068	.54343
	Walking	.3266	.44009
	Total	.2721	.48555
LogSNSIexer12	Comparison	.1065	.46845
	Walking	.0635	.39916
	Total	.0830	.42558

Between-Subjects Factors (LogSNSI)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within-Subject Effects (LogSNSI)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	1.473E-5	1	1.473E-5	.000	.986
T X A	.005	1	.005	.101	.753
T X Sm	.568	1	.568	11.553	.002*
T X G	.335	1	.335	6.805	.014*
Error(T)	1.426	29	.049		
C	1.965	2	.983	7.302	.001*
C X A	1.575	2	.787	5.851	.005*
C X Sm	.376	2	.188	1.398	.255
C X G	.241	2	.120	.894	.415
Error (C)	7.805	58	.135		

T X C	.291	2	.145	1.522	.227
T X C X A	.328	2	.164	1.716	.189
T X C X Sm	.015	2	.007	.078	.925
T X C X G	.014	2	.007	.074	.929
Error (T X C)	5.543	58	.096		
<u>Between subjects</u>					
Intercept	.921	1	.921	4.672	.039
A	.864	1	.864	4.384	.045
Sm	.044	1	.044	.224	.639
G	.766	1	.766	3.885	.058
Error	5.716	29	.197		

Tests of Within-Subject Contrasts (LogSNSI)

Source	Condition	SS	df	MS	F	P
T		4.910E-6	1	4.910E-6	.000	.986
T X A		.002	1	.002	.101	.753
T X Sm		.189	1	.189	11.553	.002*
T X G		.112	1	.112	6.805	.014*
Error (T)		.475	29	.016		
C	S vs. R	2.406	1	2.406	7.909	.009*
	E vs. R	.086	1	.086	.497	.487
C X A	S vs. R	1.912	1	1.912	6.286	.018*
	E vs. R	.074	1	.074	.426	.519
C X Sm	S vs. R	.165	1	.165	.544	.467
	E vs. R	.751	1	.751	4.319	.047*
C X G	S vs. R	.022	1	.022	.072	.791
	E vs. R	.263	1	.263	1.514	.228
Error (C)	S vs. R	8.821	29	.304		
	E vs. R	5.046	29	.174		
T X C	S vs. R	.011	1	.011	.044	
	E vs. R	.360	1	.360	1.634	
T X C X A	S vs. R	.003	1	.003	.012	
	E vs. R	.451	1	.451	2.046	
T X C X Sm	S vs. R	.021	1	.021	.082	.776
	E vs. R	.023	1	.023	.105	.749
T X C X G	S vs. R	.027	1	.027	.102	.752
	E vs. R	.002	1	.002	.010	.922
Error (T X C)	S vs. R	7.539	29	.260		
	E vs. R	6.398	29	.221		

Test of Between-Subject Contrasts (LogSNSI)

Intercept	.921	1	.921	4.672	.039
A	.864	1	.864	4.384	.045
Sm	.044	1	.044	.224	.639
G	.766	1	.766	3.885	.058
Error	5.716	29	.197		

Log Transformed SNS Indicator (LogSNSI) Comparison Group

Tests of Within-Subjects Effects – Comparison Group (LogSNSI)

Source	SS	Df	MS	F	P
T	.061	1	.061	.884	.366
T X A	.076	1	.076	1.097	.316
T x Sm	.431	1	.431	6.258	.028*
Error(T)	.827	12	.069		
C	1.241	2	.620	5.371	.012*
C X A	.988	2	.494	4.277	.026*
C X Sm	.464	2	.232	2.010	.156
Error (C)	2.772	24	.115		
T X C	.029	2	.014	.137	.872
T X C X A	.010	2	.005	.048	.953
T X C X Sm	.611	2	.305	2.942	.072
Error (T X C)	2.491	24	.104		

Tests of Within-Subjects Contrasts - Comparison Group (LogSNSI)

Source	Condition	SS	Df	MS	F	P
T		.020	1	.020	.884	.366
T X A		.025	1	.025	1.097	.316
T X Sm		.144	1	.144	6.258	.028*
Error(T)		.276	12	.023		
C	S vs. R	.995	1	.995	3.197	.099
	E vs. R	.311	1	.311	1.385	.262
C X A	S vs. R	.598	1	.598	1.922	.191
	E vs. R	.397	1	.397	1.770	.208
C X Sm	S vs. R	.710	1	.710	2.282	.157
	E vs. R	.682	1	.682	3.043	.107
Error(C)	S vs. R	3.733	12	.311		
	E vs. R	2.690	12	.224		
T X C	S vs. R	.057	1	.057	.168	.689
	E vs. R	.012	1	.012	.067	.800
T X C X A	S vs. R	.011	1	.011	.034	.857
	E vs. R	.001	1	.001	.004	.953
T X C X Sm	S vs. R	.845	1	.845	2.487	.141
	E vs. R	.982	1	.982	5.371	.039
Error (T X C)	S vs. R	4.076	12	.340		
	E vs. R	2.194	12	.183		

Tests of Between-Subjects Effects - Comparison Group (LogSNSI)

Source	SS	Df	MS	F	P
Intercept	.837	1	.837	4.654	.052
Age	.919	1	.919	5.115	.043*
Smoking	.013	1	.013	.074	.791
Error	2.157	12	.180		

Log Transformed SNS Indicator - Walking Group (LogSNSI)

Test of With-in Subject Effects

Source	SS	Df	MS	F	P
T	.086	1	.086	3.192	.094
T X A	.050	1	.050	1.849	.194
T x Sm	.163	1	.163	6.053	.027*
Error(T)	.405	15	.027		
C	.989	2	.495	3.343	.049*
C X A	.882	2	.441	2.981	.066
C X Sm	.200	2	.100	.677	.516
Error (C)	4.440	30	.148		
T X C	.531	2	.226	4.039	.036
T X C X A	.546	2	.273	4.150	.034
T X C X Sm	.287	2	.143	2.181	.1450
Error (T X C)	1.972	30	.066		

Tests of Within-Subjects Contrasts - Walking Group (LogSNSI)

Source	Condition	SS	Df	MS	F	P
T		.029	1	.029	3.192	.094
T X A		.017	1	.017	1.849	.194
T X Sm		.054	1	.054	6.053	.027*
Error (T)		.135	15	.009		
C	S vs. R	1.756	1	1.756	6.308	.024*
	E vs. R	.065	1	.065	.567	.463
C X A	S vs. R	1.638	1	1.638	5.884	.028*
	E vs. R	.110	1	.110	.968	.341
C X Sm	S vs. R	.057	1	.057	.204	.658
	E vs. R	.151	1	.151	1.325	.268
Error(C)	S vs. R	4.176	15	.278		
	E vs. R	1.708	15	.114		
T X C	S vs. R	.002	1	.002	.015	.904
	E vs. R	.745	1	.745	4.381	.054
T X C X A	S vs. R	.004	1	.004	.030	.864
	E vs. R	.7556	1	.756	4.394	.053
T X C X Sm	S vs. R	.410	1	.410	2.781	.116
	E vs. R	.450	1	.450	2.613	.127
Error (T X C)	S vs. R	2.211	15	.147		
	E vs. R	2.580	15	.172		

Tests of Between-Subjects Effects - Walking Group (LogSNSI)

Source	SS	df	MS	F	P
Intercept	.155	1	.155	.685	.421
Age	.102	1	.102	.453	.511
Smokers	.026	1	.026	.115	.740
Error	3.392	15	.226		

Performance Measures Over Time (Raw Data)Descriptive Statistics Pain Free Walking Distance (PFWD)

Variable	Group	Mean	Standard Deviation
PFWD Week 1	Comparison	118.5766	115.95750
	Walking	168.2733	90.77430
	Total	144.9780	104.69102
PFWD Week 12	Comparison	144.5982	104.70540
	Walking	233.0672	115.26600
	Total	191.5973	117.56050

Between-Subjects Factors (PFWD)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	17

Tests of With-in Subject Effects (PFWD)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	32860.943	1	32860.943	9.667	.004*
T X G	5989.672	1	5989.672	1.762	.194
Error (T)	101973.555	30	3399.118		

Tests of Between-Subject Effects (PFWD)

Source	SS	Df	MS	F	P
Intercept	1759422.40	1	1759422.40	90.354	.000*
G	76060.716	1	76060.716	3.906	.057
Error	584177.100	30	19472.570		

Descriptive Statistics - Functional Claudication Distance (FCD)

Variable	Group	Mean	Standard Deviation
FCD Week 1	Comparison	203.2965	163.31039
	Walking	284.6471	137.76662
	Total	246.5140	153.43327
FCD Week 12	Comparison	226.8003	144.18342
	Walking	418.8154	196.51232
	Total	328.8083	196.95602

Between-Subjects Factors (FCD)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	17

Tests of With-in Subject Effects (FCD)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
T	99053.522	1	99053.522	14.288	.001*
T X G	48795.069	1	48795.069	7.038	.013*
Error (T)	207984.518	30	6932.817		

Tests of Between-Subject Effects (FCD)

Source	SS	Df	MS	F	P
Intercept	5119749.04	1	5119749.04	111.476	.000*
G	297747.552	1	297747.552	6.483	.016*
Error	1377809.57	30			

Descriptive Statistics – Maximum Walking Distance (MWD)

Variable	Group	Mean	Standard Deviation
MWD Week 1	Comparison	252.0950	198.90651
	Walking	364.5273	172.58885
	Total	311.8247	191.02584
MWD Week 12	Comparison	278.0907	176.63313
	Walking	488.4990	209.54495
	Total	389.8701	219.39248

Between-Subjects Factors (MWD)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	17

Tests of With-in Subject Effects (MWD)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	89609.400	1	89609.400	15.881	.000*
T X G	38247.180	1	38247.180	6.778	.014*
Error (T)	169278.094	30	5642.603		

Tests of Between-Subject Effects (MWD)

Source	SS	Df	MS	F	P
Intercept	7623206.77	1	7623206.77	114.317	.000*
G	415275.908	1	415275.908	6.227	
Error	2000540.71	30	66684.690		

Log PFWDDescriptive Statistics Log PFWD

Variable	Group	Mean	Std. Deviation
LogPFWDWeek1	Comparison	1.9692	.27905
	Walking	2.1697	.22706
	Total	2.0757	.26855
LogPFWDWeek12	Comparison	2.0663	.29138
	Walking	2.3081	.25069
	Total	2.1947	.29293

Between-Subjects Factors (Log PFWD)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	17

Tests of Within-Subject Effects (PFWD)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
Time	.221	1	.221	10.134	.003*
Time X Group	.007	1	.007	.310	.582
Error (Time)	.654	30	.022		
<u>Between subjects</u>					
Intercept	288.771	1	288.7721	2507.275	.000
Group	.780	1	.780	6.770	.014
Error	3.455	30	.115		

Descriptive Statistics (Log FCD)

Variable	Group	Mean	Std. Deviation
Log FCDWeek1	Comparison	2.2178	.25683
	Walking	2.4079	.20656
	Total	2.3188	.25145
Log FCDWeek12	Comparison	2.2773	.27152
	Walking	2.5613	.25648
	Total	2.4282	.29663

Between-Subjects Factors (Log FCD)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	17

Tests of Within-Subject Effects (Log FCD)

Source	SS	Df	MS	F	P
<u>Within subjects</u>					
Time	.181	1	.181	10.556	.003
Time X Group	.035	1	.035	2.056	.162
Error (Time)	.513	30	.017		
<u>Between subjects</u>					
Intercept	356.889	1	356.889	3301.118	.000
Group	.896	1	.896	8.287	.007
Error	3.243	30	.108		

Descriptive Statistics (Log MWD)

Variable	Group	Mean	Std. Deviation
Log MWDWeek1	Comparison	2.3072	.28074
	Walking	2.5134	.21580
	Total	2.4168	.26563
Log MWDWeek12	Comparison	2.3593	.28816
	Walking	2.6599	.27447
	Total	2.5190	.31562

Between-Subjects Factors (Log MWD)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	17

Tests of Within-Subject Effects (Log MWD)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
Time	.157	1	.157	10.264	.003*
Time X Group	.036	1	.036	2.323	.138
Error (Time)	.459	30	.015		
<u>Between subjects</u>					
Intercept	385.776	1	385.776	3080.159	.000*
Group	1.024	1	1.024	8.173	.008*
Error	3.757	30	.125		

Difference Measures

Pain-Free Walking Distance (PFWD)Descriptive Statistics (PFWD difference over time)

Variable	Group	Mean	Std. Deviation
PFWD diff	Comparison	26.016	63.73908
	Walking	64.7939	95.87418
	Total	46.6194	83.45879

Between-Subjects Factors (PFWD diff)

	Value Label	N
Group	.00 Comparison	15
	1.00 Walking	17

Tests of Between-Subject Effects (PFWD diff)

Source	SS	df	MS	F	P
Corrected model	11979.343	1	11979.343	1.762	.194
Intercept	65721.887	1	65721.887	9.667	.004
Group	11979.343	1	11979.343	1.762	.194
Error	203947.109	30	6798.237		
Total	285474.175	32			
Corrected total	215926.453	31			

Functional Claudication Distance (FCD)Descriptive Statistics (FCD diff)

Variable	Group	Mean	Std. Deviation
FCD diff	Comparison	23.5039	119.68316
	Walking	134.1682	116.03669
	Total	82.2943	128.71063

Between-Subjects Factors (FCD diff)

	Value Label	N
Group	.00 Comparison	15
	1.00 Walking	17

Tests of Between-Subject Effects (FCD diff)

Source	SS	df	MS	F	P
Corrected model	97590.138	1	97590.138	7.038	.013
Intercept	198107.045	1	198107.045	14.288	.001
Group	97590.138	1	97590.138	7.038	.013
Error	415969.037	30	13865.635		
Total	730274.502	32			
Corrected total	513559.174	31			

Descriptive Statistics (MWD diff)

Variable	Group	Mean	Std. Deviation
MWD diff	Comparison	25.9957	94.00523
	Walking	123.9717	115.87667
	Total	78.0454	115.70967

Between-Subjects Factors (MWD diff)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	17

Tests of Between-Subject Effects (MWD diff)

Source	SS	df	MS	F	P
Corrected Model	76494.360	1	76494.360	6.778	.014
Intercept	179218.800	1	179218.800	15.881	.000
Group	76494.360	1	76494.360	6.778	.014
Error	338556.188	30	11285.206		
Total	609965.341	32			
Corrected Total	41505.548	31			

Six-minute walk test (6MWT)Descriptive Statistics (6MWT)

Variable	Group	Mean	Standard Deviation
6MWT 1 (m)	Comparison	332.8619	98.16747
	Walking	335.5272	87.28661
6MWT 12 (m)	Comparison	338.4570	66.65516
	Walking	347.6119	91.98583

Tests of Within Subject Effects (6MWT)

Source	SS	df	MS	F	P
<u>Within subjects</u>					
T	1278.711	1	1278.11	.592	.447
T X G	172.285	1	172.285	.080	.779
Error (T)	66930.411	31	2159.046		

Tests of Between-Subject Effects (6MWT)

Source	SS	df	MS	F	P
Intercept	7505004.29	1	7505004.29	576.518	.000
G	571.565	1	571.565	.044	.835
Error	403552.133	31	13017.811		

Self-Report Measures Over Time

Walking Impairment Questionnaire Distance Scores (WIQ-D)

Descriptive Characteristics (WIQ-D)

Variable	Group	Mean	Standard Deviation
WIQ-D1	Comparison	36.3150	23.76998
	Walking	51.9500	30.51217
WIQ-D12	Comparison	58.6100	31.13258
	Walking	62.6172	29.83330

Between-Subjects Factors (WIQ-D)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (WIQ-D)

Source	SS	df	MS	F	P
T	4444.806	1	4444.806	7.740	.009*
T X G	553.112	1	553.112	.963	.334
Error (T)	17803.2298	31	574.298		

Tests of Between-Subjects Effects (WIQ-D)

Source	SS	df	MS	F	P
Intercept	179537.691	1	179537.691	160.702	.000
G	1578.342	1	1578.342	1.413	.244
Error	34633.567	31	1117.212		

Walking Impairment Questionnaire Speed Scores (WIQ-S)

Descriptive Characteristics (WIQ-S)

Variable	Group	Mean	Standard Deviation
WIQ-S1	Comparison	39.9953	25.55427
	Walking	48.3683	24.17227
WIQ-S12	Comparison	43.9133	21.07576
	Walking	57.6094	22.79399

Between-Subjects Factors (WIQ-S)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (WIQ-S)

Source	SS	df	MS	F	P
T	708.391	1	708.391	3.433	.073
T X G	115.918	1	115.918	.562	.459
Error (T)	6396.697	31	206.345		

Tests of Between-Subjects Effects (WIQ-S)

Source	SS	df	MS	F	P
Intercept	147505.344	1	147505.344	164.900	.000
G	1992.460	1	1992.460	2.227	.146
Error	27729.919	31	894.514		

Walking Impairment Questionnaire Stair Climbing Ability Scores (WIQ-SC)Descriptive Characteristics (WIQ-SC)

Variable	Group	Mean	Standard Deviation
WIQ-SC1	Comparison	39.1680	21.86632
	Walking	56.7133	25.68090
WIQ-SC12	Comparison	45.2787	19.15035
	Walking	66.4389	26.48339

Between-Subjects Factors (WIQ-SC)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (WIQ-SC)

Source	SS	df	MS	F	p
T	1025.942	1	1025.942	4.234	.048
T X G	53.458	1	53.458	.221	.642
Error (T)	7511.032	31	242.291		

Tests of Between-Subjects Effects (WIQ-SC)

Source	SS	df	MS	F	P
Intercept	176307.131	1	176307.131	199.093	.000
G	6128.673	1	6128.673	6.921	.013*
Error	27452.115	31	885.552		

Walking Impairment Questionnaire Overall Scores (WIQ-O)Descriptive Characteristics (WIQ-O)

Variable	Group	Mean	Standard Deviation
WIQ-O1	Comparison	38.4950	18.40655
	Walking	52.3461	21.48616
WIQ-O12	Comparison	49.2687	17.54650
	Walking	62.2206	22.46794

Between-Subjects Factors (WIQ-O)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (WIQ-O)

Source	SS	df	MS	F	P
T	1744.137	1	1744.137	11.472	.002*
T X G	3.308	1	3.308	.022	.884
Error (T)	4713.078	31	152.035		

Tests of Between-Subjects Effects (WIQ-O)

Source	SS	df	MS	F	P
Intercept	167476.852	1	167476.852	249.955	.000
G	2938.912	1	2938.912	4.386	.044
Error	20770.278	31	670.009		

Quality of Life (SF-36) QuestionnairePhysical FunctionDescriptive Characteristics (SF-36 PF)

Variable	Group	Mean	Standard Deviation
SF-36PF1	Comparison	51.0786	15.70576
	Walking	61.6944	18.84049
SF-36PF2	Comparison	56.7857	17.82407
	Walking	70.8333	14.77777

Between-Subjects Factors (SF-36 PF)

Group	Value Label	N
.00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (SF-36-PF)

Source	SS	df	MS	F	p
T	867.843	1	867.843	10.645	.003
T X G	46.3711	1	46.371	.569	.457
Error (T)	2445.866	30	81.529		

Tests of Between-Subjects Effects (SF-36 PF)

Source	SS	df	MS	F	p
Intercept	227541.605	1	227541.605	466.334	.000
G	2395.133	1	2395.133	4.909	.034
Error	14638.104	30	487.937		

Role Limitations (SF-36RL)Descriptive Characteristics (SF-36RL)

Variable	Group	Mean	Standard Deviation
SF-36RL1	Comparison	39.3207	39.01975
	Walking	61.1111	41.61809
SF-36RL2	Comparison	57.1421	31.83528
	Walking	66.2039	41.95705

Between-Subjects Factors (SF-36 RL)

	Value Label	N
Group .00	Comparison	15
1.00	Walking	18

Tests of Within Subjects Effects (SF-36 RL)

Source	SS	df	MS	F	p
T	2067.427	1	2067.427	2.551	.121
T X G	637.948	1	637.948	.787	.382
Error (T)	24314.891	30	810.496		

Tests of Between-Subjects Effects (SF-36 RL)

Source	SS	df	MS	F	p
Intercept	197176.334	1	197176.334	86.957	.000
G	3747.928	1	3747.928	1.653	.208
Error	68025.257	30	2267.509		

Appendix S - Data Reduction

Correlation Summary Tables

Correlation Matrix – Cardiovascular measures Week 1

		HR1 (bpm)	SBP1 (mmHg)	DBP1 (mmHg)	MAP1 (mmHg)	RPP1 (bpmXmmHg)
HR1 (bpm)	Correlation Sig. (2-tailed) N = 33	1	.041 .819	.407 .019	.284 .109	.860 .000
SBP1 (mmHg)	Correlation Sig. (2-tailed) N =33	.041 .819	1	.437 .011	.817 .000	.539 .001
DBP1(mmHg)	Correlation Sig. (2-tailed) N = 33	.407 .019	.437 .011	1	.875 .000	.560 .001
MAP1 (mmHg)	Correlation Sig. (2-tailed) N =33	.284 .109	.817 .000	.875 .000	1	.648 .000
RPP1 (bpmXmmHg)	Correlation Sig. (2-tailed) N = 33	.860 .000	.539 .001	.560 .001	.648 .000	1

Correlation Matrix – Cardiovascular measures Week 12

		HR2 (bpm)	SBP2 (mmHg)	DBP2 (mmHg)	MAP2 (mmHg)	RPP2 (bpmXmmHg)
HR2 (bpm)	Correlation Sig. (2-tailed) N=33	1	.057 .754	.099 .583	.108 .549	.790 .000
SBP2 (mmHg)	Correlation Sig. (2-tailed) N=33	.057 .754	1	.337 .055	.810 .000	.649 .000
DBP2(mmHg)	Correlation Sig. (2-tailed) N= 33	.099 .583	.337 .055	1	.786 .000	.279 .116
MAP2 (mmHg)	Correlation Sig. (2-tailed) N = 33	.108 .549	.810 .000	.786 .000	1	.571 .001
RPP2 (bpmXmmHg)	Correlation Sig. (2-tailed) N =33	.790 .000	.649 .000	.279 .116	.571 .001	1

Correlation Matrix – Log of HRV measures Week 1

		LF power	HF power	Total power	PNS Ind	SNS Ind
LF power	Correlation Sig. (2-tailed) N=33	1	.743 .000	.870 .000	.127 .482	-.002 .993
HF power	Correlation Sig. (2-tailed) N=33	.743 .000	1	.845 .000	.693 .000	-.671 .000
Total power	Correlation Sig. (2-tailed) N= 33	.870 .000	.845 .000	1	.274 .123	-.298 .092
PNS ind	Correlation Sig. (2-tailed) N = 33	.127 .482	.693 .000	.274 .123	1	-.895 .000
SNS ind	Correlation Sig. (2-tailed) N =33	-.002 .993	-.671 .000	-.298 .092	-.895 .000	1

Correlation Matrix – Log of HRV measures Week 12

		LF power	HF power	Total power	PNS Ind	SNS Ind
LF power	Correlation Sig. (2-tailed) N=33	1	.733 .000	.764 .000	.106 .558	.155 .388
HF power	Correlation Sig. (2-tailed) N=33	.733 .000	1	.658 .000	.685 .000	-.558 .001
Total power	Correlation Sig. (2-tailed) N= 33	.764 .000	.685 .000	1	.182 .310	-.025 .892
LF power	Correlation Sig. (2-tailed) N = 33	.106 .558	.685 .000	.182 .310	1	-.866 .000
LF power	Correlation Sig. (2-tailed) N =33	.155 .388	-.558 .001	-.025 .892	-.866 .000	1

Correlation Matrix – Performance measures Week 1: 6MWT vs TM distance

		6MWT1 (m)	PFWD1 (m)	FCD (m)	MWD (m)
6MWT1 (m)	Correlation Sig. (2-tailed) N = 33	1	.403 .020	.486 .004	.528 .002
PFWD1(m)	Correlation Sig. (2-tailed) N = 33	.403 .020	1	.924 .000	.890 .000
FCD (m)	Correlation Sig. (2-tailed) N = 33	.486 .004	.924 .000	1	.953 .000
MWD (m)	Correlation Sig. (2-tailed) N = 33	.528 .002	.890 .000	.953 .000	1

Correlation Matrix – Performance measures Week 12: 6MWT vs TM times

		6MWT2 (m)	PFWD2 (m)	FCD2(m)	MWD2 (m)
6MWT2 (m)	Correlation Sig. (2-tailed) N = 33	1	.575 .000	.602 .000	.550 .001
PFWD2 (m)	Correlation Sig. (2-tailed) N = 33	.575 .000	1	.925 .000	.776 .000
FCD2 (m)	Correlation Sig. (2-tailed) N = 33	.602 .000	.925 .000	1	.838 .000
MWD2 (m)	Correlation Sig. (2-tailed) N = 33	.550 .001	.776 .000	.838 .000	1

Correlation Matrix – Self-report measures week 1WIQ

		WIQ-Overall1	WIQ-Distance1	WIQ-Stairs1	WIQ-Speed1
WIQ-overall1	Correlation Sig. (2-tailed) N = 33	1	.776 .000	.765 .000	.879 .000
WIQ-distance1	Correlation Sig. (2-tailed) N = 33	.776 .000	1	.283 .111	.543 .001
WIQ-stairs1	Correlation Sig. (2-tailed) N = 33	.765 .000	.283 .111	1	.605 .000
WIQ-speed1	Correlation Sig. (2-tailed) N = 33	.879 .000	.543 .001	.605 .000	1

SF-36

		WIQ-Overall1	SF-36 PF1	SF-36 RL1
WIQ-overall1	Correlation Sig. (2-tailed) N = 33	1	.555 .001	.494 .004
SF-36 PF1	Correlation Sig. (2-tailed) N = 33	.555 .001	1	.585 .000
SF-36 RL1	Correlation Sig. (2-tailed) N = 33	.494 .004	.585 .000	1

Correlation Matrix – Self-report measures week 12

Walking Impairment Questionnaire

		WIQ-Overall2	WIQ-Distance2	WIQ-Stairs2	WIQ-Speed2
WIQ-overall2	Correlation Sig. (2-tailed) N = 33	1	.768 .000	.812 .000	.862 .000
WIQ-distance2	Correlation Sig. (2-tailed) N = 33	.768 .000	1	.324 .066	.456 .008
WIQ-stairs2	Correlation Sig. (2-tailed) N = 33	.812 .000	.324 .066	1	.713 .000
WIQ-speed2	Correlation Sig. (2-tailed) N = 33	.862 .000	.456 .008	.713 .000	1

SF-36

		WIQ-Overall2	SF-36 PF2	SF-36 RL2
WIQ-overall2	Correlation Sig. (2-tailed) N = 33	1	.815 .000	.375 .031
SF-36 PF2	Correlation Sig. (2-tailed) N = 33	.815 .000	1	.608 .000
SF-36 RL2	Correlation Sig. (2-tailed) N = 33	.375 .031	.608 .000	1