METABOREFLEX RESPONSE TO ISOMETRIC HANDGRIP EXERCISE IN PEOPLE WITH PARKINSON DISEASE

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By

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Abstract

The metaboreflex is a peripheral feedback mechanism involved in the neural regulation of cardiovascular response to exercise. In young, healthy adults, this reflex responds to the accumulation of exercise- induced metabolites in active skeletal muscle, stimulating an increase in sympathetic nerve activity. This results in vasoconstriction and a significant rise in blood pressure, assisting in the maintenance of adequate muscle perfusion during physical activity (Smith, Mitchell, & Garry, 2005).

The purpose of this study was to evaluate metaboreflex response to isometric handgrip exercise in participants with idiopathic Parkinson Disease (N=10) and in an age-matched control group limited (N=3) due to difficulties with recruitment.

Metaboreflex response was evaluated using a standard protocol: heart rate and blood pressure were evaluated during (a) rest, (b) isometric handgrip at 40% of maximal voluntary contraction force, (c) post- exercise circulatory occlusion, and (d) recovery. These measurements were repeated following participation in an eight- week community exercise programme to determine the impact of initiation of regular physical activity on metaboreflex response in people with Parkinson Disease (PD).

Consistent with previous studies, participants with PD demonstrated a significant elevation in heart rate in response to isometric handgrip exercise ($p < 0.001$). Heart rate returned to baseline values upon cessation of exercise. There was no observable blood pressure response to isometric handgrip or post- exercise circulatory occlusion in either the PD or age- matched control groups suggesting a diminished metaboreflex response in both.

The diminished metaboreflex response seen in both the PD and control groups suggests impairment in peripheral response to exercise. As participants in both groups were significantly older than in previously reported literature (greater than 70 years of age compared to 55 – 66 years of age), this has important implications for future research and the monitoring of response to physical activity in older adults and people with PD, as altered responsiveness of this system may negatively impact upon fatigue and exercise tolerance in both populations.

Keywords: exercise response, metaboreflex, Parkinson disease

Dedication

This thesis is dedicated to my family for their unwavering support of my various enthusiasms.

The "Happy Gang" for the terrific holidays when I needed them most- nothing like mixing a little ditch digging, pyromania, and acrobatics; chicken catching and topsoil dancing. "There's excitement over here!"

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Sara for the marathon, non- thesis related phone calls; seven hours and counting...

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To my friends for asking and not asking how it was going through all of the above.

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Introduction

The nervous system plays a crucial role in the mediation of cardiovascular function during rest and exercise through the regulation of autonomic function. Furthering the understanding of autonomic control mechanisms and their contribution to response and tolerance of physical activity has become an area of interest in both healthy populations and in those with chronic conditions.

The integrated cardiovascular response to exercise is thought to reflect a number of factors, including cerebral cortex activation of cardiovascular related brainstem neurons, afferent input from arterial and cardiopulmonary baroreceptors, and afferent somatosensory input from contraction and metabolite- sensitive skeletal muscle receptors (Seals, 2005). The metaboreflex specifically, responds to a change in the metabolite concentration (lactic acid, hydrogen ions, potassium, among others) in skeletal muscle. The accumulation of these metabolites stimulates group IV afferent fibres and as a result, the reflex that increases sympathetic nerve activity to the muscle, stimulating vasoconstriction and a concomitant rise in blood pressure (Smith et al, 2005).

Parkinson Disease (PD) is a progressive, neurodegenerative disorder characterized by bradykinesia, tremor, rigidity, and postural instability. It has been well documented that people with Parkinson Disease (PD) are generally less active than their age- matched peers with this decrease in activity occurring prior to receiving a diagnosis of the disease (Canning, Alison, Allen, & Groeller, 1997; Chen, Zhang, Schwarzschild, Hernan, & Ascherio, 2005). Studies on cardiovascular response in people with PD have evaluated either the combined contribution of central and peripheral control of cardiovascular response, or have concentrated on central command alone (Levick, 2000).

Understanding the mechanisms controlling the response to exercise in persons with PD may be of importance in the management of cardiovascular dysfunction and fatigue in this population.

Literature Review

Parkinson Disease

Parkinson Disease (PD) is a progressive, neurodegenerative disorder characterized by bradykinesia, tremor, rigidity, and postural instability. The Parkinson Society of Canada estimates that approximately 100,000 Canadians have Parkinson Disease, with increasing age associated with increasing prevalence: one percent of the population over 65 and two percent over age 70 are currently affected (2005). Parkinson Disease is generally described as a movement disorder caused by the progressive loss of dopaminergic neurons in the basal ganglia: specifically, the substantia nigra. By the time of diagnosis, patients have typically lost 70 – 80% of these dopaminergic cells. The basal ganglia are involved in the expression of movement patterns, particularly automatic movement (for example, arm swing associated with walking). Lesions of the basal ganglia result in akinesia (difficulty initiating movement), difficulty controlling ongoing movement, rigidity, and the development of involuntary movement such as tremor or chorea (Gilman & Newman, 1996). While the motor disturbances associated with PD have been well evaluated, autonomic nervous system (ANS) dysfunction is also common and can result in impairments of the cardiovascular system (including orthostatic hypotension), bowel and bladder dysfunction, and impaired thermoregulation (Magerkurth, Schnitzer, & Braune, 2005).

Parkinson Disease is a recognized cause of primary autonomic failure with involvement of both central and peripheral autonomic nervous systems; both the sympathetic and parasympathetic systems (Senard, Brefel- Courbon, Rascol, & Montastruc, 2001). While the major features of PD are recognized to be loss of

dopaminergic neurons and the presence of Lewy bodies in the substantia nigra, neuronal cell loss and Lewy bodies occur in other areas as well: in the brainstem autonomic centres as well as post- ganglionic lesions in the periphery (Micieli, Tosi, Marchesseli, & Cavallini, 2003). Literature has indicated that over 90% of those diagnosed with PD will experience symptoms of autonomic dysfunction over the course of their disease; impacting upon not only quality of life, but also on morbidity and mortality. Therefore, it has been suggested that PD should be considered not only as a movement disorder, but as a dysautonomia as well (Dewey, 2004).

It has been demonstrated that people with Parkinson Disease (PD) are generally less active than their age- matched peers with this decrease in activity occurring prior to receiving a diagnosis of the disease (Canning, Alison, Allen, & Groeller, 1997; Chen, Zhang, Schwarzschild, Hernan, & Ascherio, 2005). Studies on cardiovascular response in people with PD have evaluated either the combined contribution of central and peripheral control of cardiovascular response, or have concentrated on central command alone (Levick, 2000). Understanding the mechanisms controlling the response to exercise in persons with PD may be of importance in the management of cardiovascular dysfunction and fatigue in this population.

The Nervous System

The integrated cardiovascular response to exercise is thought to reflect a number of factors, including cerebral cortex activation of cardiovascular related brainstem neurons, afferent input from arterial and cardiopulmonary baroreceptors, and afferent somatosensory input from contraction and metabolite- sensitive skeletal muscle receptors. The autonomic nervous system (ANS) plays a key role in this regulation through its

influence on heart rate and force of heart muscle contraction, constriction and dilation of blood vessels, and contraction and relaxation of smooth muscle in various organs (Seals, 2005). The nervous system consists of integrated central and peripheral components. The central nervous system (CNS) is comprised of the brain and spinal cord; the peripheral nervous system (PNS), all of the nervous tissue located outside of the CNS: cranial, spinal, and peripheral nerves- sensory and motor nerves that relay information to and from the periphery to the CNS. The PNS can further be divided into two functional components: the somatic nervous system (SNS) and the autonomic nervous system (ANS). The SNS consists of somatic and special sensory neurons and receptors that relay information from the periphery to the CNS as well as the motor neurons which convey output from the CNS to skeletal muscle causing muscle contraction. As a result, the somatic motor neuron system is considered to be primarily under voluntary control. The ANS consists of autonomic sensory neurons and receptors that relay information from the periphery to the CNS as well as the autonomic motor neurons which convey output from the CNS to smooth muscle, cardiac muscle, and glands. This system is primarily involuntary in nature (Waxman, 2003).

Autonomic nervous system

The ANS can be divided into three integrated operating systems based on anatomical and physiological differences: the enteric, sympathetic, and parasympathetic nervous systems. The enteric system consists of a network of neurons intrinsic to the gastrointestinal tract. The sympathetic system is generally considered to control the "fight or flight" responses to stimuli- namely pupillary dilation, increased heart and respiratory rates, and regulation of blood flow to the brain and skeletal muscle. This system

originates in preganglionic cell bodies located in the intermediolateral cell columns of the thoracic and first two lumbar segments of the spinal cord. Travelling through the ventral roots of the spinal nerves, the preganglionic axon extends to the sympathetic chain ganglia located lateral to the bodies of the thoracic and lumbar vertebrae through the white communicating rami. The preganglionic neuron then synapses with a number of postganglionic neurons at the same level, travels up or down the sympathetic trunk to synapse at higher or lower levels, passes through the trunk ganglia and out to synapse at a prevertebral ganglion, or extends and terminates in the adrenal medulla. The postganglionic fibres form the grey communicating rami and synapse at the target tissue. The parasympathetic system, in contrast, is often described as the conservation/ restoration, "rest and digest" response system; focused on the vegetative functions. This system originates in the preganglionic cell bodies located in the nuclei of cranial nerves II, VII, IX and X as well as in the grey matter of the brain stem and in sacral segments S2-4 of the spinal cord. The preganglionic neurons exit the CNS as part of a cranial nerve or as part of the anterior root of a spinal nerve and synapse with postganglionic neurons in terminal ganglia. In contrast to the sympathetic division, the terminal ganglia are located close to or within the wall of the innervated organ resulting in a more localized effect. While the functions of the sympathetic and parasympathetic systems have been described as having somewhat antagonistic features, they act in concert to maintain homeostasis at rest and during activity (Waxman, 2003; Tortora & Grabowski, 2004; Standring, 2005).

Acute Cardiorespiratory Response to Exercise

The autonomic centres in the CNS involved in cardiovascular regulation are located in the cerebral cortex, hypothalamus, and brainstem including: the rostral and caudal ventrolateral medulla, ambiguous nucleus, nucleus tractus solitarius, and are often collectively referred to as the "cardiovascular or vasomotor centres". There are four primary integrated functional areas: (a) the vasoconstrictor region located in the upper medulla and lower pons. This region sends fibres to the spinal cord activating sympathetic vasoconstrictor neurons, (b) the vasodilator region in the lower medulla. This region projects inhibitory fibres into the vasoconstrictor region, (c) the sensory region located in the nucleus tractus solitarius of the medulla and pons. This region is generally considered to be the integrating centre as it contains neurons receiving and integrating sensory input from both glossopharyngeal and vagal nerve fibres, and finally (d) the cardiac centre located in the medulla oblongata which regulates heart rate and contractility through stimulation of either sympathetic or parasympathetic neurons producing excitatory or inhibitory effects, respectively (Johnson, 1998; Levick, 2000; Ganong, 2005).

In healthy individuals, the initiation of exercise stimulates the withdrawal of cardiac vagal nerve activity. This reduction of parasympathetic activity, in combination with activation of sympathetic nerve activity, produces increases in heart rate, stroke volume, and cardiac output (cardiac output = stroke volume x heart rate). Increases in cardiac output result in increased systemic arterial blood pressure, increasing blood flow to the heart, respiratory, and active skeletal muscle in an effort to match the increase in metabolic demand within these systems (blood pressure = cardiac output x peripheral

vascular resistance). Increasing exercise intensity is accompanied by progressive vagal withdrawal until maximal exercise intensities are reached when no demonstrable cardiac vagal modulation of heart rate remains (Seals, 2005). In contrast, activation of the sympathetic nervous system generally occurs at exercise intensities associated with heart rates over 100 beats per minute (25-50% of maximum workloads). This activation also increases exponentially and has systemic effects on organs, and exercising and non-exercising muscle. Of particular importance is the sympathetically stimulated vasoconstrictor effect on exercising muscle. Activation of sympathetic nerves to arterioles produces local vasoconstriction assisting in redistribution of the increased cardiac output away from less involved structures. This local vasoconstriction supports the maintenance of cardiac output and systemic vascular resistance and consequently, systemic arterial perfusion pressure in the presence of significant, locally mediated, parasympathetically stimulated vasodilation occurring in active muscle (Seals, 2005). The interaction between sympathetically stimulated vasoconstriction and parasympathetically stimulated vasodilation assists in maintaining homeostasis of the system (Tortora & Grabowski, 2004; Seals, 2005). The current model for the cardiovascular response to exercise describes three neural control mechanisms responsible for regulation: (a) the arterial baroreflex, (b) central command, and (c) the exercise pressor reflex which includes the metaboreflex (Seals, 2005).

Baroreflex. The arterial baroreflex regulates blood pressure by modifying heart rate, stroke volume, and peripheral vascular resistance. Increased arterial blood pressure causes a "stretching" of the walls of the aortic arch and carotid sinus stimulating local mechanically- sensitive receptors. This local receptor activation signals the central

nervous system to both increase cardiac vagal modulation of heart rate and decrease sympathetic nervous system activity to the heart and vasculature, resulting in a decrease in heart rate and vascular resistance (through vasodilation), and ultimately lowered arterial blood pressure. Situations of decreased arterial blood pressure produce the opposite response. The arterial baroreflex is generally thought of as a feedback mechanism responsible for mediating acute changes in arterial blood pressure (Seals, 2005).

Central command. Central command involves activation of the cardiovascular control areas in the brainstem by the motor cortex to adjust sympathetic and parasympathetic activity during exercise. Current understanding suggests a feed- forward system of descending central motor command signals (in the primary motor cortex) generated in response to the *intent* to initiate activity. This results in activation of spinal motor units and muscle, as well as stimulation of areas of the brain involved in the regulation of ANS outflow to the periphery. Central command is thought to be primarily responsible for the initial motor and ANS responses to activity: namely, withdrawal of vagal modulation creating the resultant increase in heart rate. However, as exercise intensity or duration increases, the accompanying rise in blood pressure occurs primarily through peripheral responses- increases in sympathetic nerve activity and reductions in parasympathetic nerve activity stimulated by muscle activity; specifically, the build-up of exercise- induced metabolites. This peripheral neural drive is termed the exercise pressor reflex (Seals, 2005; Smith, Mitchell, & Garry, 2005).

Exercise pressor reflex. The exercise pressor reflex is a feedback mechanism originating in exercising muscle, and consists of an afferent and efferent arm. Activation

of the afferent arm is initiated by stimulation of mechanical and chemical- sensitive skeletal muscle receptors; mechano and metaboreflexes, respectively. Mechanoreceptors are stimulated by local pressure and active muscle tension, while metaboreceptors are activated by chemicals released during exercise. These afferent fibres (group III and group IV) project excitatory action potentials to the dorsal horn of the spinal cord and transmit sensory information to the brainstem. Although the specific pathway from the spinal cord to the brainstem is not yet fully understood, experimental studies have demonstrated both peripheral signal projection and peripheral effect on the nucleus tractus solitarius as well as the caudal and rostral ventrolateral medulla. The efferent arm of the reflex involves the projection of activated sympathetic neurons from the brainstem to the postganglionic neurons (innervating the heart and vasculature) via the preganglionic sympathetic neurons and sympathetic chain ganglia. This peripheral activation adjusts both sympathetic and parasympathetic activity during exercise: specifically, inducing tachycardia, increased myocardial contractility, and peripheral vasoconstriction resulting in increased arterial blood pressure and muscle perfusion. The exercise pressor reflex has therefore been described as a system for sensing and responding to under-perfusion of active muscle (Smith et al, 2005).

The metaboreflex specifically, responds to a change in the metabolite concentration (lactic acid, hydrogen ions, potassium, among others) in skeletal muscle. The accumulation of these metabolites stimulates group IV afferent fibres and as a result, the reflex that increases sympathetic nerve activity to the muscle, stimulating vasoconstriction and a concomitant rise in blood pressure (Smith et al, 2005).

The Metaboreflex

In 1937, Alam and Smirk published the first observations on changes in blood pressure in response to circulatory occlusion of working skeletal muscle in humans. Their results provided the first evidence of the role of accumulation of post- exercise metabolites in the maintenance of blood pressure. Elevations in blood pressure were observed in response to dynamic lower extremity exercise with a drop in blood pressure of only a few millimetres of mercury (mmHg) when cessation of exercise was accompanied by circulatory occlusion. Further, that this elevation in blood pressure was sustained until circulation was restored. Intermittent handgrip exercise with forearm cuff occlusion was also investigated, and again resulted in a rise in blood pressure during exercise with a slight drop on cessation, sustained until re- establishment of circulation. Results suggested that the initial rise in blood pressure was also dependent upon the intensity of the exercise performed. These findings pointed to the role of the accumulation of metabolites in sustaining blood pressure as well as the link between insufficient circulation, elevated blood pressure, and muscle fatigue, and were the first well- designed studies evaluating the role of the periphery alone in stimulating CNS response. Coote, Hilton, and Perez- Gonzalez (1971) later established, in animal studies, both the reflexive nature of the blood pressure response to ischemic exercise and its dependence upon exercising muscle. Using anaesthetized cats, they stimulated a blood pressure response by electrically stimulating contraction of hind limb muscle through the ventral roots of the lumbar and sacral spinal levels. On interrupting afferent input to the spinal cord through sectioning of dorsal roots at the spinal cord level or "abolishing" the dorsal root ganglion, the blood pressure response was also abolished. They further

demonstrated that ventral root stimulation without exercise (muscle work) did not stimulate a blood pressure response. Finally, their work established that occlusion of circulation exaggerated, but did not create, the observed response to ischemic muscle work: the stimulation and accumulation of exercise- induced metabolites and the resulting reflexive increase in blood pressure in response to circulatory occlusion. These findings led the authors to conclude that the increase in blood pressure seen following isometric exercise was due to the stimulation of chemical and not mechanical type III and IV afferent sensory nerve fibres. Bull, Davies, Lind, and White (1989) later investigated the individual contributions of central command and peripheral response by directly comparing the effect of voluntary and involuntary skeletal muscle work on the metaboreflex response. They found significant elevation in blood pressure and heart rate in response to two minutes of either voluntary or electrically evoked isometric contraction at 30% of maximum voluntary contraction (MVC) of the triceps surae in humans, with no significant difference between modes of muscle stimulation. Again, this study demonstrated a sustained increase in blood pressure response through the period of post- exercise circulatory occlusion. These findings supported previous works indicating that intentional or volitional exercise was not necessary to stimulate the increases in heart rate and blood pressure seen in the initial exercise response; therefore, that central command is not needed to generate this response. Further studies have indicated that the magnitude of the sympathetic response is dependent upon both mass of muscle used (though this remains controversial), and intensity of work (Khan & Sinoway, 2000; Seals, 1989).

Exercise Training

Similar to other physiological systems, ANS adaptations have been demonstrated in response to exercise training. These include: increased cardiac vagal modulation of heart rate and decreased sympathetic output. Increased cardiac vagal modulation (or vagal tone) is most clearly seen, though the mechanism is not as clearly understood, through the "training bradycardia" phenomenon: increased output from the parasympathetic nervous system resulting in lower resting and exercising heart rate and blood pressure demonstrated in the exercise- trained compared to sedentary individuals (Tortora & Grabowski, 2004; Seals, 2005).

The metaboreflex, specifically, has also been demonstrated to respond to exercise training in healthy individuals. Mostoufi- Moab, Widmaier, Cornett, Gray, and Sinoway (1998) demonstrated a decreased response to ischemic exercise in healthy adults as well as an increase in the threshold of external pressure needed to stimulate the reflex following four weeks of forearm muscle training. The findings suggested that training both reduced metabolite accumulation in exercising muscle and increased the ischemic threshold needed to stimulate the metaboreflex- a desensitization of muscle afferents to the presence of metabolites. The authors attributed their findings to increased efficiency of aerobic and decreased reliance on anaerobic metabolism with the net result being a decrease in metabolites generated, decreased stimulation/sensitization of the metaboreceptors, and therefore, a decreased sympathetic response. Results of a study by Carrington, Fisher, and White (1999) supported these findings. Comparing 400, 200, and 100m sprinters, the 400m sprinters (involved in a more anaerobic activity) demonstrated diminished blood pressure response to electrically stimulated (involuntary) exercise. This

suggests that chronic exposure to metabolic by- products of anaerobic exercise can decrease the metaboreflex response to exercise.

Autonomic Dysfunction in Parkinson Disease

The specific mechanisms underlying the impact of PD on the ANS are currently unclear. However, both anatomical and symptomatic changes have been well reported in the literature. Studies have demonstrated damage in the autonomic brain centres: hypothalamus, basal ganglia, reticular formation, dorsal nucleus of the vagus, and pre- and para- vertebral ganglia. The literature also indicates that the autonomic symptoms experienced by people with PD are wide- ranging: from orthostatic hypotension to gastrointestinal disturbances, genitourinary symptoms, and thermoregulatory dysfunction (Dewey, 2004). Orthostatic hypotension, in particular, has been widely studied due to its impact on the increased risk of falls experienced by those with PD (Chaudhuri, Healy, & Schapira, 2006).

It was previously thought that dysautonomia was a complication experienced by those in the advanced state of the disease. However, there is now a substantial body of evidence suggesting not only neuronal loss in the sympathetic nervous system, but progressive cardiac sympathetic denervation beginning in the early stages of PD (Goldstein, 2003; Bouhaddi et al., 2004; Oka et al., 2006; Chaudhuri et al., 2006). Component parts of the cardiovascular response to exercise have been examined in a small number of studies. Investigation of baroreflex response to activity in PD has demonstrated decreased baroreflex- cardiovagal function (the relationship between heart beat intervals and systolic blood pressure in response to activity) compared to age-matched controls with this impaired response further accentuated in individuals

experiencing both PD and orthostatic hypotension (Goldstein, 2003). Integrity of cardiovascular reflexes in people with PD has also been evaluated through examination of response to deep breathing and whole body tilting; an orthostatic provocation test reflecting a combination of peripheral vascular control and the ability to respond with compensatory tachycardia to stabilize blood pressure (Bouhaddi et al., 2004). Most significantly, the results indicate impairments in autonomic cardiac control occurring in the early stages of the disease (Turkka, Tolonen, & Myllyla, 1987; Martin et al., 1993; Mesec, Sega, Trost, & Pogacnik, 1999; Bouhaddi et al., 2004).

Acute Exercise Response in Parkinson Disease

Findings of dysfunction in the central command system are supported by studies evaluating response to acute bouts of exercise in patients with PD. These have generally demonstrated diminished heart rate and blood pressure response to exercise compared to age- matched controls regardless of whether workloads were measured in absolute or relative terms; for example, maximum workloads established by respiratory exchange ratios, or fatigue. While in healthy populations this might indicate the presence of a training effect or a better response to exercise, the literature indicates that people with PD demonstrate increases in submaximal heart rate and oxygen consumption during exercise and are not able to perform at the same absolute workloads compared to age- matched controls, indicating decreased exercise efficiency (Protas, Stanley, Jankovic, & MacNeill, 1996; Canning et al., 1997; Reuter, Engelhardt, Freiwaldt, & Baas, 1999; Mastrocola et al., 1999).

Isometric Exercise in Parkinson Disease

Five studies specifically comparing physiological response to isometric exercise in people with PD and controls were found in a review of the literature. The findings of all five suggest the presence of sympathetic nervous system dysfunction in this population. In 1985, Sachs, Berglund, and Kaijser compared cardiovascular responses in 20 participants with PD in the middle stages of disease severity (Hoehn & Yahr stages 2 – 4) to an age- matched control group of 15 participants. The effect of PD medication use was also evaluated, with the PD group examined both on and off PD- specific medication. Heart rate (HR) and blood pressure (BP) responses to two minutes of isometric handgrip at 33% of maximum voluntary contraction (MVC) were studied among other cardiovascular tests. Results indicated a significantly higher resting HR, significantly lower MVC of handgrip, and a significant decrease in HR and BP responses (both systolic and diastolic) in the PD group compared to controls. The diminished diastolic BP response was accentuated in participants when examined "on- medication" ($p < 0.05$ for all). The authors concluded that the results indicated impairments in central command and potentially in stimulation of peripheral receptors. In 1987, Ludin, Steiger, and Ludin compared HR and BP response to sustained isometric adduction of the thumb at 30% of MVC for five minutes in 22 participants with PD in the middle stages of disease severity (mean Hoehn & Yahr 2.7 ± 0.9) and 20 age- matched controls. Baseline BP was reported for two subgroups within the PD group: those taking, and not taking dopamine agonists, however the groups were combined for analysis. The authors again found that while both groups demonstrated significant increases in HR and BP, the response in those with PD was significantly diminished compared to controls ($p < 0.05$).

They concluded that the results indicated pathological response of, and damage to sympathetic pathways in participants with PD. In 1987, Turkka et al. examined BP response to isometric handgrip at 30% of MVC in a group of 30 participants with PD (ranging in disease severity from 2 to 18 on the Webster rating scale) and 21 age-matched controls. The PD group again demonstrated decreased diastolic BP response ($p < 0.02$) to the intervention leading the authors to conclude that, consistent with previous studies, participants with PD experience deterioration of the sympathetic ANS. Van Dijk et al. (1993) examined BP response to five minutes of isometric handgrip at 30% of MVC in 67 participants with PD and 31 age- matched controls. This study included participants with PD across the continuum of disease severity (stages 1.0 to 5.0 on the Hoehn & Yahr) and combined those on and off PD- specific medication. Baseline HR and BP was not significantly different between groups. Decreased systolic and diastolic BP responses to the intervention were demonstrated by the PD group as compared to the controls ($p < 0.01$). Regression analysis was undertaken to determine the effect of age, duration of disease, use of PD- specific medication, and disease severity on the results and demonstrated that both age and baseline BP significantly impacted upon BP response in the PD group, with increased age associated with diminished BP response. The directional impact of baseline BP was not reported. The authors concluded that the results of the study, consistent with previous literature, indicated diminished sympathetic activity in participants with PD. Finally, Martin et al. (1993) compared blood pressure response to isometric handgrip exercise at 30% of MVC for three minutes in 95 participants with PD (mean Columbia University Rating Scale for Parkinsonism (CURS) score 40.38 ± 13.63) of moderate severity and 53 age- matched controls. Participants with PD again

demonstrated decreased blood pressure response to the intervention ($p = 0.005$). Additional analysis indicated that age significantly impacted upon this response ($r = 0.29$). The authors concluded that the decreased response in the PD group contributed to the existing body of literature indicating ANS dysfunction in this population. The results of all five studies point to pathological response of the sympathetic system in PD, as evidenced by a diminished capacity to respond to physical activity, but do not distinguish between the central and peripheral contributions to this response as both pathways were operative during the interventions.

Two additional studies were found which examined BP response to handgrip in participants with PD and age- matched controls, but did not directly compare the responses between the two groups. Mesec et al. (1999) compared diastolic BP response to three minutes of isometric handgrip at 30% of MVC in 20 participants with early to moderate PD (Hoehn & Yahr stages 1-3) and 10 age- matched controls at two periods in time separated by three years. The study found a non- significant drop in blood pressure response to hand grip exercise over the three year period in both the PD and control groups, $p = 0.19$, and $p = 0.94$, respectively. The stated intention of this study was to monitor change over time in participants with PD. Therefore, the authors did not complete any comparisons between the PD and control group responses. Haapa[illegible]mi et al. (2000) examined the impact of various medication types on BP responses to a five-minute period of isometric hand grip exercise at 30% of MVC in 60 previously untreated participants with PD (median Hoehn & Yahr 1.75). The authors found a non- significant increase in BP response to hand grip exercise in participants taking levodopa ($p = 0.100$), and decreased BP response in participants taking bromocriptine and selegiline ($p = 0.076$

and $p = 0.038$, respectively). The authors concluded that PD- specific medications alter autonomic responses. Specifically, bromocriptine and selegiline decreased sympathetic response to isometric exercise, while levodopa appeared to mediate BP regulation failure while lowering BP levels at rest. Comparisons of PD and control group responses were not reported.

Although existing research has provided insight into the impairments of the ANS in PD, they do not specifically address the role of peripheral response to exercise. As previously mentioned, the current model supports the role of central command in the initial cardiovascular response to exercise- namely, immediate heart rate increases. However, with maintained contraction, the evidence suggests that afferent signals from the periphery become increasingly important. While previous studies suggest central sympathetic pathway dysfunction; by design, they are not able to delineate the individual contributions of the central and peripheral response systems particularly relevant in sustained muscle contraction. To date, there have been no studies found specifically evaluating the ability of peripheral response mechanisms, or the metaboreflex in isolation, to respond to ischemic exercise in people with PD. Due to this lack of data, the specific impact of the disease on this peripheral response system is unclear. However, studies have demonstrated that people with PD are generally less physically active than age- matched peers; demonstrate increased levels of fatigue, and decreased participation in, and tolerance of physical activity (Garber & Friedman, 2003). The ability to elevate blood pressure in response to exercise may play an important role in the tolerance of exercise as it is believed to improve perfusion in active muscle (Shoemaker, Kunselman, Silber, & Sinoway, 1998).

Research Question

The intention of this study was to evaluate metaboreflex response (as measured by mean blood pressure) to isometric handgrip exercise and post- exercise circulatory occlusion in people with Parkinson Disease. An exploratory investigation into the impact of participation in a regular exercise programme on this response in people with PD was also conducted.

Hypothesis

Metaboreflex response (as measured by mean blood pressure) to isometric handgrip exercise and post- exercise circulatory occlusion will be diminished in participants with Parkinson Disease as compared to controls.

Methods

Participants

14 participants (seven men and seven women) were recruited to participate in this study. 11 participants (six men and five women) with PD were recruited through the Northwestern Ontario Chapter of the Parkinson Society of Canada and the Movement Disorder and Neurology Day Clinics; both held at St. Joseph's Care Group (SJCG) in Thunder Bay, Ontario. Participants for the age- matched control group were solicited over a period of five months through advertisements posted at a city- run community centre for older adults, SJCG, the PD support group, local churches, and other community groups, as well as through targeted strategies aimed at family members of SJCG staff members. Due to limited success of recruitment, the age- matched control group consisted of three (3) participants (one man and two women) screened for the exclusion criteria.

Participants with PD were screened by a neurologist from the Movement Disorders Programme (London Health Sciences Centre) for the following:

Inclusion criteria: Idiopathic Parkinson Disease as diagnosed by a neurologist (UK Parkinson Disease Brain Bank criteria), Hoehn and Yahr stage 1.0 to 2.5, "on" stage of medication, stable PD medication regimen over the study period, and age 55 years and over.

Exclusion criteria: presence of an unstable medical condition, presence of other disorders that might affect balance (head injury, stroke, vestibular dysfunction, or peripheral neuropathy), current regular exercise (more than two sessions/ week with more

than 30 minutes/ session of continuous aerobic training and/or strength training), any musculoskeletal contraindications to exercise, and presence of dementia.

Experimental procedures and protocols were approved by SJCG Board Ethics Committee and Lakehead University Senate Research Ethics Board. All participants provided written, informed consent.

Measurement

Non- invasive continuous recordings of heart rate (HR), respiratory rate (RR), and blood pressure (BP) were obtained by means of a three- lead electrocardiograph (ECG), belt transducer fastened around the abdomen, and piezo- electric pulse transducer on the third finger of the left hand kept at heart level, respectively. Analog signals for blood pressure, heart rate, handgrip, and respiratory rate were continuously collected with an on- line data acquisition and analysis system (PowerLab, ADInstruments, Colorado Springs, Colorado). Maximal Voluntary Contraction (MVC) was determined for each participant prior to commencement of data collection through three trials using a handgrip dynamometer and participants positioned in supine using their right hand. MVC was defined as the peak force obtained over the three trials.

Protocol

All participants underwent standardized testing procedures between 0900 and 1200. Those with PD were scheduled during their "on" phase of medication to minimize the potential impact of the wearing- off phenomenon. Participants were positioned in supine, and MVC was determined. Isometric handgrip exercise at 40% MVC was practised by all participants prior to commencement of testing.

Following a resting baseline of five minutes (REST), participants performed two minutes of isometric handgrip at 40% of their maximal voluntary contraction force (HG). The grip force generated was displayed numerically on a screen visible to participants to allow for visual feedback of performance. Vaillancourt, Slifkin, and Newell (2002) reported increased force variability of isometric handgrip in older adults and those with PD; however, this variability was mediated by the use of visual feedback of performance. Approximately three seconds prior to the end of the handgrip period, a blood pressure cuff on the exercising arm was inflated to approximately 200 mmHg for two minutes to induce ischemia and continue stimulation of sympathoexcitatory muscle afferents (CUFF). A two- minute recovery period followed (REC). Blood pressure calibrations were performed at regular intervals throughout the protocol on the non- exercising arm (at baseline, three minutes, five minutes, 11 minutes, and at 21 minutes).

All assessments were conducted at St. Joseph's Hospital in Thunder Bay, Ontario with a physician on site. Participants with PD were evaluated at two points in time: one week prior to participation in an eight- week community exercise programme (T1), and one week immediately following completion of this programme (T2). The control group was evaluated at one point in time.

Exercise Programme

Participants with PD completed a one- hour, twice- weekly exercise programme, eight weeks in duration delivered in a city- run community centre by a community fitness facilitator trained to deliver an exercise programme to this population. The exercise class was general in nature and focused on physical impairments and functional limitations commonly experienced by people with PD: specifically, respiratory muscle weakness,

rigidity, and lower- extremity muscle weakness (Inkster, Eng, MacIntyre, & Stoessl, 2003; Paasuke et al., 2004). See Appendix 1 for specifics related to the exercise programme.

Analysis

Heart rate, respiratory rate, and mean blood pressure (MBP; 1/3 SBP + 2/3 DBP) were analyzed and compared over the course of the four intervention periods: REST, HG, CUFF, and REC (Chart software, ADInstruments, USA). Data was expressed as mean ± standard error of the mean (SEM). The changes in each parameter between interventions (REST, HG, CUFF, REC) were compared within- participants, pre- and post exercise (T1 and T2) using a two- way repeated- measures ANOVA. Post hoc comparisons were made using the Student- Newman- Keuls Method. Significance was assumed at $p < 0.05$ (Sigma Stat, Systat Software Inc., Point Richmond, CA).

Following initial analysis demonstrating non- significant findings associated with participation in the exercise programme, data associated with the PD group was pooled to maximize the number of available data collections for each of the variables: heart rate, respiratory rate, and mean blood pressure (Brown, 2002). For those participants with viable data at both T1 and T2, the mean of each variable was used. For those with only one viable data collection, this set was used for each of the variables. Merged data from the PD group was then compared to the control group with the changes in each parameter between interventions (REST, HG, CUFF, REC) evaluated using a two- way repeated-measures ANOVA. Post hoc comparisons were made using the Student- Newman- Keuls Method. Significance was assumed at $p < 0.05$ (Sigma Stat, Systat Software Inc., Point

Richmond, CA). Effect size was established using eta squared and Cohen's definition of effect size as "small, $eta^2 = 0.01$; medium, $eta^2 = 0.06$; and large, $eta^2 = 0.14$".

On completion of data analysis, secondary analysis was undertaken to verify results and control for extraneous variation between the PD and control groups at baseline. This was evaluated using an ANCOVA with significance assumed at $p < 0.05$ (SPSS for Windows, Rel. 11.0.1, SPSS Inc., Chicago, IL).

Results

Participants with Parkinson Disease

Participant characteristics are depicted in Table 1. Eleven participants with PD participated in pre- testing. One of the original 11 participants with PD was unable to attend the second testing session (T2) due to family illness. Data related to this participant was therefore not included in analysis.

Table 1.

Baseline Characteristics (SEM)	T1	T2
Participants (N)	11	10
Male/Female	6/5	6/4
Age	70.45 (1.98)	70.5 (2.20)
Mean Modified Hoehn & Yahr	2.0 (1.76)	2.0 (1.67)
Mean Disease Duration (Years)	3.27 (1.62)	3.35 (1.72)
Resting Heart Rate (HRrest)	74.10 (2.04)	72.46 (3.90)
Resting Respiratory Rate (RRrest)	15.77 (0.80)	15.62 (1.37)
Resting Mean Blood Pressure (MBPrest)	75.69 (5.20)	75.63 (1.81)
Maximum Voluntary Contraction (mV)	4.00 (0.61)	4.18 (0.83)

Handgrip

Participants with PD were able to maintain isometric handgrip for two minutes at a mean of 37.97% ± 3.15 MVC (26.45 – 64.90%) and 42.68% ± 7.61 MVC (29.41 – 110.60%) at T1 and T2 respectively. This difference was not significant, $p = 0.542$.

Changes in Heart Rate Response

Participants with PD demonstrated significant change in heart rate in response to the test interventions at both T1 and T2: $F(3, 27) = 7.00$, $p = 0.001$ with medium effect size ($eta^2 = 0.064$). See Figure 1. Post hoc analysis indicated significant elevation in heart rate from REST to HG ($p = 0.003$), a significant decrease from HG to CUFF ($p = 0.018$), and again significant decrease from HG to REC ($p = 0.003$). Participation in the eight-week supervised exercise programme did not impact significantly upon this response; there was no effect of time: $F(1, 27) = 1.37e\text{-}8$, $p = 1.00$; with no effect size demonstrated ($eta^2 = 6.75e\text{-}10$). There was further, no significant interaction between time and intervention: $F(3, 27) = 0.65$, $p = 0.59$, with effect size approaching small ($eta^2 = 0.007$).

Changes in Respiratory Rate Response

A number of participants with PD demonstrated decreased depth of respiration (as measured by decreased chest expansion) during testing sessions. As a result, six (6) of 10 complete sets of respiration rates were available for analysis at T1 and T2. Participants demonstrated a significant change in respiratory rate in response to the test interventions: $F(3, 15) = 3.74$, $p = 0.035$, with moderate to large effect size demonstrated ($eta^2 = 0.078$). See Figure 2. However, post hoc analysis indicated significant change in respiratory rate between HG and REC only ($p = 0.022$); a decrease between the two

interventions. As in the heart rate response, participation in the eight- week supervised exercise programme did not impact significantly upon respiratory rate; there was no effect of time: F (1, 15) = 0.002, p = 0.96; with no demonstrable effect size (eta^2 = 1.24e-4). There was not a significant interaction between time and intervention: F (3, 15) = 0.72, p = 0.55, with a small effect size (eta^2 = 0.01).

Changes in Blood Pressure Response

Due to the presence of significant hand tremor experienced by a number of the participants with PD, five (5) of 10 complete sets of blood pressure data were available for analysis at T1 and T2. No significant differences in mean blood pressure were observed as a result of the test interventions: F (3, 12) = 0.33, p = 0.80, with effect size approaching small (eta^2 = 0.003). See Figure 3. Post hoc analysis did not reveal any significant within- factor effects ($p < 0.05$). Again, participation in the exercise programme did not significantly impact on blood pressure response in people with PD; there was no effect of time: F (1, 12) = 0.06, p = 0.81, with a small effect size demonstrated (eta^2 = 0.01). There was not a significant interaction between time and intervention: F (3, 12) = 1.39, p = 0.29, with a small effect size (eta^2 = 0.01).

Figure 1
Heart Rate Response

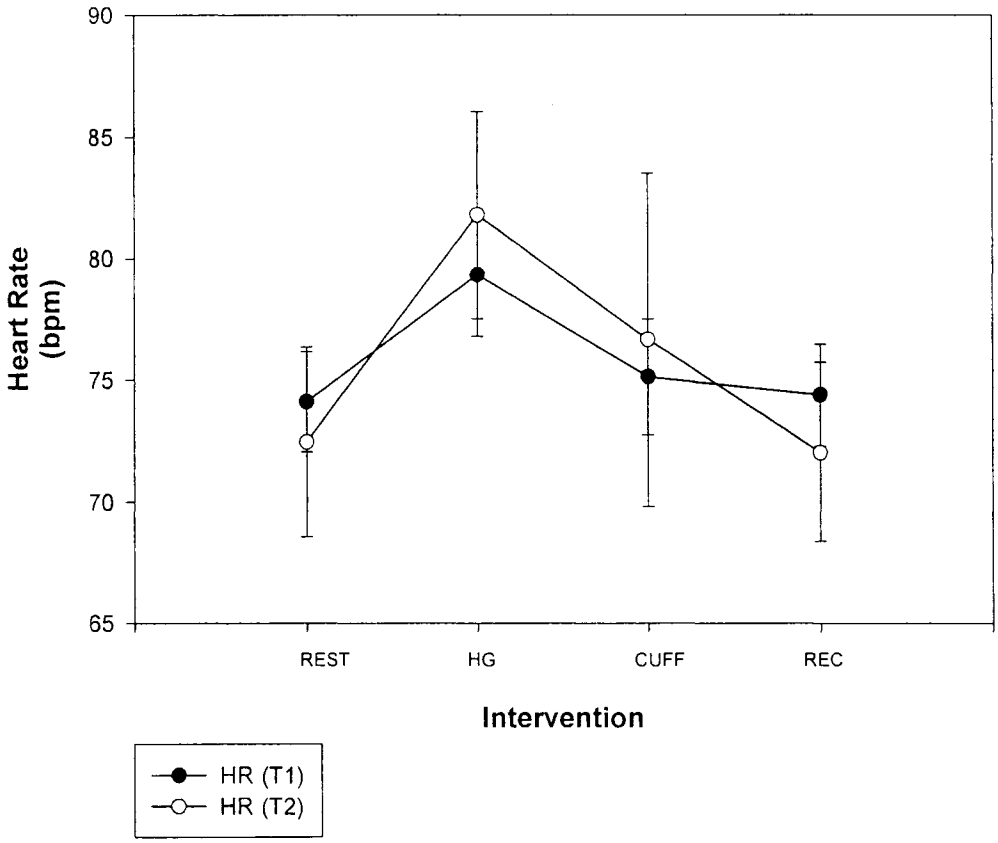


Figure 1. Heart Rate Response

Figure 2
Respiratory Rate Response

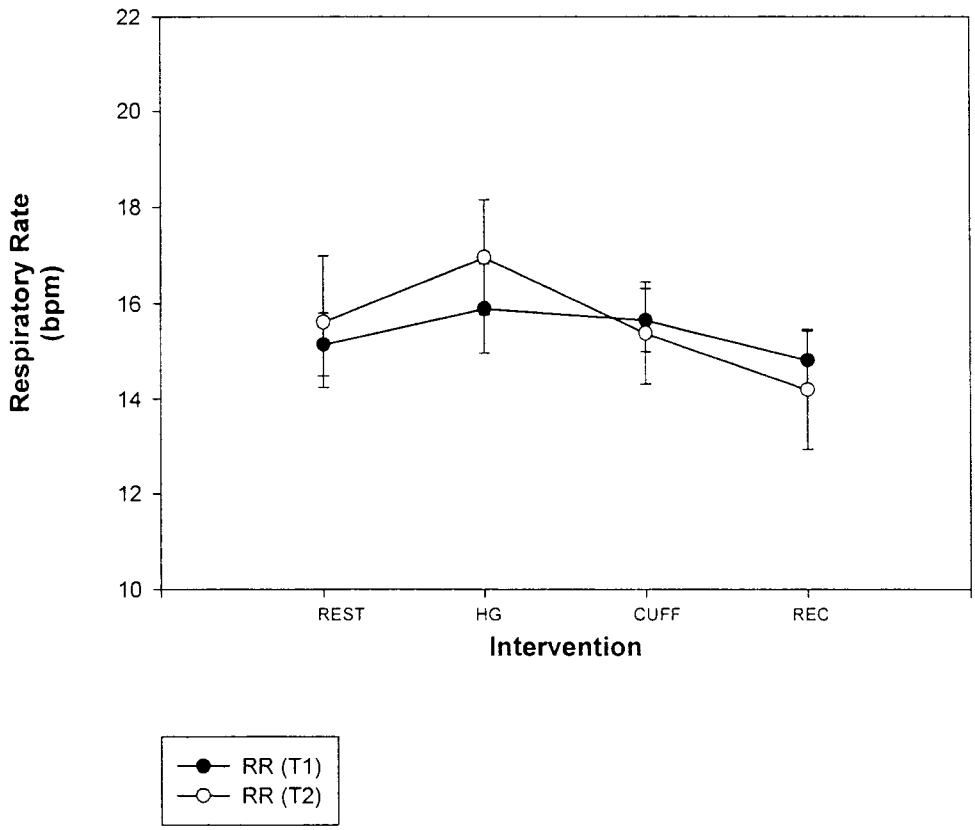


Figure 2. Respiratory Rate Response

Figure 3
Blood Pressure Response

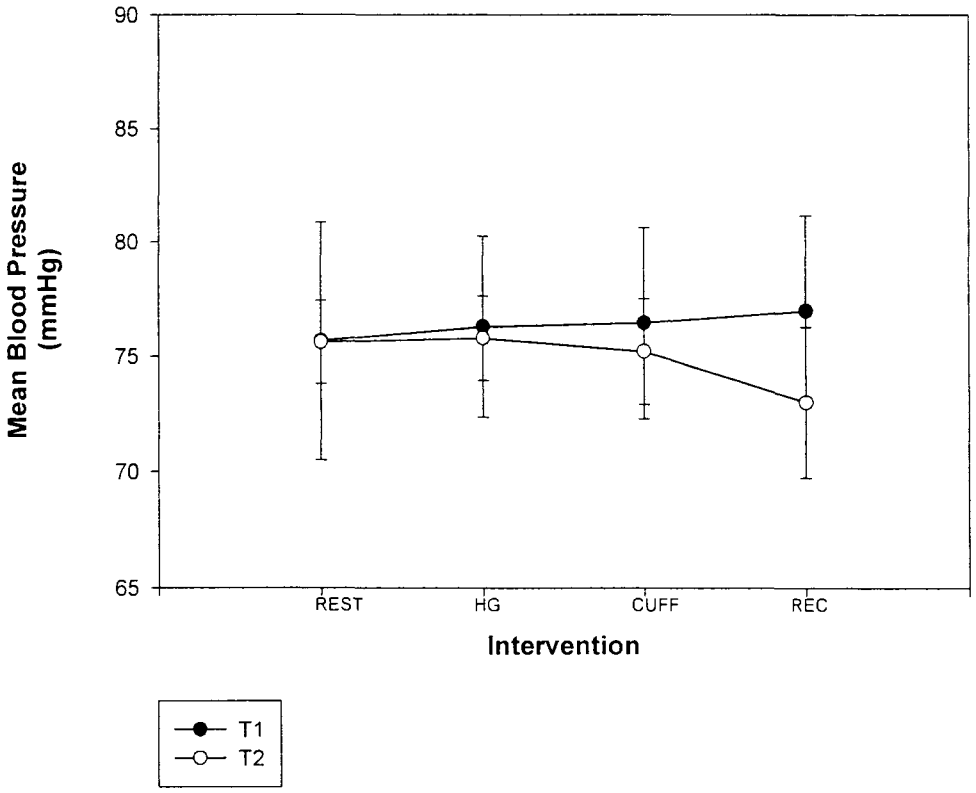


Figure 3. Blood Pressure Response

Comparison of PD and Control Groups

Pooling data from the participants with PD was completed in order to maximize the number of available data collections, correct for missing values, and increase confidence in study findings indicating a diminished metaboreflex response in the PD group. This resulted in 11 complete collections of heart rate and respiratory rate data and nine (9) complete collections of mean blood pressure data. This data was compared to that of three (3) age- matched controls. Participant characteristics are described in Table 2.

Table 2.

Baseline Characteristics (SEM)	PD	Control
Participants (N)	11	3
Male/Female	6/5	1/2
Mean Age	70.45 (1.98)	77.00 (4.51)
Mean Modified Hoehn & Yahr	2.0 (1.67)	
Mean Disease Duration (Years)	3.27 (1.62)	
Resting Heart Rate (HRrest)	72.17 (1.12)	60.49 (2.12)
Resting Respiration Rate (RRrest)	15.28 (0.35)	16.36 (1.16)
Resting Mean Blood Pressure (MBPrest)	78.80 (2.36)	75.38 (6.72)
Maximum Voluntary Contraction (mV)	4.32 (0.65)	3.00 (1.73)

Handgrip in PD and Control Groups

Participants with PD maintained isometric handgrip for two minutes at a mean of 39.81% ± 4.94 MVC (30.24 – 87.99%), while the control group maintained isometric handgrip for two minutes at a mean of 35.36% ± 1.84 MVC (31.72 – 37.59). The difference in hand grip between the two groups was not significant ($p = 0.657$).

Heart Rate Response in PD and Control Groups

There was a significant difference in heart rate between the PD and control groups: $F(1, 36) = 17.84$, $p = 0.016$, with a large effect size ($eta^2 = 0.33$). Overall, a significant change in heart rate in response to the test interventions was demonstrated with an increase in heart rate from REST to HG, and a progressive decrease in heart rate from HG to CUFF and CUFF to REC: $F(3, 36) = 4.35$, $p = 0.010$, with small to medium effect size ($eta^2 = 0.036$). See Figure 4. There was not a significant interaction between group and intervention: $F(3, 36) = 0.48$, $p = 0.70$, with effect size approaching small ($eta^2 = 0.004$).

Respiratory Rate Response in PD and Control Groups

There was no significant difference in respiratory rate response between the PD and control groups: $F(1, 36) = 5.83e\text{-}4$, $p = 0.98$, with no demonstrable effect size ($eta^2 = 3.50e\text{-}5$). The change in respiratory rate in response to the test interventions approached significance: $F(3, 36) = 2.74$, $p = 0.057$, with a small to moderate effect size ($eta^2 = 0.047$). See Figure 5. There was not a significant interaction between group and intervention: $F(3, 36) = 1.02$, $p = 0.40$, with a small effect size demonstrated ($eta^2 = 0.01$).

Blood Pressure Response in PD and Control Groups

Pooling of the data resulted in nine (9) of 11 complete sets of blood pressure available for analysis in the PD group. There was not a significant difference in blood pressure response between the PD and control groups: $F(1, 30) = 0.457$, $p = 0.52$, with a small to medium effect size ($eta^2 = 0.04$). Neither group demonstrated a significant change in mean blood pressure in response to the test interventions: $F(3, 30) = 0.237$, $p = 0.87$, with effect size approaching small ($eta^2 = 0.002$). See Figure 6. There was not a significant interaction between group and intervention: $F(3, 30) = 0.230$, $p = 0.88$, with effect size approaching zero ($eta^2 = 0.002$).

Figure 4
Heart Rate Response

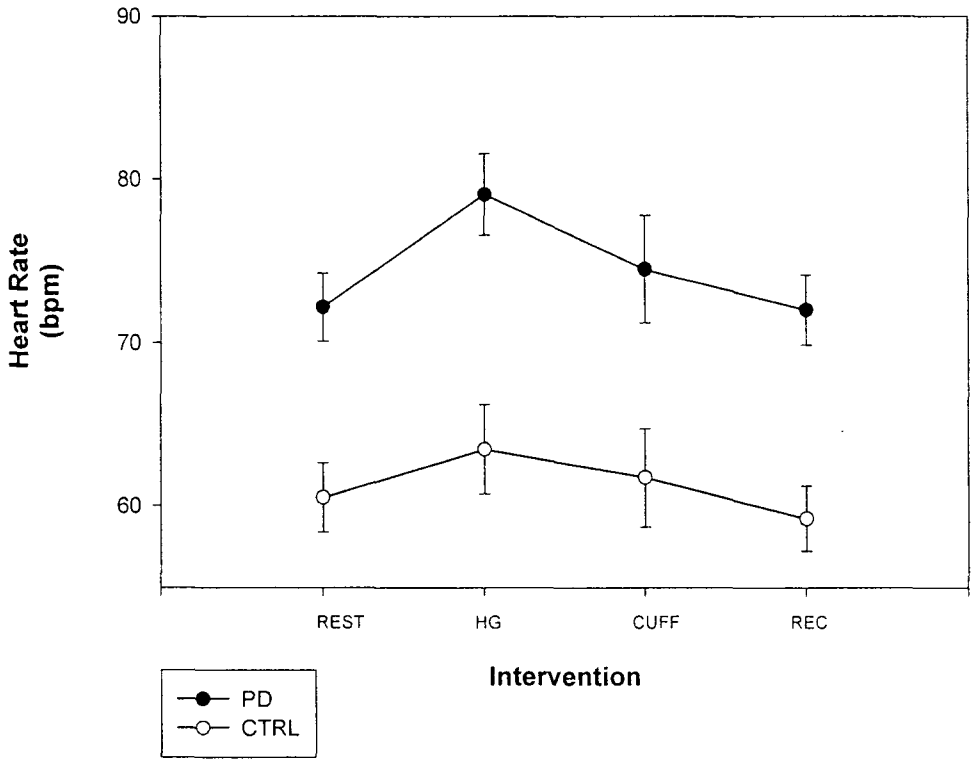


Figure 4. Heart Rate Response

Figure 5
Respiratory Rate Response

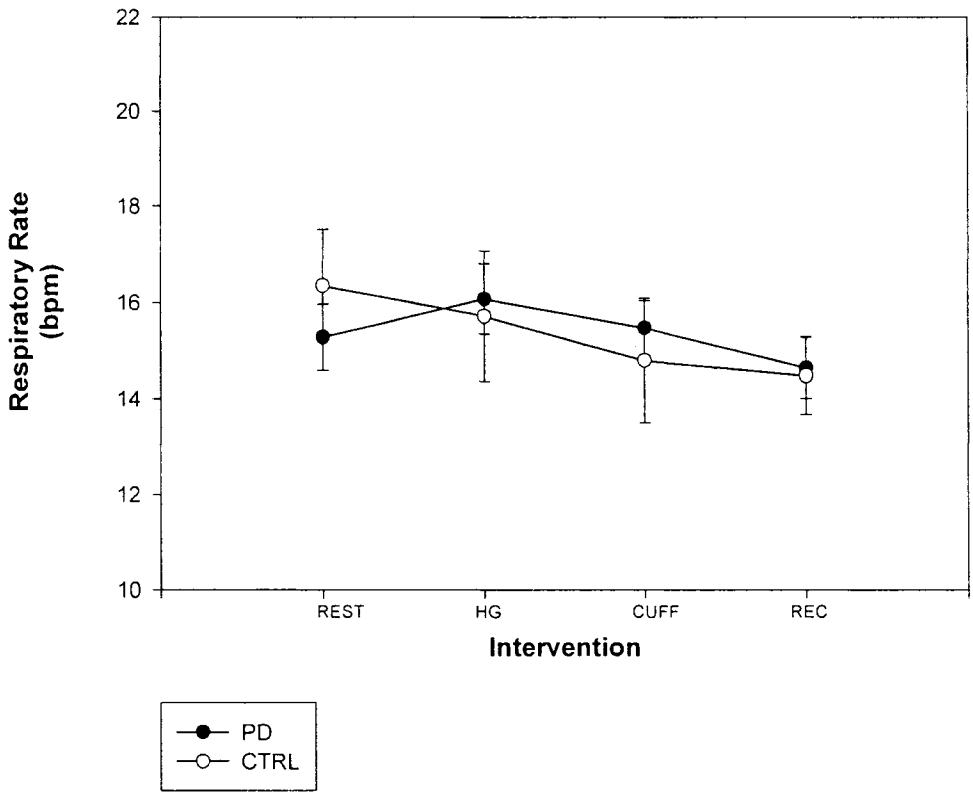


Figure 5. Respiratory Rate Response

Figure 6
Blood Pressure Response

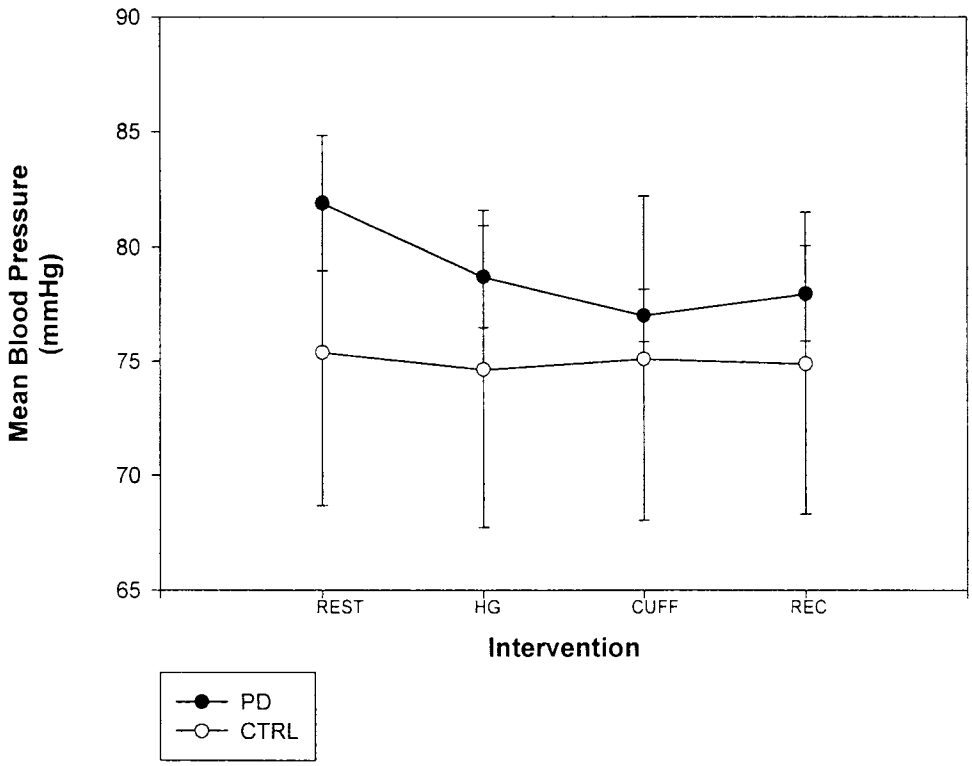


Figure 6. Blood Pressure Response

Secondary Analysis

Secondary analysis was undertaken to verify the lack of differences observed in the PD and control group intervention responses. To maximize statistical power, only baseline (REST) and HG data were used. Controlling for extraneous variation, allows for a more accurate estimation of the differences between groups. Therefore, the differences between these two time periods were analyzed using REST values as the covariates to control for baseline differences between the PD and control groups. An ANCOVA was used to produce adjusted means. After controlling for the covariates HRrest, RRrest, and MBPrest, the assumption of homogeneity of variance was met for HR: $F(1, 14) = 1.632$, $p = 0.226$, RR: $F(1, 14) = 0.238$, $p = 0.634$, and MBP: $F(1, 12) = 2.512$, $p = 0.144$. The adjusted means for change in HR were 4.537 ± 0.757 and 4.742 ± 1.670 for the PD and control groups, respectively. The difference in the means between the two groups was not statistically significant: $F(1, 14) = 0.11$, $p = 0.919$. The adjusted means for change in RR were 0.762 ± 0.467 and -0.512 ± 0.906 for the PD and control groups, respectively. Again, the difference in adjusted means between the groups was not statistically significant: RR: $F(1, 14) = 1.541$, $p = 0.240$. Finally, the adjusted means for change in MBP were -0.151 ± 0.615 and -0.951 ± 1.077 for the PD and control groups, respectively. The difference in adjusted means between the groups was not statistically significant: $F(1, 12) = 0.410$, $p = 0.538$. These results indicate that there was not a significant difference in HR, RR, or MBP response between the PD and control groups after accounting for baseline differences.

Discussion

Previous studies have evaluated the role of central command alone or peripheral response in combination with central command in regulating autonomic nervous system response in people with PD during physical activity (Bouhaddi et al., 2004; Goldstein, 2003). A review of available literature failed to find any studies specifically investigating metaboreflex response in participants with PD, isolating the role of this peripheral, afferent system in ANS dysfunction in this population.

Based on available metaboreflex literature to date, participants with PD in this study demonstrated a less than expected exercise pressor response, and as hypothesized, a decreased metaboreflex response to ischemic exercise: there was no significant increase in blood pressure in response to the handgrip exercise with maintenance of this increase during post- exercise circulatory occlusion. However, in contrast to previous studies, this diminished response was not significantly different from that demonstrated by the age-matched control group. Two potential factors may explain the difference in findings between this and previous studies. First, the literature examining physiological response to isometric exercise in people with PD is limited and methodologically problematic. Second, that due to age or inadequacy of exercise intensity, the level of post- exercise metabolite stimulation/ accumulation was inadequate to stimulate a metaboreflex response in either the PD or control group in this study.

Literature on isometric exercise in Parkinson disease

A review of the literature found only five studies investigating physiological responses to isometric exercise in participants with PD and directly comparing these responses to an age- matched control group (Sachs et al., 1985; Ludin et al., 1987;

Turkka et al., 1987; Van Dijk et al., 1993; Martin et al., 1993). None specifically addressed the role of the metaboreflex. The studies demonstrate similar methodological flaws: a) lack of homogeneity in the PD group, including reporting but not accounting for differences in PD- specific medication use, and b) lack of data or analysis related to baseline differences between PD and control groups.

Participant Homogeneity

All five studies mentioned above demonstrate challenges to participant homogeneity in the PD groups examined. This undermines confidence in study findings indicating diminished physiological response to isometric exercise in this population. Lack of clearly identified inclusion criteria, or criteria including participants with a broad range in age or disease severity affected a number of the studies. Ludin et al. (1987) examined HR and BP response to sustained isometric adduction of the thumb in participants with PD and age- matched controls. The authors concluded that the diminished HR and BP responses demonstrated by the PD group indicated both a pathological response and damage to sympathetic pathways in participants with PD. However the inclusion criteria, and specifically disease severity was not clearly defined. The mean Hoehn and Yahr score reported was 2.7 ± 0.9 indicating that the PD group included those with both mild and moderate severity of disease. Those scoring 1 or 2 on the Hoehn and Yahr are considered to be in the mild stages of the disease, experiencing either unilateral involvement or bilateral/ midline involvement without balance impairments, while those at stage 3 are considered to be at a moderate stage of the disease and demonstrate unsteadiness and restrictions in activity (Hoehn & Yahr, 1967). Although the authors reported regression analysis indicating that age, disease duration,

and disease severity did not correlate with study findings, this data and analysis was not reported.

Van Dijk et al. (1993) examined BP response to isometric handgrip in participants with PD and age- matched controls. This study included participants with PD across the continuum of disease severity (stages 1.0 to 5.0 on the Hoehn & Yahr). Again, the PD group demonstrated decreased systolic and diastolic BP responses to the intervention ($p < 0.01$). As mentioned previously, people with PD at stages 1 and 2 on the Hoehn and Yahr are considered to be in the early or mild stages of the disease, those at stage 3, moderate, while those at stages 4 and 5 are described as being "severely disabled" (Hoehn & Yahr, 1967). While regression analysis was undertaken to determine the effect of age, medication use, disease duration, and disease severity, participants from across the spectrum of disease severity were combined into a single group for analysis.

Finally, Martin et al. (1993) compared blood pressure response to isometric handgrip exercise in participants with PD and age- matched controls. While mean age was reported as 68, participants ranged in age from 45 to 91 years of age. Participants with PD again demonstrated decreased blood pressure response to handgrip exercise ($p = 0.005$), with regression analysis demonstrating that age significantly impacted upon this response. A positive relationship between age, disease severity, and ANS dysfunction has been identified in people with PD with increasing age and Hoehn & Yahr scores associated with diminished ANS responsiveness (Martin et al., 1993; Van Dijk, et al, 1993; Mesec et al., 1999; Bouhaddi et al., 2004; Dewey, 2004; Chaudhuri et al., 2006). While the literature indicates the presence of ANS dysfunction early in the disease (Oka et al., 2006; Chaudhuri et al., 2006), combining participants across broad categories of

age and disease severity assumes an equal distribution of ANS dysfunction across the continuum of age and disease process and potentially masks progression of ANS dysfunction. This assumption of equal distribution has the potential to overestimate the presence of diminished ANS responsiveness in people in the early stages of disease severity, and limits confidence in study findings.

Inconsistent reporting and analysis regarding the use of various classes of PD-specific medication is another factor affecting participant homogeneity in the studies to date on physiological response to isometric exercise in participants with PD. As mentioned previously, the literature indicates that the different classes of PD- specific medication produce varied impacts upon ANS response in this group (Haapaniemi et al., 2000). Sachs et al. (1985) examined HR and BP responses to two minutes of isometric handgrip and the effect of PD- specific medication use; levodopa in combination with a decarboxylase inhibitor. Results indicated a significantly higher resting HR, significantly lower MVC of handgrip, and a significant decrease in HR and BP responses to the handgrip exercise in the PD group as compared to controls. The attenuated diastolic BP response was further decreased in participants when "on- medication" ($p < 0.05$ for all). However, comparisons were only made between medicated and un- medicated participants with PD and between the un- medicated PD group and controls. No comparison was made between the medicated PD group and controls either at baseline, or in response to the handgrip exercise. As a result, it is not possible to determine how the use of levodopa impacted upon either baseline measures or performance in PD relative to controls.

In the 1987 study by Ludin et al., baseline data related to two subgroups within the PD group was reported, those on and off dopamine agonists. However, these subgroups were combined for analysis despite significant differences. Baseline BP (systolic and diastolic) was reported to be significantly diminished in the PD group, however this was only the case in the combined PD group and in the PD group taking a dopamine agonist. Those participants with PD not taking a dopamine agonist did not demonstrate significantly different baseline BP from the control group. On examination of baseline data, almost double the participants were taking a dopamine agonist as not ($n = 13$ versus $n = 7$), resulting in a skewing of the data toward the results found in the medicated group, and introducing wide variation in findings as evidenced by the large standard deviations. Baseline systolic and diastolic BP were reported as 143.06 ± 13.56 and 93.33 ± 8.56 in the control group, and 131.25 ± 20.42 and 85.58 ± 10.03 in the combined PD group. As only the combined group was compared with the controls, one is unable to distinguish between the effects of medication use and the disease itself on the diminished response found.

Turkka et al. (1987) examined cardiovascular reflexes in participants with PD and age- matched controls. The PD group demonstrated decreased diastolic BP response to the handgrip intervention ($p < 0.02$), leading the authors to conclude that participants with PD experience deterioration of the sympathetic ANS. Again, significant data and analysis was lacking. While the study reported no differences in performance between those treated with two different types of medication (levodopa or anticholinergics), the two groups were combined, and results and analysis were not provided.

As in the previous studies, Martin et al. (1993) and Van Dijk et al. (1993) included participants with PD on and off various types of PD- specific medication. Regression analysis failed to find a relationship between the use of PD- specific medication and results in the study by Martin et al. However, a significant difference in response between those on and off medication was demonstrated in the Van Dijk study, with those taking PD- specific medications of any class demonstrating decreased autonomic responsiveness to testing procedures. The lack of clarity regarding reporting and analysis of PD- specific medication use and its effects lessens the degree to which the individual impact of disease and disease- specific medication on ANS dysfunction can be determined.

Baseline Differences

Finally, reporting of baseline differences between PD and control groups and analysis accounting for these differences is inconsistent in the studies examining response to isometric exercise in people with PD, undermining confidence in study findings. The 1985 study by Sachs et al. indicated a significantly higher resting HR, significantly lower MVC of handgrip, and a significant decrease in HR and BP responses in the PD group compared to controls. However, analysis determining the effect of baseline differences between PD and control groups on the results was not reported. Baseline HR, and MVC of handgrip of the unmedicated PD group was significantly different than that of the control group ($p < 0.05$ for all). MVC of handgrip of the medicated PD group was not reported. Ludin et al. (1987) also reported a significant difference in baseline BP between PD and control groups ($p < 0.05$) without further analysis examining the impact of this difference on the decreased ANS response to exercise demonstrated by the participants

with PD. In addition, the ability of participants with PD to achieve MVC relative to that of the control group was not reported and the potential effect of workload on the response was, therefore, also unaddressed. Baseline values of HR, BP, and MVC were not reported for either the PD or control groups in the studies by Turkka et al. (1987) and Martin et al. (1993), again preventing analysis of the effect of possible baseline differences between groups. Van Dijk et al. (1993) also did not report baseline MVC for the PD and control groups. Therefore, the ability of participants to perform at workloads similar to age-matched controls was not established. The lack of reporting and analysis of baseline differences between PD and control groups has important implications on study findings. Without further analysis, it is not possible to determine whether the attenuated HR and BP responses demonstrated by the PD groups in these studies could have been explained by baseline differences, and whether the significantly lower MVC demonstrated by the PD groups (where reported) impacted upon these results. Studies on young, healthy participants have demonstrated that work intensity affects the magnitude of the metaboreflex response, with higher workloads generating more metabolic by- product and therefore an increased metaboreflex response than that simulated by lower intensity workloads (Cornett et al., 2000). This raises the possibility that the attenuated response demonstrated by the PD groups could have been explained by decreased workload intensity.

While the results of the present study demonstrate findings in contrast to previous literature, review of the existing research reveals inconsistencies in data reporting and analysis and generally, lack of accounting for the potential confounding factors of medication use, ability to generate force levels similar to that of age- matched controls,

and baseline differences in physiological measures. These methodological problems undermine confidence in study findings and do not allow for the isolation of the individual contributions of disease severity, medication use, and baseline differences on results indicating a diminished physiological response to isometric exercise in participants with PD as compared to controls.

Post- exercise metabolite levels

In the present study, consistent with previous literature, heart rate increased in response to isometric handgrip exercise and returned toward baseline values on cessation of exercise in both the PD and control groups (Sachs et al., 1985; Ludin et al., 1987). As the central command mechanism is thought to be primarily responsible for the initial motor and ANS responses to activity (withdrawal of suppressive, parasympathetic, cardiac vagal nerve activity causing an increase in heart rate), this result indicates that while there may be impairment in the central sympathetic pathways, some level of autonomic regulation was intact in both groups enabling this initial response to the handgrip exercise.

The absence of a true metaboreflex response to the post- exercise ischemia (as evidenced by a small decrease in MBP on cessation of exercise followed by a rebounding of MBP toward isometric handgrip levels due to accumulation of metabolites) demonstrated in this study suggests impairment in the peripheral sympathetic pathway in older adults with and without PD. Decreased stimulation/ accumulation of post- exercise metabolites in both groups of study participants due to increased age or inadequate exercise intensity are two potential mechanisms explaining this response.

Age

Age is another potential factor contributing to the difference in findings between this and earlier studies. The effects of age on the various organ systems are well documented, with older adults demonstrating progressive declines in strength and cardiovascular functioning (decreases in maximum cardiac output and aerobic capacity) among others (Frederiksen et al., 2006; Tortora & Grabowski, 2004).

Previous studies examining physiological responses to isometric exercise in participants with PD have focussed on younger participant groups than those examined in this study. As mentioned previously, two of these found age to be a significant factor in the physiological response to isometric exercise in PD (Van Dijk et al., 1993; Martin et al., 1993). A review of the literature found only one study evaluating metaboreflex response in healthy "older" populations using a similar protocol. Houssiere et al. (2006), examined the differences in metaboreflex response between 12 older (mean age 55.0) and 12 younger (mean age 22.0) participants. At baseline, the older group demonstrated increased BP and decreased MVC compared to the younger group. In response to three minutes of isometric handgrip exercise at 30% of MVC, both groups demonstrated increases in HR, with the older group demonstrating a significantly lower response compared to that of the younger group (12 ± 7 versus 19 ± 9 bpm, $p < 0.05$). BP also increased significantly in both groups in response to the handgrip exercise ($p < 0.05$), and remained elevated following post- exercise circulatory occlusion ($p < 0.01$) indicating the presence of a metaboreflex response in both the older and younger groups. The difference in BP response between groups was not significant during handgrip ($p > 0.2$), or post-exercise circulatory occlusion ($p = 0.87$). However analysis of muscle sympathetic nerve

activity (a direct measure of peripheral sympathetic nerve response) demonstrated decreased sympathetic response in the older group ($p < 0.05$). Subsequent analysis determined that baseline differences between groups (including absolute MVC) did not influence these results ($p = 0.22$). The two main findings of this study were: that a metaboreflex response was demonstrated by the older adult group as evidenced by maintenance of elevated BP during post- exercise circulatory occlusion, and that direct measurement found a diminished response in this group.

Significantly, all of the previous studies cited in this discussion examined physiological responses in populations ranging in age from a mean of 55.0 (Houssiere et al., 2006) to 66.0 (Sachs et al. 1985). The mean age of participants with PD in this study was 70.5, while the mean age of the control group was 77.0. This raises the possibility of a progressive dampening of ANS response with age and points to the need to further evaluate ANS response in older adults.

Exercise Intensity

Inadequate exercise intensity resulting in an insufficient accumulation of metabolites could explain the lack of a metaboreflex response demonstrated by both the PD and control groups. This study employed a standard protocol, evaluating metaboreflex response to post- exercise circulatory occlusion following two minutes of isometric handgrip at 30% of MVC. However, the absolute value of the handgrip force produced by the participants may have been inadequate to generate the levels of metabolites necessary to stimulate a metaboreflex response. As mentioned previously, studies in young, healthy adults demonstrated that work intensity affects the degree of the metaboreflex response, with higher workloads preferentially recruiting glycolytic fibres

thereby generating more metabolic by- product than oxidative fibres recruited by lower intensity workloads (Cornett et al., 2000). Gandevia and Hobbes (1990) demonstrated the presence of a metaboreflex in healthy participants aged 21 – 32 at work levels of 33% of maximal voluntary contraction held for only 45 seconds in duration. At this low level of work intensity and duration, the changes in heart rate and mean arterial blood pressure from rest to handgrip exercise were reported to be approximately 5 bpm and 10 mmHg, and increased to approximately 15 bpm and 18 mmHg with two minutes of handgrip at 33% MVC. Cornett et al. (2000) examined metaboreflex response in a young (23 ± 1 years of age), healthy population at handgrip levels as low as 15% of MVC. Following two minutes of handgrip exercise, heart rate and mean arterial blood pressure increased approximately 10 bpm and 20 mmHg. These results indicate that the metaboreflex can be stimulated in young, healthy populations at low levels of both work intensity and duration. Although the protocol used in this study was assumed to be of sufficient intensity and duration to stimulate a metaboreflex response (as demonstrated in previous literature), a number of studies have shown decreases in maximum voluntary grip strength associated with aging (Desrosiers, Bravo, Hebert, & Dutil, 1995; Frederiksen et al., 2006). Therefore, while the maximum voluntary contraction appeared to be adequate (participants in both the PD and control groups were able to maintain handgrip at approximately 40% of MVC), the absolute workload generated may have been insufficient. The findings of the Houssiere et al. study raise the possibility of a progressive dampening of ANS response to exercise with aging, but also demonstrate the decreased ability of older adults to achieve MVC equal to that of younger adults. These authors found significantly lower increases in heart rate in response to isometric handgrip

exercise: 12 ± 7 bpm in the older group and 19 ± 9 bpm in the younger group ($p < 0.05$). However, MVC attained by the older adult group was significantly lower than that of the younger group (32 ± 10kg versus 45 ± 8kg, $p < 0.05$). In the present study examining older participant groups, heart rate response was further diminished, increasing by only approximately 7 bpm and 3bpm in the PD and control groups, respectively. This decreased heart rate response suggests that the exercise intensity may have been insufficient to stimulate a peripheral response in either group.

In summary, consistent with the available metaboreflex literature to date, participants with PD in this study demonstrated a less than expected exercise pressor response: there was no significant increase in blood pressure in response to the handgrip exercise or maintenance of this increase during post- exercise circulatory occlusion. In contrast to previous studies, this diminished response was not significantly different from that of the age- matched control group. The limited and problematic nature of previous studies (including the combining of participants with wide- ranging ages, severity of disease, and medication classes into a single group, lack of reporting or accounting for differences in baseline measures between PD and control groups) limits the degree of confidence in these study findings. In addition, the diminished response in both groups could be explained by inadequacy of post- exercise metabolite stimulation/ accumulation due to the increased age of participants in this study, or inadequacy of exercise intensity resulting from the use of voluntary muscle contraction in this older population.

Exercise Programme

Participation in a community exercise programme did not significantly impact upon any of the physiological variables measured in the PD group, suggesting that the

intensity and/or duration of the particular programme was insufficient to impact upon autonomic nervous system response in this population. This is perhaps unsurprising given that the exercise intervention consisted of a supervised, group exercise routine that could be safely undertaken in a community setting and was, therefore, a moderate intensity programme focussed on the maintenance of global function. In addition, the exercise programme was intended to impact generally upon the physical impairments and functional limitations commonly experienced by those with PD, and was, by design, not focussed upon any one particular area of performance or physiological system. This is reflected in the lack of a "training effect" noted in either cardiovascular or autonomic nervous system functioning as would be evidenced by decreased resting/ exercise heart rate, respiratory rate, or mean blood pressure.

Future Directions

Future studies directly assessing muscle sympathetic nerve activity in both older adults and people with PD would more accurately assess the local sympathetic response to isometric exercise in these groups. Direct investigation could further determine whether metaboreflex response is generated not at all, only at very low levels and therefore not detectable in this study, or if a higher level of force generation is necessary to stimulate the accumulation of metabolites in these populations. Studies examining electrically induced muscle contraction in older adults and people with PD would establish a "true" or absolute MVC eliminating the potentially confounding variables of voluntary effort and laterality of symptoms (significant tremor or rigidity affecting predominantly one side, for example). Future studies could also investigate the effect of initiation of a generalized exercise programme on metaboreflex response in older adults

with and without PD as a measure of the impact of exercise on peripheral ANS response in an older population. Finally, comparing metaboreflex response in younger participants with PD in "on" and "off" medication states and age- matched controls could delineate the individual contributions of Parkinson Disease itself, and associated medication use to the altered metaboreflex response found in this study.

This study contributes to a body of literature highlighting global impairments experienced by people living with Parkinson Disease. Though clinical diagnosis depends upon manifestations of dopamine deficiency, non- dopaminergic, non- motor symptoms can present prior to the diagnosis of PD and increase with progression of the disease (Chaudhuri et al., 2006). These non- motor symptoms may contribute significantly to the decreased physical activity participation and tolerance levels seen in PD. Due to the role of muscle metaboreceptors in stimulating sympathetic vasoconstriction of exercising muscle, these receptors could be an important determinant of the rise in blood pressure accompanying exercise. While this study was unable to demarcate the individual contributions of age and disease, altered response of this system as demonstrated in this study could impact negatively on fatigue and exercise tolerance in people with PD as well as in older adults. Lowered blood pressure response to exercise implies decreased venous return to the heart and consequently, decreased blood flow to exercising muscle. The results of this study point to the need to proceed cautiously when evaluating response to exercise using these physiological measures in people with PD and in older adults.

Delimitations

The ability to generalize the results of this study is limited due to the inclusion criteria requiring a level 1.0 to 2.5 on the Modified Hoehn and Yahr scale. Those scoring

higher on this scale (those in a more "advanced" state of the disease) were excluded from participation. Therefore, results of this study apply only to those in the "early stages" of Parkinson Disease.

Although the participants with PD were all examined during their "on" phase of medication, they continued with their regular medication regime consisting of dopaminergic drugs among others. Medication class was not established or included in analysis of results. It has been suggested that the type of medication used to treat the symptoms of PD can both accentuate and mediate the autonomic symptoms associated with PD (Haapaniemi et al., 2000).

Limitations

This study has a number of limitations. First, the small control group limits the degree to which this study can compare the changes in heart rate, respiratory rate, blood pressure, and metaboreflex response in participants with PD with a healthy population of the same age and general characteristics.

The lack of available equipment able to continuously measure arterial blood pressure (i.e. Finapres) resulted in reliance upon a piezo- electric pulse transducer, which proved problematic despite attempts to standardize calibration with an automatic, oscillometric blood pressure cuff (Dinamap) throughout the data collection period. Due to the presence of significant hand tremor in a number of the participants, and the loss of one participant to follow- up, five (5) of 10 complete collections of blood pressure data were available for analysis at T1and T2. The impact of hand tremor (increasing variability of force production in the PD group) may have been compounded by the testing procedures which relied on the handgrip exercise being consistently performed on

the right side regardless of hand dominance or laterality of disease involvement. The increased variability in handgrip performance demonstrated by the PD group may have been decreased somewhat by stratifying the group by side of disease involvement; however this would have required a significantly larger participant group than was available. As mentioned previously, visual feedback of performance was used in an attempt to minimize variability of performance in both groups of older adults as indicated by previous authors (Vaillancourt et al., 2002). The reliance on chest expansion as a measure of respiratory rate (as measured by a belt transducer) also contributed to problems with data collection in this population, resulting in six (6) of 10 complete collections of respiration data at T1 and T2.

Finally, evaluation of the metaboreflex through monitoring of physiological responses is an indirect method of examining the peripheral component of cardiovascular response to exercise. Direct assessment of the impact of the metaboreflex requires examination of muscle sympathetic nerve activity through the use of microneurography. This testing procedure is not currently available in Thunder Bay, Ontario.

Summary

In addition to being a movement disorder caused by progressive loss of dopaminergic cells, Parkinson Disease is also a cause of primary autonomic nervous system dysfunction. Autonomic Nervous System (ANS) dysfunction is common, affecting over 90% of people with PD over the course of their disease, and can result in impairments of the cardiovascular system (including orthostatic hypotension), bowel and bladder dysfunction, and impaired thermoregulation (Dewey, 2004; Magerkurth et al., 2005).

The results of this study suggest diminished peripheral response to exercise, specifically diminished metaboreflex response to exercise in people with PD. This finding is consistent with the larger body of literature indicating impaired blood pressure response to exercise in those with PD (Sachs et al., 1984; Ludin et al., 1987; Reuter et al., 1999; Bouhaddi et al., 2004). In contrast to previous studies however, the decreased blood pressure response demonstrated by participants with PD was not significantly different from the control group. While it is not possible to distinguish between the impact of age, disease, and disease- specific medication in this study, impairments in peripheral response to exercise (and consequently decreased blood flow to the brain, heart, and exercising muscle) could, to some degree, account for the increased levels of fatigue and the general tendency toward inactivity experienced by people with PD. These factors should be taken into account during exercise prescription and monitoring in people with PD as well as in older adults, as results of this study indicate that using physiological markers such as heart rate and blood pressure may not accurately represent exercise response or tolerance in either of these groups.

References

Alam, M., & Smirk, F.H. (1937). Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *Journal of Physiology, 80*, 372-383.

Bouhaddi, M., Vuillier, F., Fortrat, J.O., Cappelle, S., Henriet, M.T., Rumbach, L., et al. (2004). Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-dopa therapy. *Journal of Autonomic Neurosciences, 116*(1-2), 30-8.

Brown, J.G. (2002). Using a Multiple Imputation Technique to Merge Data Sets *Applied Economics Letters*, 9(5), 311-14.

Bull, R.K., Davies, C.T.M., Lind, A.R., & White, M.J. (1989). The human pressor response during and following voluntary and evoked isometric contraction with occluded local blood supply. *Journal of Physiology, 411*, 63-70.

Canning, C.G., Alison, J.A., Allen, N.E., Groeller, H. (1997). Parkinson's disease: an investigation of exercise capacity, respiratory function, and gait. *Archives of Physical Medicine and Rehabilitation, 78*, 199-207.

Carrington, C.A., Fisher, W.J., & White, M.J. (1999). The effects of athletic training and muscle contractile character on the pressor response to isometric exercise of the human triceps surae. *European Journal of Applied Physiology, 80*, 337-343.

Chaudhuri, K.R., Healy, D.G., & Schapira, A.H.V. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurology, 5*, 235-245.

Chen, H., Zhang, S.M., Schwarzschild, M.A., Hernan, M.A., Ascherio, A. (2005). Physical activity and the risk of Parkinson disease. *Neurology, 64*, 664-669.

Coote, J.H., Hilton, S.M., & Perez-Gonzalez, J.F. (1971). The reflex nature of the pressor response to muscular exercise. *Journal of Physiology, 215*, 789-804.

Cornett, J.A., Herr, M.D., Gray, K.S., Smith, M.B., Yang, Q.X., & Sinoway, L.I. (2000). Ischemic exercise and the muscle metaboreflex. *Journal of Applied Physiology, 89*, 1432-1436.

Desrosiers, J., Bravo, G., Hebert, R., Dutil, E. (1995). Normative data for grip strength of elderly men and women. *The American Journal of Occupational Therapy, 49*(7), 637-644.

Dewey, R.B. (2004). Autonomic dysfunction in Parkinson's disease. *Neurologic Clinics, 24*, S127-S139.

Frederiksen, H., Hjelmborg, J., Mortensen, J., McGue, M., Vaupel, J., & Christensen, K. (2006). Age trajectories of grip strength: cross- sectional and longitudinal data among 8,342 Danes aged 46 to 102. *Annals of Epidemiology, 16*, 554-562.

Ganong, W.F. (2005). *Review of Medical Physiology*. New York: Lange Medical Books/ McGraw-Hill.

Gandevia, S.C., & Hobbs, S.F. (1990). Cardiovascular responses to static exercise in man: central and reflex contributions. *Journal of Physiology, 430*, 105-117.

Garber, C.E., & Friedman, J.H. (2003). Effects of fatigue on physical activity and function in patients with Parkinson's disease. *Neurology, 60*, 1119-1124.

Gilman, S., & Newman, S. (Eds.). (1996). *Manter and Gatz's Essentials of Clinical and Neurophysiology*. 9th Ed. F.A. Davis Company: Philadelphia.

Goldstein, D.S. (2003). Dysautonomia in Parkinson's disease: neurocardiological abnormalities. *Lancet Neurology, 2*, 669-676.

Haapaniemi, T.H., Kallio, M.A., Korpelainen, J.T., Suominen, K., Tolonen, U., Sotaniemi, K.A., et al. (2000). Levodopa, bromocriptine and selegiline modify cardiovascular responses in Parkinson's disease. *Journal of Neurology, 415*, 868-874.

Hoehn, M.M., Yahr, M.D. (1967). Parkinsonism: onset, progression, and mortality. *Neurology, 17*(5), 427-442.

Houssiere, A., Najem, B., Pathak, A., Xhaet, O., Naeije, R., & Van de Borne, P. (2006). Chemoreflex and metaboreflex responses to static hypoxic exercise in aging humans. *Medicine & Science in Sports & Exercise, 38*(2), 305-312.

Inkster, L.M., Eng, J.J., MacIntyre, D.L., & Stoessl, A.J. (2003). Leg muscle strength is reduced in Parkinson's disease and relates to the ability to rise from a chair. *Movement Disorders, 18*(2), 157-162.

Johnson, L.R. (1998). *Essential Medical Physiology*. Philadelphia: Lippincott-Raven.

Khan, M.H., & Sinoway, L.I. (2000). Muscle reflex control of sympathetic nerve activity in heart failure: the role of exercise conditioning. *Heart Failure Review, 6*, 87-100.

Levick, J.P. (2000). *An Introduction to Cardiovascular Physiology*. New York: Oxford University Press.

Ludin, S.M., Steiger, U.H., & Ludin, H.P. (1987). Autonomic disturbances and cardiovascular reflexes in idiopathic Parkinson's disease. *Journal of Neurology, 235*, 10-15.

Magerkurth, C., Schnitzer, R., & Braune, S. (2005). Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. *Clinical Autonomic Research, 15*, 76-82.

Martin, R., Manzanares, R., Molto, J.M., Canet, T., Ruiz, C., & Matias- Guiu, J. (1993). Cardiovascular reflexes in Parkinson disease. *The Italian Journal of Neurological Sciences, 14*(6), 437-42.

Mastrocola, C., Vanacore, W., Giovani, A., et al. (1999). Twenty-four-hour heart rate variability to assess autonomic function in Parkinson's disease. *Acta Neurologica Scandinavica, 99*, 245-247.

Mesec, A., Sega, S., Trost, M., & Togacnik, T. (1999). The deterioration of cardiovascular reflexes in Parkinson's disease. *Acta Neurologica Scandinavica, 100*(5), 296-9.

Miceli, G., Tosi, P., Marcheselli, S., & Cavallini, A. (2003). Autonomic dysfunction in Parkinson's disease. *Neurological Sciences, 24*, S32-S34.

Mostoufi- Moab, S., Widmaier, E.J., Cornett, J.A., Gray, K., & Sinoway, L.I. (1998). Forearm training reduces the exercise pressor reflex during ischemic rhythmic handgrip. *Journal of Applied Physiology, 84*, 277-283.

Oka, H., Mochio, S., Onouchi, K., Morita, M., Yoshioka, M., & Inoue, K. (2006). Cardiovascular dysautonomia in de novo Parkinson's disease. *Journal of the Neurological Sciences, 241*, 59-65.

Paasuke, M., Ereline, J., Gapeyeva, H., Joost, K., Mottus, K., & Taba, P. (2004). Leg- extension strength and chair- rise performance in elderly women with Parkinson's disease. *Journal of Aging & Physical Activity, 12*(4), 511-524.

Parkinson Society of Canada. What is Parkinson's Disease? (2005). Retrieved October 2005, from http://www.parkinson.ca/pd/parkinson.html

Protas, E.J., Stanley, R.K., Jankovic, J., & MacNeill, B. (1996). Cardiovascular and metabolic responses to upper- and lower- extremity exercise in men with idiopathic Parkinson's disease. *Physical Therapy, 76*(1), 34-40.

Reuter, I., Engelhardt, M., Freiwaldt, J., & Baas, H. (1999). Exercise test in Parkinson's disease. *Clinical Autonomic Research, 9*(3), 129-134.

Sachs, C., Berglund, B., & Kaijser, L. (1985). Autonomic cardiovascular responses in parkinsonism: effect of levodopa with dopa-decarboxylase inhibition. *Acta Neurologica Scandinavica, 71*, 37-42.

Seals, D.R. (1989). Influence of muscle mass on sympathetic neural activation during isometric exercise. *Journal of Applied Physiology, 67*, 1801-1806.

Seals, D.R. (2005). *American College of Sports Medicine: Advanced Exercise Physiology*, Chapter 9: The Autonomic Nervous System. (R.L. Terjung Ed.). New York: Lippincott Williams & Wilkins.

Senard, J.M., Brefel- Courbon, C., Rascol, O., & Montastruc, J.L. (2001) Orthostatic hypotension in patients with Parkinson's disease. *Drugs & Aging, 18*(7), 495-505.

Shoemaker, J.K., Kunselman, A.R., Silber, D.H., & Sinoway, L.I. (1998). Maintained exercise pressor response in heart failure. *Journal of Applied Physiology, 85*(5), 1793-1799.

Smith, S.A., Mitchell, J.H., & Garry, M.G. (2005). The mammalian exercise pressor reflex in health and disease. *Experimental Physiology, 91*(1), 89-102.

Standring, S (Ed.). (2005). *Gray's Anatomy*. 39th Ed. Toronto: Elsevier Ltd.

Tortora, G.J. & Grabowski, S.R. (2004). *Introduction to the Human Body: The Essentials of Anatomy and Physiology*. New York: John Wiley & Sons.

Turkka, J.T., Tolonen, U., & Myllyla, V.V. (1987). Cardiovascular reflexes in Parkinson's disease. *European Neurology, 26*, 104-112.

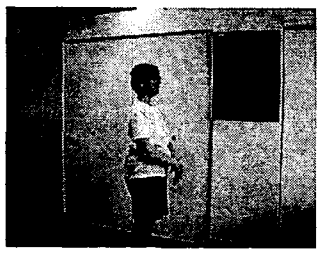
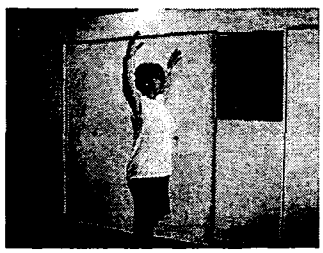
Vaillancourt, D.E., Slifkin, A.B., & Newell, K.M. (2002). Interdigit individuation and force variability in the precision grip of young, elderly, and Parkinson's disease participants. *Motor Control, 6*, 113-128.

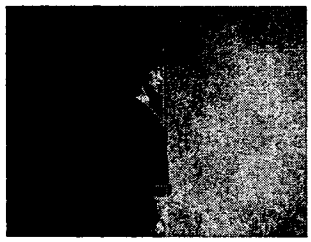
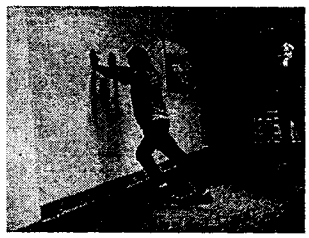
Van Dijk, J.G., Haan, J., Zwinderman, K., Kremer, B., Van Hilten, B.J., Roos, R.A. (1993). Autonomic nervous system dysfunction in Parkinson's disease: relationships with age, medication, duration, and severity. *Journal of Neurology Neurosurgery and Psychiatry, 56*, 1090-1095.

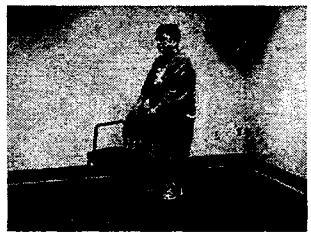
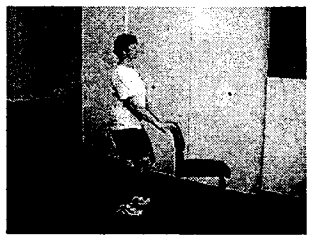
Waxman, S.G. (2003). *Clinical Neuroanatomy*. New York: Lange Medical Books/ McGraw-Hill.

Appendix 1

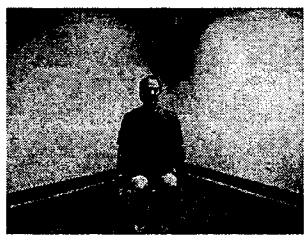
Class Quick Review

Warm-up		
1. Posture correction *Stand tall with feet shoulder width apart.* *Pull your abdominals in.* *Head and chest up.* *Shoulders rolled back.* *Chin tucked in.* *Thumbs facing forwards with palms facing sides.*		
2. Diaphragmatic Breathing *Standing, gently place palms over lower abdomen.* *Take a full breath in through nose, allowing diaphragm to expand. Abdomen will lift out.* *Slowly breathe out through mouth. Abdomen will pull in.* *Repeat 5 times.*		
3. Deep Breathing Exercise *Stand tall with feet hip width apart.* *Cross arms over one another in front of you.* *Take in a deep breath, begin lifting arms up and open.* *Breathe out, lower arms to starting position.* *Perform for 5 deep breaths.*		
4. Marching on the spot *Stand tall with feet hip width apart.* *March on the spot with small steps for1 minute. Let arms swing naturally.* *High step for 3 minutes.*		

Standing/Stretching Hold 10 seconds. Repeat 3-5 times		
1. Posture at wall *Stand back against wall, feet 2 inches away.* *Pull in abdominal muscles.* *Flatten lower back and shoulder blades against wall.* Pull chin back towards wall. Head does not need to touch wall. Errors - feet too far from wall, shoulders round, head tips up or down		
2. Wall stretch *Stand back against wall, feet 2 inches away.* *Pull in abdominal muscles.* *Flatten lower back and shoulder blades against wall.* *Pull chin back towards wall.* *Raise elbows to shoulder height and rest forearms on wall* Errors - head pokes forward, low back arches, forearms not touch wall		
3. Stretching tall *Stand back against wall, feet 2 inches away.* *Pull chin back towards wall and reach arms overhead.* *Stretch as though trying to make yourself taller.* Errors - chin pokes, rise onto toes, reach arms back		
4. Stretching arms behind back *Move away from wall.* *Stand with back straight and feet firmly on floor, hip distance apart.* *Clasp hands behind back.* *Gently lift arms up and away from back. Very little movement.* Errors - bend forward from hips, shoulders round, chin pokes		
5. Calf stretch Stand facing wall, one arms length away. Place hands on wall at shoulder height. *Step back with left foot.* *Keep left leg straight, gently bend right knee.* *Lean forward into wall.* *Repeat with opposite leg.* Errors- heels up, toes out, bend forward from hips		

Strengthening Hold 5 seconds, repeat 5-10 times each side		
1. Weight shifting *Stand behind chair, legs a little wider apart than shoulder width.* *Rest hands lightly on chair.* *Shift weight slowly onto one leg.* *Hold.* Shift weight to other leg. Hold. Errors - body twists/hip drops, foot off floor, feet too far or too close, knees buckle		
2. Backwards leg swing *Stand behind chair, feet couple inches apart.* *Rest hands lightly on chair.* *Keep right leg straight, slowly swing back from hip. Hold.* *Slowly bring leg back to starting position.* Errors - lean forward, bend knee		
3. Heel raises *Stand behind chair, feet couple inches apart.* *Rest hands lightly on chair.* *Push straight up onto toes.* *Hold.* *Slowly lower back down.* Errors - rock back onto heels or forward onto arms, push up using chair		
4. Toe lifts *Stand behind chair, feet couple inches apart.* *Rest hands lightly on chair.* *Lift toes of one foot up off floor.* *Keep knees straight, move from ankle only.* *Hold.* *Slowly lower toes back down.* Errors - lean forward at waist, bend knees		
5. Mini squats behind a chair *Stand behind chair, feet flat on floor hip distance apart.* *Rest hands lightly on chair.* *Slowly do small knee bend. Keep shoulders in line with hips.* *Knees do not bend past feet.* *Hold.* *Slowly straighten up.* Errors - lift heels, stick bottom out, pull up with arms		

6. Seated Posture correction *Sit bottom at back of chair, tuck feet slightly under knees.* *Use book or riser under feet if not touch floor.* *Sit up tall. Pull in abdominal muscles, pull chin in slightly, draw shoulders back.* *Maintain posture throughout seated exercises.* Errors - slouch, shoulders round, chin pokes		
7. Knee extensions *Sit with bottom at back of chair, feet firmly on floor.* *Slowly straighten left knee while tightening thigh muscles. Keep toes pulled up.* *Hold.* *Slowly lower leg.* Errors - quick movement, turn leg out, toes not pulled up, slouching		
8. Chair sit to stand *Scoot bottom forward to edge of chair, feet flat on floor shoulder width apart. Tuck feet slightly under knees.* *Place hands on thighs, push up into standing.* *Slowly lower back down onto chair.* Errors - rock forward, "plunk" onto chair, feet slide		
9. Triceps strengthening *Sit bottom at back of chair, feet firmly on floor. Slide bottom to right side of chair.* *Place left hand on left thigh for support. Lean forward at waist, keep back straight.* *Raise right elbow behind you to 90 degrees.* *Straighten elbow – "kickback" Keep shoulder and upper arm still.* *Hold. Bend elbow back down.* Errors - slouch, elbow drifts down, quick movement		
10. Arm raises to the side *Sit bottom at back of chair, feet firmly on floor.* *Place arms at side.* *Slowly raise left arm up to just below shoulder height.* *Keep elbow straight and palm facing floor.* *Hold.* *Slowly lower arm back down.* Errors - slouch, arm drifts forwards, shrug shoulder		

Seated/Stretching Hold 10 seconds, repeat 3-5 times each side		
1. Turtle tuck *Sit with bottom at back of chair, feet firmly on floor.* *Pull abdominal muscles in and sit up tall.* *Pull chin straight back.* *Hold.* Errors - slouch, tuck chin to chest, arch back over chair		
2. Forward stretch in chair *Sit with bottom at back of chair, feet firmly on floor.* *Slowly relax forward- roll head, shoulders and back down towards floor.* *Let arms and head hang down.* *Hold.* *Slowly roll back up to starting position. Begin with low back, upper back, shoulders and let head come up last.* Errors - poke head up on way down, lead with head on way up, slouching		
3. Backwards stretch in chair *Sit with bottom at back of chair, abdominals pulled in.* *Lightly rest fingers at base of skull.* *Slowly lean backwards over chair- keep ears in line with shoulders. Hold.* Errors - poke chin/pull head forwards, elbows drift out, slouch		
4. Side stretch in chair *Sit with bottom at back of chair, feet flat on the floor. May sit to one side of chair.* *Lift right arm up to the side and slowly reach over head to opposite wall. Anchor left arm on chair. Hold.* Errors - lean forwards, drop shoulder and tip to side, poke chin out		
5. Upper back rotation in chair *Sit with bottom at back of chair, feet flat on floor.* *Place left arm on back of chair.* *Reach around in front of you with right arm to grab back of chair on left side.* *At the same time turn head and look back over left shoulder.* *Hold.* Errors - slouch, tip head back, struggle to reach back of chair		

6. Arm raises in chair *Sit with bottom at back of chair, feet flat on floor.* *Clasp hands together in front, slowly lift arms overhead taking a deep breath in.* *Hold.* *Slowly lower arms back down as you breathe out.* *Repeat.* *Use wand or cane if available.* Errors - arch low back, round shoulders, poke chin out		
7. Hamstring stretch in sitting *Sit at edge of chair with right leg bent (foot flat on floor) and left leg straight resting on heel.* *Sit up tall, lean forward from hips .* *Hold.* Errors – slouch, knee bends, poke chin out		
8. Ankle circles *Sit with bottom at back of chair.* *Left foot on floor, lift right foot up off floor.* *Move right foot in slow complete circles.* Errors - move entire leg, small or incomplete circles		
9. Shoulder blade squeezes *Sit with bottom in middle of chair seat, feet firmly on floor.* *Tuck elbows in at sides at 90 degrees.* *Pull shoulder blades back and down in a V movement.* *Hold.* Errors - slouch, throw shoulders back, poke chin out		

Cool-down		
1. Marching *Stand tall with feet hip width apart.* *Maintain moderate stepping for 3 minutes to cool down the body.* *Keep arms swinging at sides.*		
2. Diaphragmatic Breathing *With good standing posture do 5 slow deep breaths in and out to cool the body down.*