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Cardiovascular Effects Of Exercise And Use Of Abdominal Binder In Patients Of Parkinson's Disease With Orthostatic Hypotension

Faizan Ahmed, *The University of Western Ontario*

Supervisor: Overend, Tom, *The University of Western Ontario*

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Abstract

Orthostatic hypotension (OH) is a common manifestation of autonomic dysfunction in Parkinson's Disease. It can adversely affect a patient's functional capacity, exercise tolerance and quality of life, while increasing the risk of falls, cerebrovascular disease and overall mortality. Use of an abdominal binder (AB) can help counter OH; however, this has not been sufficiently studied in patients with Parkinson's Disease (PwPD). Moreover, the hemodynamic effects of upper and lower extremity exercise are unclear in PwPD with OH. Although OH can impair the cerebral circulation, the consequences on the cerebral hemodynamics of wearing an AB or performing exercise are unknown in PwPD with OH.

This thesis aimed to generate practical evidence that is useable by the clinicians as well as the patients during the rehabilitation process of PwPD with OH. The three research studies that constitute this thesis investigated the effects of the interventions on systemic hemodynamics, cerebral hemodynamics and symptoms of orthostasis in PwPD with and without OH. The first study investigated the effects of wearing an abdominal binder (AB) and its subsequent removal in the standing position. The results showed that AB was effective in countering OH and its removal negatively affected the hemodynamics. The second study investigated the effects of performing upright self-regulated aerobic cycling exercise (SRACE). The responses to SRACE were found to be largely similar in all PwPD, regardless of OH. However, PwPD with relatively severe OH developed exercise-induced hypotension (EIH) without symptomatic deterioration. The third study investigated if performing resisted upper limb exercise (RULE) can be used to counter OH in PwPD. The results showed that RULE can be a useful adjunct for a brief quick resolution of OH.

The findings of this thesis suggest that AB and RULE can be used successfully for countering OH, that AB should not be removed while standing, and that BP should be monitored in PwPD with severe OH in order to detect EIH during exercise. These conclusions are expected to expand the knowledge base and provide greater options for the management of OH during the rehabilitation of PwPD, thereby helping in the control of OH and the prevention of potential complications of OH while providing a more tailored rehabilitation.

Keywords

Parkinson's Disease, orthostatic hypotension, hemodynamics, blood pressure, abdominal binder, aerobic exercise, resistance exercise, physical therapy, rehabilitation, cerebral blood flow, cerebral oxygenation, dizziness.

Summary for Lay Audience

Orthostatic hypotension (OH), which is an abnormal decrease in blood pressure (BP) upon assumption of upright posture (such as standing), can occur in patients with Parkinson's Disease (PwPD) due to abnormality in the regulation of blood pressure. OH can decrease the blood supply to the brain, often producing dizziness and/or fainting. These factors can have serious negative consequences on the patient's ability to lead an active lifestyle, while elevating the risk of brain disorders and early death.

Compression of the belly by wearing an abdominal binder (AB) may help counter OH, but this has not been sufficiently studied in PwPD. Moreover, the effects of performing different types of exercise on the blood pressure are largely unexplored in these patients. Furthermore, it is unclear how wearing an AB or performing exercise influence the blood flow to the brain when PwPD have OH. We undertook three research studies to fill these gaps in knowledge. The studies investigated (1) the effects of wearing and later removing an AB in the upright position, (2) performing self-regulated aerobic cycling exercise (SRACE) in which the intensity of exercise was controlled by the participant, and (3) performing resisted (using weight) upper limb exercise (RULE) in the upright position by PwPD with and without OH. It was found that both wearing an AB as well as performing RULE helped counter OH; the removal of the AB led to adverse effects on the circulation of blood in PwPD with OH; and most PwPD with and without OH responded similarly to SRACE. However, a few PwPD with relatively severe OH had an abnormal decrease in BP, called exercise-induced hypotension (EIH), during SRACE.

We have shown that wearing an AB or performing RULE are useful for countering OH in PwPD; the AB should not be removed in the standing position; and BP should be monitored while PwPD with severe OH perform aerobic exercise in order to detect the development of EIH. The findings of this thesis should be able to help make the rehabilitation programs for PwPD with OH safer and better.

Co-Authorship Statement

The literature search and review, study design and planning, application for ethical approval, recruitment of the participants, conducting the research interventions, collection of the data, statistical analysis, interpretation of the statistical analysis, synthesis of the results, drafting of all the chapters in this thesis, and revisions and finalization of all the chapters in this thesis were carried out by Faizan Ahmed, with inputs in the form of guidance, advice and review from the members of the advisory committee. The advisory committee comprised of Dr. Tom Overend (supervisor), Dr. Kurt Kimpinski (advisory committee member) and Dr. Kevin Shoemaker (advisory committee member).

Dedication

This thesis is dedicated to my parents who dedicated their lives to my better education.

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List of Abbreviations

AB	Abdominal binder
AE	Aerobic exercise
ANS	Autonomic nervous system
ARS	Autonomic reflex screening
BP	Blood pressure
CASS	Composite Autonomic Severity Score
CBF	Cerebral blood flow
CBFv	Mean cerebral blood flow velocity determined using transcranial Doppler ultrasound
CI	Confidence interval
CNS	Central nervous system
CO	Cardiac output
$crSO_2$	Regional cerebral (cortical) oxyhemoglobin saturation determined as ratio of oxygenated to de-oxygenated blood in the circulation of cerebral frontal cortex using near-infrared spectroscopy
DBP	Diastolic blood pressure
EIH	Exercise-induced hypotension, defined as decrease of ≥10 mmHg in systolic blood pressure with performance of physical exercise
HR	Heart rate
HUT	Head-up tilt
IPD	Idiopathic Parkinson's Disease

MAP	Mean arterial pressure
NIRS	Near-infrared spectroscopy
OH	Orthostatic hypotension, defined as decrease of ≥20 mmHg in systolic blood or ≥10 mmHg in diastolic pressure within 3 minutes of assumption of upright posture
OSS	Orthostatic Symptom Scale
PD	Parkinson's Disease
PwPD	Patients with Parkinson's Disease
RE	Resistance exercise
ROM	Range of motion (of the joint)
RPE	Rating of perceived exertion
RULE	Resisted upper limb exercise
SBP	Systolic blood pressure
SH	Supine hypertension, defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg after 5 minutes of assumption of supine position
SRACE	Self-regulated aerobic cycling exercise
SV	Stroke volume
SVR	Systemic vascular resistance
TCD	Transcranial Doppler (ultrasound)
ULE	Upper limb exercise

Chapter 1

1 General Introduction

1.1 Background

Parkinson's Disease (PD) was first described by Dr. James Parkinson in 1817.[1] PD ranks second among the neurodegenerative disorder for its prevalence.[2,3] Estimates of global prevalence range between 7 and 10 million people.[4] PD has both motor as well as non-motor manifestations. Motor manifestations of PD include bradykinesia, rigidity, tremors and postural instability,[5] whereas, non-motor manifestations of PD include behavioural abnormalities, and autonomic nervous system, sensory and sleep-related dysfunction.[6] In physiotherapy practice as well as in most other clinical disciplines the treatment for PD is mainly focussed on the management of motor manifestations. However, non-motor manifestations deserve equal attention as they become the major cause of disability in patients with Parkinson's Disease (PwPD) during the later stages of the disease process and are known to severely undermine the quality of life in these patients.[7,8] Cardiovascular autonomic dysfunction is a frequent non-motor manifestation of PD. It commonly presents clinically as orthostatic hypotension (OH), which is a sustained decrease of at least 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) upon assumption of upright posture.[9] This thesis aimed to expand the existing knowledge base related to the rehabilitation of PwPD with OH by producing meaningful evidence to assist clinicians in tailoring an exercise program for safer and effective rehabilitation of these patients.

1.2 The autonomic nervous system and Parkinson's Disease

The autonomic nervous system (ANS) is a functional part of the nervous system that regulates the homeostasis of the body through involuntary responses. The ANS innervates

the cardiac muscle, smooth muscle and the glandular tissue.[10] The internal body functions that are regulated by the ANS include regulation of the heart rate (HR), respiratory rate, blood pressure (BP), digestion, body temperature, urination, defecation, sexual functions, body fluid production (tears, saliva and sweat), electrolyte balance and body metabolism.[11] The efferent signals of the ANS reach the target organs through the two main branches of the ANS called the parasympathetic nervous system and the sympathetic nervous system. The two branches generally have opposite effects in the regulation of body functions. For instance, the sympathetic nervous system helps increase HR and BP, whereas, the parasympathetic nervous system helps decrease them. Failure of the ANS in regulating the homeostasis is referred to as autonomic dysfunction or dysautonomia. It can result in abnormal regulation of the body functions that are mentioned above. Dysautonomia can be the primary disorder such as in neurocardiogenic syncope and postural orthostatic tachycardia syndrome, or it can occur secondary to diseases/disorders as in case of diabetes, rheumatoid arthritis and PD.

Dysautonomia can be present in PwPD from the very onset of PD. According to the Braak staging hypothesis for PD, the dorsal motor nucleus of the glossopharyngeal and vagus nerves, the gastrointestinal submucosal plexus and the post-ganglionic sympathetic nervous system have Lewy body pathology.[12,13] These pathologies precede the nigral involvement and as a result non-motor manifestations may precede motor manifestations in PD, albeit non-motor manifestations may not be recognized as being due to PD until late after the onset of motor symptoms of PD.[12] According to Goldstein, PD is a combination of a movement disorder and a dysautonomia.[14] Both parasympathetic and sympathetic branches of the autonomic nervous system can be affected in PD. This can result in cardiovascular, thermoregulatory, urogenital and gastrointestinal dysfunction.[15] Symptoms and signs like dry mouth, constipation, urinary retention, a fixed pulse rate, and erectile dysfunction can result from the failure of the parasympathetic cholinergic system. Decreased sweating can result from the failure of the sympathetic cholinergic system, whereas, OH and the resulting symptoms of orthostasis can result from a failure of the sympathetic noradrenergic system.[16] OH results when regulation of the cardiovascular

system by the autonomic nervous system becomes dysfunctional. This is called cardiovascular autonomic dysfunction. Cardiovascular autonomic dysfunction can result in hypotension [OH, post-prandial hypotension and exercise-induced hypotension (EIH)] and/or hypertension [supine hypertension (SH)]. Despite the goal of exercise rehabilitation and physiotherapy care of PwPD customarily being the management of motor manifestations of PD, non-motor manifestations resulting from autonomic nervous system dysfunction can be disabling to a similar magnitude.[17]

Orthostatic hypotension can seriously affect the health and quality of life of PwPD: Therefore, it is necessary both to prevent and treat it. Moreover, PwPD with OH may also develop EIH during exercise, which can be dangerous for the patient and should be avoided. However, scarcity of relevant literature limits the knowledge base and hinders sound decision-making during the rehabilitation of PwPD with OH. With the intention of increasing the relevant knowledge base this thesis investigated the effects of the use of countermeasures to control OH as well as the consequences of performing exercise by PwPD with OH.

1.3 Orthostatic hypotension and its implications in PD

Orthostatic hypotension is a frequent manifestation of cardiovascular autonomic dysfunction. The prevalence of OH in PwPD is estimated to be about 30%.[18] However, there are reports of it being present at a higher percentage, up to 58% in PwPD.[19,20] OH is believed to result from a combination of three pathological changes in PD; baroreflex failure, cardiac noradrenergic denervation and extra-cardiac noradrenergic denervation.[21] Of these three, cardiac noradrenergic denervation is the hallmark feature found during sympathoneural imaging after injection of imaging agents iodine-123-metaiodobenzylguanidine and fluorine-18-labelled dopamine in PwPD with OH.[16,22] Cardiac noradrenergic denervation is also more extensive than the extracardiac noradrenergic denervation and is believed to be virtually universal in PwPD. The arterial

baroreflex mechanism has both sympathetic and parasympathetic components and the functioning of both of these is seriously diminished in PD.[21]

Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of OH that are commonly experienced by patients include light-headedness, dizziness, weakness, fatigue, blurred vision, headache, palpitations and nausea. Some other symptoms that are less commonly experienced by patients include neck and shoulder pain (coat hanger pain), chest pain, dyspnoea and syncope (fainting).[23] Symptoms of orthostasis can make it difficult for patients with OH to perform activities in the standing position. As a result, PwPD may start avoiding exercise and physical activities in the upright position to escape the symptoms of OH. If they stop or reduce activities that require standing up and walking, this can have a negative effect on their functional capacity and exercise tolerance. Not only the skeletal muscles but also the cardiac musculature may atrophy over time. Skeletal muscle atrophy leads to generalized body weakness, whereas atrophy of the cardiac musculature weakens the heart and reduces its capacity to increase the BP effectively when needed. This may result in worsening of OH and greater apprehension by the patient in assuming an upright position and performing activities in this position. As a result, the patient can fall into a vicious cycle of worsening OH which precludes physical activity, which in turn further worsens OH.[24–26] The outcome can be an ever-worsening OH and physical deconditioning. To break this cycle, it is important to control OH as well as to maintain an active lifestyle. Exercises for improving the strength of the lower limbs and non-strenuous physical activities have been suggested in the literature to prevent physical deconditioning.[25]

Patients with PD are at risk of falls due to the disease process as well as ageing.[27] OH is also known to be associated with increased risk of falls.[28–30] One of the more serious consequence of OH is syncope which can lead to falls. Although literature may suggest syncope to be a less common reason for falls, this may be due to the reason that patients in which falls were caused by syncope were not included in many studies.[31] Irrespective of the cause, falls are dangerous in the elderly, and elderly people constitute the majority of PwPD.

Orthostatic hypotension has also been implicated in causing or worsening cerebrovascular diseases like stroke and dementia.[32,33] A systematic review and meta-analysis by Angelousi et al found a strong and independent relationship between OH and the risk of ischemic cardiac events as well as cardiovascular events.[34] These investigators also implicated OH with a 36% increase in the risk of overall mortality.

OH results in multiple complications that can seriously worsen the prognosis in PwPD. These include symptoms of orthostasis, physical deconditioning, decline in functional capacity that can affect the quality of life, predisposition to greater risk of falls, increasing risk of cerebrovascular diseases and ischemic heart disease, and an increased risk of early death. There is the need for timely and adequate management of OH, to avoid harm to the patient and to ensure a better rehabilitation.

1.3.1 Strategies for the control of OH

There are pharmacological and non-pharmacological strategies for the control of OH. The mainstay for treatment of OH in PwPD is the non-pharmacological management.[35,36] This starts with the education of the patient about avoidance of factors that aggravate OH. These factors include dehydration, consumption of alcohol or heavy meal and exercising in hot environments. The next line of treatment is education about physical countermeasures that can counter OH. These include the use of external compression garments and performing physical counter-maneuvers to control OH. External compression of the abdomen and lower extremities using an abdominal binder (AB) and compression stockings, respectively, is a commonly used non-pharmacological strategy to counter OH. It is known that most of the pooling of blood during upright posture occurs in the abdomen.[37] Compression of the splanchnic (abdominal) vasculature can help reduce the cross-sectional area of the blood vessels in the abdomen, thus reducing their capacitance i.e. reducing the ability of the blood vessels to hold or store blood. This reduction in capacitance prevents pooling of blood in the abdominal vasculature and helps improve the venous return to the heart.[38–40] An increase in venous return to the heart can improve the stroke volume (SV) and eventually help in increasing the BP. Physical counter-maneuvers that can be used to

control OH include bending forwards, active tensing of the lower extremities, squatting and standing cross-legged. These counter-maneuvers have been known to increase BP and abate symptoms of OH, including prevention of syncope. Drinking water and consuming a high salt diet have been recommended to increase and maintain plasma volume that in turn helps in maintaining a higher BP.[36,41]

While non-pharmacological management may be sufficient for many patients with OH, others may need additional support through the use of medications to offset the hypotension. Pharmacological strategies include two main types of medications. The first type is the synthetic mineralocorticoid called fludrocortisone that acts by increasing the intravascular volume resulting in increased BP. Fludrocortisone shows clinical effects of treatment after about 1-2 weeks of use and therefore may not be useful for immediate control of OH.[26] The other type includes pressor agents called midodrine and droxidopa that increase SVR resulting in increased BP. Although midodrine is available, droxidopa is not readily available for treatment of OH in Canada. Unlike most non-pharmacological treatment options, the pharmacological options are not free from side effects. Although these medications help by increasing the BP in the standing position, they also increase the BP when the patient assumes recumbent position, thereby producing SH (discussed in the next section). Apart from SH, fludrocortisone can cause hypertension and hypokalemia. The long-term use is associated with renal failure and left ventricular hypertrophy. Side effects of use of midodrine include urinary retention and piloerection (goose bumps).

Conversely, non-pharmacological measures like the AB, while being effective in countering OH, are known to be free from the risk of development of SH. Moreover, there is no apparent risk of end-organ damage. The external compression devices/garments can be worn and removed as needed and do not require a latent period before the start of their action. The physical counter-maneuvers like leg muscle tensing, bending, and cross-legged standing can be used instantly to counter OH and do not require a pre-scheduled medication regimen or the need to carry or wear a compression garment. While being effective alone in milder cases, non-pharmacological strategies may be used along with medications to

counter severe OH. Severe OH might prove to be resistant to either pharmacological or non-pharmacological management alone and a combination of both the strategies may be needed to increase the BP. In other cases, the use of non-pharmacological adjuncts can also help decrease the dosage of the medication required to produce an effective control of OH. This simultaneously reduces the risk of the side-effects of the medications.

1.3.2 Supine hypertension as a complication during the management of OH

Patients with PD with OH can also develop neurogenic SH. This is defined by the consensus statement on the definition of neurogenic SH in cardiovascular autonomic failure by the American Autonomic Society and the European Federation of Autonomic Societies as SBP of 140 mmHg or more and/or DBP of 90 mmHg or more when measured after 5 minutes of rest in the supine position.[42]

As mentioned, medications that prevent OH can produce SH as a side effect because these medications increase the BP in both standing and recumbent positions. SH may produce or aggravate complications in the form of renal and cardiovascular disease.[43] The first line of treatment for SH is generally non-pharmacological by sleeping in semi-sitting position or keeping the head-end of the bed elevated. However, if these fail to control SH, i.e. if the SBP remains >180 mmHg or DBP remains >110 mmHg persistently, then the addition of an anti-hypertensive agent may be useful during times when SH is prominent (i.e. at night while sleeping). [25] Nevertheless, this solution for SH may potentially increase the risk of falls by worsening the OH during the night time when the patient may get up to go to the toilet or at the time the patient would get up from the bed in the early morning.

1.4 Autonomic regulation of cardiovascular system during exercise

Physical exercise imposes stress on the cardiovascular system to supply oxygen and nutrients to the exercising muscles. The autonomic regulation of the cardiovascular

response to exercise starts with a feed-forward mechanism called the 'central command'.[44] It is named so because all its nuclei are located in the central nervous system (CNS). The central command helps the body prepare and respond to the hemodynamic demands of the exercise at the onset of exercise and continues to exert neural control for the remaining duration of the exercise. The role of the central command is a parallel activation of the somatic (voluntary) and autonomic nuclei, which helps in simultaneous activation of the neural circuits that control the motor, cardiovascular and respiratory functions. Another autonomic regulatory mechanism is a feed-back reflex mechanism through which metabolic and mechanical receptors located in the active muscles send impulses to the centers in the brain responsible for autonomic regulation of the cardiovascular system. This is called the exercise pressor reflex. The exercise pressor reflex informs the cardiovascular centers about the metabolic demands and therefore helps determine the changes in systemic oxygen delivery. In addition to these mechanisms, two more mechanisms called the cardiopulmonary and arterial baroreflexes provide inputs to the brain for the regulation of cardiovascular system. The cardiopulmonary and arterial baroreflexes are parts of the neurally mediated negative feedback mechanism that operates to regulate the BP during exercise. During exercise, afferent inputs from these four mechanisms are coordinated and integrated by the autonomic networks in the brainstem, followed by alterations in sympathetic and parasympathetic outflow to the cardiovascular system for hemodynamic adjustments to occur in response to exercise.[44,45]

1.4.1 Cardiovascular adjustments during aerobic exercise

Patients with PD perform both aerobic and anaerobic exercise during rehabilitation. During aerobic exercise (AE) there is greater demand for oxygen compared to anaerobic exercise. With the beginning of light to moderate intensity AE, both HR and SV increase initially in proportion to the intensity of exercise, producing an initial increase in cardiac output. However, cardiac output plateaus within the next few minutes due to the achievement of steady state exercise (a level of exercise at which energy demands equal the energy supply).[46] The initial rise in HR is due to vagal withdrawal, which is followed by increase

in sympathetic outflow to the heart as the intensity of exercise increases.[47,48] Sympathetically-mediated increase in HR includes both the direct stimulation of the ventricles by the sympathetic nerves as well as by the influence of catecholamines released from the adrenal medulla. The rapid increase in the SV with the onset of AE is a result of the increased preload that occurs due to increased venous return caused by catecholamine-mediated venoconstriction of the capacitance vessels and the effects of the rhythmic contractions in the active muscles that push the venous blood towards the heart. This brings into effect the Frank-Starling mechanism and the increased force of myocardial contraction caused by the sympathetic outflow to the ventricles. During steady state AE, the HR and SV (and therefore the CO) stabilize within a few minutes of exercise. However, during incremental AE to maximal effort the plateauing of CO is delayed due to progressively increasing workload. SBP increases modestly during AE predominantly due to the substantial increase in CO that is partially offset by the large decrease in the SVR. Although SVR should increase during AE due to sympathetically mediated generalized vasoconstriction, the 'functional sympatholysis' offsets the effects of generalized vasoconstriction by local vasodilatation in the active muscles.[45,49] As a result, the SBP rises due to increase in CO, whereas, the DBP does not change substantially. Mean arterial pressure (MAP) increases slightly due to the increase in SBP. As a result of the combined effect of vasoconstriction in the inactive muscles and viscera as well as the local vasodilatation in the active muscles, the CO is diverted from the inactive muscles and viscera to the active muscles. This significantly increases the blood flow of the active muscles and helps in meeting the oxygen and nutrient requirements of the exercising musculature.

1.4.2 Cardiovascular adjustments during resistance exercise

During resistance exercise (RE) the cardiovascular responses are different from AE. RE has a major component of anaerobic exercise and is a common constituent of the exercise rehabilitation program for PwPD. The energy demand is largely decoupled from the responses of the cardiovascular system during RE. The heaviness of the load and the

number of repetitions determine the magnitude of the response of the cardiovascular system. In contrast to AE, HR increases gradually with the number of repetitions during RE, whereas SV changes little and can decrease slightly. As a result, CO increases modestly. However, due to increased SVR produced by sympathetically-mediated generalized vasoconstriction along with the increase in CO, the SBP increases gradually with the number of repetitions when the load remains constant. The DBP shows no change or it may increase. [46] MAP also increases due to increase in both SBP and DBP.[46] The pressor response, which is a rapid rise in both SBP and DBP is observed during RE due to the cardiovascular arousal elicited by the RE. Due to mechanical occlusion of the blood vessels during the static component of the RE the blood flow through the active muscles is decreased. This results in accumulation of metabolic by-products that trigger the exercise pressor reflex, eventually producing a reflex increase in BP. Unlike AE, where a modest increase in BP is observed due to large increase in CO but negligible or no change in SVR, a large increase in BP is observed with modest increase in CO during RE.[50,51]

Overall, during AE the CO increases substantially but due to a decrease in the SVR, the BP rises only modestly, whereas, during RE (anaerobic exercise) the CO increases only modestly while the BP increases substantially due to increases in both the SVR and exercise pressor response.

1.5 Gaps in knowledge

Although cardiovascular autonomic dysfunction affects a significant number of PwPD, there is scarce literature about the effects of exercise in PwPD who have OH. Moreover, literature about the effects of countermeasures for controlling OH is also limited.

1.5.1 Abdominal Binder as a countermeasure to OH in PD

Utility of the AB for countering OH has been better investigated in other neurological disorders/diseases than PD, for instance, in spinal cord injury. Although conflicting evidence exists about the utility of ABs in controlling OH in spinal cord injury, it is

commonly used for countering OH as well as for respiratory benefits (improved voice production and lung volumes).[52–56] An AB compresses the abdomen, thereby increasing the intra-abdominal pressure that is believed to reduce the pooling of blood in the splanchnic vasculature and increase the venous return to heart. This is the probable mechanism through which an AB helps increase the BP for countering OH.[40]

The AB is more effective than compression stockings. Previous studies have shown that compression of the abdomen is better than compression of the lower extremities for increasing BP in patients with OH.[53,57] The AB has certain advantages over other methods of countering OH, both pharmacological and non-pharmacological. It is easy to wear and remove, does not require any special training or assistance, and its use is usually free of serious complications, including absence of development of SH.

Literature about the use of AB in PD is very limited. A recent study by Fanciulli et al[58] showed that the AB is effective in increasing BP by 10 mmHg in PwPD with OH. Although their findings appear promising for the use of AB to control OH in PwPD, their research study needs to be interpreted with caution. This is due to the fact that the mean change in SBP in their participants was -14.8 mmHg (95% CI -27.2, -2.3) at the 3rd minute during the head-up tilt (HUT) which is lower than the OH threshold of 20 mmHg SBP. This creates the possibility that although some participants may have demonstrated a decrease of ≥20 mmHg in SBP during HUT to justify the criteria of OH, others might not have (the confidence interval ranged from -2.3 mmHg to -27.2 mmHg decrease in SBP during the 3rd minute of HUT for the participants in their study). Thus, it is unclear if all the participants in Fanciulli et al's study had clinically obvious OH based on the widely accepted definition of OH. Absence of any other study on the effects of wearing an AB in PwPD necessitates that an investigation be undertaken on the effects of wearing an AB by PwPD with OH while ensuring that all participants fulfill the widely accepted definition of OH i.e. a sustained decrease of ≥20 mmHg in SBP during the initial three minutes of HUT.[9]

Another gap in knowledge is about the effects of wearing an AB by PwPD who have symptoms of orthostasis (dizziness, light-headedness, etc.) but do not have OH. No

literature has studied whether wearing an AB by PwPD is suitable for the management of symptoms of orthostasis in the absence of clinically obvious OH. As a result, there exists ambiguity about the possible risks and benefits of wearing an AB by PwPD without OH. Although the use of an AB may appear to be benign, it may not be appropriate to reach a conclusion without objective evidence. We need to investigate if serious hemodynamic complications in the systemic or cerebral circulations can occur as a result of wearing an AB by PwPD who do not have OH. Since PwPD without OH do not need an increase in venous return to the heart as they do not have a substantial decline in BP with the assumption of upright posture, determining whether the use of AB produces any undesirable increase or decrease in the systemic BP was the primary objective of studying the effects of AB in PwPD without OH. The idea was to inform the clinician about if they can prescribe an AB to a PwPD who does not have OH without the risk of potentially serious hemodynamic complications. This will help in clinical decision making for those PwPD who obtain symptomatic relief with the use of an AB but do not have OH. Another aim was to help the clinician know whether PwPD with borderline OH should avoid wearing an AB on 'good' days when the decline in SBP is not more than 20 mmHg systolic. For instance, if a PwPD has a decrease of 25 mmHg in SBP upon standing on one day but 15 mmHg on another day, the clinician would need to be certain that wearing the AB on the day the BP fell by 15 mmHg is not expected to produce any adverse hemodynamic effects.

Lastly, it is unknown if removing the AB in the standing position has any adverse effects on systemic and cerebral hemodynamics, and if this may worsen the symptoms of orthostasis. Since the mechanism of action of AB is through controlling the pooling of blood in the abdomen through external compression, a sudden removal of the pressure may produce a sudden release of the abdominal contents, possibly allowing the capacitance vessels to expand in an uncontrolled manner. We speculated that a sudden release to allow an uncontrolled expansion in the capacitance vessels may produce exaggerated pooling of the blood in the splanchnic circulation which may produce significant worsening of OH.

1.5.2 Exercise and OH in PD

Patients with PD are normally advised to live an active lifestyle that includes regular exercise. The exercises are generally advised as a part of the exercise rehabilitation program. Most exercise rehabilitation programs include a combination of exercises that are aimed towards maintenance and improvement of joint mobility, soft-tissue flexibility, muscular strength, cardiorespiratory endurance, balance, coordination, and ambulation.[59–62] In order to maintain cardiorespiratory endurance, AE is commonly prescribed.

Aerobic exercise can be performed in different ways including walking and stationary cycling exercise. The potential benefits are not limited to improvements in cardiorespiratory endurance, rather AE also helps maintain the joint range of motion (ROM) and muscle strength of the limbs that are used during the exercise. Walking, being a common form of AE in daily life, helps maintain the muscle strength and ROM of the lower limbs. On the other hand, many activities of daily living require the use of upper limbs. This includes activities like cooking, eating, bathing, personal hygiene, overhead activities, etc. Therefore, for PwPD maintenance of ROM and muscle strength of all four limbs is generally an important objective of the exercise rehabilitation programs. PwPD usually undertake AE as well as upper limb resistance exercise to fulfill this objective. However, in PwPD it is unclear if upright AE using lower limbs can produce adverse effects due to a combined effect of OH and vasodilation in the lower limbs.

When the systemic circulation is already compromised due to OH, exercise may produce an additional and potentially exaggerated pooling of blood in the lower limbs through vasodilatation. This may prove to be catastrophic to the patient as BP could further decline up to a point that syncope (fainting) may occur. A decline in SBP of ≥10 mmHg produced by exercise is known as exercise-induced hypotension (EIH).[45] EIH is a known complication in autonomic disorders. In PD, a combination of cardiac and extra-cardiac sympathetic denervation as well as excessive vasodilatation in the exercising muscles are believed to produce EIH.[45] EIH has been associated with symptoms that are similar to those seen as a result of OH such as dizziness, fatigue, syncope and reduced physical

capacity.[45,63,64] EIH has shown to worsen OH both during and after the cessation of exercise.[65] As a result, EIH has been implicated in restricting patient's mobility and independence and predisposing the patient to a higher risk of falls that can result in serious injuries, thus worsening the prognosis and affecting the patient's quality of life.[45]

Two studies have reported EIH in PwPD.[66,67] Reuter et al reported that 3 of the 15 participants with idiopathic PD developed EIH during their study on cycle ergometry using a ramp protocol. [66] However, it is unclear if those 3 participants in their study had OH or dysautonomia as these were not reported. In a later study, Low et al found that 10 of the 17 PwPD with OH had either no change or a decrease in BP during supine cycling graded exercise test.[67] Although the findings of this study suggested that EIH occurred only in PwPD with OH, it neither specified how many of those 10 participants had decrease in BP during exercise and if this decrease was significant enough to be called EIH. Moreover, in Low et al's study[67] the participants did a supine cycling exercise test, which may not be able to suggest what can be expected during upright exercise as the effect of gravity was eliminated during supine exercise. Another notable hinderance to the clinical application of the existing literature about the effects of lower extremity exercise in PwPD is that most of the available literature is about the effects of graded exercise testing in PwPD. Clinicians generally prescribe patient-regulated AE to PwPD that, unlike the ramp protocols, hands the control of the intensity of the exercise over to the patient and relies on the patient's rating of perceived exertion to regulate the intensity of exercise. This makes it difficult for the clinicians to derive clinically meaningful knowledge from the available evidence. In short, there is lack of literature on hemodynamic responses of PwPD with OH when they perform self-regulated AE in the upright position. Given the potential complication of EIH, evidence on upright patient-regulated AE is vital for the clinical decision-making during exercise rehabilitation of PwPD with OH.

While lower extremity exercise raises the suspicion of greater complications in the form of EIH, upper extremity exercise appears to have a positive aspect due to the potential for countering OH. Resisted upper limb exercise (RULE) is generally prescribed to maintain

and improve upper limb strength, endurance and ROM. However, beyond the known motor benefits, it might also prove to be useful for increasing systemic BP, as RE is known to increase BP as well as total peripheral resistance in healthy individuals.[46,68,69] Since RE has the potential to increase BP without the need of substantial increase in CO, it may be logical to exploit this property of RE to boost BP for countering the OH without the need of increasing the cardiac preload (that requires a reduction in pooling of the venous blood in the abdomen and lower extremities).

Although the potentially beneficial effect of RE on BP may prompt an investigation about the hemodynamic advantage of performing RULE in PwPD with OH, one may argue that there exist countermeasures and counter-maneuvers that are already known and require lesser effort than RULE. Simply put, when countermeasures like AB and compression stockings or counter-maneuvers like bending forward and standing cross-legged are already known to help patients with OH, it may sound counterintuitive to search for a more challenging method like RULE that requires active effort in the form of antigravity resisted exercise. However, the existing countermeasures have certain disadvantages that may sufficiently inspire the search for a better substitute. AB and compression stockings are worn prior to assumption of upright posture for maximal benefits. This limits their benefits to only those situations where AB and compression stockings were worn in a pre-planned manner to counter OH i.e. the patient must anticipate symptoms of OH and wear the AB or compression stockings in advance. On the other hand, RULE may be used instantly whenever needed without the need of planning in advance. The other counter-maneuvers like bending forward and cross-legged standing may further compromise the already affected balance in PwPD. RULE can be done with a wide base of support and does not require bending or any such posture that may compromise the patient's postural stability during the standing position. Another distinguishing feature of RULE is that it does not target the pooling of blood in the lower extremities or the abdomen by compression or muscular pumping to increase the venous return. Rather, RULE combines the effects of static and dynamic exercise using the comparatively smaller upper limb muscles which we

hypothesized would produce a pressor response that shall prove to be potent in rapidly raising the systemic BP and attenuating the symptoms of OH.

1.5.3 Effects on cerebral circulation

When systemic BP decreases due to OH, it leads to substantial cerebral hypoperfusion, provided that the decrease in the systemic MAP is sufficient to render the cerebral autoregulatory mechanisms dysfunctional. Cerebral hypoperfusion can adversely affect the regional cerebral oxygen saturation and produce symptoms of orthostasis.[70–73] However, existing literature about exercise or physical countermeasures against OH in PwPD generally reports only the changes that occur in the systemic BP and symptoms.[66,67,74–79] It is unclear how the cerebral hemodynamics change when PwPD with OH perform exercise or use an AB in the upright position. Practically, monitoring the changes in the cerebral circulation may not be possible in the clinic during the exercise rehabilitation of PwPD, and therefore, the changes in the cerebral hemodynamics may not be of interest to most clinicians. However, this knowledge is required to understand the sequence of changes that may produce the symptoms of orthostasis. This shall expand the knowledge base and provide an understanding of the sequence of changes from systemic hemodynamics, through cerebral hemodynamics, to symptom manifestation. Hence, there is need to study the changes in cerebral blood flow and cerebral oxygenation in PwPD with OH while they perform exercise or use a device to counter OH.

Overall, lack of existing literature and significant gaps in knowledge inspired us to undertake one research study on the use of external compression (AB) to counter OH, another research study on the effects of lower extremity AE in the upright position, and a third research study on the possible use of RULE to counter OH.

1.6 Thesis objectives

The aim of this thesis was to produce clinically meaningful literature that can help expand the knowledge base of physiotherapists and other clinicians to support evidence-based

rehabilitation of the PwPD with OH. To achieve this aim this thesis investigated the effects of techniques and exercises that are commonly used during the rehabilitation of PwPD on the systemic circulation, cerebral circulation and symptoms, with a focus on PwPD with OH. The findings of this thesis are intended to help expand the knowledge base about the rehabilitation of PwPD with OH that should eventually help clinicians, especially the physiotherapists, in developing tailored rehabilitation programs for PwPD with OH as well as inform all the clinicians during the process of clinical decision making. PwPD with OH may benefit directly from the findings of this thesis by learning more about the options available to them for the management of OH as well as about the hemodynamic effects of performing exercise, thereby possibly making better informed decisions about their rehabilitation.

This thesis has three research studies, each with a different set of objectives. However, as a common approach, all the research studies studied the effects on the same dependent variables namely, SBP, MAP, DBP, HR, cerebral blood flow velocity, ratio of oxygenated to de-oxygenated blood in the cerebral frontal cortex, and symptoms of orthostasis. The systemic hemodynamics were represented by HR and SBP, DBP and mean blood pressures. Cerebral hemodynamics were represented by cerebral blood flow and cerebral oxygenation. Cerebral blood flow was represented by the mean middle cerebral artery velocity and cerebral oxygenation was represented by the regional cerebral cortical ratio of oxygenated to de-oxygenated hemoglobin. The symptoms of orthostasis were ranked using the Orthostatic Symptom Scale (OSS).[57,80]

In the first research study (chapter 2), we investigated the effects of wearing an AB by PwPD with and without OH. This study had three objectives: to investigate (1) the effects of wearing an AB by PwPD with OH; (2) the effects of wearing an AB by PwPD without OH; and (3) the effects of removing the AB in the standing position. We hypothesized that wearing an AB will alter the dependent variables in PwPD with and without OH. We also hypothesized that the removal of AB shall significantly change the values of the dependent variables in all the participants.

In the second research study (chapter 3), we investigated the effects of performing self-regulated aerobic cycling exercise (SRACE) by PwPD on the dependent variables. The objective of this study was to determine if PwPD with and without OH respond differently to SRACE. We hypothesized that the dependent variables will be altered differently by SRACE in PwPD with compared to those without OH.

In the third research study (chapter 4), we investigated the effects of performing RULE on the dependent variables, especially the systemic BP. The objective of this research was to determine if RULE can be used to counter OH in PwPD. We hypothesized that RULE will alter all the dependent variables in general and the SBP in particular.

As a whole, the three research studies in this thesis intended to explore the means to effectively counter OH and to understand the consequences of performing different types of exercise in PwPD with OH, in order to generate clinically relevant evidence that can inform and make the rehabilitation of these patients better and safer in the future.

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Chapter 2

2 Cardiovascular effects of abdominal binder in Parkinson's Disease with and without orthostatic hypotension

2.1 Introduction

Orthostatic hypotension (OH), is a common non-motor manifestation in Parkinson's Disease (PD).[1,2] OH is a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or in diastolic blood pressure (DBP) of at least 10 mmHg occurring within 3 minutes of standing up at 60 degrees or more of head-up tilt (HUT).[3] OH may be present in up to 58% of patients with PD (PwPD).[4,5] During chronic PD, non-motor problems like orthostatic hypotension, dementia, hallucinations, depression, choking and urinary incontinence become the primary cause of disability,[6] in effect becoming the dominant barriers to functional independence. Postural dizziness and light-headedness (orthostasis) caused by OH may add to pre-existing motor deficits in predisposing the patients to a greater risk of falls.[7–9]

Wearing an abdominal binder (AB) during standing to help offset the effects of OH has proven useful in various disease populations.[10–14] The relative ease of use of an AB and relatively low chance of complications makes this a good first option for management of OH. However, research regarding the effects of wearing an AB for management of OH in PD and its effects on symptoms of orthostasis is scarce. It is also unclear if improvements in systemic circulation directly translate into better blood and oxygen supply to the brain, which could result in decreased severity of orthostatic symptoms.[15–17]

This study was undertaken to investigate: (1) whether the use of an AB in PD patients with OH results in improvement of systemic BP, cerebral blood flow/oxygenation and the severity of orthostatic symptoms; (2) if an AB can be worn without the risk of hemodynamic or symptomatic complications by those PwPD who do not have OH; and (3)

the effects of removing the AB on hemodynamics and orthostatic symptoms while in the standing position.

2.2 Methods

2.2.1 Participants

Thirty-four PwPD were recruited and tested at the university campus of the London Health Sciences Centre, London, ON. Institutional ethical approval and written informed consent from each participant were obtained. Subjects abstained from alcohol and caffeine for at least 12 hours and from nicotine and a heavy meal for at least 4 hours prior to testing. The sample consisted of patients with levodopa-responsive idiopathic PD (IPD) who were between stages 2 and 4 of the Hoehn and Yahr classification,[18] 60 to 90 years old, male or female, had at least 3 years post-diagnosis history of IPD and were able to independently stand up from a sitting position and walk. Potential participants in therapy with alpha- and beta-adrenergic antagonists, anticholinergics or other medications that could interfere with the regulation of BP and heart rate were excluded from the study. Individuals with diseases that could affect autonomic function (except those with PD) or the ability to cooperate were also excluded. All participants were already on stable dopaminergic medications. No medications were withheld or changed for the purposes of this study. Anti-hypotensive medications, including midodrine and fludrocortisone were allowed to ensure that the participants would present for this study as they would present themselves for PD rehabilitation in a clinical setting.

All participants underwent autonomic reflex screening (ARS), which is a standardized set of measurements used to evaluate autonomic nervous system function.[19] The results from the ARS were reported using the composite autonomic severity score[19] (CASS), a 10 point scale that provides a quantitative value for the severity of dysautonomia.

The HUT was used to classify patients for the presence or absence of OH. As per the consensus statement on the definition of OH,[3] participants with 20 mmHg or greater reduction in SBP during the HUT component of the ARS were allocated to the PD+OH

group. Those without OH went to the PD group. The findings from HUT done during the ARS served as the control condition for comparison with the experimental condition of HUT with an AB (HUT+AB). The HUT testing in both conditions was identical, i.e. 70° HUT lasting for 5 minutes and was done on the same day for each participant. After 5 minutes in HUT+AB, the AB was removed in the 70° HUT position and the monitoring continued for the next one minute. Two BP thigh cuffs (Critikon, GE Healthcare, Finland) joined end-to-end formed a belt on the abdomen beneath the elastic AB (Appendix B). The anterior thigh cuff bladder was connected to a sphygmomanometer to measure pressure. The elastic AB (ITA MED, USA) was tightly worn over this belt and the bladder of the belt inflated to achieve 20 ± 2 mmHg pressure. The size of the elastic AB used was selected based of the abdominal girth of the participant.

2.2.2 Physiological recordings

Continuous and non-invasive beat-to-beat systemic blood pressure (BP) recordings, which included arterial systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP), were obtained from a finger held at the heart level (BMEYE Nexfin device, Amsterdam, Netherlands and WR TestWorks TM software, WR Medical Electronics Co. Stillwater, MN, USA). Middle cerebral artery velocities were recorded to represent cerebral blood flow velocity (CBFv) using transcranial doppler (TCD) ultrasound probes at 2 MHz (Multigon 500M, DWL MultiDop-T, Neuroscan, NY, USA), placed bilaterally on the sides of the head. The ratio of oxy- to deoxy-haemoglobin was used as the measure of cerebral regional oxygen saturation ($crSO_2$). Two rectangular probes of the near-infrared spectroscopy (NIRS) machine (NIRS Foresight® cerebral oximeter, CASMED, Branford, CT, USA) were placed bilaterally over the forehead to record the $crSO_2$ of each cerebral frontal cortex.

2.2.3 Scale

Symptoms were scored using the Orthostatic Symptom Scale (OSS),[11,13,20] a visual analogue scale with increasing levels of severity of symptoms of orthostasis, i.e. 0 (no symptoms), 2 (tiredness or momentary light-headedness), 4 (mental sluggishness or

difficulty concentrating), 6 (dizziness or unsteadiness), 8 (blurred vision or faintness) and 10 (syncope or pre-syncope). If a participant felt ‘somewhat light-headed’, it was scored as 1 in this study. As blurred vision is possible with orthostasis and prescription glasses are difficult to be worn along with TCD probes, the symptoms were verbally reported by the participants and corresponding values from OSS were recorded by the investigators.

2.2.4 Data Analysis

Data were visually inspected using Spike2 software (version 7, Cambridge Electronic Design, Cambridge, UK), down-sampled to 1 Hz using Spike2 software and MATLAB software (version R2017b update 9, MathWorks Co.) and analyzed using SPSS version 25 (IBM Corporation).

A three-way mixed ANOVA (including post-hoc comparison using Bonferroni corrections) was used to analyze the effects of group, type of intervention and time on parametric dependent variables. A two-way mixed ANOVA was used to analyze the effects of removal of the abdominal binder. To correct for multiple t-tests, the level of significance was set at $P = 0.05/x$, where x = the number of times the t-test was undertaken.

A Wilcoxon signed-rank test was used to analyze the effect of wearing the AB on symptoms in each group as the data obtained from the OSS (for symptoms) was ordinal level of measurement. We used a Mann-Whitney U test to analyze the effect of the removal of AB on the symptoms between the groups. Probability values of $P<0.05$ were deemed significant for all analyses.

Graphical presentation of data was done using GraphPad Prism software (version 8 for Mac, GraphPad Software, California, USA). Data was analyzed in intervals of 1 minute for HUT and HUT+AB, and in intervals of 30 seconds, i.e. 31st to 60th second of the first minute after removal of AB. For changes in variables after the removal of AB, the HUT 5th minute recordings of variables served as the baseline.

2.3 Results

Demographic data of the participants is presented in Table 2-1. Baseline (pre-HUT) values for each variable during the two forms of intervention are presented in Table 2-2 for both groups. There was no significant difference between the groups at baseline prior to HUT or prior to HUT+AB for any variable.

Table 2-1: Demographic data of participants.

	PD+OH	**PD**
n	18	16
Age (years)	74 ± 6	72 ± 6
Sex ratio (male:female)	12:6	7:9
CASS score	4.5	1.2

n = number of participants; CASS: composite autonomic severity score; PD+OH = group of participants with Parkinson's disease with orthostatic hypotension; PD = group of participants with Parkinson's disease without orthostatic hypotension.

Table 2-2: Baseline (Pre-HUT) values of variables for PD+OH and PD groups for each intervention.

	PD+OH		**PD**	
	HUT	*HUT+AB*	*HUT*	*HUT+AB*
CBFv (cm/sec)	43.54 ± 11.98	44.17 ± 10.80	37.14 ± 9.08	38.35 ± 10.49
$crSO_2$ (percent)	69.43 ± 5.19	70.19 ± 5.18	70.10 ± 4.16	70.67 ± 3.45

SBP (mmHg)	143.97 ± 19.26	146.01 ± 20.31	134.84 ± 23.43	139.75 ± 22.44
MAP (mmHg)	97.71 ± 16.46	98.70 ± 16.23	90.56 ± 12.22	94.35 ± 11.91
DBP (mmHg)	69.37 ± 13.24	70.51 ± 13.13	65.03 ± 7.13	67.93 ± 6.78

CBFv = mean middle cerebral artery velocity; crSO2 = ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation; SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure; PD+OH = group of participants with Parkinson's disease with orthostatic hypotension; PD = group of participants with Parkinson's disease without orthostatic hypotension; HUT = Head-up tilt; and HUT+AB = Head-up tilt with abdominal binder.

There was no significant three-way interaction between the independent variables group, type of intervention and time for any dependent variable. No significant interaction was found between group and type of intervention for any variable. Statistically significant ($P<0.05$) two-way interactions were found between type of intervention and time for SBP and DBP. Statistically significant ($P<0.05$) two-way interactions between group and time were observed for all the dependent variables, i.e. CBFv, $crSO_2$, SBP, MAP and DBP.

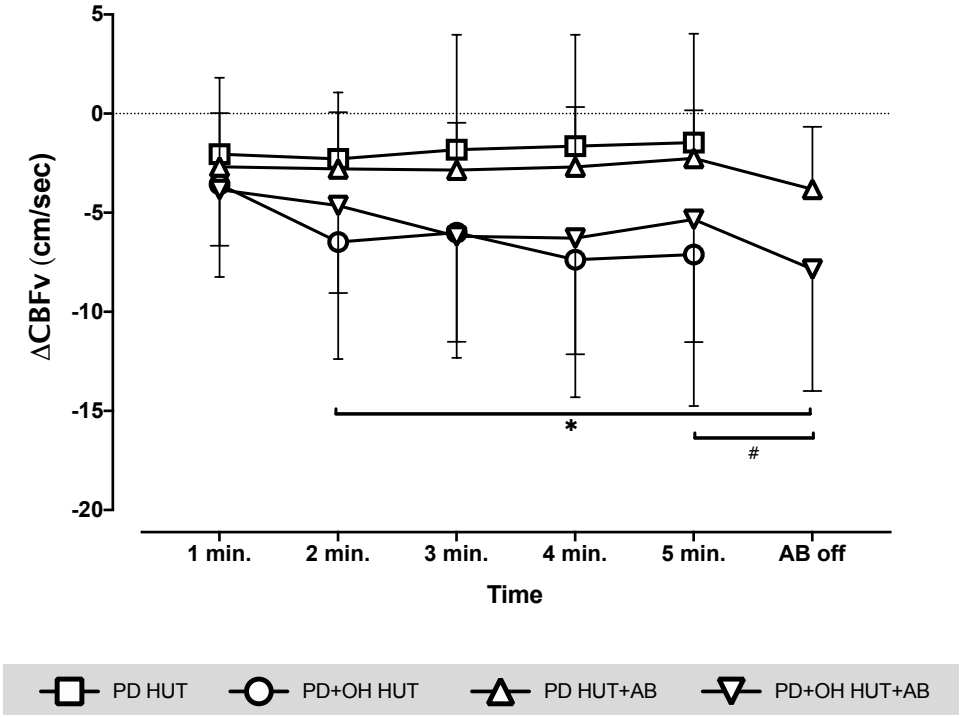
Analysis for simple main effects revealed that in the PD+OH group, the values of SBP, MAP and DBP remained significantly lower ($P<0.05$) compared to their baseline values for the entire duration of HUT. CBFv and $crSO_2$ were not affected by HUT during the first minute, after which both started to decline significantly ($P<0.05$). Use of AB during HUT significantly attenuated ($P<0.05$) the mean reduction in SBP by 7.03 mmHg, in MAP by 4.19 mmHg and in DBP by 2.76 mmHg in the PD+OH group. Similar, but not significant changes were observed in CBFv and $crSO_2$ in this group. Use of the AB delayed the time taken to reach the nadir of SBP by one minute (Figure 2-1).

On the other hand, HUT did not cause any significant changes from baseline values for SBP, MAP and CBFv in the PD group. DBP increased with HUT. This increase achieved statistical significance ($P=0.033$) at 2 minutes into HUT and persisted until the end of HUT.

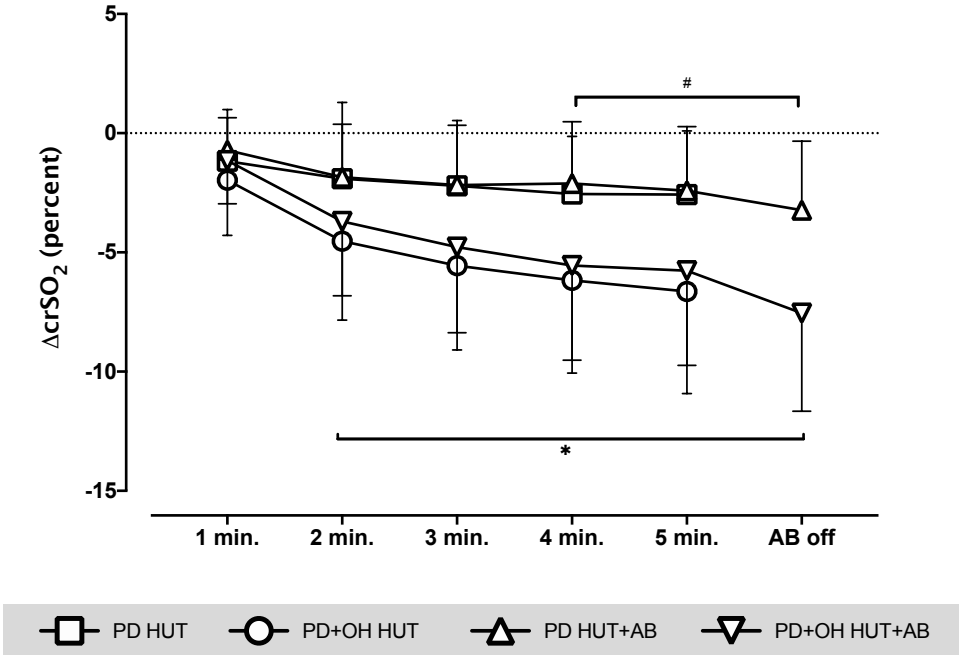
$crSO_2$ progressively decreased throughout the HUT. This decline achieved statistical significance (P=0.017) after 3 minutes into HUT. Use of the AB during HUT did not produce significant changes in any dependent variable in this group compared to HUT without the AB (Figure 2-1).

Figure 2-1: Changes in dependent variables during HUT and HUT+AB in groups PD and PD+OH.

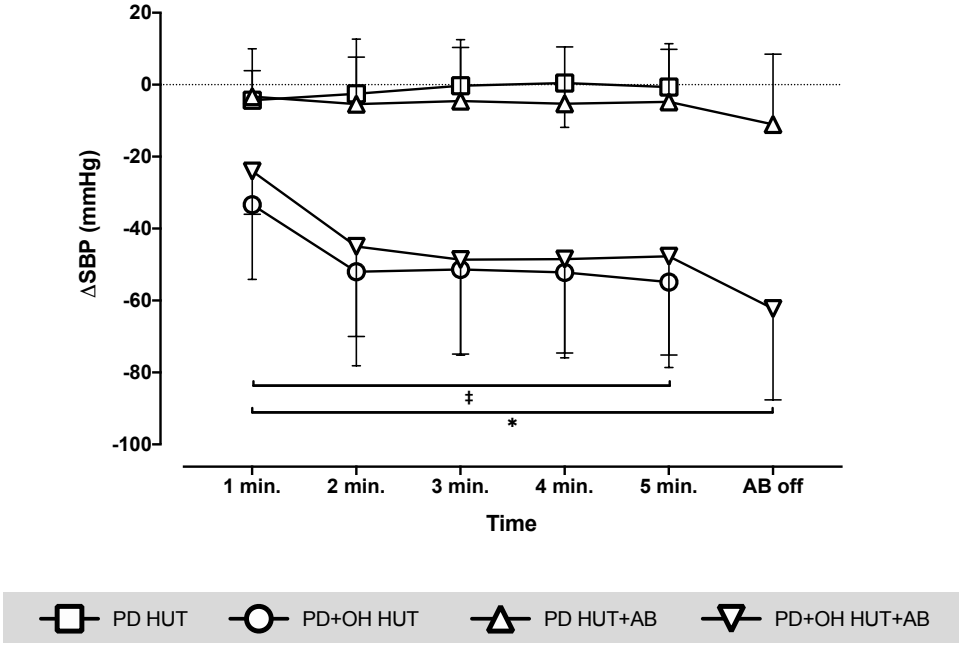
(a) Changes in CBFv during HUT and HUT+AB in groups PD and PD+OH.



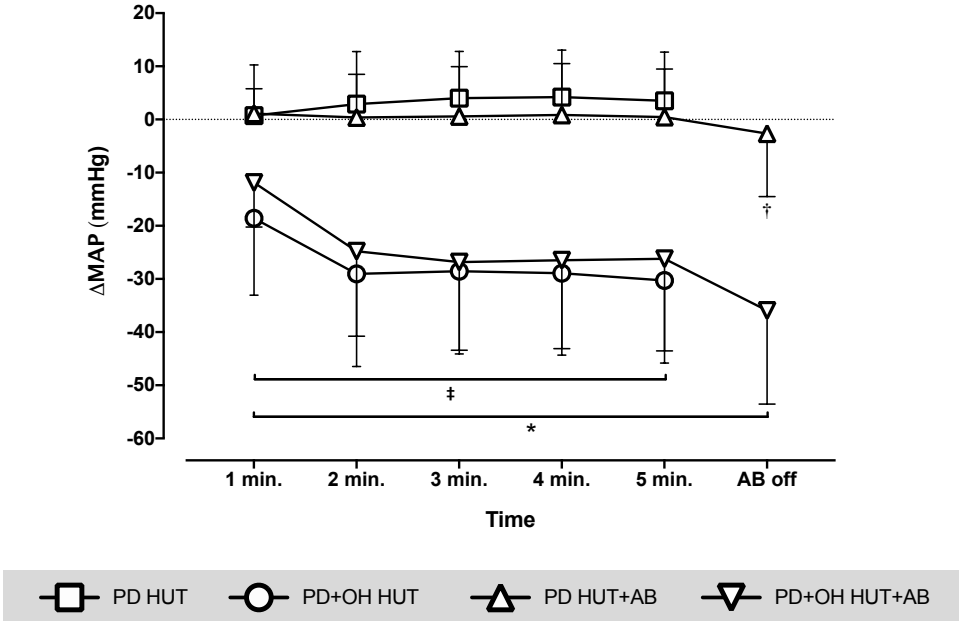
(b) Changes in $crSO_2$ during HUT and HUT+AB in groups PD and PD+OH.



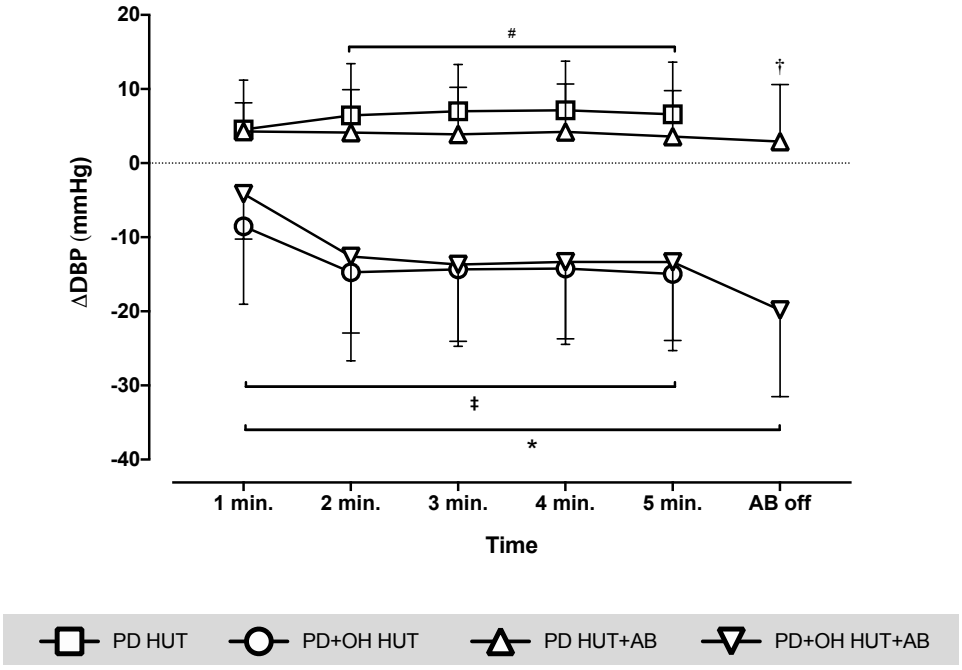
(c) Changes in SBP during HUT and HUT+AB in groups PD and PD+OH.



(d) Changes in MAP during HUT and HUT+AB in groups PD and PD+OH.



(e) Changes in DBP during HUT and HUT+AB in groups PD and PD+OH.



HUT = head-up tilt; OH = orthostatic hypotension; AB = abdominal binder; HUT+AB = head-up tilt with abdominal binder; CBFv = cerebral blood flow velocity (determined as mean middle cerebral artery velocity);

$crSO_2$ = ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation; SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure; 1 min = first minute into HUT/HUT+AB; 2 min = second minute into HUT/HUT+AB; 3 min = third minute into HUT/HUT+AB; 4 min = fourth minute into HUT/HUT+AB; 5 min = fifth minute into HUT/HUT+AB; AB off = post removal of abdominal binder. Baseline value is pre-HUT value for 5 minutes of HUT, but in case of removal of abdominal binder it is the 5th minute value of HUT+AB that served as the baseline value; * significant (P<0.05) for changes from baseline value in PD+OH group during HUT and/or significant (P<0.01) with removal of AB; # significant (P<0.05) for changes from baseline value in PD group during HUT and/or significant (P<0.01) with removal of AB; ‡ significant (P<0.05) for comparison between interventions (HUT and HUT+AB) in the PD+OH group; † significant (P<0.01) for comparison between groups after removal of AB.

CBFv (a) decreased during HUT in the PD+OH group but remained stable in the PD group. Use of the AB during HUT did not change the results in either group. crSO2 (b) decreased progressively in both the groups during HUT. Use of the AB during HUT did not control the decline in crSO2 in either group. HUT produced decrease in magnitude of SBP (c), MAP (d) and DBP (e) in the PD+OH group. On the contrary, no effect of HUT was observed on SBP (c) and MAP (d) in the PD group, while DBP (e) increased slightly above the baseline. Use of the AB during HUT effectively controlled the decrease in SBP (c), MAP (d) and DBP (e) in the PD+OH group, while in the PD group it did not change the results for these variables. The removal of the AB in the HUT position led to a decrease in the magnitudes of all the variables (a-e) in the PD+OH group, whereas, only CBFv (a) and crSO2 (b) decreased in the PD group. Overall, AB was effective in countering OH during HUT by increasing the systemic BP (c, d and e) in PwPD with OH, but it failed to control the decline in cerebrovascular measures (a and b) in these participants, while in PwPD without OH, the use of the AB during HUT was ineffective. Removal of the AB in the upright position produced adverse effects on the cerebrovascular measures (a, b) as well as the systemic BP (c, d and e) in PwPD with OH, while in PwPD without OH it negatively influenced only the cerebrovascular measures.

2.3.1 Removal of AB

There was a significant (P<0.05) interaction between group and time for CBFv, SBP and DBP. Removal of AB during standing led to significant (P<0.01) reductions in magnitudes of all variables in the PD+OH group but only CBFv and $crSO_2$ in the PD group (Table 2-3). Statistically greater reductions (P<0.01) of 7.07 and 6 mmHg were observed for MAP and DBP, respectively, in the PD+OH group compared to the PD group (Figure 2-1).

Table 2-3: Effects of removal of abdominal binder in 70° HUT position on dependent variables.

		Mean	95% CI	*t*	*P*
ΔCBFv (cm/sec)	PD+OH	-3.61	-5.19 to -2.02	-4.826	<0.001*
	PD	-1.55	-2.44 to -0.66	-3.783	0.002*

		Mean	95% CI	*t*	*P*
$\Delta crSO_2$ (percent)	PD+OH	-1.77	-2.34 to -1.20	-6.61	<0.001*
	PD	-0.81	-1.29 to -0.34	-3.674	0.003*
ΔSBP (mmHg)	PD+OH	-15.76	-21.11 to -10.4	-6.210	<0.001*
	PD	-6.26	-11.18 to -1.34	-2.714	0.016
ΔMAP (mmHg)	PD+OH	-10.20	-13.68 to -6.71	-6.176	<0.001*
	PD	-3.13	-6.16 to -0.09	-2.199	0.044
ΔDBP (mmHg)	PD+OH	-6.66	-9.15 to -4.16	-5.631	<0.001*
	PD	-0.66	-2.69 to 1.36	-0.698	0.496

Δ = change in measured value from 5th minute into HUT+AB to the second half of the first minute after removal of abdominal binder; CBFv = mean middle cerebral artery velocity; crSO2 = ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation; SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure; PD+OH = group of participants with Parkinson's disease with orthostatic hypotension; PD = group of participants with Parkinson's disease without orthostatic hypotension; CI = confidence interval; and t = calculated t-value from paired samples t-test. *significant at P<0.01

2.3.2 Symptoms

Only 8 subjects in the group PD+OH and 7 subjects in the PD group were symptomatic (Table 2-4). There was no statistically significant effect of wearing of AB on symptoms during the fifth minute of HUT nor of the removal of AB in any group or between the groups. However, some participants in each group experienced reduction in symptoms with the use of the AB (Table 2-4). Removal of the AB in HUT position worsened the symptoms for some of the participants in the PD+OH group, while subjects in the PD group remained unaffected.

Table 2-4: Presentation of symptoms during HUT, HUT+AB and removal of AB in PD+OH and PD groups.

Subject	*HUT 1 min*	*HUT 5 min*	*HUT+AB 1 min*	*HUT+AB 5 min*	*HUT (AB removed)*
A1	2	0	2	0	0
A2	2	6	0	0	4
A3	2	1	1	1	1
A4	2	8	6	6	6
A5	1	0	0	0	4
A6	0	0	0	0	4
A7	6	2	0	1	1
A8	2	0	1	1	0
B1	4	4	2	2	2
B2	4	0	2	1	1
B3	8	0	0	0	0
B4	6	0	2	0	0
B5	1	0	0	0	0
B6	1	0	2	0	0
B7	2	1	0	0	0

A = PD+OH group subjects; B = PD group subjects. Magnitude/severity of symptoms is reported on orthostatic symptoms scale (OSS). OSS is visual analogue scale with increasing levels of severity of symptoms where 0 = no symptoms, 1 = somewhat lightheaded, 2 =tiredness or momentary light-headedness, 4 = mental sluggishness or difficulty concentrating, 6 = dizziness or unsteadiness, 8 blurred vision or faintness and 10 syncope or pre-syncope. HUT 1 min = OSS value near the end of first minute during HUT; HUT 5 min = OSS value near the end of fifth minute during HUT; HUT+AB 1 min = OSS value near the end of first minute during HUT with AB; HUT+AB 5min = OSS value near the end of fifth minute during HUT with AB; and HUT (AB removed) = OSS value near the end of first minute after AB was removed while participant remained in HUT position.

2.4 Discussion

This study investigated the possible positive and negative effects of wearing an AB on systemic BP and the resulting changes on cerebral hemodynamics, cerebral oxygenation and symptoms of orthostasis in PwPD with and without OH. Additionally, we determined the hemodynamic consequences of removal of an AB in the standing posture. This is the first study to (1) investigate the effects of changes in systemic hemodynamics on cerebral circulation and symptoms in PwPD when an AB is used, (2) determine if an AB can be useful for symptomatic relief in PwPD who do not have OH, (3) investigate the effects of removal of AB in the standing position, and (4) to undertake these investigations after objectively determining the severity of autonomic dysfunction using CASS in PwPD.

In the PD+OH group, AB proved effective in attenuating orthostatic fall in BP but failed to statistically improve CBFv, $crSO_2$ or symptoms. This failure may be due to the inability of the AB to raise the systemic BP sufficiently enough to significantly influence the cerebral hemodynamics. However, even minor improvements in the MAP may be able to restore the impaired functioning of the cerebral autoregulation, leading to alleviation of symptoms of orthostasis.[15–17,21] This may explain why only some of the participants with OH in this study had lesser severity of the symptoms with the use of an AB (Table 2-4). The probable mechanism by which the AB can maintain a higher systemic BP is that the mechanical compression by the AB prevents and reduces venous pooling in the splanchnic circulation (where most of the venous pooling occurs), thereby increasing the venous return to the heart,[10,12,22,23] helping to maintain the cardiac output.

The use of an AB in the PD group was ineffectual. All the variables changed similarly during the HUT, irrespective of the use of AB. Although the changes observed in symptoms with the use of an AB were not statistically significant, some individuals benefitted symptomatically with the use of the AB (Table 2-4). Thus, an AB may be useful for PwPD with OH for control of OH, and in some cases, for symptomatic relief, while it may also be useful for some PwPD (without OH) for symptomatic relief without the risk of serious hemodynamic complications. The latter observation is particularly important for the individuals with borderline OH as they need not discontinue the use of their AB if on some days the decrease in SBP upon assumption of upright posture is less than 20mmHg. These findings, in effect, bring into question the clinical relevance of the 'gold standard' definition for OH[3] during the process of prescription of an AB by a clinician. The gold standard definition of OH[3] in the present form relies solely on the objective quantification of BP decline, with no regard for symptoms, whereas, a clinician may be inclined to consider treatment options for OH with greater emphasis on symptomatic relief than the objective improvements in BP.

Symptomatic individuals who have PD, irrespective of OH, stand to gain from the use of an AB if it successfully attenuates the severity of the symptoms as this may contribute to fall prevention.[24–27] Additionally, improved confidence in the standing position can greatly enhance functional independence in activities of daily living that might have been restricted.[15,26] Given the impending risk of syncope triggered by OH,[28] which can result in a fall,[29,30] the clinician may consider using an AB for controlling the OH. In the present study, the compression of the abdomen produced by the AB at 20 ± 2 mmHg pressure was comfortably tolerated by all the participants and no participant complained of uneasiness.

The findings of the present study are supported by the findings of the study by Smit et al[12] who found similar but greater improvements in SBP during HUT with an AB for the one minute of their testing protocol. The differences may be due to patient population and the method of orthostatic stress, i.e. active standing, in the study by Smit et al[12] compared to HUT in the present study. In a similar study, Fanciulli et al[23] found greater mean

improvements in SBP, MAP and DBP with the use of an AB during the third minute into HUT in patients with PD and symptomatic OH. These differences may be due to greater duration of time for which an AB was worn (2 hours) prior to HUT+AB, lesser angle of HUT (60°) and >3 times lesser mean decline in SBP during the third minute of HUT without the AB, compared to the present study.

Removal of AB in the 70° HUT position led to 'AB-removal hypotension' where significant reductions in the systemic and cerebral hemodynamics as well as cerebral oxygenation were observed in the PD+OH group. Although symptoms did not change statistically, these worsened in some participants in the PD+OH group (Table 2-4). The findings of the present study for the effects of AB removal are supported by Figueroa et al[11] who found worsening of OH when the pressure applied by the AB was decreased. Reductions in systemic BP with the removal of the AB reinforces the construct that an AB helps maintain higher BP by controlling pooling of the blood in the splanchnic circulation, as removal of the AB led to immediate reductions in systemic and cerebral circulations. We note that the detrimental effects of removal of the AB in the PD+OH group outweighed the benefits of wearing it by more than double. Thus, it may be appropriate to say that not wearing an AB by PD+OH patients is better than removing it in the standing position. Care should therefore be taken to never remove the AB in the standing position. In the PD group, there was no significant reduction in systemic BP with the removal of AB and the reductions in CBFv and $crSO_2$ were considerably lesser and not accompanied by worsening of symptoms. Nevertheless, it may be prudent to follow the same precautions.

2.4.1 Limitations

Head-up tilt was always followed by HUT+AB, which might have induced an order-effect. As HUT was part of the ARS, which was required for the allocation of participants into groups, counterbalancing was not possible. Male participants constituted two-thirds of participants in the PD+OH group. We conducted a two-way mixed repeated measures ANOVA to determine if gender had any interaction with the temporal effects of HUT in either group and found no significant gender interactions or main effects on any variable.

Therefore, the greater number of male participants in the PD+OH group does not appear to have compromised the external validity of this study.

2.5 Conclusions

In PwPD who have OH, an AB at a pressure of 20 ± 2 mmHg can be effectively used to attenuate the severity of OH. However, a 20 ± 2 mmHg pressure exerted by the AB may not be effective in significantly improving CBFv, CrSO2 or symptoms. Symptomatic improvement varies between patients, and if present, can be of clinical value during rehabilitation.

In those PwPD who do not have OH, an AB at a pressure of 20 ± 2 mmHg does not adversely affect systemic or cerebral hemodynamics or cerebral oxygenation. In most individuals, it seems to decrease the burden of symptoms. Therefore, AB can be a useful modality for symptomatic management of some PwPD who do not have OH and who benefit from it symptomatically, without risk of serious hemodynamic complications.

Removal of the AB in the standing position, especially in those who suffer from OH, results in adverse effects in systemic and cerebral hemodynamics. In some individuals with OH, it can worsen the symptoms of orthostasis. Therefore, removal of AB should be avoided in the standing posture.

Further studies are needed to determine if a greater AB pressure would significantly improve CBFv and $crSO_2$ and definitively cure the symptoms of orthostasis.

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Chapter 3

3 Self-regulated aerobic cycling exercise: Effects in Parkinson's Disease with orthostatic hypotension

3.1 Introduction

Physical activity and exercise in patients with Parkinson's Disease (PwPD) may be associated with benefits like attenuation of disease progression, decrease in motor symptoms and risk of falls, improved balance and gait, better ability to perform activities of daily living and improved quality of life.[1–8] In order to reap these benefits, aerobic exercise is commonly prescribed to PwPD.[9] Aerobic exercise is commonly performed as walking and stationary cycling and can be self-regulated by the patient by using their rating of perceived exertion (RPE) to determine the intensity of exercise. Self-regulated aerobic cycling exercise (SRACE) allows these patients to perform physical exercise while maintaining the intensity of exercise within safe limits by themselves, including during the times when the exercise is performed without the supervision of a health professional. Stationary cycling exercise, performed while sitting upright, can be a better tolerated alternative to walking as it less taxing to patients with orthostatic symptoms (being in a sitting position) and monitoring is easier with greater accuracy due to reduced movement of the upper body compared to walking.

Orthostatic hypotension (OH) due to dysautonomia is commonly seen in PwPD and the prevalence is estimated to be as high as 58%.[10–17] It occurs due to abnormal pooling of blood in the lower extremities and abdomen.[18] ue to the absence of relevant literature, it is unknown if during SRACE, the vasodilatation that would develop as a result of the lower extremity exercise could worsen the pooling of blood in the lower extremities, potentially accentuating hypotension, worsening orthostatic symptoms and bringing the patient to the verge of syncope. Moreover, existing literature suggests that PwPD, especially PwPD with OH, are at a risk of developing exercise-induced hypotension (EIH) during graded exercise testing.[19,20] Despite the fact that during SRACE the intensity of exercise is not intended to be maximal in nature, it still may not be benign for all PwPD with OH. This is due to the

potential risk of a combination of OH and EIH during SRACE done in upright position that may potentially deteriorate the systemic blood pressure (BP) even further and impair the cerebral blood flow and the oxygen supply to the brain.

There is uncertainty pertaining to potential adverse hemodynamic effects of SRACE in PwPD with OH, due to the lack of objective evidence in this clinical population. Therefore, this study was undertaken to compare the effects of SRACE (done as stationary cycling in the upright position) in PwPD with and without OH. Specifically, the objectives of this study were to compare i) systemic hemodynamics, ii) cerebral blood flow and oxygenation and iii) orthostatic symptoms between groups. The goal was to determine the hemodynamic and symptomatic consequences of performing SRACE in PwPD using standard physiological and clinical measures.

3.2 Methods

3.2.1 Participants

This was a prospective, interventional study with two groups. Twenty-eight PwPD were recruited and tested at the London Health Sciences Centre (University Campus), London, ON. Written informed consent from each participant and institutional ethical approval were obtained. The inclusion criteria were: PwPD between stages 2 and 4 of the Hoehn and Yahr classification,[21] consisting of idiopathic PD (IPD) patients who were levodopa-responsive, 60 to 90 years old, male or female, could walk and independently stand up from a sitting position, and a post-diagnosis history of IPD of at least 3 years. Exclusion criteria included (1) treatments (use of alpha- and beta-adrenergic antagonists or anticholinergics) and diseases that could influence the functioning of autonomic nervous system (except for PD); (2) diseases/disorders that could influence the ability of the participant to cooperate; and (3) diseases or conditions, including neurological and orthopedic conditions, that affect the ability of the participant to perform stationary cycling exercise. Participants were not asked to hold or change any medication in order to participate in this study. Stable dopaminergic medications, and if prescribed, anti-hypotensive medications, (midodrine or fludrocortisone) were continued as prescribed to replicate these patients' daily lives,

similar to how they would exercise in supervised clinics and therapy visits. We wanted to ensure that the setting of this study mimics the setting of community walking or rehabilitation clinics where participants normally undertake exercise simultaneously after these medications. Prior to testing, all participants abstained from a heavy meal and nicotine for at least 4 hours and from caffeine and alcohol for at least 12 hours.

The protocol started with testing of the autonomic nervous system using a standardized set of measurements called as the autonomic reflex screening (ARS).[22] The ARS included a head-up tilt (HUT) to evaluate participants for the presence of OH. Participants with 20 mmHg or greater fall in SBP[23] were allocated to the PD+OH group while others went to the PD group. The severity of dysautonomia was quantified using the 11-point (0 to 10) composite autonomic severity score (CASS).[22]

3.2.2 Physiological recordings

Systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP) were obtained from a finger held at heart level using the continuous, beat-to-beat and non-invasive technique (BMEYE Nexfin device, Amsterdam, Netherlands and WR TestWorks TM software, WR Medical Electronics Co. Stillwater, MN, USA). Heart rate (HR) was monitored continuously (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems Inc., Branford, CT, USA) using electrocardiography electrodes (Ambu® Blue Sensor SP, Glen Burnie, MD, USA). Transcranial doppler (TCD) ultrasound monitoring (Multigon 500M, DWL MultiDop-T, Neuroscan, NY, USA) using probes at 2 MHz placed bilaterally on the sides of the head, was undertaken to measure middle cerebral artery velocities that represented cerebral blood flow velocity (CBFv). We measured $crSO_2$ using two near-infrared spectroscopy (NIRS) (NIRS Foresight® cerebral oximeter, CASMED, Branford, CT, USA) probes placed over the forehead bilaterally.

3.2.3 Scales

A Borg CR 10 scale[24] was used for the rating of perceived exertion (RPE) by the participants. The Orthostatic Symptom Scale (OSS),[25,26] which is a visual analogue scale,

was used to score the severity of symptoms. The approximate terms for levels of severity of OSS are 0 (no symptoms), 2 (tiredness or momentary light-headedness), 4 (mental sluggishness or difficulty concentrating), 6 (dizziness or unsteadiness), 8 (blurred vision or faintness) and 10 (syncope or pre-syncope). Additionally, a perception of 'somewhat light-headed' was scored as 1. An investigator matched the symptoms reported by the participant to the categories in the OSS. This was done instead of the reporting of the numerical level of severity on the OSS by the participant due the possibility of blurred vision and the difficulty in wearing prescription glasses along with the TCD probes.

3.2.4 Protocol

Prior to the initiation of exercise, all participants were in the sitting position and procedures about the Borg CR 10 scale and the OSS were explained in detail. Participants were asked to sit on a cycle ergometer (Monark 824E Ergometic, Monark Exercise AB, Sweden) and pedal at a rate of 50 rpm by aligning to a digital metronome for a two-minute warm-up. No resistance was applied at this stage. After warm-up, resistance was applied in the form of weights while encouraging participants to maintain the pedaling rate at 50 rpm for the whole duration of cycling exercise. The resistance was modified within the first minute to achieve at least 3 and preferably 4 on the Borg CR 10 scale as per the exertion perceived by the participant. Such modifications of resistance continued thereafter till 8 minutes of exercise to continuously keep the RPE higher than 3 and as close as possible to 4. Near the end of each minute, participant's perceived exertion on the Borg CR 10 scale and the severity of symptoms on the OSS were recorded. The exercise was followed by a cool-down period of two minutes and a longer recovery period. If any participant was unable to sit on the cycle ergometer due to pain or any orthopedic limitation, a modified arm ergometer attached with pedals and placed on the ground was used while the participant remained seated in a chair. Exercise intensity was limited if the participant reached 85% of age-predicted maximal heart rate or SBP of 200 mmHg. Participants could stop the exercise if they wanted, felt extremely dyspnoeic, developed leg fatigue or chest pain, or experienced the symptoms of pre-syncope.

3.2.5 Statistical analysis

Data were visually inspected using Spike2 software (version 7, Cambridge Electronic Design, Cambridge, UK) and down-sampled using Spike2 software and MATLAB software (version R2018, Mathworks Co.). Data were analyzed using SPSS version 25 (IBM corporation). Data were analyzed in intervals of one minute for baseline, first minute, third minute, fifth minute and seventh minute. A two-way mixed ANOVA (including post-hoc comparisons using Bonferroni correction) was used to analyze the effects of group and time on dependent variables. A Wilcoxon signed rank test was used to analyze change in symptoms from baseline to the fifth minute during exercise and a Mann-Whitney U test was used to compare CASS scores.

3.3 Results

The demographic data of the participants and the baseline values of dependent variables are presented in Tables 3-1 and 3-2, respectively. Graphical representation of the results is shown in Figures 3-1 and 3-2. There were no significant interactions between the independent variables 'group' and 'time' for changes in any of the dependent variables. Analysis of the main effects of time revealed statistically significant differences in SBP ($P=0.025$), HR ($P<0.001$) and CBFv ($P=0.012$) at the different points in time, but not in MAP, DBP and $crSO_2$. On the other hand, the analysis of main effects of group revealed statistically significant differences between the groups of 42.8 mmHg for SBP (95% CI 24.5, 61.1; $P<0.001$) (Fig. 3-1a), 26.9 mmHg for MAP (95% CI 16.9, 36.9; $P<0.001$) (Fig. 3-1b), 17.3 mmHg for DBP (95% CI 10.8, 23.9; $P<0.001$) (Fig. 3-1c) and 4.8% for $crSO_2$ (95% CI 2.4, 7.3; $P<0.001$) (Fig. 3-1f) but not for HR (Fig. 3-1d) and CBFv (Fig. 3-1f). The temporal changes from baseline that were observed during pairwise comparisons were statistically significant ($P<0.05$) only for HR (Fig. 3-1d). HR increased from baseline (Table 3-2) to 1st minute by 15.5 beats.min^{-1} 95% CI [21.5, 9.4], 3rd minute by 24.2 beats.min^{-1} 95% CI [31.9, 16.5], 5th minute by 26.8 beats.min^{-1} 95% CI [34.2, 19.5] and 7th minute by 30.2 beats.min^{-1} 95% CI [38.8, 21.6] (Fig 3-1d). Participants in the PD group had a higher mean SBP of 42.8 mmHg ($P<0.001$; 95% CI [24.5, 61.1]) (Fig. 3-1a), MAP

of 26.9 mmHg (P<0.001; 95% CI [16.9, 36.9]) (Fig. 3-1b), DBP of 17.3 mmHg (P<0.001; 95% CI [10.8, 23.9]) (Fig. 3-1c) and $crSO_2$ of 4.8% (p<0.001; 95% CI [2.4, 7.3]) (Fig. 3-1f). During HUT, 6 of the 13 participants in the PD+OH group had worsening of orthostatic symptoms, whereas, none of these participants experienced the same during SRACE.

Table 3-1: Demographic data of the participants.

	PD+OH group	**PD group**
n	13	15
Age (years)	73±6	70±6
Sex ratio (male:female)	8:5	10:5
CASS score	4.62	1.0

n: number of participants; CASS: composite autonomic severity score; PD group: group of participants with Parkinson's disease without orthostatic hypotension; PD+OH: group of participants with Parkinson's disease with orthostatic hypotension.

Table 3-2: Baseline values of dependent variables.

	PD+OH group	**PD group**	***P***
SBP (mmHg)	112.8±27.8	139.3 ±20.5	0.008*
MAP (mmHg)	81.6±14.0	98.0±13.4	0.004*
DBP (mmHg)	63.6±8.4	74.5±10.8	0.007*
HR (bpm)	77.0 ±12.4	76.7 ±14.6	0.950

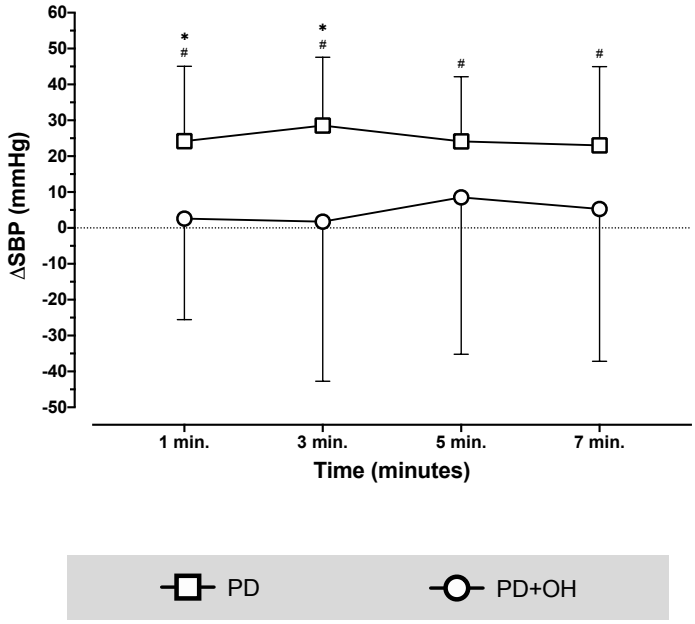
CBFv (cm/sec)	41.0±6.8	38.6±7.8	0.405
$crSO_2$ (percent)	66.5 ±2.8	70.5±4.1	0.006*

SBP: systolic blood pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure; HR: heart rate; CBFv: mean cerebral flow velocity; $crSO_2$: ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation; Values of the variables are absolute; PD group: group of participants with Parkinson's disease without orthostatic hypotension; PD+OH: group of participants with Parkinson's disease with orthostatic hypotension; *significant at $P<0.05$

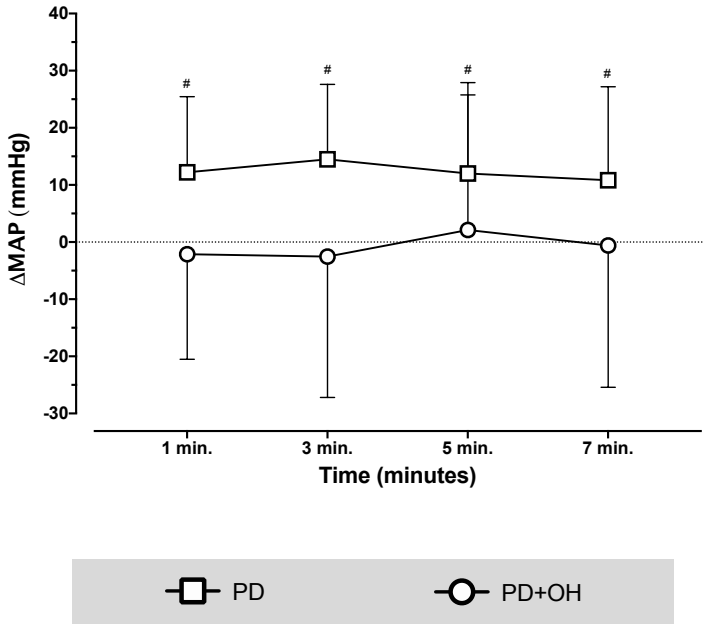
Variable responses were observed for SBP in the PD+OH group. 10 participants had an increase, while 3 participants decreased SBP with exercise (Fig. 3-2a). All 3 participants with decrease in SBP with exercise fulfilled the criteria of EIH i.e. ≥10 mmHg fall in SBP during exercise.[27] For the purpose of convenience, the 10 participants who increased SBP during exercise were labelled as PD+OH(INCREASE) subgroup and the remaining 3 participants with EIH were labelled as PD+OH(EIH) subgroup. A closer look at the 3 participants in the PD+OH(EIH) subgroup revealed that 1) they had a visible decrease in MAP (Fig. 3-2b) and DBP (Fig. 3-2c) that was similar to the decrease seen in SBP, 2) they had lesser increase in HR (Fig. 3-2d) compared to other participants, 3) the initial increase in CBFv from its baseline was absent in their case (Fig. 3-2e), 4) the $crSO_2$ declined prominently compared to the other 10 participants in the PD+OH group (Fig. 3-2f), and 5) all of them had an orthostatic decline of >75 mmHg in SBP during HUT and had a CASS score of ≥5. Given the small number of participants, no statistical analysis was undertaken for the subgroups.

Figure 3-1: Changes in dependent variables for the PD and PD+OH groups during upright stationary cycling self-regulated aerobic exercise.

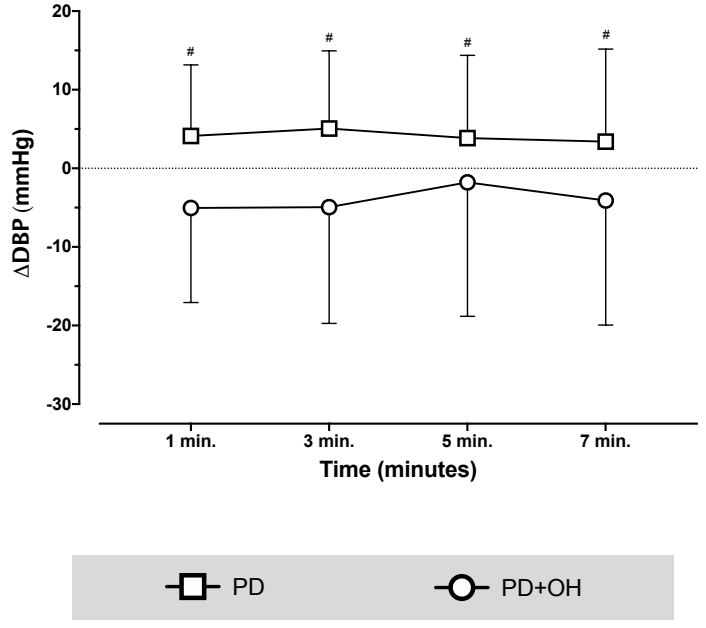
(a) Changes in SBP for PD and PD+OH groups during SRACE.



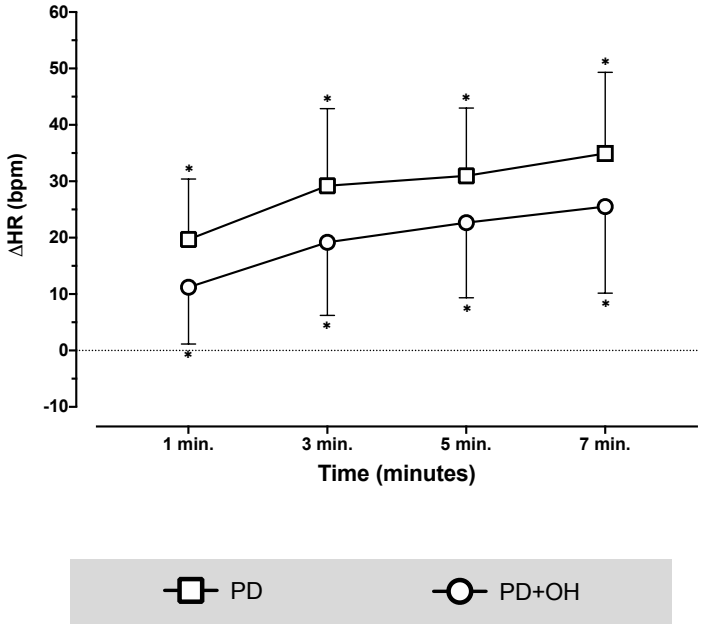
(b) Changes in MAP for PD and PD+OH groups during SRACE.



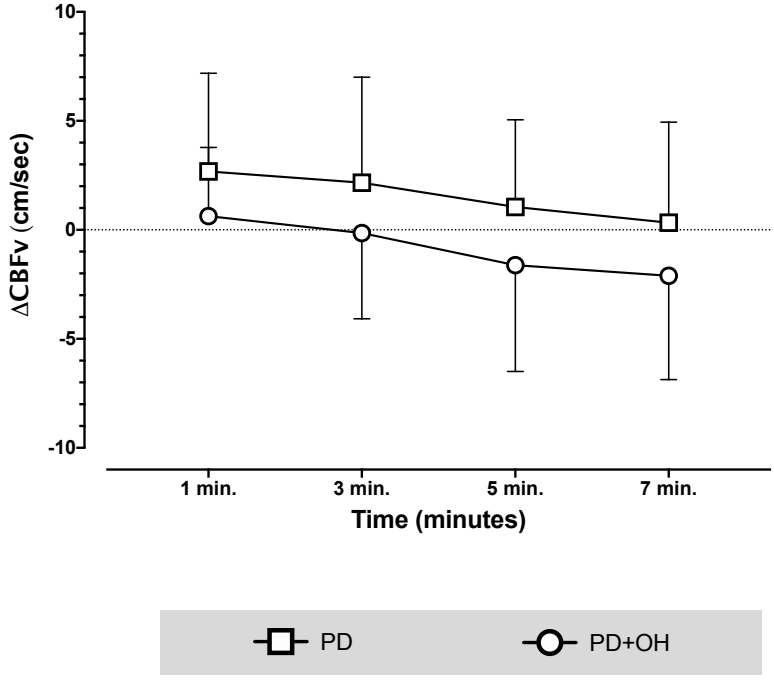
(c) Changes in DBP for PD and PD+OH groups during SRACE.



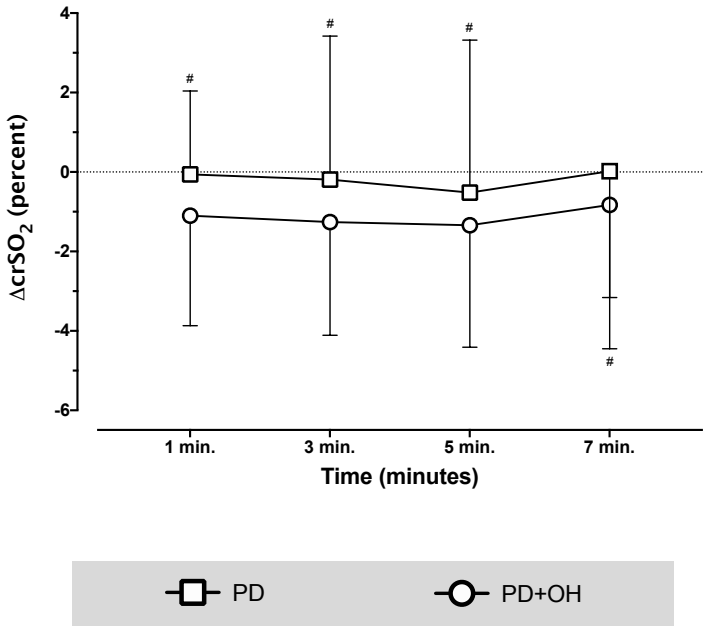
(d) Changes in HR for PD and PD+OH groups during SRACE.



(e) Changes in CBFv for PD and PD+OH groups during SRACE.



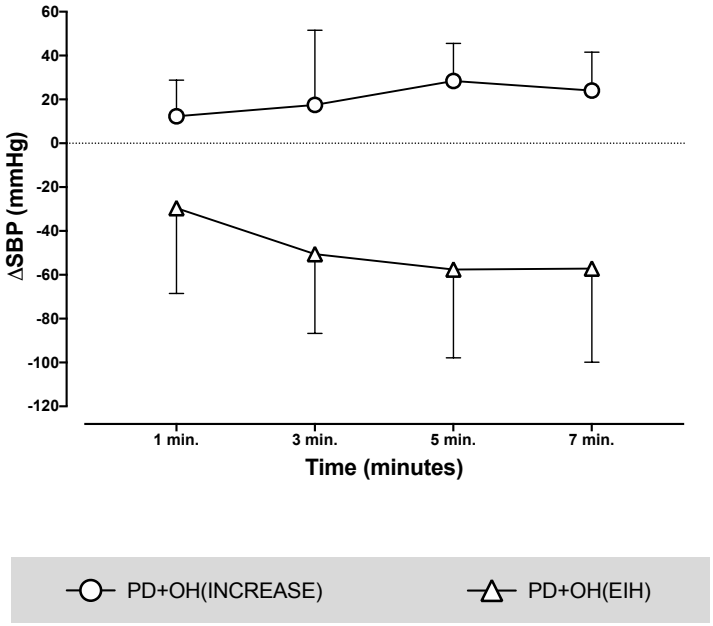
(f) Changes in $crSO_2$ for PD and PD+OH groups during SRACE.



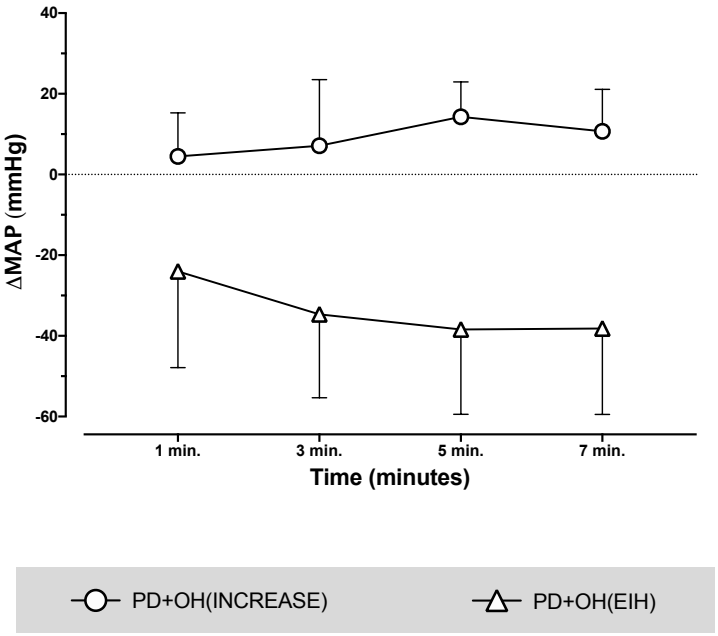
∆SBP = change in systolic blood pressure from the baseline value; ∆MAP = change in mean arterial pressure from the baseline value; ∆DBP = change in diastolic blood pressure from the baseline value; ∆HR = change in heart rate from the baseline value; ∆CBFv = change in mean cerebral blood flow velocity from the baseline value; ∆$crSO_2$ = change in ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation from the baseline value; * significant ($P<0.05$) for change from baseline value; # significant ($P<0.05$) for difference between the groups. SBP (a), MAP (b), DBP (c) and $crSO_2$ (f) differed between the groups but changed similarly over time in both the groups. HR was not different between the groups and changed similarly in both groups over time (d). CBFv neither differed between the groups nor varied over time (e). Overall, temporal changes in cardiovascular (a – d) and cerebrovascular measures (e and f) were similar in PD+OH and PD groups.

Figure 3-2: Changes in dependent variables for the PD+OH(INCREASE) and PD+OH(EIH) subgroups during upright stationary self-regulated aerobic cycling exercise.

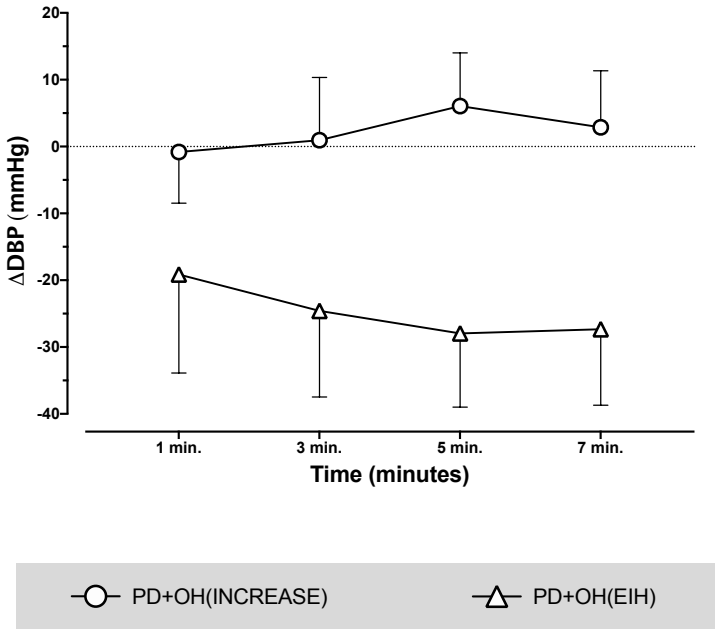
(a) Changes in SBP for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



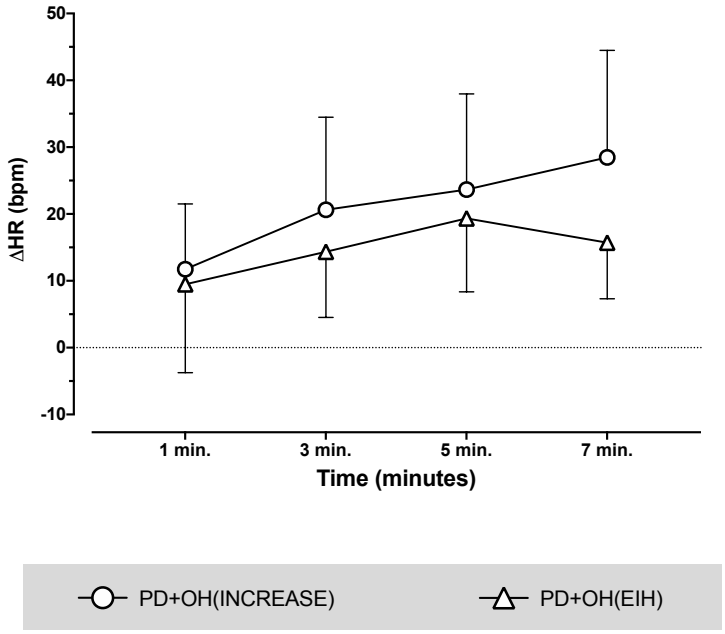
(b) Changes in MAP for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



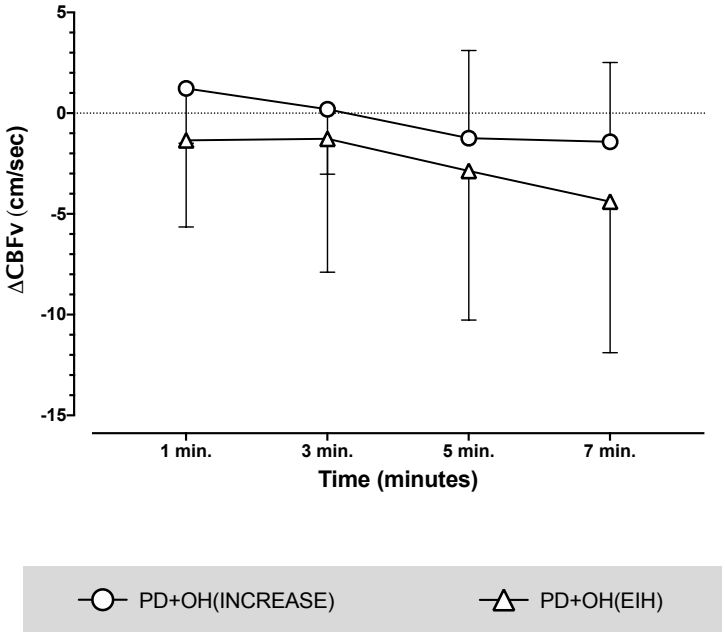
(c) Changes in DBP for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



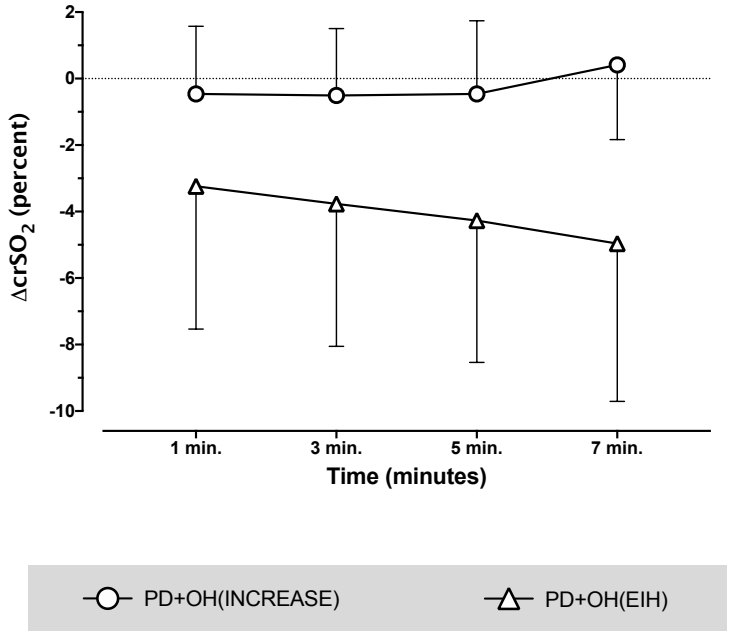
(d) Changes in HR for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



(e) Changes in CBFv for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



(f) Changes in $crSO_2$ for PD+OH(INCREASE) and PD+OH(EIH) subgroups.



∆SBP = change in systolic blood pressure from the baseline value; ∆MAP = change in mean arterial pressure from the baseline value; ∆DBP = change in diastolic blood pressure from the baseline value; ∆HR = change in heart rate from the baseline value; ∆CBFv = change in mean cerebral blood flow velocity from the baseline value; ∆$crSO_2$ = change in ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation from the baseline value. In the PD+OH(EIH) subgroup, SBP (a), MAP (b) and DBP (c) decreased progressively over time to below the baseline till the 5th minute after which all three variables stabilized. Contrary to this, an increase above the baseline was observed in the PD+OH(INCREASE) subgroup for the same variables (a, b and c). HR (d) increased and CBFv (e) decreased similarly in both the groups. $crSO_2$ decreased more in the PD+OH(EIH) subgroup (f). No statistical analysis was undertaken for the subgroups owing to the small number of participants in the PD+OH(EIH) subgroup. Overall, there was noticeably greater decline in systemic BP (a, b and c) and cerebrovascular measures (e and f) during SRACE in those PwPD who had OH and EIH than those who had OH but no EIH.

3.4 Discussion

This is the first study to determine and demonstrate the cardiovascular and cerebrovascular responses to upright SRACE in PwPD with and without OH. We investigated the effects of performing upright SRACE on systemic blood pressure, heart rate, cerebral blood flow and cerebral oxygenation in PwPD with and without OH. In general, no differences were found between the responses of PwPD with and without OH. However, a small subset of PwPD with OH developed EIH without associated worsening of orthostatic symptoms.

The absence of group and time interaction while the group differences existed for SBP, MAP and DBP suggests that significant changes in these variables over time followed a similar and almost parallel trajectory. The group differences, therefore, appear to be primarily due to the significantly different baselines, apparently owing to OH. Although systemic BP may be altered by OH prior to SRACE, the response of systemic BP to SRACE is similar in all PwPD, irrespective of OH. This suggests that the abnormality in the regulation of the cardiovascular system in PwPD with OH does not lead to a difference in systemic BP response to SRACE in comparison to PwPD without OH. However, this inference contrasts with the finding of EIH in 3 of the 13 participants in the PD+OH group in this study. A possible explanation for this discrepancy is that most participants in the PD+OH group had mild OH and as a result, had a BP response similar to what was observed in the PD group. Despite a distinctly different BP response in participants who developed EIH, their smaller number (n=3) seems to be the reason for their inability to draw the results of the statistical analysis towards a statistically significant group and time interaction. Since all the participants in the PD+OH(EIH) sub-group had substantial orthostatic drop of >75 mmHg in SBP during HUT (done to evaluate OH), while those in the PD+OH(INCREASE) subgroup had <75 mmHg decline in SBP during the HUT intervention, we speculate that OH of 75 mmHg decline in SBP is the threshold for onset of EIH or a negative response of SBP (decline in SBP which does not qualify to be called EIH i.e. decrease of <10 mmHg in SBP with exercise) during SRACE.

On the other hand, given the absence of group and time interactions for SBP and the similar trajectory of the changes in SBP above the baseline as well as over time, it may be appropriate to infer that the responses of systemic BP to upright SRACE are similar clinically in PwPD without OH and those with OH of <75 mmHg drop in SBP during HUT. Hence, only those PwPD who demonstrated relatively severe OH also displayed an abnormal cardiovascular response to exercise. This highlights the significance of the severity of dysautonomia in the manifestation of EIH. This is a known phenomenon.[20] In their study on supine cycling graded exercise test in PwPD, Low et al also concluded that the development of EIH correlated with the severity of dysautonomia.[20] This finding of the

present study is therefore supported by the findings of Low et al.[20] The main effect of time being statistically significant for SBP but not for MAP and DBP means that only SBP changed over time whereas MAP and DBP did not. This suggests that the response of PwPD without OH as well as of those with OH of <75 mmHg drop in SBP (during HUT) to SRACE is similar to what has been observed in normal healthy individuals.[28] Hence, during SRACE done by PwPD, the therapist may emphasize on the monitoring of SBP alone for changes over time and not DBP.

Orthostatic hypotension is a common manifestation of dysautonomia in PwPD. The underlying pathophysiological changes in dysautonomia in PD that can result in OH are baroreflex failure, and cardiac and extracardiac sympathetic noradrenergic denervation.[29] As a result, the HR and stroke volume may not increase on demand, pooling of blood in the capacitance vessels of the splanchnic and lower extremity circulations may compromise the venous return, and the diversion of blood from the non-exercising muscles and other parts of the body towards the exercising muscles may fail due to lack/absence of increase in systemic vascular resistance (SVR). Consequently, a combination of decreased cardiac output and decreased SVR produces OH, with the SVR playing a major role.[30] We speculate that this combination, with decreased SVR being the major contributor, is also partly responsible for the development of EIH. Additionally, an abnormal response to exercise called the 'supersensitivity' of the vasculature of the exercising muscles to metabolic by-products, is speculated to produce accentuated vasodilatation in the exercising muscles, producing a further decline in the SVR.[27] Although variable combinations of these abnormalities seem to underlie the development of EIH, we speculate that an extraordinary drop in the SVR is the most important contributor to EIH. We believe that an excessive drop in SVR further increases pooling of the blood in the gravity-dependent and exercising musculature of the lower limbs while the cardiac output is already faltering due to the cardiac noradrenergic denervation, baroreflex failure and the decreased venous return caused by pooling of blood due to the extra-cardiac noradrenergic denervation. All of these in combination eventually produce EIH.

The absence of group differences for HR suggests that a similar HR response to SRACE may be expected for all PwPD irrespective of the presence or severity of OH. This may imply that the utility of HR to define a range for SRACE intensity may be apt for all PwPD, including those with OH, given that the intensity of SRACE is similar to the present study. The findings of the present study for HR are supported by the findings of Werner et al[31] and Low et al[20], at submaximal exercise workloads during graded exercise testing.

The absence of significant differences between groups for CBFv suggests that the changes in cerebral blood flow during SRACE are not influenced by OH in PwPD, i.e. all PwPD have similar changes in CBFv resulting from SRACE, irrespective of OH. CBFv decreased similarly in both the groups (Figure 3-1e), which is the normal response of CBFv to exercise.[32] On the other hand, a significant difference between the groups for $crSO_2$ at all times suggests that cerebral oxygenation is compromised due to OH independent of SRACE, as the significant difference existed at the baseline before the start of SRACE and the response of $crSO_2$ to SRACE in both the groups was similar over time (Figure 3-1f). Thus, SRACE does not seem to adversely affect $crSO_2$ in PwPD with OH. This may be the reason why participants in the PD group or the PD+OH(INCREASE) subgroup had no onset or any worsening of orthostatic symptoms during SRACE. However, it was surprising to observe that despite the substantial fall in systemic BP and a greater mean decline in CBFv and $crSO_2$ compared to the PD+OH(INCREASE) participants, the 3 participants in the PD+OH(EIH) subgroup remained completely asymptomatic during SRACE. This finding is especially interesting as 2 of these 3 participants had complained of worsening of symptoms during HUT. Although the reasons and the exact mechanism of this discrepancy are unclear, we speculate that the difference in symptomatic manifestations may be related to the speed of onset of the stress over the cerebral circulation. In case of HUT the onset of OH is much quicker compared to the gradual increase in exercise stress and the consequent development of EIH. Perhaps the brain is able to better tolerate the stress imposed by the EIH by increasing oxygen extraction from the blood but is unable to adequate respond to the stress imposed by the sudden onset of OH. Future studies may be able to investigate and identify the mechanism of this

differential symptomatic response to the two types of hypotension. However, the finding of this study that EIH did not elicit the worsening of symptoms has important clinical implications. This suggests that EIH may not necessarily manifest symptomatically in PwPD with OH during SRACE. This is important because these patients may be able to walk or do SRACE during rehab sessions in the upright position, without feeling dizzy or light-headed. However, this does cause concern in patients with declining MAPs who might not be symptomatic until they are on the verge of syncope (fainting). This might prompt clinicians to opt for supervision during exercise rehabilitation of PwPD with OH and rely more on objective BP monitoring than patient's perception of symptoms. Given that all the 3 participants with EIH had severe orthostatic drop of >75 mmHg in SBP during HUT, the presence of OH of this severity might serve as a red flag for the possibility of development of EIH in PwPD with OH.

3.4.1 Strengths and limitations

A strength of the present study is that no dopaminergic or anti-hypotensive medication was stopped during participation in this study, which implies that participation in the present study was similar to participation in a routine exercise program with regards to control of OH and symptoms of PD. We had several limitations. First, the findings of this study are limited to the exercise duration of 7 minutes, a duration that is lesser than the usually prescribed/recommended duration of >20 minutes of SRACE. However, PwPD are frequently advised to undertake intermittent exercise, which involves short bouts of exercise, and these findings may then be relevant for a single bout of similar duration. A second limitation is that the measurement of CBFv to represent cerebral blood flow is dependent on the assumption that the diameter of the vessel being monitored always remains constant. However, OH might negatively influence the diameter of the insonated vessel producing falsely high estimates of cerebral blood flow.[33] And third, the present study did not take into account the severity of OH as a potential independent or confounding variable. Variability in severity of OH, which results from variability in severity of dysautonomia, can be studied for its effects on hemodynamics by future studies.

3.5 Conclusions

The cardiovascular and cerebrovascular responses to upright SRACE are largely the same for PwPD with and without OH. A small percentage of PwPD with relatively severe OH can, however, develop EIH without experiencing symptoms of orthostasis, thus concealing this complication unless BP is objectively measured during exercise.

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Chapter 4

4 Resisted upper limb exercise improves orthostatic hypotension in Parkinson's Disease

4.1 Introduction

Orthostatic hypotension (OH) may be present in the majority of patients with Parkinson's Disease (PwPD).[1,2] OH is a reduction in systolic blood pressure (SBP) of at least 20 mmHg or of at least 10 mmHg in diastolic blood pressure (DBP) that occurs within 3 minutes of standing up at 60 degrees or more of head-up tilt (HUT) and sustained in nature.[3] It has been implicated in causing cerebral hypoperfusion[4,5] and decreased cerebral oxygenation,[6–8] producing orthostatic symptoms like dizziness, fatigue up to syncope[9–11] as well as increasing the risk of cerebrovascular diseases like stroke and dementia.[12,13]

Physical counter-maneuvers like bending forward, cross-legged standing and activating the calf muscle pump can be used to improve OH while the patient is in the standing position.[14] However counter-maneuvers focusing on the lower extremities such as standing cross-legged and bending forward may not be as comfortable and safe for PwPD (and other disease populations affected by OH) due to the inherent fall risk in these patients. For example, cross-legged standing can decrease the base of support and bending forward brings the centre of gravity of the body closer to the edge of base of support, both of which decrease stability in the standing position which may increase fall risk. On the other hand, unilateral upper limb exercise (ULE) can be easily performed while the patient is in the standing position without the need of altering the base of support or taking the centre of gravity to the edge of the base of support.

While lower extremity exercise has the potential to cause complications in the form of worsening of OH and exercise-induced hypotension (EIH), upper extremity exercise appears to avoid this complication when used to treat OH.[14–17] Resistance exercise (RE) involves the use of static (isometric) muscular contraction to grip or hold the resistance or weight followed by dynamic concentric and eccentric contractions of muscles to elevate

and lower the resistance/weight that is being lifted.[18] RE is known to increase blood pressure (BP) and heart rate (HR),[19] which can be a desirable effect in PwPD with OH while standing. Aerobic exercise involving the lower limbs is associated with vasodilation in those limbs, potentially increasing pooling in the lower half of the body. Such vascular effects in the lower limbs can result in exacerbating OH. Upper limb RE avoids these issues.

Resisted upper limb exercise (RULE) is important for PwPD to maintain strength and muscular endurance of upper extremities, while simultaneously maintaining the range of motion. Maintaining and improving the functional abilities of the upper extremities is necessary as arms play an important role in many activities of daily living and occupational tasks.[20,21] Moreover, strengthening exercises in PwPD counter muscular weakness, unrelated to tremor and rigidity.[22] Due to scarcity of relevant literature, it is unknown if this type of exercise can also be used for hemodynamic benefits like countering OH and improving cerebral blood flow and oxygenation. Such benefits can be used for improvement of orthostatic symptoms.

This study was undertaken to examine the effects of performing overhead RULE in PwPD with and without OH. Specific objectives of this study were to determine the following: i) the effects of RULE on orthostatic BP drop in PwPD with OH; ii) if RULE results in clinically significant improvement in orthostatic symptoms; and iii) the effects of RULE on cerebral hemodynamics including cerebral oxygenation and cerebral blood flow during a HUT test.

4.2 Methods

This study was undertaken at the university campus of the London Health Sciences Centre. Thirty-nine PwPD were enrolled after obtaining written informed consent. Male and female participants with idiopathic PD, between 60 and 90 years of age, who responded to levodopa treatment and had at least a 3 year history of PD, were between 60 and 90 years of age and of either gender were included in this study, provided they were also

independent in transfer and were able to walk unsupported. Any patient who was not able to cooperate or any patient on treatment with medication/s or having a disease/disorder (except PD) that could alter the functioning of the autonomic nervous system was excluded. This study was approved by the institutional board of research ethics. All participants undertook autonomic reflex screening (ARS) in which a standardized set of tests, including the head-up tilt (HUT) are done to determine the presence and severity of OH. The findings from ARS were interpreted for evaluation using the 11-point composite autonomic severity score (CASS).[23] All participants with ≥20mmHg fall in SBP during the HUT component of the ARS were deemed to have OH[24] and were allocated to the PD+OH group (n=21) while others were allocated to the PD group (n=18). Participants in both the groups performed ULE as per the protocol mentioned below and continued to take their prescribed medications as per their schedule during the study.

4.2.1 Protocol

Each participant started in the 70° (upright) HUT position holding an unopened 500 ml water bottle (factory-filled with water; ~500g in weight) in one hand while keeping the arm by the side. This position was maintained at all times, including during the recovery period after the exercise. Overhead unilateral dynamic RULE was done starting with neutral position of the shoulder joint and full flexion of the elbow joint while holding the water bottle in hand. This was followed by complete shoulder flexion and elbow extension (hand going up) for overhead shoulder flexion and then returning to the starting position, while holding the water bottle in hand. For convenience, the movement from the starting position to the maximum overhead position shall be referred to as ‘up’ and the return to the starting position shall be referred to as ‘down’ in this manuscript. The exercise was done in rhythm with a digital metronome such that each up and down movement were done for 1 second, and consecutively for 60±2 seconds. Therefore, the frequency of the ‘up’ movement was 0.5 Hz. The post-exercise recovery period consisted of relaxed standing in the 70° HUT position with that arm by the side that performed the exercise for a period of 60±2 seconds. Throughout the study, the contralateral arm (that did not perform RULE) was positioned

with elbow flexed and the hand in-front of the chest at the heart level to ensure the accuracy of the BP monitoring.

4.2.2 Physiological recordings

Continuous HR monitoring (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems Inc., Branford, CT, USA) was done using electrocardiography electrodes (Ambu® Blue Sensor SP, Glen Burnie, MD, USA). Blood pressure (BP), heart rate (HR), mean cerebral blood flow velocity (CBFv), ratio of oxygenated to de-oxygenated blood in the circulation of cerebral frontal cortex ($crSO_2$) and symptoms were studied as the dependent variables influenced by independent variable (RULE performance). BP was measured beat-to-beat as systolic, mean and diastolic blood pressure (SBP, MAP and DBP, respectively) from a finger held at the heart level using a non-invasive technique (BMEYE Nexfin device, Amsterdam, Netherlands and WR TestWorks TM software, WR Medical Electronics Co. Stillwater, MN, USA). Near-infrared spectroscopy (NIRS) was used (NIRS Foresight® cerebral oximeter, CASMED, Branford, CT, USA) for recording of $crSO_2$. Two NIRS probes, one on each side of the forehead, were used for recording of $crSO_2$ at each of the cerebral frontal cortices. CBFv was represented by the mean middle cerebral artery velocities measured bilaterally using probes of transcranial doppler ultrasound (TCD) (Multigon 500M, DWL MultiDop-T, Neuroscan, NY, USA) placed on each side of the forehead.

4.2.3 Scale

For the ranking of severity of symptoms, the Orthostatic Symptom Scale (OSS)[25,26] was used. OSS is a visual analogue scale with increasing ranking of symptoms. The ranks are 0, 2, 4, 6, 8 and 10, and their descriptive symptoms are no symptoms, tiredness/momentary light-headedness, mental sluggishness/difficulty concentrating, dizziness/unsteadiness, blurred vision/fainting and presyncope/syncope, respectively. Additionally, ‘somewhat light-headed’ was scored as 1. In the present study, OSS was used differently. Instead of looking at the scale and reporting their symptoms, participants responded about their symptoms to an investigator’s question: “how are you feeling now?”. This was done for all

the participants as some of the participants were expected not to be able to wear their prescription glasses due to presence of TCD probes bilaterally on their temples and few others experiencing blurred vision during HUT.

4.2.4 Data analysis

Visual inspection of the collected data (physiological recordings) was done using Spike2 software (version 7, Cambridge Electronic Design, Cambridge, UK). MATLAB (version R2018, Mathworks Co.) and Spike2 software was used to down-sample the data prior to analysis. Statistical analysis of the data was done using SPSS version 25 (IBM Corporation).

Data were analyzed in intervals of one minute each for baseline before head-up tilt HUT), during the fifth minute of HUT, baseline before RULE, during RULE and during the post-exercise recovery period (referred to as 'recovery'). A Mann-Whitney U test was used to compare CASS scores. The effects of group and time over the dependent variables were analyzed using a two-way mixed ANOVA (including post-hoc comparisons using Bonferroni correction). Symptoms were compared from baseline to immediate post-exercise recovery period using the Wilcoxon signed-rank test. Comparison of baseline and fifth minute values of HUT for SBP was done using a paired samples t-test.

4.3 Results

The demographic data of the participants are presented in Table 4-1. Results are shown in the graphical form in Figure 4-1. The Shapiro-Wilks test revealed that there was absence of normal distribution of variables. After the removal of outliers (extremely high or low values of the dependent variables that affect the normality of data and may have a negative impact on the statistical test results), normal distribution was achieved. Two-way mixed ANOVA (with post-hoc analysis using Bonferroni correction) was performed with and without the outliers. The results with and without outliers did not differ for significant findings. Therefore, outliers were included in the final data analysis. During HUT, SBP decreased significantly by 47.7 mmHg (95% CI 35.5, 59.8; $P<0.001$) to produce OH in the

participants that were then allocated to the PD+OH group (Fig. 4-2). During and after RULE, there was no significant interaction between the independent variables 'group' and 'time' for changes in any of the dependent variables, except for $crSO_2$ (P=0.029). The main effects of group showed that there were significant differences between the groups of 34.9 mmHg for SBP (95% CI 19, 50.8; P<0.001), 21.3 mmHg for MAP (95% CI 11.3, 31.3; P<0.001), 14.3 mmHg for DBP (95% CI 7.1, 21.5; P<0.001) and 3.3% for $crSO_2$ (95%CI 0.5, 6.2; P=0.023), including at the baseline. No significant main effects of group were observed for HR and CBFv. Significant changes were observed as main effects of time for SBP (P<0.001), MAP (P<0.001), DBP (P<0.001), HR (P<0.001), CBFv (P=0.023) and $crSO_2$ (P<0.001).

Table 4-1: Demographic data of the participants.

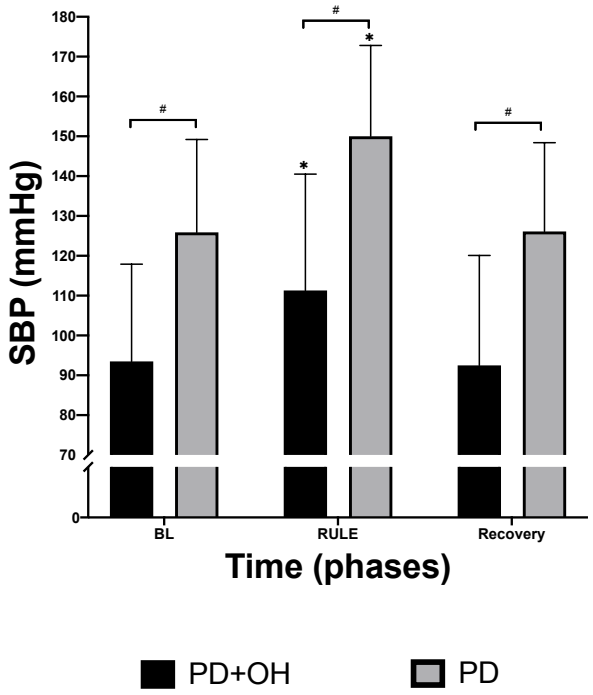
	PD+OH group	PD group
n	21	18
Age (years)	74±6	70±6
Sex ratio (M:F)	12:9	10:8
CASS score	4.6	1.0

n = number of participants, M = male, F= female, CASS = composite autonomic severity score. PD+OH = group comprising of patients with Parkinson's Disease with orthostatic hypotension, PD = group comprising of patients with Parkinson's Disease without orthostatic hypotension.

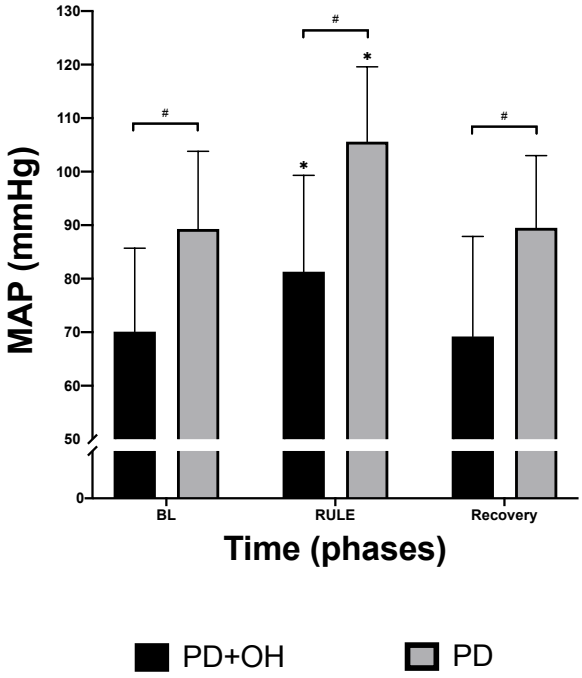
In the PD+OH group, with the performance of RULE, SBP increased significantly by 17.9 mmHg (95% CI 11.6, 24.1; P<0.001), whereas, in the recovery period, SBP decreased significantly by 18.8 mmHg (95% CI 14.7, 23; P<0.001). In 5 of the 21 PD+OH group participants, OH observed during HUT was reversed by RULE.

Figure 4-1: Effects of resisted upper limb exercise on blood pressure, heart rate and cerebral hemodynamics during Head-up Tilt.

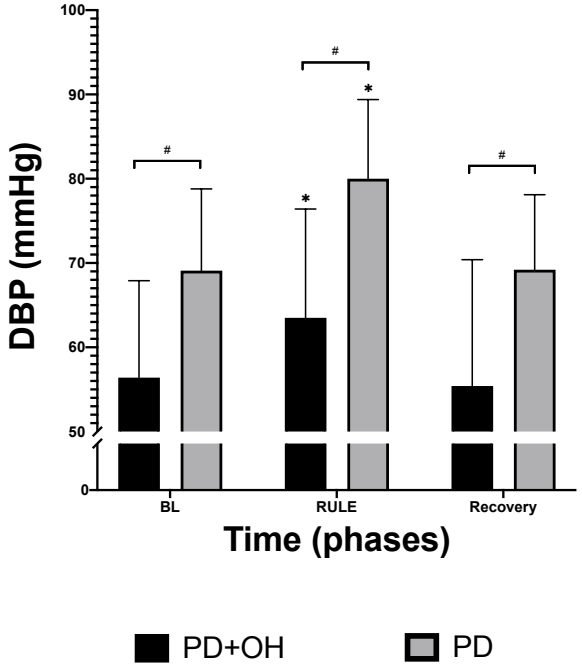
(a) Effects of RULE on SBP



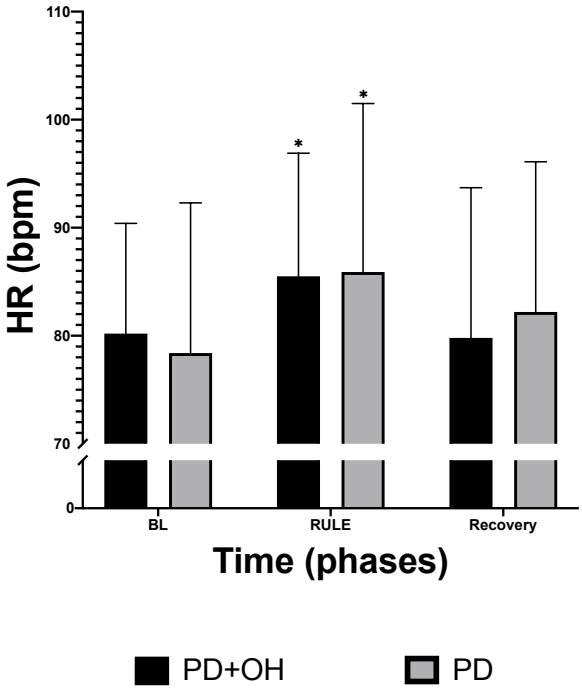
(b) Effects of RULE on MAP



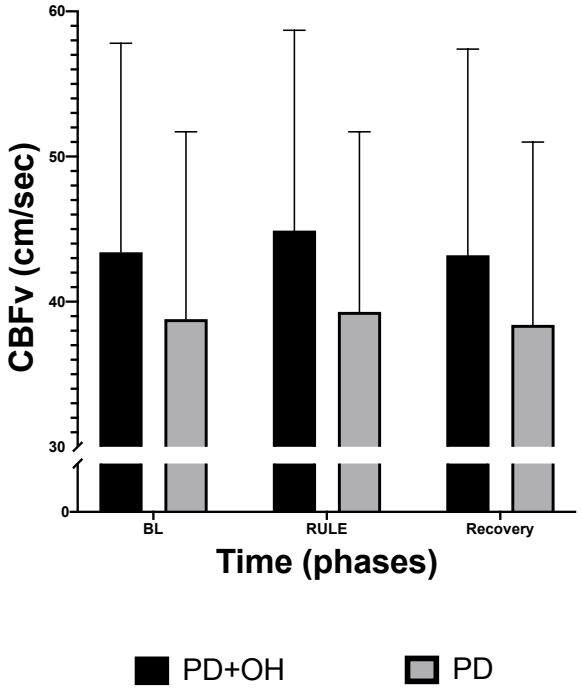
(c) Effects of RULE on DBP



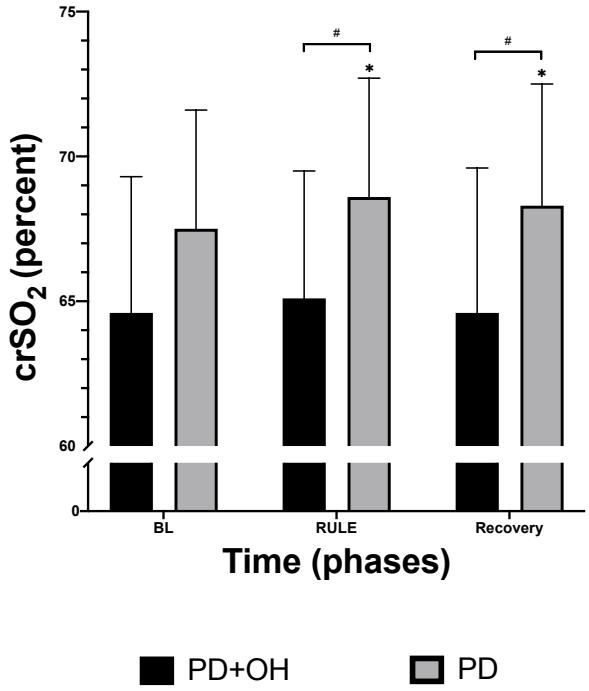
(d) Effects of RULE on HR



(e) Effects of RULE on CBFv

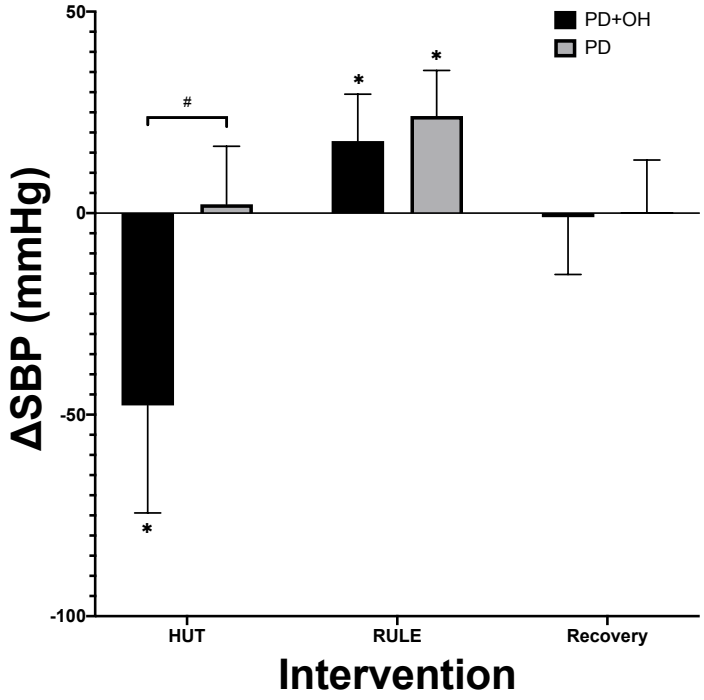


(f) Effects of RULE on $crSO_2$



PD+OH = group comprising of patients with Parkinson's Disease with orthostatic hypotension, PD = group comprising of patients with Parkinson's Disease without orthostatic hypotension, SBP = change in systolic blood pressure from the baseline value, MAP = change in mean arterial pressure from the baseline value, DBP = change in diastolic blood pressure from the baseline value, ∆HR = change in heart rate from the baseline value, CBFv = change in mean cerebral blood flow velocity from the baseline value, $crSO_2$ = change in ratio of oxy- to deoxy-haemoglobin saturation in cerebral circulation from the baseline value, BL = baseline value of the dependent variable, RULE = resisted upper limb exercise, recovery = post-RULE recovery period, *significant ($P<0.05$) for change from baseline value, $^{\#}$significant ($P<0.05$) for difference between the groups. SBP (a), MAP (b) and DBP (c) differed between the groups but changed similarly during RULE and recovery. HR was similar between the groups and changed similarly in both groups during RULE and recovery (d). CBFv was similar between the groups and did not change with RULE or during recovery (e). $crSO_2$ was different between the groups and changed differently with RULE and during recovery (f). RULE improved systemic hemodynamics to counter orthostatic hypotension but failed to influence the cerebral hemodynamics (except for $crSO_2$ increase in the PD group). The improvements in systemic hemodynamics returned to the baseline in the recovery period.

Figure 4-2: Changes in systolic blood pressure during head-up tilt and in response to resisted upper limb exercise.



PD+OH = group comprising of patients with Parkinson's Disease with orthostatic hypotension, PD = group comprising of patients with Parkinson's Disease without orthostatic hypotension, ∆SBP = change in systolic blood pressure from the baseline value, HUT = head-up tilt, RULE = resisted upper limb exercise, *significant ($P<0.05$) for change from baseline value, #significant ($P<0.05$) for difference between the groups. In the PD+OH group, SBP decreased during HUT, whereas, it increased with RULE. In the PD group, SBP remained unchanged during HUT and increased with RULE. In both the groups, SBP returned to baseline in the recovery period. SBP decreased to produce orthostatic hypotension (OH) during head-up tilt in some patients with PD (PD+OH group). Performing RULE helped increase SBP in all patients with PD, highlighting the benefit of performing RULE by PD+OH group. In both the groups, this increase in SBP diminished completely in the recovery period.

No statistically significant change in symptoms was produced by RULE in either group when changes in symptoms were analyzed over time (from baseline to immediate post-exercise recovery period) in symptomatic participants in each group.

4.4 Discussion

This is the first study to investigate the effects of RULE on systemic and cerebral hemodynamics and cerebral oxygenation in PwPD. Since both SBP and DBP increased

significantly with RULE, it is evident that this type of upper limb exercise is effective in countering OH quickly, within a minute (Fig. 4-1a,c). In 5 of the 21 participants in the PD+OH group, RULE completely reversed the OH by increasing SBP to a value greater than the magnitude of decline observed during HUT. This study adds an important non-pharmacological intervention for OH.

In order to control the effects of OH, passive support can be provided by external compression devices like abdominal binders[25–28] and pressure stockings,[29–32] while active maneuvers[14,33] include tensing the muscles of the legs, bending forward, squatting and crossing legs. All of these countermeasures target the pooling of blood in the abdomen or the lower extremities[25,34] and aid in improving the venous return to the heart so that stroke volume, cardiac output and BP are increased.[25,36] Use of exercise as a countermeasure against OH is largely unexplored, including activation of calf muscles during standing.[33] This is more true for exercise that does not target the pooling of blood and therefore, does not depend upon improvement of venous return to the heart to increase BP. In the present study, RULE has shown to increase BP, in some cases enough to reverse OH, without repeated contractions of the lower limb or core muscles. Therefore, it may be useful for the patient to increase the BP when they cannot target improvements in venous return through lower extremity counter-maneuvers, such as in situations of prolonged standing like standing in a queue, standing bathing, standing in public transit, etc. Similarly, upper extremity resistance exercises would be of benefit to patients during transfers from the toilet seat, transfers from wheelchair or getting off the bed in the morning, etc. In all these situations RULE can be performed easily, without the need of decreasing the base of support or of bringing the center of gravity closer to the edge of the base of support for countering OH.

Furthermore, RULE can also contribute as another adjunct in combination with the other counter-maneuvers to control OH. We speculate that a combination of active counter-maneuvers like leg-crossing and RULE may be more effective at countering OH than each

individually. Maximizing the use of counter-maneuvers by studying what combinations may be most synergistic is an important avenue of future research studies.

Non-significant changes were observed for MCAv in PD+OH group with RULE (Fig. 4-1e). Although MAP increased by an average of 16% from its baseline value, MCAv increased only by an average of 3.43%. It is unclear if this difference was due to the regulatory effect of the cerebral autoregulation or if the duration of exercise, being only 1 minute, was insufficient for the changes in systemic hemodynamics to be reflected over the cerebral hemodynamics. Although all the participants in the PD+OH group had OH, it is unlikely that the regulatory effect of cerebral autoregulation was compromised, since recurrent exposure to low BP can trigger adaptations in cerebral autoregulation to remain functional during OH.[4,37] Similar to CBFv, $crSO_2$ did not change significantly with RULE (Fig. 4-1f). These findings suggest that unilateral RULE performed for 1 minute neither changes cerebral blood flow nor the cerebral oxygenation, which may explain why none of the participants had changes in symptoms with RULE.

Absence of group and time interaction implies that there was no significant effect of OH on changes in any of the dependent variables, except in case of $crSO_2$. This suggests that presence of OH in PwPD does not influence the cardiovascular and cerebrovascular responses to RULE. RULE does directly affect the cerebral oxygenation during and after RULE as PwPD with OH had lower values of $crSO_2$ than those without OH during and after RULE, but not at the baseline. However, the statistically significant findings for $crSO_2$ do not seem to have substantial clinical value. This is because the statistically significant increase from the baseline to the recovery period in the PD group was <1% and the statistically significant decline that was observed during the recovery period in the PD+OH group actually brought the $crSO_2$ back to near its baseline value (Fig. 4-1f).

Since systemic BP (SBP, MAP and DBP) differed between the groups without group and time interaction, but with significant changes over time, the two groups appear to have maintained a parallel trajectory for changes during and after the exercise. The significantly lower baseline values of SBP, MAP and DBP in the PD+OH group were as expected, since

these participants had OH. HR, being similar between the groups and changing similarly over time (no group and time interaction), suggests that the HR response to RULE is not compromised due to OH. These findings contradict the findings of Miyasato et al[38] who found significant blunting of SBP and HR in PwPD compared to paired control participants during knee extension resistance exercise. The reasons for the differences may be related to the exercising limb (upper limb in the present study versus lower limb in their study), muscle mass (smaller muscle mass in the present study versus larger muscle mass in their study), comparison with controls (no comparison with healthy controls in the present study), and the segregation and group allocation based on a clinical measure of dysautonomia (group allocation based on OH in the present study versus PwPD compared to controls, irrespective of OH in their study).

The absence of significant difference between the values of the dependent variables at baseline and recovery shows that each variable returned to near its baseline value within a minute after RULE (Fig. 4-1a-e), except for $crSO_2$ in the PD group which remained higher than the baseline during the recovery period (Fig. 4-1f). This suggests that although the benefits of RULE can be rapidly activated, they fade away equally rapidly. Perhaps, a RULE session with intermittent exercise may be useful to achieve and maintain the benefits observed in systemic BP over a longer time period. Future studies should investigate the possibility of this hypothesis.

4.4.1 Limitations

This study used ~500g weight (in the form of 500 mL disposable water bottles) as the resistance, irrespective of the percentage of the repetition maximum (RM) this weight was for any participant. It is known that hemodynamic responses to resistance exercise depend upon the relative intensity of the effort. Possible variations in the relative intensity of the effort of the participants in the present study can negatively influence the internal validity of the study. However, the purpose in this study was to use a resistance device that is readily available. Moreover, resistance exercise prescriptions by physiotherapists are not always based on RM testing. Rather, such prescriptions generally start with a very light to light

resistance and may vary based on the comfort and acceptance of the patient. Future studies may determine if using a percentage of RM is superior to the use of a standard resistance item with a fixed mass like the disposable water bottle used in our study.

4.5 Conclusion

Resisted upper limb exercise done using ~500g resistance for 1 minute at 0.5 Hz can significantly and instantaneously increase the systemic BP (SBP, MAP and DBP) in PwPD with OH, resulting in attenuation, and in some cases complete reversal of OH. The use of upper limb resistance exercises is likely to be an important intervention for patients with OH, where such improvement of BP is helpful to complete daily activities involving a transition from a supine to a more upright position. Additionally, RULE is likely to be an important adjunct to lower limb counter-maneuvers directed towards OH as they involve different mechanisms and therefore likely to be synergistic.

4.6 References

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Chapter 5

5 General Discussion and Future Direction

5.1 Overview of the thesis and implications on clinical practice

The aim of this thesis was to improve the rehabilitation care of patients with Parkinson's Disease (PwPD) who suffer from orthostatic hypotension (OH). We did this by exploring methods to counter OH and by determining the hemodynamic effects of routine but potentially hazardous exercise. OH is a common manifestation in Parkinson's Disease (PD) and can be present in up to 58% of PwPD.[1,2] However, there is little literature on the effects of OH during the rehabilitation of PwPD and this justifies the need for more research in this area. We anticipated that the findings from the investigations in this thesis will help expand the knowledge base for the development of tailored rehabilitation programs for PwPD with OH. Countering OH is expected to reduce the symptom burden from orthostasis, improve balance and decrease the risk of falls. Prevention of hemodynamic complications during potentially hazardous aerobic exercise is expected to prevent serious reductions in blood pressure (BP) during exercise. This avoids worsening of symptoms of orthostasis and reducing the risk of syncope.

We investigated the utility of wearing an abdominal binder (AB) as a device to control OH. Second, we investigated the hemodynamic effects of self-regulated aerobic cycling exercise (SRACE). And third, we investigated the utility of performing resisted upper limb exercise (RULE) as a counter-maneuver to control OH. All studies compared PwPD with and without OH to develop an understanding of how the presence of OH influences the changes in the variables under observation in this clinical population. The specific objectives in this thesis were to determine (1) the effects of wearing an AB and its removal in standing position, (2) the effects of performing SRACE done as stationary cycling exercise in the upright position, and (3) the effects of RULE done in standing position. The

effects were studied on systemic BP, heart rate (HR), cerebral blood flow velocity (CBFv), cerebral oxygenation ($crSO_2$) and symptoms of orthostasis.

In our first study, we demonstrated that an AB is a useful modality for the control of OH in PwPD. This suggests that a clinician can prescribe an AB for countering OH. If the increase in systolic blood pressure (SBP) is desired to be ~7 mmHg then AB alone may be sufficient for the treatment. An AB may also be used in combination with other modalities for a possible greater increase in BP. Although this thesis did not find a statistically significant change in symptoms of orthostasis with the use of AB, some participants in both the groups (PwPD with OH and PwPD without OH) showed lesser burden of symptoms with the use of AB. This indicates that symptomatic improvement with the use of AB varies between individual PwPD and may be unpredictable. Since relief from symptoms of orthostasis can help improve confidence in the standing position and in performing activities of daily living, it may be reasonable for the clinician to prescribe AB to those PwPD who benefit from it symptomatically, without regard to presence or absence of OH.[3] Such a prescription would be based on demonstrated benefit in symptoms in a PwPD with the use of an AB, as this benefit varies between individual PwPD. Hemodynamic changes were minimal with the use of AB by those PwPD who do not have OH, thus indicating the use of an AB is safe in PwPD in the absence of OH. Another clinically important finding of this thesis was about the removal of AB after it was worn for 5 minutes. We demonstrated that the removal of AB in the standing position led to severe decline in the cardiovascular and cerebrovascular measures. The magnitude of this decline was greater than the magnitude of improvement associated with the wearing of an AB in PwPD with OH. This suggests that if a patient must remove their AB in the standing position, they may be better advised not to wear it at all, as the complications of removal of the AB in the standing position outweigh the benefits of wearing it. To avoid removing the AB in the standing position is an important precaution that every clinician should suggest to their patient, especially those with OH, to prevent serious deterioration in systemic and cerebral hemodynamics.

In our second study we demonstrated that in general, PwPD with and without OH respond similarly to upright self-regulated aerobic cycling exercise (SRACE). However, a small fraction of PwPD with OH can develop exercise-induced hypotension (EIH). We showed that about a quarter of PwPD with OH developed EIH. These findings indicate that for most of the PwPD with and without OH, there were no differences in the cardiovascular and cerebrovascular changes during SRACE. We found that only those PwPD with OH who had a decrease in SBP of >75 mmHg during HUT developed EIH. Despite the presence of EIH, these PwPD did not experience onset or worsening of symptoms. Therefore, due to lack of symptomatic changes during EIH, it may not be appropriate to rely on patient's perception of symptoms. Rather, objective monitoring of BP is recommended for these patients. The findings of this chapter can prove helpful to the clinicians in planning a safe and effective exercise rehabilitation program for PwPD, especially those with OH.

We demonstrated in our third study that resisted upper limb exercise (RULE) done while holding a ~500g weight in the hand, in the upright position can effectively attenuate OH in PwPD, and in some cases it can even reverse OH. The improvements in SBP were found to be isolated and without significant changes in cerebral hemodynamics. The increase in SBP occurred rapidly in response to RULE but the gains were short lived, fading rapidly after the cessation of exercise. We also demonstrated that the systemic and cerebral hemodynamic changes that occur in response to RULE are similar in all PwPD, irrespective of the presence of OH. The one exception to this was cerebral oxygenation, for which the presence of OH was associated with a blunted increase in $crSO_2$ during RULE and subsequently a greater decline post exercise. RULE provides the clinician with another option that can be used to increase SBP rapidly when PwPD with OH need this response. Conditions like standing in a crowded public transit or being in the middle of a flight of stairs or on an escalator can be some examples where other counter-maneuvers involving the lower extremities may be difficult to perform. Moreover, since PwPD suffer from decreased balance control, a maneuver that does not require them to decrease their base of support or to bring their centre of gravity closer to the edge of their base of support can be

better tolerated. RULE does not require any shift of base of support or centre of gravity to raise BP and thus may be a safer alternative for countering OH in PwPD with advanced balance deficit. Additionally, RULE may also be a useful adjunct to other counter-maneuvers for increasing the BP. This intervention will likely be useful during other daily activities like getting up from bed in the morning or rising from the toilet seat.

5.1 Strengths of this thesis

There are several strengths of this thesis. All the variables studied in this thesis were monitored non-invasively, using technology that is readily available in most hospitals around the world. Thus, it allows for easy reproduction of the studies in this thesis without serious concerns about patient safety, patient comfort, and infection transmission. No changes were made to the medication schedules of the participants and no medications were stopped for participation in this study. Therefore, participation in these studies by PwPD was similar to participation in rehabilitation programs, and thus reflects the practicality of application of the findings. The age range of the participants in this thesis was 60 to 90 years old, which is meant to include most of the PwPD in the population who may develop OH as well as undertake exercise rehabilitation.[4,5] Thus, this thesis has a reasonable generalizability for PwPD and therefore, has decent external validity with regard to the age range of the PD patients.

All the participants were assessed for OH and segregated into groups based on presence or absence of OH prior to the start of interventions. This is unlike most of the available literature on effects of exercise in PD. This segregation enabled the researchers to differentiate and report those findings that were observed exclusively due to the presence of OH in this patient population. In the existing literature, PwPD are generally compared to age-matched controls for investigating the hemodynamic effects of exercise. For instance, existing literature suggests blunted SBP response to graded exercise tests in PwPD compared to age-matched controls. However, a majority of these studies does not report the presence or absence of dysautonomia/OH in their participants.[6–9] As a result, the conclusions are drawn about hemodynamic abnormalities that appear to be due to the

disease process of PD, whereas such hemodynamic abnormalities may be attributable to dysautonomia. Clinical decision making based on such evidence may misguide the prescription of the rehabilitation exercise program for PD. If we had not segregated participants based on OH (that was due to dysautonomia), we might have concluded that any individual with PD can develop EIH during SRACE, instead of the actual finding that only PwPD with OH should be expected to develop EIH.

All the dependent variables in this thesis were continuously measured and analyzed in intervals of one minute each. This thesis used the universally accepted definition of OH and therefore limited the assessment to BP changes for determination of OH to the first three minutes of HUT (as per the consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome).[10] However, because CASS scoring of the severity of autonomic dysfunction requires the analysis of BP during the first five minutes after the HUT, the investigators analyzed the changes in BP as well as the other variables for an additional period of two minutes of HUT i.e. for the first five minutes of HUT for the purpose of CASS scoring.[11] Although a variant of OH called 'delayed OH' can occur after three minutes of HUT, its clinical significance is unknown.[10] Moreover, since clinical assessments for the determination of OH are limited to the first three minutes after HUT or standing, an inclusion of longer periods for determination of OH in this thesis would have resulted in the inclusion of those PwPD who would otherwise not be considered to have OH in a real-life clinical assessment.[10,12] This might negatively influence the clinical applicability of the findings of this thesis and was therefore avoided.

All the studies in this thesis were conducted as per the routine protocol for studies on autonomic function testing with respect to avoidance of food, alcohol and caffeine prior to the experiment, maintenance of ambient temperature, etc. These measures control for possible flaws in this thesis due to confounding variables and thus improve the internal validity of this thesis.

This thesis is the first to study the cerebrovascular effects of the AB, SRACE and RULE in PwPD with OH. Changes in CBFv and $crSO_2$ can occur in response to changes in systemic hemodynamics that occur due to OH as well as in response to different postures. These changes in turn can influence the patient's perceived symptoms. From the findings of this thesis, clinicians shall be able to understand the instantaneous changes in cardiovascular, cerebrovascular, and symptomatic measures with the three interventions. This can help clinicians develop a better understanding of these changes which is expected to ultimately improve the care they provide to PwPD.

Existing literature is mostly focused on the hemodynamic effects of graded exercise tests in PwPD. However, in graded exercises tests the intensity of the exercise is not controlled by the patient, which is unlike the real-life scenario where most individuals regulate the intensity of their physical activities by themselves. For instance, walking pace in the community is generally maintained by people based on the perception of their level of exertion and is sometimes limited by symptoms of pain, breathlessness, dizziness, etc. Similar is the case when clinicians prescribe aerobic exercise based on the rating of perceived exertion (RPE) of their patient during the process of rehabilitation. The RPE is the most practical method of regulating the intensity of exercise during rehabilitation as well as during the activities of daily living of the patient. This thesis investigated the effects of aerobic exercise such that the intensity of the exercise was self-regulated by the participant using the RPE scale. This will provide direct evidence about the effects of patient-regulated aerobic exercise to the clinician so that he/she can utilize the evidence more easily compared to the evidence derived from graded exercise tests.

Lastly, very little literature exists about EIH in PwPD. Existing literature is either silent about the presence of OH/dysautonomia in the participants of those studies or it is focused on the effects of exercise performed in the supine/recumbent position. As a result, no literature except this thesis has investigated if EIH can occur during an exercise that is performed in the upright position, which is also the position for OH to happen. Physical activity like aerobic exercise is commonly performed by PwPD in the upright position, for

instance, walking at a good pace in the community. The novel findings of this thesis shall help clinicians better understand the risk of development of EIH in PwPD with OH.

5.2 Limitations and future research

There are certain limitations of this thesis. The first limitation is that the sampling method was a 'sample of convenience' which means that the patients attending the movement disorders clinic were enrolled if they were willing to participate. This is unlike a random selection of participants and therefore, may not be reflective of the entire population of PwPD. Thus, there is some risk of sampling error. However, random selection of PwPD is an ambitious goal and most literature at present that pertains to biological interventions does not employ it.

We have two limitations resulting from the allocation of the participants to the groups being based on the decrease in SBP of ≥20 mmHg during HUT. The first of these limitations is that PwPD with slightly greater or lesser than 20 mmHg decrease in SBP were placed on either side of this division i.e. they were allocated to either group, which meant that PwPD with 22 mmHg decrease in SBP during HUT were assumed to be fundamentally different from PwPD with 18 mmHg decrease. However, dysautonomia and its implications, including OH, are a continuous spectrum. Moreover, the present threshold of 20 mmHg for the diagnosis of OH is not always reflective of the clinical symptomatology of OH. The second of these two limitations is that the clinical presentations and complications of OH may vary with the severity of OH and therefore, not all PwPD with ≥20 are similar. As a result, if the participants in the PD+OH group had a greater proportion of PwPD with greater severity of OH (producing greater adverse effects over the dependent variables over time), then the findings may potentially show statistically significant interaction of group and time, and if there is a greater proportion of PwPD with milder OH then there may be absence of group and time interaction. As this influences the results of the investigations, it might have adversely affected the internal validity of the research studies in this thesis. Future studies may control for this difference in severity of OH and either enrol within a narrow range of severity of OH for a sample comparable to the studies in this thesis or

segregate the PwPD with OH into subgroups with defined range of OH for studies with reasonably large sample sizes.

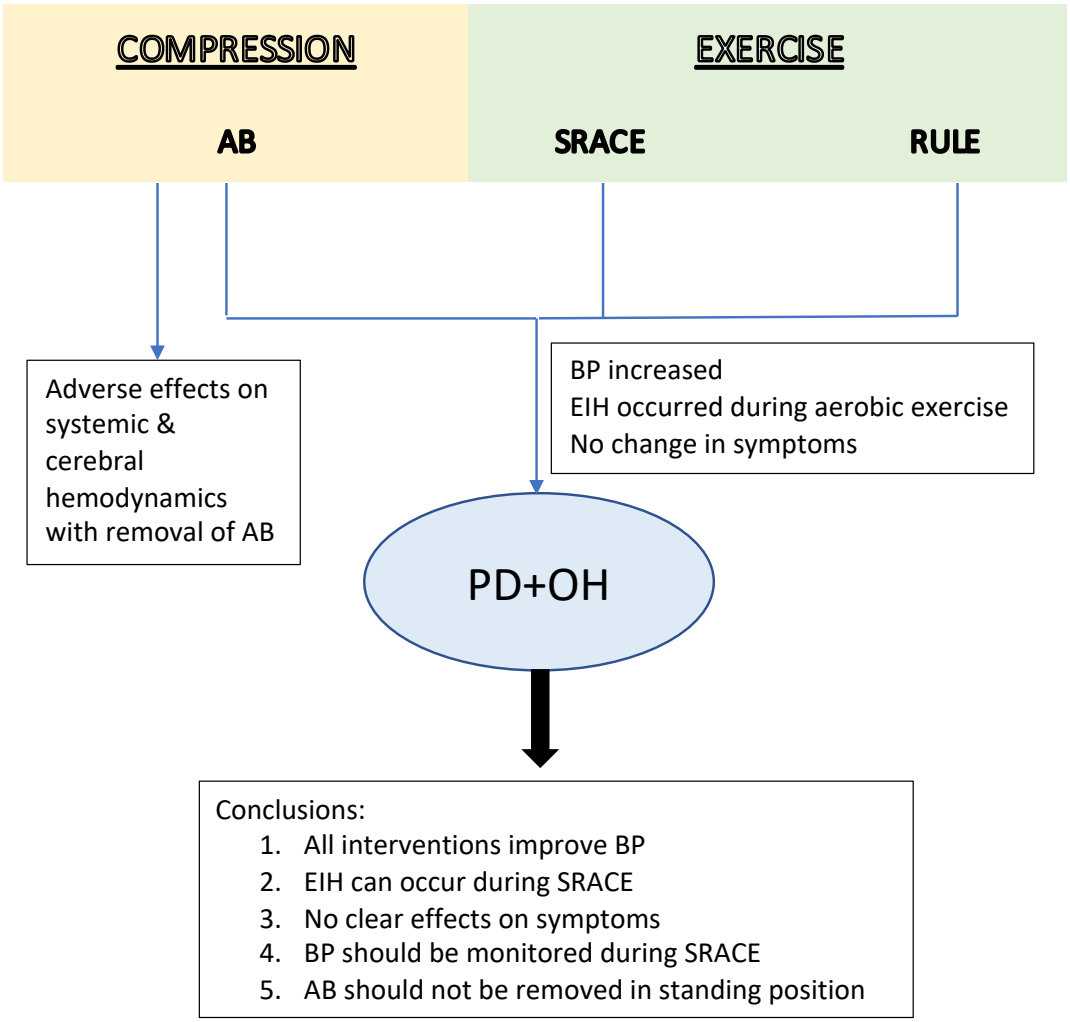
The fourth limitation is that all the investigations were carried out for a short duration of time and as a result reflect the short-term effects of the intervention. Future research can study the effects of longer durations of monitoring of the effects of the interventions studied in this thesis.

The fifth limitation is that BP is known to be influenced by the time of the day as well as by behavioural factors.[13] It also varies day-to-day.[14,15] We did only one session of the experiment which may not reflect day-to-day and intra-day variability in the hemodynamic responses. Although controlling for behavioural factors may not be completely feasible, future studies can address the limitation of intra-day and day-to-day variability by performing the intervention at the same time of day for all participants and repeating the intervention on different days.

Since the participants were not required to stop or alter their prescribed medications to participate in the research studies in this thesis, this raises concerns about potential confounding effects of medications over changes in the dependent variables, particularly the BP. It might seem that consumption of medications, especially those that increase BP to counter OH, could change the findings of this thesis or alter the group allocation criteria by altering the decrease in BP during HUT. However, medications like midodrine and fludrocortisone increase BP in all positions, not only the standing position.[16] This means that supine as well as standing BPs increase as a result of consumption of these medications. As a result, the difference between the standing/upright and the supine lying positions remains fairly constant. For instance, if a PwPD with OH obtains an improvement of 15 mmHg in SBP with the consumption of midodrine, then he/she may have SBPs as 110 mmHg during supine lying and 80 mmHg during standing/upright position after consumption of midodrine compared to a state without midodrine in which SBPs would be expected to be 95 mmHg during supine lying position and 65 mmHg during standing/upright position. Thus, consumption of midodrine would be expected to shift the

SBP changes en-block to higher values without affecting the absolute difference between the supine and standing SBP. In other words, midodrine increases the standing BP but it does not change the difference between the standing and lying down SBP as it increases SBP similarly in all positions. This phenomenon has been proved by research and discussed in a systematic review and meta-analysis.[17] Consequently, consumption of medications that counter OH including midodrine is not expected to affect the group allocation criteria of ≥20 mmHg decrease in SBP as decrease in SBP during HUT is not affected by consumption of midodrine or other medications (including fludrocortisone) used for the same purpose. Although antiparkinsonian medications (including levodopa/sinemet) may decrease BP, participants in both groups consumed these medications similarly and this would nullify any confounding effects these medications may have on the dependent variables. Therefore, consumption of medications is not expected to negatively influence the internal validity of this thesis by influencing the allocation of participants to groups. However, since midodrine and other similar medications that help counter OH increase the standing BP, such an increase in BP may lead to higher MAP at the cerebral level, thus preventing a decrease in MAP to substantially low levels that could render the cerebral autoregulation dysfunctional and produce symptoms of orthostasis. Such a possibility has the potential to prevent the onset of symptoms and may be considered a limitation of this thesis with regards to sensitivity of symptomatic presentation during HUT.

Figure 5-1: Summary of interventions and findings in this thesis



Compression of the abdomen using the abdominal binder (AB) and performing exercise in the form of resisted upper limb exercise (RULE) helped counter orthostatic hypotension (OH) by increasing the blood pressure (BP). Performing self-regulated aerobic cycling exercise (SRACE) increased BP in most participants with Parkinson's Disease and OH (PD+OH) but led to exercise-induced hypotension (EIH) in those with severe OH.

5.3 Conclusions

Orthostatic hypotension can be countered using AB as well as RULE in PwPD. Each of these interventions uses a different mechanism to increase BP. SRACE does not generally produce different responses in PwPD with and without OH, although, in PwPD with

relatively severe OH, SRACE can produce EIH. Through the findings of this thesis clinicians should be better enabled to decide if an AB should be prescribed to a PwPD for the control of OH or for the control of symptoms or for both. The clinician may advise RULE to the patient when an AB, or another such modality or posture, may not be feasible or suitable. During the process of exercise rehabilitation, the clinician may use the findings of this thesis while prescribing SRACE to PwPD with OH and in deciding if regular monitoring of BP is warranted for their patients. Overall, the findings of this thesis should be instrumental in providing the clinician with a deeper understanding of the implications of the presence of OH during the rehabilitation of PwPD as well as in equipping them with a greater choice of strategies for countering OH.

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Appendices

Appendix A: Research ethics approval

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice **RE-ISSUED**

Principal Investigator: Dr. Kurt Kimpinski
Department & Institution: Schulich School of Medicine and Dentistry\Neurology,London Health Sciences Centre

Review Type: Full Board
HSREB File Number: 109386
Study Title: Exercise and its cardiovascular effects in patients of Parkinson's Disease with cardiovascular autonomic dysfunction.

HSREB Initial Approval Date: November 29, 2017
HSREB Expiry Date: November 29, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Letter of Information & Consent		2017/08/22
Data Collection Form/Case Report Form	Received September 22, 2017	
Instruments	Dizziness Handicap Inventory	
Instruments	Orthostatic hypotension questionnaire (OHQ)	
Instruments	Orthostatic Determination and Severity Scale.	
Instruments	Autonomic Symptom Profile Questionnaire	
Data Collection Form/Case Report Form	Exercise log sheet (stage 2)	2017/09/20
Other	Exercise Training Description Sheet - stage 2.	2017/09/20
Revised Western University Protocol	(NCT# included)	2017/09/20

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Appendix B: Abdominal belt and binder

Figure B1: Abdominal belt formed by joining two thigh cuffs (a) inner side and (b) outer side.

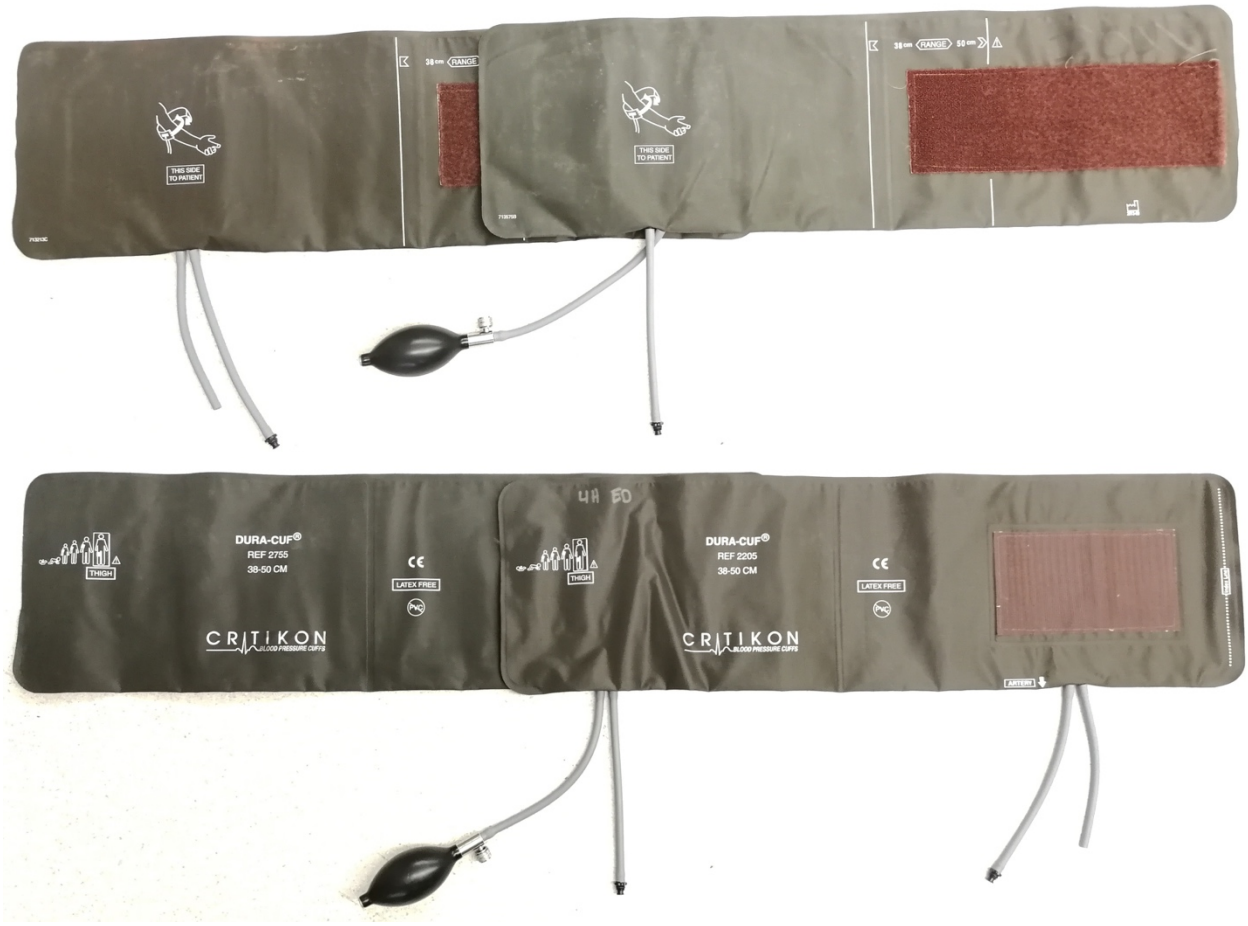
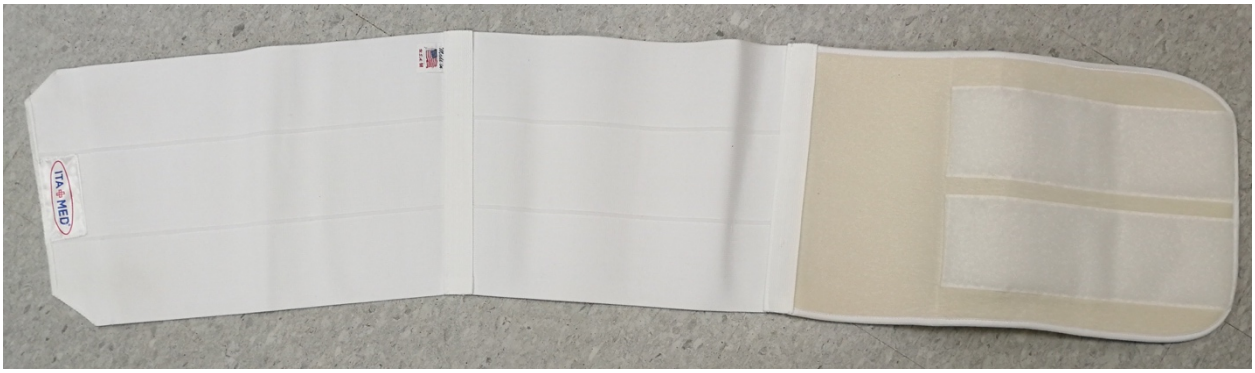


Figure B2: The elastic abdominal binder. (Only the medium size is shown here)



Appendix C: Clinical trial registration

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Trial record **1 of 1** for: NCT03343574

Previous Study | Return to List | Next Study

Cardiovascular Effects of Exercise in Patients With Parkinson's Disease

ClinicalTrials.gov Identifier: NCT03343574

Recruitment Status : Active, not recruiting
First Posted : November 17, 2017
Last Update Posted : November 21, 2019

Sponsor:
Faizan Ahmed

Information provided by (Responsible Party):
Faizan Ahmed, Lawson Health Research Institute

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Tracking Information
First Submitted Date ICMJE
November 10, 2017

Curriculum Vitae

Name: Faizan Ahmed

Post-secondary Education and Degrees:

Guru Gobind Singh Indraprastha University
New Delhi, India
2001-2006 Bachelor of Physiotherapy

Jamia Hamdard (Hamdard University)
New Delhi, India
2006-2008 Master of Physiotherapy (Cardiopulmonary)

Western University
London, Ontario, Canada
2015-2020 PhD Health & Rehabilitation Sciences (PT field)

Professional Affiliations:

Registered Physiotherapist, Ontario, Canada
Member, Canadian Physiotherapy Association, Canada
Member, Indian Association of Physiotherapists, India

Honours and Awards:

Ontario Graduate Scholarship
2017-18, 2018-19

2nd prize in poster competition
InterACTION2019 (Ontario PT Association annual conference)
2019

Related Work Experience

Teaching Assistant
Western University
2017

Lecturer of Physiotherapy
Jazan University, Jizan, KSA
2013-15

Assistant Professor of Physiotherapy (Cardiopulmonary)
Jamia Hamdard (Hamdard University), New Delhi, India
2009-13

Publications:

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