The development of a self-regulated isometric handgrip training protocol and its effects on blood pressure (resting and ambulatory), markers of autonomic function and adherence in pre-hypertensive and stage 1 hypertensive adults (≥55years).

By

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List of commonly used abbreviations

Δ = change

ABPM = ambulatory blood pressure monitoring

Ang-II = angiotensin II

ANCOVA = analysis of covariance

ANOVA = analysis of variance

BP = blood pressure

BPV = blood pressure variability

BRS = baroreflex sensitivity

CR-10 = category ratio 10 scale

CV% = coefficient of variation

DBP = diastolic blood pressure

ECG = electrocardiography

EMG = electromyography

EMG_{peak} = peak of electromyography signal

HRV = heart rate variability

HR ($b.min^{-1}$) = heart rate

HFnu = high frequency spectral component of heart rate variability (normalised units)

IHG = isometric handgrip

LFnu = low frequency spectral component of heart rate variability (normalised units)

LF(mmHg) = low frequency spectral component of systolic blood pressure variability

LF% = low frequency spectral component of systolic blood pressure variability (percentage of total spectra

LF/HF = ratio of low and high frequency spectral components of heart rate variability

Ln = natural logarithm

mmHg = millimetres of mercury

MVC = maximal voluntary contraction

MAP = mean arterial pressure

pNN50% = the percentage of adjacent NN intervals differing by more than 50ms

RAAS = renin angiotensin aldosterone system

RPE = rate of perceived exertion

rMSSD = root mean square of successive differences

SD = standard deviation

SBP = systolic blood pressure

SDNN = SDNN, standard deviation of all NN intervals

SDANN = average standard deviation across each 5-minute segment of NN intervals

TE = typical error

CR-10 = category ratio scale

Publications arising from this thesis

Morrin, N. M. *et al.* (2018) 'The use of the CR-10 scale to allow self-regulation of isometric exercise intensity in pre-hypertensive and hypertensive participants', *European Journal of Applied Physiology*, 118(2), pp. 339–347.

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Abstract

Isometric exercise training is gaining recognition for its blood pressure (BP) lowering effects. The current thesis had four primary purposes, to: i) assess the reproducibility of various BP and heart rate variability (HRV) measures (ii) validate the CR-10 scale as a novel method for self-regulating the intensity of isometric handgrip (IHG) exercise and iii) determine the effects of self-regulated IHG exercise on resting and 24-hour ambulatory BP iv) investigate levels of participant adherence to self-regulated IHG training. Secondary to these purposes, indirect measures of autonomic function were recorded to provide insight into a possible mechanistic pathway for BP reductions.

Study 1 (Chapter 4) assessed the reproducibility of 24-hour ambulatory BP, 24-hour HRV, resting HRV and resting systolic blood pressure variability (BPV). It was shown that i) the typical error in ambulatory systolic BP recordings reduced over consecutive pairs of measurements (3.8-2.8mmHg) and would therefore benefit from familiarisation periods ii) 24-hour HRV provided superior reproducibility to resting measurements and iii) resting systolic BPV displayed poor reproducibility (coefficient of variation, 27-60%) .

Study 2 (Chapter 5) determined the validity of self-regulating IHG exercise as an alternative to the commonly-prescribed 30% maximal voluntary contraction (MVC). Findings showed that exercising at "Level-6" on the category-ratio scale (CR-10) enabled participants to produce an appropriate IHG exercise intensity (mean 33% MVC). Thus, the CR-10 scale provides a valid means for participants to self-regulate the intensity of IHG exercise.

Study 3 (Chapter 6) implemented an IHG training programme in a 2-phase training study design. Phase 1 showed that 10-weeks of self-regulated IHG training (at CR-10 "Level 6") induced clinically-relevant reductions in resting systolic BP (-6mmHg). However, no changes were observed in 24-hour ambulatory BP. The data also displayed trending changes in autonomic modulation of both heart (HRV) and systolic BP (BPV), these findings could offer some explanation for the reductions in resting BP. Phase 2 revealed excellent adherence (average, 95%) during both shorter-term (14 weeks) and longer-term (24 weeks) self-regulated, home-based, unsupervised IHG training. However, despite excellent adherence, the longer-term exercise group did not maintain their reduced resting BP upon completion of 24-weeks of isometric exercise training.

Taken together, these findings demonstrate the appropriateness of self-regulated IHG training as a non-pharmacological intervention for lowering resting BP. However, it seems that the reductions in resting BP may be lost with prolonged training and further investigation into the long-term effects of isometric exercise training on resting and ambulatory BP is required.

Chapter 1: Introduction

Blood pressure (BP) is the hydrostatic pressure that blood exerts onto the vasculature (Pappano and Wier 2013). Following left ventricular contraction, blood is ejected into the aorta where maximal pressure is reached; this is termed systolic blood pressure (SBP). As the ventricle relaxes and refills, the pressure in the aorta falls to its lowest level; this is termed diastolic blood pressure (DBP) (Klabunde 2012). Normal resting SBP is classified at ≤120mmHg and normal resting DBP is classified at ≤80mmHg (Mancia, Fagard, Narkiewicz, et al. 2013). Hypertension is the persistent elevation of BP. In adults (≥18years), a systolic value of ≥140mmHg and/or a diastolic value of ≥90mmHg would be defined as hypertension (Mancia, Fagard, Narkiewicz, et al. 2013; Chobanian, Bakris, Black, et al. 2003).

Hypertension can be categorised into two primary types; essential hypertension and secondary hypertension. Essential hypertension does not have a clear cause and accounts for more than 90% of cases (Oparil, Zaman, and Calhoun 2003; Rimoldi, Scherrer, and Messerli 2014). In contrast secondary hypertension is due to an identifiable cause (i.e. obstructive sleep apnoea, renal artery stenosis, thyroid disease, Cushing's syndrome) and only accounts for 5-10% of cases (Rimoldi, Scherrer, and Messerli 2014). The prevalence of hypertension (primary and secondary) in adults (≥18 years) is approximately 30-45% (Piepoli, Hoes, Agewall, et al. 2016), with a steep rise associated with advancing age (Knott and Mindell 2011; Piepoli, Hoes, Agewall, et al. 2016; Franklin, Gustin, Wong, et al. 1997; Chobanian, Bakris, Black, et al. 2003); for example, 44% of 55-64 year olds have hypertension, this prevalence rises to 72.6% of people aged ≥75years (Knott and Mindell 2011).

Accounting for 9.4 million deaths in 2010 (Lim, Vos, Flaxman, et al. 2012) and 10.4 million deaths in 2013 (Forouzanfar, Alexander, Anderson, et al. 2015) the impact of hypertension on mortality rates is a growing concern worldwide. Bearing an independent and continuous relationship with the incidence of stroke, heart failure, peripheral artery disease and chronic kidney disease (Mancia, Fagard, Narkiewicz, et al. 2013), hypertension is considered one of the top five risk factors for death and disability . The treatment and management of hypertension-related conditions are estimated to cost the National Health Service £2.1 billion per year (Optimity Matrix 2014), with a further £1 billion on antihypertensive drug costs (NICE 2011). Its economic burden and risk to quality of life and mortality ensures that appropriate diagnosis, management and prevention remains an important medical issue.

Without exception, the management of hypertension includes the recommendation of appropriate lifestyle interventions (Mancia, Fagard, Narkiewicz, et al. 2013; NICE 2011; Piepoli, Hoes, Agewall, et al. 2016). Aerobic exercise is one the most widely recommended non-pharmacological therapeutic strategies. International guidelines suggest that those needing to lower their BP should engage in ≥30 minutes of moderate intensity aerobic exercise on 5-7 days of the week (Ghadieh and Saab 2015; Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013; Brook, Appel, Rubenfire, et al. 2013; James, Oparil, Carter, et al. 2014). However, with low compliance and dropout rates high between 3-6 months of exercise initiation

(Dishman, Sallis, and Orenstein 1984) aerobic exercise is reported as the most difficult lifestyle recommendation to be implemented (Riegel, Moreira, Fuchs, et al. 2012; Baynouna, Neglekerke, Ali, et al. 2014; Ohta, Tsuchihashi, and Kiyohara 2011; Montesi, Moscatiello, Malavolti, et al. 2013). Common barriers to aerobic type exercise include access difficulties, inflexible work schedules, time commitment, competing priorities and lack of convenience (Bethancourt, Rosenberg, Beatty, et al. 2014; Franco, Tong, Howard, et al. 2015; Jefferis, Sartini, Lee, et al. 2014). In addition, older people whom are at the highest risk of hypertension, present with further aerobic exercise barriers including mobility issues, chronic health conditions and fear of injury (Jefferis, Sartini, Lee, et al. 2014; Franco, Tong, Howard, et al. 2015). It is therefore of no surprise that physical activity has been found to be particularly low in older adults (Jefferis, Sartini, Lee, et al. 2014). Recent research identified, as a top priority, a need to determine the optimal prescription of exercise that emphasises alternatives to walking/running for older individuals with and without arthritis or other health problems (Khan, Bacon, Khan, et al. 2017). This emphasises a clear public interest in exploring additional exercise options that are more accessible to a variety of population groups.

Research findings suggest that isometric training programmes, utilising handgrip exercises or bilateral quadriceps contractions, can successfully lower resting BP in young healthy adults (Wiley et al. 1992; Ray & Carrasco 2000; Howden et al. 2002; Millar et al. 2008; Wiles et al. 2010; Devereux et al. 2010; Devereux et al. 2011; Badrov, Bartol, et al. 2013; Devereux & Wiles 2015; Gill et al. 2015), non-medicated hypertensives and pre-hypertensives (Peters, Alessio, Hagerman, et al. 2006; Baross, Wiles, and Swaine 2012, 2013) and medicated hypertensives (Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; McGowan, Visocchi, Faulkner, et al. 2007; Badrov, Horton, Millar, et al. 2013; Millar, Levy, Mcgowan, et al. 2013). The typical isometric exercise programme prescribes three weekly exercise sessions, each lasting a total of 20 minutes. As compared with aerobic exercise recommendations, isometric exercise therefore poses a simple, time-effective alternative for the non-pharmacological management of hypertension.

To date, the majority of isometric training has been prescribed using a percentage of maximal voluntary contraction (%MVC). Thirty percent is most typical and consistently effective after 6-10 weeks of training (Wiley, Dunn, Cox, et al. 1992; Taylor, McCartney, Kamath, et al. 2003; McGowan, Visocchi, Faulkner, et al. 2007; Millar, Bray, McGowan, et al. 2007; Badrov, Horton, Millar, et al. 2013) with lower intensities showing a blunted or insignificant effect (Baross, Wiles, & Swaine, 2012; Devereux & Wiles, 2015; Gill et al., 2015). Unfortunately, this method of exercise prescription is currently limited to lab-based dynamometers or expensive programmable dynamometers that calculate and visually display the percentage of an individual's MVC. Not only does this pose a financial barrier, the requirement of 2-3 maximal contractions prior to an exercise session is limited in some groups, particularly those with frailty.

The problem of expensive monitoring of appropriate exercise intensity is not uncommon in aerobic exercise where the use of heart rate (HR) monitors provides accurate, real-time information on exercise intensity. For

this reason, the American College of Sports Medicine promotes the use of the Borg 6-20 perceived exertion scale for self-regulating exercise for the management of hypertension (Pescatello, Franklin, Fagard, et al. 2004a). It would seem pertinent to determine the validity and effectiveness of using perceived exertion in the prescription of isometric exercise (Chapter 5). This would provide cost effectiveness and remove the necessity of maximal contractions.

Although findings have revealed positive effects of isometric exercise on resting BP in both healthy and hypertensive populations, the effects on ambulatory BP measurements have not been fully determined. The National Institute for Clinical Excellence (NICE) recommends ambulatory BP monitoring (ABPM) as a gold standard measure for diagnosing hypertension and assessing treatment effects (NICE 2011). To date, only five studies have measured ambulatory BP (Stiller-Moldovan, Kenno, and McGowan 2012; Somani, Baross, Levy, et al. 2017; Ash, Taylor, Thompson, et al. 2016; Pagonas, Vlatsas, Bauer, et al. 2017; Goessler, Buys, VanderTrappen, et al. 2018) following isometric handgrip training over 8-10 weeks. Despite a similar exercise prescription amongst studies, findings have been contradictory with positive effects (Somani, Baross, Levy, et al. 2017), no effects (Stiller-Moldovan, Kenno, and McGowan 2012; Pagonas, Vlatsas, Bauer, et al. 2017; Goessler, Buys, VanderTrappen, et al. 2018) and negative effects (Ash, Taylor, Thompson, et al. 2016) all being reported. Considering the limited use of ambulatory measurements following an isometric training intervention it would be prudent to determine the effect of isometric exercise alongside resting measurements (Chapter 6). In addition, determining the variability within a 24-hour measurement and the need to habituate participants to the ambulatory monitoring process requires determination (Chapter 4).

Little is known about the precise mechanisms responsible for isometric exercise induced reductions in resting BP. The autonomic nervous system is central to the regulation of BP (Chapter 2, section 2.02.i). For this reason the possible link between BP reductions and improved autonomic regulation has attracted the attention of some researchers (Taylor, McCartney, Kamath, et al. 2003; Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013; Stiller-Moldovan, Kenno, and McGowan 2012). However, research to date has produced equivocal findings. Further investigation into autonomic regulation prior to and following an isometric training intervention is required (Chapter 6). Considering the large variation in resting measurements of autonomic function (Pinna, Maestri, Torunski, et al. 2007) it would be important to firstly determine the reproducibility and importance of habituation prior to the measurement of autonomic function (Chapter 4).

Considering the simplicity, time-effectiveness and home-based possibilities of isometric exercise, it has been proposed that the prescription of isometric exercise would result in exercise sustainability and adherence as compared with aerobic exercise (Inder, Carlson, Dieberg, et al. 2016; Carlson, Dieberg, Hess, et al. 2014; McGowan, Proctor, Swaine, et al. 2017). However, to date, adherence to un-supervised, isometric exercise

has not been recorded. The long-term appropriateness and feasibility of isometric exercise is therefore unknown and is in need of investigation (Chapter 6).

Understanding BP regulation and the pathophysiology of hypertension is central to gaining mechanistic insight into the effects of isometric exercise on BP. An overview of this is provided in chapter 2 (section 2.0). In addition, chapter 2 will detail: 1) previous research on the use of exercise for BP management, 2) The autonomic effects of exercise, 3) exercise adherence, 4) self-regulation of exercise. A particular emphasis will be placed on isometric exercise throughout.

Chapter 2: Literature review

2.0 Blood pressure regulation and pathophysiology of hypertension

The relationship between arterial blood pressure (BP) and haemodynamics is clearly established. Cardiac output (heart rate*stroke volume) and total peripheral resistance (TPR; resistance offered by all systemic vasculature) are the two primary factors contributing to arterial BP (Pappano and Wier 2013). These factors are not constant; changes in behaviour (e.g. exercise, feeding, postural change), the environment (i.e. thermoregulation) and emotion (i.e. fright) (Guyenet 2006) alter circulatory demands. These demands are met by alterations in blood distribution which are mediated by changes in cardiac output and TPR. The influence of isometric exercise on circulatory demands is described in detail in section 2.6.

There are a number of mechanisms that contribute to BP regulation. These mechanisms can be divided into three main categories: neural, humoral and vascular. Hypertension, a sustained rise in BP, is a sign that there is a dysfunction in one or more of the key mechanisms regulating BP (Navar 2010). As a way of further understanding this cardiovascular disease, the following section (2.0) will describe the key BP regulation pathways and how they may be involved in the development of hypertension.

2.i Neural factors

The autonomic nervous system has a key role to play in BP regulation. In a healthy organism, BP is tightly regulated by the dynamic interplay and relative balance between parasympathetic and sympathetic nerve activity (Shaffer, Mccraty, Zerr, et al. 2014).

Sympathetic nerves innervate blood vessels and the sinoatrial (SA) node and myocardium of the heart (Klabunde 2012). Cardiovascular sympathetic activity is altered based on afferent sensory information received by the rostral ventrolateral medulla (RVLM) of the brainstem (Dampney, Coleman, Fontes, et al. 2006). Efferent nerve impulses prompt the release of the neurotransmitter norepinephrine which binds to post synaptic alpha-adrenergic receptors in the vasculature and beta-adrenergic receptors in the heart and the juxtaglomerular apparatus of the kidneys (Klabunde 2012). Efferent sympathetic nerve activity produces systemic vasoconstriction and cardiac stimulation which results in increased cardiac conduction velocity in addition to increased rate and strength of cardiac contractions.

The parasympathetic nervous system assists in regulating BP via vagal nerve fibres which innervate the atrioventricular (AV) and SA nodes of the heart. Afferent sensory information is received by cell bodies located within the medulla in the brain. The integration of this information results in parasympathetic efferent nerve impulses which trigger the release of acetylcholine, a neurotransmitter, that binds to muscarinic receptors in the heart (Klabunde 2012). This parasympathetic nerve activity acts to reduce SA

node firing and slow AV node conduction – both contributing to a slowing of heart rate (HR) and a reduction in the strength of contraction.

The cardiovascular regulation centre in the medulla is responsible for making adjustments in the balance between levels of sympathetic and parasympathetic nerve activity. Adjustments are based on the integration of information from both the high brain centres and afferent sensory signals (Klabunde 2012). Afferent sensory signals originate from neural reflexes; these are negative feedback mechanisms that contribute to short term changes in BP that are necessary to meet metabolic demands. The primary neural reflexes include the baroreceptor and chemoreceptor reflexes, these are discussed in section 2.i.a.

2.i.a Role of neural reflexes in the regulation of blood pressure

The baroreflex is activated by cardiopulmonary and arterial baroreceptors that sense volume and pressure changes respectively. Cardiopulmonary baroreceptors are located in the walls of the atria and ventricles and the arterial baroreceptors are located in the carotid sinus and aortic arch. The arterial baroreceptors are the main contributors to the autonomic reflex control of both the heart (cardiac reflex) and blood vessels (vascular reflex) (Zimmer 2004). These were discovered by Heinrich Ewald Hering in 1924 (Zimmer 2004). Hering's experimental work led to the discovery that pressure on the carotid sinus and aortic arch sent signals via the glossopharyngeal and vagus nerves, which led to decreases in HR, cardiac contractility, vascular resistance, venous return and thus an alteration in autonomic balance (a decrease in sympathetic activity and increase in parasympathetic activity) (Zimmer, 2004). In contrast to these discoveries, a reduction in pressure on the carotid sinus and aortic arch results in unloading of the baroreceptors (Kougias, Weakley, Yao, et al. 2010). This unloading, reduces the firing rate and leads to an increase in sympathetic outflow and therefore an increase in peripheral vascular resistance and cardiac tissue activity (increase rate and strength of contraction and conduction velocity).

Under conditions whereby BP is required to increase to enable adequate blood flow (e.g. during exercise), the baroreceptor mechanism adjusts and operates around the prevailing BP (see section 2.6.3). This acute resetting is short-lived and the operating pressure returns to previous resting levels following the return of homeostasis.

The second reflex involved in the neural regulation of BP is the chemoreceptor reflex. Chemoreceptors are also located within the aortic arch and carotid artery with their afferent fibres also running in the glossopharyngeal and vagus nerves (Klabunde 2012). Peripheral chemoreceptors primarily function to regulate respiration and thus maintain appropriate oxygen, carbon dioxide and pH within a narrow physiologic range. The chemoreceptors increase their firing rate in response to a fall in arterial PO_2 and an increase in arterial PCO_2 and hydrogen ion concentration. They reflexively increase ventilation and sympathoexcitation of cardiac tissue and blood vessels (Dampney, Coleman, Fontes, et al. 2006; Schultz, Li,

and Ding 2007). The increase in ventilation and sympathetic activity of the heart ensures that excess carbon dioxide is expired and oxygen is replenished, whilst the constriction of most vascular beds (excluding the brain and heart) aids in the conservation of available oxygen (Dampney, Coleman, Fontes, et al. 2006).

2.i.b Role of neural reflexes in the pathophysiology of hypertension

A reduction in baroreceptor sensitivity increases the pressure threshold required to activate a stretch sensitive baroreceptor. This phenomenon is known as chronic baroreceptor resetting and is thought to be responsible for sustained increases in BP (Carthy 2014). A lower sensitivity would result in reduced baroreceptor signalling in response to increased BP, which would in turn cause a reduction in the activation of parasympathetic efferent activity and inhibition of sympathetic outflow (Carthy 2014). Chronic baroreceptor resetting has been highlighted in the aetiology of essential hypertension (Kougias, Weakley, Yao, et al. 2010) with strong negative associations found between mean arterial pressure (MAP) and baroreceptor sensitivity (Hesse, Charkoudian, Liu, et al. 2007; Charkoudian and Rabbitts 2009). Research has also shown that the sensitivity of baroreceptors in those with essential hypertension is decreased (Parati, Di Rienzo, Bertinieri, et al. 1988; Grassi, Cattaneo, Seravalle, et al. 1998; Mussalo, Vanninen, Ikaheimo, et al. 2002).

One of the most widely accepted theories for chronic baroreceptor resetting/decreased baroreceptor sensitivity is reduced vascular compliance (Thrasher 2004). In the case of both aging and atherosclerosis there is a stiffening of the arteries (Sun 2014). This reduces the deformation of stretch sensitive receptors in response to increases in pressure. Research has highlighted the negative association between arterial stiffness and baroreflex sensitivity (Mattace-Raso, van den Meiracker, Bos, et al. 2007; Okada, Galbreath, Shibata, et al. 2012). These findings provide strong evidence for the role of aortic stiffness in the lowering of baroreceptor sensitivity and therefore its role in sustaining increases in BP.

Chemoreceptor sensitivity has been found to be high in hypertensive populations (Tafil-Klawe, Trzebski, and Klawe 1985; Somers, Mark, and Abboud 1988) and therefore has also been proposed as a factor involved in the aetiology of essential hypertension (Schultz, Li, and Ding 2007; Paton, Ratcliffe, Hering, et al. 2013). Although the primary function of chemoreceptor activity is to increase alveolar ventilation and ensure adequate oxygen perfusion of vital organs, it also increases sympathetic activity to areas where oxygen is not urgently needed (i.e. muscles, splanchnic and renal beds). If chemoreceptor activity is enhanced in those with hypertension, this may in turn lead to tonic elevation of sympathetic outflow to some vascular and renal beds (Oparil, Zaman, and Calhoun 2003). Whether increased sympathetic drive originating from the chemoreceptors is contributing to the development of hypertension or whether chemoreceptors are active as a result of hypertension is a subject of debate (Schultz, Li, and Ding 2007).

Some research findings in favour of causation focus primarily on individuals with sleep apnoea; a condition characterised by a cessation of breathing due to airway obstruction during sleep (Narkiewicz and Somers 1999; Smith and Pacchia 2007). Sleep apnoea has been shown to cause chronic intermittent hypoxic episodes and enhance chemoreceptor activity that lasts much longer than the hypoxic episode itself (Narkiewicz and Somers 1999; Smith and Pacchia 2007). In a rat model researchers induced intermittent hypoxic episodes and showed that hypertension ensued from the repeated hypoxic episodes (Fletcher 2001). This research provided compelling evidence to support the contributory role of heightened chemoreceptor activity in the development of hypertension.

Other theories, taken from findings in chronic heart failure patients and animal models suggest that the presence of sympathetic overdrive and Angiotensin II (Ang II) (see section 2.02.ii) in addition to a reduction in nitric oxide (NO) (see section 2.02.iii) would heighten the chemoreflex response (Ding, Li, and Schultz 2011; Schultz 2011; Li, Sun, Overholt, et al. 2004). This response would be a direct result of a reduction in carotid body blood flow which would in turn stimulate a response from the chemoreceptors suggestive of reduced oxygen levels.

Either way, augmented chemoreceptor drive contributes to enhanced sympathetic neural drive (Schultz, Li, and Ding 2007). Its' contributing role, either in the manifestation or maintenance of high BP is becoming more certain. Recent evidence supporting this showed that surgical excision of the carotid body in spontaneously hypertensive rats showed marked decreases in both BP and sympathetic activity (McBryde, Abdala, Hendy, et al. 2013).

2.ii Hormonal factors

Many hormones have vasoactive and neural properties, this means that they can influence BP through changes in vascular and autonomic tone. In addition, antidiuretic hormones influence reabsorption of fluid; regulating BP through increases in fluid volume. The characteristics of these hormones not only influence their significance in BP regulation but also in the pathophysiology of hypertension. The renin-angiotensin-aldosterone system (RAAS) is the most influential hormone system involved in the long-term regulation of BP (Dampney, Coleman, Fontes, et al. 2006); aside from its' system generated hormone (Ang II) it influences the secretion of antidiuretic hormones (aldosterone and vasopressin) in addition to the sympathetic neurotransmitter norepinephrine (Klabunde 2012). Natriuretic peptide hormones are counter regulatory to the hormones established through the RAAS and are therefore also important long-term regulators of BP (Volpe, Rubattu, and Burnett 2014).

2.ii.a The role of the renin-angiotensin-aldosterone system in blood pressure regulation

The RAAS is a powerful regulator of blood volume, sodium and potassium balance and systemic arterial BP (Pacurari, Kafoury, Tchounwou, et al. 2014). Blood pressure is regulated via three primary effectors of this system; renin, angiotensin and aldosterone. Renin is an active proteolytic enzyme that is released from the juxtaglomerular apparatus of the kidney. The release of renin initiates a cascade of molecular events that work to maintain homeostasis. Renin acts upon and cleaves a component of the protein angiotensinogen which alters its molecular status to angiotensin I. Angiotensin I is subsequently converted to Ang II by the actions of the angiotensin converting enzyme (ACE) (Klabunde 2012). The many actions of Ang II contribute to an elevation of fluid volume and BP (Harrison-bernard 2009). Angiotensin II directly constricts vascular smooth muscle cells, facilitates release of norepinephrine from the adrenal medulla and sympathetic nerve endings, increases sympathetic nervous activity, stimulates thirst and the release of vasopressin from the pituitary gland (Klabunde 2012). Vasopressin is an antidiuretic hormone responsible for increasing fluid retention in the kidneys in addition to its direct vasoconstrictor properties (Klabunde 2012). The final effector of the RAAS is another antidiuretic hormone; aldosterone. Angiotensin II stimulates the release of this hormone from the adrenal medulla which causes salt retention and fluid volume expansion (Stiefel, Vallejo-Vaz, García Morillo, et al. 2011).

Due to the wide-ranging actions of both angiotensin and aldosterone, the release of renin has a major influence on regulating BP. There are three mechanisms responsible for signalling renin release; 1) a decrease in glomerular filtration rate is detected by the juxtaglomerular cells; 2) a reduction in sodium chloride concentrations detected within the distal tubule of the macula densa; 3) increased renal sympathetic nerve activity which act on β1 adrenergic receptors on the juxtaglomerular apparatus. Renin release can also be stimulated indirectly by sympathetic nerve innervation of the α1 adrenoceptors on the renal arterioles (Johns 2013). This innervation causes vasoconstriction which in turn reduces glomerular filtration stimulating renin release. Lastly, independent of renin, sympathetic nerve innervation of the renal tubules contributes to the regulation of BP by decreasing urinary water and sodium excretion by stimulating an increase in sodium and water reabsorption throughout the nephron (DiBona 2000).

2.ii.b The role of the RAAS in the pathophysiology of hypertension

The influence of renin on the development of hypertension was originally proposed in 1947 by Harry Goldblatt (Goldblatt 1947). Goldblatt found that renal ischemia stimulated renin secretion and led to an increase in arterial BP; an effect not observed during ischemia of the femoral or splenic arteries (Goldblatt 1947). Since this discovery, the RAAS has been the subject of intense research into the development of hypertension. In 1972, Guyton and co-workers demonstrated that abnormal kidney function and consequent

dysregulation of fluid influences chronic elevations in BP (Guyton, Coleman, Cowley, et al. 1972). It is now widely accepted that heightened activation of the RAAS is one of the major pathophysiologic mechanisms of hypertension (Esler, Lambert, and Schlaich 2010) with increased levels of Ang II (Higuchi, Ohtsu, Suzuki, et al. 2007) and aldosterone (Stiefel, Vallejo-Vaz, García Morillo, et al. 2011) being specifically implicated in its development.

One of the key contributors to over-activation of the RAAS is increased renal sympathetic nerve activity (Esler 2014). Although sympathetic innervation of the kidneys was proposed by Claude Bernard in 1859, the existence and contribution of these nerves to BP regulation were not fully understood until the 1960's (Muller and Barajas 1972). It is now understood that the juxtaglomerular apparatus, afferent and efferent arterioles and renal tubules are extensively innervated by sympathetic nerves (DiBona and Kopp 1997). This knowledge has advanced therapeutic treatment modalities for hypertension including ablation of renal sympathetic nerves (Barrett 2015) and pharmacological blockade of this system (Bader 2010).

In the presence of heightened activity of renal sympathetic nerve activity a persistence of renin excretion prevails. This in turn leads to chronic increases in Ang II production (Klabunde 2012). Augmented levels of this vasoactive peptide have been implicated in leading to sustained elevations in BP through its continued actions of vasoconstriction, aldosterone secretion and increased sympathetic nerve activity (Oparil, Zaman, and Calhoun 2003). In addition, increased levels of Ang II can play a crucial role in vascular inflammation, remodelling and endothelial dysfunction, thus mediating the development of hypertension (Pacurari, Kafoury, Tchounwou, et al. 2014) (see section 2.3).

Elevated levels of aldosterone are also implicated in the pathophysiology of hypertension. In addition to its classic actions of sodium and fluid retention, aldosterone contributes to increased vascular inflammation and fibrosis (Martinez 2010). These actions promote vascular remodelling and therefore can contribute to the development of atherosclerosis and hypertension (Martinez 2010).

Some researchers oppose the idea that sympathetic activation is the sole contributory mechanism affecting the kidney and therefore elevating BP (Esler, Lambert, and Schlaich 2010). Instead the intrarenal system and the interaction between Ang II and AT-1 receptors may be implicated in the development of hypertension (Crowley, Gurley, Herrera, et al. 2006). This interaction within the kidney has been shown to be associated with renal vasoconstriction and anti natriuresis (Crowley, Gurley, Herrera, et al. 2006) and researchers argue that it is this effect that is dominant in the pathophysiology of hypertension. Of course, it is recognised that heightened angiotensin II activity is due in part to elevated sympathetic tone, however research has also shown the angiotensin-II levels are high despite ACE inhibition (Navar, Kobori, and Prieto-Carrasquero 2003) supporting the theory that intrarenal angiotensin II can be formed locally (Navar, Imig, Zou, et al. 1997). Their actions may therefore be involved in the pathophysiology of hypertension in the absence of autonomic dysfunction.

2.ii.c Role of Natriuretic Peptides in regulation of blood pressure

In 1981, Adolfo J De Bold discovered that atrial extracts had both natriuretic and vasodilatory properties. Later came the identification of atrial natriuretic peptide (ANP) and B-type/brain natriuretic peptide (BNP), both involved in long-term regulation of BP and fluid balance (de Bold 2011). These hormones are stored in the atrial myocytes and are secreted in response to both mechanical (atrial distension) and neurohumoral (Ang II, endothelin, sympathetic stimulation) factors (de Bold 2011). The actions of natriuretic peptides (NP) are in opposition to that of angiotensin II, their functions are therefore counter-regulatory to the RAAS.

The secretion of NP facilitates natriuresis (excretion of sodium) and diuresis (urine production) via an increase in glomerular filtration rate. This process reduces renin release and as a result reduces Ang II formation, subsequently reducing aldosterone release from the adrenal cortex. Collectively, these actions reduce blood volume, leading to a fall in central venous pressure, cardiac output and arterial BP (Klabunde 2012).

2.ii.d Role of natriuretic peptides in the pathophysiology of hypertension

The participation of ANP and BNP in the pathophysiology of hypertension is still up for debate. In animal models, it has been shown that a deliberate disruption of ANP receptor genes resulted in hypertension (John, Krege, Oliver, et al. 1995). In addition, rats with hypertension showed a lower peptide response to atrial distension (Onwochei and Rapp 1989). In contrast, levels of ANP in hypertensive rats and humans have been shown to be elevated above normal (Schiffrin, St-Louis, and Essiambre 1988; Sagnella, Markandu, Buckley, et al. 1991) however, this may indicate reduced binding of ANP onto vascular receptors thus disenabling its BP lowering effects.

The study of gene types associated with NP has gained some momentum. Chandra and colleagues recently found that ANP gene expression was down-regulated in patients with essential hypertension (Chandra, Saluja, Narang, et al. 2015). In addition, researchers have shown specific gene variations associated with increased levels of circulating NP and consequently a lowered risk of developing hypertension (Newton-Cheh, Larson, Vasan, et al. 2012).

Research into the association between NP and hypertension continues. In the meantime, the development of NP therapeutic strategies are currently under rigorous development and clinical experiments (Volpe, Rubattu, and Burnett 2014).

2.iii Vascular factors

The endothelium, consisting of endothelial cells is located on the inner lining of all blood vessels. Although not generally classified as a short or long-term BP regulating mechanism, the responsiveness and therefore healthy functioning of the endothelium is of prime importance when it comes to regulating appropriate

vascular tone when under the influence of vasoactive hormones (Ang II, norephinephrine) detailed within the earlier parts of this chapter (see section 2.ii).

Investigations into the role of the endothelium in regulating vascular tone and therefore BP saw a surge in the late 1970's. In 1980, Furchgott and Zawadski were instrumental in discovering the vital role played by the endothelium in producing an endothelial-derived relaxing factor (EDRF) resulting in the relaxation of the arterial wall (Furchgott and Zawadzki 1980). Following on from this discovery, Furchgott suggested that the EDRF was nitric oxide (NO) and later in 1988 Palmer and colleagues confirmed his suggestions and later discovered it to be generated from its antecedent L-arginine by endothelial NO synthase (Palmer, Ashton, and Moncada 1988). In the late 1980's research highlighted the ability of the endothelium to induce vasodilation in response to increases in blood flow (shear stress), a process now known as endothelium-dependent flow mediated vasodilation (FMD) (Pohl, Holtz, Busse, et al. 1986). The effects of shear stress were recognised to effect the production of vasodilating substances like NO (Tinken, Thijssen, Hopkins, et al. 2010) and prostacyclin (Eskurza, Seals, DeSouza, et al. 2001). The importance of NO in BP regulation has been shown in a number of animal and human studies whereby NO synthase was pharmacologically inhibited. This inhibition has been shown to result in vasoconstriction and a rise in systemic BP (Chowdhary and Townend 2001).

As a way of maintaining homeostasis, an endothelin-derived constricting factor (EDCF), endothelin-1 (ET-1), works to oppose the effects of NO. This powerful vasoconstricting peptide was discovered by researchers in Japan in 1988 (Yanagisawa, Kurihara, Kimura, et al. 1988). The synthesis of ET-1 is stimulated by a number of factors including Ang II (see section 2.ii) and thrombin; a blood coagulating factor whose activity is heightened during periods of inflammation (González, Valls, Brito, et al. 2014).

2.iii.a Role of vascular factors in the pathophysiology of hypertension

Endothelial dysfunction (ED) is characterised by a disturbance in the pathway that promotes the synthesis of the anti-inflammatory and vasoactive dilators like NO and prostacyclin; thus leading to a predominance of pro-inflammatory vasoconstrictors like ET-1 and Ang-II. With studies showing reduced vasodilating capabilities in hypertensive subjects (Linder, Kiowski, Buhler, et al. 1990; Panza, Casino, Kilcoyne, et al. 1993). The association between ED and hypertension has been established, the question remains whether hypertensive subjects have an impaired ability to synthesise the predominant vasodilator NO or whether its reduced bioavailability is secondary to hypertension that is originating from autonomic dysfunction and/or humoral factors.

Studies in the early 90's showed an impaired response to the neurotransmitter acetylcholine in hypertensive subjects, suggesting an abnormality of vascular NO bioactivity in hypertension (Linder, Kiowski, Buhler, et al. 1990; Panza, Casino, Kilcoyne, et al. 1993). However, this response is not consistent with other studies and

in a larger trial by Cockroft and colleagues results showed no impairment in vasodilator responses to muscarinic agonists (Cockroft, Chowienczyk, Benjamin, et al. 1994). This larger investigation alongside similar findings by the same research group (Kneale, Chowienczyk, Brett, et al. 1999) has led to the suggestion that a reduction in the synthesis of NO is not a cause of hypertension but an effect (Chowdhary and Townend 2001). In support of this suggestion, Milgard and Lind showed that endothelium-dependent dilation is immediately impaired by acute increases in BP in healthy normotensive participants (Millgard and Lind 1998)

Because hypertension is widely associated with endothelial dysfunction (e.g. decreased NO bioavailability) in addition to increased levels of sympathetic activity, it has been suggested that the autonomic nervous system may be an important factor affecting the behaviour of endothelial function (Amiya, Watanabe, and Komuro 2014). However, the mechanism for this effect has not been widely documented. In 2002, Hijmering and colleagues set upon linking sympathetic nerve activity and endothelial dysfunction (Hijmering, Stroes, Olijhoek, et al. 2002). They found that increased levels of sympathetic activity blunted flow mediated dilation and subsequently NO release. It was suggested that there was indeed a link between the sympathetic system and the production of the endothelium derived relaxing factor, NO.

The decrease in the bioavailability of NO and its negative effects on endothelial function may ultimately lead to the development of hypertension via a couple of mechanisms. Firstly, ET-I is no longer exposed to the counterproductive effects of NO and therefore its vasoconstricting actions become predominant. Secondly without the anti-oxidant and anti-inflammatory actions of NO, the vasculature becomes exposed to the pro-oxidant and pro-inflammatory actions of Ang-II and ET-1, therefore leading to an increase in reactive oxygen species (ROS) and thus oxidative stress and inflammation. Markers of oxidative stress have been shown to be elevated in hypertensive individuals indicating that oxidative stress is involved in the pathophysiology of hypertension (Rodrigo, Prat, Passalacqua, et al. 2007).

The production of ROS, namely superoxide anion (González, Valls, Brito, & Rodrigo, 2014), encourages structural alterations of vascular smooth muscle cells including cell proliferation, growth and hypertrophy, in addition to the promotion of adhesion molecules to endothelial cells (Fortuño, San José, Moreno, et al. 2005). These actions contribute to the narrowing and stiffening of the arterial lumen and furthermore to increased peripheral resistance and therefore increased BP (Fortuño, San José, Moreno, et al. 2005).

Whilst the reduction of NO may be a result of increased sympathetic activity (Hijmering, Stroes, Olijhoek, et al. 2002), the increased presence of ET-1 and Ang-II seen in hypertensive subjects (Mancia et al., 1999; Saito, Nakao, Mukoyama, & Imura, 1990) may also be due to autonomic dysfunction. Heightened sympathetic activity, leading to RAAS over-activation (see section 2.ii.b) contributes to the increase in Ang-II and therefore in oxidative stress and inflammation (González, Valls, Brito, et al. 2014; Hitomi, Kiyomoto, and Nishiyama 2007). This not only encourages the production of ROS but it also functions to mobilise ET-1 which in turn participates in the production of ROS (González, Valls, Brito, et al. 2014). The actions of ROS and the resulting

effects on the stiffening of the arterial lumen (Wu, Xia, Kalionis, et al. 2014; Sun 2014) may also contribute to reduced baroreflex sensitivity – thus continually reducing sympathetic withdrawal in response to high arterial pressure (see section 2.i.a).

2.iv Summary

Blood pressure is regulated by neural, hormonal and local vascular factors. The baroreflex and chemoreflex are key negative feedback systems that regulate BP through changes in the autonomic nervous system. The RAAS is the most influential hormonal system involved in the long-term regulation of BP; the RAAS is active in the kidneys and regulates fluid volume. Natriuretic peptide hormones are counter regulatory to the RAAS. Endothelial function is a key vascular factor that influences BP regulation. The responsiveness and therefore healthy functioning of the endothelium is of prime importance when it comes to regulating appropriate vascular tone. Vasodilating and vasoconstricting substances ensure the appropriate regulation of vascular tone and therefore BP.

Whilst these factors are key BP regulators, a dysfunction in one or more of these can predispose an individual to sustained rises in BP and therefore hypertension. As described in section 2.i a reduction in the sensitivity of the baroreflexes or heightened sensitivity of chemoreflexes can alter the effective responsiveness of the autonomic nervous system affecting appropriate autonomic balance. Hormonal factors such as heightened activation of the RAAS can also contribute to the development of hypertension (Esler, Lambert, and Schlaich 2010); with increased levels of Ang II (Higuchi, Ohtsu, Suzuki, et al. 2007) and aldosterone (Stiefel, Vallejo-Vaz, García Morillo, et al. 2011) specifically implicated in its development. Finally ED can lead to hypertension due to the reduction in anti-inflammatory and vasoactive dilators like NO and prostacyclin and a resulting predominance of pro-inflammatory vasoconstrictors like ET-1 and Ang-II.

The autonomic nervous system is effected and/or affected by all three regulatory mechanisms. Therefore a derangement in one or more of these mechanisms can cause or be caused by an imbalance in the autonomic nervous system (i.e. heightened sympathetic nerve activity and suppression of cardio-vagal nerve activity). This places the autonomic nervous system central to the pathophysiology of hypertension (Thayer, Yamamoto, and Brosschot 2010). The influence of exercise on this system may therefore provide key mechanistic insight into BP management strategies. The effects of exercise, in particular isometric exercise on the function of the autonomic nervous system are discussed in section 2.6.

2.1 Exercise prescription for blood pressure management

International guidelines recommend that hypertensive adults engage in aerobic exercise at a moderate (Ghadieh and Saab 2015; Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013) or moderate-vigorous (James, Oparil, Carter, et al. 2014; Brook, Appel, Rubenfire, et al. 2013) intensity for 30-60 minutes on 5-7 days of the week. In addition to aerobic exercise training, dynamic resistance on 2-3 days per week is recommended by some organisations (Ghadieh and Saab 2015; James, Oparil, Carter, et al. 2014; Mancia, Fagard, Narkiewicz, et al. 2013; Pescatello, Franklin, Fagard, et al. 2004a). Isometric exercise is currently only recommended as an adjunct therapy by the American Heart Association (James, Oparil, Carter, et al. 2014) and Hypertension Canada (Ghadieh and Saab 2015); however, in light of consistently positive findings (Inder, Carlson, Dieberg, et al. 2016) this recommendation is likely to be included in future international guidelines. The following sections review each exercise modality and its effect on BP following a single exercise session (acute effects) and a period of exercise training (chronic effects). A more detailed review on isometric exercise training and BP management is provided.

2.1.1 Aerobic exercise

Aerobic exercise is the most widely researched and recommended exercise modality for BP management (Pescatello, Macdonald, Lamberti, et al. 2015). One of the reasons that aerobic exercise is recommended for most days of the week is because BP has been shown to be lower in the hours following an exercise bout (Pescatello, Macdonald, Lamberti, et al. 2015). This phenomenon is called post exercise hypotension (PEH) (Thompson, Crouse, Goodpaster, et al. 2001; Cardoso, Gomides, Queiroz, et al. 2010; Park, Rink, and Wallace 2006) and has been shown to occur in both normotensive and hypertensive participants (Pescatello, Franklin, Fagard, et al. 2004a; Carpio-Rivera 2016) following a single aerobic exercise session of varying intensities (40-100% VO_2 max) and durations (15-50 minutes) (Pescatello, Macdonald, Lamberti, et al. 2015). For this reason, PEH is considered to be an important physiological phenomenon playing a crucial role in BP management (Kenney and Seals 1993).

The magnitude of resting systolic and diastolic BP reductions following aerobic exercise cessation is approximately -6/4mmHg (Carpio-Rivera 2016). However the magnitude and duration of the BP response varies widely between studies (Cardoso, Gomides, Queiroz, et al. 2010; Carpio-Rivera 2016) suggesting that mode of measurement (resting or ambulatory), participant and exercise characteristics are likely to influence the findings. Findings have shown that baseline BP influences the magnitude of PEH, with hypertensive participants benefiting from larger systolic BP reductions as compared with normotensive and pre-hypertensive participants (Cardoso, Gomides, Queiroz, et al. 2010). Ambulatory recordings show a wide range of responses; findings have revealed that hypertensive participants experience a BP reduction ranging

from -2 to -12mmHg over a period of 2-24 hours (Pescatello and Kulikowich 2001; Brandao Rondon, Alves, Braga, et al. 2002; Cardoso, Gomides, Queiroz, et al. 2010; Thompson, Crouse, Goodpaster, et al. 2001) whilst the majority of studies on normotensive participants do not find an ambulatory effect (Cardoso, Gomides, Queiroz, et al. 2010).

The influence of aerobic exercise intensity on the magnitude of PEH is controversial with a meta-analysis reporting reductions following low, moderate and high-intensity exercise (Cardoso, Gomides, Queiroz, et al. 2010). Recent findings suggest that individuals with resistant hypertension benefit from similar BP reductions in the 5 hours following both light and moderate intensity exercise; however, the reduction following light intensity exercise was sustained over a longer period of time (10 hours) (Santos, Moraes, Vieira, et al. 2016). In contrast, De Morais and colleagues found that a maximal exercise bike ergometer test reduced 24-hour average, daytime and night-time ambulatory BP whereas moderate intensity exercise (20minutes @ 90% lactate threshold) did not have an effect (De Morais, SALES, De Almeida, et al. 2015) in pre-hypertensive participants.

Aside from PEH being advantageous in contributing to day to day BP management, the merits of PEH are further supported by studies showing that the BP response to acute exercise is strongly correlated with chronic BP reductions following aerobic training (Kiviniemi, Hautala, Karjalainen, et al. 2015; Liu, Goodman, Nolan, et al. 2012). This strong correlation suggests that PEH could be used as a screening tool to identify hypertensive individuals who will respond to exercise as antihypertensive treatment.

Meta-analyses have shown that aerobic training programmes lasting up to 24 weeks have revealed reductions in resting systolic and diastolic BP (-3 to -4/-2 to -3mmHg) (Cornelissen and Fagard 2005; Cornelissen and Smart 2013). Similar to PEH, a more pronounced reduction in resting BP has been found in hypertensive participants (-7 to -11/-5mmHg) (Cornelissen and Fagard 2005; Cornelissen and Smart 2013; Börjesson, Onerup, Lundqvist, et al. 2016). Börjesson and colleagues conducted the largest analysis of aerobic activity and BP in hypertensives (n=1480). When compared with other reviews their findings revealed a larger systolic BP reduction of -10.8mmHg (Börjesson, Onerup, Lundqvist, et al. 2016). The augmented systolic effect could be related to the fact that the trials included in this review were of a moderate and high exercise intensity only. Low intensity trials were excluded. Evidence suggests that moderate or high intensity exercise training elicits similar chronic adaptations (Millar and Goodman 2014) whereas exercise training at low intensities reduces its effectiveness (Cornelissen and Smart 2013). The inclusion of low intensity studies in previous meta-analyses may have contributed to the reduced effect reported in hypertensive adults (Cornelissen and Fagard 2005; Cornelissen and Smart 2013).

Findings from other studies have also reported chronic reductions in daytime ambulatory BP (-3.3/-3.5mmHg) (Cornelissen and Fagard 2005, Cardoso et al. 2010, Cornelissen et al. 2013). Unlike observations on resting BP data, larger reductions in ambulatory BP have not been observed in hypertensive participants

as compared with normotensives (Cornelissen et al. 2013); however, the smaller number of studies assessing ambulatory BP limits the conclusiveness of this finding.

2.1.2 Dynamic resistance exercise

In comparison to the widely recommended use of aerobic training as a non-pharmacological antihypertensive therapy, the use of dynamic resistance exercise training is not normally recommended as a stand-alone exercise therapy but only recommended by some organisations as an adjunct therapy in BP management (Ghadieh and Saab 2015; James, Oparil, Carter, et al. 2014; Mancia, Fagard, Narkiewicz, et al. 2013; Pescatello, Franklin, Fagard, et al. 2004a).

Research to date supports the existence of PEH in response to an acute bout of dynamic resistance exercise in both normotensive (Keese, Farinatti, Pescatello, et al. 2011; Moraes, Bacurau, Ramalho, et al. 2007; Moreira, Cucato, Terra, et al. 2016; Queiroz, Sousa, Cavalli, et al. 2015) and hypertensive (Queiroz, Sousa, Cavalli, et al. 2015; Mota, Oliveira, Dutra, et al. 2013; De Brito, Rezende, Da Silva, et al. 2015; Hardy and Tucker 1998) individuals. A meta-analysis carried out in 2016 indicated that hypertensive participants experience a reduction of -9/-5mmHg following an acute bout of resistance exercise, whilst normotensives experience a smaller hypotensive response (-3/2.7mmHg) (Casonatto, Goessler, Cornelissen, et al. 2016). However, unfortunately these BP reductions have only been observed in the 60-90 minutes after an acute bout of dynamic resistance training (Casonatto, Goessler, Cornelissen, et al. 2016) and the lasting effect of PEH, as measured by ambulatory BP, is not well supported (Moraes, Bacurau, Ramalho, et al. 2007; Hardy and Tucker 1998; Queiroz, Sousa, Cavalli, et al. 2015; Cardoso, Gomides, Queiroz, et al. 2010); further investigation, particularly amongst hypertensive participants is required (Casonatto, Goessler, Cornelissen, et al. 2016).

Although the evidence supports a short-term hypotensive response following a bout of dynamic resistance training, research supporting dynamic resistance training is weak. Several meta-analyses have been carried out with varying conclusions. Four meta-analyses have concluded that dynamic resistance training performed over a number of weeks has no beneficial effect on resting or ambulatory BP in hypertensive and normotensive participants (Cornelissen and Smart 2013; Börjesson, Onerup, Lundqvist, et al. 2016; Cardoso, Gomides, Queiroz, et al. 2010; Cornelissen and Fagard 2005). In contrast to hypertensive and normotensive adults, the meta-analysis carried out in 2013 suggests that pre-hypertensive adults experience a reduction in resting BP (-4/-3.8mmHg) following training carried out over a number of weeks (Cornelissen and Smart 2013). These findings on pre-hypertensive adults are in agreement with another meta-analysis carried out by MacDonald et al., (2016). However, in addition, findings from this meta-analysis also showed that hypertensives reduced their BP by 6/5mmHg; this finding disagrees with those of previous meta-analyses (Cornelissen and Smart 2013; Börjesson, Onerup, Lundqvist, et al. 2016; Cardoso, Gomides, Queiroz, et al.

2010; Cornelissen and Fagard 2005). This discrepancy is curious but might be explained by the small number of trials analysed (lowering the power of the meta-analyses) and the inclusion of well-controlled hypertensive participants (Cornelissen and Smart 2013; Börjesson, Onerup, Lundqvist, et al. 2016; Cardoso, Gomides, Queiroz, et al. 2010; Cornelissen and Fagard 2005); this would negate the potentially greater impact of resistance training on those with a higher baseline BP. In support of this, MacDonald and colleagues (2016) studied a larger number of trials (n=71) and although findings showed an overall BP decrease in hypertensives a sub-group analysis found no effect on medicated (i.e. well-controlled) hypertensives.

In addition, findings from individual studies have shown that those with higher baseline BP respond most positively to dynamic resistance training (Moraes, Bacurau, Ramalho, et al. 2007; Moreira, Cucato, Terra, et al. 2016) and therefore add strength to this theory. However, the evidence support the chronic effects of dynamic resistance training still remains relatively weak and further research is warranted on this topic (MacDonald, Johnson, Huedo-Medina, et al. 2016).

2.1.3 Isometric exercise

To date, meta-analyses have revealed consistent reductions in resting BP following isometric training programmes (Cornelissen et al. 2013, Carlson et al. 2014, Cornelissen et al. 2011, Inder et al. 2016). However, due to the limited research, the American Heart Association (James, Oparil, Carter, et al. 2014) and Hypertension Canada (Ghadieh and Saab 2015) are currently the only organisations that recommend isometric exercise for antihypertensive benefits.

As compared with aerobic and dynamic resistance exercise, research on the effects of isometric exercise on PEH is limited and findings are varied. Some studies have reported the presence of PEH (Stewart, Montgomery, Glover, 2007; Millar *et al.*, 2009; Van Assche *et al.*, 2016) and others have not found an acute hypotensive effect (Ash et al. 2016, Goessler et al. 2016, Olher et al. 2013). Overall, exercise protocols are varied and have included 4x2minute handgrip contractions at 30% MVC (Millar et al. 2009a, Ash et al. 2016, Van Assche et al. 2017, Goessler et al. 2016), a single 2-minute handgrip contraction at 35% MVC (Stewart, Montgomery, Glover, et al. 2007) and 20 x 10 second handgrip contractions at 30 and 50% MVC (Olher, Bocalini, Bacurau, et al. 2013). Out of the three studies that reported hypotensive effects of isometric exercise, one measured ambulatory BP (Van Assche *et al.*, 2016) whilst two studies only measured hypotensive effects at 5 minutes (Millar, Bray, MacDonald, et al. 2009) and 1 minute (Stewart, Montgomery, Glover, et al. 2007) post exercise. The reductions seen in the early minutes following exercise can be attributed to the sudden perfusion of previously occluded muscle mass (Macdonald 2002). This mechanism results in a transient pressure undershoot and has been suggested that the hypotension as a result of this should not be defined as PEH (Macdonald 2002). Measuring beyond the very early post exercise stage, ambulatory recordings carried out by Van Assche and colleagues observed a SBP hypotensive response (-

5.4mmHg) recorded for 6 hours post isometric exercise (Van Assche, Buys, De Jaeger, et al. 2017). However, despite a similar population group, Ash et al., (2016) did not echo these findings and reported no BP reductions over a 19-hour ambulatory recording despite observing hypotensive effects following an aerobic exercise bout. In summary, only one study has documented a PEH response beyond the first 5 minutes of completing isometric exercise (Van Assche, Buys, De Jaeger, et al. 2017) and therefore the existence of this phenomenon in isometric exercise remains under debate.

In contrast to the mixed findings on PEH following an acute bout of isometric exercise, meta-analyses provide strong evidence in support of chronic BP adaptations following isometric training programmes (Cornelissen et al. 2013, Carlson et al. 2014, Cornelissen et al. 2011, Inder et al. 2016). Findings from these meta-analyses are varied with isometric exercise training showing reductions of -13.5/-6.1mmHg (Cornelissen et al. 2011), -10.9/-6.2mmHg (Cornelissen et al. 2013), -6.7/-3.9mmHg (Carlson et al. 2014) and -5.2/-3.91mmHg (Inder et al. 2016) (Table 2.1). Whilst these papers suggest that the magnitude of BP reductions has decreased over time, it is important to note that the size of each meta-analysis increased over time and therefore as time has progressed each analysis benefited from more data, thus making the process more rigorous and more representative of isometric training effects. For example, Cornelissen et al., (2011) included the three isometric training randomised control trials (n=81) available at the time of analysis whilst five years later, Inder et al., (2016) included the 11 isometric training randomised control trials available (n=302).

Due to the small number of studies available to analyse, subgroup analysis between population groups (normotensive, pre-hypertensive, unmedicated hypertensive, medicated hypertensive) was not attempted until 2016 (Inder et al. 2016). Findings from Inder et al. showed that hypertensive individuals experienced a larger decrease in mean arterial pressure (-5.91mmHg) as compared to normotensive individuals (-3.01mmHg). There remains a paucity of data for further subgroup analysis between medicated and non-medicated hypertensives.

Table 2.1: Summary of a meta-analysis carried out on the effects of isometric exercise training on resting blood pressure (Inder *et al.,* 2016).

Reference	Included studies	Blood pressure status	Participant (N)	Major findings
Inder et al., 2016	Badrov et al., 2013	Normotensive	302	SBP -5.2mmHg
	Badrov et al., 2013	Hypertensive (Medicated)		DBP -3.91mmHg
	Baross et al., 2013	Pre-hypertensive and hypertensive (non-medicated)		**Subgroup analyis**
	Baross et al., 2012	Pre-hypertensive and hypertensive (non-medicated)		
	Devereaux et al., 2011	Normotensive		Hypertensive
	Gill et al., 2015	Normotensive		MAP -5.91
	Millar et al., 2008	Normotensive		
	Stillar-Maldoven et al., 2012	Hypertensive (medicated)		Normotensive
	Taylor et al., 2003	Hypertensive (medicated and non-medicated)		MAP -3.01
	Wiles et al., 2010	Normotensive		
	Wiley et al., 1992	Pre-hypertensive		

However, it is important to note that, to date, only ten studies have specifically investigated the effects of isometric training in pre-hypertensive and hypertensive (medicated and unmedicated) populations (Table 2.2). Studies carried out on these population groups have found significant resting SBP reductions ranging from -5mmHg to -13mmHg and DBP reductions ranging from -5mmHg to -15mmHg. Only one study reported no significant changes in SBP (Stiller-Moldovan, Kenno, and McGowan 2012) whilst six studies reported no significant changes in DBP (Taylor, McCartney, Kamath, et al. 2003; McGowan, Visocchi, Faulkner, et al. 2007; Stiller-Moldovan, Kenno, and McGowan 2012; Baross, Wiles, and Swaine 2012, 2013). Changes in mean arterial pressure (MAP) are not commonly reported; however, some studies report reductions between -11mmHg and -5mmHg (Taylor, McCartney, Kamath, et al. 2003; Baross, Wiles, and Swaine 2012, 2013; Badrov, Horton, Millar, et al. 2013; Millar, Levy, Mcgowan, et al. 2013) with others reporting no change (McGowan, Levy, Millar, et al. 2006). Mean arterial pressure is an important variable in the measurement of BP as it represents the average pressure during each cardiac cycle and alongside SBP and DBP is strongly associated with cardiovascular disease risk (Hadaegh, Shafiee, Hatami, et al. 2012; Sesso, Stampfer, Rosner, et al. 2000). This thesis will investigate changes in MAP in addition to systolic and diastolic BP.

Reasons for varied responses between training studies in the pre-hypertensive and hypertensive population have yet to be fully defined. However, taking the findings on the medicated hypertensive population (Taylor, McCartney, Kamath, et al. 2003; McGowan, Visocchi, Faulkner, et al. 2007; Stiller-Moldovan, Kenno, and McGowan 2012; Badrov, Horton, Millar, et al. 2013; Millar, Levy, Mcgowan, et al. 2013) the impact of pre-training blood pressure values is worthy of mention. These five studies are consistent in terms of intensity (30% MVC), duration (2minutes), number of repetitions (4 repetitions) and isometric exercise type (handgrip) but differences in pre-training BP levels vary widely. For example, Taylor et al. (2003) recruited participants whose baseline BP was 156±9.4/82.3±9.3mmHg and Millar et al. (2013) recruited participants with baseline values of 125±3/78 ± 2mmHg (Table 2.2). The reduction in SBP reported in these studies was -19mmHg and -5mmHg respectively. In addition, Stiller-Moldovan recruited medicated participants whose mean baseline values were within optimal BP ranges (113±12.7/60.7±11.6mmHg). They found no significant effects of alternate handgrip isometrics on resting BP. However, this finding is in contrast to studies that recruited young healthy participants with baseline values within similar ranges (Wiley, Dunn, Cox, et al. 1992; Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Bartol, Dibartolomeo, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015).

In the case of the well-controlled hypertensive participant the effects of anti-hypertensive medication may involve an overlap between the mechanisms mediating the effects of isometric training (Millar, Bray, McGowan, et al. 2007); this could explain the lack of change in the well-controlled hypertensive participant as compared with normotensives who are not medicated. However, insufficient information is currently available with regards to specific medications and their relationship with an individual's responsiveness to

isometric exercise training. This thesis will not attempt to determine medication effects or delineate BP responses in medicated or un-medicated participants but will recruit older individuals (>55years) with a low cardiovascular risk who are displaying baseline BP within the pre-hypertension and stage 1 hypertension ranges (130-159/85-99). Isometric exercise is recommended as an alternative exercise modality for BP management in this specific population group (James, Oparil, Carter, et al. 2014) and they are therefore most likely to be prescribed it within the clinic environment (McGowan, Proctor, Swaine, et al. 2017). Considering the small number of randomised controlled studies conducted on individuals with baseline BP within this range (Wiley, Dunn, Cox, et al. 1992; Taylor, McCartney, Kamath, et al. 2003; Baross, Wiles, and Swaine 2013; Millar, Levy, Mcgowan, et al. 2013), continued research on this population group is required.

Another reason for varied BP responses could be related to differences in the training stimulus which is made up of the relative exercise intensity (% MVC), muscle mass recruited (handgrip, bilateral legs) and programme length (number of weeks) (Hess, Carlson, Inder, et al. 2016; Lawrence, Cooley, Huet, et al. 2014). The independent effect of isometric exercise intensity remains unclear. Handgrip intensity is normally set at 30% MVC (Wiley, Dunn, Cox, et al. 1992; Taylor, McCartney, Kamath, et al. 2003; McGowan, Visocchi, Faulkner, et al. 2007; Millar, Bray, McGowan, et al. 2007; Badrov, Bartol, Dibartolomeo, et al. 2013); however some bilateral leg training protocols have found beneficial effects using intensities as low as ~10%MVC in normotensive (Wiles, Coleman, and Swaine 2010) and ~14% in pre-hypertensive and hypertensive participants (Baross, Wiles, and Swaine 2012).

To understand the effects of isometric exercise intensity, some studies that have made side by side comparisons of varying exercise intensities have been carried out on bilateral leg isometric protocols (Gill, Arthur, Swaine, et al. 2015; Baross, Wiles, and Swaine 2012; Wiles, Coleman, and Swaine 2010; Hess, Carlson, Inder, et al. 2016). Findings have shown that isometric exercise performed at both 21% MVC and 10% MVC elicits significantly positive BP reductions in normotensive males (Wiles, Coleman, and Swaine 2010). However, Gill et al., (2015) found that differing contraction intensities impacted on BP reductions with contractions carried out at 34% MVC eliciting positive reductions whilst those at 23% MVC did not improve BP. Similarly Baross et al., (2012) found BP improvements following isometric leg contractions at 14% MVC but not at 7% MVC. Some of these differences could be explained by total exercise volume (contraction duration X number of repetitions X sessions per week X total number of weeks). The training volume prescribed by Gill and colleagues (2015), who found that the lower intensity (24% MVC) did not lower resting BP, equalled 72minutes, this was compared to 192minutes prescribed by Wiles et al., (2010) who found that the lower intensity (10% MVC) still elicited a positive change. This suggests that isometric contraction intensity may be compensated for by increased training volume. However, despite a comparable exercise volume (192minutes) to that of Wiles et al., (2010) findings from Baross *et al*., (2012) showed that bilateral leg exercise at 8% MVC did not elicit any change thus suggesting that a certain stimulus level is likely to be required.

To date, the only isometric handgrip intensity prescribed to pre-hypertensive adults and hypertensive adults has been 30% MVC (Wiley, Dunn, Cox, et al. 1992; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; McGowan, Visocchi, Faulkner, et al. 2007; Stiller-Moldovan, Kenno, and McGowan 2012; Badrov, Horton, Millar, et al. 2013; Millar, Levy, Mcgowan, et al. 2013; Ash, Taylor, Thompson, et al. 2016) and 50% MVC (Peters, Alessio, Hagerman, et al. 2006). Although this method has been successful to date (Table 2.2) it presents some limitations, especially within this population group. Firstly, specialised programmable handgrip devices or dynamometers, designed to calculate %MVC prior to the beginning of each exercise session, are required. These are somewhat expensive and some dynamometers can only be used in the laboratory. Secondly, the calculation of %MVC requires 2-3 all-out maximal efforts, which might present a limitation in some groups of participants, especially in those with frailty. Some older adults are limited in maximal gripping, due to the prevalence of varying degrees of arthritic pain in the hand (Arthritis Research UK 2017). In addition, maximal contractions pose a risk of carrying out a Valsalva manoeuvre (O'Connor, Sforzo, and Frye 1989) in addition to causing large and abrupt increases in SBP (Pescatello *et al.*, 2004b). Maximal contractions should therefore be avoided in those at high cardiovascular risk (Pescatello, Franklin, Fagard, et al. 2004b). If this type of exercise is to benefit older people with hypertension (or who are at risk of hypertension) then it must be simple to use, affordable, home-based and ideally it must avoid maximal effort. There has been little exploration of alternative ways to regulate isometric handgrip intensity for the management of BP. Considering that the ACSM recommend the use of the rate of perceived exertion to regulate aerobic exercise for BP management it would seem pertinent to explore the validity of this method of exercise prescription (Chapter 5).

Table 2.2: Studies examining the effects of isometric exercise training on resting blood pressure in pre-hypertensive and hypertensive (medicated and unmedicated) participants

Reference	Participants	Age	Baseline BP (SBP/DBP)	BP status	Method of BP determination	Exercise mode	Exercise programme	Intensity	Duration	Major findings
Wiley (1992)	Ex: 8 Con:10	20-35	134.1±0.95 /86.5±2.01 134±3.3/83.4 ±6.7	Pre-hypertensive	Automated oscillometric device	Unilateral IHG	4x2min, 3-min rest, 3x/week	30% MVC	8 wks	SBP -13mmHg DBP -15mmHg
Baross et al., (2012)	Ex: 10	54.6 ±5.5	139.1± 2.2 /78.9 ± 10.3	Pre-hypertensive and unmedicated hypertensive	Continuous non-invasive recording	Bilateral leg extension	4x2min, 2-min rest, 3x/week	85% HRpeak	8 wks	SBP -11mmHg No change DBP MAP-5mmHg
	Ex:10 Con:10	53.6 ±5.5 53.6 ±4.5	137.3±5.3 /78.3± 5.5 138.7± /78.2±5.5					70% HRpeak		No change BP
Baross et al., (2013)	Ex: 10 Con:10	53±5 55±6	139±7 /85±14 139±8 /85±7	Pre-hypertensive and unmedicated hypertensive	Continuous non-invasive recording	Bilateral leg extension	4x2min, 2-min rest, 3x/week	85% HRpeak (~14% MVC)	8 wks	SBP -11mmHg No change DBP MAP -5mmHg
Ash et al., (2016)	Ex:5	43±5 .3	134±2.7/78.4 ±2.3	Pre-hypertensive and unmedicated Hypertensive	Automated oscillometric device	Bilateral IHG	4x2min, 2-min rest, 3x/week	30% MVC	8wks	No change ABP Night DBP +7.7mmHg

Table 2.2 (continued). Studies examining the effects of isometric exercise training on resting blood pressure in pre-hypertensive and hypertensive (medicated and unmedicated) participants

Reference	Participants	Age	Baseline BP (SBP/DBP)	BP status	Method of BP determination	Exercise mode	Exercise programme	Intensity	Duration	Major findings
Peters et al., (2006)	Ex: 10	52±5	146± 11 /90±7	Unmedicated Hypertensive	Not reported	Alternating unilateral IHG	4x45s, 1-min rest, 3x/week	50% MVC	6 wks	SBP -13mmHg No change DBP
Taylor et al., (2003)	Ex: 9	69±6	156±9.4 /82.3±9.3	Medicated hypertensive	Not reported	Alternating unilateral IHG	4x2min, 1-min rest, 3x/week	30% MVC	10 wks	SBP -19mmHg MAP -11mmHg No change DBP
	Con: 8	64.2 ±5.5	152±7.8/87. 1±10.8							
McGowan et al., (2006)	Ex: 17	67±6	126.9 ±2.4 /72.2 ± 2.0	Medicated hypertensive	Not reported	Unilateral IHG	4x2min, 4-min rest, 3x/week	30% MVC	8 wks	No change MAP
McGowan et al., (2007)	Ex: 7	62 ±11	133.9 ±5 /73.2±3.2	Medicated hypertensive	Automated oscillometric device	Alternating unilateral IHG	4x2min, 1-min rest, 3x/week	30% MVC	8 wks	SBP -15mmHg No change DBP
	Ex: 9	66±1 9	141.6±3.8 /79.6±3.8	Medicated hypertensive		Unilateral IHG	4x2min, 4-min rest, 3x/week	30% MVC	8 wks	SBP -9mmHg No change DBP
Stiller-Moldovan et al., (2012)	Ex: 11	60±9	113.9±12.7 /60.7±11.6	Medicated hypertensive	Automated oscillometric device	Alternating unilateral IHG	4x2min, 1-min rest, 3x/week	30%MVC	8 wks	No change resting BP No change ABP
	Con: 9	62.7 ±6.1	117.8±14.3 /67.5±4.2							

IHG, isometric handgrip; SBP, systolic blood pressure; DBP, diastolic blood pressure; Ex, exercise; Con, control; MVC, maximal voluntary contraction; ABP,

Ambulatory blood pressure. **NOTE:** no study reported changes in maximal contraction strength post intervention.

Although a reduction in resting BP is a common outcome of isometric exercise training, its effect on ABPM has not been thoroughly investigated. To date, four studies have measured ambulatory BP (Ash, Taylor, Thompson, et al. 2016; Goessler, Buys, VanderTrappen, et al. 2018; Stiller-Moldovan, Kenno, and McGowan 2012; Somani, Baross, Levy, et al. 2017) following isometric handgrip training over 8-10 weeks. All studies instructed participants to carry out 4x2minute contractions at 30% MVC, 3 times per week. Consistent with their findings in resting BP, Stiller-Moldovan et al., (2012) found no significant 24-hour ambulatory BP change in well controlled medicated hypertensive participants. In addition, Ash and colleagues showed no significant change in 19-hr ambulatory systolic BP recordings in a small group of unmedicated pre-hypertensive and stage 1 hypertensives (Ash *et al.*, 2016). However, night time diastolic BP increased (Ash *et al.*, 2016). In contrast to their findings in isometric exercise training, Ash et al., did report significant BP reductions following an aerobic training stimulus, however, subject numbers in each exercise type were small (n=5) and not supported by a non-exercising control group; this should be considered a limitation and further investigation is required (Ash *et al.*, 2016). Although Stiller-Moldovan and colleagues (2012) found no significant changes in ambulatory systolic BP, night time and 24 hour average values showed a promising decrease of 3mmHg and 4mmHg respectively (Stiller-Moldovan, Kenno and McGowan, 2012). More recently, published findings by Somani et al., (2017) reported that 10 weeks of isometric handgrip training significantly induced ambulatory BP reductions in healthy, normotensive participants (Somani *et al.*, 2017) whilst Goessler and colleagues found no change in ambulatory BP in a similar population group (Goessler, Buys, VanderTrappen, et al. 2018). The slightly longer training intervention prescribed by Somani and colleagues (10 weeks versus 8 weeks) may have influenced these disparate findings. However, considering resting BP reductions have been shown following as little as 4 weeks of isometric training (Devereux, Wiles, and Swaine 2010) this would require further investigation. As ambulatory monitoring is arguably a more clinically relevant measurement (NICE 2011), further evidence on the impact of isometric exercise training on both resting and ambulatory BP within a pre-hypertensive and/or mild hypertensive population would be an important progression of the literature to date. This thesis will use 24-hr ambulatory BP monitoring as a key measurement in the detection of BP changes following isometric training (Chapter 6).

2.1.4 Summary of acute and chronic effects of exercise on blood pressure

Currently aerobic exercise is the preferred exercise modality for BP management with a number of organisations recommending that hypertensive patients should participate in at least 30 minutes of moderate intensity (Ghadieh and Saab 2015; Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013) or moderate-vigorous (James, Oparil, Carter, et al. 2014; Brook, Appel, Rubenfire, et al. 2013) intensity exercise on most days of the week. Although aerobic exercise provides the most evidence for an acute hypotensive and chronic hypotensive response to exercise, it is also recommended by some organisations that hypertensive individuals carry out dynamic resistance training as an adjunct to aerobic

exercise (Ghadieh and Saab 2015; James, Oparil, Carter, et al. 2014; Mancia, Fagard, Narkiewicz, et al. 2013; Pescatello, Franklin, Fagard, et al. 2004a).

For the first time, the American Heart Association (James, Oparil, Carter, et al. 2014) and Hypertension Canada (Ghadieh and Saab 2015) has recommended isometric exercise as an alternative approach to hypertension management (Pescatello, Macdonald, Lamberti, et al. 2015). Due to limited data, this recommendation is not wholly supported (Mancia, Fagard, Narkiewicz, et al. 2013) and further evidence supporting its effect on both resting and ambulatory BP monitoring is required. This thesis will contribute to the body of literature examining the effects of isometric exercise on pre-hypertensive and hypertensive participants.

2.2 Adherence to exercise recommended for the management of blood pressure

Despite the plethora of research supporting aerobic training as an effective exercise modality for the management of BP, research suggests that the majority of hypertensive individuals do not participate in the recommended levels of physical activity. For example four studies administered questionnaires to large groups of individuals with hypertension with the aim of determining the adherence rates to healthy lifestyle interventions (Ohta, Tsuchihashi, and Kiyohara 2011; Al-Kaabi, Al-Maskari, Afandi, et al. 2009; Riegel, Moreira, Fuchs, et al. 2012; Baynouna, Neglekerke, Ali, et al. 2014). Findings showed that only 3-33% of individuals participated in the recommended aerobic exercise guidelines. Females and those with a higher body mass index (Riegel *et al.*, 2012) or waist circumference (Al-Kaabi *et al.*, 2009) were significantly less likely to meet the recommended guidelines. Increasing levels of physical activity within the population remains a challenge (Heath, Parra, Sarmiento, et al. 2016).

There are a number of barriers that limit the proportion of adults engaging in aerobic-type exercise. Research has consistently shown time commitment to be a primary barrier to engaging in physical exercise (Dishman, Sallis, and Orenstein 1984). Considering the proportion of time required to meet the recommended aerobic exercise guidelines is it perhaps of no surprise that adherence to this exercise modality is poor. Additional barriers to engaging with aerobic exercise include a lack of self-motivation, pain, lack of enjoyment, poor neighbourhood conditions, cost and lack of convenience (Bethancourt, Rosenberg, Beatty, et al. 2014; Franco, Tong, Howard, et al. 2015; Jefferis, Sartini, Lee, et al. 2014). Physical activity is reported to be particularly low in older people where it is reported that only 15% of men and 10% of women aged between 70-93 years are engaging in >150 minutes of moderate-vigorous physical activity per week (Jefferis, Sartini, Lee, et al. 2014). Further barriers prevent older people from engaging in exercise and physical activity. These barriers have included, fear of injury, lack of mobility, concern about slowing others down and chronic health

conditions (Jefferis, Sartini, Lee, et al. 2014; Franco, Tong, Howard, et al. 2015). Considering the prevalence of hypertension amongst older individuals (Knott and Mindell 2011) it is imperative that accessible and alternative options are available to them.

The simplicity of isometric exercise, alongside the small time commitment required, makes it possible that adherence to this type of training may be superior to that of aerobic training (Carlson, Dieberg, Hess, et al. 2014; McGowan, Proctor, Swaine, et al. 2017). In addition, isometric exercise has the potential to be carried out in a comfortable seated position, at home; these options remove many of the barriers to physical activity that older people face.

However, given that cost and lack of convenience are commonly cited as exercise barriers these must also be considered in the effective prescription of isometric exercise training. The prescription of isometric exercise in training studies has not been cost-effective nor convenient; specialised equipment that is expensive or lab-based is required to record MVC and to also regulate the exercise intensity at 30% MVC. A simpler and more cost-effective method of regulating isometric exercise requires exploration (Chapter 5). Together with the additional benefits of isometric exercise training (time effectiveness, ease of exercise) it is hoped that long-term adherence to this type of exercise regime would be high. To date, research has not addressed long-term adherence levels to isometric exercise training. This thesis will examine adherence to unsupervised, home-based, isometric exercise training (Chapter 6).

2.3 Regulating the intensity of exercise for blood pressure management

Exercise intensity is described as one of the most important exercise prescription variables required to improve physical fitness and maintain health benefits. In relation to BP management, studies on aerobic exercise generally prescribe exercise intensity based on a percentage of an individual's maximal oxygen uptake (VO_2max), heart rate reserve or maximal heart rate (HRmax) (Cornelissen and Smart 2013; Cornelissen, Buys, and Smart 2013). Studies investigating the effects of resistance training prescribe a percentage of one repetition maximum (dynamic resistance) or maximal voluntary contraction (isometric) (Cornelissen and Smart 2013; MacDonald, Johnson, Huedo-Medina, et al. 2016; Millar, Bray, McGowan, et al. 2007).

These exercise prescription methods are useful because they ensure that the prescribed exercise intensity is accurate and consistent – this is useful in research settings. However, the need for specialised equipment could limit the prescription of this exercise to large population groups. In addition, considering that cost and lack of convenience are cited as barriers to adhering to exercise regimes (Bethancourt, Rosenberg, Beatty, et

al. 2014; Franco, Tong, Howard, et al. 2015; Jefferis, Sartini, Lee, et al. 2014), these methods of exercise prescription might not be long-term solutions for BP management.

An increasingly popular way of prescribing intensity is the use of the rating of perceived exertion (RPE) scale (Parfitt, Evans, and Eston 2012). Accepted for its validity in 1973 Borg's tool for rating perceived exertion is now a widely known psychophysiological tool. The 15-point/6-20 scale and category ratio (CR-10) scale are two of the most widely used.

During aerobic exercise, strong linear relationships between HR (Marriott and Lamb 1996; Borg, Hassmén, and Lagerström 1987; Ueda and Kurokawa 1995; Borg and Kaijser 2006; Scherr, Wolfarth, Christle, et al. 2013) lactate (Borg, Hassmén, and Lagerström 1987; Scherr, Wolfarth, Christle, et al. 2013), VO_2 (Goslin and Rorke 1986; Chen, Fan, and Moe 2002) and ventilation (Chen, Fan, and Moe 2002; Utter, Robertson, Green, et al. 2004) have been found. These associations allow an individual's subjective perception of exertion to be used as a secondary measure for determining exercise load/stress (Garber, Blissmer, Deschenes, et al. 2011).The use of the RPE scale in this way is termed the estimation mode – in this condition, RPE is monitored as a dependent response variable during an exercise task (Winter, Jones, Davison, et al. 2007). Research investigating the subjective estimation of exercise intensity has provided reference points along the scales that correspond to a range of important physiological markers of intensity. For example; an RPE of 12-13 on the 6-20 RPE scale corresponds to 64-76% HR max or 46-63% VO_2 max (Garber, Blissmer, Deschenes, et al. 2011). For this reason the American College of Sports Medicine promotes the use of the Borg 6-20 perceived exertion scale for self-regulating exercise for the management of hypertension (Pescatello, Franklin, Fagard, et al. 2004a). However, despite studies successfully eliciting fitness improvements following training programmes using RPE to prescribe intensity, research has not investigated the effectiveness of RPE regulated exercise for BP management.

For this reason researchers must continue to investigate the scales' usefulness as an independent intensity regulator and therefore its potential as an exercise prescription tool. Faulkner and Eston advocate the use of an estimation-production protocol for the prescription of RPE regulated exercise (Faulkner and Eston 2008). Using this protocol, individuals are requested to actively self-regulate exercise intensity (production mode) in order to produce a pre-determined RPE (estimation mode). The ability of an individual to reproduce a pre-determined marker of intensity using RPE is noted. To date, researchers have successfully shown that individuals are able to reproduce markers of cardiorespiratory stress (Marriott and Lamb 1996; Green, Michael, and Solomon 1999; Dunbar, Robertson, Baun, et al. 1992; Eston, Davies, and Williams 1987; Paulson, Bishop, Leicht, et al. 2013; Goosey-Tolfrey, Lenton, Goddard, et al. 2010) and physical capacity (Goosey-Tolfrey, Lenton, Goddard, et al. 2010; Paulson, Bishop, Leicht, et al. 2013; Marriott and Lamb 1996) during a production task. Whilst higher intensities would seem to be more reproducible (Marriott and Lamb 1996,

Goosey-Tolfrey 2010, Green Michael 1999) lower intensities improve with a practice period (Eston and Williams, 1988).

As compared with aerobic exercise, research on RPE and resistance exercise (dynamic and isometric) is limited. To date, research in this area has primarily focused on the relationship between resistance load and RPE. Evidence is building for the validity of RPE with positive associations existing between intensity of isometric contraction and rating on the CR-10 scale (Pincivero, Coelho, and Erikson 2000; Tiggemann, Korzenowski, Brentano, et al. 2010) and the 6-20 scale (O'Connor, Poudevigne, and Pasley 2002). With regards to investigating the ability of RPE to regulate resistance exercise, Lagally and Amorose carried out an estimation-production protocol with dynamic resistance exercises to good effect thus, recommending the scale as a useful method of prescribing the intensity of resistance exercise for training purposes (Lagally and Amorose 2007).

It would seem that the use of the RPE scale to regulate intensity of exercise for BP management could be feasible. However, studies have not yet used this as a tool in BP management research protocols. This thesis will investigate the possibility of utilising RPE as an isometric exercise intensity regulator (Chapter 5).

2.4 The influence of exercise on the pathophysiological pathways involved in the development of hypertension

The effects of exercise on the pathophysiological pathways involved in the development of hypertension have been widely studied. As described in sections 2.i, 2.ii, 2.iii, hypertension can result from a derangement in one or more of the BP regulating mechanisms (neural, humoral, and vascular) (section 2.0). As a way of understanding why exercise leads to reductions in BP, alterations to these mechanisms following exercise regimes have been studied widely.

To date, research has shown that exercise can have positive effects on the vasculature (Pescatello, Franklin, Fagard, et al. 2004a; Gkaliagkousi, Gavriilaki, and Douma 2015). Research findings have shown that aerobic exercise can increase arterial compliance (Tanaka, Dinenno, Monahan, et al. 2000; Pierce, Harris, Seals, et al. 2016; Vaitkevicius, Fleg, Engel, et al. 1993; Heffernan, Collier, Kelly, et al. 2007), reduce vascular responsiveness to endothelin 1 (a powerful vasoconstrictor) (Pescatello, Franklin, Fagard, et al. 2004a), reduce oxidative stress (Krause, Rodrigues-Krause, O'Hagan, et al. 2014; Nojima, Watanabe, Yamane, et al. 2008) and increase the expression of NO synthase (Niebauer and Cooke 1997; Krause, Rodrigues-Krause, O'Hagan, et al. 2014) which in turn enhances endothelium-dependent vasodilation (Niebauer and Cooke 1997; Green, Maiorana, O'Driscoll, et al. 2004). The effects of dynamic resistance training on the vasculature have not been extensively studied. Research has shown improvements in endothelial function (Umpierre and Stein 2007) whilst this type of training has also been associated with reduced arterial compliance (Umpierre

and Stein 2007; Miyachi 2013). In relation to isometric exercise training, a limited number of findings have shown reductions in markers of oxidative stress (Peters, Alessio, Hagerman, et al. 2006) and increased endothelial-dependent vasodilation (McGowan, Visocchi, Faulkner, et al. 2007; McGowan, Levy, Millar, et al. 2006; Badrov, Freeman, Zokvic, et al. 2016). To date, findings do not suggest that isometric training has any effect on arterial stiffness (Pagonas, Vlatsas, Bauer, et al. 2017). Although limited, the research discussed suggests that some differences might exist between exercise modalities and their influence on the vasculature.

In relation to humoral activity, aerobic exercise has been shown to reduce plasma renin activity – suggesting a role for the RAAS in the reduction in BP following an aerobic exercise regime (Goessler, Polito, and Cornelissen 2016; Fagard 2006). Considering the effects of renin release on the production of Ang-II (a powerful vasoconstrictor) this is a likely contributor to reduced BP following training. However, although aerobic exercise has been shown to reduce Ang-II in healthy subjects, these findings have not been consistent in hypertensives (Goessler, Polito, and Cornelissen 2016) and therefore the total contribution of the RAAS to BP reductions remains to be clarified. The effects of dynamic resistance training on the RAAS has not been thoroughly investigated. To date, findings suggest that there are no effects (Goessler, Polito, and Cornelissen 2016). With regards to isometric training, its effects on the RAAS has not yet come under scrutiny.

Changes to the autonomic nervous system have been widely investigated during and following exercise training. As has been described in sections 2.i, 2.ii, 2.iii, the autonomic nervous system effects and/or is affected by neural, hormonal, and vascular processes responsible for regulating BP and therefore stands central to the pathophysiology of hypertension (Thayer, Yamamoto, and Brosschot 2010) and a key target for BP treatment approaches (Fisher, Young, and Fadel 2009).

Sympathetic hyperactivity/autonomic dysfunction depends on a variety of internal mechanisms (Grassi and Ram 2016); these have been described in detail (2.i.b, 2.ii.b, 2.ii.d, 2.iii.a) and include reduced baroreflex sensitivity, heightened chemoreflex sensitivity, over activation of the RAAS and the consequential increase in Ang-II and aldosterone, increases in ROS and ET-1, reduced production of NO and finally reduced effectiveness of natriuretic peptides (Fisher, Young, and Fadel 2009; Grassi and Ram 2016). The stimulus for this dysfunction and therefore hypertension may be linked to a variety of factors including genetics (Grassi and Ram 2016), aging (Hart and Charkoudian 2014), chronic stress (De Vente, Olff, Van Amsterdam, et al. 2003; Aguilera, Kiss, and Sunar-Akbasak 1995) and poor lifestyle choices such as obesity (Lohmeier and Iliescu 2013) and physical inactivity (Thayer, Yamamoto, and Brosschot 2010).

Considering the increased vagal tone observed in athletes, it is understood that repeated metabolic stress and stimulation of the sympathetic nervous system induced during a training bout (see section 2.5) results in a reflex increase in parasympathetic nerve activity (supercompensation) and a resulting improvement in sympathovagal balance (Stanley, Peake, and Buchheit 2013; Plews, Laursen, Stanley, et al. 2013). The

stimulation of the autonomic nervous system during exercise (see section 2.5) and changes in autonomic function that follow an acute or chronic bout of exercise training (see sections 2.6 & 2.7) may therefore provide mechanistic insight into BP reductions.

The effect of exercise on the ANS can be summarised in three categories; autonomic regulation during a bout of exercise (acute stimulation), autonomic regulation directly after a single bout of exercise (acute effects), and autonomic regulation after a long-term exercise programme (chronic effects). Understanding the stimulation, recovery and adaptation of the ANS is of primary importance when trying to determine whether autonomic mechanisms are responsible for BP reductions following exercise training regimes.

The following sections will detail the specific autonomic adjustments to an exercise stimulus (aerobic, dynamic resistance and isometric), acute autonomic responses upon exercise (aerobic, dynamic resistance and isometric) cessation and chronic autonomic changes in response to exercise training (aerobic, dynamic resistance and isometric).

2.5 Autonomic regulation during a bout of exercise

During dynamic (aerobic, dynamic resistance) or static (isometric) physical exercise, the autonomic nervous system facilitates both ventilatory and cardiovascular adjustments necessary to meet the metabolic needs of the working muscles (Fadel and Raven 2012). In general, parasympathetic withdrawal and sympathetic nerve activation increases HR, cardiac contractility, BP, and ventilation. While parasympathetic withdrawal is aimed at allowing HR to increase, sympathetic activation works to increase HR, myocardial contractility and thus stroke volume (Nobrega, Leary, Silva, et al. 2014). In addition, efferent sympathetic signalling induces venoconstriction and vasoconstriction (non-exercising muscle tissue, splanchnic, renal, skin) aimed at improving venous return and redirecting cardiac output for perfusion of active muscles (Nobrega, Leary, Silva, et al. 2014; Fisher, Young, and Fadel 2015).

The specific responses to isometric exercise are well established and differ substantially to that of dynamic exercise (Lind and McNicol 1967a). During dynamic exercise at a constant workload, HR will increase to a steady state value. In contrast, HR during isometric exercise at a constant workload will continually rise (Fisher, Young, and Fadel 2015) albeit at a more modest magnitude (Lind & McNicol 1967). The BP response to the different exercise modalities is perhaps the most notable. The intermittent rhythmical nature of dynamic exercise encourages local vasodilation and blood flow (Fisher et al. 2015). Whilst SBP rises, local vasodilation results in a fall in TPR which contributes to DBP remaining relatively unchanged or decreasing (Lind & McNicol 1967). In contrast, isometric exercise which involves sustained mechanical compression of the intramuscular vasculature results in a more substantial increase in SBP (Fisher, Young, and Fadel 2015;

Lind and McNicol 1967a; Goodwin, McCloskey, and Mitchell 1972). Unlike dynamic exercise, intermittent vasodilation of the active muscles does not occur and therefore TPR increases, eliciting a concomitant increase in DBP (Lind & McNicol 1967).

The primary mechanisms responsible for the autonomic shift towards sympathetic dominance are the combined effects of central command, the exercise pressor reflex (mechanoreflex and metaboreflex) and their interactions with the arterial baroreflexes (Gallagher 2006). Specifically, during an isometric contraction these reflexes elicit significant decreases in levels of parasympathetic nerve activity (Goulart, Cabiddu, De Borba Schneiders, et al. 2017; Taylor, Wiles, Coleman, et al. 2017) and increases in sympathetic nerve activity (Boulton, Taylor, Macefield, et al. 2016). It is thought that the activation of these reflexes, in particular the metaboreflex, are mechanistically linked to the BP lowering effects of isometric exercise (Brook, Appel, Rubenfire, et al. 2013). The following sections will discuss the primary reflexes responsible for the stimulation of the autonomic nervous system during exercise (central command, exercise pressor reflex, arterial baroreceptors). Evidence relating to autonomic changes following exercise (acute and chronic) will also be highlighted; a specific focus will be placed on isometric exercise.

2.5.1 The role of central command

Central command, originally termed cortical irradiation (Krogh and Lindhard 1913) is classically defined as a feedforward mechanism, where descending neural signals from higher brain centres stimulate both the motor pathways and cardiovascular centres (Goodwin, McCloskey, and Mitchell 1972). Central command has been associated with effort-related cognitive processes (Williamson 2010) and therefore influence an individual's cardiovascular response (arterial BP, HR, ventilation etc.) in anticipation of exercise and in accordance with the level of perceived effort during exercise (Williamson 2010).

At the onset of isometric exercise, central command is responsible for increasing HR, arterial BP and ventilation (Williamson, McColl, Mathews, et al. 2002). The increase in HR is mediated by the immediate withdrawal of vagal control (Freyschuss 1970). The role of central command on vascular vasoconstriction at the onset of exercise is largely unknown, however increases in BP suggest a centrally mediated mechanism (Green and Paterson 2008). As isometric contractions are sustained beyond the initial few seconds, central command continues to bear influence over these hemodynamic variables (Fisher, Young, and Fadel 2015). This has been demonstrated using imagined static exercise (Williamson, McColl, Mathews, et al. 2002) and neuromuscular blockade during static contractions (Mitchell, Reeves, Rogers, et al. 1989); each study showed increases in both HR and arterial BP throughout the exercise and therefore confirmed the influence of central command on these variables. It is generally accepted that central command does not increase sympathetic nerve activity to inactive muscles (Mark, Victor, Nerhed, et al. 1985), however, comparing voluntary and

electrically evoked muscle contractions, recent findings suggest that this reflex is responsible for increases in muscle sympathetic nerve activity (MSNA) in the active muscle (Boulton, Taylor, Macefield, et al. 2016).

In addition to its primary feedforward functionality, it has been proposed that somatosensory feedback (pressor reflex) arising from the working musculature continually bears influence over an individual's perception of effort and therefore levels of central command (Nobrega, Leary, Silva, et al. 2014). Using hypnosis, perception of effort has been increased whilst cycling at a steady workload (Williamson 2010). Hypnosis increased cardiovascular adjustments in accordance with the increase in perceived exertion clarifying the role of perceived exertion on central command (Williamson 2010). A sustained isometric task results in a gradual increase in an individual's perception of effort (Pincivero and Gear 2000) and muscle electromyography (Mitchell, Reeves, Rogers, et al. 1989). These changes indicate a progressive role for central command output (Amann, Sidhu, Weavil, et al. 2015; Williamson, McColl, Mathews, et al. 2002; Mitchell 2012) which is mediated by feedback arising from the active musculature (pressor reflex).

2.5.2 The role of the pressor reflex

Alongside central command, peripheral feedback mechanisms work to alter the level of cardiovascular response required to meet the metabolic demands of the working tissues. Krogh and Lindhard were amongst the first researchers to identify that neural reflexes originating from the contracting musculature could induce cardiovascular changes (Krogh and Lindhard 1913). These neural reflexes are elicited due to mechanical (mechanoreflex) and metabolic (metaboreflex) changes within the working musculature; their combined effects are now widely known as the exercise pressor reflex (Fisher, Young, and Fadel 2015). The exercise pressor reflex relays afferent information to the cardiovascular control centre along thinly myelinated group III and unmyelinated group IV afferent neurons (McCloskey and Mitchell 1972).

The mechanoreflex stimulates increases in BP and HR in response to the distortion of mechanoreceptors during muscle stretch and muscle contraction (Hayes 2005). Using an electrically evoked muscle stretch, these cardiovascular changes were explained by a withdrawal of cardiovagal activity (Gladwell, Fletcher, Patel, et al. 2005; Gladwell and Coote 2002). The peripheral effects of the mechanoreflex are not well understood – although a voluntary isometric quadriceps contraction has been shown to elicit an immediate increase in muscle SNA (Herr, Imadojemu, Kunselman, et al. 1999), the contribution of central command and/or the metaboreflex cannot be ruled out. The isolation of the mechanoreflex during an isometric contraction is difficult to achieve and therefore its total contribution to alterations in neural control is not clear.

The metaboreflex was first isolated by Alam and Smirk using cuff occlusion (Alam and Smirk 1937). Despite the cessation of exercise, these researchers showed that BP remained elevated whilst metabolites were trapped within the muscle following isometric handgrip exercise. This procedure eliminated the influence of

central command and isolated what is now commonly known as the metaboreflex. In comparison with aerobic and dynamic resistance exercise, the metaboreflex is thought to be most active during isometric exercise. During isometric exercise the sustained compression of the intramuscular vasculature introduces an ischeamic challenge and therefore a continuous accumulation of muscle metabolites (lactate, potassium, adenosine, arachidonic acid, deprotonated phosphate, prostaglandins) (Fisher, Young, and Fadel 2015; Kaufman and Hayes 2002; Devereux, Coleman, Wiles, et al. 2012). Lactate in particular has been shown to play a major role in stimulating skeletal muscle afferents (Kaufman, Hayes, Adreani, et al. 2002). In a physiological attempt to restore muscle blood flow the metaboreflex undergoes a potent stimulus (McCloskey and Mitchell 1972; Kaufman and Hayes 2002; Mitchell, Reeves, Rogers, et al. 1989; Iellamo, Massaro, Raimondi, et al. 1999; Ichinose, Saito, Kondo, et al. 2008) whereby efferent sympathetic nerve activity is strongly initiated eliciting large increases in arterial pressure.

The repeated stimulation of the metaboreflex, is thought to be one of the primary mechanisms for the BP lowering effects of isometric exercise (Brook, Appel, Rubenfire, et al. 2013). Given the ischemic nature of isometric exercise, exercise cessation introduces an immediate increase in blood flow (McGowan, Levy, Millar, et al. 2006), also known as reactive hyperaemia. Reactive hyperaemia causes an increase in shear stress on the endothelium which is associated with NO production (Green, Maiorana, O'Driscoll, et al. 2004). The level of ischaemia present during isometric exercise has led researchers to believe that repetitive episodes of ischaemia and stimulation of the metaboreflex would act to improve endothelial-dependent vasodilation; potentially linked to chronic increases in the bioavailability of NO and improved antioxidant activity (McGowan, Levy, McCartney, et al. 2007). Findings from McGowan et al., have shown that isometric handgrip training improved brachial artery flow mediated dilation but this was present in the trained arm only, and it was therefore concluded that systemic BP reductions were unlikely to be related to changes in improvements in flow mediated dilation (McGowan, Visocchi, Faulkner, et al. 2007). However, Peters et al., showed increases in blood antioxidant activity following 8 weeks of isometric training (bilateral handgrip) this finding indicated that endothelial exposure to harmful reactive oxygen species was minimised (Peters, Alessio, Hagerman, et al. 2006). Unfortunately a control group was not included within this study and therefore care must be taken when interpreting the results.

In addition to the potential endothelial benefits related to the repeated exposure to the metaboreflex,the stimulation of the autonomic nervous system via the metaboreflex (and central command) could elicit parasympathetic supercompensation, a well-known phenomenon in aerobic training (Stanley, Peake, and Buchheit 2013; Carter, Banister, and Blaber 2003; Hautala, Kiviniemi, and Tulppo 2009). For the purposes of hypertension management, this regular autonomic stimulus is therefore regarded as an important aspect of exercise training. Current findings related to chronic autonomic changes following isometric training can be found in section 2.6. This thesis will aim to further explore the effects of isometric training on autonomic function.

2.5.3 The role of the arterial baroreflex

At rest, the arterial baroreflex (as discussed in section 2.i.a) is an important reflex mechanism that maintains BP at its original set point value. In response to increases or decreases in pressure, baroreceptors alter afferent neuronal firing which mediates changes in parasympathetic and sympathetic nerve activity (Fadel and Raven 2012) and therefore arterial BP.

Before the 1990's it was generally accepted that the baroreflex was switched off or inhibited during exercise; this was to allow the concomitant increases in HR and BP required to meet the metabolic demands of the exercising muscle (Raven, Fadel, and Ogoh 2006). However, in a landmark study in 1990, Sheriff and colleagues showed that increases in BP became unrestrained during metaboreflex stimulation following sino-aortic baroreceptor denervation (Sheriff, O'Leary, Scher, et al. 1990). Convincing evidence is now available for the resetting of the baroreflex operating point during exercise; this enables the reflex mechanism to continue modulating exercise induced increases in BP and sympathetic nerve activity (Potts, Shi, and Raven 1993; Ogoh, Fisher, Dawson, et al. 2005). The contributing neural mechanisms responsible for the resetting include both central command and the exercise pressor reflex (Gallagher, Fadel, Smith, et al. 2006); afferent signals from the baroreflex, central command and the exercise pressor reflex converge centrally within the medulla oblongata. The processing of this information acts to alter parasympathetic and sympathetic efferent signalling (Figure 2.1), appropriate to the exercise demands.

Specifically, during isometric exercise the sensitivity of the baroreflex control of muscle sympathetic nerve activity increases in an intensity dependent manner (Ichinose, Saito, Kondo, et al. 2008). This demonstrates an important neural interaction between central command, the metaboreflex and the baroreflex in the control of excessive increases in sympathetic nerve activity and arterial BP. The influence of the baroreflex on the pathophysiology of hypertension (see section 2.i.b) has led researchers to investigate changes in baroreflex sensitivity following the immediate cessation of different exercise modalities and following longer term exercise programmes (see sections 2.6.1 & 2.6.2).

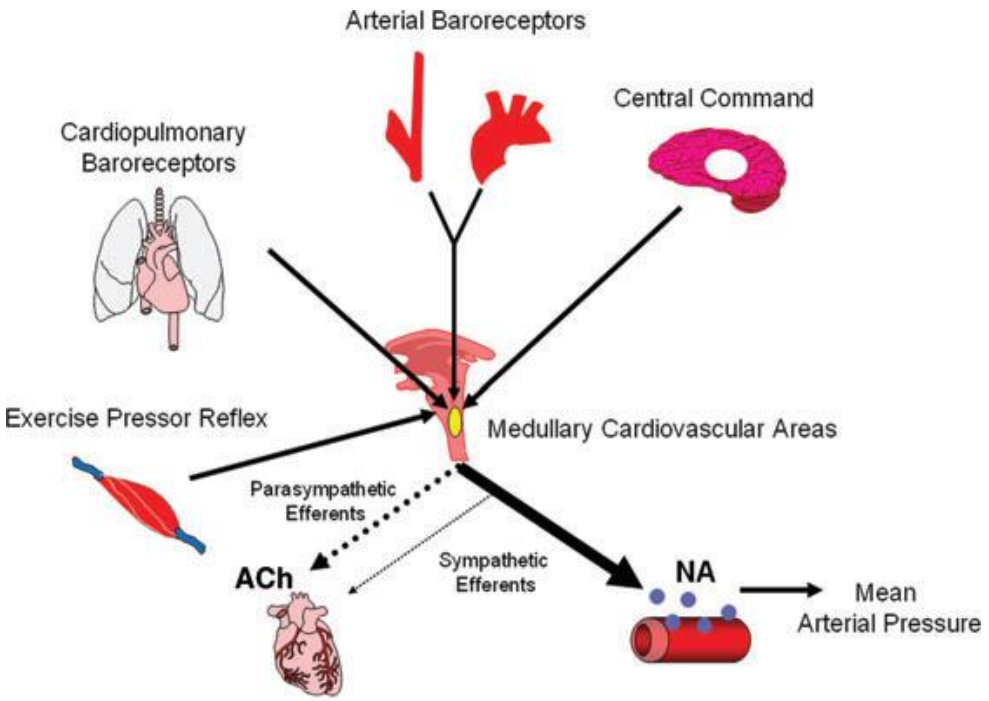

Figure 2.1. A schematic representation of the neural mechanisms mediating the neural cardiovascular adjustments to exercise.

During exercise, neural signals originating from the brain (central command), the baroreflexes and skeletal muscle (exercise pressor reflex) contribute to the intensity dependent modulation of sympathetic and parasympathetic nerve activity during exercise. These signals converge centrally within the cardiovascular control centres of the medulla oblongata. The modulation of neural activity mediates changes in heart rate and the diameter of resistance and capacitance vessels – these changes are required to meet the metabolic demands of the exercise. (Figure from Fadel & Raven 2012).

2.5.4 Summary

During exercise, central command, the exercise pressor reflex and the arterial baroreflex all work together to regulate the autonomic nervous system and therefore facilitate the ventilatroy and cardiovascular adjustments necessary to meet the metabolic needs of the working muscles. Due to the ischemic nature of isometric exercise it is thought that the metaboreflex (part of the exercise pressor reflex) is strongly stimuluated in an attempt to restore muscle blood flow. The repeated stimulation of this reflex is thought to be mechanistically linked to the BP lowering effects of isometric exercise (Brook, Appel, Rubenfire, et al. 2013).

Regardless of exercise type, it is suggested that the repeated stimulation of the autonomic nervous system during exercise could lead to favourable changes in autonomic balance over the long-term. The following

sections will highlight the evidence relating to autonomic changes following exercise (acute and chronic); a specific focus will be placed on isometric exercise.

2.6 The acute and chronic effects of exercise on autonomic function

As previously discussed (see section 2.5), an exercise (aerobic, isometric, dynamic resistance) stimulus induces marked changes in autonomic regulation of both HR and BP. These changes have led researchers to investigate the role of the autonomic nervous system in chronic BP reductions. Studies have investigated both the acute autonomic changes upon exercise cessation and longer term autonomic changes that may occur as a result of different exercise modalities.

2.6.1 The acute effects of exercise on autonomic function

The autonomic imbalance (heightened sympathetic activity and depressed parasympathetic activity) present during an exercise stimulus has been shown to persist following a single bout of aerobic (Terziotti, Schena, Gulli, et al. 2001; Cote, Bredin, Phillips, et al. 2015; Legramante, Galante, Massaro, et al. 2002; Anaruma, Ferreira, Sponton, et al. 2016) and dynamic resistance exercise (Kliszczewicz, Esco, Quindry, et al. 2016; Heffernan, Collier, Kelly, et al. 2007; Rezk, Marrache, Tinucci, et al. 2006; Teixeira, Ritti-Dias, Tinucci, et al. 2011; Niemela, Kiviniemi, Hautala, et al. 2008). In contrast, improvements in autonomic balance have been found following isometric exercise cessation (Taylor, Wiles, Coleman, et al. 2017; Millar, MacDonald, Bray, et al. 2009). In relation to aerobic and dynamic resistance exercise, it is thought that sympathetic modulation remains high to override the vasodilator and hypotensive effects of the previous exercise (Stanley, Peake, and Buchheit 2013; Teixeira, Ritti-Dias, Tinucci, et al. 2011). It has also been suggested that sympathetic modulation may remain high due to the metabolites accumulated during the exercise stimulus (Stanley, Peake and Buchheit, 2013) and cardiovagal nerve activity remains supressed due to a reduced venous return/blood volume and a consequential unloading of baroreceptors (Stanley, Peake and Buchheit, 2013).

In relation to aerobic exercise, Terziotti and colleagues showed that 20 minutes of light (50% of anaerobic threshold) and moderate (80% of anaerobic threshold) intensity aerobic exercise induced a PEH response that was associated with an increase in the low frequency component of systolic BP variability (BPV) (sympathetic vasomotor tone; see Chapter 3, section 3.5.2 for definition) and decrease in the high frequency component of heart rate variability (HRV) (cardiovagal tone; see Chapter 3, section 3.5.1 for definition) 15 minutes post exercise (Terziotti, Schena, Gulli, et al. 2001). The increase in sympathetic vasomotor tone, as detected by an increase in LF BPV is consistent with other studies carried out on healthy males (Cote, Bredin, Phillips, et al. 2015) and mild essential hypertensives (Legramante, Galante, Massaro, et al. 2002). Terziotti showed that these markers of vasomotor sympathetic nerve activity had returned to pre exercise levels

within 60 minutes, however, other findings in mild essential hypertensives showed that the LF component of BPV remained elevated at 60 minutes (Legramante, Galante, Massaro, et al. 2002). Although the prescription of a higher exercise intensity by Legramante and colleagues may explain this discrepancy, a slower return to pre exercise levels in individuals whose autonomic function may be compromised is consistent with research in diabetics where a reduction in cardiovagal tone was found (Anaruma, Ferreira, Sponton, et al. 2016).

Alongside vagal suppression and an increase in sympathetic tone, the sensitivity of cardiovagal baroreflexes has been shown to decrease following aerobic exercise (Terziotti, Schena, Gulli, et al. 2001; Heffernan, Collier, Kelly, et al. 2007; Studinger, Lénárd, Kováts, et al. 2003). This is perhaps due to unloading or the maintenance of a higher operating point induced by the exercise stimulus (see section 2.5.3). Similar to other autonomic markers, studies have shown that BRS returned to baseline values within 60-minutes (Terziotti, Schena, Gulli, et al. 2001; Studinger, Lénárd, Kováts, et al. 2003; Legramante, Galante, Massaro, et al. 2002).

Despite the evidence showing transient autonomic imbalance following exercise cessation, MSNA has shown positive reductions following aerobic exercise in healthy participants (Aprile, Oneda, Gusmao, et al. 2016; Halliwill, Taylor, and Eckberg 1996) and those with chronic kidney disease (Aprile, Oneda, Gusmao, et al. 2016). However, these acute reductions were not replicated in chronic heart failure participants following moderate continuous exercise and high intensity interval exercise (Nobre, Groehs, Azevedo, et al. 2016). Further research on clinical populations with exaggerated MSNA is required.

Similar to aerobic exercise, recordings of HRV suggest that an episode of dynamic resistance exercise causes a reduction in cardiovagal activity and increased dominance of sympathetic activity (Kliszczewicz, Esco, Quindry, et al. 2016; Heffernan, Collier, Kelly, et al. 2007; Rezk, Marrache, Tinucci, et al. 2006; Teixeira, Ritti-Dias, Tinucci, et al. 2011; Niemela, Kiviniemi, Hautala, et al. 2008). The acute effects of resistance training have been primarily tested in young healthy men and women and measurements most commonly take place between 15-90 minutes post exercise. Findings from Rezk et al., (2006) and Teixeira et al., (2011) showed that 6 resistance exercises at 40% (Rezk, Marrache, Tinucci, et al. 2006) , 80% (Rezk, Marrache, Tinucci, et al. 2006) and 50% (Teixeira, Ritti-Dias, Tinucci, et al. 2011) 1RM reduced the HF spectral component of HRV in healthy normotensive individuals. The reduction in cardiovagal tone persisted for 20-75 minutes following exercise cessation (Rezk, Marrache, Tinucci, et al. 2006; Teixeira, Ritti-Dias, Tinucci, et al. 2011).

Studies have also found a reduction in BRS following resistance training (Niemela, Kiviniemi, Hautala, et al. 2008; Heffernan, Collier, Kelly, et al. 2007), increases in the LF component of BPV and plasma catecholmines (epinephrine and norepinephrine; Kliszczewicz *et al.*, 2016). As is consistent with aerobic training, these findings support the autonomic imbalance induced by acute resistance exercise.

In contrast to aerobic and dynamic resistance exercise, the acute effects of a single isometric exercise training session on autonomic function remains largely unexplored. However, findings to date are in contrast with

that of aerobic and resistance exercise training. In 2009, Millar et al., was the first to investigate acute changes in HRV following 4x2 minute isometric handgrip contractions performed at 30% MVC. Using a non-linear HRV analysis method findings showed that there was a shift in neurocardiac autonomic balance towards an increase in vagal tone 10 minutes after exercise cessation (Millar, MacDonald, Bray, et al. 2009). These cardiac autonomic changes were accompanied by significant decreases in BP observed 5 minutes post exercise cessation (Millar *et al.*, 2009).

Recently, Taylor and colleagues (2017) investigated the effects of a single isometric exercise wall squat training session on HRV and BRS in pre-hypertensive males. During a 5-minute recovery period, the researchers found that vagal tone increased alongside a decrease in the LF:HF ratio and BRS increased (Taylor, Wiles, Coleman, et al. 2017). Together with the findings from Millar et al., (2009) it would seem that an acute bout of isometric exercise initiates an immediate parasympathetic super-compensation. However, further research is needed to clarify the lasting effects of this autonomic change following an acute bout of isometric exercise.

Researchers suggest that these acute changes may be mechanistically linked to chronic BP reductions following isometric exercise training (Millar, MacDonald, Bray, et al. 2009). However this link has not yet been clarified (see section 2.7.2). Curiously, the acute effects of isometric exercise are in contrast with aerobic and dynamic resistance exercise where parasympathetic modulation and BRS has remained suppressed following an acute bout of exercise. These discrepancies could be related to the differences in mechanical and neural responses to varying exercise modalities. For example research has shown that isometric exercise preserves carotid artery diameter (Black, Stohr, Stone, et al. 2016) whereas aerobic exercise decreases it (Willie, Ainslie, Taylor, et al. 2011). In addition, research findings have shown that isolating the metaboreflex (using post exercise ischemia) after an isometric contraction results in a quick return of HR back to baseline levels – this shows that the primary stimulus involved in isometric exercise (metaboreflex) does not have a large effect on cardiac vagal withdrawal (Fisher, Seifert, Hartwich, et al. 2010) and therefore the loss of central command and/or mechanoreflex immediately following isometric exercise has been suggested to have an overwhelming effect on cardiac parasympathetic reactivation (Fisher, Seifert, Hartwich, et al. 2010).

2.6.2 The chronic effects of exercise on autonomic function

Research has shown that a bout of aerobic training (16 weeks) reduces MSNA in never treated hypertensive (Laterza, De Matos, Trombetta, et al. 2007) and heart failure patients (Roveda, Middlekauff, Rondon, et al. 2003; de Mello Franco, Santos, Rondon, et al. 2006). Remarkably the magnitude of reduction is such that baseline levels following an exercise regime have been matched to age-matched healthy control subjects (Laterza, De Matos, Trombetta, et al. 2007). Although BP is not always a measured outcome of these studies, Laterza showed that an attenuated MSNA was accompanied with reductions in both systolic and diastolic BP

(Laterza, De Matos, Trombetta, et al. 2007); providing support for the benefit of improving autonomic balance in human hypertension.

In support of reductions in peripheral sympathetic nerve traffic in hypertensives, researchers have also found a reduced LF component of BPV following aerobic exercise regimes lasting between 4 weeks and 4 months in mild hypertensives (Collier, Kanaley, Carhart, et al. 2009) and never treated hypertensives (Laterza, De Matos, Trombetta, et al. 2007; Izdebska, Cybulska, Izdebski, et al. 2004); each study found associated reductions in BP. Similar to findings in MSNA following aerobic exercise training (Carter 2003), reductions in this marker of efferent sympathetic nerve activity is not reported in normotensive participants (Izdebska, Cybulska, Izdebski, et al. 2004; Alex, Lindgren, Shapiro, et al. 2013b).

Whilst the reduction in sympathetic nerve activity (as measured by MSNA and the LF component of systolic BPV) is evident in hypertensive adults as compared with normotensive adults, the effects of aerobic training on increased vagal tone in both healthy and hypertensive participants is well supported. The chronic improvements of vagal activity following exercise training is associated with an induced resting bradycardia (Sandercock, Bromley and Brodie, 2005). Cardiovagal tone and sympathovagal balance, characterised by baroreflex sensitivity HF, rMSSD, pNN50% and the LF:HF ratio, have been shown to improve following aerobic training in healthy individuals (Tulppo, Hautala, Mäkikallio, et al. 2003; Pigozzi, Alabiso, Parisi, et al. 2001; Hallman, Holtermann, Søgaard, et al. 2017; Melanson and Freedson 2001; Ueno and Moritani 2003; Monahan, Dinenno, Tanaka, et al. 2000) and hypertensive individuals (Collier, Kanaley, Carhart, et al. 2009; Laterza, De Matos, Trombetta, et al. 2007). However, other aerobic training studies have not found improvements in resting HRV in mild hypertensives (Davy, Willis, and Seals 1997) and type II diabetics (Kang, Ko, and Baek 2016) despite BP reductions (Davy, Willis, and Seals 1997; Kang, Ko, and Baek 2016). Studies reporting changes are strengthened by larger participant pools and in some cases 24-hour monitoring (Pigozzi, Alabiso, Parisi, et al. 2001; Hallman, Holtermann, Søgaard, et al. 2017; Tulppo, Hautala, Mäkikallio, et al. 2003). This measurement is more specific to the day-to-day stresses of real life and has been shown to be more reproducible than 5-10 minute resting measurements (Pitzalis, Mastropasqua, Massari, et al. 1996). This measurement could therefore provide greater sensitivity to changes following aerobic exercise training. The reproducibility of resting and 24-hour measurements of HRV are explored in Chapter 4.

In contrast to aerobic training, dynamic resistance training performed over a period of 8 weeks to 6 months does not appear to improve cardiovagal activity in healthy adults (Heffernan, Collier, Kelly, et al. 2007; Karavirta, Costa, Goldberger, et al. 2013; Cooke and Carter 2005; Madden, Levy, and Stratton 2006) and mildly hypertensive adults (Collier, Kanaley, Carhart, et al. 2009). These findings are despite some studies showing significant changes in BP following resistance training interventions (Collier, Kanaley, Carhart, et al. 2009; Cooke and Carter 2005). Although the effects of resistance training on BP remain inconclusive, these findings may indicate an alternative mechanism in the event of BP reductions following dynamic resistance

training. However, there is a limited amount of research investigating HRV post resistance training (Kingsley and Figueroa 2016). In addition, the use of resting measurement techniques (Heffernan, Collier, Kelly, et al. 2007; Karavirta, Costa, Goldberger, et al. 2013; Cooke and Carter 2005) as opposed to 24-hour measurements may cause small training effects to go undetected (Pitzalis, Mastropasqua, Massari, et al. 1996).

Although changes in HRV have not been found following dynamic resistance training, research has found reductions in LF systolic BPV following resistance training in mild hypertensives; this reduction was associated with BP reductions suggesting a training-induced reduction in vasomotor sympathetic nerve activity in hypertensive patients (Collier, Kanaley, Carhart, et al. 2009). In contrast, other studies have found no change in LF systolic BPV following 8 (Cooke and Carter 2005) and 12 weeks (Alex, Lindgren, Shapiro, et al. 2013b) of resistance training. However, participants were normotensive and it could be suggested that peripheral sympathetic nerve activity may not undergo changes in healthy vessels. Similarly research findings have shown that MSNA did not decrease in young healthy adults following resistance training – this was despite a reduction in BP (Carter, Ray, Downs, et al. 2003) . The precise autonomic changes responsible for BP changes following resistance training therefore remains inconclusive. There remains a need for further research to determine the autonomic effects of dynamic resistance training in hypertensive populations whilst measuring both BP and autonomic changes synchronously.

The effects of isometric exercise training on autonomic function has been investigated via MSNA (Ray and Carrasco 2000), systolic BPV (Taylor, McCartney, Kamath, et al. 2003), baroreflex sensitivity (Devereux and Wiles 2015) and HRV (Stiller-Moldovan, Kenno, and McGowan 2012; Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013). Ray and Carrasco (2000) measured the effects of handgrip isometric training on BP and MSNA and found no changes in MSNA in normotensive participants following 5 weeks of training. The lack of effect of exercise on MSNA in normotensives is consistent with findings in aerobic exercise (Carter, Ray, Downs, et al. 2003). However, it is important to note that no changes in SBP were found (Ray and Carrasco 2000) and therefore reductions in this autonomic variable would not have been expected. It would be important to note that the training intervention was only 5 weeks in duration. Although short isometric training programmes (4-5 weeks) have previously shown positive reductions in SBP these studies used bilateral leg exercises (Howden, Lightfoot, Brown, et al. 2002; Devereux, Wiles, and Swaine 2010). This type of exercise employs a much greater muscle mass and may therefore stimulate the exercise pressor reflex to a greater extent allowing positive effects to be gained following short exercise programmes (Lawrence, Cooley, Huet, et al. 2014).

Research investigating the effects of isometric exercise on autonomic function is currently limited and inconclusive. To date only one study has measured the effects of isometric training on systolic BPV (Taylor, McCartney, Kamath, et al. 2003). The researchers found a significant decrease in the LF:HF ratio of BPV which

was reported to indicate a reduction in vasomotor sympathetic tone (Taylor, McCartney, Kamath, et al. 2003).

In relation to HRV, Taylor et al., (2003) reported a non-significant decrease in the LF:HF ratio and a significant increase in the HF parameter; these results indicate a positive change in vagal modulation (Taylor, McCartney, Kamath, et al. 2003). In contrast, Wiles et al., (2010), Badrov et al., (2013) and Stillar-Maldovan et al., (2014) reported no changes in the spectral analysis of HRV despite some studies reporting significant decreases in BP (Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013). The differences in baseline BP values could have influenced the discrepant findings. Taylor et al., (2003) recruited individuals with baseline SBP of 156.0 ± 9.4 mmHg and DBP of 82.3 ± 9.3 mmHg. This value is higher than the baseline values in the other studies where individuals were within normal BP range (≤120/≤80mmHg) (Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013; Stiller-Moldovan, Kenno, and McGowan 2012). Considering that changes in autonomic function accompany hypertension (Mancia and Grassi 2014) it seems logical to suggest that positive changes might only be observed in a population whose BP is out of normal range. However, aerobic training has had positive effects on autonomic function in both healthy (Tulppo, Hautala, Mäkikallio, et al. 2003; Pigozzi, Alabiso, Parisi, et al. 2001; Hallman, Holtermann, Søgaard, et al. 2017; Melanson and Freedson 2001; Ueno and Moritani 2003; Monahan, Dinenno, Tanaka, et al. 2000) and hypertensive populations (Laterza, De Matos, Trombetta, et al. 2007; Collier, Kanaley, Carhart, et al. 2009).

Findings related to changes in autonomic function following isometric exercise are very limited and for now an autonomic mechanism for BP reductions remains speculative. To date, studies have only carried out short-term measurements (5-minute HRV recordings). As discussed earlier, these measurements are associated with a lot of day-to-day variability (Ginsburg, Bartur, Peleg, et al. 2011; Hojgaard, Holstein-Rathlou, Agner, et al. 2005; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Pinna, Maestri, Torunski, et al. 2007; Ponikowski, Piepoli, Amadi, et al. 1996) and therefore may not provide a measurement sensitive enough to detect long-term changes; this thesis will explore whether 24-hour recordings of autonomic function provide greater reproducibility and therefore provide a more sensitive measurement of autonomic function (Chapter 4).

In an attempt to add further knowledge on this topic, this thesis will explore autonomic nervous system changes following an isometric training programme.

2.6.3 Summary of acute and chronic autonomic effects of exercise

The acute and chronic effects of exercise on autonomic function have been viewed as a mechanistic link to BP reductions following exercise training regimes. Whilst acute bouts of aerobic and dynamic resistance training have been shown to increase sympathetic activity, aerobic (Terziotti, Schena, Gulli, et al. 2001; Cote,

Bredin, Phillips, et al. 2015; Legramante, Galante, Massaro, et al. 2002; Anaruma, Ferreira, Sponton, et al. 2016; Kliszczewicz, Esco, Quindry, et al. 2016; Heffernan, Collier, Kelly, et al. 2007; Rezk, Marrache, Tinucci, et al. 2006; Teixeira, Ritti-Dias, Tinucci, et al. 2011; Niemela, Kiviniemi, Hautala, et al. 2008) training regimes lasting a number of weeks have been shown to elicit increases in vagal tone and/or reductions in sympathetic activity; indicative of improved autonomic balance. In contrast to these training modalities, the effects of isometric exercise training on autonomic function is largely under-researched. Findings suggest that an acute bout of training improves vagal modulation (Taylor, Wiles, Coleman, et al. 2017; Millar, MacDonald, Bray, et al. 2009) whereas only one study supports the chronic effects of isometric training on autonomic function (Taylor, McCartney, Kamath, et al. 2003). It is possible that more sensitive measures of autonomic function are required for the detection of training adaptations. Chapter 4 explores this aspect in more detail.

2.7 Thesis aims

The study of isometric exercise training and its effects on the regulation of BP is still young. This thesis will focus on three important and novel elements that will progress and develop this area of research. The aims of this thesis are to i) develop an appropriate, cost-effective and accessible isometric hand-grip exercise ii) measure the effectiveness of isometric hand-grip exercise on BP and autonomic function iii) assess adherence levels to an isometric training programme. The aim of investigating these individual elements is to improve accessibility to isometric exercise by developing a cost-effective method of regulating exercise intensity, determine the potential for participant adherence to isometric exercise, provide further evidence for the effectiveness of isometric exercise training on BP and finally provide mechanistic insight into BP reductions following isometric exercise training.

The principle purpose of isometric exercise training is to reduce BP. Although isometric exercise training is considered a simple, time-effective approach to a non-pharmacological method of anti-hypertensive therapy, exercise prescription guidelines state that isometric training should be carried out at a specific percentage of an individuals' MVC. This method requires individuals to execute regular maximal contractions whilst also having access to specialised equipment (often lab-based dynamometers) that displays force recordings – the cost implication of this equipment would be considered a barrier to exercise participation. This thesis will develop a simple and cost-effective method of regulating isometric exercise intensity (Chapter 5); this method will lend itself to unsupervised, home-based exercise that can be carried out in a familiar and comfortable environment. The measurement of participant compliance to this simple method of isometric exercise will provide insight into the long-term viability of isometric exercise training for people with hypertension (Chapter 6).

The BP and autonomic effects of isometric hand-grip training will be investigated. The majority of studies have only explored the effects of isometric exercise training on resting BP and its effects on 24-ambulatory BP remains largely unexplored. Considering that 24-hour recordings are the gold standard for BP measurement (NICE 2011) it is important that this measure is taken in addition to the more common resting measurements (Chapter 6). In an attempt to understand the mechanistic pathways behind BP reductions studies have measured autonomic function, however, only short-term measurements (mainly 5-minute HRV recordings) have been taken. These measurements are associated with a lot of day-to-day variability and therefore may not provide a measurement sensitive enough to detect long-term changes; this thesis will explore whether 24-hour recordings of autonomic function provide greater reproducibility and therefore provide a more sensitive measurement of autonomic function (Chapter 4).

In summary, the overall aim of this thesis was to develop a simple method of self-regulating isometric exercise intensity and determine its effectiveness in relation to participant compliance, BP and autonomic function. The hypotheses of this thesis are that the CR-10 scale will provide an effective method for isometric hand-grip intensity regulation, self-regulated isometric handgrip exercise will reduce resting and ambulatory BP and improve autonomic function and finally participant compliance to self-regulated isometric exercise will be high.

The primary objectives of this thesis were to:

1) Determine the viability of utilising the rate of perceived exertion chart to regulate isometric handgrip intensity.
2) Assess the chronic adaptations in BP (resting and 24-hour ambulatory) to 10 weeks of isometric exercise.
3) Measure levels of participant adherence during short and long term training programmes.

The secondary objective of this thesis was to:

1) Assess the chronic adaptions in autonomic function to 10 weeks of isometric exercise

Chapter 3: General Methods

3.1 Introduction

This chapter will detail the general methods that were used within the current thesis. Specifics relating to their application within each investigation will be detailed in Chapters 4 (section 4.2.5), 5 (section 5.2.2) and 6 (section 6.2.2). The general methods include:

- Participants
- Resting blood pressure measurement
- 24-hour ambulatory blood pressure measurement
- Measurements of autonomic function (resting and ambulatory)
    - Resting and ambulatory heart rate variability
    - Resting systolic blood pressure variability
- Operation of the PowerLab handgrip dynamometer
- Use of the Category-Ratio 10 scale
- A comparative analysis between the lab-based PowerLab handgrip dynamometer (Powerlab 26T, AD instruments LTD, Sydney, Australia) (Figure 3.9) and the ergonomic hand exerciser (Rolyan, Patterson Medical, Nottinghamshire, UK) (Figure 3.10) using electromyography.

3.2 Research outline

Study 1 (Chapter 4) assessed the reproducibility, and therefore, normal day-to-day variability, of resting and 24-hour recordings of autonomic function and 24-hour ambulatory blood pressure (BP). The assessment of reproducibility determines the retest reliability and therefore typical measurement error and day-to-day variability when a measurement is repeated (Hopkins, 2000). In addition, the measurement of reproducibility determines the need for participant familiarisation sessions. The reproducibility procedures are described in Section 4.2. The measurement of reproducibility allowed for the determination of measurement precision and the need for familiarisation trials. Interpretation of the data provided typical day-to-day variation and also suggested that there is a benefit to carrying out familiarisation sessions when measuring these specific physiological variables. Study 2 (Chapter 5) determined the validity of self-regulating isometric handgrip exercise using the Category-Ratio 10 (CR-10) scale. The measurement of validity ensured that the CR-10 scale was an appropriate method of regulating isometric exercise intensity as compared with the more common method of %MVC. The validity procedures are described in Chapter 5, Section 5.2.2. The ability of participants to reproduce a %MVC and/or systolic BP (SBP) response whilst self-regulating isometric exercise was of particular interest. Study 3 (Chapter 6) implemented an isometric training plan using a 2-phase design (Chapter 6). During phase I, experimental participants engaged in a 10-week self-regulated isometric

handgrip (IHG) training programme – changes to BP (resting and 24-hour ambulatory) and autonomic function were assessed on completion of the exercise programme. During phase II experimental participants continued to exercise (longer-term exercise group) and the control participants embarked on the isometric hand-grip training programme (shorter-term exercise group) for the duration of 16 weeks. Adherence to unsupervised, self-regulated IHG training was analysed and compared in both groups whilst the maintenance of physiological adaptations was assessed in the longer-term exercise group.

The quantitative research approach was chosen based on its ability to measure cause and effect. Chapter 6 used a randomised controlled trial design as it is considered to provide the most reliable evidence on the effectiveness of interventions (Field 2009).

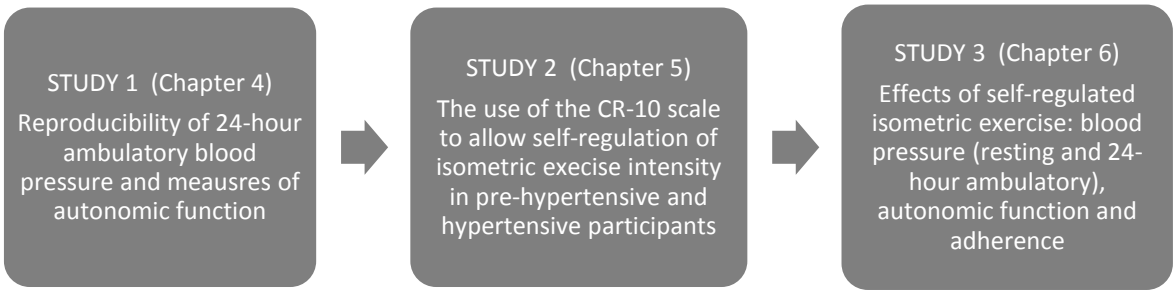

Figure 3.1: Schematic of the research design

3.3 Participants and recruitment

Ethical approval for each individual study (study 1, UEP2015May01; study 2, UEP2015Nov02; study 3, UEP2016Apr02) was granted from the local research ethics committee (Appendix 3). Thirty-one (17 females, 14 males) pre-hypertensive and hypertensive adults with a mean age of 64.6±5.8yrs, body mass of 78.3±17.6kg and height 169.3±12.1cm participated. As defined by the European Society of Hypertension (Table 3.1, Mancia *et al.*, 2013) participants were either pre-hypertensive or hypertensive (stage 1) (SBP; 138.7±7.0mmHg, DBP; 83±8.7mmHg). Aside from mild hypertension, participants were otherwise "healthy". Participants were apparently low cardiovascular risk and were therefore considered for isometric exercise prescription (Brook, Jackson, Giorgini, et al. 2015). Cardiovascular risk was assessed via questionnaire. Smokers and diabetics, individuals with a history of cardiovascular (CV) events (angina, myocardial infarction, and atrial fibrillation) or with a knowledge of hypertensive sleep apnoea, chronic heart failure or coronary artery disease were excluded from participation. Further laboratory tests such as blood sampling, diagnostic echocardiogram or an echo scan were not carried out to confirm the cardiovascular status of participants. In

addition to the above criteria, participants were required to be free from any musculoskeletal injury that might affect exercise participation. Physical activity levels were not part of the inclusion criteria and therefore it is assumed that participants ranged in fitness status prior to participation.

Table 3.1: Resting blood pressure of suitable participants (Mancia, Fagard, Narkiewicz, et al. 2013)

	Systolic (mmHg)		**Diastolic (mmHg)**
Resting blood pressure			
Pre-hypertensive/high normal	130-139	and/or	85-89
Hypertensive (stage 1)	140-159	and/or	90-99

Participants were recruited in a number of ways:

1) Recruitment posters were displayed in local pharmacies and within Buckinghamshire New University
2) Recruitment email sent bi-monthly via the Buckinghamshire New University digest emails (delivered to all campus staff)
3) Leaflets were delivered to local houses
4) Recruitment information was printed in the local newsletters of Bucks 50 plus forum and University of the 3rd age
5) Recruitment leaflets were handed out at local bowling and Movers and Shakers groups
6) Recruitment talk delivered to the V valley plus group (Marlow, Buckinghamshire)

To ensure all participants met the criteria, prospective participants were screened before data collection. Pre-participation screening included three resting BP measurements (to determine pre-hypertension/stage 1 hypertension status), in accordance with the protocols described in section 3.4, together with an exclusion criteria checklist and a physical activity readiness questionnaire (PAR-Q plus; Appendix 1) (Jamnik, Warburton, Makarski, et al. 2011). The study procedures were explained in detail and information sheets for each specific study was provided. An example of an information sheet can be found in Appendix 2. If any exclusion criteria were highlighted during pre-participation screening the participant was not invited to participate in the study.

3.4 Resting and 24-hour blood pressure recording

3.4.1 Equipment

Cardiotens and Card(X) plore 24-hour holter devices were used to take both resting and 24-hour BP measurements (Meditech, Hungary) (Figures 3.2 & 3.3). These devices are fully automatic, oscillometric BP monitors and have been clinically validated (against the gold standard mercury sphygmomanometer) by the British Hypertension Society (BHS) and the US Association for the Advancement of Medical Instrumentation (AAMI) validation protocols (Barna, Keszei, and Dunai 1998). Annual servicing was carried out on the automatic devices to ensure they continued to meet the validation criteria. The reproducibility of 24-hour ambulatory BP across four separate time points are presented in Chapter 4 (Table 4.5).

Oscillometric devices are non-invasive and measure BP by occluding an artery by the automatic inflation of a pneumatic cuff. When no pulsatile blood flow is detected, the cuff pressure begins to decrease – as pressure decreases, blood begins to pass back through the artery, thus creating pulsatile blood flow (Babbs 2012). The cuff is able to monitor the change in pulsatile blood flow via the detection of oscillations. These oscillations increase in amplitude until the mean arterial pressure (MAP) is reached, they then start to decrease until

blood flow becomes normal (Babbs 2012). The systolic and diastolic values are then calculated with the help of an algorithm.

3.4.2 Fitting procedures

To fit the BP cuff, participants were seated with their non-dominant arm supported at the elbow and forearm positioned at mid sternum level (O'Brien, Asmar, Beilin, et al. 2003). Their back was supported and legs were uncrossed. The mid portion of the bicep was measured with a flexible measurement tape and the appropriate sized cuff was chosen (Table 3.2). The brachial artery was palpated and the midline of the bladder was placed at this point. The cuff was then wrapped and secured around the arm by means of Velcro which was attached to its adjoining surfaces.

Table 3.2: Blood pressure cuff fitting guide adapted from Meditech Cardiotens, 1998. Ambulatory blood pressure and ECG monitoring system: Users Guide.

Name	**Arm Circumference Range**
Normal adult	24-32cm
Small adult (child)	Under 24cm
Large adult	32-42cm

3.4.3 Measurement

Resting BP measurements were consistently taken with the fully automatic, oscillometric BP monitors (section 3.4.1) following 10 minutes of seated rest (Pickering, Hall, Appel, et al. 2005). During the measurement the arm was supported at the elbow and forearm positioned at mid sternum level (O'Brien, Asmar, Beilin, et al. 2003), the participant was seated comfortably with the back supported and legs uncrossed with feet flat on the floor (Pickering, Hall, Appel, et al. 2005). Measurements were taken three times on the non-dominant arm; each measurement was separated by 1 minute (O'Brien, Asmar, Beilin, et al. 2003). An average of the two lowest measurements was recorded as the resting BP (NICE 2011). Due to the effects of external variables on BP, participants were requested to avoid food (4 hours), caffeine (12 hours) and alcohol (24 hours) prior to a laboratory visit (Badrov, Bartol, Dibartolomeo, et al. 2013). Because of the known effects of bladder distension on resting BP, participants were also asked to void their bladder in advance of the testing session (Fagius and Karhuvaara 1989).

Ambulatory BP measurements were also taken with the fully automated BP monitors (section 3.4.1). The monitor was fitted to the non-dominant arm (section 3.4.2). This ensured consistency with resting measurements and also assisted with the continuation of normal day-to-day activities. The 24-hour device was programmed with the CardioVisions software programme (Version 1.20.0, Meditech, Hungary) to record BP at 30-minute intervals throughout the day and every 60 minutes at night (O'Brien et al., 2003). To ensure accurate recordings participants were advised to stop what they were doing, free their hand of any items and relax it by their side during each measurement. Caffeine and alcohol were avoided during 24-hour monitoring periods. Participants were also asked to complete a physical activity diary (Bouchard et al., 1983) (Appendix 3) for the 24-hour period. This tool determined the time the participants went to bed and got up. Participants were requested not to engage in organised sport activity and vigorous exercise.

3.5 Measurement of autonomic activity

The variability in cardiovascular parameters such as heart rate (HR) and SBP were used to provide indirect measurement of autonomic nervous system activity. Indirect measurements of autonomic function are popular due to their ease of measurement and limited invasiveness. Heart rate variability (HRV) and systolic blood pressure variability (BPV) provide information on autonomic activity via the examination of oscillations and rhythms that occur as a result of autonomic control of cardiac tissue (HRV) and vasomotor tone (systolic BPV). The following sections describe the physiological

interpretations of HRV and systolic BPV (section 3.5.1, section 3.5.2) and measurement techniques (section 3.6, section 3.7).

3.5.1 Heart rate variability

Heart rate variability is the beat-beat time variation recorded between consecutive heartbeats recorded on an electrocardiogram (ECG) in normal sinus rhythm (Routledge, Campbell, McFetridge-Durdle, et al. 2010). The time between successive beats, and therefore HRV, is influenced by a complex, dynamic interaction between neural and hormonal control systems, in addition to the mechanical effects of breathing (e.g. stretching of the atria, changing thoracic pressure) (Shaffer, Mccraty, Zerr, et al. 2014; Billman 2011). Heart rate variability reflects the responsiveness of the autonomic nervous system when faced with internal and external environmental demands (McMillan 2002). The more responsive a heart is (i.e. greater beat-beat variation) the more reflective it is of a healthy heart (Shaffer, Mccraty, Zerr, et al. 2014; Routledge, Campbell, McFetridge-Durdle, et al. 2010). Reduced HRV typically represents an attenuated regulatory capacity and therefore a decline in the ability of the autonomic nervous system to respond to change (Shaffer, Mccraty, Zerr, et al. 2014).

The clinical significance of these subtle variations in cardiac activity was described in 1965 when an association between reduced HRV of the fetal heart and fetal stress was discovered by Hon and Lee (Hon & Lee 1963). Heart rate variability was detected before an appreciable change in HR and could therefore identify abnormalities in autonomic function. Reduced HRV is associated with hypertension (Singh, Larson, Tsuji, et al. 1998; Kaftan and Kaftan 2000; Mussalo, Vanninen, Ikäheimo, et al. 2001) amongst other clinical conditions such as chronic heart failure, diabetes, obesity and myocardial infarction (Routledge, Campbell, McFetridge-Durdle, et al. 2010; Billman 2011; Thayer, Yamamoto, and Brosschot 2010). Low HRV correlates with all-cause mortality and is a predictor of future coronary health risk (Thayer, Yamamoto, and Brosschot 2010; Tsuji, Venditti, Manders, et al. 1994; Janszky, Ericson, Mittleman, et al. 2004; Vinik, Maser, and Ziegler 2011). The beneficial effects of isometric exercise on HRV in a hypertensive population is therefore of particular interest.

Heart rate variability recordings are most commonly taken over a period of 5-minutes to 24-hrs (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). The two major procedures for analysing HRV are frequency domain analysis and time domain analysis. Frequency domain analysis illustrates HRV as a function of frequency. The analysis reveals the cyclical nature behind the time lag between each QRS waveform (beat-beat interval/N-N interval) and plots the frequencies with which the length of the N-N interval changes (Routledge, Campbell, McFetridge-Durdle, et al. 2010) this provides an index of total power, and the

distribution of and ratio between low frequency (0.04-0.15 Hz) and high frequency (0.15-0.4 Hz) power activity.

The physiological interpretation of these frequencies remains a subject of debate and investigation (Heathers 2014; Billman 2013, 2011). Studies have shown that HF power is a useful marker of parasympathetic influences on the heart (Pagani, Lombardi, Guzzetti, et al. 1984; Malliani, Pagani, Lombardi, et al. 1991; Saul, Berger, Albrecht, et al. 1991; Akselrod, Gordon, Ubel, et al. 1981; Pagani, Lombardi, Guzzetti, et al. 1986). However, it has also been shown that sympathetic neural activity can modulate the HF component and therefore may not be categorically representative of parasympathetic activity (Taylor, Myers, Halliwill, et al. 2001). The interpretation of LF power has been controversial and although it has been previously labelled as a marker of sympathetic nerve activity, this is no longer accepted (Heathers 2012; Billman 2011, 2013; Heathers 2014). It is mostly concluded that the LF power represents a complex mix of sympathetic and parasympathetic activity (Saul, Berger, Albrecht, et al. 1991; Billman 2013); other likely contributors to this frequency band include baroreceptor (Laborde, Mosley, and Thayer 2017) and renin angiotensin aldosterone system activity (RAAS) (Akselrod, Gordon, Ubel, et al. 1981).

Considering the long held beliefs that the LF and HF frequencies were exclusively representative of specific autonomic branches, the ratio between these frequencies (LF/HF) has been assumed to represent sympathovagal balance (Malliani, Pagani, Lombardi, et al. 1991; Pagani, Lombardi, Guzzetti, et al. 1986). However, this representation is based on the assumption that the LF component reflects sympathetic activity, the HF component reflects parasympathetic activity and these autonomic branches work together in a linear and reciprocal way (Billman 2013). Although the reciprocal relationship between the autonomic branches is true during specific orthostatic challenges (Shaffer, Mccraty, Zerr, et al. 2014) recent reviews illustrate the need to apply caution when interpreting this variable unless it is representative of a relative relationship between sympathetic and parasympathetic activity during specific autonomic regulatory tasks (Shaffer, Mccraty, Zerr, et al. 2014; Heathers 2014).

Time domain analysis detects changes in the N-N intervals over time (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). Common time domain indices include SDNN (standard deviation of all normal N-N intervals), rMSSD (square root of the mean of the sum of squares of successive N-N interval differences) and pNN50% (number of successive N-N intervals differing by >50 ms divided by the total number of successive N-N intervals). The SDNN is a marker of overall variability, whilst rMSSD and pnn50% have been found to correlate strongly with HF (Kleiger, Stein, and Bigger 2005; Shaffer, Mccraty, Zerr, et al. 2014; Massin, Derkenne, and von Bernuth 1999) and are therefore interpreted as markers of vagal tone (Laborde, Mosley, and Thayer 2017).

3.5.2 Systolic blood pressure variability

Blood pressure is not a constant variable; rather, it shows spontaneous fluctuations beat-beat, minute-minute, hour-hour, day-to-day (Höcht 2013). Blood pressure variability (BPV) is a representation of a complex interplay amongst different neurohumoral systems. In normal physiological conditions BP fluctuations indicate an adaptive response to environmental, behavioural and emotional stimuli occurring in daily life. As discussed in Chapter 2, (section 2.0) the physiological mechanisms responsible for these adaptive responses are changes in central sympathetic drive, afferent transmission from arterial and cardio-pulmonary reflexes and circulating hormones (angiotensin II, bradykinin, endothelin-1, insulin and nitric oxide). However, excessive fluctuations have been shown as independent contributors to cardiovascular events and mortality (Eguchi 2016; Hansen, Thijs, Li, et al. 2010). In 2010, Rothwell showed that hypertensive patients with higher BPV were at increased risk of cardiovascular events (Rothwell, Howard, Dolan, et al. 2010) whilst other studies have highlighted the elevated risk of target organ damage (Parati, Pomidossi, Albini, et al. 1987; Palatini, Penzo, Racioppa, et al. 1992; Frattola, Parati, Cuspidi, et al. 1993; Mancia, Parati, Hennig, et al. 2001).

Systolic blood pressure variability is frequently assessed in the very short term (beat-beat) following exercise interventions (Kingsley and Figueroa 2016). The mechanisms behind large fluctuations in these measurements are suggested to indicate increases in central sympathetic drive and decreased arterial/cardiopulmonary reflexes (Parati, Ochoa, Lombardi, et al. 2013). Beat-beat variation can be analysed using a time domain measure (coefficient of variation or standard deviation) and via spectral analysis. Spectral analysis of BPV has become a popular tool for the estimation of neural influences on vasomotor tone and therefore BP regulation. It has been shown that LF power (0.077– 0.15Hz) of systolic BPV reflects vascular sympathetic tone (Cevese, Grasso, Poltronieri, et al. 1995; Montano, Lombardi, Gnecchi Ruscone, et al. 1992; Stafford, Harris, and Weissler 1970) and closely correlates with muscle sympathetic nerve activity during sympathetic activation (Pagani, Montano, Porta, et al. 1997). It has also been shown that LF systolic BPV is raised in hypertensive patients (Lucini, Mela, Malliani, et al. 2002).

It has been suggested that autonomic modulation of HR is not an important determinant of BP powers in the LF regions (Parati, Saul, Di Rienzo, et al. 1995). This was highlighted by Saul *et al*., (1991) who found that cardiac autonomic blockade eliminated only a fraction of BPV at frequencies lower than 0.15Hz (Saul, Berger, Albrecht, et al. 1991). Whilst hypertensive patients often display autonomic dysfunction that manifests as reduced HRV and increased BPV, the neural mechanisms responsible for the BP lowering effects of exercise therapy are still widely debated (Kingsley and Figueroa 2016). Considering that the autonomic regulation of HRV and BPV are independent of each other it would be

considered important to measure both variables to help determine the autonomic effects of IHG exercise (Chapter 6).

3.6 Measurement of heart rate variability

Throughout the current thesis, HRV was assessed at rest (Chapter 4) and during 24-hour ambulatory recordings (Chapter 4, Chapter 6). Heart rate variability was recorded and analysed using electrocardiography (ECG) taken from a 2-lead (Cardiotens, Meditech, Hungary) (Figure 3.2) or 3 lead (Card(X)plore, Meditech, Hungary) (Figure 3.3) configuration recommended by the Holter device manufacturer (Figure 3.4). To ensure within-subject consistency, participants were fitted with the same model unit throughout data collection.

Using time and frequency domain analysis, HRV was calculated using the CardioVisions software (Version 1.20.0, Meditech, Hungary). The analysis is based on the Task Force document created by the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). This will be further described in sections 3.6.3 and 3.6.4.

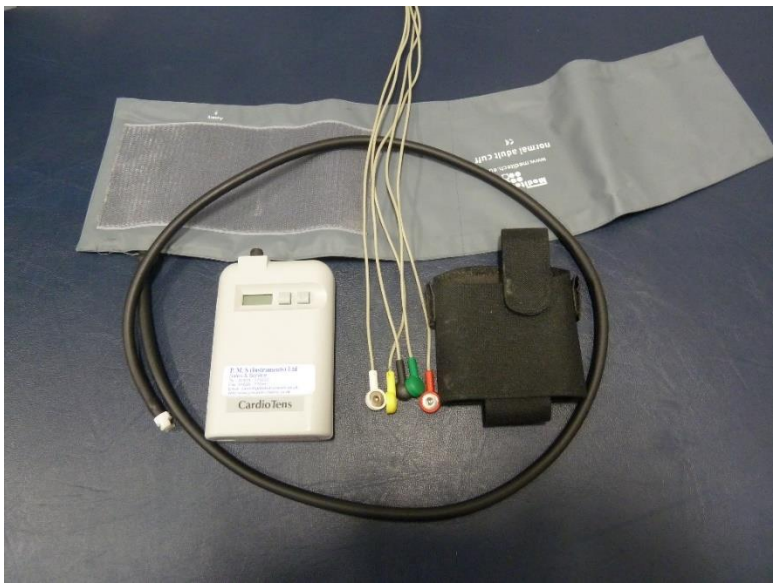

Figure 3.2: Cardiotens ambulatory blood pressure and ECG recorder (Cardiotens, Meditech, Hungary)

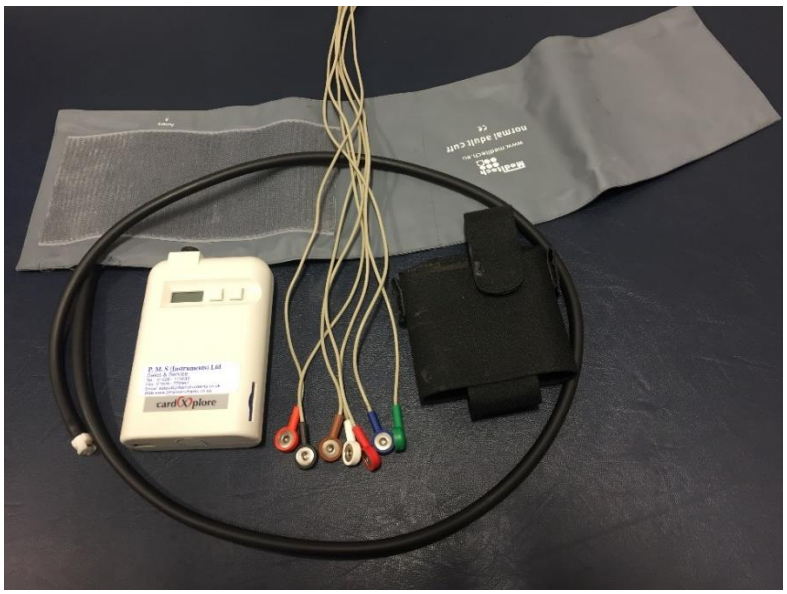

Figure 3.3: Card (X) plore ambulatory blood pressure and ECG monitor (Card(X)plore, Meditech, Hungary)

3.6.2 Electrode fitting

Due to the possibility of interference from static electricity, participants were asked to avoid wearing synthetic clothes (viscose, acrylic, nylon and polyester) during monitoring. Whilst participants were lying supine their skin was prepared with sterile wipes and the shaving of chest hair (if necessary). Depending on the device, a two (Figure 3.4A, Box 3.1) or three lead (Figure 3.4B, Box 3.1) ECG electrode configuration was chosen based on the manufacturer's recommendations. To ensure correct placement, an online observation of the ECG signal was carried out using the CardioVisions software (Version 1.20.0, Meditech, Hungary). With the participant remaining supine, resting measurements were taken upon completion of participant set-up. The monitor was set to record for ten minutes in which the last 5 minute segment was used within the analysis. Participants were requested to rest quietly during this period.

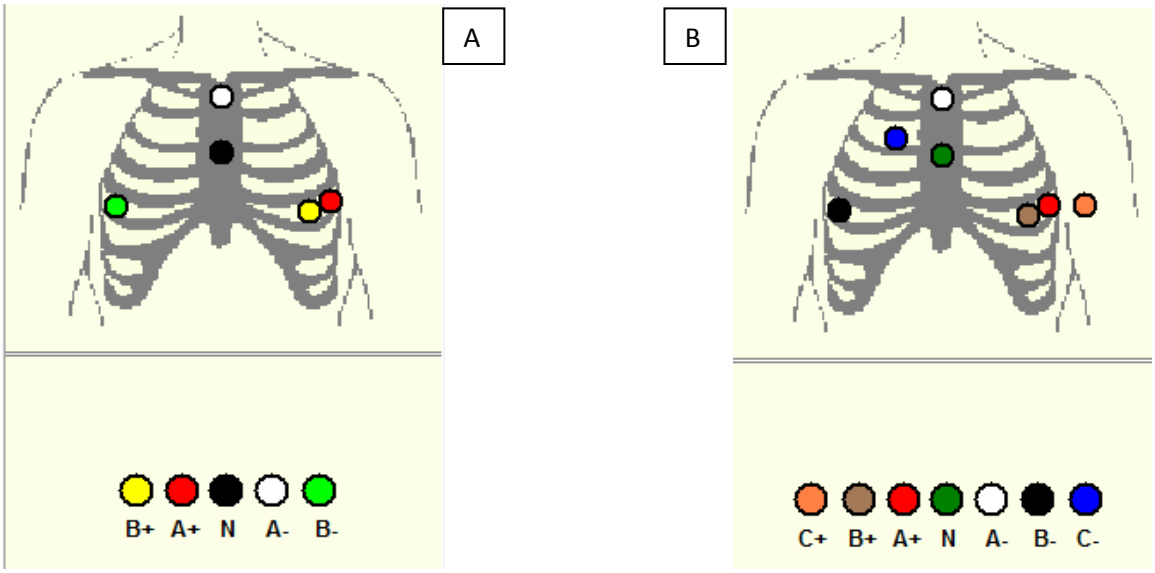

Figure 3.4: (A) 2 lead ECG electrode configuration for Cardiotens (Meditech) set-up. (B) 3 lead ECG electrode configuration for Card(X)plore (Meditech) set-up.

Box 3.1 ECG electrode placement

2-lead placement (Cardiotens, Meditech, Hungary)

- Yellow: left anterior axillary line, intercostal space 5
- Red: left anterior axillary line, intercostal space 5
- Black: sternum
- White: manubrium sterni
- Green: Right anterior axillary line, intercostal space 5

3-lead placement (Card(X)plore, Meditech, Hungary)

- Orange: left posterior axillary line, intercostal space 5
- Brown: left anterior axillary line, intercostal space 5
- Red: left anterior axillary line, intercostal space 5
- Green: sternum
- White: manubrium sterni
- Black: right anterior axillary line, intercostal space 5
- Blue: right sternal border, 2nd rib

Ambulatory ECG recordings were taken continuously throughout a 24-hour period. As described in section 3.4.3, caffeine and alcohol were avoided during 24-hour monitoring periods and participants were also asked to complete a physical activity diary (Bouchard, Tremblay, Leblanc, et al. 1983) (Appendix 3) for the 24-hour period.

There is continuing debate with regards to the benefits of controlling breathing frequency during resting autonomic function measurements (Thayer, Loerbroks, and Sternberg 2011). Researchers

believe that a low breathing frequency (≤ 8.5 breaths per minute/0.1 Hz) disturbs the LF component of spectral analysis (Aubert, Seps, and Beckers 2003) and may cause both the LF and HF to overlap – thus making interpretation of LF difficult. Regardless of paced breathing, the interpretation of the LF spectral component is difficult because it represents both branches of the autonomic system – its use in determining autonomic function is therefore not particularly useful. On the other hand, the HF band, strongly representative of the vagal branch of the autonomic system, would not seem to be affected by breathing frequency (Bloomfield, Magnano, Bigger, et al. 2001; Pinna, Maestri, La Rovere, et al. 2006; Sinnreich, Kark, Friedlander, et al. 1998). However, others suggest that the use of a metronome to control breathing frequency may unintentionally change the acute functioning of the autonomic nervous system (Bloomfield, Magnano, Bigger, et al. 2001). Paced breathing is thought to stimulate parasympathetic activity (Laborde, Mosley, and Thayer 2017). Altering the autonomic system in this way may elicit invalid results and any beneficial changes to the vagal branch of the autonomic system following a therapeutic intervention may therefore not be revealed. Tracking changes in vagal-related indices (i.e. HF frequency) is of great interest from a clinical and health perspective (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996) and it is this frequency band that is of particular interest to the current research. For these reasons controlled breathing was not implemented into the resting HRV procedures.

3.6.3 Time-Domain analysis

Time domain statistical analysis detects and interprets the time differences between normal heart beats. All normal heart beats consist of a QRS waveform, representing ventricular depolarisation. The time between each QRS waveform is termed the R-R interval. Because the R wave is the most prominent part of the QRS complex, its peak is used to detect the inter-beat interval (milliseconds) between successive beats. Peak detection is realised by a pre-programmed algorithm (Cardiovisions, Version 1.20.0, Meditech, Hungary). Beat-beat intervals were considered valid for analysis if they were different from the previous interval by less than 20%. The ECG processing algorithms are successfully tested on the MIT-BIH arrhythmia database and provide 99.8 % beat detection accuracy. Despite pre-programmed algorithms, data was screened for unusual ECG rhythms; frequent missed beats (e.g. 2nd and 3rd degree heart block) were not always disregarded by the programme and therefore needed to be visually detected.

Once the distance between all peaks was calculated, a time event series or tachogram is generated (Figure 3.5); a time event series enables SDNN, rMSSD, pNN50% to be calculated based on the time (millisecond) differences between the inter-beat intervals (Figure 3.6)

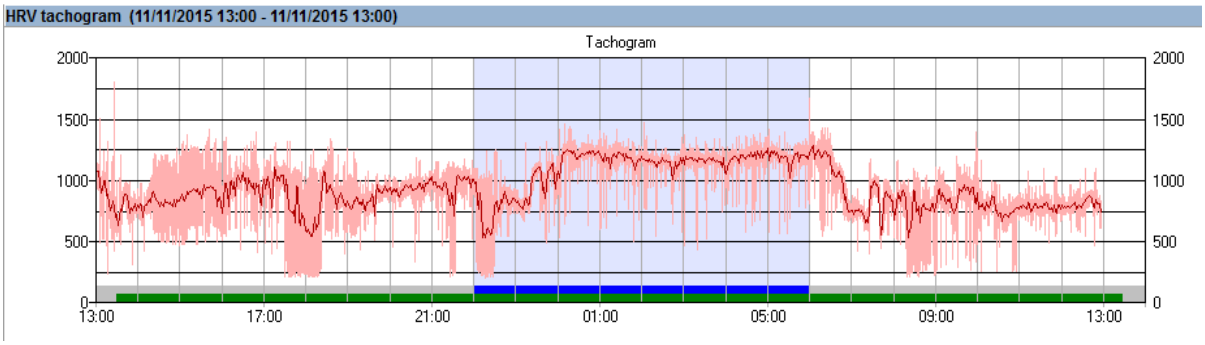

Figure 3.5: A tachogram representing the change in R-R intervals throughout an entire 24-hr period

Figure 3.6: R-R intervals are represented by two black bi-directional arrows, indicating the time distance between each peak within the QRS complex. The time in milliseconds is outlined along the x axis

3.6.4 Frequency domain analysis

Frequency domain analysis, by definition, decomposes any steady, stationary, fluctuating time-dependent signal into its sinusoidal components (Aubert, Seps, and Beckers 2003). The tachogram plotting the length of each R-R interval against the duration of the recording is based on individual beats and is therefore erratic and not steady. A software algorithm provided equidistant sampling and power spectral analysis (fast fourier transform) then computed the signal over time into a frequency spectrum (Cardiovisions, version 1.20.0, Meditech, Hungary). The frequency regions applied for the LF component of HRV was 0.04 – 0.15 Hz and 0.15 – 0.4 Hz for the HF component (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). Figure 3.7 provides an illustrative representation of these frequency components.

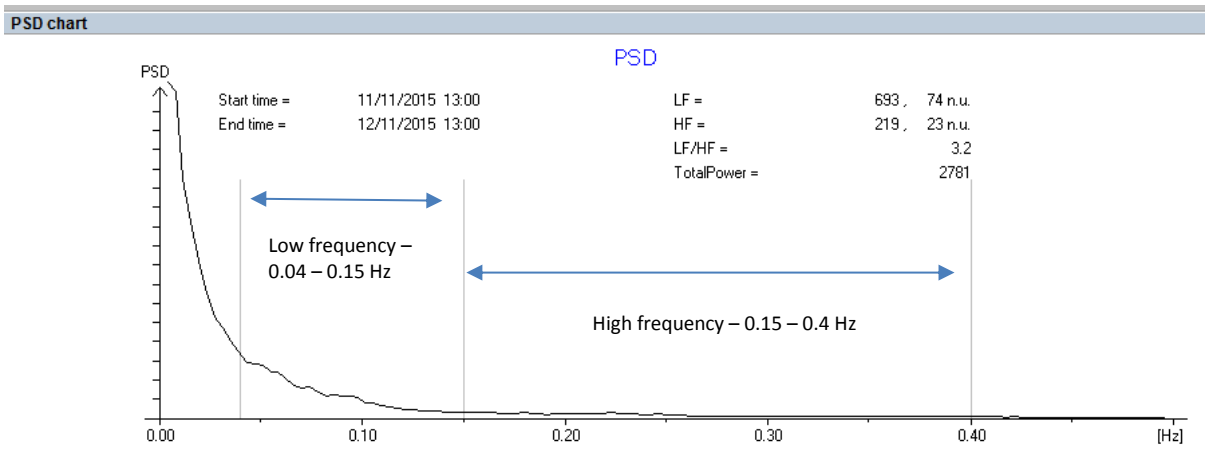

Figure 3.7: An example of heart rate variability spectra taken from a 24-hr ambulatory electrocardiogram reading. The power spectral density graph highlights the low frequency and high frequency bands. Each frequency component is calculated as the area under the curve

3.7 Systolic blood pressure variability

Beat to beat measurements of BP were taken with the Finometer MIDI device (Finapres, TNO Instruments, Amsterdam, Netherlands). This device carries out its measurements using the volume clamp method. This method was developed by Penaz in 1973 and has since been used in many commercially available, non-invasive continuous BP systems (Bogert and van Lieshout 2005). Blood flow creates dynamic pulsatile loading and unloading, thus constantly varying the arterial diameter. The volume clamp method ensures that the diameter of the measured artery is kept constant.

The Finometer (Finometer MIDI, Finapres, TNO Instruments, Amsterdam, Netherlands) utilises a finger cuff comprised of a 50µm plastic bladder – this bladder inflates and deflates via a short air hose that is

connected to a microprocessor block attached (via Velcro straps) to the participants wrist (Wesseling, de Wit, van der Hoeven, et al. 1995). Any change in the diameter of the artery created by changes in blood flow is detected by infrared photo-plethysmograph, this is housed within the finger cuff (Bogert and van Lieshout 2005). Photo-plethysmography detects changes in blood flow and therefore arterial diameter. For example, during systole there is an increase in blood within the artery, this change in blood volume (and therefore vessel diameter) activates a fast servo-controller system which regulates finger cuff pressure and thus prevents any change in vessel diameter.

This fast servo-controller system ensures that the transmural pressure (difference between intra-arterial and cuff pressure) is kept at zero. It is proposed therefore that when the transmural pressure equals zero the intra-arterial pressure equals the cuff pressure (Bogert and van Lieshout 2005). To ensure the values provided represent brachial artery BP levels a height sensor is used to calibrate for the height discrepancy between the digital artery and the brachial artery.

3.7.1 Set-up and calibration

Lying supine, the microprocessor block was attached to the participant's wrist on their dominant side. The dominant side was selected due to the attachment of the 24-hour ambulatory blood pressure monitor on the non-dominant side (Section 3.4.3). Based on Figure 3.8 an appropriate cuff size was selected. The finger cuff was then precisely fitted to the intermediate phalange of the middle finger. Care was taken to ensure that the infrared sensors were placed at either side of the finger; this was to ensure they were placed alongside the location of the digital arteries. Once the cuff was attached a firm pull was applied to ensure a secure fitting.

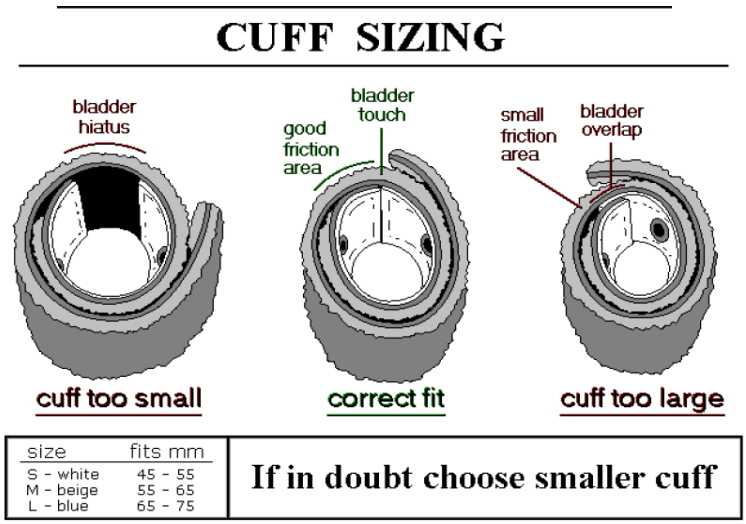

Figure 3.8: Fitting guide for finger cuff. Illustration taken from the Finometer user guide (Finapres Medical Systems BV 2002)

Height sensor nulling is an important feature of the Finometer MIDI calibration. As BP is most accurately measured at the level of the heart (O'Brien, Asmar, Beilin, et al. 2003) a height correction system is used to sense the position of the finger with respect to the heart. Whilst holding the transducers together, a height nulling procedure is carried out. The two transducers were then positioned at the finger cuff and onto a Velcro strap attached to the arm at heart level. The height of the liquid column running between the sensors is measured by a pressure transducer – this height is automatically subtracted from the finger pressure. Due to the supine orientation of the participants the height difference was consistently small and maintained (between -1mmHg and +1mmHg). The monitor was set to record for ten minutes in which the last five minute segment was used within the analysis. Participants were requested to rest quietly during this period

Cold hands can cause problems for the accurate functioning of the Finometer MIDI device. If fingers are cold, the arteries are contracted and circulation in the hand becomes prohibited (Wesseling, de Wit, van der Hoeven, et al. 1995). To prevent problematic recordings caused by cold hands, a rubber water bottle was filled with warm water, the participants' hand rested on this for the duration of each measurement.

When compared to intra-arterial pressure recordings, diastolic and mean pressure measurements taken with the Finometer MIDI have met the validity criteria for the American Association for the Advancement of Medical Instrumentation criteria (AAMI) (Guelen, Westerhof, Van der Sar, et al. 2003). To meet this criteria measurements as compared with intra-arterial recordings need to be within 5mmHg with a standard deviation of 8mmHg (Schutte, Huisman, van Rooyen, et al. 2004). However, as compared with the Finometer Midi, superior validity has been found in the Finometer PRO device (Guelen, Westerhof, Van der Sar, et al. 2003; Schutte, Huisman, van Rooyen, et al. 2004), this is owing to the return to flow calibration procedure (Schutte, Huisman, van Rooyen, et al. 2004). Despite this finding, the Finometer MIDI is regarded as a particularly useful device to detect the dynamics of the cardiovascular system and thus relative changes in BP and therefore BPV (Imholz, Imholz, Wieling, et al. 1998; Bos, Imholz, van Goudoever, et al. 1992; Omboni, Parati, Frattola, et al. 1993). As compared with intra-arterial recordings the validity of spectral measures within the LF and HF domain have been tested on the Finapres device (a predecessor of the more advanced Finometer). Validity was established for diastolic and mean BP variability but not systolic variability within the LF domain (Omboni, Parati, Frattola, et al. 1993). Despite low validity, systolic BPV is most commonly associated with long-term health conditions (Höcht 2013); determining the reproducibility of this would therefore be important prior to its use in assessing post intervention changes in this variable (Chapter 4).

3.7.2 Analysis

Spectral analysis of beat to beat BP data was analysed using an online software programme (Cardioseries v2.4, Brazil). All tachograms were visually inspected for abnormally shaped and ectopic beats which were subsequently replaced by a linear interpolation algorithm. Systolic BP data was resampled at 2Hz and Fast Fourier transform was applied to 128-point sections of the 5-minute resting recording. Power densities in the low frequency ranged between 0.07-0.15 Hz (Höcht 2013).

3.8 Isometric handgrip

Lab based isometric handgrip tests (Chapter 5, section 5.2, Chapter 6, section 6.2) were carried out using a grip force transducer (Powerlab, AD instruments, Sydney Australia). The force (measured in Newtons) output was detected by linear load cells located within the transducer and recorded by a data acquisition system (Powerlab, AD instruments, Sydney Australia) which was interfaced with a data analysis software programme (LabChart Pro 7, AD instruments, Sydney, Australia).

The interfacing of the acquisition system with the data analysis programme allowed for the measurement of maximal voluntary contractions (MVC). In addition, the force displacement, displayed on a computer screen enabled participants to monitor force when a specific force output was required (for example 30% MVC).

Isometric handgrip exercise was always carried out on the non-dominant side using a standardised position (Roberts, Denison, Martin, et al. 2011). Participants were seated with their back supported and non-dominant arm adducted with 90 degrees of flexion at the elbow joint (Alkurdi and Dweiri 2010). The transducer was held in the hand which was kept in a neutral position. During isometric contractions participants were instructed to maintain the position of the body and to breathe evenly throughout the exercise in order to avoid the Valsalva manoeuvre.

The non-dominant hand was kept consistent throughout this thesis due to the concurrent measurement of BPV (see section 3.7) on the dominant hand during lab-based tasks (Chapter 5 & 6). Both alternating isometric handgrip training (Badrov, Bartol, Dibartolomeo, et al. 2013; McGowan, Visocchi, Faulkner, et al. 2007; Peters, Alessio, Hagerman, et al. 2006; Taylor, McCartney, Kamath, et al. 2003) and unilateral isometric handgrip training (Wiley, Dunn, Cox, et al. 1992; McGowan, Levy, Millar, et al. 2006; McGowan, Visocchi, Faulkner, et al. 2007; Millar, Levy, Mcgowan, et al. 2013) has been prescribed in earlier studies. Both training methods have resulted in significant improvements in resting SBP and only one study has directly compared these training methods (McGowan, Visocchi, Faulkner, et al. 2007). In this study findings showed that unilateral training reduced SBP by -8mmHg

and alternating unilateral handgrip training showed a superior reduction of -15mmHg. However, other studies using unilateral handgrip training have found similarly large reductions in resting SBP (Table 4.4) and therefore the superiority of bilateral handgrip training remains unconfirmed.

3.8.1 A comparative analysis between the PowerLab handgrip dynamometer and the ergonomic hand exerciser using electromyography.

Chapter 5 describes the validation of the use of the CR-10 perceived exertion scale (Figure 3.9) to self-regulate isometric handgrip exercise. The validation was carried out on a lab-based handgrip dynamometer (Figure 3.8) (Powerlab 26T, AD instruments LTD, Sydney, Australia). Following validation, exercises were prescribed to participants using a portable, ergonomic hand exerciser (Figure 3.10) (Rolyan, Patterson Medical, Nottinghamshire, UK) and the CR-10 scale (Borg, 1982) (Chapter 5).

The ergonomic hand exerciser (Figure 3.10) was chosen based on its design which replicated the shape of the lab-based handgrip dynamometer (Figure 3.9) (Powerlab 26T, AD instruments LTD, Sydney, Australia). To ensure that the biomechanical advantage provided by the ergonomic hand exerciser was similar to that of the lab-based handgrip dynamometer electromyography (EMG) was recorded from the flexor carpi ulnaris during a 2-minute self-regulated (CR-10, “Level-6”) isometric handgrip exercise.

Following the completion of the validation procedures outlined in Chapter 5, six participants returned to the laboratory (within 7 days) on one occasion. Participants were seated comfortably whilst prepared for EMG recordings. Electrical activity of the flexor carpi ulnaris was recorded using a surface EMG system (Powerlab, AD instruments, Sydney Australia). Firstly the skin was prepared; ethanol was used to clean the skin and excess hair was removed if necessary. Positive and negative electrodes were placed 10mm apart on the muscle belly (on the line between the medial epicondyle of the elbow and styloid process of the ulna) of the non-dominant arm, in the direction of the muscle fibres. The reference electrode was placed over the styloid process of the ulna.

Whilst retaining their comfortable seated position (back supported, legs uncrossed, feet flat on the floor) participants held the handgrip dynamometer in their non-dominant hand whilst holding their arm adducted with 90 degrees of flexion at the elbow joint (Alkurdi and Dweiri 2010). A brief isometric handgrip warm-up was then completed using three, 15 second contractions at approximately 50%, 75% and 90% of maximal effort. On completion of the warm-up, the CR-10 scale (Figure 3.9) was introduced. The following explanation was given to participants to read;

"During the exercise bout, I want you to pay close attention to how hard you feel the exercise is. The feeling should reflect your total amount of fatigue, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as arm pain, shortness of breath or exercise intensity but try to concentrate on your total, over all feeling of exertion. Try not to underestimate or overestimate your feelings of exertion; be as accurate as you can" (Modified from Faulkner and Eston, 2007).

Rating	**Descriptor**
0	Nothing at all
1	Very light
2	Light
3	Moderate
4	Somewhat hard
5	Hard
6	
7	Very hard
8	
9	
10	Maximal

Figure 3.9: Category Ratio Scale (CR-10 Scale)

An anchoring procedure was then used to assist the participant in putting into context the sensations of exercise intensity (Nobel and Robertson, 1996). Resuming their arm (90 degrees of flexion at the elbow joint) and comfortable seating position (back supported, legs uncrossed, feet flat on the floor), participants held the dynamometer loosely and were asked to *"think about your feelings of exertion and assign a rating of 0 to those feelings".* Following this, participants were instructed to maximally grip the handgrip device for 3-5 seconds (breathing evenly throughout). Prior to the contraction, participants were asked to *"think about the feelings of exertion at the end of the contraction and to assign a rating of 10 to those feelings"*. The maximal exertion task was repeated 2 more times with a 1-minute rest in between. The participants' MVC and EMG_{peak} were recorded. EMG_{peak} was determined by establishing the highest torque value and calculating the average EMG activity recorded 0.25 seconds prior to maximum torque (Wiles, Allum, Coleman, et al. 2008).

Finally, participants were asked to carry out 2 x 2 minute contractions, self-regulated at an intensity level of CR-10 "Level-6" (Chapter 5). A 10-minute rest was provided between contractions. One contraction was carried out on a portable, ergonomic hand exerciser (Figure 3.10) (Rolyan, Patterson Medical, Nottinghamshire, UK) and the other contraction was carried out on a handgrip dynamometer (Figure 3.9) (Powerlab 26T, AD instruments LTD, Sydney, Australia). These were carried out in a randomised order.

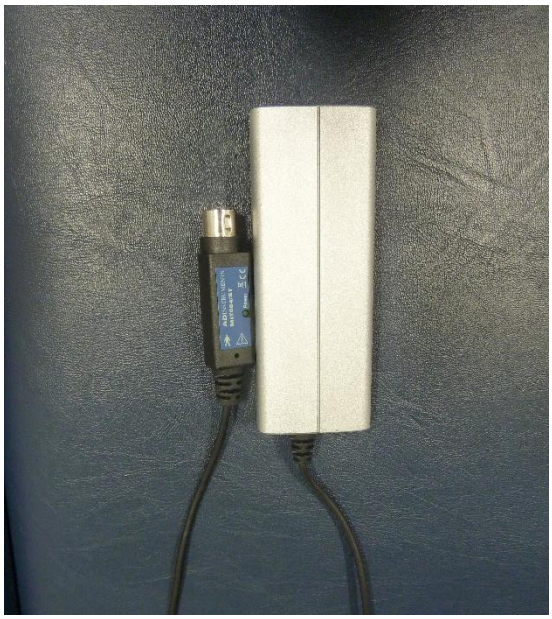

Figure 3.9: Handgrip dynamometer (Powerlab 26T, AD instruments LTD, Sydney, Australia)

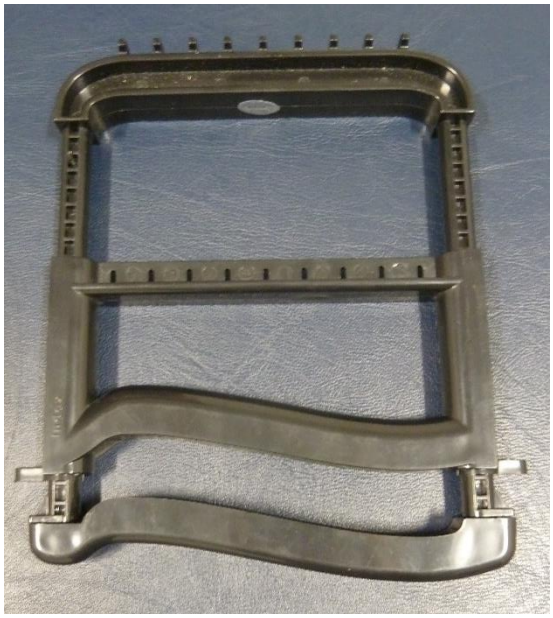

Figure 3.10: Ergonomic hand exercise (Rolyan, Patterson Medical, Nottinghamshire, UK)

The raw EMG signal was recorded by a data acquisition system (Powerlab, AD instruments, Sydney Australia) which was interfaced with a data analysis software programme (LabChart Pro 7, AD instruments, Sydney, Australia). The signal was recorded at a sample rate of 1000Hz and filtered using band-pass filters with cut off frequencies set at 10Hz and 500Hz which were then full wave rectified (Remaley, Fincham, McCullough, et al. 2015). Average EMG was determined for each 2-minute

contraction and its percentage of EMG_{peak} was calculated. The agreement between %EMG for each handgrip tool was assessed using Bland–Altman plots with 95% limits of agreement (LOA).

Figure 3.11 illustrates the individual (black circles) and average differences (dotted line) in %EMG achieved whilst carrying out 1 x 2 minute isometric contraction on each dynamometer. The dotted line shows that %EMG during a 2-minute isometric contraction on the ergonomic hand exerciser (Rolyan, Patterson Medical, Nottinghamshire, UK) may differ from the handgrip dynamometer (Powerlab 26T, AD instruments LTD, Sydney, Australia) by an average of -1.2% (range -4.6 – 0.5). These differences are small and the range of values fall well within the LOA (Figure 3.11). It can be concluded that the ergonomic hand exerciser (Rolyan, Patterson Medical, Nottinghamshire, UK) provides similar biomechanical advantage over the handgrip dynamometer (Powerlab 26T, AD instruments LTD, Sydney, Australia) when performing a 2-minute self-regulated isometric hand grip contraction. This agreement showed that participants regulated the isometric exercise intensity with similar levels of muscle recruitment. Considering the relationship between EMG and MVC (Wiles, Coleman, and Swaine 2010) it can therefore be assumed that self-regulated force will remain relatively consistent when performing the isometric contraction on the ergonomic hand exerciser (Rolyan, Patterson Medical, Nottinghamshire, UK).

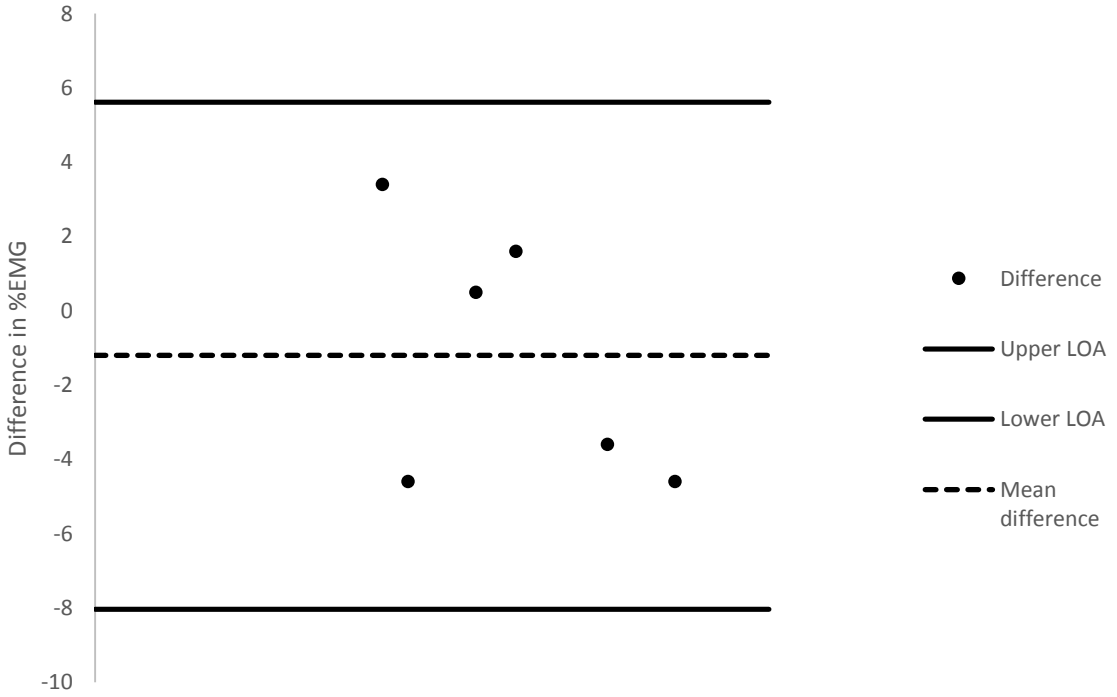

Figure 3.11: Bland Altman plot displaying differences in %EMG during an isometric handgrip contraction performed on the Powerlab dynamometer and ergonomic hand exerciser. Difference: difference between %EMG measurements (ergonomic hand exerciser – powerlab dynamometer). The dashed line displays the mean difference score. The solid black lines display the mean difference ± 1.96*SD (Limits of agreement, LOA)

Chapter 4: Reproducibility of 24-hour ambulatory blood pressure and measures of autonomic function

4.1 Introduction

As discussed in Chapter 2, (section 2.0) hypertensive adults display a persistent elevation of systolic and/or diastolic BP, alongside a deterioration of optimal autonomic functioning characterised by a reduction in parasympathetic activity and an increase in sympathetic tone (Carthy 2014; Mussalo, Vanninen, Ikäheimo, et al. 2001, 2003). Chapter 3, (section 3.5) detailed two indirect methods of assessing an individuals' autonomic function; HRV and systolic BPV. The detection of meaningful changes to both blood pressure (BP) and markers of autonomic function is a pre-requisite for the proper interpretation of post treatment or intervention findings (Dietrich, Rosmalen, Althaus, et al. 2010). The study of these variables has obvious disadvantages with mood, alertness, time of day and nutritional intake all having a significant impact on the result (Verdecchia 2000). Isolating true biological variation from these confounding factors has proven difficult, with research to date showing limited consistency in the reliability of these variables (Sandercock, Bromley, and Brodie 2005; Reino-González, Pita-Fernández, Cibiriain-Sola, et al. 2015).

Although BP is traditionally measured at rest within a clinic environment, this method is commonly associated with the phenomena of white coat and masked hypertension whereby BP presents itself as artificially high or low (Keren, Leibowitz, Grossman, et al. 2015). Additionally, the placebo effect, observer bias and poor reproducibility limit the application of clinic measurements in the assessment of a therapeutic intervention (Pickering, Hall, Appel, et al. 2005; Mancia, Omboni, Parati, et al. 1995).

Ambulatory BP monitoring (ABPM) takes BP measurements at pre-set (e.g. 15 minutes or 30 minutes) intervals during a patients usual daily activities (O'Brien, Asmar, Beilin, et al. 2003). This type of measurement is popular because it removes observer bias and has been shown to minimise the influence of white coat hypertension (De La Sierra, Segura, Banegas, et al. 2011) and the placebo effect (Felício, Pacheco, Ferreira, et al. 2007; Mancia, Omboni, Parati, et al. 1995). Ambulatory BP monitoring could be more representative of true BP because it provides measurements during daily life activities, stresses and sleep all within the participant's familiar home environment. Recent findings provide clinical support for ambulatory monitoring which has been found to be better at predicting cardiovascular mortality (Dolan, Stanton, Thijs, et al. 2005). The National institute for Clinical Excellence now recommends ABPM as a gold standard measure for diagnosing hypertension and assessing treatment effects (NICE 2011). Despite this, relatively few studies use ABPM to evaluate the effects of exercise interventions, in particular isometric exercise interventions (Chapter 2; section 2.2.3).

Ambulatory BP monitoring has also been repeatedly shown to be more reproducible than resting measurements (Campbell, Ghuman, Wakefield, et al. 2010; Fotherby and Potter 1993; Mansoor,

McCabe, and White 1994; Stergiou, Baibas, Gantzarou, et al. 2002; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001; van der Steen, Lenders, Graafsma, et al. 1999) the typical error (TE; an estimate of the degree of uncertainty surrounding consecutive measurements) within resting measurements has been found to range from 12.5-7mmHg for systolic and 7-4.6mmHg for diastolic. This compares to ABPM where a TE of 8.2-2.3mmHg has been found for systolic readings and 4.6-1.5mmHg for diastolic (Campbell, Ghuman, Wakefield, et al. 2010; Fotherby and Potter 1993; Mansoor, McCabe, and White 1994; Stergiou, Baibas, Gantzarou, et al. 2002; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001; van der Steen, Lenders, Graafsma, et al. 1999).

Despite superior reproducibility in ABPM, differences in study design lead to large variances between studies. For example, those with poorer reproducibility typically recruited untreated stage 2 hypertensives (Stergiou, Baibas, Gantzarou, et al. 2002; van der Steen, Lenders, Graafsma, et al. 1999). It would seem that better reproducibility is found within normotensives (Ash, Walker, Olson, et al. 2013; Stergiou, Alamara, Salgami, et al. 2005) and treated hypertensives (Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001).

Although participant status likely influences reproducibility, the effect of familiarisation has not yet been evaluated. The novelty of wearing an ambulatory device for the first time might initiate a pressor effect (Calvo, Hermida, Ayala, et al. 2003; Hermida, Calvo, Ayala, et al. 2002). The superior reproducibility detected by Wendelin-Saarenhovi and colleagues could be attributed to a familiarisation trial included within the research design (2001). However, the data from the familiarisation trial was not included in the analysis and therefore its impact on subsequent measurements remains unknown (Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001). A study carried out by Musso and colleagues (1997) would suggest that familiarisation periods are required. They found that the average BP decreased over four successive monitoring periods (Musso, Vergassola, Barone, et al. 1997). However, TE was not reported, this measure of absolute reliability is fundamental for calculating appropriate sample size and for interpreting post intervention findings. Further investigation is required to determine consistency of ABPM across several successive trials.

As compared with BP, the reproducibility of indirect measures of autonomic function, in particular over the course of 24-hours, has received less attention. Resting HRV measurements have been frequently investigated with little consistency in the findings. Reliability based on intraclass correlation coefficients (ICCs) is often reported as good-excellent (ICC, 0.7-0.9) (Bertsch, Hagemann, Naumann, et al. 2012; Ginsburg, Bartur, Peleg, et al. 2011; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Pinna, Maestri, Torunski, et al. 2007; Sacre, Jellis, Marwick, et al. 2012). Whilst a high ICC between repeated measures is typically accepted to indicate a high level of reliability, it could also be an artefact of high between-subject variability (Pinna, Maestri, Torunski, et al. 2007; Hallman, Srinivasan, and

Mathiassen 2015). It is not uncommon for the same study to report a high ICC alongside large coefficients of variation (TE expressed as a percentage) (Ginsburg, Bartur, Peleg, et al. 2011; Hojgaard, Holstein-Rathlou, Agner, et al. 2005; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Pinna, Maestri, Torunski, et al. 2007; Ponikowski, Piepoli, Amadi, et al. 1996) suggesting high levels of biological variation and instances of random error (Hallman, Srinivasan, and Mathiassen 2015) In contrast, low coefficients of variation (CV) for both time (6-8%) and frequency domain (6-12%) have been reported in a large group of healthy individuals (n=70) (Sinnreich, Kark, Friedlander, et al. 1998) and a small sample of stage 1 hypertensives (n=8) (Parati, Omboni, Villani, et al. 2001). It has been suggested (Sandercock, Bromley, and Brodie 2005) that clinical populations (chronic heart failure, type 2 diabetics) display poorer levels of reliability (Lord, Senior, Das, et al. 2001; Ponikowski, Piepoli, Amadi, et al. 1996; Sacre, Jellis, Marwick, et al. 2012), however, given the small CV reported in stage 1 hypertensives (Parati, Omboni, Villani, et al. 2001) further analysis on this population is required. Whilst a much smaller volume of research exists, resting measures of beat-beat systolic BPV has shown similar inconsistencies with poor (Zöllei, Csillik, Rabi, et al. 2007; Hojgaard, Holstein-Rathlou, Agner, et al. 2005), good (Parati, Omboni, Villani, et al. 2001; Bartels, Jelic, Gonzalez, et al. 2004) and excellent (Ditor, Kamath, Macdonald, et al. 2005) reliability being reported for the LF component of systolic BPV. The limited findings in addition to variations within the chosen statistical calculations pose problems for comparison across studies.

Unlike resting HRV measurements, a smaller amount of research exists on ambulatory recordings of autonomic function. Direct comparisons between resting and ambulatory recordings have shown that longer ambulatory recordings display lower variability (Pitzalis, Mastropasqua, Massari, et al. 1996; Tarkiainen, Timonen, Tiittanen, et al. 2005). To the researcher's knowledge, only 3 studies have measured the reproducibility of HRV recorded over 24-hours. These specific studies found CV for time domain components ranging from 10-53% (Kleiger, Bigger, Bosner, et al. 1991; Pitzalis, Mastropasqua, Massari, et al. 1996) and 16-40% (Bigger, Fleiss, Rolnitzky, et al. 1992; Kleiger, Bigger, Bosner, et al. 1991) for frequency domain components. Although these results reflect superior reliability to those generally found during resting measurements (Ginsburg, Bartur, Peleg, et al. 2011; Hojgaard, Holstein-Rathlou, Agner, et al. 2005; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Pinna, Maestri, Torunski, et al. 2007; Ponikowski, Piepoli, Amadi, et al. 1996) these studies are limited by the recruitment of healthy individuals only. In addition, studies recording 24-hour autonomic function or indeed resting measurements are limited by a lack of familiarisation trials and an exploration of the effect of habituation.

In light of the limited and confounding reliability data on non-invasive cardiovascular function measurements, this study will aim to assess the reproducibility of resting measurements of autonomic function (systolic BPV and HRV) and 24-hour ABPM and HRV in pre-hypertensive and hypertensive adults. The effects of familiarisation across four trials will be determined. Results will be used to determine small and moderate detectable changes and to calculate appropriate sample size estimates for randomised controlled trials.

4.2 Methodology

4.2.3 Participants

Eleven pre-hypertensive and hypertensive adults (≥ 55years) participated in the study. A detailed description of the recruitment process can be found in Figure 4.1. Ethical approval was obtained by the local research ethics committee and written informed consent was obtained from all participants prior to the beginning of the study.

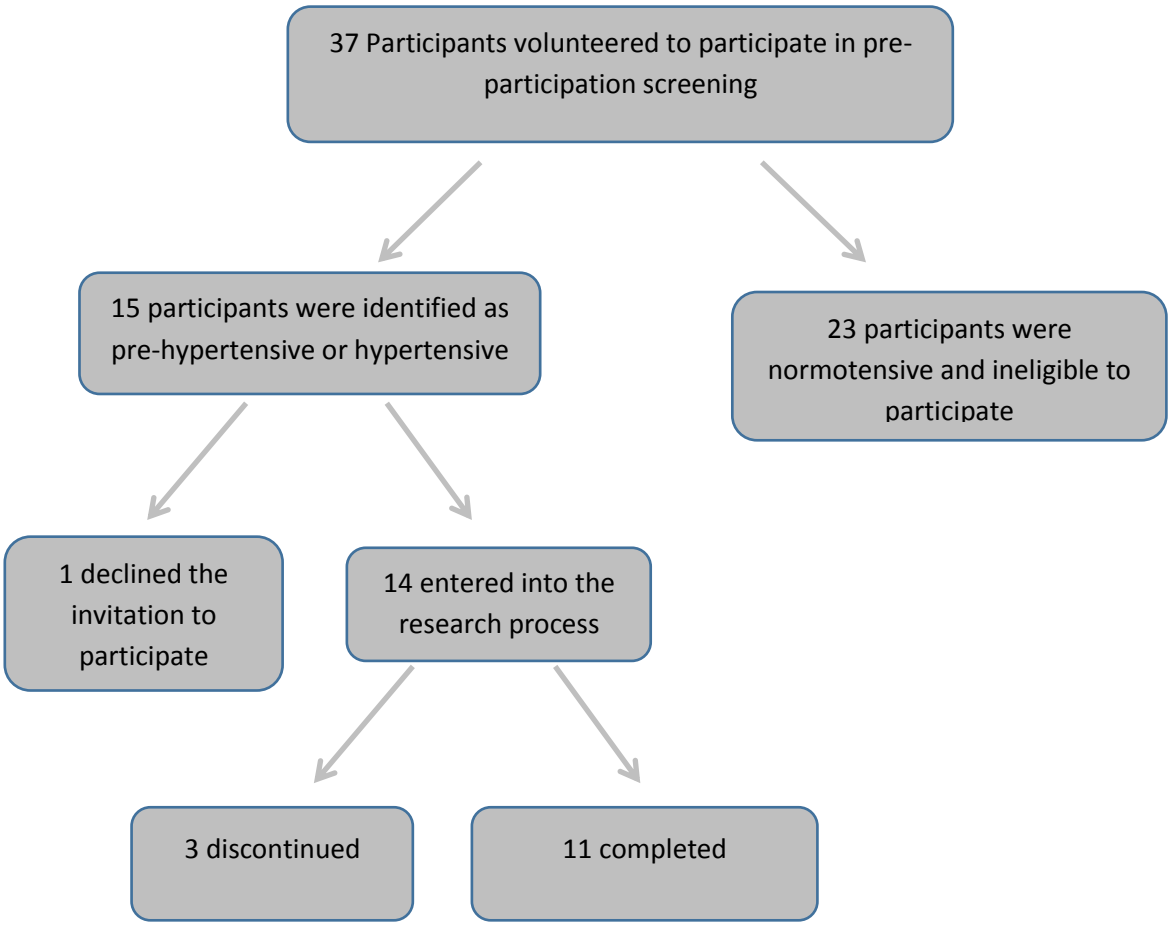

Figure 4.1: Recruitment process

Table 4.1: Participant baseline characteristics. Values are mean±SD

Characteristic	Participants (n = 11)
Gender	
Male	2
Female	9
Age (years)	67.2±4.7
Body mass (kg)	67.5±12
Height (cm)	162.4±8.3
Body mass index (BMI)	27.1±4.5
RSBP(mmHg)	141.7±8.9
RDBP (mmHg)	83.0±10.9
Medication classification	
ACE inhibitor	2
Diuretic	1
Alpha blocker	1

RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure.

Note: Six participants were classed as having isolated systolic pre-hypertension/hypertension and was therefore the most common phenotype within this population group.

4.2.4 Research design

Participants attended the laboratory on 4 separate occasions for repeat measurements of resting HRV, systolic BPV and 24-hour ambulatory BP and HRV. Pre-visit conditions were standardised with each participant avoiding food (4 hours), caffeine (12 hours) and alcohol (24 hours) prior to each laboratory

visit (Badrov, Bartol, Dibartolomeo, et al. 2013). Because of the known effects of bladder distension on resting BP, participants were also asked to void their bladder in advance of the testing session (Fagius and Karhuvaara 1989). All measurements for each participant took place on their designated weekday and the timing of each visit was standardised to within 2 hours of the first visit. Each session was separated by a minimum of 7 days and maximum of 14.

4.2.5 Procedures

Stature and mass were measured on arrival at the laboratory (Seca, Bonn, Germany). Participants were then instructed to lay supine in a temperature controlled room (21 degrees) whilst they were prepared for resting measurements. For HRV, electrode placement followed a 2-lead (Cardiotens, Meditech, Hungary) or 3 lead (Card(X)plore, Meditech, Hungary) configuration recommended by the Holter device manufacturer. To ensure within subject consistency each participant was fitted with the same device model. Systolic BPV was measured beat-beat using a non-invasive Finometer device (Finometer MIDI, Finapres, TNO Instruments, Amsterdam, The Netherlands). All systolic BPV recordings were measured from the middle finger on the dominant hand. For a detailed explanation of participant preparation for HRV and systolic BPV please see Chapter 3, sections 3.5 and 3.6. Upon completion of participant set-up both monitors were set to record for ten minutes in which the last five minute segment was used within the analysis. Participants were requested to rest quietly during this period.

Following resting measures the participants were prepared for ambulatory measurements. Ambulatory BP and HRV was measured using the Cardiotens and Card(X)plore devices (Meditech, Hungary). A pneumatic cuff was attached to the upper portion of the participant's non-dominant arm (Chapter 3, section 3.4), and the participants retained chest electrode placement from the earlier resting measurements. The ambulatory units were then attached to participants using a holter case clipped around the waist. The holter device was set to record BP every 30 minutes between 06.00 and 22.00 and every hour between 22.00 and 06.00. Participants were instructed to stop what they were doing, free their hand of any items and relax their arm down by their side during each BP recording. Caffeine and alcohol were avoided during the 24-hour monitoring period. Participants were also asked to complete a physical activity diary (Bouchard, Tremblay, Leblanc, et al. 1983) (Appendix 3) for the 24-hour period. This tool determined the time the participants went to bed and got up. Participants were urged to try and maintain a similar daily routine (i.e. meal times, bed time) and requested not to engage in organised sport activity and vigorous exercise.

4.2.6 Data processing

Heart rate variability: The ECG signals collected from the Cardiotens and Card(X)plore were analysed (Cardiovisions, version 1.2, Meditech, Hungary) using time domain and frequency domain analysis. Detailed ECG data processing methods are described elsewhere (Chapter 3, sections 3.6.3 & 3.6.4). The following time frames were used for complete analysis; 5-minute resting measurement, 24 hour average, daytime average and night-time average. Daytime and night-time segments were interpreted using the Bouchard Physical Activity diary (Appendix 3).

Systolic blood pressure variability: Spectral analysis of beat to beat systolic blood pressure data was analysed using an online software programme (Cardioseries v2.4, Brazil). Detailed data processing methods are described elsewhere (Chapter 3, section 3.7.2).

24-hour ambulatory blood pressure monitoring: Blood pressure readings were divided into a series of specific time points for analysis; 24-hr average, daytime average and night-time average. The night-time period included measurements taken between the hours that the participant went to bed and got up (as determined by the Bouchard Physical Activity Diary). A measurement was deemed successful if there were 7 successful night time recordings and 14 successful daytime recordings (O'Brien 2003).

4.2.7 Statistical analysis

Typical error of measurement/coefficient of variation

All variables were assessed for normality using the Shapiro Wilk test. A specifically designed spreadsheet was then used to assess the reproducibility of each physiological measurement (Hopkins 2000). Consecutive pairs of measurements (1-2, 2-3, 3-4) were analysed and TE and CV was calculated. If the measurement did not meet the criteria for normality ($p \leq 0.05$) the CV was calculated on 100*log transformed data (100*ln) – this substantially reduces non-uniform errors (Al Haddad, Laursen, Chollet, et al. 2011). Uncertainty in the difference between successive measurements was reported using 90% confidence limits.

Prior to these calculations, all data was assessed for outliers using the statistics package for social sciences (IBM, version 23, Armonk, NY). Outliers were removed and not included in the analysis.

Detectable changes and sample size estimates

The between subject standard deviation (average across all 4 trials) was used to calculate both small and moderate detectable changes (Hopkins 2000).

Small detectable change = 0.2*between subject standard deviation

Moderate detectable change = 0.5*between subject standard deviation

The typical error and detectable changes (small and moderate) were then used to calculate sample size estimates for a randomised controlled trial with a power of 0.8 (80%) at a 0.05 significance (5%) level.

4.3 Results

Descriptive statistics for all variables (mean ±SD) are presented in Tables 4.1-4.4**.** The TE for each variable across consecutive pairs of measurements is shown in Table 4.5. For ease of comparison across the literature the TE within systolic BPV and HRV is reported as a CV. All HRV and systolic BPV variables displayed non-normality and heteroscedasticity and therefore CV is reported after log transformation.

Table 4.2: Descriptive statistics (mean±SD) of average, daytime and night time blood pressure (mmHg) during 24-hour monitoring.

	Trial 1	**Trial 2**	**Trial 3**	**Trial 4**
24- hour SBP	136.4 ± 8.9	138.3 ± 12.9	136 ± 10.7	136.4 ± 9.6
24-hour DBP	78.2 ± 7.3	77.5 ± 8.9	76.7 ± 8.1	76.6 ± 7.6
24-hour MAP	97.8 ± 6.8	97.7 ± 8.7	96.5 ± 7.3	96.5 ± 7
Daytime SBP	141 ± 11.1	142.6 ± 13.5	141.4 ± 11.6	141.9 ± 10
Daytime DBP	81.2 ± 7.6	80.4 ± 8.4	80 ± 8.7	80.6 ± 8.3
Daytime MAP	101.2 ± 7.6	101.2 ± 9	100.5 ± 8.1	100.9 ± 7.7
Night-time SBP	125.6 ± 9.1	125.3 ± 12.8	120.4 ± 11.1	121.9 ± 11.9
Night-time DBP	69.4 ± 6.6	68.9 ± 9.8	67.1 ± 7.7	67.6 ± 7.2
Night-time MAP	88.1 ± 5.7	87.7 ± 9.6	84.9 ± 7.7	85.7 ± 7.7

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure

Table 4.3: Descriptive statistics (mean±SD) of average 24-hour time and frequency domain heart rate variability

	Trial 1	**Trial 2**	**Trial 3**	**Trial 4**
rMSSD (ms)	24.4±12.3	28.9±17.5	26.2±14.1	27.3±14.4
SDNN (ms)	71.3±17.1	74.1±21.4	73.7±23.7	70.0±17.8
pNN50 (%)	5.0±7.4	5.0±6.8	5.7±8	6.2±8
HF (ms^2)	226.5±224.9	346.8±417.9	260.0±227.9	267.7±236.6
HF nu	22.5±9.3	29.4±10.2	26.8±9.0	28.0±9.9
LF (ms^2)	509.0±314.3	603.5±479.8	585.6±433.1	534.2±319.4
LF nu	69.8±10.4	66.4±10.6	70.1±8.0	67.2±11.3
LF/HF	2.7±2.7	2.7±1.4	3.1±1.3	2.8±1.5

rMSSD, root mean square of successive differences; SDNN, standard deviation of all NN intervals; SDANN, average standard deviation across each 5-minute segment of NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; LF, low frequency; HF, high frequency; nu, normalised units.

Table 4.4: Descriptive statistics (mean±SD) of average resting time and frequency domain heart rate and systolic blood pressure variability

	Trial 1	**Trial 2**	**Trial 3**	**Trial 4**
rMSSD (ms)	21.7±12.6	22.5±16.9	21.5±15.7	23.2±18.6
SDNN (ms)	31.8±15.3	35.4±19.2	33.9±18	35.6±17.3
pNN50%	3.1±4.6	3.1±5.1	3.4±4.8	3.7±7.9
HF (ms^2)	172.4±139.2	199.7±208.6	133.6±139.9	85.2±55.6
HF nu	43.1±13.8	41.8±14.5	33.7±12.8	36.6±15.5
LF (ms^2)	221.7±224.7	287.3±279.5	186.3±171.0	228.6±201.9
Lf nu	52.6±14.4	54.6±15.1	59.9±17.3	59.4±17.1
LF/HF	1.5±1.2	1.5±1.1	2.2±1.4	2.1±1.4
LF ($mmHg^2$)	13.2±9.8	14.9±7.9	12.7±7.5	21.3±12.2
LF (%)	46.8±13.2	45±10.3	41.7±10.7	50.3±7.1

rMSSD, root mean square of successive differences; SDNN, standard deviation of all NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; LF, low frequency; HF, high frequency; nu, normalised units; SD, standard deviation.

The variability within 24-hour average SBP showed a small but progressive decline across measurements (Table 4.5). The TE between measures 1-2 was 3.8mmHg (90% CI 2.6-6.1), between measures 2-3 was 3.1mmHg (90% CI 2.3-4.9), and between measures 3-4 was 2.8mmHg (90% CI 2.05-4.42) (Table 4.5). The TE for daytime and night-time SBP showed a similar pattern, with the magnitude of TE reducing across pairs of measurements (Table 4.5). In general the TE for DBP and MAP was smaller than that found in SBP. Night time measures of DBP displayed progressive reductions in TE across measurements (Table 4.5) – however, this was not consistent with average and daytime measurements. Night-time BP measurements exhibited the largest TE; for SBP, TE between trials 1-2 was 5.4mmHg (90% CI 3.9-8.5), for DBP it was 3.6mmHg (90% CI 2.7-5.8) and for MAP it was 4.2mmHg (90% CI 3.1-6.7).

As compared with 24-hour measurements, resting HRV displayed larger magnitudes of error (Table 4.5) and sample size estimates (Table 4.6). Aside from 24-hour average recordings of rMSSD, the TE across pairs of autonomic measurements did not show a pattern of decline across measurements.

Table 4.5: Reproducibility of 24-hour ambulatory blood pressure, 24-hour heart rate variability and short term blood pressure variability and heart rate variability.

	Trial 2-1 (TE±90% CI)	**Trial 3-2 (TE±90% CI)**	**Trial 4-3 (TE±90% CI)**
24 hour SBP			
Average	3.8 (2.8-6.1)	3.1 (2.3-4.9)	2.8 (2.1-4.4)
Daytime	4.9 (3.7-7.9)	3.9 (2.8-6.2)	2.8 (2.1-4.5)
Night-time	5.4 (3.9-8.5)	4.4 (3.2-7.0)	3.6 (2.7-5.8)
24 hour DBP			
Average	1.7 (1.3-2.7)	1.9 (1.4-3.0)	1.5 (1.0-2.3)
Daytime	1.4 (1.0-2.2)	2.1 (1.6-3.4)	2.0 (1.5-3.2)
Night-time	3.8 (2.8-6.0)	2.7 (2.0-4.3)	1.7 (1.3-2.8)
24 hour MAP			
Average	2.2 (1.6-3.5)	2.2 (1.6-3.5)	1.6 (1.2-2.6)
Daytime	2.2 (1.7-3.6)	2.6 (1.9-4.1)	1.9 (1.4-3)
Night	4.2 (3.1-6.7)	3.1 (2.3-4.9)	1.8 (1.3-2.8)
	Trial 2-1 (CV±90% CI)	**Trial 3-2 (CV±90% CI)**	**Trial 4-3(CV±90% CI)**
24 hour average HRV			
rMSSD (ms) ln	14.1 (10-23)	11.8(9-20)	10.9(8-18)
SDNN(ms) ln	7.7 (6-13)	6.8 (5-11)	9.9 (7-16)
pNN50% ln	47.1 (33-89)	49.5 (34-44)	41.3 (29-74)

HF (ms^2)ln	16.9 (12-29))	19.6 (14-34.3)	17.3 (12.5-28.9)
HF nu ln	12.8 (9-21)	16.3 (12-27)	6.6 (5-11)
LF (ms^2) ln	24.6 (18-42)	26.1 (19-45)	22.8 (16-39)
LF nu ln	4.2 (3-7)	8.5 (6-14)	7.9 (6-13)
Lf/HF ln	12.6 (9-22)	27.7 (20-48)	20.7 (14-35)
Daytime HRV			
rMSSD (ms) ln	12.1 (9-20)	10.4 (8-17)	14.6(11-24)
SDNN (ms) ln	9.5 (7-16)	9.0 (7-15)	12.8 (9-21)
pNN50% (ln)	28.4 (20-49)	53.4 (37-98)	56.4 (39-104)
HF (ms^2) ln	31.9 (23-56)	31.6 (23-55)	25.3 (18-43)
HF nu ln	12.7 (9-21)	11.9 (9-20)	15.2 (11-25)
LF (ms^2) ln	40.5 (29-72)	41.2 (29-73)	24.5 (18-42)
LF nu ln	7.3 (5-12)	8.1 (6-13)	7.2 (5-12)
LF/HF ln	18.7 (14-31)	21.3 (15-36)	23.6 (17-40)
Night-time HRV			
rMSSD (ms) ln	12.6 (9-21)	8.3 (6-14)	9.7 (7-16)
SDNN (ms)	18.7 (14-31)	21.3 (15-36)	24 (17-40)
pNN50%	81.1 (54-166)	56.1 (38-108)	37 (26-67)
HF (ms^2) ln	13.9 (10-24)	21.1 (15-37)	14.6 (11-24)
HF nu ln	18.4 (13-31)	22.7 (16-39)	9.3 (7-16)
LF (ms^2) ln	28.8 (21-49)	37.0 (26-65)	21.0 (5-36)
LF nu ln	9.6 (7-16)	11.5 (8-19)	7.2 (5-12)
LF/HF	29.3 (21-51)	34.8 (25-61)	15 (11-25)

Short-term HRV			
rMSSD (ms) ln	19.7 (14-33)	19.7 (14-33)	24.3 (17-41)
SDNN (ms) ln	28.0 (20-48)	29.7 (21-51)	32.8 (23-57)
pNN50% ln	51.0 (35-97)	41.9 (29-78)	117.3 (74-277)
HF (ms^2) ln	35.5 (25-65)	115.4 (75-254)	88.4 (58-196)
HF nu ln	36.1 (26-63)	39.6 (28-70)	20.7 (15-36)
LF (ms^2) ln	50.9 (36-93)	91 (61-181)	65.4 (44-129)
LF nu ln	28.9 (21-50)	28.1 (20-48)	22.7 (16-40)
LF/HF ln	76.3 (52-147)	98.6 (67-198)	39.0 (28-69)
Short-term systolic BPV			
LF (%) ln	30.1 (21-52)	24.1 (17-41)	26.8 (19-46)
LF ($mmHg^2$) ln	66.8 (46-126)	55.4 (39-102)	59.1 (41-110)

SBP, systolic blood pressure; DBP, diastolic blood pressure; rMSSD, root mean square of successive differences; SDNN, standard deviation of all NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; LF, low frequency; HF, high frequency; nu, normalised units; ln, log transformed; SD, standard deviation.

Table 4.6: Detectable change and sample size estimates

	24-hour average BP							
	SBP	DBP	MAP					
Smallest detectable change *	2.1	1.6	1.5					
Moderate detectable change **	5.2	3.9	3.7					
Sample size ***	24	17	22					
	Resting HRV							
	rMSSD (ms)	SDNN (ms)	pNN50%	HF (ms^2)	Hf nu	Lf (ms^2)	LF nu	LF/HF
Smallest detectable change *	3.2	3.5	1.1	29.2	2.8	44.6	3.2	0.26
Moderate detectable change **	8	8.75	2.9	73	7.1	111.7	8	0.65
Sample size ***	25	81	23	107	152	65	147	125
	24-hour average HRV							
	rMSSD (ms)	SDNN	pNN50%	HF (ms^2)	HF nu	LF (ms^2)	LF nu	LF/HF
Smallest detectable change *	2.9	4	1.5	58	1.9	78.6	2	0.26
Moderate detectable change **	7.2	10	3.8	145	4.8	196.7	5	0.65
Sample size ***	25	31	26	84	32	78	44	112
	Resting systolic BPV							
	LF %	LF ($mmHg^2$)						
Smallest detectable change *	2.2	1.84						
Moderate detectable change **	5.4	4.6						
Sample size ***	187	138						

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, rMSSD, root mean square of successive differences; SDNN, standard deviation of all NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; LF, low frequency; HF, high frequency; nu, normalised units; SD, standard deviation.

*=0.2*between subject standard deviation; **=0.5*between subject standard deviation; ***=sample size based on moderate detectable change

4.4 Discussion

The primary aim of this study was to conduct a pairwise analysis across four consecutive 24-hour ambulatory BP and HRV measurements. The first novel finding of this study was that the TE during 24-hour ambulatory BP measurements was smaller than that previously reported in resting measurements (Campbell, Ghuman, Wakefield, et al. 2010; Fotherby and Potter 1993; Mansoor, McCabe, and White 1994; Stergiou, Baibas, Gantzarou, et al. 2002; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001; van der Steen, Lenders, Graafsma, et al. 1999) and smaller than a moderate detectable change; thus making this measurement sensitive enough to detect changes to 24-hr BP following a therapeutic exercise intervention.

The TE for SBP reduced slightly across consecutive pairs of measurements, thus indicating that the procedure displays increased sensitivity following one habituation period and furthermore with two. The increased sensitivity was more evident during the night-time measurements compared with daytime only or 24-hour average. As is consistent with this study, night-time measurements commonly show poorer reproducibility as compared with 24-hour average and daytime recordings (Ash, Walker, Olson, et al. 2013; Campbell, Ghuman, Wakefield, et al. 2010; Fotherby and Potter 1993; Stergiou, Alamara, Salgami, et al. 2005; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001). The TE during night-time measurements in hypertensive adults has been reported to range from 6.5-11.3mmHg for SBP (Stergiou, Baibas, Gantzarou, et al. 2002; Eguchi, Hoshide, Hoshide, et al. 2010; van der Steen, Lenders, Graafsma, et al. 1999). A limitation of these studies is the assessment of ambulatory BP on only two occasions. Following two habituation trials the current study showed a TE of 3.6mmHg which is the lowest reported in hypertensive adults. This finding shows a particular benefit of personal adaptation to wearing the device at night.

Diastolic BP showed similar improvements in reliability across consecutive night-time measurements with little change during 24-hour or daytime measurements. However, as compared with SBP, a smaller magnitude of error during diastolic measurement was found. This finding is consistent with previous 24-hour ABPM studies and resting BP studies (Campbell, Ghuman, Wakefield, et al. 2010; Stergiou, Baibas, Gantzarou, et al. 2002; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001). There has been limited discussion in the literature with regards to the specific reasons for this. However, SBP has been shown to be influenced to a greater degree during tasks such as silent reading, reading aloud, and mental stress (Bernardi, Wdowczyk-szulc, Valenti, et al. 2000) and exercise (Mitchell 2012). Therefore different circumstances during each recording will influence SBP to a greater degree. It has been suggested that the lower variability in DBP may simply be related to the fact that DBP is

measured with a reduced arm cuff pressure and with a short time delay following the systolic measurement (Musini and Wright 2009). Patients may become more relaxed during each diastolic measurement.

Interestingly, regardless of trial number, the TE for 24-ABPM was lower in this present study compared with those reported previously (Eguchi, Hoshide, Hoshide, et al. 2010; Fotherby and Potter 1993; Stergiou, Alamara, Salgami, et al. 2005; van der Steen, Lenders, Graafsma, et al. 1999). This likely reflects the fact that participants in the present study had a lower baseline BP. Mean baseline SBP within the current study was 142mmHg, this compares with other research recruiting individuals with average SBP values of 155mmHg (Mansoor, McCabe, and White 1994), 165mmHg (van der Steen, Lenders, Graafsma, et al. 1999) and 178mmHg (Fotherby and Potter 1993), with another study limiting their recruitment to individuals with SBP over 180mmHg (Stergiou, Baibas, Gantzarou, et al. 2002). Variability in BP is generally proportional to BP values (Parati, Ochoa, Lombardi, et al. 2013) and therefore the day to day variability and thus TE may increase as the severity of hypertension increases. In addition, evidence for the standardisation of activities in previous research is limited with the exclusion of caffeine and advice regarding levels of physical activity lacking. The findings of the current study align more closely with results from studies in normotensive individuals (Ash, Walker, Olson, et al. 2013).

In relation to HRV, the second novel finding of this study showed that the CV for both time and frequency domain parameters was lower during 24-hour ambulatory recordings in comparison to 5-minute resting recordings. In addition, the TE for all 24-hour HRV parameters was consistently lower than a moderate detectable change suggesting that the measurement has sufficient sensitivity for detecting statistical significance if post intervention changes are of a moderate magnitude. In contrast, owing to the large day-day variation observed during resting recordings, a moderate detectable change was not consistently smaller than the TE and therefore resting measurements provide substantially less sensitivity. Large day-to-day variations in resting HRV recordings, is consistent with previous research (Hojgaard, Holstein-Rathlou, Agner, et al. 2005; Pinna, Maestri, Torunski, et al. 2007; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Ponikowski, Piepoli, Amadi, et al. 1996; Tarkiainen, Timonen, Tiittanen, et al. 2005). Despite large variations (CV; 19-117.3%), the reproducibility of time domain parameters was similar to that of post MI and stroke patients (Ginsburg, Bartur, Peleg, et al. 2011; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010).

Whilst previous research has reported the reproducibility of 24-hour HRV recordings (Bigger, Fleiss, Rolnitzky, et al. 1992; Hohnloser, Klingenheben, Zabel, et al. 1992; Kleiger, Stein, and Bigger 2005; Pitzalis, Mastropasqua, Massari, et al. 1996); this is the first study to investigate changes following

habituation, and report absolute reliability (CV) during both day and night periods. Although 24-hour measures of rMSSD showed a consistent decline in CV across measurements, this finding was not consistently evident in the other HRV parameters and therefore the need for habituation remains questionable.

However, when compared with the current study, 24-hour measurements on healthy volunteers found similar levels of reproducibility for the time domain vagal component, rMSSD (Kleiger, Stein, and Bigger 2005; Pitzalis, Mastropasqua, Massari, et al. 1996). In contrast, CV for SDNN (6.8-9.9%) was much smaller to that reported by Pitzalis and colleagues (1996) where the CV for SDNN was reported as 20%. The recruitment of young healthy individuals who have large variances in their heart rates and therefore larger overall variability (SDNN) may have contributed to poorer reproducibility. It is well known that HRV is reduced in clinical and older populations (Carthy 2014; Umetani, Singer, McCraty, et al. 1998) and may therefore display less variation within this particular variable. Further comparisons between young healthy adults and clinical populations is required.

Finally, the current findings show large day-day variation in BPV parameters with no obvious benefit of habituation. The CV reported in the current study is much larger to that previously reported by Parati et al., (2001). This difference in findings could be related to the longer recordings (15 minutes) employed (Parati, Omboni, Villani, et al. 2001). Alternatively the younger pool of participants (29-54 years) recruited by Parati et al., (2001) could have contributed to the superior reproducibility. Older hypertensives have been shown to have greater levels of muscle sympathetic nerve activity when compared to younger hypertensives (Yamada, Miyajima, Tochikubo, et al. 1989). It is therefore possible that the participants in the current study had a greater level of sympathetic nerve activity which may have contributed to the large day-day variations. The current findings suggest that detecting changes in the LF component of systolic BPV following a therapeutic intervention may prove problematic.

4.5 Conclusion

When compared with other research, ambulatory BP monitoring provides greater measurement sensitivity as compared with resting measurements. The current study shows that wearing an ambulatory device for the first time may induce error into BP recordings. It is recommended that at least one habituation period is provided; especially if night-time recordings are of interest. For HRV, 24-hour measurements as compared with resting measurements offer better reproducibility with the benefit of habituation remaining questionable. Resting measures of systolic BPV showed poor reproducibility.

Although resting BP measurements and short term HRV recordings have specific advantages, namely quick measurement and controlled conditions; 24 hour measurements offer superior reproducibility and where possible should be utilised in the design of intervention studies.

Chapter 5: The use of the CR-10 scale to allow self-regulation of isometric exercise intensity in pre-hypertensive and hypertensive participants.

5.1 Introduction

As reviewed in Chapter 2, section 2.2.3 isometric exercise has been shown to lower blood pressure (BP) in healthy adults (Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Wiley, Dunn, Cox, et al. 1992; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Bartol, Dibartolomeo, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015), hypertensive (non-medicated and medicated) and pre-hypertensive adults (Wiley, Dunn, Cox, et al. 1992; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; Peters, Alessio, Hagerman, et al. 2006; McGowan, Visocchi, Faulkner, et al. 2007; Baross, Wiles, and Swaine 2012, 2013; Millar, Levy, Mcgowan, et al. 2013; Badrov, Horton, Millar, et al. 2013).

Studies that have been carried out in pre-hypertensive and hypertensive participants have mostly used isometric handgrip exercises. Training programmes typically prescribe 4 x 2 minute contractions (performed unilaterally or by alternating hands), repeated 3 times per week for 8-10 weeks (Millar, McGowan, Cornelissen, et al. 2014). To date, the majority of isometric training programmes have prescribed a percentage of maximal voluntary contraction (%MVC) to regulate the exercise intensity (Taylor, McCartney, Kamath, et al. 2003; McGowan, Visocchi, Faulkner, et al. 2007; Stiller-Moldovan, Kenno, and McGowan 2012; Millar, Levy, Mcgowan, et al. 2013; Ash, Taylor, Thompson, et al. 2016; Badrov, Horton, Millar, et al. 2013). This method requires a device (e.g. handgrip, hand dynamometer) that displays the magnitude of force exerted which then allows the exercise participant to visualise force output (on a computer screen or the device itself) and maintain it at a pre-set target. Calculating %MVC also requires the performance of 2-3 short maximal efforts to firstly establish MVC. The most common target handgrip exercise intensity is 30% MVC. Specifically, this training intensity has been effective at lowering resting systolic SBP by 6-19mmHg and resting DBP by 3-15mmHg in pre-hypertensives and hypertensive adults (Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, McCartney, et al. 2007; Wiley, Dunn, Cox, et al. 1992; Badrov, Horton, Millar, et al. 2013; Millar, Bray, McGowan, et al. 2007).

Although regulating isometric exercise using %MVC has proven effective, regulating isometric exercise in this way presents a number of limitations. Firstly, specialised programmable handgrip devices or dynamometers, designed to calculate %MVC prior to the beginning of each exercise session, are required. These are somewhat expensive and some dynamometers can only be used in the laboratory which limits accessibility. Secondly, the calculation of %MVC requires 2-3 all-out maximal efforts, which might present a limitation in some groups of participants, especially in those with frailty. Some older adults are limited in maximal gripping, due to the prevalence of varying degrees of arthritic pain

in the hand (Arthritis Research UK 2017). If this type of exercise is to benefit older people with hypertension (or who are at risk of hypertension) then it must be simple to use, affordable, home-based and ideally it must avoid maximal effort. There has been little exploration of alternative ways to regulate isometric exercise intensity.

As reviewed in Chapter 2, section 2.4, studies provide support for the use of the rate of perceived exertion (RPE) scale as an effective exercise prescription tool. During cardiorespiratory exercise (e.g. cycling, running, rowing), perceived exertion charts (Borg 1973) have been shown to correlate strongly with physiological markers of intensity such as heart rate (HR) and oxygen consumption (VO_2) (Scherr, Wolfarth, Christle, et al. 2013; Ueda and Kurokawa 1995; Borg and Kaijser 2006). Using an estimation-production model researchers have also shown that participants can replicate specific markers of intensity (HR, VO_2, power output) by producing a given level of perceived exertion (Soriano-Maldonado, Romero, Femia, et al. 2013; Marriott and Lamb 1996; Green, Crews, Bosak, et al. 2002; Goosey-Tolfrey, Lenton, Goddard, et al. 2010; Eston, Davies, and Williams 1987; Paulson, Bishop, Leicht, et al. 2013).

The CR-10 scale (Figure 3.9) is a perceived exertion chart and was developed by Gunnar Borg with the intention of using verbal expressions that are easy to understand (Borg 1982). With regard to isometric exercise, a strong linear relationship has been previously determined between the Borg CR-10 scale and %MVC during 5-second contractions (Pincivero, Coelho, and Erikson 2000). However, its relationship with %MVC during longer isometric contractions is unknown. In addition, the use of perceived exertion and its relationship with cardiovascular responses during isometric exercise remains unexplored. Recent findings show that an individual's SBP reactivity (ΔSBP) in response to a single 2-minute isometric handgrip task at 30% MVC is related to the magnitude of training-induced BP reductions in hypertensive individuals (Badrov, Horton, Millar, et al. 2013). Within this sample (n=12) findings showed that those with a small ΔSBP (~10mmHg) responded less positively to isometric training whilst individuals with a larger ΔSBP (up to 50mmHg) responded most positively (Badrov, Horton, Millar, et al. 2013). Considering the wide range of SBP changes observed during isometric exercise and its potential impact on training adaptations, further examination of the ΔSBP and its relationship to the CR-10 scale and %MVC is required.

The purpose of this research was to primarily determine the validity of regulating isometric exercise intensity using perceived exertion. Specifically, an estimation task examined the relationship between the Borg CR-10 scale and both %MVC and ΔSBP. Based on the initial findings, the research determined whether individuals could reproduce (production task) %MVC and its corresponding ΔSBP using an imposed numerical value from the CR-10 scale. Three production trials were carried out to assess

whether practice trials are necessary to improve an individual's accuracy at producing a specific exercise intensity.

5.2 Methodology

5.2.1 Participants

Fourteen (9 females, 5 males) pre-hypertensive and stage 1 hypertensive adults (SBP; 141±6.6mmHg, DBP; 84±6.4mmHg) with a mean age of 64.4±5.7 years, body mass of 73.3±16kg, stature of 166±12.4cm and body mass index of 28.6±4.3 participated in the study. Five participants were taking anti-hypertensive medication which included diuretics (n=1), ACE inhibitors (n=2), calcium channel blockers (n=1) and alpha blockers (n=1). All participants conformed to the selection criteria detailed in Chapter 3, section 3.3. Ethical approval was granted by the local research ethics committee and written informed consent was obtained from all individual participants included in the study.

5.2.2 Research design

Participants attended the laboratory on five occasions. Each visit was separated by a minimum of 48 hours and maximum of 7 days. Pre-visit conditions were standardised with each participant avoiding food (2 hours), caffeine (12 hours) and alcohol (24 hours) prior to each laboratory visit.

Familiarisation session

Stature and mass were measured on arrival at the laboratory (Seca, Bonn, Germany). This was followed by completion of a Physical Activity Readiness Questionnaire; PAR-Q+ (Jamnik, Warburton, Makarski, et al. 2011) (Appendix 1). Participants were then instructed to sit comfortably in a chair (back supported, legs uncrossed, feet flat on the floor) whilst BP was measured during 10 minutes of quiet rest. Blood pressure was measured using a non-invasive Finometer device (Finometer MIDI, Finapres Medical Systems, Amsterdam, Netherlands) which was attached to the middle phalanx of the third digit on the dominant hand. Detailed information on the Finometer is provided in Chapter 3, section 3.7. An average of the final two minutes of recording was used for the baseline BP (day-of BP). Throughout all testing procedures, the acute ΔSBP was calculated based on day-of BP.

Following the resting period, participants were instructed on how to use an isometric handgrip dynamometer (AD instruments LTD, Sydney, Australia). Whilst retaining their comfortable seated position, participants held the handgrip device in their non-dominant hand whilst holding their arm adducted with 90 degrees of flexion at the elbow joint. A brief isometric hand-grip warm-up was then completed using three, 15 second contractions at approximately 50%, 75% and 90% of maximal effort.

The handgrip dynamometer was connected to an 8-channel chart recorder (Powerlab 26T, AD instruments LTD, Sydney, Australia) and interfaced with a computer analysis system (LabChart Pro 7 software, AD instruments LTD, Sydney, Australia).

On completion of the warm-up, the CR-10 was introduced. The following explanation was given to participants to read;

"During the exercise bout, I want you to pay close attention to how hard you feel the exercise is. The feeling should reflect your total amount of fatigue, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as arm pain, shortness of breath or exercise intensity but try to concentrate on your total, over all feeling of exertion. Try not to underestimate or overestimate your feelings of exertion; be as accurate as you can" (Modified from Faulkner and Eston, 2007).

An anchoring procedure was then used to assist the participant in putting into context the sensations of exercise intensity (Nobel and Robertson, 1996). Resuming their comfortable seating position and holding the dynamometer loosely, participants were asked to *"think about your feelings of exertion and assign a rating of 0 to those feelings".* Following this, participants were asked to maximally grip the handgrip device for 3-5 seconds (breathing evenly throughout). Prior to the contraction, participants were asked to *"think about the feelings of exertion at the end of the contraction and to assign a rating of 10 to those feelings"*. The maximal exertion task was repeated 2 more times with a 1-minute rest in between. The maximal value attained was recorded as the participant's MVC.

To complete familiarisation, three handgrip intensities ranging from 15% to 35% were calculated and randomly assigned. With the assistance of a force output visual display participants carried out 2-minute contractions at the assigned intensity with 4-minute rests in between each contraction. During each 2-minute repetition participants were requested to provide a rating from the CR-10 scale every 30 seconds.

Estimation task

The baseline BP measurement, warm-up and anchoring procedures all followed the same protocol as the familiarisation session. Following three MVCs (1-minute rest between each effort) participants undertook eight, 2-minute contractions at randomised intensities ranging from 10% to 40% MVC (5% increments). A force-output visual display screen was used to assist participants in maintaining the correct intensity. Each contraction was separated by a 4-minute rest period. Participants were requested to provide a rating from the CR-10 scale every 30 seconds. Blood pressure was measured throughout using the Finometer device (Finometer MIDI, Finapres Medical Systems, Amsterdam,

Netherlands) and ΔSBP was calculated by subtracting day-of SBP from the average SBP during each 2-minute contraction.

Production task

All eight contraction intensities provided 32 ratings from the CR-10 scale (every 30 seconds during each 2-minute contraction). A linear regression was carried out on the CR-10 ratings and the calculated average of the corresponding %MVC and ΔSBP. The linear regression revealed that CR-10 "Level-6" aligned with an average relative force value of 33% MVC (95% CI; 36.2%, 30%) and an average ΔSBP of 38mmHg (95% CI; 44mmHg, 32mmHg). Level-6 was subsequently used in the production tasks (trials 1-3), each separated by 7 days.

Day-of BP, warm-up and anchoring procedures were all repeated before each production task. Participants were then asked to carry out four, 2-minute isometric handgrip contractions whilst maintaining the CR-10 rating at "Level-6". A 4-minute rest was provided between each contraction. The participant was blinded to the force output display. Apart from the time elapsed, no feedback was provided to the participant.

5.2.3 Statistical analysis

Data were analysed using the statistics package for social sciences (IBM, version 23, Armonk, NY). Analyses were carried out specifically for the *estimation task*, *estimation task v's production task (trials 1-3), and production task (trials 1-3)*.

Estimation task

The relationships between CR-10 and %MVC and CR-10 and ΔSBP were subjected to linear regression.

Estimation task v's production task (trials 1-3)

Average values for ΔSBP and %MVC were calculated across each 2-minute contraction (repetitions 1-4) carried out during the production trials. For each production trial, a 1-way analysis of variance (ANOVA) was used to detect differences between CR-10 "Level-6" estimation and CR-10 "Level-6" production; post hoc analysis was performed using a Bonferroni test for pairwise comparisons. The alpha level was set at 0.05. Effect size (ES) was also calculated (Cohen's d) for significant findings. Values of 0.1, 0.3 and 0.5 were considered small, moderate, and large effects, respectively (Field 2009).

Production task (trials 1-3)

For each production trial, average force was calculated for four separate time segments of the 2-minute isometric contraction (0-30s, 30-60s, 60-90s, and 90-120s); each time segment was averaged across all four contractions. Pearson correlations assessed the relationship between segments of time and force. A repeated measures ANOVA with Bonferroni adjustments was used to detect between-trial differences at each time segment. The alpha level was set at 0.05.

5.3 Results

Estimation task

Significant linear relationships (Figure 5.1) were observed between the CR-10 scale and the calculated average of the corresponding %MVC (r=0.845) and ΔSBP (r=0.784). Level-6 on the CR-10 scale aligned with an average ΔSBP of 38mmHg (95% CI; 44mmHg, 32mmHg) and an average relative force value of 33% MVC (95% CI; 36.2%, 30%). Therefore, the common prescription of 30% MVC was deemed to be closest to "Level 6" and was adopted for use in the isometric production trials.

Estimation task vs production task (trials 1-3)

One-way ANOVA with Bonferroni adjustment showed that there was no significant differences (p>0.05) in relative force between the estimation task and all repetitions in all three trials of the production task (Figure 5.2).

In production trial 1, the ΔSBP was significantly lower than the estimation task during repetition 1 (p=0.000, ES=2.00), 2 (p=0.000, ES=1.82) and 3 (p=0.000, ES=1.35). In production trial 2, the change in SBP was significantly lower than the estimation task during repetition 1 (p=0.000, ES=2.13), 2 (p=0.000, ES=1.64) and 3 (p=0.003, ES=1.31). In production trial 3, the ΔSBP was significantly lower than the estimation task during repetition 1 (p=0.000, ES=1.65) and repetition 2 (p=0.025, ES=1.05) (Figure 5.2).

Production task (trials 1-3)

Figure 5.4 shows that %MVC decreased in a moderately linear fashion (relative to segments of time) in trial 1 (r=0.583), trial 2 (r=0.594) and trial 3 (r=0.645). Between-trial differences were detected with a significant interaction for time*day. Percent MVC during the first time segment (0-30s) was significantly greater in trial 3 as compared with trial 1 (p=0.021, ES=0.354).

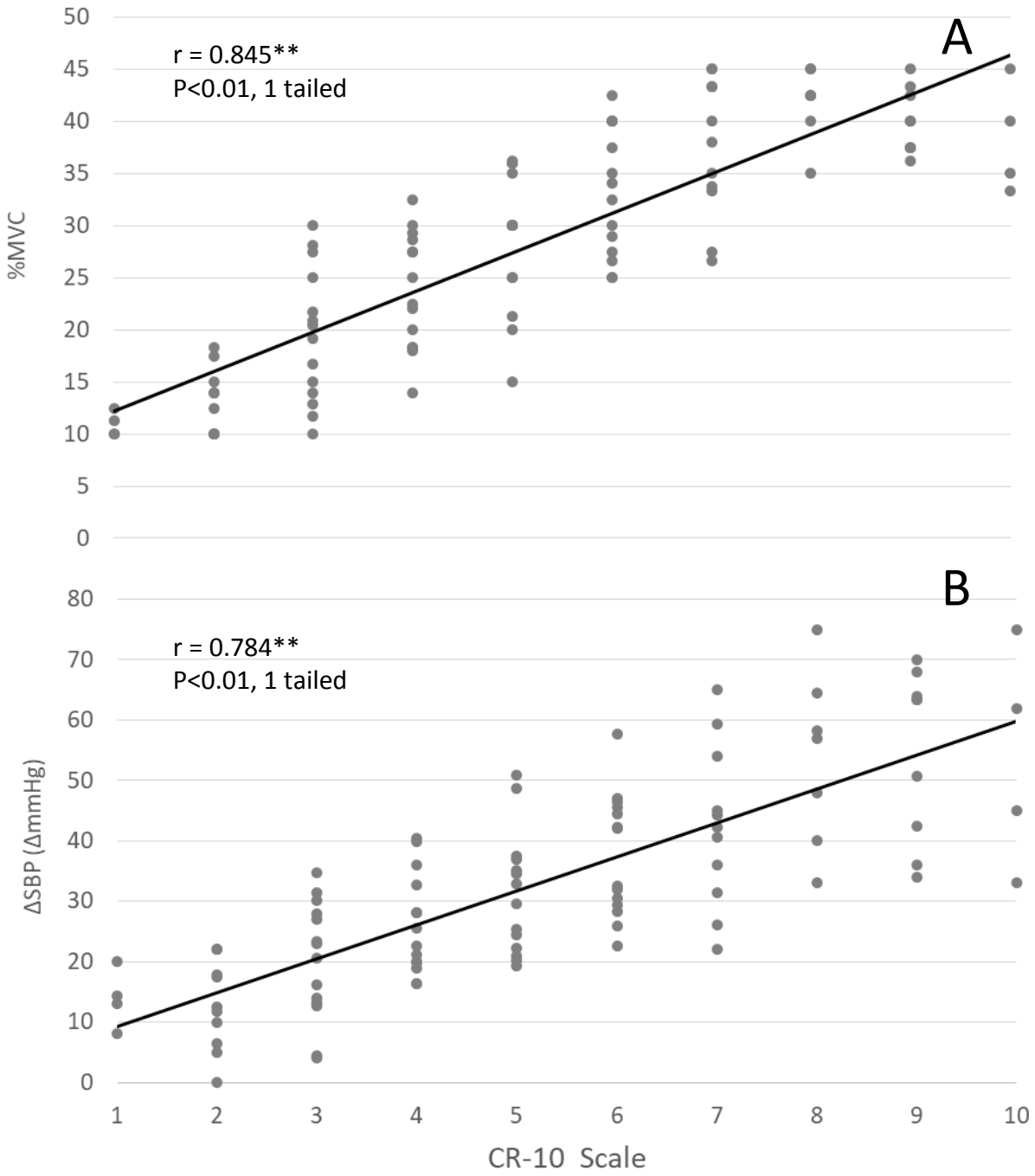

Figure 5.1: Regression analysis between A) CR-10 scale and % MVC B) CR-10 scale and ΔSBP during the estimation trial (** = p>0.01)

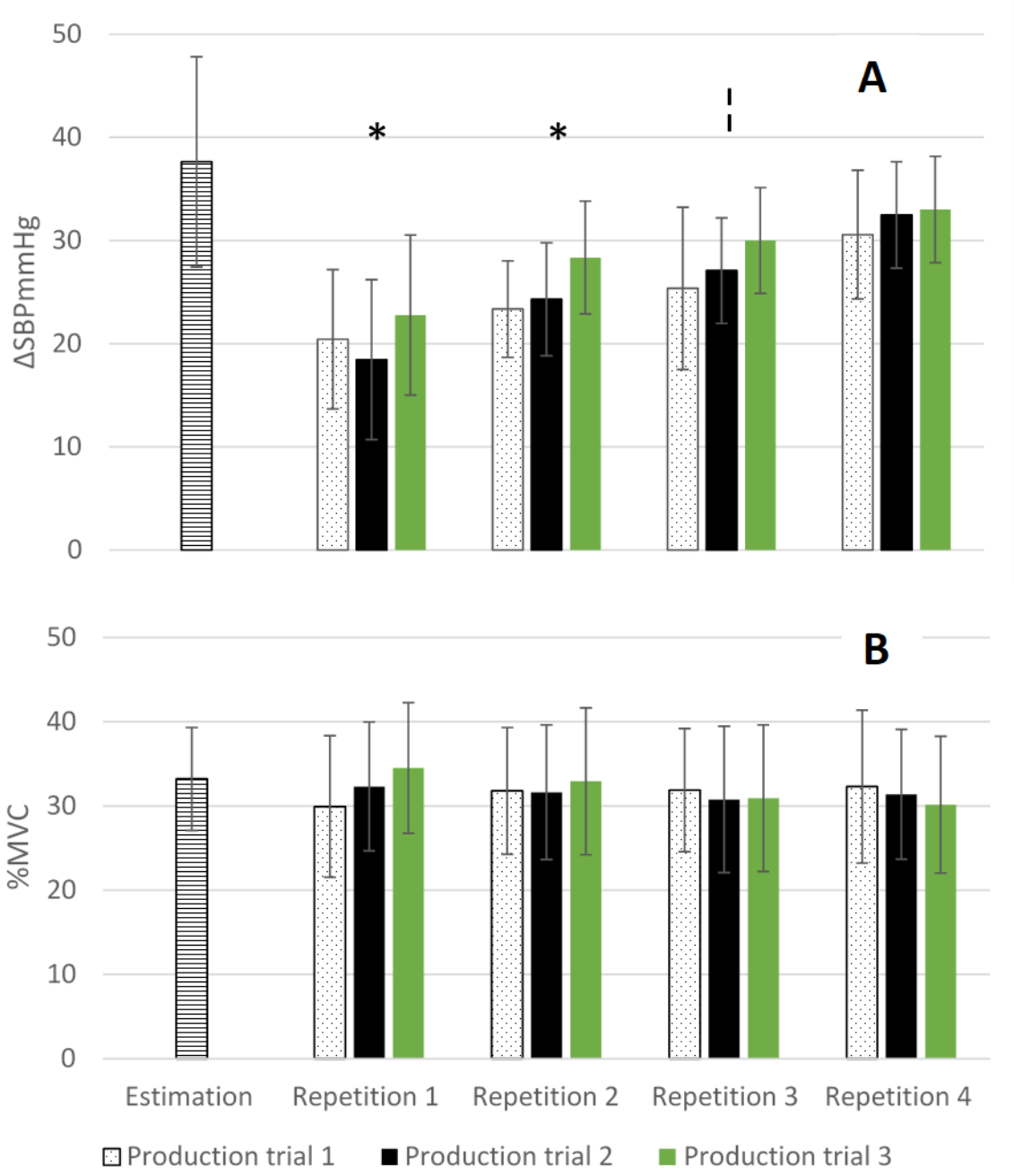

Figure 5.2: One-way ANOVA between ΔSBP (mean±SD) and %MVC (mean±SD) during the estimation task and production trials 1-3. **Panel A)*** = significant differences between production trials 1-3 and estimation task ($p<0.05$). ¦= significant differences between estimation task and production trials 1-2 ($p<0.05$). **Panel B)** No significant differences between %MVC estimation task and %MVC production trials 1-3, reps 1-4

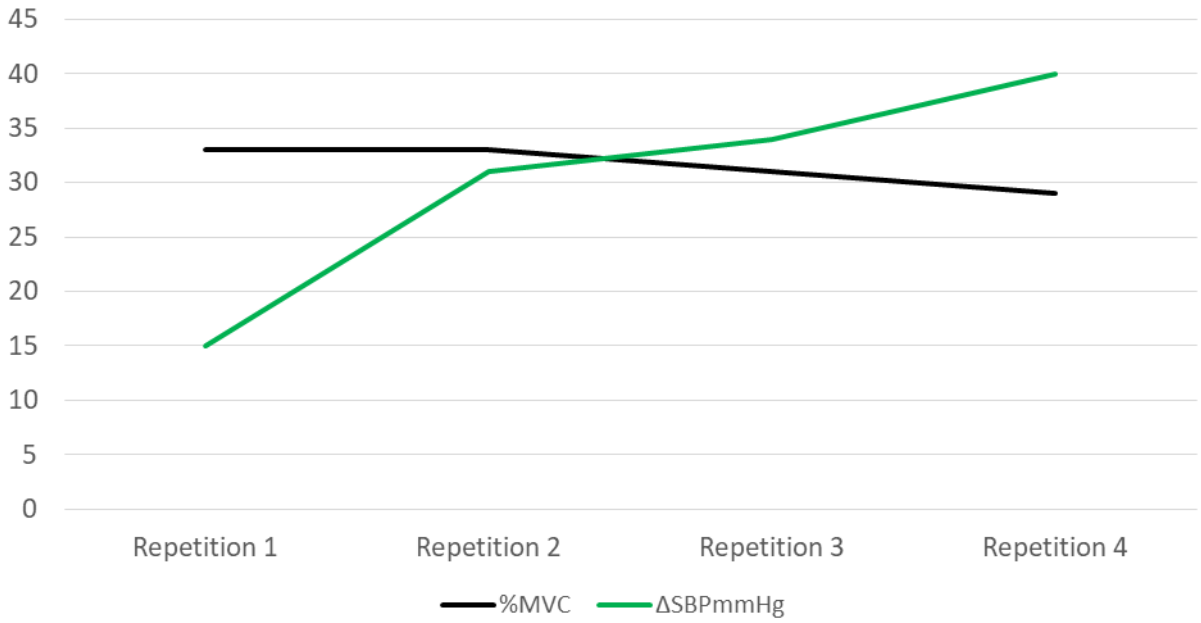

Figure 5.3: Typical %MVC and SBPmmHg response in one participant undertaking a repeated 2-minute contraction at CR-10 Level 6. Typically each 2-minute isometric contraction showed a decrease in %MVC and increase in SBPmmHg.

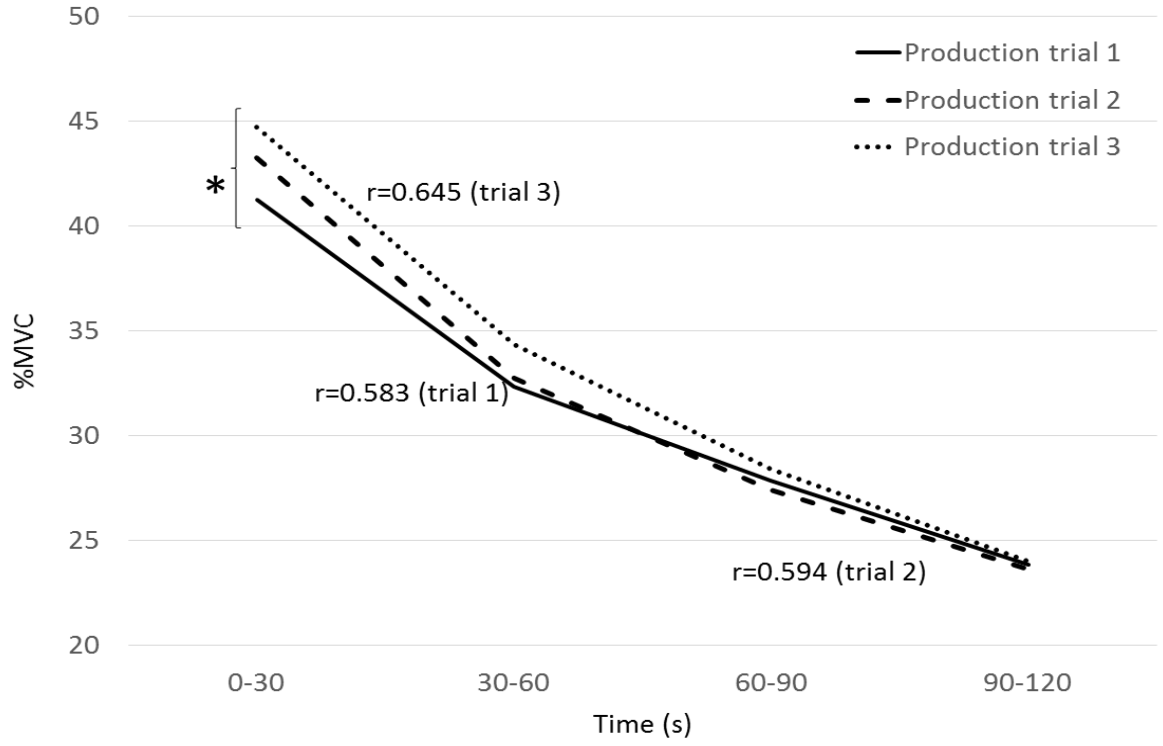

Figure 5.4: Relationships between %MVC and isometric contraction duration. Between trial differences showed significant differences between segment 1, trial 1 and segment 1 trial 3 (* = $p<0.05$). Values are means for 14 subjects calculated for each time segment and averaged across the four repetitions carried out during each trial.

5.4 Discussion

The aims of this study were two-fold. Firstly, the study aimed to establish whether a relationship exists between the CR-10 scale and either %MVC or ΔSBP (estimation task). Secondly, the study aimed to assess whether, when using a specific number on the CR-10 scale, participants were able to produce an exercise intensity that equated to a specific %MVC and which elicited a sizeable ΔSBP. Results from the estimation task indicated that a strong linear relationship exists between the CR-10 scale and both %MVC and ΔSBP (Figure 5.1). Specifically, the estimation task revealed that "Level- 6" on the CR-10 scale aligned with an average %MVC of 33% (95% CI; 36.2%, 30%) and an average ΔSBP of 38mmHg (95% CI; 44mmHg, 32mmHg). The most common isometric exercise prescription, aimed at lowering BP in previous studies, has been set at 30% MVC (Millar, Bray, McGowan, et al. 2007; Taylor, McCartney, Kamath, et al. 2003; Wiley, Dunn, Cox, et al. 1992; Badrov, Horton, Millar, et al. 2013). Based on the positive reductions in BP observed after these training interventions prescribed at 30% MVC, the findings from the estimation task indicated that the CR-10 "Level-6" would most closely approximate the exercise intensity that has been used previously. Therefore, it was concluded that this CR-10 level would be the most appropriate level for isometric exercise prescription within the production task (trials 1-3).

The production task trials revealed that it was possible for participants to adequately self-regulate their exercise intensity (%MVC) using "Level-6" on the CR-10 scale (Figure 5.2). Further, familiarisation trials are not necessary to improve the accuracy of participants' ability to produce the intensity that was observed during the estimation task (average 33% MVC) at CR-10 "Level 6". This is the first study to demonstrate the ability of individuals to self-regulate isometric exercise effort (force) by using a rating of perceived exertion scale. The ability to self-regulate isometric exercise intensity, without the need to establish maximal voluntary contraction (MVC), would potentially offer greater access to this type of exercise for some groups (especially those with frailty or arthritic pain of the hand). Indeed, using this self-regulation method would allow participants to perform isometric exercise in a self-regulated (controlled) way, whilst using a variety of different types of resistance (other than squeezing with the hand). Any 'immovable object' around the home or workplace could be utilised. Of course, further validation studies would be required before this is possible.

In contrast to the current study, inaccuracies in reproducing a given exercise intensity in an exercise-related production task have been reported (Marriott and Lamb 1996). As compared with an estimation task, cyclists overproduced their power at an RPE level of 11 ("light"), 13 ("somewhat hard") and 15 ("hard"). However, power output at an RPE of 17 ("very hard") was produced successfully (Marriott and Lamb, 1996) . Within the current study, CR-10 "Level 6" indicated an effort level somewhere between "hard" and "very hard". Although it is difficult to compare aerobic and isometric exercise, it could be suggested that it is easier to

self-regulate exercise intensity when it is above what is described on the rating of perceived exertion scale as “hard”.

Despite the reproducibility of %MVC using an imposed CR-10 “Level 6”, its corresponding physiological parameter (ΔSBP) determined during the estimation task was under-produced across each production task; this was particularly evident in the first 2 repetitions of all production trials (Figure 5.2). These findings suggest that although ΔSBP is significantly related to increasing CR-10 levels during an estimation task, this physiological response is not readily produced during a 2-minute isometric handgrip task despite the accuracy of %MVC reproduction. There are two potential explanations for this difficulty in achieving this physiological change during the production protocol.

Firstly, the calculation of the ΔSBP during estimation and production tasks were inherently different. Whilst the ΔSBP during the production task was calculated for each 2-minute period of exercise, the estimation task value represents the ΔSBP averaged across a number of periods of exercise. The latter is therefore representative of a cumulative hemodynamic effect. The cumulative effect of previous periods of isometric exercise is evident in repetition number 4 in all production trials, where ΔSBP was not different to the estimation task value (Figure 5.2). Although previous research has shown that SBP increases over the course of single periods of isometric exercise lasting varying lengths of time (Smolander, Aminoff, Korhonen, et al. 1998; Lind and McNicol 1967b; Greaney, Wenner, and Farquhar 2015), the current research is the first to show that despite a 4-minute rest between repetitions, the hemodynamic response accumulates and is still evident during consecutive periods of isometric exercise. This response may be related to progressive muscle fatigue and accumulation of metabolic by-products. In contrast to repetition number 4, the ΔSBP during repetition number 1 was not influenced by an accumulation of prior exercise and revealed a wide range of individual SBP responses (6-35mmHg). This wide range is in agreement with findings from Badrov, Horton *et al*., (2013). To reiterate their findings; lower responses (~10mmHg) to a single isometric handgrip task predicted smaller BP benefits following 8 weeks of isometric handgrip training. The findings of the current study are important because it clarifies the existence of inter-individual differences in response to a single isometric exercise contraction (repetition 1, production trials 1, 2 and 3). This finding supports the notion that there is potential for isometric exercise to benefit some individuals more than others (Badrov, et al. 2013b), however, more research is warranted. The interplay of a number of factors may be responsible for the individual variations. Differences in central command output, sensitivity of mechano- and metabo-reflexes or baroreflex function, are likely candidates for varied responses amongst different individuals (Smith 2010). In addition, hypertension status (pre-hypertension and stage 1) and anti-hypertensive medications (which have been shown to dampen levels of reactivity) (Benschop, Nieuwenhuis, Tromp, et al. 1994) may have contributed to this inter-individual variation.

Secondly, the estimation task was regulated by a consistent force output (%MVC) whilst the production task was entirely self-regulated (CR-10 “Level-6”). In contrast to a consistent force output, this study showed that

self-regulation of intensity using the CR-10 scale resulted in a time-dependent decrease in force (Figure 5.4). This may have acted to minimise increases in central command, thereby, reducing cardiovascular drift (i.e. ΔSBP) during the 2-minute period of isometric exercise (Williamson 2010). Isometric exercise regulated by %MVC is thought to gradually increase levels of central command in response to fatigue, resulting in a continual upward drift in cardiovascular parameters (Wiles, Allum, Coleman, et al. 2008). This drift was likely to be more evident in the estimation task as opposed to the production task. However, considering the high pressor response experienced by some hypertensive individuals in response to isometric exercise (Badrov, Horton, Millar, et al. 2013; Delaney, Greaney, Edwards, et al. 2010) the use of the CR-10 scale should be effective in minimising this upward drift in cardiovascular parameters.

5.5 Conclusion

In conclusion, the current research shows that the use of CR-10 "Level-6" is a novel and cost-effective way of self-regulating consistent and appropriate hand-grip isometric exercise intensity (%MVC) in pre-hypertensive and hypertensive participants. Findings showed that following familiarisation, individuals can reproduce appropriate percentages of their maximal voluntary contraction without the need for practice trials.

Chapter 6: Effects of self-regulated isometric exercise: blood pressure (resting and 24-hour ambulatory), autonomic function and adherence.

6.1 Introduction

As reviewed in Chapter 2, section 2.2.3 isometric exercise training has been shown to reduce resting blood pressure (BP) (Cornelissen, Smart, and Survey 2013; Carlson, Dieberg, Hess, et al. 2014; Börjesson, Onerup, Lundqvist, et al. 2016; Inder, Carlson, Dieberg, et al. 2016) following 4-10 weeks of training in normotensive, pre-hypertensive and hypertensive individuals. The largest and most recent meta-analysis of randomised control trials (n=302) revealed post-training reductions in resting systolic (-5.2mmHg) and diastolic (3.91mmHg) BP with hypertensive participants showing a significantly larger decrease in MAP (-5.91mmHg) as compared with healthy participants (Inder, Carlson, Dieberg, et al. 2016). Although resting measures are classically used to assess the impact of an intervention on an individual's BP status, ambulatory BP is arguably a more clinically relevant and reproducible measurement (Fotherby and Potter 1993; Mansoor, McCabe, and White 1994; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001; Stergiou, Baibas, Gantzarou, et al. 2002; Campbell, Ghuman, Wakefield, et al. 2010). Studies exploring the effects of isometric exercise on 24-hour ambulatory BP are limited (Stiller-Moldovan, Kenno, and McGowan 2012; Somani, Baross, Levy, et al. 2017; Ash, Taylor, Thompson, et al. 2016; Pagonas, Vlatsas, Bauer, et al. 2017) and to date have produced mixed findings (Chapter 2, section 2.2.3). The effect of isometric exercise on this measure therefore requires further investigation.

To date, training protocols typically include 4 x 2 minutes of isometric handgrip (unilateral or alternative bilateral) or bilateral leg contractions at 30% MVC, repeated 3-5 times per week. A short exercise duration and the availability of portable programmable handgrip devices provide exercising individuals with the flexibility in relation to exercise location and time of day; this makes isometric exercise an attractive option for pre-hypertensive and hypertensive adults. Research has shown that only 3-33% of individuals participate in the recommended aerobic exercise guidelines recommended for BP management (Ohta, Tsuchihashi, and Kiyohara 2011; Riegel, Moreira, Fuchs, et al. 2012; Al-Kaabi, Al-Maskari, Afandi, et al. 2009; Baynouna, Neglekerke, Ali, et al. 2014). The simplicity of isometric exercise should remove many of the common barriers associated with aerobic training regimes (Chapter 2, section 2.3). Taking this into consideration, a number of researchers have hypothesised that adherence to isometric training would therefore be higher than the commonly prescribed aerobic training (Inder, Carlson, Dieberg, et al. 2016; Carlson, Dieberg, Hess, et al. 2014; McGowan, Proctor, Swaine, et al. 2017). However, since computerised devices (that are required to program the correct training intensity (i.e. 30% MVC) can be expensive, this may constitute a barrier to participant uptake. Research into more cost-effective alternatives which can offer greater flexibility about how this type of exercise can be performed, has the potential to reach larger population numbers. Chapter 5 details the validation of the CR-10 perceived exertion scale (Borg 1982) to self-regulate isometric handgrip exercise intensity. Using an estimation-production protocol, findings showed that self-regulating isometric handgrip

exercise intensity at CR-10 “Level-6” produced a relative exercise intensity of approximately 33% MVC (Figure 5.2). Following the establishment of this system of training, it is logical to explore the effects of a self-regulated isometric handgrip exercise training programme on both resting and ambulatory BP.

Considering the lack of isometric adherence data (Chapter 2, section 2.3) it would also be prudent to explore this aspect of isometric training for BP management. The validation of a self-regulated isometric training method (Chapter 5) enables the prescription of a low cost, home-based isometric training regime. This provides opportunity to, for the first time, monitor adherence to unsupervised isometric handgrip training.

In addition to exploring the effect of a self-regulated training programme, there is a need to explore the mechanisms associated with attenuated BP levels following training. Indeed, the mechanisms responsible for reduced BP after isometric training are still under debate. Researchers have proposed improvements to markers of oxidative stress (Peters, Alessio, Hagerman, et al. 2006), improved endothelial function (Badrov, Freeman, Zokvic, et al. 2016; McGowan, Levy, Millar, et al. 2006; McGowan, Visocchi, Faulkner, et al. 2007; Badrov, Bartol, Dibartolomeo, et al. 2013) augmented cardiovagal control (Taylor, McCartney, Kamath, et al. 2003) and reduced sympathetic vasomotor tone (Taylor, McCartney, Kamath, et al. 2003). Considering that the autonomic nervous system influences and/or is influenced by a number of blood pressure regulating processes (neural, hormonal and vascular) it is plausible to propose that a perturbation in these can contribute to heightened sympathetic nerve activity and suppression of vagal nerve activity; this change in autonomic function could contribute to the development and maintenance of hypertension through autonomic stimulation of the heart, peripheral vasculature and kidneys (see Chapter 2, sections 2.i, 2.ii, 2.iii). Thus, the measurement of autonomic nervous system activation may provide key mechanistic insight into the causes of the BP reductions following isometric exercise training. As reviewed in Chapter 2 (section 2.5.2) autonomic function has been previously measured following isometric training (Taylor, McCartney, Kamath, et al. 2003; Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013; Stiller-Moldovan, Kenno, and McGowan 2012). The majority of studies have found no changes in indirect measures of autonomic function (Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013; Stiller-Moldovan, Kenno, and McGowan 2012) despite significant decreases in BP . One of the primary limitations of this previous research is the measurement of heart rate variability (HRV) over a short time period (5-10 minutes) which has been shown to be highly variable across consecutive measurements (Ginsburg, Bartur, Peleg, et al. 2011; Hojgaard, Holstein-Rathlou, Agner, et al. 2005; Maestri, Raczak, Danilowicz- Szymanowicz, et al. 2010; Pinna, Maestri, Torunski, et al. 2007; Ponikowski, Piepoli, Amadi, et al. 1996). Findings from published works included in the current thesis (Chapter 4) showed that 24-hour ambulatory HRV measurements provide more reliable measurements (Morrin, Stone, and Henderson 2017) as compared with resting HRV. The smaller error associated with 24-hour measurements therefore provide a greater possibility of detecting autonomic changes following a therapeutic intervention.

This study was divided into 2 key phases. Phase 1 was designed to establish whether the use of CR-10 "Level-6" to regulate isometric handgrip training intensity can be used to effectively reduce resting and 24-hour ambulatory BP in pre-hypertensive and stage 1 hypertensive adults, over the course of a 10-week exercise programme. In addition, phase 1 would provide mechanistic insight into potential BP changes through the indirect measurement of autonomic function (systolic BPV and HRV). Phase 2 aimed to determine the levels of participant adherence during unsupervised, home-based, self-regulated isometric exercise.

6.2 Methodology

6.2.1 Participants

Seventeen (9 males, 8 females) pre-hypertensive and stage 1 hypertensive adults were randomly allocated to a control or experimental group (Table 6.1). All participants met the inclusion criteria outlined in Chapter 3, (section 3.3). Ethical approval was granted by Buckinghamshire New University research ethics committee. Prior to participation, each participant received a printed information sheet detailing the procedures and any potential risks involved. Written informed consent was obtained from all participants and appropriateness to exercise was determined by the completion of a Physical Activity Readiness Questionnaire; PAR-Q+ (Jamnik, Warburton, Makarski, et al. 2011) (Appendix 1). It was intended that all participants would participate in phase 1 and phase 2 of the study. One participant from the control group (phase 1) did not participate in phase 2 due to personal reasons; their data was removed from the phase 2 analysis (Tables 6.9, 6.10).

Table 6.1: Baseline characteristics of the participants. Values are presented as mean ± SD

	Experimental (n=9)	**Control (n=8)**	**p value**
Females (n)	5	3	-
Males (n)	4	5	-
Age (yrs)	63.8±6.4	66±5.6	0.484
Height (cm)	172±15.4	171±5.9	0.828

Weight (kg)	81.1±20.8	83.8±16.1	0.767
Body mass index	26.9±3.8	28.7±5.5	0.44
RSBP (mmHg)	139.4±7.5	134.3±6.1	0.140
RDBP (mmHg)	85.6±9.5	78±10	0.147
RMAP (mmHg)	103.5±7.93	97±7.7	0.135
RHR (bpm)	62.3±6.8	69.4±11.3	0.139
24-hr SBP (mmHg)	137.8±8.3	129.8±7.8	0.031*
24-hr DBP (mmHg)	82.4±9.6	75.7±8.8	0.156
24-hr MAP (mmHg)	101±8.73	93.5±6.9	0.075
Antihypertensive medication			
Calcium channel blockers	n=2	n=2	
Angiotensin II antagonist	n= 1	n=1	
Diuretic	n=1		
Alpha adrenergic blocker	n=1		
ACE inhibitor	n=1		
Proportion of group on medication	44.4%	25%	0.402

RSBP, resting systolic blood pressure; RDBP, resting diastolic blood pressure; RMAP, resting mean arterial blood pressure; RHR, resting heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure

6.2.2 Research design

The data collection period was 28 weeks in duration and was split into 2 phases *(phase 1 and phase 2)*. Phase 1 was a randomised controlled trial and incorporated a familiarisation session, pre-intervention measurements, a 10-week part-supervised isometric handgrip training intervention and post-intervention measurements (Table 6.1). Phase 2 included 2 x 7 weeks of unsupervised home-based training with measurements taken at the end of each training 7-week period (Figure 6.1)

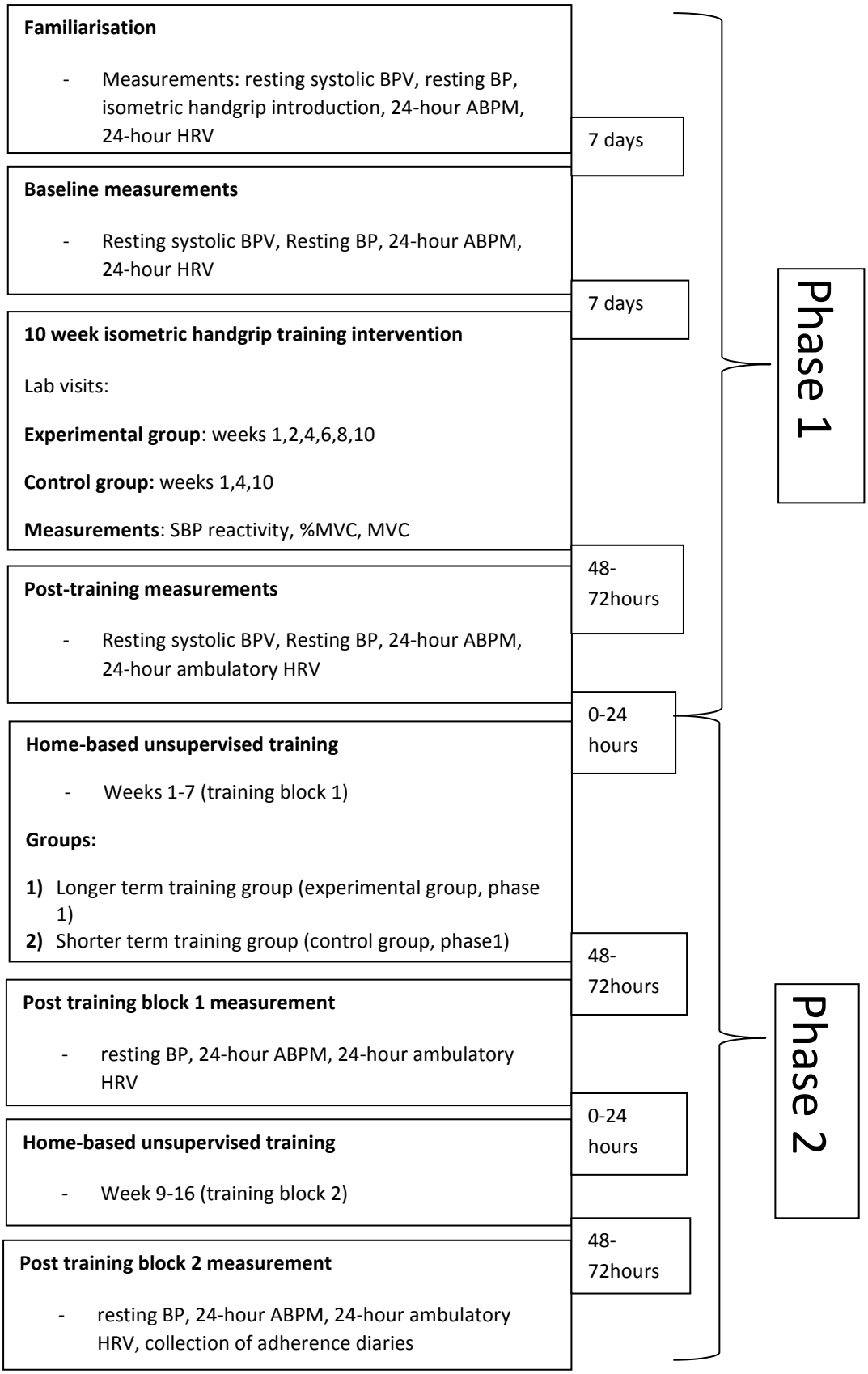

Figure 6.1: Schematic illustration of phase 1 and phase 2 of self-regulated isometric handgrip exercise training intervention. BPV; blood pressure variability, BP, blood pressure; HRV, heart rate variability; ABPM, ambulatory blood pressure monitoring.

6.2.3 Phase 1

The experimental and control participants visited the lab on 9 and 6 occasions respectively (Figure 6.1). Each visit was standardised to take place at the same time of day (+/- 2 hours) with participants avoiding food (2 hours), caffeine (12 hours) and alcohol (24 hours) prior to each laboratory visit.

6.2.3.1 Familiarisation

Stature and mass were measured on arrival at the laboratory (Seca, Bonn, Germany). Familiarisation included the measurement of **i)** resting systolic BP variability (BPV); **ii)** introduction to self-regulation of isometric exercise intensity; **iii)** resting and 24-hour ambulatory BP, and **iv)** 24-hour ambulatory HRV.

- ***Resting systolic BPV***

Lying supine, beat-to-beat systolic BPV was measured using a non-invasive Finometer MIDI device (Finapres, TNO Instruments, Amsterdam, Netherlands). All systolic BPV recordings were measured from the middle finger on the dominant hand. Participants were allowed to rest quietly for 10 minutes during the recording. This procedure is described in detail in Chapter 3 (section 3.7).

- ***Introduction to self-regulation of isometric exercise intensity***

Participants were seated comfortably in a chair (back supported, legs uncrossed, feet flat on the floor) whilst holding a handgrip dynamometer (non-dominant hand) which was connected to an 8-channel recorder (Powerlab 26T, AD instruments LTD, Sydney, Australia) and interfaced with a computer analysis system (LabChart Pro 7 software, AD instruments LTD, Sydney, Australia). With their arm adducted to 90 degrees of flexion at the elbow joint. Participants completed an isometric handgrip warm-up (three 15-second contractions at approximately 50%, 75%, and 90% of maximal effort) followed by three brief maximal contractions (3-5 seconds). One minute of rest was allowed between each maximal contraction. Using an estimation-production procedure, participants were then introduced to self-regulation of isometric handgrip intensity; this is described in detail in Chapter 5, section 5.2.2.

Briefly, the highest MVC value was recorded and used to calculate 15%, 25% and 35% MVC. Using a visual force output display (Powerlab 26T, AD instruments LTD, Sydney, Australia) participants carried out three 2-minute contractions at each intensity (randomised) with 4-minute rest periods in between each contraction. During each 2-minute period of exercise, participants were requested to provide a

rating from the CR-10 scale (Borg 1982) at 30-second intervals (estimation task). Following the estimation task, participants were blinded to the force output display on the handgrip device and instructed to carry out two 2-minute contractions at CR-10 "Level-6"; a four minute rest was allowed between repetitions (production task).

- ***24-hour ambulatory BP and HRV***

Ambulatory BP and HRV were measured using the Cardiotens and Card(X)plore devices (Meditech, Hungary). For BP measurements, a pneumatic cuff was attached to the participant's non-dominant upper arm; detailed fitting methods are provided in detail in Chapter 3, (section 3.4.2). For HRV, electrode placement followed a 2-lead (Cardiotens, Meditech, Hungary) or 3-lead (Card(X)plore, Meditech, Hungary) configuration, as recommended by the Holter device manufacturer (detailed fitting procedures can be found in Chapter 3, (section 3.6.2). To ensure within-subject consistency, each participant was fitted with the same device model on each measurement occasion. The ambulatory units were then attached to participants using a holter case, clipped around the waist. The holter device was set to record BP every 30 minutes between 06.00 and 22.00 and every hour between 22.00 and 06.00. Participants were instructed to free their hand of any items and relax their arm down by their side during each BP recording. Caffeine and alcohol were avoided during the 24-hour monitoring period. Participants were also asked to complete a physical activity diary (Bouchard et al., 1983) for the same 24-hour period (Appendix 3). This tool determined the time that the participants went to bed and got up the following morning. Participants were urged to try to maintain a similar daily routine (i.e. meal times, bed time) and were requested not to engage in organised sport activity or vigorous exercise.

The processing of electrocardiograms is described in detail in Chapter 3 (section 3.6.3 & 3.6.4); beat-to-beat intervals were considered valid if they were different from the previous interval by less than 20% (Cardioseries V4, meditech, Hungary). One of the 24-hour HRV samples was deemed unacceptable for analysis (phase 1 experimental group) due to the presence of persistent ECG tracings that were representative of 2nd degree heart block; this elongated the RR interval at regular intervals causing false HRV calculations. All HRV data belonging to this participant was removed from the analysis.

- ***Resting BP***

Before leaving the laboratory, three resting BP measurements were recorded. Participants were seated comfortably with their elbow supported and forearm rested at heart level. Each measurement was separated by 1-minute of quiet rest (Chapter 3, section 3.4.3).

6.2.3.2 Baseline and post intervention measurements

Within 7 days of completing the familiarisation protocol participants returned to the lab for pre-intervention measurements. Firstly, participants were positioned supine and prepared for a systolic BPV measurement which took place during 10-minutes of quiet rest (Chapter 3, section 3.5.2). Participants were then seated comfortably for a resting BP measurement (Chapter 3, section 3.4.3) which was taken following a further 5 minutes of rest. Finally participants were prepared for 24-hour ambulatory BP and HRV measurements (Chapter 3, section 3.4 & 3.6).

All measurements were repeated in the same format following the completion of 10 weeks of self-regulated isometric handgrip training. The experimental group underwent these measurements within 48-72 hours of completing their final training session.

6.2.3.3. 10 week self-regulated isometric hand-grip training intervention

Participants randomised to the IHG training group, trained on three occasions per week for 10 weeks. Training consisted of four bouts of 2-minutes of unilateral contractions, performed with the non-dominant hand on an ergonomic hand exerciser (Rolyan, Patterson Medical, Nottinghamshire, UK) (Figure 3.10). Training intensity was self-regulated using the CR-10 “Level-6”. Experimental participants were requested to attend one lab-based training session on weeks 1, 2, 4, 6, 8 and 10; the time of day (+/- 2hours) of the visit was standardised and caffeine (12 hours), food (2 hours) and alcohol (24 hours) were avoided prior to each visit. The laboratory-based training session in week one marked the beginning of the training. For subsequent visits (weeks 2, 4, 6, 8 and 10), participants were instructed to have completed their last training session within 24-48 hours of the scheduled visit. Control participants visited the laboratory for one laboratory-based exercise session on weeks 1, 4 and 10. Within-session measurements included SBP reactivity, MVC and the relative intensity (%MVC) of self-regulated isometric exercise.

- ***SBP reactivity***

On arrival at the laboratory, participants were seated comfortably (back supported, legs uncrossed, feet flat on the floor). Using the finometer midi (Finapres, TNO Instruments, Amsterdam, Netherlands), BP was continuously recorded for 10 minutes during quiet rest. The resting BP was calculated as the average of the final two minutes of the seated rest. The finometer midi remained attached and continuously recorded the BP, for the duration of the exercise session. The baseline value (resting BP) was utilised to calculate SBP reactivity to each isometric exercise contraction. Reactivity was calculated by subtracting the resting BP from the average SBP over the course of each 2-minute isometric contraction.

- ***MVC and relative training intensity (%MVC)***

Following a brief warm-up (three 15-second contractions @ 50%, 75%, 90% maximal effort) and three brief (3-5 seconds) MVCs (1-minute rest in between) participants carried out a full training session which was self-regulated by using the CR-10 “Level-6”. The relative intensity of the training session was recorded (Powerlab 26T, AD instruments LTD, Sydney, Australia).

6.2.4 Phase 2

Following phase 1, both experimental and control participants engaged in two 7-week periods of home-based self-regulated isometric handgrip training. For the duration of this phase the experimental group are referred to as the 'longer-term training' group and the control group are referred to as the 'shorter-term training' group. Training intensity was self-regulated using CR-10 "Level-6". Resting BP and 24-hour ambulatory BP and HRV were measured on completion of each 7-week training period (Figure 6.1). Measurements took place within 48-72 hours of completing the final exercise session of each training period. Participants were required to record each exercise session in their 'training log' and adherence was calculated as:

$$\frac{\text{Number of exercise sessions completed}}{\text{Number of exercise sessions prescribed}} \text{ X } 100$$

6.2.5 Statistical analysis

Data were analysed using the statistics package for social sciences (SPSS; IBM, version 23, Armonk, NY). All data were firstly assessed for normality using the Shapiro-Wilk test. Non-normally distributed data were log transformed by calculating the natural logarithm (Ln). In the event of variables maintaining non-normality following transformation, non-parametric statistical analysis was carried out.

Phase 1

One-way analysis of variance (ANOVA) was carried out on age, height, weight and baseline measures of BP (resting and 24-hour average). Small differences were evident between groups in initial baseline BP scores at the onset of the study. The majority of differences were non-significant ($p>0.05$). However, the difference in 24-hour average SBP reached statistical significance ($p = 0.031$) (Table 6.1). Due to these differences and the previous findings that have highlighted the association between reductions in BP and initial scores (Millar, Bray, McGowan, et al. 2007), analysis of covariance (ANCOVA) was used to assess whether change scores in the experimental and control groups were significantly different. Baseline scores were used as the covariate. An alpha level of 0.05 was accepted as being statistically significant and the Bonferroni post-hoc procedure was used to explore any

significant differences that were detected by the ANCOVA. In the case of non-normality, data were rank-transformed prior to running the ANCOVA test (Fan and Zhang 2017).

A 2x3 repeated measures ANOVA was carried out on %MVC, MVC and SBP reactivity (repetition 1) to detect between-group differences at training weeks 1, 4, and 10. An alpha level of 0.05 was accepted as being statistically significant and the Bonferroni post-hoc procedure was used to explore any significant differences that were identified by the factorial ANOVA.

Pearson correlation coefficients were calculated (experimental group only) to detect correlations between:

i) Change in maximal voluntary contraction (average MVC [weeks 1, 2, 4] - average MVC [weeks 6, 8, 10]) and change in resting SBP (post intervention - baseline)

ii) Change in SBP reactivity during repetition 4 (average SBP reactivity [weeks 1, 2, 4] – average SBP reactivity [weeks 6, 8, 10]) and change in resting SBP (post intervention - baseline)

iii) Change in SBP reactivity during repetition 4 (average systolic blood pressure response [weeks 1, 2, 4] – average SBP reactivity [weeks 6, 8, 10]) and average change in MVC (average MVC [weeks 1,2,4] – average MVC [weeks 6,8,10])

iv) Baseline SBP (mmHg) and change in SBP following 10 weeks of isometric handgrip training.

v) Age and change in SBP following 10 weeks of IHG training.

vi) Systolic blood pressure reactivity and change in SBP following 10 weeks of isometric handgrip training.

Phase 2

A 2x3 repeated measures ANOVA was used to determine differences in levels of adherence between the shorter-term and longer-term training groups (group*time) and within groups (time) during weeks 1-7 (phase 2), weeks 9-16 (phase 2) and weeks 1-16 (overall adherence).

A one-way repeated measures ANOVA was used to determine differences in change scores (BP and HRV) within the longer-term exercise group. Change scores were calculated by subtracting measurements taken at **i)** post-intervention (phase 1), **ii)** following weeks 1-7 (phase 2), **iii)** following weeks 9-16 (phase 2) from baseline measurements (phase 1). An alpha level of 0.05 was accepted as being statistically significant and again, the Bonferroni post-hoc procedure was used to explore any significant differences identified by the ANOVA. In the case of non-normality, a Friedman test for related samples was used to determine statistically significance.

In addition, a one-way repeated measures ANOVA was used to determine whether changes occurred from phase 1 to phase 2 (training block 1 and training block 2) within the shorter-term exercise group. As above, an alpha level of 0.05 was accepted as being statistically significant and again, the Bonferroni post-hoc procedure was used to explore any significant differences. Variables displaying non-normality were analysed using the Friedman test for related samples.

6.3 Results

Phase 1

Resting BP and HR

Following 10 weeks of self-regulated IHG exercise training the experimental group experienced reductions in SBP (-6.16mmHg, 95% CI -13.25, 0.92), DBP (-1.8mmHg, 95% CI -9.133,1.265) and MAP (-4.13, 95% CI -8.816, 0.556). However, these changes were not statistically different ($p>0.05$).

There was a small decrease in resting heart rate (1 beat.minute^{-1}), which was not statistically different to the changes observed in the control group ($p>0.05$). Results are shown in Table 6.2.

Of note, all participants successfully completed the IHG exercise training protocol without experiencing clinical abnormalities or inappropriate symptoms during or immediately after isometric exercise.

24-hour ambulatory BP and HR

Following 10 weeks of self-regulated isometric handgrip exercise training, there were no significant differences in 24-hour average, day-time, night-time ambulatory BP (SBP, DBP, MAP) and HR between the experimental and control groups ($p>0.05$). Results are shown in Table 6.3.

Autonomic function

Despite the experimental group showing increases in 24-hour average and daytime markers of vagal tone (HF, HFnu, pNN50%, rMSSD) and decreases in LF, LFnu and LF/HF, no significant differences in the pre- post-training change were observed between groups across all HRV indices ($P>0.05$). In addition, despite decreases within the experimental group, no significant between-group differences were observed in markers of vasomotor sympathetic tone (LF%, LF absolute).These results are presented in Table 6.4 and 6.5.

***Table 6.2**: Baseline-post differences (phase 1) in resting measures of heart rate, systolic, diastolic and mean arterial blood pressure. Values are mean ± SD*

	Baseline (week 0, phase 1)	Post (Week 10, phase 1)	Mean Difference	P value
SBP (mmHg)				
Experimental	139.4±7	133.3±6	- 6.1±9	0.676
Control	134.3±6.1	131.9±6	- 2.4±6	
DBP (mmHg)				
Experimental	85.6±9	83.7±9	-1.8±6	0.127
Control	78.3±10.3	80.0±11	1.8±3	
MAP (mmHg)				
Experimental	103.5±8	100.2±7	-3.2±6	0.329
Control	96.9±7.7	97.29±9	0.4±4	
HR (bpm)				
Experimental	63.4±6.6	62.3±6.9	-1.0±3.7	0.829
Control	69.0±11.3	69.4±11.3	0.3±4.8	

No significant differences in change were observed between the experimental and control group following 10-weeks of self-regulated isometric handgrip training.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

Table 6.3: Baseline-post differences (phase 1) in 24-hour, daytime and night-time ambulatory HR and BP (SBP, DBP, MAP). Values are mean ± SD.

	Baseline (Week 0, phase 1)	Post (Week 10, phase 1)	Mean difference	P value
24-hour average ambulatory blood pressure				
SBP (mmHg)				
Experimental	137.8±8.3	139.1±9.4	1.3±4.9	0.804
Control	129.1±6.6	129.7±8.0	0.6±4.1	
DBP (mmHg)				
Experimental	82.5±9.7	82.2±9.5	-0.3±3.3	0.709
Control	75.8±8.8	75.6±7.8	-0.2±2.5	
MAP (ln mmHg)				
Experimental	4.611±0.086	4.613±0.088	0.002±0.029	0.720
Control	4.536±0.074	4.537±0.070	0.001±0.026	
MAP (mmHg)				
Experimental	100.9±8.7	101.2±8.9	0.2±3.6	
Control	93.5±7.0	93.62±6.7	-0.1±2.3	
HR (bpm)				

Experimental	71.5±11.7	70.6±11.7	-0.9±4.5	0.548
Control	72.0±10.1	72.6±11.0	0.6±5.3	
Daytime ambulatory blood pressure				
SBP (mmHg)				
Experimental	141.8±9.8	143.0±9.9	1.2±5.0	0.684
Control	133.9±6.7	134.5±8.6	0.5±4.6	
DBP (mmHg)				
Experimental	86.0±10.9	85.3±9.7	-0.7±4.6	0.809
Control	79.2±9.7	80.0±9.4	0.8±3.0	
MAP (mmHg)				
Experimental	104.6±10.0	104.5±9.2	-0.1±4.5	0.902
Control	97.5±7.8	98.1±8.0	0.6±2.4	
HR (bpm)				
Experimental	75.5±12.4	73.6±11.5	-1.9±5.8	0.256
Control	75.3±3.5	77.2±4.1	1.9±6.7	
Night-time ambulatory blood pressure				
SBP (mmHg)				
Experimental	126.9±10.5	127.4±12.3	0.5±14.0	0.729

Control	112.2±7.3	118.0±8.6	5.8±5.1	
DBP (mmHg)				
Experimental	73.5±9.6	72.8±11.3	-0.7±8.1	0.908
Control	64.2±6.0	65.2±6.0	1.1±2.8	
MAP (mmHg)				
Experimental	91.3±9.4	91.0±11.1	-0.2±9.9	0.894
Control	80.1±4.7	82.8±5.3	2.6±3.6	
HR (bpm)				
Experimental	61.7±9.3	63.8±13.09	2.1±6.1	0.537
Control	61.6±10.8	62.1±10.4	0.4±3.7	

No significant differences in change were observed between the experimental and control group following 10 weeks of self-regulated isometric exercise training

SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure; HR, heart rate, Ln, natural logarithm.

Table 6.4: Baseline-post differences (phase 1) in 24-hour, daytime and night-time ambulatory HRV. Values are mean ± SD.

24-hour average ambulatory HRV	Baseline (Week 0, phase 1)	Post (Week 10, phase 1)	Mean change	P Value
SDNN				
Experimental	140.9±32.9	136±20.9	-4.88±29.4	0.695
Control	132.7±44.5	135.6±49.3	2.9±27.0	
~pNN50 %				
Experimental	5.9±7.9	7.6±11.4	1.8±4.1	0.597
Control	2.6±2.7	3.6±4.7	1.0±2.3	
rMSSD				
Experimental	28.8±14.9	33.6±23.5	4.9±9.9	
Control	21.4±8.3	22.7±10.3	1.3±3.2	
rMSSD ln				
Experimental	3.26±0.4	3.38±0.5	0.11±0.2	0.620
Control	3.00±0.4	3.04±0.4	0.04±0.2	
LF (ms^2)				
Experimental	790.9±551.4	673.8±419.1	-117.1±156.2	
Control	478.8±323.7	598.3±475.5	119.5±197.3	
LF (ms^2) Ln				
Experimental	6.51±0.56	6.39±0.50	-0.13(0.15)	0.113
Control	5.96±0.74	6.05±0.95	0.09±0.35	
LF nu				
Experimental	72.75±9.9	67.75±10.8	-5.0±6.3	0.225
Control	72.5±9.9	71.13±10.2	-1.4±4.6	
HF (ms^2)				
Experimental	320.3±432.4	386.0±559.4	65.8±142.4	
Control	162.0±130.1	209±191.2	47.0±73.7	

HF (ms^2) Ln				
Experimental	5.33±0.84	5.48±0.89	0.15±0.39	0.941
Control	4.8±0.81	4.9±0.94	0.16±0.38	
HF nu				
Experimental	23.63±9.2	28.25±10	4.6±5.7	0.196
Control	24.13±8.3	25.5±8.9	1.4±3.1	
LF/HF				
Experimental	3.54±1.4	2.71±1.1	-0.8±0.9	0.130
Control	3.53±1.9	3.44±2.2	-0.1±0.9	
	Baseline (Week 0, phase 1)	**Post (Week 10, phase 1)**	**Mean difference**	**P value**
Daytime ambulatory HRV				
SDNN				
Experimental	101.5±29.3	103.3±23.9	1.9±28.4	0.966
Control	102.7±32.2	103.4±42.9	0.7±34.8	
~pNN50%				
Experimental	4.5±8.2	6.0±9.3	1.5±1.7	0.224
Control	2.0±2.5	2.5±4.4	0.5±2.0	
~rMSSD				
Experimental	25.6±16.1	29.3±15.3	3.7±5.0	0.115
Control	20.3±8.5	21.2±10.8	0.9±3.2	
LF (ms^2)				
Experimental	726.7±723.2	534.5±267.2	-192.2±516.5	
Control	418.6±289.2	426±364.7	8.2±155.3	
LF (ms^2) Ln				
Experimental	6.29±0.77	6.18±0.45	-0.11±0.39	0.797
Control	5.81±0.73	5.76±0.86	-0.06±0.43	
LF nu*				
Experimental	70.7±10.8	64.8±16.4	-5.9±12.0	0.365

Control	71.9±11.4	73.1±10.9	1.2±8.9	
HF (ms^2)				
Experimental	296.0±494.3	311.1±413.3	15.2±97.7	
Control	148.0±140.1	152.6±157.1	4.6±45.5	
HF (ms^2) Ln				
Experimental	5.07±0.96	5.31±0.85	0.24±0.34	0.155
Control	4.65±0.87	4.65±0.93	0.00±0.43	
HF nu				
Experimental	24.03±11.2	26.8±7	2.8±6.7	0.551
Control	23.6±8.9	25±8.3	1.5±5.4	
LF/HF				
Experimental	3.8±2.0	2.8±1.2	-1.0±1.2	0.149
Control	3.8±2.3	3.6±2.0	-0.2±1.4	
	Baseline (Week 0, phase 1)	**Post (Week 10, phase 1)**	**Mean difference**	**P Value**
Night-time ambulatory HRV				
SDNN (ms)				
Experimental	104.4±27.8	101.5±28.5	-2.9±15.7	0.789
Control	92.3±40.6	101.1±51.1	8.8±57.0	
~pNN50 %				
Experimental	8.0±9.2	9.0±13.6	1.0±7.2	0.673
Control	2.98±3.6	5.18±7.2	2.2±4.1	
rMSSD (ms)				
Experimental	32.1±15.3	37±30.2	4.9±18.3	
Control	23.1±8.9	25.8±11.2	2.7±4.1	
rMSSD Ln				
Experimental	3.38±0.4	3.43±0.5	0.05±0.3	0.621
Control	3.07±0.4	3.16±0.4	0.10±0.2	
LF (ms^2)				

Experimental	914.5±479.3	1101.6±1284.5	187.1±924.3	
Control	613.1±473.8	799.4±655.5	186.3±225.5	
LF (ms^2) Ln				
Experimental	6.71±0.49	6.69±0.71	-0.02±0.4	0.296
Control	6.13±0.85	6.29±1.08	0.15±0.49	
LF nu				
Experimental	71.9±8.7	69.1±10.3	-2.8±7.4	0.890
Control	74.6±7.8	71.4±10.2	-3.3±4.8	
HF (ms^2)				
Experimental	370.0±373.9	743.9±1462.5	373.9±1112.0	
Control	174.1±112.8	262.8±225.1	88.6±132.1	
HF (ms^2) Ln				
Experimental	5.59±0.81	5.74±1.13	0.15±0.65	0.453
Control	4.92±0.79	5.21±0.97	0.29±0.41	
HF nu				
Experimental	24.6±7.9	27.8±9.9	3.1±6.0	0.551
Control	23.5±7.2	25.6±9.2	2.1±4.2	
LF/HF				
Experimental	3.3±1.3	2.9±1.4	-0.4±1.1	
Control	3.7±1.9	3.4±2.1	-0.3±0.7	
LF/HF Ln				
Experimental	1.12±0.4	0.95±0.5	-0.17±0.4	0.819
Control	1.21±0.5	1.07±0.6	-0.13±0.2	

No significant differences in change were observed between the experimental and control group following 10 weeks of self-regulated isometric exercise training. ~, non-parametric test; HRV, heart rate variability; SDNN, standard deviation of all NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; rMSSD, root mean square of successive differences; LF, low frequency; HF, high frequency; nu, normalised units; ln, natural logarithm

Table 6.5: Baseline-post differences (phase 1) in resting systolic BPV. Values are displayed as mean ±SD.

	Baseline (Week 0, phase 1)	Post (Week 10, phase 1)	Mean difference	P value
LF $mmHg^2$				
Experimental	6.57±3.5	5.17±2.5	-1.39±4.8	
Control	4.68±5.4	5.13±4.8	0.32±1.4	
LF $mmHg^2$ Ln				
Experimental	1.76±0.5	1.54±0.5	-0.22±0.8	0.632
Control	1.07±1.2	1.27±0.9	0.27±0.5	
LF (%)				
Experimental	24.44±7.9	20.56±6.4	-3.89±8.4	0.241
Control	17.42±9.3	20.0±6.4	2.57±5.5	

No significant differences in change were observed between the experimental and control group following 10 weeks of self-regulated isometric exercise training

BPV, blood pressure variability; LF, low frequency; Ln, natural logarithm

Maximal voluntary contraction (MVC).

Within the experimental group, MVC increased from 268.89±98.0 N (baseline) to 286.89±87.9 N (week 10). As compared with the control group, this increase in maximal handgrip strength was not statistically significant ($p>0.05$).

Within the experimental group, a moderate correlation (-0.517, $p = 0.90$) was found between the change in MVC (average MVC [weeks 1, 2 and 4] – average MVC [weeks 6, 8 and 10]) and reductions in resting SBP. This correlation did not reach statistical significance (Figure 6.2).

Self-regulated %MVC

No interaction effects (group x time) or main effects (time) were observed for the self-regulated %MVC training intensity, following the training intervention (Table 6.6). Within the experimental group, average training intensity ranged from 32.81±5.2% (week 1) to 31.97±3.8% (week 10).

SBP reactivity

No interaction effects (group x time) or main effects (time) were observed for SBP reactivity (repetition 1) following the training intervention (Table 6.6).

Within the experimental group a significant correlation (-0.741, $p = 0.022$) was observed between the change in SBP reactivity during repetition 4 (average SBP reactivity [weeks 1, 2, 4] – average SBP reactivity [weeks 6, 8, 10]) and change in resting SBP (week 10 - baseline) (Figure 6.3).

In addition, a significant correlation (0.699, $p = 0.039$) was observed (experimental group) between change in SBP reactivity during repetition 4 (average SBP reactivity [weeks 1, 2 and 4] – average SBP reactivity [weeks 6, 8 and 10]) and change in MVC (average MVC [weeks 1, 2 and 4] – average MVC [weeks 6, 8 and 10]) (Figure 6.4).

Participant characteristics and physiological response to isometric exercise as predictors of isometric handgrip training effectiveness

In the training group, Pearson correlations showed that baseline systolic BP was significantly associated with the training-induced reductions in resting systolic BP (Figure 6.5a). Systolic BP reactivity and age were not significantly associated with training induced reductions in resting systolic BP (Figure 6.5b, Figure 6.5c).

Table 6.6: SBP reactivity, MVC and %MVC measured at baseline, week 4 and week 10. Values are mean ± SD.

	Training week 1	Training week 4	Training week 10	P value (group x time)	P value (time)
SBP reactivity (repetition 1)					
Experimental	22.61±13.0	23.56±16.8	24.55±16.46	0.759	0.976
Control	25.00±14.5	24.75±9.3	23.75±13.4		
MVC (Newtons)					
Experimental	268.89±98.0	273.44±87.2	286.89±87.9	0.355	0.310
Control	277.25±104.6	283.00±91.6	279.50±102.7		
%MVC					
Experimental	32.81±5.2	32.47±3.5	31.97±3.8	0.303	0.661
Control	30.94±8.7	32.88±9.0	32.66±6.8		

No significant main or interaction effects observed for SBP reactivity (repetition 1), MVC or %MVC.

SBP reactivity, systolic blood pressure reactivity; MVC, maximal voluntary contraction; %MVC, percentage of maximal voluntary contraction.

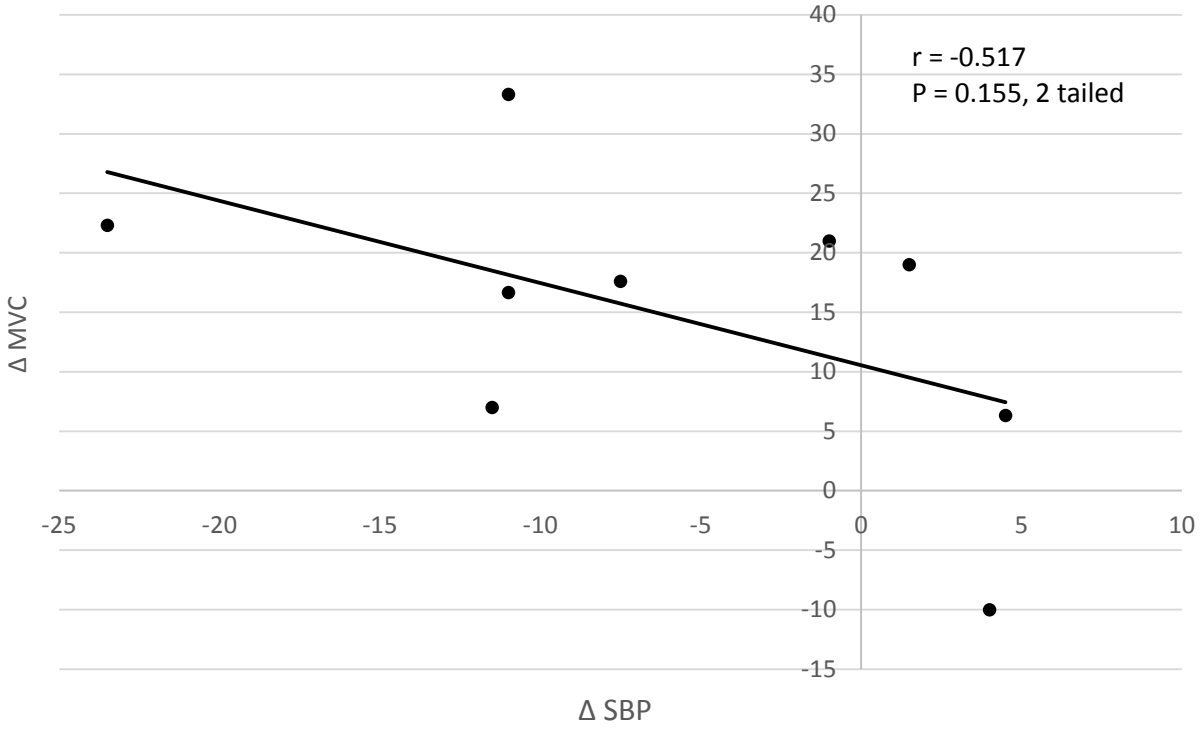

Figure 6.2: Correlation between the change in maximal voluntary contraction (average MVC [weeks 1, 2, 4] - average MVC [weeks 6, 8, 10]) and change in resting SBP (post intervention - baseline)

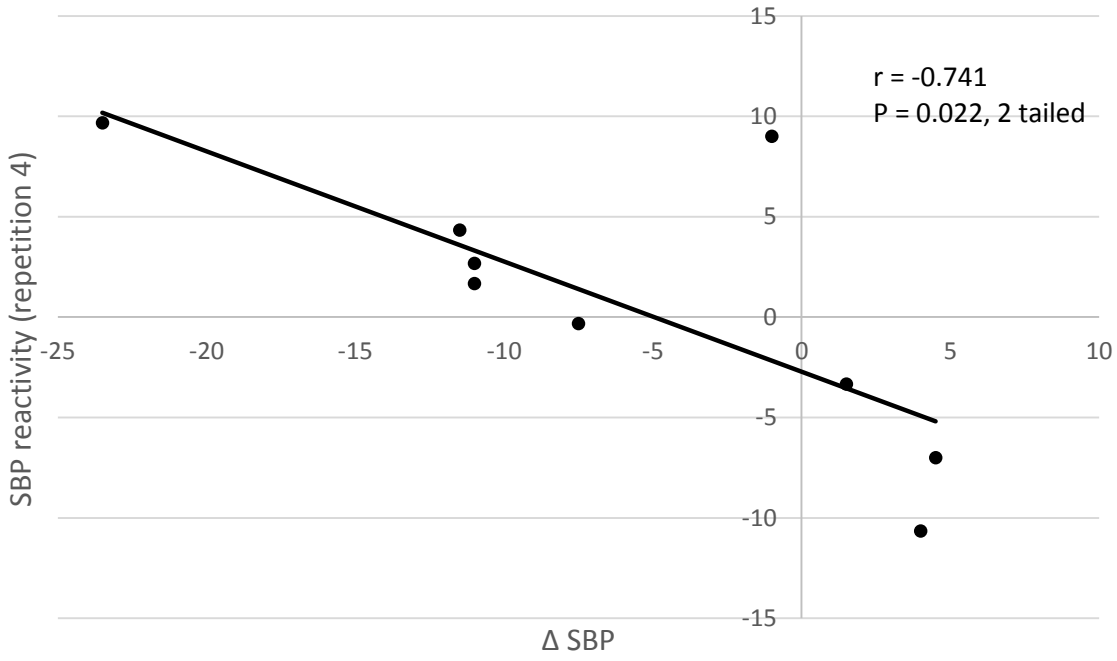

Figure 6.3: Correlation between the change in SBP reactivity (systolic blood pressure reactivity) during repetition 4 (average SBP reactivity [weeks 1, 2, 4] – average SBP reactivity [weeks 6, 8, 10]) and change in resting SBP (post intervention - baseline)

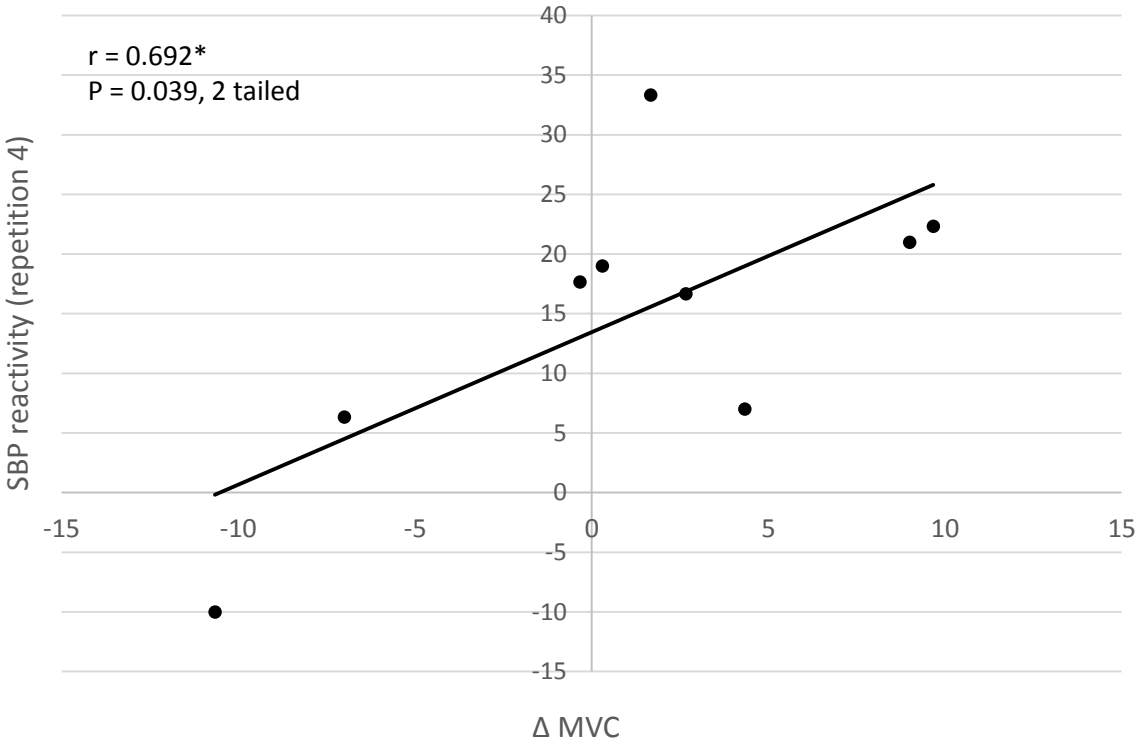

Figure 6.4: Correlation between the change in SBP reactivity during repetition 4 (average systolic blood pressure reactivity [weeks 1, 2, 4] – average systolic blood pressure reactivity [weeks 6, 8, 10]) and average change in MVC (average MVC [weeks 1,2,4] – average MVC [weeks 6,8,10])

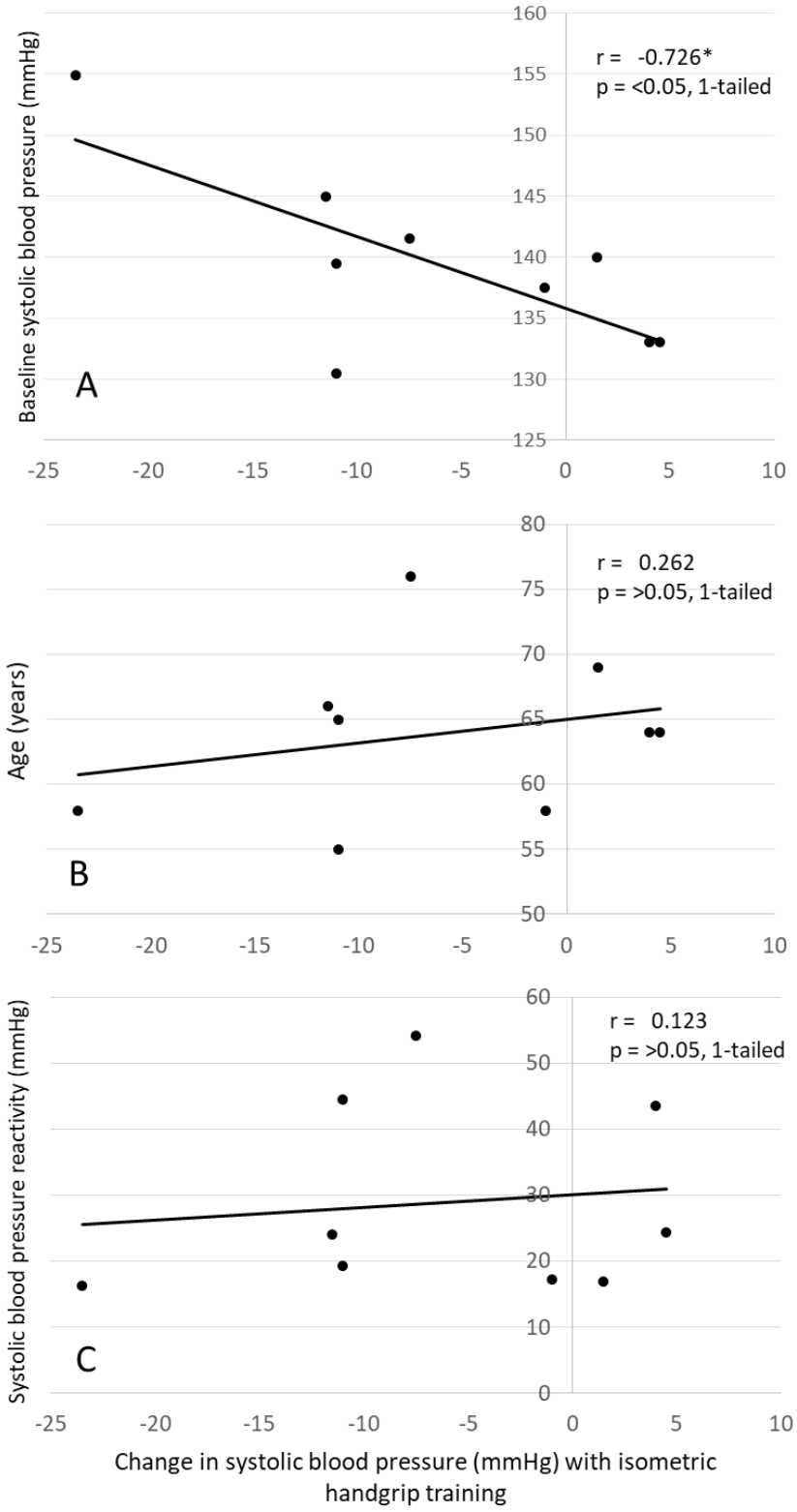

Figure 6.5: Correlation analysis between **A)** Baseline systolic blood pressure (mmHg) and change in systolic blood pressure following 10 weeks of isometric handgrip training. **B)** Age and change in systolic blood pressure following 10 weeks of isometric handgrip training. **C)** Systolic blood pressure reactivity and change in systolic blood pressure following 10 weeks of isometric handgrip training. * = significant correlation ($p<0.05$).

Phase 2

Adherence

Participant retention in both the longer-term (phase 1 experimental group) and shorter-term exercise groups (phase 1 control group) was 100% (Figure 6.6). Adherence during weeks 1-7 was lower in the longer-term training group (89±14.6%) as compared with the shorter-term training group (98.6±2.3%). However, there was no group x time interaction effects (df = 1, F=1.483, p = 0.196). In addition, there was no main effect for time (df = 1, F = 0.485, p=0.498). During weeks 9-16 similar adherence rates were observed in both the longer-term and shorter-term training groups (95.5±5.6%, 96.5±4.5% respectively; Figure 6.6).

Physiological changes from baseline (Phase 1); longer-term training group only.

No statistically significant differences were found between the mean differences from baseline measurements and measurements taken at the end of phase 1, end of training period 1 (phase 2), and end of training period 2 (phase 2) (Table 6.7). However, resting SBP showed a strong trend of returning back towards baseline levels, by the end of training period 2 (phase 2). Similarly, markers of vagal tone (rMSSD, pNN50%, HFnu) showed a strong trend of returning back towards baseline levels by the end of training period 2 (phase 2) (Table 6.8). Twenty-four-hour average and daytime ambulatory BP recordings showed a trend towards increasing above baseline values by the end of training period 2 (phase 2) (Table 6.7).

Blood pressure and autonomic function; shorter-term training group only

No main effect for time was found within any BP or autonomic variable (HRV, systolic BPV; Table 6.9 and Table 6.10). However, the pattern of change within a number of variables between baseline and the end of training period 1 were similar to the changes observed in the experimental group during phase 1 of the study. These patterns include; **i)** decreases in resting SBP, DBP, MAP, 24-hour average LFnu and 24-hour average LF/HF; **ii)** increases in 24-hour average rMSSD, pNN50%, HFnu and HF; **iii)** no change in 24-hour average SBP, DBP, MAP, daytime SBP, DBP, MAP and night-time SBP, DBP or MAP.

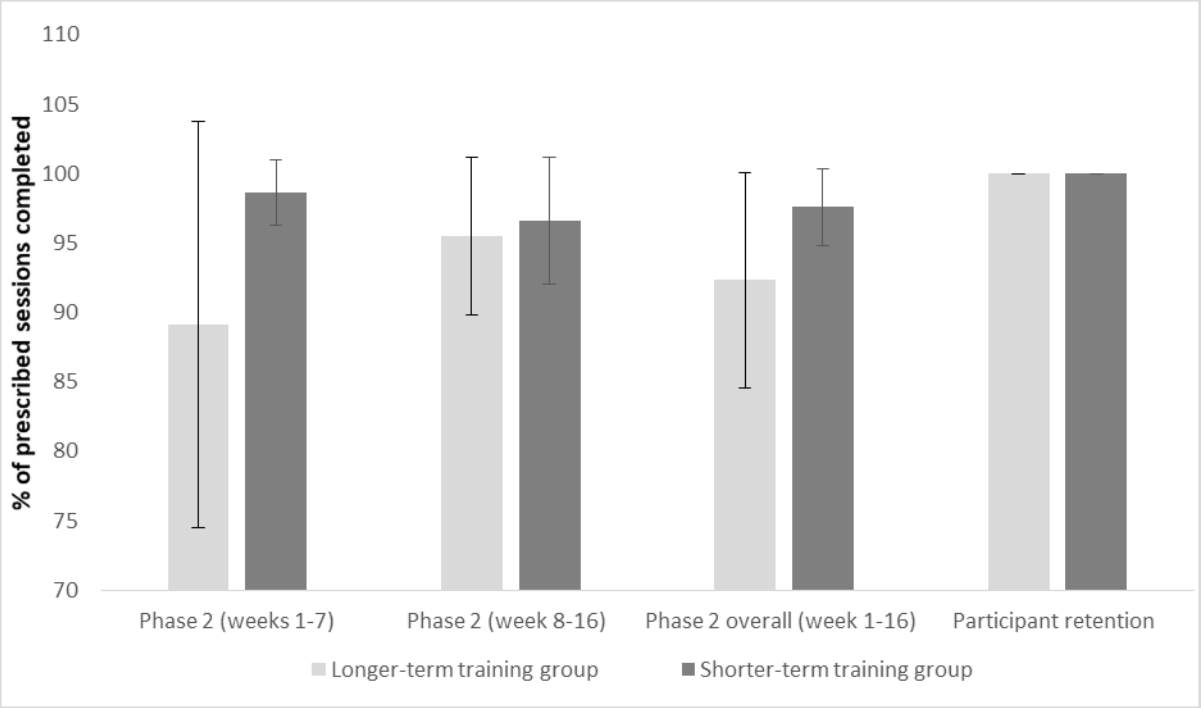

Figure 6.6: Participant retention and percentage of completed exercise sessions during weeks 1-7 (phase 2), weeks 9-16 (phase 2) and overall (phase 2) in the longer-term training group and shorter-term training group. Values are percentage of prescribed sessions completed ±SD. No significant differences were observed within (time) and between (group x time) both training groups.

Table 6.7: Calculated differences in resting and ambulatory blood pressure following phase 1 and phase 2 of study in the longer-term training group. Values are mean (95% confidence intervals).

	Mean difference (10 weeks [phase 1] – baseline)	Mean difference (training block 1 [phase 2] – baseline)	Mean difference (training block 2 [phase 2] – baseline)	Effect for time (P value)
Resting blood pressure				
SBP (mmHg)	-6.167 (-13.253, 0.920)	-7.722 (-15.521, 0.077)	-0.944 (-4.336, 2.447)	0.107
DBP (mmHg)	-1.833 (-6.521, 2.854)	-2.314 (-6.973, 2.344)	-3 (-6.641, 0.641)	0.971
MAP (mmHg)	-3.278 (-8.028, 1.473)	-4.117 (-9.228, 0.994)	-2.499 (-5.613, 0.615)	0.651
24-hour ambulatory blood pressure				
SBP (mmHg)	1.453 (-2.766, 5.671)	2.651 (-1.215, 6.516)	5.519 (0.377, 10.661)	0.277
DBP (mmHg)	-0.236 (-3.176, 2.704)	2.424 (0.042, 4.806)	2.516 (-1.546, 6.578)	0.233
MAP (mmHg)	0.326 (-2.856, 3.508)	2.500 (-0.147, 5.146)	3.517 (-0.844, 7.878)	0.262
Daytime ambulatory blood pressure				
SBP (mmHg)	2.507 (-1.963, 6.077)	4.426 (-1138, 9.990)	3.517 (-0.844, 7.878)	0.167
DBP (mmHg)	-0.280 (-4.131, 3.571)	2.964 (-1.256, 7.185)	3.646 (0.341, 6.952)	0.109
MAP (mmHg)	0.499 (3.452, 4.996)	3.452 (-0.957, 7.860)	4.996 (1.303, 8.689)	0.121

Night-time ambulatory blood pressure				
SBP (mmHg)	-1.200 (-12.671, 10.271)	-2.786 (-10.642, 5.070)	-2.066 (-10.249, 6.117)	0.831
DBP (mmHg)	-1.811 (-8.403, 4.782)	1.077 (-4.765, 6.918)	-2.993 (-10.244, 4.257)	0.325
MAP (mmHg)	-1.607 (-9.680, 6.466)	1.077 (-4.765, 6.918)	-2.722 (-8.226, 2.781)	0.405

No significant differences in change from baseline between phase 1 and phase 2 of intervention study

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure;

Table 6.8: Calculated change scores in 24-hour average ambulatory heart rate variability between baseline measurements and phase 1 and phase 2 of intervention (longer-term training group only)

	Mean difference (10 weeks [phase 1] – baseline)	**Mean difference (training block 1 [phase 2] – baseline)**	**Mean difference (training block 2 [phase 2] – baseline)**	**Effect for time (P value)**
SDNN (ms)	-4.88 (-29.487, 19.737)	6.00 (-10.431, 22.431)	-12.13*(-33.001,8.751)	0.027
pNN50%	1.75 (-1.646, 5.146)	3.13 (-1.420, 7.670)	-1.50 (-4.291, 1.291)	
pNN50% Ln	0.23 (-0.342, 0.799)	0.45 (-0.533, 1.430)	-0.13 (-0.732, 0.473)	0.192
rMSSD (ms)	4.88 (-3.382, 13.132)	5.50 (-3.096, 14.096)	-3.13 (-6.980, 0.730)	0.100
LF nu	-5.00 (-10.287, 0.287)	-7.38 (-12.623, -2.127)	-0.88 (-8.156, 0.406)	0.095
HF nu	4.63 (-0.145, 9.395)	5.63 (1.861, 9.389)	0.88 (-5.340, 7.090)	
HF nu Ln	0.19 (-0.342, 0.799)	0.24 (-0.533, 1.430)	0.072 (-0.732, 0.473)	0.098
LF/HF	-0.83 (-1.599, -0.051)	-1.11 (-2.043, -0.182)	-0.39 (-1.364, 0.589)	0.113

Data is presented as average change scores between baseline measurements and phase 1 and 2 (training block 1 and training block 2) of the intervention

* =significant difference between training block 2 [phase 2] minus baseline

SDNN, standard deviation of all NN intervals, pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; rMSSD, root mean square of successive differences; LF, low frequency; HF, high frequency; nu, normalised units; Ln, natural logarithm

Table 6.9: Resting, 24-hour average, daytime and night-time HR and BP (SBP, DBP, MAP) in shorter-term training group only. Values are mean ± SD

	Baseline (phase 1)	Post (phase 1)	Training block 1 (phase 2)	Training block 2 (phase 2)	Effect for Time (P value)
Resting blood pressure					
SBP (mmHg)	132.4±3.5	131.4±5.8	124.4±12	126.3±8.3	0.112
DBP (mmHg)	78.4±11.2	80.0±12.1	74.4±11.2	78.4±10.3	0.080
MAP (mmHg)	96.4±8.2	97.1±9.2	91.0±10.5	94.3±9.5	0.082
HR ($b.min^{-1}$)	69.4±11.4	69.0±10.5	68.3±10.4	69.4±11.6	0.324
24-hour average ambulatory blood pressure					
SBP (mmHg)	129.4±8.0	129.6±7.8	129.7±13.1	128.7±9.1	0.921
DBP (mmHg)	75.3±9.4	75.3±8.4	75.4±9.4	73.9±10.0	0.561
MAP (mmHg)	93.1±7.5	93.6±7.2	93.5±9.4	92.2±8.9	0.692
HR ($b.min^{-1}$)	73.1±10.4	72.8±11.9	69.9±9.2	68.9±10.4	
HR ($b.min^{-1}$) ln	4.28±0.14	4.28±0.17	4.24±0.13	4.22±0.15	0.123
Daytime ambulatory blood pressure					
SBP (mmHg)	134.0±7.3	134.9±9.2	134.7±14.6	132.9±10.4	0.829
DBP (mmHg)	78.8±10.4	79.2±9.9	79.5±9.8	77.0±9.8	0.430
MAP (mmHg)	97.2±8.4	97.7±8.6	97.9±10.3	95.6±10.2	0.564
HR ($b.min^{-1}$)	76.4±10.3	76.8±12.6	72.8±10.5	71.2±10.7	0.160
Night-time ambulatory blood pressure					
SBP (mmHg)	111.5±7.6	117.6±9.1	110.8±3.9	115.7±5.8	0.052
DBP (mmHg)	63.5±6.1	65.0±6.5	62.5±8.5	65.1±6.6	0.324
MAP (mmHg)	79.5±4.7	82.6±5.7	78.6±6.3	82.0±5.2	0.129
HR ($b.min^{-1}$)	62.9±11.0	62.9±11.0	62.0±8.0	61.9±9.8	
HR ($b.min^{-1}$) Ln	4.13±0.17	4.13±0.17	4.12±0.13	4.11±0.16	0.762

No significant main effects for time were found.

SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure; HR, heart rate.

Table 6.10: 24-hour average ambulatory heart rate variability and resting systolic blood pressure variability in shorter-term training group only. Values are mean ±SD.

	Pre (phase 1)	Post (phase 1)	Training block 1 (phase 2)	Training block 2 (phase 2)	Effect for time (P value)
24-hour ambulatory HRV					
SDNN (ms)	139.0±44.0	148.6±35.5	136.4±31.1	130.9±30.1	0.295
pNN50%	2.6±2.9	3.9±5.0	3.6±2.4	3.6±3.5	
pnn50% Ln	0.61±0.78	0.84±1.00	1.04±0.78	0.94±0.86	0.136
rMSSD (ms)	20.9±8.8	22.3±11.0	28.7±10.1	23.1±8.4	0.084
LF (ms^2)	453.7±341.2	598.3±513.6	578.1±400.8	575.4±509.8	0.192
LF nu	72.4±10.8	71.7±10.8	65.6±15.4	70.9±12.2	0.088
HF (ms^2)	153.7±138.2	202.1±205.4	232.6±141.3	164.0±117.8	
HF (ms^2) Ln	4.72±0.84	4.88±1.00	5.28±0.66	4.88±0.71	0.116
HF nu	24.1±9.0	25.0±9.5	29.1±12.3	25.4±10.0	0.183
LF/HF	3.6±2.0	3.6±2.3	3.1±2.4	3.5±2.3	
LF/HF Ln	1.15±0.55	1.12±0.59	0.89±0.73	1.09±0.63	0.178
Resting systolic BPV					
LF ($mmHg^2$)	4.7±5.4	5.0±4.8	3.8±2.9	6.6±7.7	0.221
LF %	17.4±9.3	20.0±6.4	15.7±6.9	21.1±10.5	0.181

No significant main effects for time were found

SDNN, standard deviation of all NN intervals; pNN50%, the percentage of adjacent NN intervals differing by more than 50ms; rMSSD, root mean square of successive differences; LF, low frequency; HF, high frequency; nu, normalised units; Ln, natural logarithm; BPV, blood pressure variability

6.4 Discussion

The purpose of this 2-phase study was to determine the physiological effectiveness and practicality of prescribing self-regulated isometric exercise training. Phase 1 aimed to determine the effects of self-regulated IHG training on resting and 24-hour ambulatory BP. In addition, phase 1 aimed to determine whether alterations in markers of autonomic function (24-hour HRV and resting systolic BPV) may be contributory factors in any BP changes. Phase 2 primarily aimed to assess levels of adherence to home-based, unsupervised isometric exercise training. In addition, the maintenance of physiological changes that occurred during phase 1 was measured during phase 2.

Phase 1

Resting and ambulatory blood pressure

The results showed that 10-weeks of self-regulated IHG exercise (phase 1) induced non-significant reductions in resting SBP (-6.16mmHg, 95% CI -13.25, 0.92), DBP (-1.8mmHg, 95% CI -9.133, 1.265) and mean arterial pressure (-4.13, 95% CI -8.816, 0.556). Although the magnitude of SBP reduction is consistent with other research (Millar, Levy, Mcgowan, et al. 2013; Badrov, Bartol, Dibartolomeo, et al. 2013; Millar, Bray, McGowan, et al. 2007) carried out on hypertensive participants the reasons for the changes not reaching statistical significance was probably due to the reduction (-2mmHg) observed in the control group. It is difficult to explain why the control group experienced these small reductions in resting blood pressure but the most plausible explanation is that this change reflected inadvertent changes in physical activity and diet, made by participants following the diagnosis of pre-hypertension or stage 1 hypertension. Despite this, the magnitude of change in resting BP has, for the first time, revealed that isometric exercise training can be carried out successfully in a self-regulated way at home. Self-regulated isometric exercise training, using the CR-10 scale, provides the pre-hypertensive and hypertensive patient with a simple means of performing training in a carefully-controlled way that is suitable to be carried out on affordable and portable equipment that does not need regular recalibration with maximal voluntary contractions. However, although 66% of individuals showed clinically relevant (≥2mmHg) (Pescatello, Franklin, Fagard, et al. 2004a) decreases in SBP (-7mmHg, - -23mmHg), 34% of individuals did not show a change (-1mmHg - +4mmHg). These disparate findings within population groups are not uncommon (Millar, McGowan, Cornelissen, et al. 2014) and require further understanding. The current study revealed correlations between **i)** changes in MVC and reductions in resting SBP (Figure 6.2) and **ii)** SBP reactivity during repetition 4 and reductions in resting SBP (Figure 6.3). These findings are discussed in Chapter 7, section 7.3.

In contrast to the trends observed in relation to resting BP, 24-hour average, daytime and night-time ambulatory BP did not show any changes. Although the literature exploring ambulatory BP changes, following

isometric training interventions is scarce, these findings are consistent with those of other isometric training interventions carried out on pre-hypertensive and hypertensive participants (Stiller-Moldovan, Kenno, and McGowan 2012; Ash, Taylor, Thompson, et al. 2016; Pagonas, Vlatsas, Bauer, et al. 2017). In contrast to these previous findings and those of the current study, findings by Somani et al., (2017) reported that 10 weeks of isometric handgrip training induced significant reductions in ambulatory BP in healthy, normotensive participants (Somani, Baross, Levy, et al. 2017).

Taken together with previous findings and those of the current study, isometric training has yet to show improvements in ambulatory BP in those with pre-hypertension and hypertension (medicated and un-medicated). In contrast to resting BP, ambulatory measurements capture an individual's BP fluctuations during daily life activities. These activities include a range of physical and mental stressors and therefore reflects an individual's BP responses to numerous stimuli and therefore their ability to control BP during ambulatory conditions (Schultz and Sharman 2013). It is possible that the physiological mechanism responsible for hypertensive responses (i.e. reduced baroreceptor sensitivity) was not affected by the isometric handgrip training and therefore changes in ambulatory BP was not observed. This is supported by the lack of change observed in SBP reactivity (repetition 1; Table 6.6). Discussion of these findings can be found in Chapter 7, section 7.5.

Heart rate and systolic blood pressure variability

Despite increases in markers of cardiovagal tone and decreases in LF and LF/HF following 10-weeks of isometric exercise training, findings from the current study showed that the between-group changes were not significantly different for all HRV indices (Table 6.4). Similar patterns of change were observed during phase 2 (training period 1) in the shorter-term exercise group (Table 6.10). Similar to the current findings, Taylor et al., (2003) reported a trend towards a decrease in LF/HF in addition to a significant increase in HF in hypertensive participants. The researchers concluded that there was an improvement in vagal control of the heart and improved sympathovagal balance (Taylor, McCartney, Kamath, et al. 2003). In contrast to these changes, other studies involving normotensive populations and well-controlled hypertensives have reported no significant changes in HRV (Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013; Stiller-Moldovan, Kenno, and McGowan 2012). Taken together, these limited findings suggest that an alteration to the autonomic control of the heart may play a role in reducing resting BP in pre-hypertensive and hypertensive adults, but perhaps not in normotensive and well-controlled hypertensive adults. However, due to the poor reproducibility of resting HRV measurements (Morrin, Stone, and Henderson 2017) the lack of sensitivity in this measurement may not allow the detection of small changes (Wiles, Coleman, and Swaine 2010; Badrov, Bartol, Dibartolomeo, et al. 2013) following isometric training.

Similar to the findings in HRV, the current study found that the changes in sympathetic vasomotor tone (LF, LF %) following training were not significantly different to the changes observed following a control period.

However, the experimental group displayed decreases in the LF components of systolic BPV whilst the control group experienced a slight increase. These small changes were observed within the control group after the first seven week period of training, during phase 2. Considering the poor reproducibility of 5-minute recordings of systolic BPV (Chapter 4) the non-significant findings of the current study are not conclusive and warrant further investigation. However, these findings lend some support to the significant reduction in the LF component of systolic BPV found by Taylor and colleagues (Taylor, McCartney, Kamath, et al. 2003) in hypertensive adults.

The potential mechanisms responsible for BP reductions are discussed more thoroughly in Chapter 7 (section 7.6).

Phase 2

The current research is the first to design a study with an unsupervised home-based isometric exercise phase. The levels of adherence (Figure 6.4) reported within the current thesis demonstrate the ease of isometric exercise training completion. Following the completion of phase 1, the longer-term training group (phase 1; experimental group) showed a reduced exercise completion rate during training period 1 (phase 2) as compared with the shorter-term training group. This difference was not statistically significant but highlights the potential for training "fatigue" following the completion of phase 1. Despite the lower level of adherence observed in the longer-term training group, the reductions in resting BP (SBP, DBP, MAP) and changes to rMSSD, pNN50%, LF nu, HF nu and LF/HF were maintained following training period 1 (Table 6.7 & Table 6.8) and therefore, the reduction in adherence during training period 1 would not appear to have been detrimental to the sustainability of the changes in resting BP and HRV.

Adherence during training period 2 was excellent in both the longer-term and shorter-term training groups (95.5% and 96.5% respectively). Despite this, the reductions in resting SBP and MAP observed in the longer-term exercise group showed a trend of returning back towards baseline whilst, 24-hour average and daytime blood pressures showed a trend towards increased levels, compared with baseline. These findings are discussed in Chapter 7 (section 7.4).

6.5 Conclusion

In conclusion, 10 weeks of self-regulated isometric exercise induced reductions in resting BP which were similar in magnitude to previously reported findings. These findings lend support to the clinical relevance of isometric handgrip exercise training. However, 24-hour ambulatory BP was not altered, thereby suggesting that there might be a different mechanism responsible for controlling resting and ambulatory BP. The data also displayed a trend towards changes in autonomic control of both heart rate (HRV) and vasculature (systolic BPV); this, could offer some explanation for the observed reductions in resting BP.

Adherence to self-regulated isometric exercise training was excellent, overall. Despite these adherence levels the longer-term training group did not maintain the positive changes in SBP, MAP, and HRV upon completion of training period 2.

Chapter 7: General discussion

7.1 Introduction and summary of main findings

The primary aims of this thesis were to i) Determine a method of self-regulating isometric hand-grip (IHG) exercise, ii) Measure the effectiveness of self-regulated IHG exercise on 24-hour ambulatory BP and resting BP and iii) Assess adherence levels to an unsupervised, self-regulated isometric training programme. The secondary aim of this thesis was to add insight into the effectiveness of a self-regulated IHG training programme on autonomic function.

To achieve these aims in an effective manner, three individual studies were carried out. Chapter 4 determined the reproducibility of 24-hour ambulatory BP, HRV and systolic BPV and the need for familiarisation sessions prior to data collection. Chapter 5 focused on validating the use of the CR-10 scale for self-regulation of isometric hand-grip exercise. Chapter 6 implemented the use of a self-regulated isometric exercise in a 2-phase training intervention. Phase 1 measured the effects of a 10-week, part supervised, self-regulated isometric handgrip training programme on BP (24-hour ambulatory and resting) and autonomic function. Phase 2 measured adherence to an unsupervised, home-based isometric training programme and compared this in a longer-term training group (24 weeks) and shorter-term training group (14 weeks). In addition, the maintenance of physiological change during longer-term isometric training was assessed.

The main findings of the studies included in this thesis were:

1) The CR-10 “Level-6” was shown to be a valid method by which individuals can self-regulate their isometric exercise intensity, and is thus useful for isometric training purposes.
2) A 10-week, part-supervised, self-regulated isometric handgrip training programme did not induce changes in ambulatory BP (systolic, diastolic, mean arterial pressure) but did induce clinically significant reductions in resting SBP (mean -6mmHg) that were similar in magnitude to those previously reported.
3) The group changes in resting SBP, after this training, were not statistically significant, largely because the control group experienced a mean reduction of -2 mmHg in their resting SBP.
4) This training programme induced small, non-significant improvements in markers of cardiovagal tone, as measured by 24-hour HRV. In addition, small, non-significant reductions in the LF component of systolic BPV (indicative of a reduction in sympathetic vasomotor tone) was found.
5) Self-reported compliance with the training programme, indicated that self-regulated isometric training is well adhered to in both shorter-term and longer-term training groups. Adherence was superior in participants who were new to the training regime (shorter-term training group) than those who had already completed 10-weeks of exercise (longer-term training group).

6) The longer term training group maintained resting BP changes following training block 1 (phase 2) whilst a trend for resting BP returning back to baseline was observed following training block 2 (phase 2).
7) Whilst resting SBP returned back towards baseline, daytime and 24-hour average BP showed a trend towards increasing above baseline levels.

7.2 Finding: The CR-10 "Level-6" was shown to be a valid method by which individuals can self-regulate their isometric exercise intensity, and is thus useful for isometric training purposes.

Question: What are the benefits of using the RPE scale for self-regulation of exercise, in particular isometric exercise?

Chapter 5 employed an estimation-production protocol to determine whether participants were able to effectively utilise the CR-10 scale to self-regulate IHG exercise intensity. Results from the estimation task indicated that there was a strong linear relationship between the CR-10 scale and %MVC (Figure 5.1) and that "Level- 6" aligned with an average %MVC of 33% (95% CI; 36.2%, 30%). Considering that the most common isometric exercise prescription, aimed at lowering BP in previous studies, has been set at 30% MVC (Millar, Bray, McGowan, et al. 2007; Taylor, McCartney, Kamath, et al. 2003; Wiley, Dunn, Cox, et al. 1992; Badrov, Horton, Millar, et al. 2013) these findings indicated that the CR-10 "Level-6" would most closely approximate the exercise intensity that has been used previously. Following the estimation task, the production task revealed that participants were able to adequately self-regulate their exercise intensity (%MVC) using "Level-6" on the CR-10 scale (Figure 5.2). As discussed in Chapter 2 (section 2.4), strong linear relationships have also been found between the different levels on an RPE scale and markers of aerobic exercise intensity (Borg, Hassmén, and Lagerström 1987; Ueda and Kurokawa 1995; Marriott and Lamb 1996; Borg and Kaijser 2006; Scherr, Wolfarth, Christle, et al. 2013; Goslin and Rorke 1986; Chen, Fan, and Moe 2002; Utter, Robertson, Green, et al. 2004) and dynamic resistance exercise training (Lagally and Amorose 2007; Tiggemann, Korzenowski, Brentano, et al. 2010; Row, Knutzen, and Skogsberg 2012). With regard to isometric exercise, one previous study had shown a strong linear relationship between the Borg CR-10 scale and %MVC during 5-second contractions (Pincivero, Coelho, and Erikson 2000). However, its relationship with %MVC during longer isometric contractions was until now, unknown.

However, it is important to note, that although studies have highlighted that exercise interventions regulated by perceived exertion have been successful in increasing aerobic capacity (Fujiwara, Asakuma, and Iwasaki

2000; Kobayashi, Hosoi, Takeuchi, et al. 2001; Parfitt, Evans, and Eston 2012), anaerobic capacity (Fujiwara, Asakuma, and Iwasaki 2000) and muscular strength (Allen, Canning, Sherrington, et al. 2010; Dibble, Hale, Marcus, et al. 2006) studies have not investigated whether exercise programmes designed for BP management are successful when self-regulated using a perceived exertion scale. Despite this, the most recent guidelines for exercise and BP management suggest that moderate aerobic exercise can be self-regulated using RPE 11-13 (Pescatello, Macdonald, Lamberti, et al. 2015) on the Borg 6-20 scale. Considering the relative importance of exercise intensity for BP management (Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013; Ghadieh and Saab 2015; Brook, Appel, Rubenfire, et al. 2013; James, Oparil, Carter, et al. 2014) it would seem prudent for more studies to verify the effectiveness of RPE regulated exercise on BP management exercise programmes. Chapter 6 describes the first study to utilise a perceived exertion chart (CR-10 scale) for the primary purpose of regulating isometric exercise prescribed with the intention of aiding BP management. This novel study showed that self-regulation of isometric exercise was effective in reducing resting SBP in pre-hypertensive and hypertensive individuals (Table 6.2).

The use of perceived exertion scales in the prescription of exercise for BP management has a number of benefits; 1) Cost effectiveness 2) Simplicity 3) Individualised training 4) Reduced need for the recalculation of training zones 5) Exercise flexibility 6) Improved exercise adherence.

Cost effectiveness

RPE scales are freely available online. This cost-effective resource therefore provides opportunity to large portions of the population to self-regulate a prescribed exercise intensity without the need for specialised equipment such as isometric handgrip devices, physiological monitoring instruments (e.g. gas analysis systems or HR monitors), gym-based resistance machines and an exercise professional who can assist individuals with identifying the correct training loads for exercise training.

Simplicity

RPE scales are simple to understand and use. However, considering the importance of exercise intensity in the prescription of BP management training regimes (Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013; Ghadieh and Saab 2015; Brook, Appel, Rubenfire, et al. 2013; James, Oparil, Carter, et al. 2014) the ability to reproduce markers of exercise intensity is of paramount importance for the successful application of perceived exertion charts. The necessity for familiarisation protocols prior to successful self-regulation is debatable. It has been argued that the reproduction of a prescribed intensity will be more accurate following instructor led feedback during production trials (Dishman 1994). A study carried out by Soriano-Maldonado and colleagues (2013) showed that practice trials improved individuals ability to reproduce target HR's using the 6-20 RPE scale (Soriano-Maldonado, Romero, Femia, et al. 2013). However, other researchers have concluded that individuals are able to reproduce markers of cardiorespiratory stress

(Marriott and Lamb 1996; Green, Michael, and Solomon 1999; Dunbar, Robertson, Baun, et al. 1992; Eston, Davies, and Williams 1987; Paulson, Bishop, Leicht, et al. 2013; Goosey-Tolfrey, Lenton, Goddard, et al. 2010), physical capacity (Goosey-Tolfrey, Lenton, Goddard, et al. 2010; Paulson, Bishop, Leicht, et al. 2013; Marriott and Lamb 1996) and resistance training load (Lagally and Amorose 2007) during a single production task and therefore others conclude that familiarisation sessions are not necessary.

Findings from Chapter 5 showed that the accuracy of isometric exercise intensity production did not improve over the course of three separate production trials (Figure 5.2). This finding would suggest that individuals are able to self-regulate isometric exercise intensity without the need for feedback from an exercise professional. However, it is important to note that all individuals underwent a detailed introduction to the CR-10 scale which involved anchoring procedures led by the primary researcher (Chapter 5, section 5.2.2). Future studies will need to determine whether a brief and self-instructed anchoring procedure would be sufficient to familiarise participants with the CR-10 "Level-6". This would further enhance the simplicity and accessibility of a self-regulated isometric exercise.

Participant led training intensity

The use of perceived exertion to regulate exercise intensity as opposed to prescribing a specific intensity calculated from an individual's maximum capacity allows the intensity of exercise to be participant led. Imposing a relative exercise intensity on exercise participants could introduce prescription error and cause individuals to work at a too low or too high an exercise intensity. For example, aerobic exercise intensities based off HR can cause some problems. One common procedure of calculating HR max is to use age-predicted HR max (220-age); this calculation can introduce errors of approximately 11 beats.min^{-1} above or below the true maximum (Arena, Myers, and Kaminsky 2016). In addition, hypertensive adults on beta blockers have a blunted HR response at rest and during exercise (Wonisch, Hofmann, Fruhwald, et al. 2003). Exercise prescription based off HR is therefore of limited accuracy and again may cause individuals to exercise at too high a level in order to meet the prescribed HR zone. In this scenario it could be healthier to use methods of self-perception to control intensity (di Blasio, Sablone, Civino, et al. 2009).

In relation to isometric exercise prescription, the use of maximal contractions to prescribe exercise intensity is limited and could also introduce significant prescription errors. For example, individuals with arthritis or frailty may be unable to carry out a true maximal contraction. The calculation of %MVC would therefore be based on an inaccurate maximal contraction and would result in individuals working below the prescribed intensity.

Instead of imposing a relative exercise that could introduce significant prescription errors, Parfitt et al., (2012) argues that participant led intensity regulation, using an RPE scale, encourages autonomy which is an

important component of developing an individual's intrinsic motivation which is linked with long-term exercise adherence (Ryan, Fredrick, Lepes, et al. 1997).

Reduced need for recalculation of training zones

The use of the RPE scale reduces the necessity for regular recalculation of training zones. For example, isometric exercise training will increase strength (Table 6.6) and therefore relative exercise intensity is traditionally recalculated prior to commencing each exercise session. This typically involves 3 x maximal isometric contractions (Chrysant 2010). As discussed, the use of maximal contractions is limited in older adults due to frailty and arthritis. It is also recommended that abrupt increases in SBP should be avoided in those at cardiovascular risk (Pescatello, Franklin, Fagard, et al. 2004b). The use of the RPE scale avoids the need for recalculation of training zones. Findings from Chapter 6 showed that as individuals got stronger the %MVC elicited at CR-10 "Level-6" did not significantly change (Table 6.6). This finding proves that individuals adjust their self-regulated power outputs in accordance with strength gains; removing the need to regularly recalculate training zones.

This benefit is also applicable to dynamic resistance exercise prescription where an individual's 1RM would naturally improve during the course of training. Without regular recalculation of training zones through a 1RM test, individuals could end up exercising at too low an intensity and may not, therefore, achieve the desirable benefits.

Exercise flexibility

The use of a perceived exertion chart also provides individuals with exercise flexibility. Although isometric exercise already offers flexibility (i.e. short exercise timeframe, portable exercise devices) the use of perceived exertion to self-regulate isometric handgrip exercise enables individuals to carry out the exercise on any immoveable object found in the workplace or home. In relation to other exercise modalities, the use of the RPE scale to regulate intensity offers individuals the opportunity to engage in exercise without the need to access gym equipment and/or an exercise professional that could assist in monitoring exercise intensity for them. For example, the use of perceived exertion for the regulation of dynamic resistance training would allow individuals to carry out the exercises in the home using cost-effective items like resistance bands or free weights.

Improved exercise adherence

Finally, the use of RPE scales in the prescription of exercise for BP management has the potential to elicit improved exercise adherence. As previously mentioned the possibility of instilling intrinsic motivation by providing autonomy could be linked to improved adherence (Ryan, Fredrick, Lepes, et al. 1997). Also, considering that cost and lack of convenience (Bethancourt, Rosenberg, Beatty, et al. 2014; Franco, Tong,

Howard, et al. 2015; Jefferis, Sartini, Lee, et al. 2014) are common barriers associated with poor exercise adherence it could be suggested that the cost effectiveness and reduced necessity to access specialist equipment would encourage continued exercise participation. Findings from Chapter 6 showed that adherence to isometric training was excellent (Figure 6.6). It is unknown whether exercise adherence outside the confines of a research study would be of the same quality – however the small time commitment and the ability to self-regulate isometric exercise on any immovable object in the home or workplace would suggest that individuals should be able to participate in and comply with isometric exercise.

7.3 <u>Finding:</u> A 10-week self-regulated isometric training programme induced clinically-significant reductions in resting SBP that were similar in magnitude to those previously reported. However, these changes were not statistically significant, largely because the control group experienced a mean -2 mmHg change in their resting SBP.

<u>Question</u>: Do figures 6.2, 6.3 and 6.4 provide insight into inter-individual differences in resting BP reductions following 10-weeks of self-regulated isometric exercise training?

Despite the reported poor reproducibility for measurement of resting BP (Campbell, Ghuman, Wakefield, et al. 2010; Fotherby and Potter 1993; Mansoor, McCabe, and White 1994; Stergiou, Baibas, Gantzarou, et al. 2002; Wendelin-Saarenhovi, Isoaho, Hartiala, et al. 2001; van der Steen, Lenders, Graafsma, et al. 1999) the majority of previous isometric training studies have employed well controlled RCTs or crossover trials and have shown significant reductions in resting SBP (Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Wiley, Dunn, Cox, et al. 1992; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Horton, Millar, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; Baross, Wiles, and Swaine 2013).

In all of these previous studies, the isometric training intensity has been regulated by 'feedback' during the exercise, to which the participant responds by adjusting their effort until they match a predetermined target. The feedback is usually either exercising force (e.g. 30% MVC), but it has also been exercising EMG (Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2010). These methods of regulating isometric training intensity require an exercise device that can measure force, and display it, so that the participant can view it. This has invariably involved relatively expensive exercise devices. It also requires a degree of 'cognitive ability', to interpret the force display and respond to it. Therefore, these devices might not be

suitable for some people (e.g. the very elderly). The current thesis employed a self-regulated isometric handgrip training protocol (Chapter 5). This protocol does not require an exercise device that measures force and provides continuous feedback to the participant. Despite a sizeable decrease in resting SBP in the isometric training group (-6mmHg), this change was not significantly different to the change observed in the control group (-2mmHg).

The largest and most recent meta-analysis of randomised control trials (n=302) revealed post-training reductions in resting systolic BP of -5.2mmHg (Inder, Carlson, Dieberg, et al. 2016). Specifically research on hypertensive adults with similar baseline BP to that of the participants within the current thesis found that isometric handgrip training successfully reduced systolic BP by between 5 and 8 mmHg (Badrov, Horton, Millar, et al. 2013; Millar, Levy, Mcgowan, et al. 2013). These findings are similar to those of the current thesis and therefore suggests that the self-regulated isometric exercise training programme did work.

However, it is important to note that there was wide inter-individual responses amongst those within the experimental group (Figure 7.1); 66% (n=6) reduced their systolic BP (range from -23.5 to -7mmHg) whilst 34% (n=3) experienced a very small reduction or increase (range -1.0 to -4.5mmHg). Large inter-individual variability in the magnitude of BP changes is not unusual and has been observed in previous studies (Millar, Bray, McGowan, et al. 2007; Millar, Bray, MacDonald, et al. 2008; Devereux, Coleman, Wiles, et al. 2012; Badrov, Horton, Millar, et al. 2013). To date, studies have shown that participant characteristics (Millar, Bray, McGowan, et al. 2007; Millar, Bray, MacDonald, et al. 2008) and physiological responses to a single period (usually 2 minutes) of isometric exercise (Devereux, Coleman, Wiles, et al. 2012; Badrov, Horton, Millar, et al. 2013) are related to BP reductions following a period of regular isometric exercise.

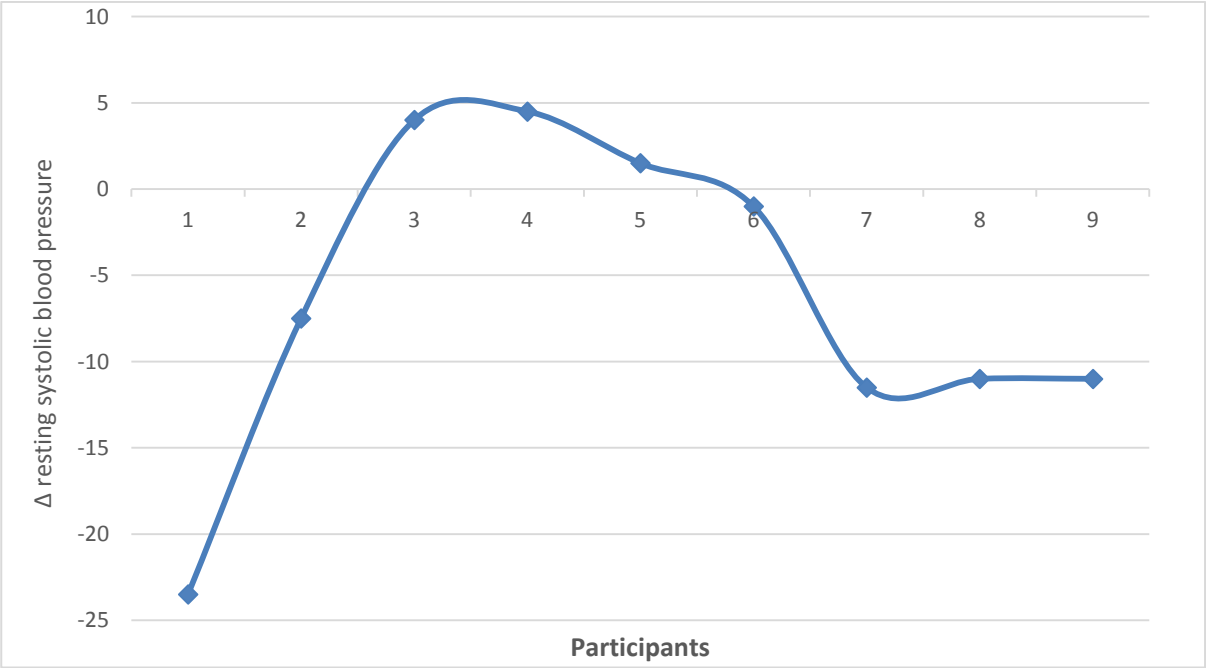

Figure 7.1: Area graph displaying individual changes in resting systolic blood pressure following 10-weeks of self-regulated isometric handgrip training. Resting systolic BP changes ranged from -23mmHg – 4.5mmHg

With regards to participant characteristics, older individuals (Millar, Bray, MacDonald, et al. 2008) and those with a higher baseline BP (Millar, Bray, McGowan, et al. 2007) experience greater BP reductions following an isometric training intervention. Physiological responses such as SBP reactivity (Badrov, Horton, Millar, et al. 2013) and lactate production (Devereux, Coleman, Wiles, et al. 2012) have been shown to be related to the magnitude of resting BP reductions following training. As discussed in Chapter 5, Badrov et al., (2013) found that SBP reactivity to a single isometric task was positively correlated with BP reductions. In relation to lactate production, findings have shown a positive relationship between reduced SBP following 4-weeks of isometric training and training lactate levels (Devereux, Coleman, Wiles, et al. 2012). This provides evidence that isometric training intensity needs to be sufficiently high enough to induce local muscle anaerobiosis and accumulation of metabolites (i.e. lactate) (Lawrence, Cooley, Huet, et al. 2014). The accumulation of metabolites is known to induce the metaboreflex (Kaufman and Hayes 2002); the repeated stimulation of this reflex via the type III afferents is believed to be related to BP reductions (Brook, Appel, Rubenfire, et al. 2013).

The data from the 10-week training intervention revealed that baseline SBP significantly correlated with baseline BP reductions (Figure 6.5a). On the other hand this study does not support the relationship between age, SBP reactivity and reductions in resting SBP (Figure 6.5b. Figure 6.5c). This suggests that a number of other factors may play a role. For example an individual's physical and physiological adaptations to an isometric training programme and its impact on reductions in resting SBP have not been explored. Findings from previous studies have shown that 4-weeks of rhythmic isometric exercise decreases lactate accumulation during ischemic exercise (Mostoufi-Moab, Widmaier, Cornett, et al. 1998), suggesting that adaptations to training can raise the 'ischemic threshold'. In addition, other forms of resistance training have been shown to increase the activation of oxidative enzymes (Frontera, Meredith, O'Reilly, et al. 1990), mitochondrial proteins (Frank, Andersson, Pontén, et al. 2016; Andersson, Frank, Ponten, et al. 2017), shift muscle fibre characteristics towards a more oxidative profile (Frank, Andersson, Pontén, et al. 2016) and improve lactate clearance following a resistance exercise session (Juel, Klarskov, Nielsen, et al. 2004). These adaptations indicate an increase in muscle aerobic capacity and would therefore result in reduced lactate accumulation at a given exercise intensity (Kraemer and Ratamess 2004). Given the evidence suggesting that the production of blood lactate is related to BP reductions (Devereux, Coleman, Wiles, et al. 2012), and isometric training improves muscle oxidative capacity (Mostoufi-Moab, Widmaier, Cornett, et al. 1998) it would be pertinent to use this discussion to explore how individual training adaptations to 10-weeks of self-regulated isometric training may have contributed to the wide variability in BP reductions.

Figure 6.2 shows a moderate negative correlation between changes in strength (as measured by MVC) and reductions in resting SBP. This finding indicates that individuals who increased their MVC during the second half of the training programme (weeks 6, 8 and 10) as compared with the first half of the training programme (weeks 1, 2 and 4) benefited from greater resting SBP reductions following 10-weeks of isometric handgrip training. Research supports inter-individual differences in isometric strength gains following a resistance training programme (Hubal, Gordish-Dressman, Thompson, et al. 2005; Erskine, Jones, Williams, et al. 2010). Inter-individual differences in isometric strength adaptations could provide insight into inter-individual BP responses. It would seem that those who do not increase their MVC in the second half of the training programme are less likely to experience reductions in resting SBP. In contrast, those whose strength increased were more likely to benefit from BP reductions. This finding provides us with some evidence for the need of continued overload to increase the likelihood of strength adaptations and potentially maximise BP reductions.

To further support the influence of training adaptations on reductions in resting SBP, Figure 6.3 shows a significant negative correlation between changes in how much the BP reacts (SBP reactivity) to a single period of exercise (repetition 4) and reductions in resting SBP. This finding indicates that individuals who maintained or increased their pressor response (SBP reactivity, repetition 4) during the 2nd half of the training programme were more likely to benefit from reduced resting SBP pre- to post-training. Findings from Chapter 5 (Figure 5.2) showed that the SBP response to isometric exercise gradually increased throughout an isometric training session (four repetitions). As discussed in Chapter 5 the larger pressor responses observed during repetition 4 are likely to be the result of an accumulation of metabolic by-products which would also be associated with muscle fatigue. The maintenance or increase in pressor response (significantly raised BP, during the training) would therefore indicate that the exercise stimulus was continuing to induce sufficient metabolic stress. This indication of continued metabolic stress, during training, seems to occur quite differently in different individuals.

Finally, the data reveals a significant correlation (Figure 6.4) between changes in MVC and changes in 'SBP reactivity' (in response to repetition 4) – this correlation suggests that those individuals who increased their MVC were experiencing maintained or possibly increased metabolic stress as the training programme progressed; an important component of BP reductions (Devereux, Coleman, Wiles, et al. 2012).

In summary, the findings presented in Figure 6.2, 6.3 and 6.4 indicate that individuals who do not experience continued increases in isometric strength adaptations (plateau) also experience a reduced 'SBP reactivity' during repetition 4 (indicative of reduced metabolic stress) and a lack of SBP reduction following isometric training. Individual training adaptations to the isometric training stimulus could be an important area of further study; this would further advance the understanding of inter-individual differences in adaptations to isometric training programmes.

7.4 Finding (1): Self-reported compliance with the training programme indicated that the participants engaged well, with the self-regulated isometric training. This was evident in both the shorter-term (16-weeks) and the longer-term (24-weeks) training groups. Compliance was superior in participants who were new to the training regime (in the shorter-term training group) than those who had already completed 10-weeks of exercise (the longer-term training group).

Finding (2): The longer term training group maintained resting BP reductions following training block 1 (phase 2) whilst a trend for resting BP to return back to baseline was observed following training block 2 (phase 2).

Question: What is the long-term applicability (compliance and maintenance of physiological adaptations) of unsupervised, self-regulated isometric training?

The current thesis is the first to record isometric exercise compliance levels and compare them between a longer-term training group (24-weeks) and a shorter-term training group (14-weeks). Exercise compliance was recorded using a multi-method approach combining self-reporting alongside objective measures (HRV, systolic BPV, resting BP, 24-hour ambulatory BP) (De Geest and Sabaté 2003).

The novel use of self-regulated isometric exercise (Chapter 5) made it possible to prescribe a cost-effective, home-based, unsupervised, isometric exercise programme (Chapter 6). Considering the high compliance reported in phase 2 of this training programme (Figure 6.6) it could be concluded that the isometric training regime was well-accepted and sustainable, within both the shorter-term and longer-term training groups. In addition, no drop-outs were observed, in either training group (Figure 6.6). This is in contrast to a number of previous longer-term aerobic training studies where drop-out rates can be as high as 50% (Nam, Dobrosielski, and Stewart 2012; Schmidt, Gruman, King, et al. 2000; Stiggelbout, Hopman-Rock, Tak, et al. 2005; Young and Stewart 2006).

Considering the high compliance levels it is reassuring to show that the longer-term training group maintained their resting BP reductions following training block 1 (Table 6.7). However, despite continued compliance during training block 2, findings show that the average resting BP in the longer-term training group (total training duration; 24 weeks) increased back towards baseline BP. Previous studies have shown

that 4-10 weeks of isometric training is effective in inducing reductions in resting BP (Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Wiley, Dunn, Cox, et al. 1992; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Horton, Millar, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; Baross, Wiles, and Swaine 2013) but no previous study has examined whether continued isometric training maintains those physiological adaptions. Considering the high adherence recorded in Chapter 6, the return of BP back toward baseline at the end of 24 weeks of training requires further discussion. The following 2 sub-sections will expand on the possible explanations for the loss of training-induced reductions in resting BP with longer-term isometric training (i) lack of compliance (despite self-reported compliance being high) and (ii) physiological adaptation. This might help steer the development of future isometric training studies.

Lack of compliance, as an explanation for the loss of isometric training-induced reductions in resting blood pressure

As the current thesis is the first to utilise a longer-term (24-week) isometric training intervention, there are few previous studies with which to compare the findings. Most other previous isometric training studies have utilised interventions of 4-10 weeks in duration (Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Wiley, Dunn, Cox, et al. 1992; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Horton, Millar, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; Baross, Wiles, and Swaine 2013). However, in contrast to isometric exercise, many studies have measured BP changes following longer-term aerobic training (≥24 weeks). Interestingly meta-analyses have shown that the magnitude of BP reductions diminish in accordance with longer (≥24 weeks) training interventions (Lee, Watson, Mulvaney, et al. 2010; Cornelissen and Smart 2013; Cornelissen and Fagard 2005). In a review examining the effects of walking interventions, Lee et al., (2010) found that only four out of twelve interventions lasting 6 to 12 months had a significant positive effect on BP. Authors conducting meta-analyses suggest that this finding is due to a lack of compliance during long-term aerobic training regimes (Lee, Watson, Mulvaney, et al. 2010; Cornelissen and Smart 2013; Cornelissen and Fagard 2005).

Unfortunately, the limitation of assessing compliance through self-reporting, is of concern (Bollen, Dean, Siegert, et al. 2014; Prince, Adamo, Hamel, et al. 2008). In comparison with direct measures, self-reporting has been shown to underestimate or overestimate participation levels (Prince, Adamo, Hamel, et al. 2008). However, in contrast to self-recalling and self-reporting of day-to-day levels of other types of exercise (e.g. aerobic exercise), isometric training programmes have the advantage of being of a simple structure (e.g. 4 x 2 minutes of exercise). Therefore, isometric training is likely to be recalled more accurately. Other types of day-to-day exercises can span a variety of activities, from structured and planned exercise sessions to

unplanned chores (walking to shops, housework). Exercise can take place numerous times throughout the day at a range of differing intensities and therefore accurate recall of exercise type, duration, distance and intensity can be more challenging than that for isometric training. Indeed, self-reporting of the isometric training sessions in the work of this thesis required a simple “yes” or “no”.

In addition, recall bias and desire to avoid criticism may lead to over exaggeration (De Geest and Sabaté 2003) of exercise completion. To assist with this, participants were not required to add any personal information to the diary and were informed that the real life compliance with isometric exercise was of great importance. For these reasons, it is therefore likely that this will have enabled accurate self-report measurement.

In contrast to the self-reported completion of the exercise sessions in the isometric training programmes (compliance), the maintenance of appropriate intensity during self-regulated isometric training could not be verified in the same way. In phase 1 of the exercise intervention (Chapter 6) an attempt was made to verify whether individuals maintained an appropriate relative exercise intensity whilst self-regulating at CR-10 “Level-6”. The findings showed that, despite some small overall increases in absolute strength (Table 6.6), the use of the CR-10 scale to regulate intensity ensured that participants adjusted their relative exercise intensity appropriately (Table 6.6). This enabled them to meet the perceived exercise intensity. However, this was only verified every 2 weeks, for 10 weeks (phase 1). Due to the unsupervised, “hands-off” approach in phase 2 (Chapter 6), strength changes and thus verification of the relative exercise intensity whilst using the scale over a longer period of time, was not possible.

Research involving longer-term training that is self-paced or regulated by perceived exertion, is scarce. It appears that, objective verification of training intensity during self-regulated interventions have not been carried out previously. However, it would seem that outcome measures such as improvements in physical fitness are used to monitor the appropriateness of ‘exercise effectiveness’. For example, studies have shown that exercise interventions regulated by perceived exertion (Fujiwara, Asakuma, and Iwasaki 2000; Kobayashi, Hosoi, Takeuchi, et al. 2001) or self-selected walking pace (Arthur, Smith, Kodis, et al. 2002) have been successful in increasing aerobic (Fujiwara, Asakuma, and Iwasaki 2000; Kobayashi, Hosoi, Takeuchi, et al. 2001; Arthur, Smith, Kodis, et al. 2002) and anaerobic (Fujiwara, Asakuma, and Iwasaki 2000) capacity following 6 (Arthur, Smith, Kodis, et al. 2002; Kobayashi, Hosoi, Takeuchi, et al. 2001) and 12 months (Fujiwara, Asakuma, and Iwasaki 2000) of aerobic training. In addition, Creasy and colleagues (2017) showed that home-based, self-regulated exercise using the Borg 6-20 perceived exertion chart had the same physiological benefits (aerobic capacity) to a centre-based, heart-rate-controlled training intervention (Creasy, Rogers, Davis, et al. 2017), and Tang et al., (2017) showed that RPE-guided, home-based exercise elicited the same cardiovascular response as a centre-based, heart rate controlled, training programme. Unfortunately, both of these studies (Creasy, Rogers, Davis, et al. 2017; Tang, Zwisler, Berg, et al. 2017) took place over 12 weeks, and therefore they do not add to the debate about self-regulated training intensity and

the longer-term appropriateness of regulating exercise with a perceived exertion chart (Fujiwara, Asakuma, and Iwasaki 2000; Kobayashi, Hosoi, Takeuchi, et al. 2001; Arthur, Smith, Kodis, et al. 2002). Further studies on longer term compliance to a prescribed exercise intensity whilst self-regulating exercise, using a perceived exertion chart, is required.

Physiological explanations for the loss of training-induced blood pressure reductions, with longer-term isometric training

Although poor exercise compliance is a plausible and accepted reason for the reduced effectiveness of longer-term training programmes on resting BP, this theory may not fully explain the important findings of previous meta-analyses relating to other types of exercise (Lee, Watson, Mulvaney, et al. 2010; Cornelissen and Smart 2013; Cornelissen and Fagard 2005) and that of the current study which indicate an attenuated effect of training on resting BP with longer-term (≥24 weeks) training (Table 6.7).

For example, despite some studies (Church, Earnest, Skinner, et al. 2007; Dobrosielski, Gibbs, Ouyang, et al. 2012) reporting high exercise compliance (~95%), neither study found decreases in resting BP following 6 months of aerobic training. In addition, longer-term training studies aimed at lowering BP, commonly include strictly-supervised training sessions, whereby adherence and drop-outs are closely monitored. Drop-out rates are sometimes accounted for, by using an 'intention to treat' analysis (Liu-Ambrose, Best, Davis, et al. 2016) but other studies have simply excluded those who only comply partially from the final analysis (Swift, Johannsen, Tudor-locke, et al. 2012). The influence of compliance on final outcomes could therefore be questionable.

Curiously, longer-term studies reporting no change in BP, almost invariably show increases in aerobic exercise capacity (Church, Earnest, Skinner, et al. 2007; Dobrosielski, Gibbs, Ouyang, et al. 2012; Cononie, Graves, Pollock, et al. 1991; Santa-Clara, Szymanski, and Fernhall 2003; Georgiades, Sherwood, Gullette, et al. 2000; Babbitt, Perkins, Diaz, et al. 2017). This indicates an appropriate exercise prescription and maintenance of 'exercise quality' throughout the training intervention. In addition, short-term aerobic training studies, aimed at reducing BP, have prescribed similar exercise programmes and have found significantly reduced BP (Cornelissen and Smart 2013). It is therefore important to scrutinise long-term training programmes and understand why BP benefits are smaller or non-existent following long-term training programmes.

As already discussed the self-regulation of isometric training, using the CR-10 method, aims to ensure that individuals continually adapt their relative exercise intensity as absolute strength changes. However, section 7.2 of this discussion has highlighted that a plateau in training adaptations (e.g. strength gains) could have a bearing on the magnitude of BP reductions. Alongside the relative intensity (self-regulated), training volume (4 x 2minutes), inter-rep rest (4 minutes) and body part (non-dominant hand) all remained constant throughout the training. Taking the potential negative impact of training plateaus into consideration, the

downfall of this training programme is that it lacks potential for progressive overload through variation of training volume – these are known training components believed to be essential for optimising a training stimulus (Kraemer and Ratamess 2004). It is very likely that by the end of training block 2 (Chapter 6, phase 2) a sufficient training stimulus had ceased in all individuals, causing resting BP to revert back towards baseline (rather like 'detraining'). The need to alter components of a longer-term training programme designed to reduce BP or maintain BP reductions, does not seem to have been discussed to date.

In support of the progressive overload theory, longer-term aerobic training studies (≥24 weeks) that have shown reductions in resting BP have often used a progressive overload training programme whereby training volume (e.g. number of repetitions and/or training intensity) are increased over the course of the training regime; (Cononie, Graves, Pollock, et al. 1991; Cox, Burke, Morton, et al. 2001; Ketelhut, Franz, and Scholze 2004; Liu-Ambrose, Best, Davis, et al. 2016; Braith, Pollock, Lowenthal, et al. 1994). Indeed, longer-term training studies that maintain a constant training intensity and training session duration do not always demonstrate resting BP reductions (Church, Earnest, Skinner, et al. 2007; Dobrosielski, Gibbs, Ouyang, et al. 2012; Swift, Johannsen, Tudor-locke, et al. 2012; Georgiades, Sherwood, Gullette, et al. 2000). Although this type of exercise prescription is suitable for the maintenance of exercise performance adaptations (i.e. VO_2 peak), it seems that a plateau (whereby no further adaptations will occur) will inevitably be reached (Kraemer, Ratamess, and French 2002). With regards to resting BP, the influence of this training plateau occurring early in a 10-week training programme (Section 7.2) or later in a 24-week training programme, could inevitably reduce the training-induced reductions in resting BP after isometric training. It could be suggested that, due to training adaptations, the metabolic stress/anaerobiosis required for a sufficient stimulus of the metaboreflex is no longer being reached.

As discussed in section 7.2, recent evidence suggests that the production of blood lactate is an important training component that is linked with reductions in resting BP. Considering the evidence that isometric training improves muscle oxidative capacity and reduces metaboreflex activity (Mostoufi-Moab, Widmaier, Cornett, et al. 1998) it would be pertinent to determine whether the principle of overload is a mandatory part of long-term isometric exercise prescription that is aimed at reducing resting BP.

Overload can be introduced by changes in training intensity and volume. In resistance training, manipulating rest intervals, and number of repetitions has been shown to overload the muscle, placing greater stress on the glycolytic system (Abdessemed, Duche, Hautier, et al. 1999; Rogatzki, Wright, Mikat, et al. 2014). Thereby resulting in increased reliance on anaerobic energy pathways and therefore lactate production. In specific reference to isometric training, increasing the number of repetitions, reducing rest between repetitions, or altering body part being exercised, are potential methods of manipulating the overload in relation to isometric training.

7.5 Finding(1): A 10-week, part-supervised, self-regulated isometric handgrip training programme did not induce changes in ambulatory BP (systolic, diastolic, mean arterial pressure).

Finding(2): A 10-week self-regulated isometric training programme introduced clinically significant reductions in resting SBP that were similar in magnitude to those previously reported. These changes were not statistically significant.

Question: How might the effects of self-regulated isometric exercise differ between resting and 24-hour ambulatory blood pressure?

Findings from Chapter 4 (Table 4.5) showed that 24-hr ABPM is more reproducible as compared with previously reported variability in resting BP measurements – the increased sensitivity associated with 24-hr BP monitoring should therefore make the detection of post-intervention changes easier. In addition to its superior reproducibility (Chapter 4), ABPM is applicable to real-life activities, removes the potential of a placebo effect, observer bias and white coat hypertension (De La Sierra, Segura, Banegas, et al. 2011; Felício, Pacheco, Ferreira, et al. 2007; Mancia, Omboni, Parati, et al. 1995). For these reasons, ABPM is widely recommended for the diagnosis of hypertension and the assessment of anti-hypertensive treatments (NICE 2011)

Despite the disadvantages of resting BP measurements, the ability to control the environment, position of the patient and pre-measurement resting conditions, it remains a popular method when assessing post-intervention changes in BP. The majority of isometric training studies have carried out well-designed randomised control trials (RCTs) or crossover trials and have almost consistently revealed larger BP changes in the training group compared with a control group (Ray and Carrasco 2000; Howden, Lightfoot, Brown, et al. 2002; Wiley, Dunn, Cox, et al. 1992; Millar, Bray, MacDonald, et al. 2008; Wiles, Coleman, and Swaine 2010; Devereux, Wiles, and Swaine 2011; Badrov, Horton, Millar, et al. 2013; Devereux and Wiles 2015; Gill, Arthur, Swaine, et al. 2015; Taylor, McCartney, Kamath, et al. 2003; McGowan, Levy, Millar, et al. 2006; Baross, Wiles, and Swaine 2013). The work of the current thesis employed a RCT design and although changes in resting BP (SBP, DBP, MAP) were not statistically significant (Table 6.2) larger decreases were observed in the experimental group. In contrast to resting BP measurements, 24hr-average, daytime and night-time BP did not show any significant changes.

As introduced in Chapter 2 (section 2.2.3) the literature exploring changes in ambulatory BP, following isometric training interventions, is scarce. Despite positive reductions in ambulatory BP found in healthy

normotensive participants following isometric training (Somani, Baross, Levy, et al. 2017), the current findings add to the body of literature reporting a lack of change in ambulatory BP in those with pre-hypertension and hypertension (medicated and un-medicated) (Pagonas, Vlatsas, Bauer, et al. 2017; Stiller-Moldovan, Kenno, and McGowan 2012; Ash, Taylor, Thompson, et al. 2016). Unfortunately, the concomitant measurement of resting and ambulatory BP following isometric exercise is not commonly employed. It appears that only one study measured both resting and ambulatory BP (Stiller-Moldovan, Kenno, and McGowan 2012) and reported no significant reductions in either measurement.

However, the disparate findings between resting and ambulatory BP following other training regimes are not in isolation. Meta-analyses show that the effect of aerobic exercise training on ambulatory BP is consistently smaller than resting measurements (Sosner, Guiraud, Gremeaux, et al. 2017; Cornelissen, Buys, and Smart 2013; Cardoso, Gomides, Queiroz, et al. 2010). In addition, aerobic training studies carried out on pre-hypertensive and hypertensive individuals have found similarly conflicting outcomes (Seals and Reiing 1991; Seals, Tanaka, Clevenger, et al. 2001; Bursztyn, Ben-Ishay, Shochina, et al. 1993) to that of the work of this thesis, where reductions in resting BP were observed, without ambulatory BP changes.

When taken together, findings from previous research and that of the work of this thesis, suggest that 24-hour ambulatory BP recordings can provide quite different information on training intervention effects. It would seem that resting measurements may not reflect training-induced changes in arterial pressure during ambulatory conditions. Despite this, there remains a link between lowering resting BP and reduced CV risk (Ettehad, Emdin, Kiran, et al. 2016). Therefore, it is unclear whether discrepancies in training-induced BP reductions seen during resting and ambulatory conditions, affect the clinical importance of the findings.

Considering the discrepancies between findings on resting and ambulatory BP, a discussion between the inherent differences in these measurements is required. In contrast to resting BP, ambulatory BP measurements capture an individual's BP during daily life activities. This ambulatory state includes a range of physical and mental stressors and therefore reflects an individual's hypertensive responses to stimuli and their ability to control BP during ambulatory conditions (Schultz and Sharman 2013). Research suggests that pre-hypertensive and hypertensive individuals and those with a family history of hypertension have exaggerated sympathetic and pressor responses to physical (Greaney, Matthews, Boggs, et al. 2014; Delaney, Greaney, Edwards, et al. 2010; Vongpatanasin, Wang, Arbique, et al. 2011; Schultz and Sharman 2013) and mental stressors (Armario, Del Rey, Martin-Baranera, et al. 2003; Fredrikson and Matthews 1990) with a number of studies showing direct relationships between an individual's hypertensive responses to exercise/lab-based tasks and ambulatory BP monitoring in real life conditions (Leite, Melo, Mello, et al. 2010; Lima, Spritzer, Herkenhoff, et al. 1995; Miyai, Arita, Morioka, et al. 2005; McKinney, Miner, Rüddel, et al. 1985). For example, despite no differences in resting BP measurements, Leite and colleagues (2010) showed that those with an increased SBP response to an exercise treadmill test had significantly greater average,

daytime and night-time systolic BP values. With this in mind, the ability of exercise interventions to lower resting BP and not ambulatory BP, may be associated with a limited effect on the mechanisms responsible for exaggerated pressor responses/systolic BP reactivity during tasks of daily living. This is commonly observed in pre-hypertensive and hypertensive adults (Greaney, Matthews, Boggs, et al. 2014; Delaney, Greaney, Edwards, et al. 2010; Vongpatanasin, Wang, Arbique, et al. 2011; Schultz and Sharman 2013). The mechanisms responsible for these exaggerated hypertensive responses are not yet fully understood. However, researchers have proposed an impairment of endothelial dependent vasodilation, arterial stiffness and neuro-humoral factors (e.g. increased levels of Angiotensin II) as possible contributors (Kim and Ha 2016). The impact of arterial stiffness is particularly relevant to older populations where it is more commonly observed (Pinto 2007; Tanaka, Dinenno, Monahan, et al. 2000). Arterial stiffness would reduce the buffering capacity of the vascular system, to changes in BP and therefore individuals will experience heightened BP reactivity to physical and mental stressors during ambulatory conditions. The potential impact of isometric training on arterial stiffness is discussed more thoroughly in section 7.5.

Findings from Chapter 6 showed that SBP reactivity to repetition 1 of the isometric exercise session was unaffected following 10 weeks of training (Table 6.6). It could be hypothesised that this finding is related to the lack of change in ambulatory BP recordings. In contrast to this finding, Badrov et al., (2013) found a reduction in SBP reactivity in a similar population group following a comparable handgrip isometric training intervention. However, 24-hr ABP was not measured and therefore the link between changes in 'SBP reactivity' and ambulatory BP cannot be determined.

7.6 <u>Finding:</u> A 10 week self-regulated isometric handgrip training programme induced small, non-significant improvements in markers of cardio-vagal tone as measured by 24-hour HRV. In addition, small, non-significant reductions were observed in the LF component of systolic BPV, which is indicative of a reduction in sympathetic vasomotor tone.

<u>Question:</u> Does the current thesis offer further insight into the physiological mechanisms responsible for resting blood pressure reductions following isometric training?

The mechanisms responsible for resting BP reductions following a period of isometric exercise training continue to remain elusive. Proposed mechanisms include vascular and neural adaptations (Millar, McGowan, Cornelissen, et al. 2014). In relation to vascular adaptations, findings have shown reductions in markers of oxidative stress (Peters, Alessio, Hagerman, et al. 2006) and increased endothelial dependent vasodilation (McGowan, Visocchi, Faulkner, et al. 2007; McGowan, Levy, Millar, et al. 2006; Badrov, Freeman,

Zokvic, et al. 2016). Considering the impact of autonomic dysfunction on the development of hypertension (see Chapter 2, section 2.i), the potential effects of isometric exercise on autonomic function is a common line of enquiry. To date, findings are mixed (Wiles, Coleman, and Swaine 2010; Ray and Carrasco 2000; Stiller-Moldovan, Kenno, and McGowan 2012; Millar, Levy, Mcgowan, et al. 2013; Badrov, Bartol, Dibartolomeo, et al. 2013).

The work of this thesis used indirect measurements of autonomic function (HRV, systolic BPV) as a means of providing mechanistic insight into the effects of isometric training on BP. Chapter 6 demonstrated that 24-hour HRV was not significantly altered following 10-weeks of this type of training. However, there was a trend towards an increase in 'vagal HRV parameters' (pNN50%, rMSSD, HFnu) and an improvement in the ratio between LF and HF (LF:HF) in the experimental group (Chapter 6, phase 1). A common interpretation of the LF:HF ratio is an improvement in sympatho-vagal balance (Malliani, Pagani, Lombardi, et al. 1991; Pagani, Lombardi, Guzzetti, et al. 1986) although there is recent controversy with regards to its true physiological meaning (Shaffer et al. 2014; Heathers, 2014). In relation to systolic BPV changes were not significantly different following 10-weeks of isometric handgrip training but showed a trend towards a decrease in LF% in the experimental group, indicating reduced levels of sympathetic vasomotor activity (Cevese, Grasso, Poltronieri, et al. 1995; Montano, Lombardi, Gnecchi Ruscone, et al. 1992; Stafford, Harris, and Weissler 1970). In the work of this thesis, similar trends in both systolic BPV and HRV were observed in the shorter-term training group (Table 6.10) following 7-weeks of isometric training.

Considering the day-to-day variability in these indirect measurements, the sample size within the work of the present thesis (Chapter 6) did not provide sufficient power to enable the detection of statistically significant differences (Chapter 4, Table 4.6). However, similar to the findings of Chapter 6, Taylor and colleagues (2003) reported changes in HRV. Their findings revealed a trend towards a reduced LF:HF and a significant increase in the HF spectral band. These findings suggested an increase in cardio-vagal tone (Taylor, McCartney, Kamath, et al. 2003). However, considering the large random variation associated with the HF frequency band (Chapter 4, Table 4.5) it is unfortunate that the less variable time domain measures (Chapter 4; Table 4.5) were not reported; this would have provided further support for their findings (Taylor, McCartney, Kamath, et al. 2003). In addition, Millar et al., (2013) found increases in non-linear heart rate complexity, a measure known for its ability to detect subtle changes in vagal modulation (Millar, Cotie, Amand, et al. 2010). No changes were observed in the traditional HRV measurements (Millar, Levy, Mcgowan, et al. 2013). Participants in both studies (Taylor, McCartney, Kamath, et al. 2003; Millar, Levy, Mcgowan, et al. 2013) included hypertensive males and females aged 60-80 years and are therefore comparable to the population of pre-hypertensive and hypertensive males and females aged between 55-77 years used in the work of this thesis. In contrast, other findings have revealed no significant or trending changes in HRV in young healthy males (Wiles, Coleman, and Swaine 2010), young healthy women (Badrov, Bartol, Dibartolomeo, et al. 2013) and well-controlled hypertensives (Stiller-Moldovan, Kenno, and McGowan 2012) following isometric

training. Overall, the findings from the current thesis and previous research indicate that isometric training could make a small contribution to a change in cardio-vagal tone in older participants. However, whilst small changes may be observed in HRV, the limited data available does not provide strong evidence in support of modified HRV as the primary mechanism responsible for resting BP reductions.

The inconclusive findings within the isometric training literature is compared to aerobic training where there is growing support for its positive influence on both resting (Melanson and Freedson 2001; Collier, Kanaley, Carhart, et al. 2009; Cozza, Di Sacco, Mazon, et al. 2012) and 24hr HRV (Pigozzi, Alabiso, Parisi, et al. 2001; Tulppo, Hautala, Mäkikallio, et al. 2003; Hallman, Holtermann, Søgaard, et al. 2017; Kiviniemi, Tulppo, Eskelinen, et al. 2014; Kiviniemi, Hautala, Makikallio, et al. 2006; Madden, Levy, and Stratton 2006) in healthy (Tulppo, Hautala, Mäkikallio, et al. 2003; Pigozzi, Alabiso, Parisi, et al. 2001; Melanson and Freedson 2001; Hallman, Holtermann, Søgaard, et al. 2017; Kiviniemi, Tulppo, Eskelinen, et al. 2014; Kiviniemi, Hautala, Makikallio, et al. 2006) and hypertensive participants (Cozza, Di Sacco, Mazon, et al. 2012; Collier, Kanaley, Carhart, et al. 2009). Similar to the findings in isometric training, studies provide little evidence in support of changes in HRV following dynamic resistance training (Karavirta, Costa, Goldberger, et al. 2013; Cooke and Carter 2005; Madden, Levy, and Stratton 2006; Kingsley and Figueroa 2016). However, the majority of studies have recruited healthy individuals (Cooke and Carter 2005; Karavirta, Costa, Goldberger, et al. 2013; Madden, Levy, and Stratton 2006) and more research involving hypertensive individuals is required. Some studies have directly compared HRV following aerobic and dynamic resistance training and found that aerobic training had a positive effect on HRV, whilst dynamic resistance did not (Collier, Kanaley, Carhart, et al. 2009; Karavirta, Costa, Goldberger, et al. 2013; Madden, Levy, and Stratton 2006). Interestingly, these disparate findings between exercise modalities are consistent with those for training-induced bradycardia – a common adaptation associated with aerobic training (Rivera-Brown and Frontera 2012) and not dynamic resistance (Fleck 1988; Schmidt, Hansen, Andersen, et al. 2014; Morra, Zaniqueli, Rodrigues, et al. 2014; Rossow, Fahs, Thiebaud, et al. 2014) or isometric training (Wiles, Coleman, and Swaine 2010; Badrov, Horton, Millar, et al. 2013; Badrov, Bartol, Dibartolomeo, et al. 2013; Taylor, McCartney, Kamath, et al. 2003). The findings of the current thesis are in agreement with these findings (Chapter 6, Table 6.2).

The different mechanical stimuli offered by aerobic and resistance training (isometric, dynamic resistance) could provide some insight into the disparate mechanistic findings between aerobic and resistance (dynamic and isometric) training. For example, it has been suggested that aerobic exercise offers a continuous pulsatile stretching of collagen fibres within the vasculature, whereas resistance training induces abrupt and sustained pressor effects (Madden, Levy, and Stratton 2006) resulting from mechanical compression of the intramuscular vasculature (Fisher, Young, and Fadel 2015; Lind and McNicol 1967b; Goodwin, McCloskey, and Mitchell 1972). It could be hypothesised that the stress placed on the heart during aerobic training provides a unique mechanical stimulus that is not as prominent during resistance training.

For example, in addition to improved HRV, aerobic training is also associated with improved baroreflex sensitivity (BRS; (Iwasaki, Zhang, Zuckerman, et al. 2003; Iellamo, Legramante, Massaro, et al. 2000; Collier, Kanaley, Carhart, et al. 2009) and arterial compliance (Tanaka, Dinenno, Monahan, et al. 2000; Pierce, Harris, Seals, et al. 2016; Vaitkevicius, Fleg, Engel, et al. 1993; Heffernan, Collier, Kelly, et al. 2007). Considering the relationship between BRS and arterial stiffness (Mattace-Raso, van den Meiracker, Bos, et al. 2007; Okada, Galbreath, Shibata, et al. 2012; Pierce, Harris, Seals, et al. 2016) it could be hypothesised that the unique mechanical stimulus induced during aerobic training is responsible for the commonly observed increases in arterial compliance (Tanaka, Dinenno, Monahan, et al. 2000; Pierce, Harris, Seals, et al. 2016; Vaitkevicius, Fleg, Engel, et al. 1993) and therefore improved BRS (Mattace-Raso, van den Meiracker, Bos, et al. 2007; Okada, Galbreath, Shibata, et al. 2012; Pierce, Harris, Seals, et al. 2016). In turn, improved BRS would subsequently lead to improved HRV through better signalling by the baroreceptors (Carthy 2014). These physiological changes, commonly associated with aerobic training, are in contrast to dynamic resistance and isometric training where changes in arterial stiffness (Rossow, Fahs, Thiebaud, et al. 2014; Cortez-Cooper, DeVan, Anton, et al. 2005; Heffernan, Collier, Kelly, et al. 2007; Pagonas, Vlatsas, Bauer, et al. 2017) BRS (Cooke and Carter 2005; Collier, Kanaley, Carhart, et al. 2009) and HRV (Collier, Kanaley, Carhart, et al. 2009; Karavirta, Costa, Goldberger, et al. 2013; Madden, Levy, and Stratton 2006; Wiles, Coleman, and Swaine 2010; Stiller-Moldovan, Kenno, and McGowan 2012; Badrov, Bartol, Dibartolomeo, et al. 2013) are not as readily observed.

However, it is important to note that, increases in both HRV and BRS have been recorded following an acute bout of isometric exercise (Taylor, Wiles, Coleman, et al. 2017). In addition, Devereux and colleagues showed that BRS following an acute bout of isometric exercise improved following training (Devereux and Wiles 2015). These changes, however, have only been observed in the acute post exercise phase; and do not lend support for training-related adaptations. Instead, these observations could be simply related to 'reactive hyperaemia', a phenomenon associated with an acute bout of isometric exercise. Reactive hyperaemia is associated with a surge in NO bioavailability which has a positive association with vagal tone (Chowdhary and Townend 1999, 2001). Researchers have hypothesised that the acute changes in autonomic activity following acute isometric exercise provides insight into the mechanisms responsible for chronic BP adaptations (Taylor, Wiles, Coleman, et al. 2017). However, these acute changes are not observed following aerobic training (Chapter 2, section 2.7.1) where evidence undoubtedly suggests that BRS and HRV improve following training – therefore the relationship between acute autonomic effects and chronic autonomic effects of training should therefore remain as speculative.

Alongside the current thesis, one previously-published study has measured systolic BPV following a period of isometric training (Taylor, McCartney, Kamath, et al. 2003). Findings from the work of the current thesis and that of Taylor and colleagues suggest a decrease in the LF component of systolic BPV and therefore a decrease in vasomotor sympathetic activity (Cevese, Grasso, Poltronieri, et al. 1995; Montano, Lombardi, Gnecchi

Ruscone, et al. 1992; Stafford, Harris, and Weissler 1970). In addition, whilst changes in HRV were not observed following dynamic resistance training improvements in the LF component of BPV was observed in hypertensives following 4 weeks training (Collier, Kanaley, Carhart, et al. 2009). In contrast to these findings others have found no change in LF systolic BPV following 8 (Cooke and Carter 2005) and 12 (Alex, Lindgren, Shapiro, et al. 2013a) weeks of resistance training. However, participants were normotensive and it could be suggested that peripheral sympathetic nerve activity is less likely to undergo changes in healthy vessels.

As discussed in detail in Chapter 2, endothelial dysfunction and autonomic nervous system imbalance are inter-related. For example, a dysfunctional endothelium undergoes a reduction in the bioavailability of NO which exposes it to the pro-inflammatory and vasoconstrictor effects of ROS, angiotensin II and endothelin 1 (Chapter 2, section 2.iii). Considering the positive influence of isometric training on endothelium dependent vasodilation (McGowan, Visocchi, Faulkner, et al. 2007; McGowan, Levy, Millar, et al. 2006; Badrov, Freeman, Zokvic, et al. 2016), it could be hypothesised that, if isometric training decreases vasomotor sympathetic tone, it could do this via improvements in endothelial function. Improvements in endothelial function following handgrip (IHG) training has been suggested to be related to an increase in nitric oxide bioavailability and/or improved oxidative stress (Green, Maiorana, O'Driscoll, et al. 2004). Oxidative stress has previously been shown to improve following IHG training (Peters, Alessio, Hagerman, et al. 2006). This theory, connecting improvements in endothelium function and vasomotor sympathetic activity, remains speculative and further analysis using more sensitive measures of vasomotor sympathetic tone is required.

This system of isometric exercise training provides the clinical and elderly populations with an opportunity to engage with isometric exercise as an additional option for BP management. Although aerobic exercise is still the most widely recommended exercise modality for BP management (Ghadieh and Saab 2015; Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013; Brook, Appel, Rubenfire, et al. 2013; James, Oparil, Carter, et al. 2014) research suggests that compliance is poor (Ghadieh and Saab 2015; Pescatello, Franklin, Fagard, et al. 2004a; Mancia, Fagard, Narkiewicz, et al. 2013; Brook, Appel, Rubenfire, et al. 2013; James, Oparil, Carter, et al. 2014). In specific reference to the elderly patient, there are a number of barriers that prevent the uptake and long-term engagement with aerobic exercise. For example, lack of mobility, chronic conditions and fear of injury are cited as common barriers to aerobic exercise participation in this population group (Jefferis, Sartini, Lee, et al. 2014; Franco, Tong, Howard, et al. 2015). Considering that the prevalence of hypertension increases with age (Knott and Mindell 2011; Piepoli, Hoes, Agewall, et al. 2016; Franklin, Gustin, Wong, et al. 1997; Chobanian, Bakris, Black, et al. 2003), the opportunity to participate in an alternative exercise option that is easy to self-regulate, cost-effective and chair based should be welcomed by these individuals.

With reference to clinical populations, individuals recovering from cardiovascular events (e.g. myocardial infarction and stroke) are advised to engage in long-term exercise participation (Rand, Eng, Tang, et al. 2009;

Dalal, Doherty, and Taylor 2015). However, it has been shown that large numbers of individuals recovering from cardiovascular events continue to lead sedentary lives (Rand, Eng, Tang, et al. 2009; Dalal, Doherty, and Taylor 2015). The primary barriers associated with exercise participation following stroke are physical impairments, lack of motivation and environmental factors (Damush, Plue, Bakas, et al. 2007). For patients required to engage in a cardiac rehabilitation programmes, geographical location, access to transport and a dislike of group-based exercise sessions are cited as common barriers to participation (Dalal, Doherty, and Taylor 2015). Although engaging in aerobic exercise has a number of social and physical benefits for these clinical populations, the option to engage in a self-regulated isometric exercise training programme should at least provide these individuals with an opportunity to participate in an effective exercise intervention for BP management and therefore aid in the prevention of future cardiovascular events.

As compared with aerobic exercise, it has been previously proposed that the simplicity, time-effectiveness and home-based possibility of isometric exercise would result in superior exercise sustainability (Inder, Carlson, Dieberg, et al. 2016; Carlson, Dieberg, Hess, et al. 2014; McGowan, Proctor, Swaine, et al. 2017). However, research also suggests that compliance to other seemingly simple approaches to BP management (e.g. medications, dietary changes) are also associated with poor adherence (Riegel, Moreira, Fuchs, et al. 2012; Rajpura and Nayak 2014; Brook, Jackson, Giorgini, et al. 2015). It was therefore important for this study to measure levels of isometric exercise adherence. The validation of the CR-10 scale provided the opportunity to prescribe a home-based, unsupervised isometric exercise programme and assess participant's levels of exercise adherence over 24 weeks. Compliance to this self-regulated, home-based isometric exercise was excellent (Figure 6.6) and therefore highlights that the development of the CR-10 "Level-6" isometric exercise system provides individuals with an effective, easy to complete exercise with the potential for long-term exercise adherence.

7.7 Thesis limitations and future directions

Considering the prevalence of hypertension, levels of mortality and costs to the economy (Chapter 1) the prescription of CR-10 "Level-6" must be easily applied to large portions of the population. In order to introduce the participants to the use of the CR-10 scale, the current thesis used a familiarisation protocol (see section 6.2.3). Future studies are required to determine whether a brief and self-instructed 'anchoring procedure' would be sufficient to familiarise participants with the CR-10 scale. This would obviate the necessity for an exercise professional to train participants in relation to the use of the scale and provide the general practitioner with a simple prescription procedure (e.g. instruction pamphlet). This would further enhance the simplicity and accessibility of the self-regulated isometric exercise method.

The current thesis provided each participant with a basic ergonomic handgrip exerciser (Figure 3.10) (Rolyan, Patterson Medical, Nottinghamshire, UK) for the performance of self-regulated isometric handgrip training.

Despite the low cost of these handgrip exercisers, it is important to further enhance the accessibility of self-regulated isometric exercise; future studies are required to test the effectiveness of isometric exercises that might be performed on immovable items commonly found within the home, in addition to isometric exercises that may not even require equipment (e.g. hand clasp).

Appropriate management of BP requires life-long lifestyle changes. Considering that the results of this thesis indicated a loss of resting BP effects (Table 6.7) during longer-term exercise training (24 weeks), further research is required to clarify the long-term applicability of self-regulated isometric handgrip exercise on BP management. A long-term RCT study should be carried out to clarify whether a loss of training-induced BP changes does indeed occur. As suggested in section 7.4, isometric exercise carried out beyond the traditional 8-10 week exercise programme may need progressive exercise training where overload is consistently applied through changes in rest duration, number of repetitions or intensity of contraction. The effect of adding an overload component should be compared with a traditional training protocol (which doesn't usually have this type of progressive overload).

The work of this thesis highlighted inter-individual differences in resting BP reductions following 10-weeks of self-regulated isometric exercise training (Figure 7.1). Section 7.3, discusses some key individual differences in isometric training adaptations (e.g. strength changes and pressor response during repetition 4) and how they could be related to changes in resting SBP. In order to understand individual differences in BP response, the study of individual training adaptations and their effect on BP changes is an important area of further study.

Although the work of this thesis indicated a trend towards changes in autonomic nervous system regulation of BP following isometric exercise training, the inherent variability within these measurements alongside the small sample size means that the findings have not provided conclusive evidence in relation to the role of changes in autonomic function when BP is reduced after training. Further, indirect measures of autonomic function, such as those used in the current thesis (HRV and systolic BPV) may not be sensitive enough to detect small changes. Although 24-hour ambulatory BP measurements were found to be more reproducible than 5-minute resting measurements (Chapter 4), further research on more-reliable indices of autonomic function are needed, to clarify the effects of isometric handgrip training on these variables.

Finally, little is still known about the influence of isometric training on 24-hour ambulatory BP measurements. Findings from the current thesis suggest that ambulatory BP does not change in a group of pre-hypertensive and hypertensive adults following isometric handgrip training (Chapter 6). However, other limited research suggests that normotensive adults experience ambulatory BP reductions following isometric training (Somani, Baross, Levy, et al. 2017). Further research is therefore required to directly compare the 24-hour

ambulatory BP effects of isometric training on normotensives, pre-hypertensives, medicated hypertensives and non-medicated hypertensives. As discussed in section 7.5, pre-hypertensive and hypertensive adults display exaggerated pressor responses during physical and mental tasks associated with daily living (Greaney, Matthews, Boggs, et al. 2014; Delaney, Greaney, Edwards, et al. 2010; Vongpatanasin, Wang, Arbique, et al. 2011; Schultz and Sharman 2013; Fredrikson and Matthews 1990; Armario, Del Rey, Martin-Baranera, et al. 2003); these responses may be due to an impairment of endothelial-dependent vasodilation, arterial stiffness and/or neuro-humoral factors (e.g. increased levels of Angiotensin II) (Kim and Ha 2016). Further understanding of the influence of isometric training on ambulatory BP in individuals with differing BP status could begin to offer further insight into some of the potential mechanisms unaffected by isometric training (e.g. endothelial dependent vasodilation, arterial stiffness and neuro-humoral factors).

7.8 Conclusion

Isometric exercise is a simple, time-efficient, non-pharmacological approach to lowering BP (McGowan, Proctor, Swaine, et al. 2017). However, the current methods of isometric handgrip intensity prescription (%MVC) are not suitable and easily accessible to all members of the population. This is especially true for clinical and elderly populations where the performance of maximal isometric contractions is contraindicated or limited due to frailty or arthritis. In addition, the cost of specialised digital devices that measure force imposes a financial barrier to isometric exercise participation.

This thesis provides strong support for the use of the CR-10 scale to self-regulate isometric handgrip exercise intensity at “Level-6”, whilst also proving effective for BP management in pre-hypertensive and hypertensive participants. This new system of isometric intensity regulation eliminates the need for regular maximal contractions and provides the exerciser with the flexibility to perform isometric handgrip training on non-specialist handgrip instruments. This thesis therefore provides an important step forward in providing an alternative method for intensity regulation which will make the prescription and execution of isometric handgrip exercise training easier for both medical staff and patients.

References

Abdessemed, D., Duche, P., Hautier, C., Poumarat, G., and Bedu, M. (1999) 'Effect of Recovery Duration on Muscular Power and Blood Lactate during the Bench Press Exercise.' *International Journal of Sports Medicine* 20 (6), 368–373

Aguilera, G., Kiss, A., and Sunar-Akbasak, B. (1995) 'Hyperreninemic Hypoaldosteronism after Chronic Stress in the Rat'. *Journal of Clinical Investigation* 96 (3), 1512–1519

Akselrod, S., Gordon, D., Ubel, F., Shannon, D., Berger, A., and Cohen, R. (1981) 'Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of Beat-to-Beat Cardiovascular Control'. in *Science* [online] vol. 213 (4504). 220–222. available from <http://www.sciencemag.org/cgi/doi/10.1126/science.6166045>

Al-Kaabi, J., Al-Maskari, F., Afandi, B., Parkar, H., and Nagelkerke, N. (2009) 'Physical Activity and Reported Barriers to Activity among Type 2 Diabetic Patients in the United Arab Emirates'. *The Review of Diabetic Studies* [online] 6 (4), 271–278. available from <http://www.soc-bdr.org/content/e4/e887/volRdsVolumes7102/issRdsIssues7152/chpRdsChapters8088/strRdsArticles8107/index_en.html?preview=preview>

Alam, M. and Smirk, F. (1937) 'Observations in Man upon a Blood Pressure Raising Reflex Arising from the Voluntary Muscles'. *Journal of Physiology* 89 (4), 372–383

Alex, C., Lindgren, M., Shapiro, P. a, Mckinley, P.S., Elizabeth, N., Myers, M.M., Zhao, Y., and Sloan, R.P. (2013a) 'Aerobic Exercise and Strength Training Effects on Cardiovascular Sympathetic Function in Healthy Adults: A Randomized Control Trial'. *Psychosomatic Medicine* 75 (4), 375–381

Alex, C., Lindgren, M., Shapiro, P.A., Mckinley, P.S., Brondolo, E.N., Myers, M.M., Zhao, Y., Sloan, R.P., Elizabeth, N., Myers, M.M., Zhao, Y., and Sloan, R.P. (2013b) 'Aerobic Exercise and Strength Training Effects on Cardiovascular Sympathetic Function in Healthy Adults: A Randomized Controlled Trial.' *Psychosomatic Medicine* 75 (4), 375–381

Alkurdi, Z.D. and Dweiri, Y.M. (2010) 'A Biomechanical Assessment of Isometric Handgrip Force and Fatigue at Different Anatomical Positions'. *Journal of Applied Biomechanics* 26 (2), 123–133

Allen, N.E., Canning, C.G., Sherrington, C., Lord, S.R., Latt, M.D., Close, J.C.T., O'Rourke, S.D., Murray, S.M., and Fung, V.S.C. (2010) 'The Effects of an Exercise Program on Fall Risk Factors in People with Parkinson's Disease: A Randomized Controlled Trial.' *Movement Disorders : Official Journal of the Movement Disorder Society* 25 (9), 1217–1225

Amann, M., Sidhu, S.K., Weavil, J.C., Mangum, T.S., and Venturelli, M. (2015) 'Autonomic Responses to Exercise: Group III/IV Muscle Afferents and Fatigue'. *Autonomic Neuroscience: Basic and Clinical* [online] 188, 19–23. available from <http://dx.doi.org/10.1016/j.autneu.2014.10.018>

Amiya, E., Watanabe, M., and Komuro, I. (2014) 'The Relationship between Vascular Function and the

Autonomic Nervous System.' *Annals of Vascular Diseases* [online] 7 (2), 109–19. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4072858&tool=pmcentrez&rendertype=abstract>

Anaruma, C.P., Ferreira, M.J., Sponton, C.H.G., Delbin, M.A., and Zanesco, A. (2016) 'Heart Rate Variability and Plasma Biomarkers in Patients with Type 1 Diabetes Mellitus: Effect of a Bout of Aerobic Exercise.' *Diabetes Research and Clinical Practice* 111, 19–27

Andersson, E.A., Frank, P., Ponten, M., Ekbm, B., Ekblom, M., Moberg, M., and Sahlin, K. (2017) 'Improving Strength, Power, Muscle Aerobic Capacity, and Glucose Tolerance through Short-Term Progressive Strength Training among Elderly People.' *Journal of Visualized Experiments:JoVE* (125)

Aprile, D.C.B., Oneda, B., Gusmao, J.L., Costa, L.A.R., Forjaz, C.L.M., Mion, D.J., and Tinucci, T. (2016) 'Post-Exercise Hypotension Is Mediated by a Decrease in Sympathetic Nerve Activity in Stages 2-3 CKD.' *American Journal of Nephrology* 43 (3), 206–212

Arena, R., Myers, J., and Kaminsky, L. (2016) 'Revisiting Age-Predicted Maximal Heart Rate: Can It Be Used as a Valid Measure of Effort'. *American Heart Journal* 173, 49–56

Armario, P., Del Rey, R.H., Martin-Baranera, M., Almendros, M.C., Ceresuela, L.M., and Pardell, H. (2003) 'Blood Pressure Reactivity to Mental Stress Task as a Determinant of Sustained Hypertension after 5 Years of Follow-Up'. *Journal of Human Hypertension* 17 (3), 181–186

Arthritis Research UK (2017) *State of Musculoskeletal Health* [online] available from <file:///Users/mariellabaxter/Downloads/State-of-musculoskeletal-health-2017.PDF>

Arthur, H.M., Smith, K.M., Kodis, J., and McKelvie, R. (2002) 'A Controlled Trial of Hospital versus Home-Based Exercise in Cardiac Patients'. *Medicine and Science in Sports and Exercise* [online] 34 (10), 1544–1550. available from <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=2002360039%5Cnhttp://sfx.scholarsportal.info/uhn?sid=OVID:embase&id=pmid:&id=doi:&issn=0195-9131&isbn=&volume=34&issue=10&spage=1544&pages=1544-1550&date=2002&title=Medicine+and>

Ash, G., Walker, T., Olson, K., Stratton, J., Gómez, A., Kraemer, W., Volek, J., and Pescatello, L. (2013) 'Reproducibility of Ambulatory Blood Pressure Changes from the Initial Values on Two Different Days'. *Clinics* [online] 68 (14), 1509–1515. available from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3840371/>

Ash, G.I., Taylor, B.A., Thompson, P.D., MacDonald, H. V, Lamberti, L., Chen, M.-H., Farinatti, P., Kraemer, W.J., Panza, G.A., Zaleski, A.L., Deshpande, V., Ballard, K.D., Mujtaba, M., White, C.M., and Pescatello, L.S. (2016) 'The Antihypertensive Effects of Aerobic versus Isometric Handgrip Resistance Exercise'. *Journal of Hypertension* [online] 35 (2), 291–299. available from <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L613339509%5Cnhttp://dx.doi.org/10.1097/HJH.0000000000001176%5Cnhttp://findit.library.jhu.edu/resolve?sid=EMBASE&issn=14735598&id=doi:10.1097%2FHJH.0000000000001176&atitle=The+antihy>

Van Assche, T., Buys, R., De Jaeger, M., Coeckelberghs, E., and Cornelissen, V. (2017) 'One Single Bout of Low Intensity Isometric Handgrip Exercise Reduces Blood Pressure during Daily Activities in Healthy Pre- and Hypertensive Individuals.' *The Journal of Sports Medicine and Physical Fitness* 57 (4), 469–475

Aubert, A.E., Seps, B., and Beckers, F. (2003) 'Heart Rate Variability in Athletes'. *Sports Medicine* 33 (12), 889–919

Babbitt, D.M., Perkins, A.M., Diaz, K.M., Feairheller, D.L., Sturgeon, K.M., Veerabhadrappa, P., Williamson, S.T., Kretzschmar, J., Ling, C., Lee, H., Grim, H., and Brown, M.D. (2017) 'Adherence to Exercise Prescription and Improvements in the Clinical and Vascular Health of African Americans.' *International Journal of Exercise Science* [online] 10 (2), 246–257. available from <http://www.ncbi.nlm.nih.gov/pubmed/28344738%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5360370>

Babbs, C.F. (2012) 'Oscillometric Measurement of Systolic and Diastolic Blood Pressures Validated in a Physiologic Mathematical Model'. *BioMedical Engineering OnLine* [online] 11 (1), 56. available from <BioMedical Engineering OnLine>

Bader, M. (2010) 'Tissue Renin-Angiotensin-Aldosterone Systems: Targets for Pharmacological Therapy.' *Annual Review of Pharmacology and Toxicology* 50, 439–465

Badrov, M.B., Bartol, C.L., Dibartolomeo, M.A., Millar, P.J., McNevin, N.H., and McGowan, C.L. (2013) 'Effects of Isometric Handgrip Training Dose on Resting Blood Pressure and Resistance Vessel Endothelial Function in Normotensive Women'. *European Journal of Applied Physiology* 113, 2091–2100

Badrov, M.B., Freeman, S.R., Zokvic, M.A., Millar, P.J., and McGowan, C.L. (2016) 'Isometric Exercise Training Lowers Resting Blood Pressure and Improves Local Brachial Artery Flow-Mediated Dilation Equally in Men and Women.' *European Journal of Applied Physiology* 116 (7), 1289–1296

Badrov, M.B., Horton, S., Millar, P.J., and Mcgowan, C.L. (2013) 'Cardiovascular Stress Reactivity Tasks Successfully Predict the Hypotensive Response of Isometric Handgrip Training in Hypertensives'. *Psychophysiology* 50, 407–414

Barna, I., Keszei, A., and Dunai, A. (1998) 'Evaluation of Meditech ABPM-04 Ambulatory Blood Pressure Measuring Device According to the British Hypertension Society Protocol.' *Blood Pressure Monitoring* 3 (6), 363–368

Baross, A.W., Wiles, J.D., and Swaine, I.L. (2013) 'Double-Leg Isometric Exercise Training in Older Men.' *Open Access Journal of Sports Medicine* [online] 4, 33–40. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3871900&tool=pmcentrez&rendertype=abstract>

Baross, A.W., Wiles, J.D., and Swaine, I.L. (2012) 'Effects of the Intensity of Leg Isometric Training on the Vasculature of Trained and Untrained Limbs and Resting Blood Pressure in Middle-Aged Men'. *International Journal of Vascular Medicine* 2012, 1–8

Barrett, C.J. (2015) ‘Renal Sympathetic Nerves - What Have They Got to Do with Cardiovascular Disease?’ *Experimental Physiology* [online] 100, 359–365. available from <http://doi.wiley.com/10.1113/expphysiol.2014.080176>

Bartels, M.N., Jelic, S., Gonzalez, J.M., Kim, W., and De Meersman, R.E. (2004) ‘Reproducibility of Heart Rate and Blood Pressure Variability in Patients with Chronic Obstructive Pulmonary Disease.’ *Clinical Autonomic Research: Official Journal of the Clinical Autonomic Research Society* 14, 194–196

Baynouna, L.M., Neglekerke, N.J.D., Ali, H.E., ZeinAlDeen, S.M., and Al Ameri, T.A. (2014) ‘Audit of Healthy Lifestyle Behaviors among Patients with Diabetes and Hypertension Attending Ambulatory Health Care Services in the United Arab Emirates’. *Global Health Promotion* [online] 21 (4), 44–51. available from <http://journals.sagepub.com/doi/10.1177/1757975914528248>

Benschop, R.J., Nieuwenhuis, E.E., Tromp, E.A., Godaert, G.L., Ballieux, R.E., and van Doornen, L.J. (1994) ‘Effects of Beta-Adrenergic Blockade on Immunologic and Cardiovascular Changes Induced by Mental Stress.’ *Circulation* 89 (2), 762–769

Bernardi, L., Wdowczyk-szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., and Sleight, P. (2000) ‘Effects of Controlled Breathing, Mental Activity and Mental Stress with or without Verbalization on Heart Rate Variability’. *Journal of the American College of Cardiology* 35 (6)

Bertsch, K., Hagemann, D., Naumann, E., Schächinger, H., and Schulz, A. (2012) ‘Stability of Heart Rate Variability Indices Reflecting Parasympathetic Activity’. *Psychophysiology* 49 (5), 672–682

Bethancourt, H.J., Rosenberg, D.E., Beatty, T., and Arterburn, D.E. (2014) ‘Barriers to and Facilitators of Physical Activity Program Use among Older Adults’. *Clinical Medicine & Research* [online] 12 (1–2), 10–20. available from <http://www.clinmedres.org/cgi/doi/10.3121/cmr.2013.1171>

Bigger, J., Fleiss, J., Rolnitzky, L., and Steinman, R. (1992) ‘Stability over Time of Heart Period Variability in Patients with Previous Myocardial Infarction and Ventricular Arrhythmias’. *American Journal of Cardiology* 69, 718–723

Billman, G.E. (2013) ‘The LF/HF Ratio Does Not Accurately Measure Cardiac Sympatho-Vagal Balance’. *Frontiers in Physiology* 4, 1–5

Billman, G.E. (2011) ‘Heart Rate Variability - a Historical Perspective’. *Frontiers in Physiology* [online] 2 (November), 1–13. available from <http://journal.frontiersin.org/article/10.3389/fphys.2011.00086/abstract>

Black, J.M., Stohr, E.J., Stone, K., Pugh, C.J.A., Stembridge, M., Shave, R., and Esformes, J.I. (2016) ‘The Effect of an Acute Bout of Resistance Exercise on Carotid Artery Strain and Strain Rate.’ *Physiological Reports* 4 (17)

di Blasio, A., Sablone, A., Civino, P., D’Angelo, E., Gallina, S., and Ripari, P. (2009) ‘Arm vs. Combined Leg and Arm Exercise: Blood Pressure Responses and Ratings of Perceived Exertion at the Same Indirectly

Determined Heart Rate'. *Journal of Sports Science and Medicine* 8, 401–409

Bloomfield, D.M., Magnano, A., Bigger, J.T., Rivadeneira, H., Parides, M., and Steinman, R.C. (2001) 'Comparison of Spontaneous vs. Metronome-Guided Breathing on Assessment of Vagal Modulation Using RR Variability.' *American Journal of Physiology. Heart and Circulatory Physiology* 280 (3), H1145–H1150

Bogert, L.W.J. and van Lieshout, J.J. (2005) 'Non-Invasive Pulsatile Arterial Pressure and Stroke Volume Changes from the Human Finger'. *Experimental Physiology* [online] 90 (4), 437–446. available from <http://doi.wiley.com/10.1113/expphysiol.2005.030262>

de Bold, A.J. (2011) 'Thirty Years of Research on Atrial Natriuretic Factor: Historical Background and Emerging Concepts.' *Canadian Journal of Physiology and Pharmacology* 89 (8), 527–531

Bollen, J.C., Dean, S.G., Siegert, R.J., Howe, T.E., and Goodwin, V.A. (2014) 'A Systematic Review of Measures of Self-Reported Adherence to Unsupervised Home-Based Rehabilitation Exercise Programmes, and Their Psychometric Properties.' *BMJ Open* 4 (6)

Borg, E. and Kaijser, L. (2006) 'A Comparison between Three Rating Scales for Perceived Exertion and Two Different Work Tests'. *Scandinavian Journal of Medicine and Science in Sports* 16, 57–69

Borg, G. (1982) 'Psychophysical Bases of Perceived Exertion.' *Medicine and Science in Sports and Exercise* 14 (5), 377–381

Borg, G. (1973) 'Perceived Exertion: A Note on "History" and Methods.' *Medicine & Science in Sports & Exercise* 5 (2), 90–93

Borg, G., Hassmén, P., and Lagerström, M. (1987) 'Perceived Exertion Related to Heart Rate and Blood Lactate during Arm and Leg Exercise'. *European Journal of Applied Physiology* 65, 679–685

Börjesson, M., Onerup, A., Lundqvist, S., and Dahlöf, B. (2016) 'Physical Activity and Exercise Lower Blood Pressure in Individuals with Hypertension: Narrative Review of 27 RCTs.' *British Journal of Sports Medicine* 50 (6), 356–61

Bos, W.J., Imholz, B.P., van Goudoever, J., Wesseling, K.H., and van Montfrans, G.A. (1992) 'The Reliability of Noninvasive Continuous Finger Blood Pressure Measurement in Patients with Both Hypertension and Vascular Disease.' *American Journal of Hypertension* 5 (8), 529–535

Bouchard, C., Tremblay, A., Leblanc, C., Lortie, G., Savard, R., and Theriault, G. (1983) 'A Method to Assess Energy Expenditure in Children and Adults.' *The American Journal of Clinical Nutrition* 37 (3), 461–467

Boulton, D., Taylor, C.E., Macefield, V.G., and Green, S. (2016) 'Contributions of Central Command and Muscle Feedback to Sympathetic Nerve Activity in Contracting Human Skeletal Muscle'. *Frontiers in Physiology* [online] 7, 1–9. available from <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00163/abstract>

Braith, R.W., Pollock, M.L., Lowenthal, D.T., Graves, J.E., and Limacher, M.C. (1994) 'Moderate- and High-Intensity Exercise Lowers Blood Pressure in Normotensive Subjects 60 to 79 Years of Age.' *The American Journal of Cardiology* 73 (15), 1124–1128

Brandao Rondon, M.U.P., Alves, M.J.N.N., Braga, A.M.F.W., Teixeira, O.T.U.N., Barretto, A.C.P., Krieger, E.M., and Negrao, C.E. (2002) 'Postexercise Blood Pressure Reduction in Elderly Hypertensive Patients'. *Journal of the American College of Cardiology* 39 (4), 676–682

De Brito, L.C., Rezende, R.A., Da Silva, N.D., Tinucci, T., Casarini, D.E., Cipolla-Neto, J., and Forjaz, C.L.M. (2015) 'Post-Exercise Hypotension and Its Mechanisms Differ after Morning and Evening Exercise: A Randomized Crossover Study'. *PLOS ONE* 10 (7), 1–16

Brook, R.D., Appel, L.J., Rubenfire, M., Ogedegbe, G., Bisognano, J.D., Elliott, W.J., Fuchs, F.D., Hughes, J.W., Lackland, D.T., Staffileno, B.A., Townsend, R.R., and Rajagopalan, S. (2013) 'Beyond Medications and Diet: Alternative Approaches to Lowering Blood Pressure.' *Hypertension* 61 (6), 1360–1383

Brook, R.D., Jackson, E.A., Giorgini, P., and McGowan, C.L. (2015) 'When and How to Recommend "alternative Approaches" in the Management of High Blood Pressure'. *The American Journal of Medicine* [online] 128 (6), 567–570. available from <http://dx.doi.org/10.1016/j.amjmed.2014.12.029>

Bursztyn, M., Ben-Ishay, D., Shochina, M., Mekler, J., and Raz, I. (1993) 'Disparate Effects of Exercise Training on Glucose Tolerance and Insulin Levels and on Ambulatory Blood Pressure in Hypertensive Patients.' *Journal of Hypertension* 11 (10), 1121–1125

Calvo, C., Hermida, R.C., Ayala, D.E., Lopez, J.E., Fernandez, J.R., Dominguez, M.J., Mojon, A., and Covelo, M. (2003) 'The "ABPM Effect" Gradually Decreases but Does Not Disappear in Successive Sessions of Ambulatory Monitoring.' *Journal of Hypertension* 21 (12), 2265–2273

Campbell, P., Ghuman, N., Wakefield, D., Wolfson, L., and White, W. (2010) 'Long-Term Reproducibility of Ambulatory Blood Pressure Is Superior to Office Blood Pressure in the Very Elderly'. *Journal of Human Hypertension* 24 (11), 749–754

Cardoso, C.G., Gomides, R.S., Queiroz, A.C.C., Pinto, L.G., da Silveira Lobo, F., Tinucci, T., Mion, D., and de Moraes Forjaz, C.L. (2010) 'Acute and Chronic Effects of Aerobic and Resistance Exercise on Ambulatory Blood Pressure.' *Clinics (Sao Paulo, Brazil)* 65 (3), 317–325

Carlson, D.J., Dieberg, G., Hess, N.C., Hons, B., Millar, P.J., and Smart, N. a (2014) 'Isometric Exercise Training for Blood Pressure'. *Mayo Clinic Proceedings* [online] 89 (3), 1–8. available from <http://dx.doi.org/10.1016/j.mayocp.2013.10.030>

Carpio-Rivera (2016) 'Acute Effects of Exercise on Blood Pressure: A Meta-Analytic Investigation'. *Arquivos Brasileiros de Cardiologia* [online] 106 (5), 422–433. available from <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2016005013101&lng=en&nrm=iso&tlng=en>

Carter, J.B., Banister, E.W., and Blaber, A.P. (2003) 'Effect of Endurance Exercise on Autonomic Control of Heart Rate.' *Sports Medicineedicine* 33 (1), 33–46

Carter, J.R., Ray, C.A., Downs, E.M., and Cooke, W.H. (2003) 'Strength Training Reduces Arterial Blood Pressure but Not Sympathetic Neural Activity in Young Normotensive Subjects'. *Journal of Applied Physiology* [online] 94 (6), 2212–2216. available from <http://www.physiology.org/doi/10.1152/japplphysiol.01109.2002>

Carthy, E.R. (2014) 'Autonomic Dysfunction in Essential Hypertension: A Systematic Review'. *Annals of Medicine and Surgery* [online] 3 (1), 2–7. available from <http://dx.doi.org/10.1016/j.amsu.2013.11.002>

Casonatto, J., Goessler, K.F., Cornelissen, V.A., Cardoso, J.R., and Polito, M.D. (2016) 'The Blood Pressure-Lowering Effect of a Single Bout of Resistance Exercise: A Systematic Review and Meta-Analysis of Randomised Controlled Trials'. *European Journal of Preventive Cardiology* 23 (16), 1700–1714

Cevese, A., Grasso, R., Poltronieri, R., and Schena, F. (1995) 'Vascular Resistance and Arterial Pressure Low-Frequency Oscillations in the Anesthetized Dog.' *The American Journal of Physiology* 268 (1 Pt 2), H7-16

Chandra, S., Saluja, D., Narang, R., Bhatia, J., and Srivastava, K. (2015) 'Atrial Natriuretic Peptide and Aldosterone Synthase Gene in Essential Hypertension: A Case-Control Study.' *Gene* 567 (1), 92–97

Charkoudian, N. and Rabbitts, J. a (2009) 'Sympathetic Neural Mechanisms in Human Cardiovascular Health and Disease.' *Mayo Clinic Proceedings* [online] 84 (9), 822–30. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2735432&tool=pmcentrez&rendertype=abstract>

Chen, M.J., Fan, X., and Moe, S.T. (2002) 'Criterion-Related Validity of the Borg Ratings of Perceived Exertion Scale in Healthy Individuals: A Meta-Analysis.' *Journal of Sports Sciences* [online] 20 (11), 873–899. available from <http://www.tandfonline.com/doi/abs/10.1080/026404102320761787>

Chobanian, A. V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L. a., Izzo, J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., and Roccella, E.J. (2003) 'Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure'. *Hypertension* 42 (6), 1206–1252

Chowdhary, S. and Townend, J.N. (2001) 'Nitric Oxide and Hypertension: Not Just an Endothelium Derived Relaxing Factor!' *Journal of Human Hypertension* 15, 219–227

Chowdhary, S. and Townend, J.N. (1999) 'Role of Nitric Oxide in the Regulation of Cardiovascular Autonomic Control.' *Clinical Science (London, England : 1979)* 97 (1), 5–17

Chrysant, S.G. (2010) 'Current Evidence on the Hemodynamic and Blood Pressure Effects of Isometric Exercise in Normotensive and Hypertensive Persons'. *Journal of Clinical Hypertension* 12 (9), 721–726

Church, T.S., Earnest, C.P., Skinner, J.S., and Blair, S.N. (2007) 'Effects of Different Doses of Physical Activity

on Cardiorespiratory Fitness among Sedentary, Overweight or Obese Postmenopausal'. *JAMA* 297 (19), 2081–2091

Cockroft, J.R., Chowienczyk, P.J., Benjamin, N., Ritter, J.M., and Phil, D. (1994) 'Preserved Endothelium-Dependent Vasodilation in Patients with Essential Hypertension'. *The New England Journal of Medicine* 330 (15), 1036–1040

Collier, S.R., Kanaley, J. a., Carhart, R., Frechette, V., Tobin, M.M., Bennett, N., Luckenbaugh, a. N., and Fernhall, B. (2009) 'Cardiac Autonomic Function and Baroreflex Changes Following 4 Weeks of Resistance versus Aerobic Training in Individuals with Pre-Hypertension'. *Acta Physiologica* 195, 339–348

Cononie, C.C., Graves, J.E., Pollock, M.L., Phillips, M.I., Sumners, C., and Hagberg, J.M. (1991) 'Effect of Exercise Training on Blood Pressure in 70- to 79-Yr-Old Men and Women.' in *Medicine and Science in Sports and Exercise* [online] vol. 23 (4). 505–511. available from <http://www.ncbi.nlm.nih.gov/pubmed/2056908%5Cnhttp://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2056908>

Cooke, W.H. and Carter, J.R. (2005) 'Strength Training Does Not Affect Vagal-Cardiac Control or Cardiovagal Baroreflex Sensitivity in Young Healthy Subjects'. *European Journal of Applied Physiology* 93 (5–6), 719–725

Cornelissen, V. a, Buys, R., and Smart, N. a (2013) 'Endurance Exercise Beneficially Affects Ambulatory Blood Pressure: A Systematic Review and Meta-Analysis.' *Journal of Hypertension* 31 (4), 639–48

Cornelissen, V.A. and Fagard, R.H. (2005) 'Effects of Endurance Training on Blood Pressure, Blood-Pressure Regulating Mechanisms, and Cardiovascular Risk Factors'. *Hypertension* 46, 667–675

Cornelissen, V.A., Fagard, R.H., Coeckelberghs, E., and Vanhees, L. (2011) 'Impact of Resistance Training on Blood Pressure and Other Cardiovascular Risk Factors: A Meta-Analysis of Randomized, Controlled Trials'. *Hypertension* 58 (5), 950–958

Cornelissen, V.A. and Smart, N.A. (2013) 'Exercise Training for Blood Pressure: A Systematic Review and Meta-Analysis.' *Journal of the American Heart Association* 2 (1)

Cornelissen, V.A., Smart, N.A., and Survey, N.E. (2013) 'Exercise Training for Blood Pressure : A Systematic Review and Meta- Analysis'. *Journal of the American Heart Association* 2 (1), 1–9

Cortez-Cooper, M.Y., DeVan, A.E., Anton, M.M., Farrar, R.P., Beckwith, K.A., Todd, J.S., and Tanaka, H. (2005) 'Effects of High Intensity Resistance Training on Arterial Stiffness and Wave Reflection in Women'. *American Journal of Hypertension* 18 (7), 930–934

Cote, A.T., Bredin, S.S.D., Phillips, A.A., Koehle, M.S., and Warburton, D.E.R. (2015) 'Greater Autonomic Modulation during Post-Exercise Hypotension Following High-Intensity Interval Exercise in Endurance-Trained Men and Women.' *European Journal of Applied Physiology* 115 (1), 81–89

Cox, K.L., Burke, V., Morton, a R., Gillam, H.F., Beilin, L.J., and Puddey, I.B. (2001) 'Long-Term Effects of Exercise on Blood Pressure and Lipids in Healthy Women Aged 40-65 Years: The Sedentary Women Exercise Adherence Trial (SWEAT).' *Journal of Hypertension* 19 (10), 1733–1743

Cozza, I.C., Di Sacco, T.H.R., Mazon, J.H., Salgado, M.C.O., Dutra, S.G. V, Cesarino, E.J., and Souza, H.C.D. (2012) 'Physical Exercise Improves Cardiac Autonomic Modulation in Hypertensive Patients Independently of Angiotensin-Converting Enzyme Inhibitor Treatment.' *Hypertension Research* 35 (1), 82–87

Creasy, S.A., Rogers, R.J., Davis, K.K., Gibbs, B.B., Kershaw, E.E., and Jakicic, J.M. (2017) 'Effects of Supervised and Unsupervised Physical Activity Programmes for Weight Loss'. *Obesity Science & Practice* [online] 3 (2), 143–152. available from <http://doi.wiley.com/10.1002/osp4.107>

Crowley, S.D., Gurley, S.B., Herrera, M.J., Ruiz, P., Griffiths, R., Kumar, A.P., Kim, H.-S., Smithies, O., Le, T.H., and Coffman, T.M. (2006) 'Angiotensin II Causes Hypertension and Cardiac Hypertrophy through Its Receptors in the Kidney.' *Proceedings of the National Academy of Sciences of the United States of America* 103 (47), 17985–17990

Dalal, H.M., Doherty, P., and Taylor, R.S. (2015) 'Cardiac Rehabilitation.' *BMJ (Clinical Research Ed.)* 29 (351), h5000

Dampney, R.A.L., Coleman, M.J., Fontes, M.A.P., Hirooka, Y., Horiuchi, J., Polson, J.W., Potts, P.D., Tagawa, T., Dampney, R.A.L., Coleman, M.J., Fontes, M.A.P., Hirooka, Y., Horiuchi, J., Polson, J.W., Potts, P.D., and Tagawa, T. (2006) 'Central Mechanisms Underlying Short Term and Long Term Regulation of the Cardiovascular System'. *Proceedings of the Australian Physiological and Pharmacological Society* [online] 32 (1), 1–12. available from <http://aups.org.au/Proceedings/32-1/dampney/dampney.pdf>

Damush, T.M., Plue, L., Bakas, T., Schmid, A., and Williams, L.S. (2007) 'Barriers and Facilitators to Exercise among Stroke Survivors.' *Rehabilitation Nursing : The Official Journal of the Association of Rehabilitation Nurses* 32 (6), 253–260

Davy, K., Willis, W., and Seals, D. (1997) 'Influence of Exercise Training on Heart Rate Variability in Post-Menopausal Women with Elevated Arterial Blood Pressure.' *Clinical Physiology* [online] 17 (1), 31–40. available from <http://www.ncbi.nlm.nih.gov/pubmed/9015656>

Delaney, E.P., Greaney, J.L., Edwards, D.G., Rose, W.C., Fadel, P.J., and Farquhar, W.B. (2010) 'Exaggerated Sympathetic and Pressor Responses to Handgrip Exercise in Older Hypertensive Humans: Role of the Muscle Metaboreflex.' *American Journal of Physiology. Heart and Circulatory Physiology* 299, H1318–H1327

Devereux, G.R., Coleman, D., Wiles, J.D., and Swaine, I. (2012) 'Lactate Accumulation Following Isometric Exercise Training and Its Relationship with Reduced Resting Blood Pressure'. *Journal of Sports Sciences* 30 (11), 1141–1148

Devereux, G.R. and Wiles, J.D. (2015) 'Immediate Post-Isometric Exercise Cardiovascular Responses Are Associated with Training-Induced Resting Systolic Blood Pressure Reductions'. *European Journal of Applied Physiology* 115, 327–333

Devereux, G.R., Wiles, J.D., and Swaine, I. (2011) 'Markers of Isometric Training Intensity and Reductions in Resting Blood Pressure.' *Journal of Sports Sciences* 29 (7), 715–724

Devereux, G.R., Wiles, J.D., and Swaine, I.L. (2010) 'Reductions in Resting Blood Pressure after 4 Weeks of Isometric Exercise Training'. *European Journal of Applied Physiology* 109, 601–606

Dibble, L.E., Hale, T.F., Marcus, R.L., Droge, J., Gerber, J.P., and LaStayo, P.C. (2006) 'High-Intensity Resistance Training Amplifies Muscle Hypertrophy and Functional Gains in Persons with Parkinson's Disease.' *Movement Disorders : Official Journal of the Movement Disorder Society* 21 (9), 1444–1452

DiBona, G.F. (2000) 'Nervous Kidney. Interaction between Renal Sympathetic Nerves and the Renin-Angiotensin System in the Control of Renal Function.' *Hypertension* 36 (6), 1083–1088

DiBona, G.F. and Kopp, U.C. (1997) 'Neural Control of Renal Function'. *Physiological Reviews* [online] 77 (1), 75–197. available from <http://www.ncbi.nlm.nih.gov/pubmed/9016301>

Dietrich, A., Rosmalen, J.G.M., Althaus, M., van Roon, A.M., Mulder, L.J.M., Minderaa, R.B., Oldehinkel, A.J., and Riese, H. (2010) 'Reproducibility of Heart Rate Variability and Baroreflex Sensitivity Measurements in Children'. *Biological Psychology* [online] 85 (1), 71–78. available from <http://dx.doi.org/10.1016/j.biopsycho.2010.05.005>

Ding, Y., Li, Y.-L., and Schultz, H.D. (2011) 'Role of Blood Flow in Carotid Body Chemoreflex Function in Heart Failure.' *The Journal of Physiology* 589 (Pt 1), 245–258

Dishman, R.K. (1994) 'Prescribing Exercise Intensity for Healthy Adults Using Perceived Exertion'. *Medicine and Science in Sports and Exercise* 26 (9), 1087–1094

Dishman, R.K., Sallis, J.F., and Orenstein, D.R. (1984) 'The Determinants of Physical Activity and Exercise.' *Public Health Reports (Washington, D.C. : 1974)* 100 (2), 158–71

Ditor, D.S., Kamath, M. V, Macdonald, M.J., Bugaresti, J., McCartney, N., and Hicks, A.L. (2005) 'Reproducibility of Heart Rate Variability and Blood Pressure Variability in Individuals with Spinal Cord Injury.' *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society* 15 (6), 387–393

Dobrosielski, D.A., Gibbs, B.B., Ouyang, P., Bonekamp, S., Clark, J.M., Wang, N.Y., Silber, H.A., Shapiro, E.P., and Stewart, K.J. (2012) 'Effect of Exercise on Blood Pressure in Type 2 Diabetes: A Randomized Controlled Trial'. *Journal of General Internal Medicine* 27 (11), 1453–1459

Dolan, E., Stanton, A., Thijs, L., Hinedi, K., Atkins, N., McClory, S., Hond, E. Den, McCormack, P., Staessen, J.A., and O'Brien, E. (2005) 'Superiority of Ambulatory over Clinic Blood Pressure Measurement in Predicting Mortality: The Dublin Outcome Study'. *Hypertension* 46 (1), 156–161

Dunbar, C.C., Robertson, R.J., Baun, R., Blandin, M.F., Metz, K., Burdett, R., and Goss, F.L. (1992) 'The

Validity of Regulating Exercise Intensity by Ratings of Perceived Exertion'. *Medicine & Science in Sports and Exercise* 24 (1), 94–99

Eguchi, K. (2016) 'Effects of Antihypertensive Therapy on Blood Pressure Variability'. *Current Hypertension Reports* [online] 18 (10), 16–19. available from <http://dx.doi.org/10.1007/s11906-016-0680-3>

Eguchi, K., Hoshide, S., Hoshide, Y., Ishikawa, S., Shimada, K., and Kario, K. (2010) 'Reproducibility of Ambulatory Blood Pressure in Treated and Untreated Hypertensive Patients'. *Journal of Hypertension* 28 (5), 918–924

Erskine, R.M., Jones, D.A., Williams, A.G., Stewart, C.E., and Degens, H. (2010) 'Inter-Individual Variability in the Adaptation of Human Muscle Specific Tension to Progressive Resistance Training'. *European Journal of Applied Physiology* 110 (6), 1117–1125

Eskurza, I., Seals, D.R., DeSouza, C.A., and Tanaka, H. (2001) 'Pharmacologic versus Flow-Mediated Assessments of Peripheral Vascular Endothelial Vasodilatory Function in Humans.' *The American Journal of Cardiology* 88 (9), 1067–1069

Esler, M. (2014) 'Sympathetic Nervous System Moves toward Center Stage in Cardiovascular Medicine from Thomas Willis to Resistant Hypertension'. *Hypertension* 63 (3), 25–33

Esler, M., Lambert, E., and Schlaich, M. (2010) 'Point : Counterpoint: The Dominant Contributor to Systemic Hypertension'. *Journal of Applied Physiology* 109 (6), 1996–1998

Eston, R.G., Davies, B.L., and Williams, J.G. (1987) 'Use of Perceived Effort Ratings to Control Exercise Intensity in Young Healthy Adults'. *European Journal of Applied Physiology* 56, 222–224

Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., Chalmers, J., Rodgers, A., and Rahimi, K. (2016) 'Blood Pressure Lowering for Prevention of Cardiovascular Disease and Death: A Systematic Review and Meta-Analysis.' *Lancet (London, England)* 387 (10022), 957–967

Fadel, P.J. and Raven, P.B. (2012) 'Human Investigations into the Arterial and Cardiopulmonary Baroreflexes during Exercise'. *Experimental Physiology* 97 (1), 39–50

Fagard, R.H. (2006) 'Exercise Is Good for Your Blood Pressure: Effects of Endurance Training and Resistance Training'. *Clinical and Experimental Pharmacology and Physiology* 33 (9), 853–856

Fagius, J. and Karhuvaara, S. (1989) 'Sympathetic Activity and Blood Pressure Increases with Bladder Distension in Humans.' *Hypertension* 14, 511–517

Fan, C. and Zhang, D. (2017) 'Rank Repeated Measures Analysis of Covariance'. *Communications in Statistics - Theory and Methods* [online] 46 (3), 1158–1183. available from <https://doi.org/10.1080/03610926.2015.1014106>

Faulkner, J. and Eston, R.G. (2008) 'Perceived Exertion Research in the 21st Century: Developments, Reflections and Questions for the Future.' *Journal of Exercise Science & Fitness* 6 (1), 1–14

Felício, J.S., Pacheco, J.T., Ferreira, S.R., Plavnik, F., Kohlmann, O., Ribeiro, A.B., and Zanella, M.T. (2007) 'Reproducibility of Ambulatory Blood Pressure Monitoring in Hypertensive Patients with Type 2 Diabetes Mellitus.' *Arquivos Brasileiros de Cardiologia* 88 (2), 206–211

Field, A. (2009) *Discovering Statistics Using SPSS (3rd Edition)*. London: Sage

Fisher, J., Seifert, T., Hartwich, D., Young, C., Secher, N., and Fadel, P. (2010) 'Autonomic Control of HR by Metabolically Sensitive Skeletal Muscle Afferents in Humans Autonomic Control of Heart Rate by Metabolically Sensitive Skeletal Muscle Afferents in Humans'. *Journal of Physiology* 588 (Pt 7), 1117–1127

Fisher, J.P., Young, C.N., and Fadel, P.J. (2015) 'Autonomic Adjustments to Exercise in Humans.' *Comprehensive Physiology* 5 (2), 475–512

Fisher, J.P., Young, C.N., and Fadel, P.J. (2009) 'Central Sympathetic Overactivity:Maladies and Mechanisms'. *Autonomic Neuroscience* 148 (1–2), 5–15

Fleck, S.J. (1988) 'Cardiovascular Adaptations to Resistance Training.' *Medicine and Science in Sports and Exercise* 20 (5 Suppl), S146-51

Fletcher, E.C. (2001) 'Invited Review: Physiological Consequences of Intermittent Hypoxia: Systemic Blood Pressure'. *Journal of Applied Physiology* 90 (4), 1600–1605

Forouzanfar, M.H., Alexander, L., Temesgen, A.M. et al. (2015) 'Global, Regional, and National Comparative Risk Assessment of 79 Behavioural, Environmental and Occupational, and Metabolic Risks or Clusters of Risks in 188 Countries, 1990-2013: A Systematic Analysis for the Global Burden of Disease Study 2013'. *The Lancet* 386 (10010), 2287–2323

Fortuño, A., San José, G., Moreno, M.U., Díez, J., and Zalba, G. (2005) 'Oxidative Stress and Vascular Remodelling.' *Experimental Physiology* 90 (4), 457–462

Fotherby, M.D. and Potter, J.F. (1993) 'Reproducibility of Ambulatory and Clinic Blood Pressure Measurements in Elderly Hypertensive Subjects.' *Journal of Hypertension* 11 (5), 573–579

Franco, M.R., Tong, A., Howard, K., Sherrington, C., Ferreira, P.H., Pinto, R.Z., and Ferreira, M.L. (2015) 'Older People's Perspectives on Participation in Physical Activity: A Systematic Review and Thematic Synthesis of Qualitative Literature'. *British Journal of Sports Medicine* [online] 49 (19), 1268–1276. available from <http://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2014-094015>

Frank, P., Andersson, E., Pontén, M., Ekblom, B., Ekblom, M., and Sahlin, K. (2016) 'Strength Training Improves Muscle Aerobic Capacity and Glucose Tolerance in Elderly'. *Scandinavian Journal of Medicine & Science in Sports* 26 (7), 764–773

Franklin, S.S., Gustin, W., Wong, N.D., Larson, M.G., Weber, M.A., Kannel, W.B., and Levy, D. (1997) 'Hemodynamic Patterns of Age-Related Changes in Blood Pressure - the Framingham Heart Study'. *Circulation* 96 (1), 308–15

Frattola, A., Parati, G., Cuspidi, C., Albini, F., and Mancia, G. (1993) 'Prognostic Value of 24-Hour Blood Pressure Variability.' *Journal of Hypertension* 11 (10), 1133–1137

Fredrikson, M. and Matthews, K.A. (1990) 'Cardiovascular Responses to Behvioral Stress and Hypertension: A Meta-Analytic Review'. *Annals of Behavioral Medicine* [online] 12 (1), 30–39. available from <http://hinarilogin.research4life.org/uniquesigpsycnet.apa.org/uniquesig0/psycinfo/1990-25811-001>

Freyschuss, U. (1970) 'Elicitation of Heart Rate and Blood Pressure Increase on Muscle Contraction.' *Journal of Applied Physiology* 28 (6), 758–761

Frontera, W.R., Meredith, C.N., O'Reilly, K.P., and Evans, W.J. (1990) 'Strength Training and Determinants of VO2max in Older Men.' *Journal of Applied Physiology* 68 (1), 329–333

Fujiwara, M., Asakuma, S., and Iwasaki, T. (2000) 'Long-term effects of non-supervised home exercise therapy on quality of life in patients with myocardial infarction.' *Journal of Cardiology* 36 (4), 213–219

Furchgott, R.F. and Zawadzki, J. V (1980) 'The Obligatory Role of Endothelial Cells in the Relaxation of Arterial Smooth Muscle by Acetylcholine.' *Nature* 288 (5789), 373–376

Gallagher, K.M., Fadel, P.J., Smith, S.A., Strømstad, M., Ide, K., Secher, N.H., and Raven, P.B. (2006) 'The Interaction of Central Command and the Exercise Pressor Reflex in Mediating Baroreflex Resetting during Exercise in Humans'. *Experimental Physiology* 91 (1), 79–87

Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B. a., Lamonte, M.J., Lee, I.M., Nieman, D.C., and Swain, D.P. (2011) 'Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise'. *Medicine and Science in Sports and Exercise* 43 (7), 1334–1359

De Geest, S. and Sabaté, E. (2003) 'Adherence to Long-Term Therapies : Evidence for Action'. *European Journal of Cardiovascular Nursing* 2 (4), 323

Georgiades, A., Sherwood, A., Gullette, E., Babyak, M., Hinderliter, A., Waugh, R., Tweedy, D., Craighead, L., Bloomer, R., and Blumenthal, J. (2000) 'Effects of Exercise and Weight Loss on Mental Stress-Induced Cardiovascular Responses in Individuals with High Blood Pressure.' *Hypertension* [online] 36 (2), 171–176. available from <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/085/CN-00299085/frame.html>

Ghadieh, A.S. and Saab, B. (2015) 'Evidence for Exercise Training in the Management of Hypertension in Adults.' *Canadian Family Physician* [online] 61 (3), 233–9. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4369613&tool=pmcentrez&rendertype=abstract>

Gill, K.F., Arthur, S.T., Swaine, I., Devereux, G.R., Huet, Y.M., Cordova, M.L., and Howden, R. (2015) 'Intensity-Dependent Reductions in Resting Blood Pressure Following Short-Term Isometric Exercise Training'. *Journal of Sports Sciences* 33 (6), 37–41

Ginsburg, P., Bartur, G., Peleg, S., Vatine, J.J., and Katz-Leurer, M. (2011) 'Reproducibility of Heart Rate Variability during Rest, Paced Breathing and Light-to-Moderate Intense Exercise in Patients One Month after Stroke'. *European Neurology* 66 (2), 117–122

Gkaliagkousi, E., Gavriilaki, E., and Douma, S. (2015) 'Effects of Acute and Chronic Exercise in Patients with Essential Hypertension: Benefits and Risks'. *American Journal of Hypertension* 28 (4), 429–439

Gladwell, V.F. and Coote, J.H. (2002) 'Heart Rate at the Onset of Muscle Contraction and during Passive Muscle Stretch in Humans: A Role for Mechanoreceptors'. *Journal of Physiology* 540 (3), 1095–1102

Gladwell, V.F., Fletcher, J., Patel, N., Elvidge, L.J., Lloyd, D., Chowdhary, S., and Coote, J.H. (2005) 'The Influence of Small Fibre Muscle Mechanoreceptors on the Cardiac Vagus in Humans'. *Journal of Physiology* 567 (2), 713–721

Goessler, K., Buys, R., and Cornelissen, V. (2016) 'Low Intensity Isometric Handgrip Exercise Has No Transient Effect on Blood Pressure in Patients with Coronary Artery Disease'. *Journal of the American Society of Hypertension* [online] 10 (8), 633–639. available from <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004872-201609002-01046>

Goessler, K., Polito, M., and Cornelissen, V.A. (2016) 'Effect of Exercise Training on the Renin-Angiotensin-Aldosterone System in Healthy Individuals: A Systematic Review and Meta-Analysis'. *Hypertension Research* 39 (3), 119–126

Goessler, K.F., Buys, R., VanderTrappen, D., Vanhumbeeck, L., and Cornelissen, V.A. (2018) 'A Randomized Controlled Trial Comparing Home-Based Isometric Handgrip Exercise versus Endurance Training for Blood Pressure Management.' *Journal of the American Society of Hypertension* 12 (4), 285–293

Goldblatt, H. (1947) 'The Renal Origin of Hypertension.' *Physiological Reviews* 27 (1), 120–165

González, J., Valls, N., Brito, R., and Rodrigo, R. (2014) 'Essential Hypertension and Oxidative Stress: New Insights.' *World Journal of Cardiology* [online] 6 (6), 353–66. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4072825&tool=pmcentrez&rendertype=abstract>

Goodwin, G.M., McCloskey, D.I., and Mitchell, J.H. (1972) 'Cardiovascular and Respiratory Responses to Changes in Central Command during Isometric Exercise at Constant Muscle Tension.' *The Journal of Physiology* 226 (1), 173–190

Goosey-Tolfrey, V., Lenton, J., Goddard, J., Oldfield, V., Tolfrey, K., and Eston, R. (2010) 'Regulating Intensity Using Perceived Exertion in Spinal Cord-Injured Participants'. *Medicine and Science in Sports and Exercise*

[online] 42 (3), 608–613. available from <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005768-201003000-00028>

Goslin, B.R. and Rorke, S.C. (1986) 'The Perception of Exertion during Load Carriage.' *Ergonomics* 29 (5), 677–686

Goulart, C. da L., Cabiddu, R., De Borba Schneiders, P., Antunes San Martin, E., Trimer, R., Borghi-Silva, A., and da Silva, A.L.G. (2017) 'Is Cardiac Autonomic Modulation during Upper Limb Isometric Contraction and Valsalva Maneuver Impaired in COPD Patients?' *International Journal of Chronic Obstructive Pulmonary Disease* [online] 13 (12), 849–857. available from <https://www.dovepress.com/is-cardiac-autonomic-modulation-during-upper-limb-isometric-contractio-peer-reviewed-article-COPD>

Grassi, G., Cattaneo, B.M., Seravalle, G., Lanfranchi, a, and Mancia, G. (1998) 'Baroreflex Control of Sympathetic Nerve Activity in Essential and Secondary Hypertension.' *Hypertension* 31 (1), 68–72

Grassi, G. and Ram, V.S. (2016) 'Evidence for a Critical Role of the Sympathetic Nervous System in Hypertension.' *Journal of the American Society of Hypertension* 10 (5), 457–466

Greaney, J.L., Matthews, E.L., Boggs, M.E., Edwards, D.G., Duncan, R.L., and Farquhar, W.B. (2014) 'Exaggerated Exercise Pressor Reflex in Adults with Moderately Elevated Systolic Blood Pressure: Role of Purinergic Receptors.' *American Journal of Physiology. Heart and Circulatory Physiology* [online] 306 (1), H132-41. available from <http://www.ncbi.nlm.nih.gov/pubmed/24163081>

Greaney, J.L., Wenner, M.M., and Farquhar, W.B. (2015) 'Exaggerated Increases in Blood Pressure during Isometric Muscle Contraction in Hypertension: Role for Purinergic Receptors.' *Autonomic Neuroscience : Basic & Clinical* [online] 188, 51–57. available from <http://dx.doi.org/10.1016/j.autneu.2014.12.003>

Green, A.L. and Paterson, D.J. (2008) 'Identification of Neurocircuitry Controlling Cardiovascular Function in Humans Using Functional Neurosurgery: Implications for Exercise Control'. *Experimental Physiology* 93 (9), 1022–1028

Green, D.J., Maiorana, A., O'Driscoll, G., and Taylor, R. (2004) 'Effect of Exercise Training on Endothelium-Derived Nitric Oxide Function in Humans'. *Journal of Physiology* 561 (1), 1–25

Green, J.M., Crews, T.R., Bosak, A.M., and Peveler, W. (2002) 'Physiological Responses at 0% and 10% Treadmill Incline Using the RPE Estimation-Production Paradigm.' *The Journal of Sports Medicine and Physical Fitness* 42 (1), 8–13

Green, J.M., Michael, T., and Solomon, A.H. (1999) 'The Validity of Ratings of Perceived Exertion for Cross-Modal Regulation of Swimming Intensity'. *Journal of Sports Medicine and Physical Fitness* [online] 39 (3), 207–212. available from <http://www.ncbi.nlm.nih.gov/pubmed/10573662>

Guelen, I., Westerhof, B.E., Van der Sar, G.L., van Montfrans, G.A., Kiemeneji, F., Wesseling, K.H., and Bos, W.J. (2003) 'Finometer, Finger Pressure Measurements with the Possibility to Reconstruct Brachial

Pressure'. *Blood Pressure Monitoring* 8 (1), 27–30

Guyenet, P.G. (2006) 'The Sympathetic Control of Blood Pressure.' *Nature Reviews. Neuroscience* 7 (5), 335–346

Guyton, A.C., Coleman, T.G., Cowley, A.V.J., Scheel, K.W., Manning, R.D.J., and Norman, R.A.J. (1972) 'Arterial Pressure Regulation. Overriding Dominance of the Kidneys in Long-Term Regulation and in Hypertension.' *The American Journal of Medicine* 52 (5), 584–594

Hadaegh, F., Shafiee, G., Hatami, M., and Azizi, F. (2012) 'Systolic and Diastolic Blood Pressure, Mean Arterial Pressure and Pulse Pressure for Prediction of Cardiovascular Events and Mortality in a Middle Eastern Population'. *Blood Pressure* 21 (1), 12–18

Al Haddad, H., Laursen, P., Chollet, D., Ahmaidi, S., and Buchheit, M. (2011) 'Reliability of Resting and Postexercise Heart Rate Measures'. *International Journal of Sports Medicine* [online] 32 (08), 598–605. available from <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0031-1275356>

Halliwill, J.R., Taylor, J.A., and Eckberg, D.L. (1996) 'Impaired Sympathetic Vascular Regulation in Humans after Acute Dynamic Exercise'. *Journal of Physiology* 495 (1), 279–288

Hallman, D.M., Holtermann, A., Søgaard, K., Krustrup, P., Kristiansen, J., and Korshøj, M. (2017) 'Effect of an Aerobic Exercise Intervention on Cardiac Autonomic Regulation: A Worksite RCT among Cleaners'. *Physiology and Behavior* [online] 169, 90–97. available from <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L613459937%5Cnhttp://dx.doi.org/10.1016/j.physbeh.2016.11.031%5Cnhttp://findit.library.jhu.edu/resolve?sid=EMBASE&issn=1873507X&id=doi:10.1016%2Fj.physbeh.2016.11.031&atitle=Effect+o>

Hallman, D.M., Srinivasan, D., and Mathiassen, S.E. (2015) 'Short- and Long-Term Reliability of Heart Rate Variability Indices during Repetitive Low-Force Work.' *European Journal of Applied Physiology* 115 (4), 803–812

Hansen, T.W., Thijs, L., Li, Y., Boggia, J., Kikuya, M., Björklund-Bodegård, K., Richart, T., Ohkubo, T., Jeppesen, J., Torp-Pedersen, C., Dolan, E., Kuznetsova, T., Stolarz-Skrzypek, K., Tikhonoff, V., Malyutina, S., Casiglia, E., Nikitin, Y., Lind, L., Sandoya, E., Kawecka-Jaszcz, K., Imai, Y., Wang, J., Ibsen, H., O'Brien, E., and Staessen, J.A. (2010) 'Prognostic Value of Reading-to-Reading Blood Pressure Variability over 24 Hours in 8938 Subjects from 11 Populations'. *Hypertension* 55 (4), 1049–1057

Hardy, D.O. and Tucker, L.A. (1998) 'The Effects of a Single Bout of Strength Training on Ambulatory Blood Pressure Levels in 24 Mildly Hypertensive Men.' *American Journal of Health Promotion : AJHP* 13 (2), 69–72

Harrison-bernard, L.M. (2009) 'The Renal Renin-Angiotensin System'. *Advances in Physiology Education* 33 (4), 270–274

Hart, E.C.J. and Charkoudian, N. (2014) 'Sympathetic Neural Regulation of Blood Pressure: Influences of Sex and Aging.' *Physiology (Bethesda, Md.)* [online] 29 (1), 8–15. available from

<http://physiologyonline.physiology.org/content/29/1/8.long>

Hautala, A.J., Kiviniemi, A.M., and Tulppo, M.P. (2009) 'Individual Responses to Aerobic Exercise: The Role of the Autonomic Nervous System'. *Neuroscience and Biobehavioral Reviews* 33 (2), 107–115

Hayes, S.G. (2005) 'Comparison between the Effect of Static Contraction and Tendon Stretch on the Discharge of Group III and IV Muscle Afferents'. *Journal of Applied Physiology* [online] 99 (5), 1891–1896. available from <http://jap.physiology.org/cgi/doi/10.1152/japplphysiol.00629.2005>

Heath, G., Parra, D., Sarmiento, O., Anderson, B., Owen, N., Goenka, S., Montes, F., and Brownson, R. (2016) 'Evidence-Based Intervention in Physical Activity: Lessons from around the World'. *Lancet* 380 (9838), 272–281

Heathers, J.A.J. (2014) 'Everything Hertz: Methodological Issues in Short-Term Frequency-Domain HRV'. *Frontiers in Physiology* 5 (177), 1–15

Heathers, J.A.J. (2012) 'Sympathovagal Balance from Heart Rate Variability: An Obituary'. *Experimental Physiology* [online] 97 (4), 556–556. available from <http://doi.wiley.com/10.1113/expphysiol.2011.063867>

Heffernan, K.S., Collier, S.R., Kelly, E.E., Jae, S.Y., and Fernhall, B. (2007) 'Arterial Stiffness and Baroreflex Sensitivity Following Bouts of Aerobic and Resistance Exercise'. *International Journal of Sports Medicine* 28 (3), 197–203

Hermida, R.C., Calvo, C., Ayala, D.E., Fernández, J.R., Ruilope, L.M., and López, J.E. (2002) 'Evaluation of the Extent and Duration of the "ABPM Effect" in Hypertensive Patients'. *Journal of the American College of Cardiology* 40 (4), 710–717

Herr, M.D., Imadojemu, V., Kunselman, A.R., and Sinoway, L.I. (1999) 'Characteristics of the Muscle Mechanoreflex during Quadriceps Contractions in Humans'. *Journal of Applied Physiology* 86 (2), 767–772

Hess, N.C.L., Carlson, D.J., Inder, J.D., Jesulola, E., Mcfarlane, J.R., and Smart, N.A. (2016) 'Clinically Meaningful Blood Pressure Reductions with Low Intensity Isometric Handgrip Exercise. A Randomized Trial'. *Physiological Research* 65 (3), 461–468

Hesse, C., Charkoudian, N., Liu, Z., Joyner, M.J., and Eisenach, J.H. (2007) 'Baroreflex Sensitivity Inversely Correlates with Ambulatory Blood Pressure in Healthy Normotensive Humans'. *Hypertension* 50 (1), 41–46

Higuchi, S., Ohtsu, H., Suzuki, H., Shirai, H., Frank, G.D., and Eguchi, S. (2007) 'Angiotensin II Signal Transduction through the AT1 Receptor: Novel Insights into Mechanisms and Pathophysiology.' *Clinical Science (London, England : 1979)* 112 (8), 417–428

Hijmering, M.L., Stroes, E.S.G., Olijhoek, J., Hutten, B.A., Blankestijin, P.J., and Rabelink, T.J. (2002) 'Sympathetic Activation Markedly Reduces Endothelium-Dependent, Flow-Mediated Vasodilation'. *Journal*

of the American College of Cardiology 39 (4), 683–688

Hitomi, H., Kiyomoto, H., and Nishiyama, A. (2007) 'Angiotensin II and Oxidative Stress.' *Current Opinion in Cardiology* 22 (4), 311–315

Höcht, C. (2013) 'Blood Pressure Variability: Prognostic Value and Therapeutic Implications'. *ISRN Hypertension* [online] 16. available from <http://www.hindawi.com/journals/isrn/2013/398485/ref/>

Hohnloser, S.H., Klingenheben, T., Zabel, M., Schroder, F., and Hanjorg, J. (1992) 'Intraindividual Reproducibility of Heart Rate Variability'. *Pacing and Clinical Electrophysiology : PACE* 15 (11 Pt 2), 2211–2214

Hojgaard, M. V, Holstein-Rathlou, N.-H., Agner, E., and Kanters, J.K. (2005) 'Reproducibility of Heart Rate Variability, Blood Pressure Variability and Baroreceptor Sensitivity during Rest and Head-up Tilt.' *Blood Pressure Monitoring* 10 (1), 19–24

Hon, E.H. and Lee, S.T. (1963) 'Electronic Evaluation of Fetal Heart Rate. VIII. Patterns Preceding Fetal Death, Further Observations.' *American Journal of Obstetrics and Gynecology* 87, 814–826

Hopkins, W.G. (2000) 'Measures of Reliability in Sports Medicine and Science.' *Sports Medicine* 30 (1), 1–15

Howden, R., Lightfoot, J.T., Brown, S.J., and Swaine, I.L. (2002) 'The Effects of Isometric Exercise Training on Resting Blood Pressure and Orthostatic Tolerance in Humans'. *Exprerimental Physiology* 87 (4), 507–515

Hubal, M.J., Gordish-Dressman, H., Thompson, P.D., Price, T.B., Hoffman, E.P., Angelopoulos, T.J., Gordon, P.M., Moyna, N.M., Pescatello, L.S., Visich, P.S., Zoeller, R.F., Seip, R.L., and Clarkson, P.M. (2005) 'Variability in Muscle Size and Strength Gain after Unilateral Resistance Training'. *Medicine and Science in Sports and Exercise* 37 (6), 964–972

Ichinose, M., Saito, M., Kondo, N., and Nishiyasu, T. (2008) 'Baroreflex and Muscle Metaboreflex: Control of Muscle Sympathetic Nerve Activity'. *Medicine and Science in Sports and Exercise* 40 (12), 2037–2045

Iellamo, F., Legramante, J.M., Massaro, M., Raimondi, G., and Galante, A. (2000) 'Effects of a Residential Exercise Training on Baroreflex Sensitivity and Heart Rate Variability in Patients with Coronary Artery Disease'. *Circulation* 102 (21), 2588–2593

Iellamo, F., Massaro, M., Raimondi, G., Peruzzi, G., and Legramante, J.M. (1999) 'Role of Muscular Factors in Cardiorespiratory Responses to Static Exercise: Contribution of Reflex Mechanisms.' *Journal of Applied Physiology* 86 (1), 174–180

Imholz, B.P., Imholz, B.P., Wieling, W., Wieling, W., van Montfrans, G. a, van Montfrans, G. a, Wesseling, K.H., and Wesseling, K.H. (1998) 'Fifteen Years Experience with Finger Arterial Pressure Monitoring: Assessment of the Technology.' *Cardiovascular Research* [online] 38 (3), 605–616. available from <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=97

47429>

Inder, J.D., Carlson, D.J., Dieberg, G., Hess, N.C., Millar, P.J., and Smart, N.A. (2016) 'Isometric Exercise Training for Blood Pressure Management: A Systematic Review and Meta-Analysis to Optimize Benefit'. *Hypertension Research* [online] 39 (2), 88–94. available from <http://www.scopus.com/inward/record.url?eid=2-s2.0-84898670812&partnerID=40&md5=f02036652a8116dc218136ada7c31b15>

Iwasaki, K.-I., Zhang, R., Zuckerman, J.H., and Levine, B.D. (2003) 'Dose-Response Relationship of the Cardiovascular Adaptation to Endurance Training in Healthy Adults: How Much Training for What Benefit?' *Journal of Applied Physiology* 95 (4), 1575–1583

Izdebska, E., Cybulska, I., Izdebski, J., Makowieka-Ciesla, M., and Trzebski, A. (2004) 'Effects of Moderate Physical Training on Blood Pressure Variability and Hemodynamic Pattern in Mildly Hypertensive Subjects'. *Journal of Physiology and Pharmacology* 55 (4), 713–724

James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., Handler, J., Lackland, D.T., LeFevre, M.L., MacKenzie, T.D., Ogedegbe, O., Smith, S.C., Svetkey, L.P., Taler, S.J., Townsend, R.R., Wright, J.T., Narva, A.S., and Ortiz, E. (2014) 'Evidence-Based Guideline for the Management of High Blood Pressure in Adults'. *JAMA* [online] 311 (5), 507–20. available from <http://jama.jamanetwork.com/article.aspx?articleid=1791497%5Cnhttp://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.284427>

Jamnik, V.K., Warburton, D.E.R., Makarski, J., McKenzie, D.C., Shephard, R.J., Stone, J. a, Charlesworth, S., and Gledhill, N. (2011) 'Enhancing the Effectiveness of Clearance for Physical Activity Participation: Background and Overall Process'. *Applied Physiology, Nutrition, and Metabolism* [online] 36 (Suppl 1), S3–S13. available from <http://www.ncbi.nlm.nih.gov/pubmed/21800946>

Janszky, I., Ericson, M., Mittleman, M.A., Wamala, S., Al-Khalili, F., Schenck-Gustafsson, K., and Orth-Gomer, K. (2004) 'Heart Rate Variability in Long-Term Risk Assessment in Middle-Aged Women with Coronary Heart Disease: The Stockholm Female Coronary Risk Study'. *Journal of Internal Medicine* 255 (1), 13–21

Jefferis, B.J., Sartini, C., Lee, I.-M., Choi, M., Amuzu, A., Gutierrez, C., Casas, J.P., Ash, S., Lennnon, L.T., Wannamethee, S.G., and Whincup, P.H. (2014) 'Adherence to Physical Activity Guidelines in Older Adults, Using Objectively Measured Physical Activity in a Population-Based Study'. *BMC Public Health* [online] 14 (382), 1–9. available from <http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-14-382>

John, S.W., Krege, J.H., Oliver, P.M., Hagaman, J.R., Hodgin, J.B., Pang, S.C., Flynn, T.G., and Smithies, O. (1995) 'Genetic Decreases in Atrial Natriuretic Peptide and Salt-Sensitive Hypertension.' *Science (New York, N.Y.)* 267 (5198), 679–681

Johns, E.J. (2013) 'Autonomic Regulation of Kidney Function.' *Handbook of Clinical Neurology* 117, 203–214

Juel, C., Klarskov, C., Nielsen, J.J., Krustrup, P., Mohr, M., and Bangsbo, J. (2004) 'Effect of High-Intensity

Intermittent Training on Lactate and H+ Release from Human Skeletal Muscle.' *American Journal of Physiology. Endocrinology and Metabolism* 286 (2), E245–E251

Kaftan, A.H. and Kaftan, O. (2000) 'QT Intervals and Heart Rate Variability in Hypertensive Patients.' *Japanese Heart Journal* 41 (2), 173–182

Kang, S.-J., Ko, K.-J., and Baek, U.-H. (2016) 'Effects of 12 Weeks Combined Aerobic and Resistance Exercise on Heart Rate Variability in Type 2 Diabetes Mellitus Patients.' *Journal of Physical Therapy Science* [online] 28 (7), 2088–93. available from <http://www.ncbi.nlm.nih.gov/pubmed/27512271>

Karavirta, L., Costa, M.D., Goldberger, A.L., Tulppo, M.P., Laaksonen, D.E., Nyman, K., Keskitalo, M., Häkkinen, A., and Häkkinen, K. (2013) 'Heart Rate Dynamics after Combined Strength and Endurance Training in Middle-Aged Women: Heterogeneity of Responses'. *PLOS ONE* 8 (8), 1–8

Kaufman, M.P. and Hayes, S.G. (2002) 'The Exercise Pressor Reflex.' *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society* 12 (6), 429–439

Kaufman, M.P., Hayes, S.G., Adreani, C.M., and Pickar, J.G. (2002) 'Discharge Properties of Group III and IV Muscle Afferents.' *Advances in Experimental Medicine and Biology* 508, 25–32

Keese, F., Farinatti, P., Pescatello, L., and Monteiro, W. (2011) 'A Comparison of the Immediate Effects of Resistance, Aerobic, and Concurrent Exercise on Postexercise Hypotension.' *Journal of Strength and Conditioning Research* 25 (5), 1429–1436

Kenney, M.J. and Seals, D.R. (1993) 'Brief Review Postexercise Hypotension'. *Hypertension* 22 (5), 653–664

Keren, S., Leibowitz, A., Grossman, E., and Sharabi, Y. (2015) 'Limited Reproducibility of 24-h Ambulatory Blood Pressure Monitoring'. *Clinical and Experimental Hypertension* 37 (7), 599–603

Ketelhut, R.G., Franz, I.W., and Scholze, J. (2004) 'Regular Exercise as an Effective Approach in Antihypertensive Therapy.' *Medicine and Science in Sports and Exercise* [online] 36 (1), 4–8. available from <http://www.ncbi.nlm.nih.gov/pubmed/14707760>

Khan, N., Bacon, S.L., Khan, S., Perlmutter, S., Gerlinsky, C., Dermer, M., Johnson, L., Alves, F., Mclean, D., Laupacis, A., Pui, M., Berg, A., and Flowitt, F. (2017) 'Hypertension Management Research Priorities from Patients, Caregivers, and Healthcare Providers: A Report from the Hypertension Canada Priority Setting Partnership Group'. *Journal of Clinical Hypertension* 19 (11), 1063–1069

Kim, D. and Ha, J.-W. (2016) 'Hypertensive Response to Exercise: Mechanisms and Clinical Implication.' *Clinical Hypertension* [online] 22 (17), 1–4. available from <http://dx.doi.org/10.1186/s40885-016-0052-y>

Kingsley, J.D. and Figueroa, A. (2016) 'Acute and Training Effects of Resistance Exercise on Heart Rate Variability'. *Clinical Physiology and Functional Imaging* 36 (3), 179–187

Kiviniemi, A.M., Hautala, A.J., Karjalainen, J.J., Piira, O.-P., Lepojärvi, S., Ukkola, O., Huikuri, H. V, and Tulppo, M.P. (2015) 'Acute Post-Exercise Change in Blood Pressure and Exercise Training Response in Patients with Coronary Artery Disease.' *Frontiers in Physiology* [online] 5, 1–7. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4290526&tool=pmcentrez&rendertype=abstract>

Kiviniemi, A.M., Hautala, A.J., Makikallio, T.H., Seppanen, T., Huikuri, H. V, and Tulppo, M.P. (2006) 'Cardiac Vagal Outflow after Aerobic Training by Analysis of High-Frequency Oscillation of the R-R Interval.' *European Journal of Applied PhysiologyEuropean Journal of Applied Physiology* 96 (6), 686–692

Kiviniemi, A.M., Tulppo, M.P., Eskelinen, J.J., Savolainen, A.M., Kapanen, J., Heinonen, I.H.A., Huikuri, H. V., Hannukainen, J.C., and Kalliokoski, K.K. (2014) 'Cardiac Autonomic Function and High-Intensity Interval Training in Middle-Age Men'. *Medicine and Science in Sports and Exercise* 46 (10), 1960–1967

Klabunde, R. (2012) *Cardiovascular Physiological Concepts*. Second Edi. Baltimore: Lippincott Williams & Williams

Kleiger, R., Bigger, J., Bosner, M., Chung, M., Cook, J., Rolnitzky, L., Steinman, R., and Fleiss, J. (1991) 'Stability over Time of Variables Measuring Heart Rate Variability in Normal Subjects'. *American Journal of Cardiology* 68 (6), 626–630

Kleiger, R.E., Stein, P.K., and Bigger, J.T. (2005) 'Heart Rate Variability: Measurement and Clinical Utility.' *Annals of Noninvasive Electrocardiology* [online] 10 (1), 88–101. available from <http://www.ncbi.nlm.nih.gov/pubmed/15649244>

Kliszczewicz, B.M., Esco, M.R., Quindry, J.C., Blessing, D.L., Oliver, G.D., Taylor, K.J., and Price, B.M. (2016) 'Autonomic Responses to an Acute Bout of High-Intensity Body Weight Resistance Exercise vs. Treadmill Running.' *Journal of Strength and Conditioning Research* 30 (4), 1050–1058

Kneale, B.J., Chowienczyk, P.J., Brett, S.E., Cockcroft, J.R., and Ritter, J.M. (1999) 'Forearm Vasoconstriction in Response to Noradrenaline and NG-Monomethyl-L-Arginine in Essential Hypertension.' *Clinical Science (London, England : 1979)* 97 (3), 277–282

Knott, C. and Mindell, J. (2011) *Hypertension*. vol. 1

Kobayashi, Y., Hosoi, T., Takeuchi, T., and Aoki, S. (2001) 'Benefits of a Convenient, Self-Regulated 6-Month Walking Program in Sedentary, Middle-Aged Women'. *Japanese Journal of Physical Fitness and Sports Medicine* [online] 50 (3), 313–323. available from <https://www.jstage.jst.go.jp/article/jspfsm1949/50/3/50_3_313/_article>

Kougias, P., Weakley, S.M., Yao, Q., Lin, P.H., and Chen, C. (2010) 'Arterial Baroreceptors in the Management of Systemic Hypertension.' *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research* 16 (1), RA1-A8

Kraemer, W.J. and Ratamess, N.A. (2004) 'Fundamentals of Resistance Training: Progression and Exercise

Prescription'. *Medicine and Science in Sports and Exercise* 36 (4), 674–688

Kraemer, W.J., Ratamess, N.A., and French, D.N. (2002) 'Resistance Training for Health and Performance'. *Current Sports Medicine Reports* [online] 1 (3), 165–171. available from <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00149619-200206000-00007>

Krause, M., Rodrigues-Krause, J., O'Hagan, C., Medlow, P., Davison, G., Susta, D., Boreham, C., Newsholme, P., O'Donnell, M., Murphy, C., and De Vito, G. (2014) 'The Effects of Aerobic Exercise Training at Two Different Intensities in Obesity and Type 2 Diabetes: Implications for Oxidative Stress, Low-Grade Inflammation and Nitric Oxide Production.' *European Journal of Applied Physiologyhysiology* 114 (2), 251–260

Krogh, A. and Lindhard, J. (1913) 'The Regulation of Respiration and Circulation during the Initial Stages of Muscular Work'. *The Journal of Physiology* 47 (1–2), 112–136

De La Sierra, A., Segura, J., Banegas, J.R., Gorostidi, M., De La Cruz, J.J., Armario, P., Oliveras, A., and Ruilope, L.M. (2011) 'Clinical Features of 8295 Patients with Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring'. *Hypertension* 57 (5), 898–902

Laborde, S., Mosley, E., and Thayer, J.F. (2017) 'Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting'. *Frontiers in Psychology* 8, 1–18

Lagally, K.M. and Amorose, A.J. (2007) 'The Validity of Using Prior Ratings of Perceived Exertion to Regulate Resistance Exercise Intensity'. *Perceptual and Motor Skills* 104 (2), 534–542

Laterza, M.C., De Matos, L.D.N.J., Trombetta, I.C., Braga, A.M.W., Roveda, F., Alves, M.J.N.N., Krieger, E.M., Negr??o, C.E., and Rondon, M.U.P.B. (2007) 'Exercise Training Restores Baroreflex Sensitivity in Never-Treated Hypertensive Patients'. *Hypertension* 49 (6), 1298–1306

Lawrence, M.M., Cooley, I.D., Huet, Y.M., Arthur, S.T., and Howden, R. (2014) 'Factors Influencing Isometric Exercise Training-Induced Reductions in Resting Blood Pressure'. *Scandinavian Journal of Medicine and Science in Sports* 25 (2), 1–12

Lee, L.L., Watson, M.C., Mulvaney, C.A., Tsai, C.C., and Lo, S.F. (2010) 'The Effect of Walking Intervention on Blood Pressure Control: A Systematic Review'. *International Journal of Nursing Studies* 47 (12), 1545–1561

Legramante, J.M., Galante, A., Massaro, M., Attanasio, A., Raimondi, G., Pigozzi, F., and Iellamo, F. (2002) 'Hemodynamic and Autonomic Correlates of Postexercise Hypotension in Patients with Mild Hypertension.' *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 282 (4), R1037–R1043

Leite, P.H., Melo, R.C., Mello, M.F., Silva, E. Da, Borghi-Silva, A., and Catai, A.M. (2010) 'Heart Rate Responses during Isometric Exercises in Patients Undergoing a Phase III Cardiac Rehabilitation Program.' *Revista Brasileira de Fisioterapia (São Carlos (São Paulo, Brazil))* 14 (5), 383–389

Li, Y.-L., Sun, S.-Y., Overholt, J.L., Prabhakar, N.R., Rozanski, G.J., Zucker, I.H., and Schultz, H.D. (2004) 'Attenuated Outward Potassium Currents in Carotid Body Glomus Cells of Heart Failure Rabbit: Involvement of Nitric Oxide.' *The Journal of Physiology* 555 (Pt 1), 219–229

Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., Amann, M., Anderson, R.H., Andrews, K.G., Aryee, M., and Atkinson, C. (2012) 'A Comparative Risk Assessment of Burden of Disease and Injury Attributable to 67 Risk Factors and Risk Factor Clusters in 21 Regions, 1990–2010: A Systematic Analysis for the Global Burden of Disease Study 2010'. *The Lancet* 380 (9859), 2224–2260

Lima, E.G., Spritzer, N., Herkenhoff, F.L., Bermudes, A., and Vasquez, E.C. (1995) 'Noninvasive Ambulatory 24-Hour Blood Pressure in Patients with High Normal Blood Pressure and Exaggerated Systolic Pressure Response to Exercise.' *Hypertension (Dallas, Tex. : 1979)* 26 (6 Pt 2), 1121–1124

Lind, A.R. and McNicol, G.W. (1967a) 'Circulatory Responses to Sustained Hand-Grip Contractions Performed during Other Exercise, Both Rhythmic and Static'. *The Journal of Physiology* [online] 192 (3), 595–607. available from <http://doi.wiley.com/10.1113/jphysiol.1967.sp008319>

Lind, A.R. and McNicol, G.W. (1967b) 'Muscular Factors Which Determine the Cardiovascular Responses to Sustained and Rhythmic Exercise.' *Canadian Medical Association Journal* 96 (12), 706–715

Linder, L., Kiowski, W., Buhler, F.R., and Luscher, T.F. (1990) 'Indirect Evidence for Release of Endothelium-Derived Relaxing Factor in Human Forearm Circulation in Vivo. Blunted Response in Essential Hypertension.' *Circulation* 81 (6), 1762–1767

Liu-Ambrose, T., Best, J.R., Davis, J.C., Eng, J.J., Lee, P.E., Jacova, C., Boyd, L.A., Brasher, P.M., Munkacsy, M., Cheung, W., and Hsiung, G.-Y.R. (2016) 'Aerobic Exercise and Vascular Cognitive Impairment: A Randomized Controlled Trial.' *Neurology* [online] 87 (20), 2082–2090. available from <http://www.ncbi.nlm.nih.gov/pubmed/27760869%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/27760869>

Liu, S., Goodman, J., Nolan, R., Lacombe, S., and Thomas, S.G. (2012) 'Blood Pressure Responses to Acute and Chronic Exercise Are Related in Prehypertension'. *Medicine and Science in Sports and Exercise* 44 (9), 1644–1652

Lohmeier, T.E. and Iliescu, R. (2013) 'The Sympathetic Nervous System in Obesity Hypertension'. *Current Hypertension Reports* 15 (4), 409–416

Lord, S.W., Senior, R.R., Das, M., Whittam, a M., Murray, A., and McComb, J.M. (2001) 'Low-Frequency Heart Rate Variability: Reproducibility in Cardiac Transplant Recipients and Normal Subjects.' *Clinical Science (London, England : 1979)* 100 (1), 43–46

Lucini, D., Mela, G.S., Malliani, A., and Pagani, M. (2002) 'Impairment in Cardiac Autonomic Regulation Preceding Arterial Hypertension in Humans: Insights from Spectral Analysis of Beat-by-Beat Cardiovascular Variability'. *Circulation* 106 (21), 2673–2679

MacDonald, H. V., Johnson, B.T., Huedo-Medina, T.B., Livingston, J., Forsyth, K.C., Kraemer, W.J., Farinatti,

P.T.V., and Pescatello, L.S. (2016) 'Dynamic Resistance Training as Stand-Alone Antihypertensive Lifestyle Therapy: A Meta-Analysis'. *Journal of the American Heart Association* 5 (10), 1–35

Macdonald, J.R. (2002) 'Potential Causes, Mechanisms, and Implications of Post Exercise Hypotension'. *Journal of Human Hypertension* 16 (4), 225–236

Madden, K.M., Levy, W.C., and Stratton, J.R. (2006) 'Exercise Training and Heart Rate Variability in Older Adult Female Subjects'. *Clinical & Investigative Medicine* [online] 29 (1), 20–28. available from <http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=106471574&site=ehost-live>

Maestri, R., Raczak, G., Danilowicz- Szymanowicz, L., Torunski, A., Sukiennik, A., Kubica, J., La Rovere, M.T., and Pinna, G.D. (2010) 'Reliability of Heart Rate Variability Measurements in Patients with a History of Myocardial Infarction'. *Clinical Science (London, England : 1979)* [online] 118 (3), 195–201. available from <http://www.ncbi.nlm.nih.gov/pubmed/20310082>

Malliani, A., Pagani, M., Lombardi, F., and Cerutti, S. (1991) 'Cardiovascular Neural Regulation Explored in the Frequency Domain.' *Circulation* 84 (2), 482–492

Mancia, G., Fagard, R., Wood, D. a. et al. (2013) '2013 ESH/ESC Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)'. *European Heart Journal* 34 (28), 2159–2219

Mancia, G. and Grassi, G. (2014) 'The Autonomic Nervous System and Hypertension'. *Circulation Research* 114 (11), 1804–1814

Mancia, G., Grassi, G., Giannattasio, C., and Seravalle, G. (1999) 'Sympathetic Activation in the Pathogenesis of Hypertension and Progression of Organ Damage.' *Hypertension* 34 (4 Pt 2), 724–728

Mancia, G., Omboni, S., Parati, G., Ravogli, A., Villani, A., and Zanchetti, A. (1995) 'Lack of Placebo Effect on Ambulatory Blood Pressure.' *American Journal of Hypertension* 8 (3), 311–315

Mancia, G., Parati, G., Hennig, M., Flatau, B., Omboni, S., Glavina, F., Costa, B., Scherz, R., Bond, G., and Zanchetti, A. (2001) 'Relation between Blood Pressure Variability and Carotid Artery Damage in Hypertension: Baseline Data from the European Lacidipine Study on Atherosclerosis (ELSA).' *Journal of Hypertension* 19 (11), 1981–1989

Mansoor, G.A., McCabe, E.J., and White, W.B. (1994) 'Long-Term Reproducibility of Ambulatory Blood Pressure.' *Journal of Hypertension* 12 (6), 703–708

Mark, A.L., Victor, R.G., Nerhed, C., and Wallin, B.G. (1985) 'Microneurographic Studies of the Mechanisms of Sympathetic Nerve Responses to Static Exercise in Humans'. *Circulation Research* 57 (3), 461–469

Marriott, H.E. and Lamb, K.L. (1996) 'The Use of Ratings of Perceived Exertion for Regulating Exercise Levels

in Rowing Ergometry'. *European Journal of Applied Physiology and Occupational Physiology* [online] 72 (3), 267–271. available from <http://link.springer.com/10.1007/BF00838650>

Martinez, F.A. (2010) 'Aldosterone Inhibition and Cardiovascular Protection: More Important than It Once Appeared.' *Cardiovascular Drugs and Therapy* 24 (4), 345–350

Massin, M.M., Derkenne, B., and von Bernuth, G. (1999) 'Correlations between Indices of Heart Rate Variability in Healthy Children and Children with Congenital Heart Disease.' *Cardiology* 91 (2), 109–113

Mattace-Raso, F.U.S., van den Meiracker, A.H., Bos, W.J., van der Cammen, T.J.M., Westerhof, B.E., Elias-Smale, S., Reneman, R.S., Hoeks, A.P.G., Hofman, A., and Witteman, J.C.M. (2007) 'Arterial Stiffness, Cardiovagal Baroreflex Sensitivity and Postural Blood Pressure Changes in Older Adults: The Rotterdam Study.' *Journal of Hypertension* 25 (7), 1421–1426

McBryde, F.D., Abdala, A.P., Hendy, E.B., Pijacka, W., Marvar, P., Moraes, D.J.A., Sobotka, P.A., and Paton, J.F.R. (2013) 'The Carotid Body as a Putative Therapeutic Target for the Treatment of Neurogenic Hypertension'. *Nature Communications* 4 (2395)

McCloskey, D.I. and Mitchell, J.H. (1972) 'Reflex Cardiovascular and Respiratory Responses Originating in Exercising Muscle'. *The Journal of Physiology* 224 (1), 173–186

McGowan, C.L., Levy, A.S., McCartney, N., and MacDonald, M.J. (2007) 'Isometric Handgrip Training Does Not Improve Flow-Mediated Dilation in Subjects with Normal Blood Pressure.' *Clinical Science (London, England : 1979)* 112 (7), 403–409

McGowan, C.L., Levy, A.S., Millar, P.J., Guzman, J.C., Morillo, C. a, McCartney, N., and Macdonald, M.J. (2006) 'Acute Vascular Responses to Isometric Handgrip Exercise and Effects of Training in Persons Medicated for Hypertension.' *American Journal of Physiology. Heart and Circulatory Physiology* 291 (4), H1797–H1802

McGowan, C.L., Proctor, D.N., Swaine, I., Brook, R.D., Jackson, E.A., and Levy, P.D. (2017) 'Isometric Handgrip as an Adjunct for Blood Pressure Control: A Primer for Clinicians'. *Current Hypertension Reports* [online] 19 (6), 51. available from <http://link.springer.com/10.1007/s11906-017-0748-8>

McGowan, C.L., Visocchi, A., Faulkner, M., Verduyn, R., Rakobowchuk, M., Levy, A.S., McCartney, N., and MacDonald, M.J. (2007) 'Isometric Handgrip Training Improves Local Flow-Mediated Dilation in Medicated Hypertensives'. *European Journal of Applied Physiology* 99 (3), 227–234

McKinney, M.E., Miner, M.H., Rüddel, H., McIlvain, H.E., Witte, H., Buell, J.C., Eliot, R.S., and Grant, L.B. (1985) 'The Standardized Mental Stress Test Protocol: Test-Retest Reliability and Comparison with Ambulatory Blood Pressure Monitoring'. *Psychophysiology* [online] 22 (4), 453–463. available from <http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8986.1985.tb01632.x/abstract%5Cnhttp://doi.wiley.com/10.1111/j.1469-8986.1985.tb01632.x>

McMillan, D.E. (2002) 'Interpreting Heart Rate Variability Sleep/Wake Patterns in Cardiac Patients.' *The*

Journal of Cardiovascular Nursing 17 (1), 69–81

Melanson, E.L. and Freedson, P.S. (2001) 'The Effect of Endurance Training on Resting Heart Rate Variability in Sedentary Adult Males'. *European Journal of Applied Physiology* 85 (5), 442–449

de Mello Franco, F.G., Santos, A.C., Rondon, M.U.P., Trombetta, I.C., Strunz, C., Braga, A.M.W., Middlekauff, H., Negrão, C.E., and Pereira Barretto, A.C. (2006) 'Effects of Home-Based Exercise Training on Neurovascular Control in Patients with Heart Failure'. *European Journal of Heart Failure* 8 (8), 851–855

Millar, P.J., Bray, S.R., MacDonald, M.J., and McCartney, N. (2009) 'Cardiovascular Reactivity to Psychophysiological Stressors: Association with Hypotensive Effects of Isometric Handgrip Training.' *Blood Pressure Monitoring* 14 (5), 190–195

Millar, P.J., Bray, S.R., MacDonald, M.J., McCartney, N., Millar PJ, SR, B., MJ, M., and N, M. (2008) 'The Hypotensive Effects of Isometric Handgrip Training Using an Inexpensive Spring Handgrip Training Device.' *Journal of Cardiopulmonary Rehabilitation and Prevention* 28 (3), 203–207

Millar, P.J., Bray, S.R., McGowan, C.L., MacDonald, M.J., McCartney, N., PJ, M., SR, B., CL, M., MJ, M., and N, M. (2007) 'Effects of Isometric Handgrip Training among People Medicated for Hypertension: A Multilevel Analysis'. *Blood Pressure Monitoring* 12 (5), 307–14

Millar, P.J., Cotie, L.M., Amand, T.S., McCartney, N., and Ditor, D.S. (2010) 'Effects of Autonomic Blockade on Nonlinear Heart Rate Dynamics'. *Clinical Autonomic Research* 20 (4), 241–247

Millar, P.J. and Goodman, J.M. (2014) 'Exercise as Medicine: Role in the Management of Primary Hypertension'. *Journal of Applied Physiology, Nutrition and Metabolism* 39 (7), 856–8

Millar, P.J., Levy, a. S., Mcgowan, C.L., Mccartney, N., and Macdonald, M.J. (2013) 'Isometric Handgrip Training Lowers Blood Pressure and Increases Heart Rate Complexity in Medicated Hypertensive Patients'. *Scandinavian Journal of Medicine and Science in Sports* 23 (5), 620–626

Millar, P.J., MacDonald, M.J., Bray, S.R., and McCartney, N. (2009) 'Isometric Handgrip Exercise Improves Acute Neurocardiac Regulation.' *European Journal of Applied Physiology* 107 (5), 509–515

Millar, P.J., McGowan, C.L., Cornelissen, V. a, Araujo, C.G., and Swaine, I.L. (2014) 'Evidence for the Role of Isometric Exercise Training in Reducing Blood Pressure: Potential Mechanisms and Future Directions.' *Sports Medicine (Auckland, N.Z.)* [online] 44 (3), 345–56. available from <http://www.ncbi.nlm.nih.gov/pubmed/24174307>

Millgard, J. and Lind, L. (1998) 'Acute Hypertension Impairs Endothelium-Dependent Vasodilation.' *Clinical Science (London, England : 1979)* 94 (6), 601–607

Mitchell, J., Reeves, D., Rogers, H., Secher, N., and Victor, R. (1989) 'Autonomic Blockade and Cardiovascular Responses to Static Exercise in Partially Curarized Man'. *Journal of Physiology* [online] 413,

433–445. available from <http://doi.wiley.com/10.1111/j.1467-9515.2006.00499.x>

Mitchell, J.H. (2012) 'Neural Control of the Circulation during Exercise: Insights from the 1970-1971 Oxford Studies'. *Experimental Physiology* [online] 97 (1), 14–19. available from <http://doi.wiley.com/10.1113/expphysiol.2011.058156>

Miyachi, M. (2013) 'Effects of Resistance Training on Arterial Stiffness: A Meta-Analysis'. *British Journal of Sports Medicine* 47 (6), 393–396

Miyai, N., Arita, M., Morioka, I., Takeda, S., and Miyashita, K. (2005) 'Ambulatory Blood Pressure, Sympathetic Activity, and Left Ventricular Structure and Function in Middle-Aged Normotensive Men with Exaggerated Blood Pressure Response to Exercise.' *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research* 11 (10), CR478-84

Monahan, K.D., Dinenno, F. a, Tanaka, H., Clevenger, C.M., DeSouza, C. a, and Seals, D.R. (2000) 'Regular Aerobic Exercise Modulates Age-Associated Declines in Cardiovagal Baroreflex Sensitivity in Healthy Men.' *The Journal of Physiology* [online] 529 Pt 1, 263–71. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2270167&tool=pmcentrez&rendertype=abstract>

Montano, N., Lombardi, F., Gnecchi Ruscone, T., Contini, M., Finocchiaro, M.L., Baselli, G., Porta, A., Cerutti, S., and Malliani, A. (1992) 'Spectral Analysis of Sympathetic Discharge, R-R Interval and Systolic Arterial Pressure in Decerebrate Cats.' *Journal of the Autonomic Nervous System* 40 (1), 21–31

Montesi, L., Moscatiello, S., Malavolti, M., Marzocchi, R., and Marchesini, G. (2013) 'Physical Activity for the Prevention and Treatment of Metabolic Disorders'. *Internal and Emergency Medicine* 8 (8), 655–666

Moraes, M.R., Bacurau, R.F.P., Ramalho, J.D.S., Reis, F.C.G., Casarini, D.E., Chagas, J.R., Oliveira, V., Higa, E.M.S., Abdalla, D.S.P., Pesquero, J.L., Pesquero, J.B., and Araujo, R.C. (2007) 'Increase in Kinins on Post-Exercise Hypotension in Normotensive and Hypertensive Volunteers'. *Biological Chemistry* 388 (5), 533–540

De Morais, P., SALES, M.M.M., De Almeida, J., Motta-Santos, D., De Sousa, C., Simoes, H., MORAIS, P.K. DE, SALES, M.M.M., ALMEIDA, J.A. DE, Motta-Santos, D., SOUSA, C.V. DE, GUSTAVO, H., and SIMÕES (2015) 'Effects of Aerobic Exercise Intensity on 24-h Ambulatory Blood Pressure in Individuals with Type 2 Diabetes and Prehypertension'. *Journal of Physical Therapy Science* 27 (1), 51–56

Moreira, S.R., Cucato, G.G., Terra, D.F., and Ritti-Dias, R.M. (2016) 'Acute Blood Pressure Changes Are Related to Chronic Effects of Resistance Exercise in Medicated Hypertensives Elderly Women'. *Clinical Physiology and Functional Imaging* 36 (3), 242–248

Morra, E.A., Zaniqueli, D., Rodrigues, S.L., El-Aouar, L.M., Lunz, W., Mill, J.G., and Carletti, L. (2014) 'Long-Term Intense Resistance Training in Men Is Associated with Preserved Cardiac Structure/Function, Decreased Aortic Stiffness, and Lower Central Augmentation Pressure.' *Journal of Hypertension* 32 (2), 286–293

Morrin, N.M., Stone, M.R., and Henderson, K.J. (2017) 'Reproducibility of 24-h Ambulatory Blood Pressure and Measures of Autonomic Function.' *Blood Pressure Monitoring* 22 (3), 169–172

Mostoufi-Moab, S., Widmaier, E.J., Cornett, J. a, Gray, K., and Sinoway, L.I. (1998) 'Forearm Training Reduces the Exercise Pressor Reflex during Ischemic Rhythmic Handgrip.' *Journal of Applied Physiology (Bethesda, Md. : 1985)* 84 (1), 277–283

Mota, M., Oliveira, R., Dutra, M., Pardono, E., Terra, D., Lima, R., Simoes, H., and Da Silva, F. (2013) 'Acute and Chronic Effects of Resistive Excercise on Blood Pressure in Hypertensive Elderly Women'. *Journal of Strength and Conditioning Research* 27 (12), 3475–80

Muller, J. and Barajas, L. (1972) 'Electron Microscopic and Histochemical Evidence for a Tubular Innervation in the Renal Cortex of the Monkey.' *Journal of Ultrastructure Research* 41 (5), 533–549

Musini, V.M. and Wright, J.M. (2009) 'Factors Affecting Blood Pressure Variability : Lessons Learned from Two Systematic Reviews of Randomized Controlled Trials'. *PLoS ONE* 4 (5), 1–6

Mussalo, H., Vanninen, E., Ikäheimo, R., Laitinen, T., and Hartikainen, J. (2003) 'Short-Term Blood Pressure Variability in Renovascular Hypertension and in Severe and Mild Essential Hypertension.' *Clinical Science (London, England : 1979)* 105 (5), 609–614

Mussalo, H., Vanninen, E., Ikaheimo, R., Laitinen, T., Laakso, M., Lansimies, E., and Hartikainen, J. (2002) 'Baroreflex Sensitivity in Essential and Secondary Hypertension.' *Clinical Autonomic Research* 12 (6), 465–471

Mussalo, H., Vanninen, E., Ikäheimo, R., Laitinen, T., Laakso, M., Länsimies, E., and Hartikainen, J. (2001) 'Heart Rate Variability and Its Determinants in Patients with Severe or Mild Essential Hypertension'. *Clinical Physiology* 21 (5), 594–604

Musso, N.R., Vergassola, C., Barone, C., and Lotti, G. (1997) 'Ambulatory Blood Pressure Monitoring: How Reproducible Is It?' *American Journal of Hypertension* 10 (8), 936–939

Nam, S., Dobrosielski, D.A., and Stewart, K.J. (2012) 'Predictors of Exercise Intervention Dropout in Sedentary Individuals with Type 2 Diabetes'. *Journal of Cardiopulmonary Rehabilitation and Prevention* 32 (6), 370–378

Narkiewicz, K. and Somers, V.K. (1999) 'Obstructive Sleep Apnea as a Cause of Neurogenic Hypertension.' *Current Hypertension Reports* 1 (3), 268–273

Navar, L.G. (2010) 'Last Word on Counterpoint: Activation of the Intrarenal Renin-Angiotensin System Is the Dominant Contributor to Systemic Hypertension.' *Journal of Applied Physiology (Bethesda, Md. : 1985)* 109, 2015

Navar, L.G., Imig, J.D., Zou, L., and Wang, C.T. (1997) 'Intrarenal Production of Angiotensin II.' *Seminars in*

Nephrology 17 (5), 412–422

Navar, L.G., Kobori, H., and Prieto-Carrasquero, M. (2003) 'Intrarenal Angiotensin II and Hypertension.' *Current Hypertension Reports* 5 (2), 135–143

Newton-Cheh, C., Larson, M.G., Vasan, R.S., Bloch, K.D., Surti, A., Guiducci, C., and Kathiresan, S. (2012) 'Europe PMC Funders Group Association of Common Variants in NPPA and NPPB with Circulating Natriuretic Peptides and Blood Pressure'. *Nature Genetics* 41 (3), 348–353

NICE (2011) *Hypertension - Clinical Management of Primary Hypertension in Adults*.

Niebauer, J. and Cooke, J.P. (1997) 'Cardiovascular Effects of Exercise: Role of Endothelial Shear Stress'. *Journal of the American College of Cardiology* [online] 28 (7), 1652–1660. available from <http://dx.doi.org/10.1016/S0735-1097(96)00393-2>

Niemela, T.H., Kiviniemi, A.M., Hautala, A.J., Salmi, J.A., Linnamo, V., and Tulppo, M.P. (2008) 'Recovery Pattern of Baroreflex Sensitivity after Exercise'. *Medicine and Science in Sports and Exercise* 40 (5), 864–870

Nobel, B.J. and Robertson, R.J. (1996) *Perceived Exertion*. Champaign, Illinois: Human Kinetics

Nobre, T., Groehs, R., Azevedo, L., Antunes-Correa, L., Martinez, D., Alves, M., and Negrao, C. (2016) 'Post-Exercise Neurovascular Control in Chronic Heart Failure Patients'. *International Journal of Sports Medicine* [online] 37 (13), 1073–1079. available from <http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/498/CN-01342498/frame.html>

Nobrega, A.C.L., Leary, D.O., Silva, B.M., Marongiu, E., Piepoli, M.F., and Crisafulli, A. (2014) 'Neural Regulation of Cardiovascular Response to Exercise : Role of Central Command and Peripheral Afferents'. *BioMed Research International*

Nojima, H., Watanabe, H., Yamane, K., Kitahara, Y., Sekikawa, K., Yamamoto, H., Yokoyama, A., Inamizu, T., Asahara, T., and Kohno, N. (2008) 'Effect of Aerobic Exercise Training on Oxidative Stress in Patients with Type 2 Diabetes Mellitus.' *Metabolism: Clinical and Experimental* 57 (2), 170–176

O'Brien, E., Asmar, R., Beilin, L., Imai, Y., Mallion, J.M., Mancia, G., Mengden, T., Myers, M., Padfield, P., Palatini, P., Parati, G., Pickering, T., Redon, J., Staessen, J., Stergiou, G., and Verdecchia, P. (2003) 'European Society of Hypertension Recommendations for Conventional, Ambulatory and Home Blood Pressure Measurement'. *Journal of Hypertension* [online] 21 (5), 821–848. available from <http://www.ncbi.nlm.nih.gov/pubmed/12714851>

O'Connor, P., Sforzo, G.A., and Frye, P. (1989) 'Effect of Breathing Instruction on Blood Pressure Responses during Isometric Exercise.' *Physical Therapy* 69 (9), 757–761

O'Connor, P.J., Poudevigne, M.S., and Pasley, J.D. (2002) 'Perceived Exertion Responses to Novel Elbow Flexor Eccentric Action in Women and Men'. *Medicine and Science in Sports and Exercise* 34 (5), 862–868

Ogoh, S., Fisher, J.P., Dawson, E.A., White, M.J., Secher, N.H., and Raven, P.B. (2005) 'Autonomic Nervous System Influence on Arterial Baroreflex Control of Heart Rate during Exercise in Humans'. *The Journal of Physiology* [online] 566 (2), 599–611. available from <http://doi.wiley.com/10.1113/jphysiol.2005.084541>

Ohta, Y., Tsuchihashi, T., and Kiyohara, K. (2011) 'Relationship between Blood Pressure Control Status and Lifestyle in Hypertensive Outpatients'. *Internal Medicine* [online] 50 (19), 2107–2112. available from <http://joi.jlc.jst.go.jp/JST.JSTAGE/internalmedicine/50.5321?from=CrossRef>

Okada, Y., Galbreath, M.M., Shibata, S., Jarvis, S.S., Vangundy, T.B., Meier, R.L., Vongpatanasin, W., Levine, B.D., and Fu, Q. (2012) 'Relationship between Sympathetic Baroreflex Sensitivity and Arterial Stiffness in Elderly Men and Women'. *Hypertension* 59 (1), 98–104

Olher, R.D.R.V., Bocalini, D.S., Bacurau, R.F., Rodriguez, D., Figueira, A., Pontes, F.L., Navarro, F., Simões, H.G., Araujo, R.C., and Moraes, M.R. (2013) 'Isometric Handgrip Does Not Elicit Cardiovascular Overload or Post-Exercise Hypotension in Hypertensive Older Women'. *Clinical Interventions in Aging* 8, 649–655

Omboni, S., Parati, G., Frattola, A., Mutti, E., Di Rienzo, M., Castiglioni, P., and Mancia, G. (1993) 'Spectral and Sequence Analysis of Finger Blood Pressure Variability. Comparison with Analysis of Intra-Arterial Recordings.' *Hypertension* 22 (1), 26–33

Onwochei, M.O. and Rapp, J.P. (1989) 'Hyposecretion of Atrial Natriuretic Factor by Prehypertensive Dahl Salt-Sensitive Rat.' *Hypertension* 13 (5), 440–448

Oparil, S., Zaman, M.A., and Calhoun, D.A. (2003) 'Pathogenesis of Hypertension'. *Annals of Internal Medicine* 139 (9), 761–776

Optimity Matrix (2014) *Cost-Effectiveness Review of Blood Pressure Interventions*. (November)

Pacurari, M., Kafoury, R., Tchounwou, P.B., and Ndebele, K. (2014) 'The Renin-Angiotensin-Aldosterone System in Vascular Inflammation and Remodeling'. *International Journal of Inflammation* 2014

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., and Piccaluga, E. (1986) 'Power Spectral Analysis of Heart Rate and Arterial Pressure Variabilities as a Marker of Sympatho-Vagal Interaction in Man and Conscious Dog.' *Circulation Research* 59 (2), 178–193

Pagani, M., Lombardi, F., Guzzetti, S., Sandrone, G., Rimoldi, O., Malfatto, G., Cerutti, S., and Malliani, A. (1984) 'Power Spectral Density of Heart Rate Variability as an Index of Sympatho-Vagal Interaction in Normal and Hypertensive Subjects.' *Journal of Hypertension. Supplement : Official Journal of the International Society of Hypertension* 2 (3), S383-5

Pagani, M., Montano, N., Porta, A., Malliani, A., Abboud, F.M., Birkett, C., and Somers, V.K. (1997) 'Relationship between Spectral Components of Cardiovascular Variabilities and Direct Measures of Muscle Sympathetic Nerve Activity in Humans.' *Circulation* 95 (6), 1441–1448

Pagonas, N., Vlatsas, S., Bauer, F., Seibert, F.S., Zidek, W., Babel, N., Schlattmann, P., and Westhoff, T.H. (2017) 'Aerobic versus Isometric Handgrip Exercise in Hypertension: A Randomized Controlled Trial.' *Journal of Hypertension* 35 (11), 2199–2206

Palatini, P., Penzo, M., Racioppa, A., Zugno, E., Guzzardi, G., Anaclerio, M., and Pessina, A.C. (1992) 'Clinical Relevance of Nighttime Blood Pressure and of Daytime Blood Pressure Variability.' *Archives of Internal Medicine* 152 (9), 1855–1860

Palmer, R.M., Ashton, D.S., and Moncada, S. (1988) 'Vascular Endothelial Cells Synthesize Nitric Oxide from L-Arginine.' *Nature* 333 (6174), 664–666

Panza, J.A., Casino, P.R., Kilcoyne, C.M., and Quyyumi, A.A. (1993) 'Role of Endothelium-Derived Nitric Oxide in the Abnormal Endothelium-Dependent Vascular Relaxation of Patients with Essential Hypertension.' *Circulation* 87 (5), 1468–1474

Pappano, A. and Wier, W.G. (2013) *Cardiovascular Physiology: Mosby Physiology Monograph Series*. 10th edn. ed. by Pappano, A.J. and Wier, W.G. Philadelphia: Elsevier Inc.

Parati, G., Ochoa, J.E., Lombardi, C., and Bilo, G. (2013) 'Assessment and Management of Blood-Pressure Variability.' *Nature Reviews. Cardiology* [online] 10 (3), 143–55. available from <http://www.nature.com/nrcardio/journal/v10/n3/full/nrcardio.2013.1.html>

Parati, G., Omboni, S., Villani, A., Glavina, F., Castiglioni, P., Di Rienzo, M., and Mancia, G. (2001) 'Reproducibility of Beat-by-Beat Blood Pressure and Heart Rate Variability.' *Blood Pressure Monitoring* 6 (4), 217–220

Parati, G., Pomidossi, G., Albini, F., Malaspina, D., and Mancia, G. (1987) 'Relationship of 24-h Blood Pressure Mean and Variability to Severity of Target Organ Damage in Hypertension'. *Journal of Hypertension* 5 (1), 93–98

Parati, G., Di Rienzo, M., Bertinieri, G., Pomidossi, G., Casadei, R., Groppelli, a, Pedotti, a, Zanchetti, a, and Mancia, G. (1988) 'Evaluation of the Baroreceptor-Heart Rate Reflex by 24-Hour Intra-Arterial Blood Pressure Monitoring in Humans.' *Hypertension* 12 (2), 214–222

Parati, G., Saul, J.P., Di Rienzo, M., and Mancia, G. (1995) 'Spectral Analysis of Blood Pressure and Heart Rate Variability in Evaluating Cardiovascular Regulation : A Critical Appraisal'. *Hypertension* [online] 25 (6), 1276–1286. available from <http://hyper.ahajournals.org/cgi/content/long/25/6/1276> [11 March 2015]

Parfitt, G., Evans, H., and Eston, R. (2012) 'Perceptually Regulated Training at RPE 13 Is Pleasant and Improves Physical Health'. *Medicine & Science in Sports & Exercise* [online] 44 (8), 1613–1618. available from <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005768-201208000-00026>

Park, S., Rink, L.D., and Wallace, J.P. (2006) 'Accumulation of Physical Activity Leads to a Greater Blood Pressure Reduction than a Single Continuous Session, in Prehypertension.' *Journal of Hypertension* 24 (9),

1761–1770

Paton, J.F.R., Ratcliffe, L., Hering, D., Wolf, J., Sobotka, P. a., and Narkiewicz, K. (2013) 'Revelations about Carotid Body Function through Its Pathological Role in Resistant Hypertension'. *Current Hypertension Reports* 15 (4), 273–280

Paulson, T. a. W., Bishop, N.C., Leicht, C. a., and Goosey-Tolfrey, V.L. (2013) 'Perceived Exertion as a Tool to Self-Regulate Exercise in Individuals with Tetraplegia'. *European Journal of Applied Physiology* [online] 113 (1), 201–209. available from <http://link.springer.com/10.1007/s00421-012-2426-5>

Pescatello, L.S., Franklin, B. a, Fagard, R., Farquhar, W.B., Kelley, G. a, and Ray, C. a (2004a) 'American College of Sports Medicine Position Stand. Exercise and Hypertension.' *Medicine and Science in Sports and Exercise* 36 (3), 533–553

Pescatello, L.S., Franklin, B. a, Fagard, R., Farquhar, W.B., Kelley, G. a, and Ray, C. a (2004b) 'Exercise and Hypertension.' *Medicine and Science in Sports and Exercise* 36 (3), 533–553

Pescatello, L.S. and Kulikowich, J.M. (2001) 'The after Effects of Dynamic Exercise on Ambulatory Blood Pressure'. *Medicine and Science in Sports and Exercise* [online] 33 (11), 1855–1861. available from <http://www.ncbi.nlm.nih.gov/pubmed/11689735>

Pescatello, L.S., Macdonald, H. V, Lamberti, L., and Johnson, B.T. (2015) 'Exercise for Hypertension : A Prescription Update Integrating Existing Recommendations with Emerging Research'. *Current Hypertension Reports* 17 (11), 87–97

Peters, P.G., Alessio, H.M., Hagerman, A.E., Ashton, T., Nagy, S., and Wiley, R.L. (2006) 'Short-Term Isometric Exercise Reduces Systolic Blood Pressure in Hypertensive Adults: Possible Role of Reactive Oxygen Species'. *International Journal of Cardiology* 110 (2), 199–205

Pickering, T.G., Hall, J.E., Appel, L.J., Falkner, B.E., Graves, J.W., Hill, M.N., Jones, D.H., Kurtz, T., Sheps, S.G., and Roccella, E.J. (2005) 'Recommendations for Blood Pressure Measurement in Humans: An AHA Scientific Statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee.' *Journal of Clinical Hypertension (Greenwich, Conn.)* 7 (2), 102–109

Piepoli, M.F., Hoes, A.W., Gale, C. et al. (2016) '2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice'. *European Heart Journal* 37 (29), 2315–2381

Pierce, G.L., Harris, S.A., Seals, D.R., Casey, D.P., Barlow, P.B., and Stauss, H.M. (2016) 'Estimated Aortic Stiffness Is Independently Associated with Cardiac Baroreflex Sensitivity in Humans: Role of Aging and Habitual Endurance Exercise'. *Journal of Human Hypertension* [online] 30 (9), 513–520. available from <http://www.nature.com/authors/editorial_policies/license.html#terms>

Pigozzi, F., Alabiso, A., Parisi, A., Di Salvo, V., Di Luigi, L., Spataro, A., and Iellamo, F. (2001) 'Effects of Aerobic Exercise Training on 24 Hr Profile of Heart Rate Variability in Female Athletes.' *The Journal of Sports Medicine and Physical Fitness* 41 (1), 101–107

Pincivero, D.., Coelho, A.., and Erikson, W.. (2000) 'Perceived Exertion during Isometric Quadriceps Contraction'. *Journal of Sports Medicine and Physical Fitness* 40 (4), 319–326

Pincivero, D. and Gear, W. (2000) 'Quadriceps Activation and Perceived Exertion during a High Intensity, Steady State Contraction to Failure'. *Muscle Nerve* 23 (4), 514–520

Pinna, G.D., Maestri, R., La Rovere, M.T., Gobbi, E., and Fanfulla, F. (2006) 'Effect of Paced Breathing on Ventilatory and Cardiovascular Variability Parameters during Short-Term Investigations of Autonomic Function.' *American Journal of Physiology. Heart and Circulatory Physiology* 290 (1), H424–H433

Pinna, G.D., Maestri, R., Torunski, A., Danilowicz-Szymanowicz, L., Szwoch, M., La Rovere, M.T., and Raczak, G. (2007) 'Heart Rate Variability Measures: A Fresh Look at Reliability.' *Clinical Science (London, England : 1979)* 113 (3), 131–140

Pinto, E. (2007) 'Blood Pressure and Ageing'. *Postgraduate Medical Journal* [online] 83 (976), 109–114. available from <http://pmj.bmj.com/cgi/doi/10.1136/pgmj.2006.048371>

Pitzalis, M. V, Mastropasqua, F., Massari, F., Forleo, C., Di Maggio, M., Passantino, A., Colombo, R., Di Biase, M., and Rizzon, P. (1996) 'Short- and Long-Term Reproducibility of Time and Frequency Domain Heart Rate Variability Measurements in Normal Subjects.' *Cardiovascular Research* 32 (96), 226–233

Plews, D.J., Laursen, P.B., Stanley, J., Kilding, A.E., and Buchheit, M. (2013) 'Training Adaptation and Heart Rate Variability in Elite Endurance Athletes: Opening the Door to Effective Monitoring'. *Sports Medicine* 43 (9), 773–781

Pohl, U., Holtz, J., Busse, R., and Bassenge, E. (1986) 'Crucial Role of Endothelium in the Vasodilator Response to Increased Flow in Vivo.' *Hypertension (Dallas, Tex. : 1979)* 8 (1), 37–44

Ponikowski, P., Piepoli, M., Amadi, A.A., Chua, T.P., Harrington, D., Volterrani, M., Colombo, R., Mazzuero, G., Giordano, A., and Coats, A.J. (1996) 'Reproducibility of Heart Rate Variability Measures in Patients with Chronic Heart Failure.' *Clinical Science (London, England : 1979)* 91 (4), 391–398

Potts, J.T., Shi, X.R., and Raven, P.B. (1993) 'Carotid Baroreflex Responsiveness during Dynamic Exercise in Humans.' *The American Journal of Physiology* 265 (6 Pt 2), H1928-38

Prince, S.A., Adamo, K.B., Hamel, M.E., Hardt, J., Connor Gorber, S., and Tremblay, M. (2008) 'A Comparison of Direct versus Self-Report Measures for Assessing Physical Activity in Adults: A Systematic Review'. *International Journal of Behavioral Nutrition and Physical Activity* 5 (56), 1–24

Queiroz, A.C.C., Sousa, J.C.S., Cavalli, A.A.P., Jr, N.D.S., Costa, L.A.R., Tobaldini, E., Montano, N., Silva, G. V, Ortega, K., Jr, D.M., Tinucci, T., and Forjaz, C.L.M. (2015) 'Post-Resistance Exercise Hemodynamic and Autonomic Responses : Comparison between Normotensive and Hypertensive Men'. *Scandinavian Journal of Medicine and Science in Sports* 25 (4), 486–494

Rajpura, J. and Nayak, R. (2014) 'Medication Adherence in a Sample of Elderly Suffering from Hypertension: Evaluating the Influence of Illness Perceptions, Treatment Beliefs, and Illness Burden.' *Journal of Managed Care Pharmacy : JMCP* 20 (1), 58–65

Rand, D., Eng, J.J., Tang, P.F., Jeng, J.S., and Hung, C. (2009) 'How Active Are People with Stroke?: Use of Accelerometers to Assess Physical Activity.' *Stroke* 40 (1), 163–168

Raven, P.B., Fadel, P.J., and Ogoh, S. (2006) 'Arterial Baroreflex Resetting during Exercise: A Current Perspective.' *Experimental Physiology* 91 (1990), 37–49

Ray, C. and Carrasco, D. (2000) 'Isometric Handgrip Training Reduces Arterial Pressure at Rest without Changes in Sympathetic Nerve Activity.' *American Journal of Physiology. Heart and Circulatory Physiology* 279 (1), H245–H249

Reino-González, S., Pita-Fernández, S., Cibiriain-Sola, M., Seoane-Pillado, T., López-Calviño, B., Pértega-Díaz, S., Reino-Gonzalez, S., Pita-Fernandez, S., Cibiriain-Sola, M., Seoane-Pillado, T., Lopez-Calvino, B., Pertega-Diaz, S., Reino-González, S., Pita-Fernández, S., Cibiriain-Sola, M., Seoane-Pillado, T., López-Calviño, B., and Pértega-Díaz, S. (2015) 'Validity of Clinic Blood Pressure Compared to Ambulatory Monitoring in Hypertensive Patients in a Primary Care Setting'. *Blood Pressure* [online] 24 (2), 111–118. available from <http://informahealthcare.com/doi/abs/10.3109/08037051.2014.992197>

Remaley, D.T., Fincham, B., McCullough, B., Davis, K., Nofsinger, C., Armstrong, C., and Stausmire, J.M. (2015) 'Surface Electromyography of the Forearm Musculature during the Windmill Softball Pitch'. *Orthopaedic Journal of Sports Medicine* [online] 3 (1), 1–8. available from <http://ojs.sagepub.com/cgi/content/long/3/1/2325967114566796>

Rezk, C.C., Marrache, R.C.B., Tinucci, T., Mion, D.J., and Forjaz, C.L.M. (2006) 'Post-Resistance Exercise Hypotension, Hemodynamics, and Heart Rate Variability: Influence of Exercise Intensity.' *European Journal of Applied Physiology* 98 (1), 105–112

Riegel, G., Moreira, L.B., Fuchs, S.C., Gus, M., Nunes, G., Correa, V., Wiehe, M., Gon??alves, C.C., Fernandes, F.S., and Fuchs, F.D. (2012) 'Long-Term Effectiveness of Non-Drug Recommendations to Treat Hypertension in a Clinical Setting'. *American Journal of Hypertension* 25 (11), 1202–1208

Rimoldi, S.F., Scherrer, U., and Messerli, F.H. (2014) 'Secondary Arterial Hypertension: When, Who, and How to Screen?' *European Heart Journal* 35 (19), 1245–1254

Rivera-Brown, A.M. and Frontera, W.R. (2012) 'Principles of Exercise Physiology: Responses to Acute Exercise and Long-Term Adaptations to Training'. *The Journal of Injury, Function and Rehabilitation* 4 (11), 797–804

Roberts, H.C., Denison, H.J., Martin, H.J., Patel, H.P., Syddall, H., Cooper, C., and Sayer, A.A. (2011) 'A Review of the Measurement of Grip Strength in Clinical and Epidemiological Studies: Towards a Standardised Approach'. *Age and Ageing* [online] 40 (4), 423–429. available from <http://www.ageing.oxfordjournals.org/cgi/doi/10.1093/ageing/afr051>

Rodrigo, R., Prat, H., Passalacqua, W., Araya, J., Guichard, C., and Bachler, J.P. (2007) 'Relationship between Oxidative Stress and Essential Hypertension.' *Hypertension Research : Official Journal of the Japanese Society of Hypertension* 30 (12), 1159–1167

Rogatzki, M.J., Wright, G.A., Mikat, R.P., and Brice, A.G. (2014) 'Blood Ammonium and Lactate Accumulation Response to Different Training Protocols Using the Parallel Squat Exercise.' *Journal of Strength and Conditioning Research* 28 (4), 1113–1118

Rossow, L.M., Fahs, C.A., Thiebaud, R.S., Loenneke, J.P., Kim, D., Mouser, J.G., Shore, E.A., Beck, T.W., Bemben, D.A., and Bemben, M.G. (2014) 'Arterial Stiffness and Blood Flow Adaptations Following Eight Weeks of Resistance Exercise Training in Young and Older Women'. *Experimental Gerontology* [online] 53, 48–56. available from <http://dx.doi.org/10.1016/j.exger.2014.02.010>

Rothwell, P.M., Howard, S.C., Dolan, E., Brien, E.O., Dobson, J.E., Dahlöf, B., Sever, P.S., and Poulter, N.R. (2010) 'Prognostic Significance of Visit-to-Visit Variability, Maximum Systolic Blood Pressure, and Episodic Hypertension'. *The Lancet* [online] 375 (9718), 895–905. available from <http://dx.doi.org/10.1016/S0140-6736(10)60308-X>

Routledge, F.S., Campbell, T.S., McFetridge-Durdle, J. a, and Bacon, S.L. (2010) 'Improvements in Heart Rate Variability with Exercise Therapy'. *Canadian Journal of Cardiology* [online] 26 (6), 303–312. available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2903986&tool=pmcentrez&rendertype=abstract%5Cnhttp://linkinghub.elsevier.com/retrieve/pii/S0828282X10703950>

Roveda, F., Middlekauff, H.R., Rondon, M.U.P.B., Reis, S.F., Souza, M., Nastari, L., Barretto, A.C.P., Krieger, E.M., and Negrão, C.E. (2003) 'The Effects of Exercise Training on Sympathetic Neural Activation in Advanced Heart Failure: A Randomized Controlled Trial'. *Journal of the American College of Cardiology* 42 (5), 854–860

Row, B.S., Knutzen, K.M., and Skogsberg, N.J. (2012) 'Regulating Explosive Resistance Training Intensity Using the Rating of Perceived Exertion.' *Journal of Strength and Conditioning Research* 26 (3), 664–671

Ryan, R.M., Fredrick, C.M., Lepes, D., Rubio, N., and Sheldon, K.M. (1997) 'Intrinsic Motivation and Exercise Adherence'. *International Journal of Sport Psychology* 28 (4), 335–354

Sacre, J.W., Jellis, C.L., Marwick, T.H., and Coombes, J.S. (2012) 'Reliability of Heart Rate Variability in Patients with Type 2 Diabetes Mellitus'. *Diabetic Medicine* 29 (7), 33–40

Sagnella, G.A., Markandu, N.D., Buckley, M.G., Miller, M.A., Singer, D.R., Cappuccio, F.P., and MacGregor, G.A. (1991) 'Atrial Natriuretic Peptides in Essential Hypertension: Basal Plasma Levels and Relationship to Sodium Balance.' *Canadian Journal of Physiology and Pharmacology* 69 (10), 1592–1600

Saito, Y., Nakao, K., Mukoyama, M., and Imura, H. (1990) 'Increased Plasma Endothelin Level in Patients with Essential Hypertension.' in *The New England Journal of Medicine*. vol. 322 (3). 205

Sandercock, Bromley, P.D., and Brodie, D.A. (2005) 'The Reliability of Short-Term Measurements of Heart

Rate Variability'. *International Journal of Cardiology* 103 (3), 238–247

Sandercock, G.R., Bromley, P.D., and Brodie, D.A. (2005) 'Effects of Exercise on Heart Rate Variability: Inferences from Meta-Analysis'. *Medicine and Science in Sports and Exercise* 37 (3), 433–439

Santa-Clara, H., Szymanski, L., and Fernhall, B. (2003) 'Effect of Exercise Training on Blood Pressure in Postmenopausal Caucasian and African-American Women'. *The American Journal of Cardiology* [online] 91 (8), 1009–1011. available from <http://linkinghub.elsevier.com/retrieve/pii/S0002914903001280>

Santos, L.P., Moraes, R.S., Vieira, P.J.C., Ash, G.I., Waclawovsky, G., Pescatello, L.S., and Umpierre, D. (2016) 'Effects of Aerobic Exercise Intensity on Ambulatory Blood Pressure and Vascular Responses in Resistant Hypertension: A Crossover Trial.' *Journal of Hypertension* 34 (7), 1317–1324

Saul, J.P., Berger, R.D., Albrecht, P., Stein, S.P., Chen, M.H., and Cohen, R.J. (1991) 'Transfer Function Analysis of the Circulation: Unique Insights into Cardiovascular Regulation.' *The American Journal of Physiology* 261 (4 Pt 2), H1231–H1245

Scherr, J., Wolfarth, B., Christle, J.W., Pressler, A., Wagenpfeil, S., and Halle, M. (2013) 'Associations between Borg's Rating of Perceived Exertion and Physiological Measures of Exercise Intensity'. *European Journal of Applied Physiology* 113 (1), 147–155

Schiffrin, E.L., St-Louis, J., and Essiambre, R. (1988) 'Platelet Binding Sites and Plasma Concentration of Atrial Natriuretic Peptide in Patients with Essential Hypertension.' *Journal of Hypertension* 6 (7), 565–572

Schmidt, J.A., Gruman, C., King, M.B., and Wolfson, L.I. (2000) 'Attrition in an Exercise Intervention: A Comparison of Early and Later Dropouts.' *Journal of the American Geriatrics Society* 48 (8), 952–960

Schmidt, J.F., Hansen, P.R., Andersen, T.R., Andersen, L.J., Hornstrup, T., Krustrup, P., and Bangsbo, J. (2014) 'Cardiovascular Adaptations to 4 and 12 Months of Football or Strength Training in 65- to 75-Year-Old Untrained Men.' *Scandinavian Journal of Medicine & Science in Sports* 24 (Suppl 1), 86–97

Schultz, H.D. (2011) 'Angiotensin and Carotid Body Chemoreception in Heart Failure'. *Current Opinion in Pharmacology* 11 (2), 144–149

Schultz, H.D., Li, Y.L., and Ding, Y. (2007) 'Arterial Chemoreceptors and Sympathetic Nerve Activity: Implications for Hypertension and Heart Failure'. *Hypertension* 50 (1), 6–13

Schultz, M.G. and Sharman, J.E. (2013) 'Exercise Hypertension'. *Pulse* [online] 1 (3–4), 161–176. available from <http://www.karger.com?doi=10.1159/000360975>

Schutte, A., Huisman, H., van Rooyen, J., Malan, N., and Schutte, R. (2004) 'Validation of the Finometer Device for Measurement of Blood Pressure in Black Women.' *Journal of Human Hypertension* 18 (2), 79–84

Seals, D.R. and Reiing, M.J. (1991) 'Effect of Regular Exercise on 24-Hour Arterial Pressure in Older Hypertensive Humans.' *Hypertension* [online] 18 (5), 583–92. available from <http://www.ncbi.nlm.nih.gov/pubmed/1937660>

Seals, D.R., Tanaka, H., Clevenger, C.M., Monahan, K.D., Reiling, M.J., Hiatt, W.R., Davy, K.P., and DeSouza, C.A. (2001) 'Blood Pressure Reductions with Exercise and Sodium Restriction in Postmenopausal Women with Elevated Systolic Pressure: Role of Arterial Stiffness'. *Journal of the American College of Cardiology* [online] 38 (2), 506–513. available from <http://dx.doi.org/10.1016/S0735-1097(01)01348-1>

Sesso, H.D., Stampfer, M.J., Rosner, B., Hennekens, C.H., Gaziano, J.M., Manson, J.E., and Glynn, R.J. (2000) 'Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease Risk in Men'. *Hypertension* [online] 36 (5), 801–807. available from <http://hyper.ahajournals.org/cgi/doi/10.1161/01.HYP.36.5.801>

Shaffer, F., Mccraty, R., Zerr, C.L., and Medical, D.V. a (2014) 'A Healthy Heart Is Not a Metronome: An Integrative Review of the Heart ' s Anatomy and Heart Rate Variability'. *Frontiers in Physiology* 5 (1040), 1–19

Sheriff, D.D., O'Leary, D.S., Scher, A.M., and Rowell, L.B. (1990) 'Baroreflex Attenuates Pressor Response to Graded Muscle Ischemia in Exercising Dogs.' *The American Journal of Physiology* 258 (2 Pt 2), H305-10

Singh, J.P., Larson, M.G., Tsuji, H., Evans, J.C., O'Donnell, C.J., and Levy, D. (1998) 'Reduced Heart Rate Variability and New-Onset Hypertension: Insights into Pathogenesis of Hypertension: The Framingham Heart Study.' *Hypertension* 32 (2), 293–297

Sinnreich, R., Kark, J.D., Friedlander, Y., Sapoznikov, D., and Luria, M.H. (1998) 'Five Minute Recordings of Heart Rate Variability for Population Studies: Repeatability and Age-Sex Characteristics.' *Heart (British Cardiac Society)* 80 (2), 156–162

Smith, M.L. and Pacchia, C.F. (2007) 'Sleep Apnoea and Hypertension: Role of Chemoreflexes in Humans.' *Experimental Physiology* 92 (1), 45–50

Smith, S.A. (2010) 'Exercise in Hypertension: Do Skeletal Muscle Reflexes Make This a Dangerous Proposition?' *American Journal of Physiology. Heart and Circulatory Physiology* 299 (5), H1302–H1303

Smolander, J., Aminoff, T., Korhonen, I., Tervo, M., Shen, N., Korhonen, O., and Louhevaara, V. (1998) 'Heart Rate and Blood Pressure Responses to Isometric Exercise in Young and Older Men'. *European Journal of Applied Physiology and Occupational Physiology* 77 (5), 439–444

Somani, Y., Baross, A., Levy, P., Zinszer, K., Milne, K., Swaine, I., and McGowan, C. (2017) 'Reductions in Ambulatory Blood Pressure in Young Normotensive Men and Women after Isometric Resistance Training and Its Relationship with Cardiovascular Reactivity.' *Blood Pressure Monitoring* 22 (1), 1–7

Somers, V.K., Mark, a L., and Abboud, F.M. (1988) 'Potentiation of Sympathetic Nerve Responses to Hypoxia in Borderline Hypertensive Subjects.' *Hypertension* 11 (6 Pt 2), 608–612

Soriano-Maldonado, A., Romero, L., Femia, P., Roero, C., Ruiz, J., and Gutierrez, A. (2013) 'A Learning Protocol Improves the Validity of the Borg 6–20 RPE Scale during Indoor Cycling'. *International Journal of Sports Medicine* [online] 35 (5), 379–384. available from <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0033-1353166>

Sosner, P., Guiraud, T., Gremeaux, V., Arvisais, D., Herpin, D., and Bosquet, L. (2017) 'The Ambulatory Hypotensive Effect of Aerobic Training: A Reappraisal through a Meta-Analysis of Selected Moderators'. *Scandinavian Journal of Medicine and Science in Sports* 27 (3), 327–341

Stafford, R.W., Harris, W.S., and Weissler, A.M. (1970) 'Left Ventricular Systolic Time Intervals as Indices of Postural Circulatory Stress in Man.' *Circulation* 41 (3), 485–492

Stanley, J., Peake, J.M., and Buchheit, M. (2013) 'Cardiac Parasympathetic Reactivation Following Exercise: Implications for Training Prescription'. *Sports Medicine* 43 (12), 1259–1277

van der Steen, M., Lenders, J., Graafsma, S., Arend, J. den, Thien, T., den Arend, J., and Thien, T. (1999) 'Reproducibility of Ambulatory Blood Pressure Monitoring in Daily Practice'. *Journal of Human Hypertension* 13 (5), 303–308

Stergiou, G., Alamara, C., Salgami, E., Vaindirlis, I., Dacou-Voutetakis, C., and Mountokalakis, T. (2005) 'Reproducibility of Home and Ambulatory Blood Pressure in Children and Adolescents'. *Blood Pressure Monitoring* 10 (3), 143–147

Stergiou, G.S., Baibas, N.M., Gantzarou, A.P., Skeva, I.I., Kalkana, C.B., Roussias, L.G., and Mountokalakis, T.D. (2002) 'Reproducibility of Home, Ambulatory, and Clinic Blood Pressure: Implications for the Design of Trials for the Assessment of Antihypertensive Drug Efficacy.' *American Journal of Hypertension* 15 (2 Pt 1), 101–104

Stewart, J., Montgomery, L., Glover, J., and Medow, M. (2007) 'Changes in Regional Blood Volume and Blood Flow during Static Handgrip'. *American Journal of Physiology - Heart and Circulatory Physiology* 292 (1), H215–H223

Stiefel, P., Vallejo-Vaz, a J., García Morillo, S., and Villar, J. (2011) 'Role of the Renin-Angiotensin System and Aldosterone on Cardiometabolic Syndrome.' *International Journal of Hypertension* 2011 (685238), 1–8

Stiggelbout, M., Hopman-Rock, M., Tak, E., Lechner, L., and van Mechelen, W. (2005) 'Dropout from Exercise Programs for Seniors: A Prospective Cohort Study.' *Journal of Aging and Physical Activity* 13 (4), 406–421

Stiller-Moldovan, C., Kenno, K., and McGowan, C.L. (2012) 'Effects of Isometric Handgrip Training on Blood Pressure (Resting and 24 h Ambulatory) and Heart Rate Variability in Medicated Hypertensive Patients'. *Blood Pressure Monitoring* 17, 55–61

Studinger, P., Lénárd, Z., Kováts, Z., Kocsis, L., and Kollai, M. (2003) 'Static and Dynamic Changes in Carotid Artery Diameter in Humans during and after Strenuous Exercise.' *The Journal of Physiology* 550 (Pt 2), 575–

Sun, Z. (2014) 'Aging, Arterial Stiffness, and Hypertension'. *Hypertension* [online] 65 (2), 252–256. available from <http://hyper.ahajournals.org/cgi/doi/10.1161/HYPERTENSIONAHA.114.03617>

Swift, D.L., Johannsen, N.M., Tudor-locke, C., Conrad, P., Johnson, W.D., Blair, S.N., Sénéchal, M., and Church, T.S. (2012) 'Exercise Training and Habitual Physical Activity; A Randomised Controlled Trial'. *American Journal of Preventative Medicine* 43 (6), 629–635

Tafil-Klawe, M., Trzebski, A., and Klawe, J. (1985) 'Contribution of the Carotid Chemoreceptor Reflex to the Mechanism of Respiratory Sinus Arrhythmia in Young Healthy and Hypertensive Humans.' *Acta Physiologica Polonica* 36 (1), 59–64

Tanaka, H., Dinenno, F. a, Monahan, K.D., Clevenger, C.M., DeSouza, C. a, and Seals, D.R. (2000) 'Aging, Habitual Exercise, and Dynamic Arterial Compliance.' *Circulation* 102 (11), 1270–1275

Tang, L.H., Zwisler, A.-D., Berg, S.K., Doherty, P., Taylor, R.S., and Langberg, H. (2017) 'Is the Cardiovascular Response Equivalent between a Supervised Center-Based Setting and a Self-Care Home-Based Setting When Rating of Perceived Exertion Is Used to Guide Aerobic Exercise Intensity during a Cardiac Rehabilitation Program?' *American Journal of Physical Medicine & Rehabilitation* 96 (6), 381–387

Tarkiainen, T.H., Timonen, K.L., Tiittanen, P., Hartikainen, J.E.K., Pekkanen, J., Hoek, G., Ibald-Mulli, A., and Vanninen, E.J. (2005) 'Stability over Time of Short-Term Heart Rate Variability.' *Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society* 15 (6), 394–399

Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) 'Guidelines Heart Rate Variability'. *European Heart Journal* [online] 17, 354–381. available from <http://circ.ahajournals.org/content/93/5/1043.short>

Taylor, A.C., McCartney, N., Kamath, M. V., and Wiley, R.L. (2003) 'Isometric Training Lowers Resting Blood Pressure and Modulates Autonomic Control'. *Medicine and Science in Sports and Exercise* 35 (251), 251–256

Taylor, J.A., Myers, C.W., Halliwill, J.R., Seidel, H., and Eckberg, D.L. (2001) 'Sympathetic Restraint of Respiratory Sinus Arrhythmia: Implications for Vagal-Cardiac Tone Assessment in Humans.' *American Journal of Physiology. Heart and Circulatory Physiology* 280 (6), H2804-14

Taylor, K.A., Wiles, J.D., Coleman, D.D., Sharma, R., and O'Driscoll, J.M. (2017) 'Continuous Cardiac Autonomic and Haemodynamic Responses to Isometric Exercise.' *Medicine and Science in Sports and Exercise* 49 (8), 1511–1519

Teixeira, L., Ritti-Dias, R.M., Tinucci, T., Mion Junior, D., and Forjaz, C.L. de M. (2011) 'Post-Concurrent Exercise Hemodynamics and Cardiac Autonomic Modulation.' *European Journal of Applied Physiology* 111 (9), 2069–2078

Terziotti, P., Schena, F., Gulli, G., and Cevese, A. (2001) 'Post-Exercise Recovery of Autonomic Cardiovascular Control: A Study by Spectrum and Cross-Spectrum Analysis in Humans'. *European Journal of Applied Physiology* 84 (3), 187–194

Thayer, J.F., Loerbroks, A., and Sternberg, E.M. (2011) 'Inflammation and Cardiorespiratory Control: The Role of the Vagus Nerve'. *Respiratory Physiology & Neurobiology* [online] 178 (3), 387–394. available from <http://linkinghub.elsevier.com/retrieve/pii/S1569904811001996>

Thayer, J.F., Yamamoto, S.S., and Brosschot, J.F. (2010) 'The Relationship of Autonomic Imbalance, Heart Rate Variability and Cardiovascular Disease Risk Factors'. *International Journal of Cardiology* [online] 141 (2), 122–131. available from <http://dx.doi.org/10.1016/j.ijcard.2009.09.543>

Thijs, L., Staessen, J., Fagard, R., Zachariah, P., and Amery, A. (1994) 'Number of Measurements Required for the Analysis of Diurnal Blood Pressure Profile'. *Journal of Human Hypertension* 8 (4), 239–244

Thompson, P.D., Crouse, S.F., Goodpaster, B., Kelley, D., Moyna, N., and Pescatello, L. (2001) 'The Acute versus the Chronic Response to Exercise.' *Medicine and Science in Sports and Exercise* 33 (6 Suppl), S438–S445

Thrasher, T.N. (2004) 'Baroreceptors, Baroreceptor Unloading, and the Long-Term Control of Blood Pressure.' *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 288 (4), R819–R827

Tiggemann, C.L., Korzenowski, A.L., Brentano, M. a, Tartaruga, M.P., Alberton, C.L., Kruel, L.F.M., C.L., T., A.L., K., M.a., B., M.P., T., C.L., A., and L.F.M., K. (2010) 'Perceived Exertion in Different Strength Exercise Loads in Sedentary, Active, and Trained Adults.' *Journal Of Strength And Conditioning Research* [online] 24 (8), 2032–2041. available from <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=20634752%5Cnhttp://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=20634752&site=ehost-live>

Tinken, T.M., Thijssen, D.H.J., Hopkins, N., Dawson, E. a., Cable, N.T., and Green, D.J. (2010) 'Shear Stress Mediates Endothelial Adaptations to Exercise Training in Humans'. *Hypertension* 55 (2), 312–318

Tsuji, H., Venditti, F.J., Manders, E.S., Evans, J.C., Larson, M.G., Feldman, C.L., and Levy, D. (1994) 'Reduced Heart Rate Variability and Mortality Risk in an Elderly Cohort. The Framingham Heart Study.' *Circulation* 90 (2), 878–883

Tulppo, M.P., Hautala, A.J., Mäkikallio, T.H., Laukkanen, R.T., Nissilä, S., Hughson, R.L., and Huikuri, H. V (2003) 'Effects of Aerobic Training on Heart Rate Dynamics in Sedentary Subjects'. *Journal of Applied Physiology* [online] 95 (1), 364–372. available from <http://dx.doi.org/10.1152/japplphysiol.00751.2002>

Ueda, T. and Kurokawa, T. (1995) 'Relationships between Perceived Exertion and Physiological Variables during Swimming'. *International Journal of Sports Medicine* 16 (6), 385–389

Ueno, L.M. and Moritani, T. (2003) 'Effects of Long-Term Exercise Training on Cardiac Autonomic Nervous

Activities and Baroreflex Sensitivity.' *European Journal of Applied Physiology* [online] 89 (2), 109–14. available from <http://www.ncbi.nlm.nih.gov/pubmed/12665972>

Umetani, K., Singer, D.H., McCraty, R., and Atkinson, M. (1998) 'Twenty-Four Hour Time Domain Heart Rate Variability and Heart Rate: Relations to Age and Gender over Nine Decades'. *Journal of the American College of Cardiology* 31 (3), 593–601

Umpierre, D. and Stein, R. (2007) 'Hemodynamic and Vascular Effects of Resistance Training: Implications for Cardiovascular Disease.' *Arquivos Brasileiros de Cardiologia* 89 (4), 256–262

Utter, A.C., Robertson, R.J., Green, J.M., Suminski, R.R., McAnulty, S.R., and Nieman, D.C. (2004) 'Validation of the Adult OMNI Scale of Perceived Exertion for Walking/Running Exercise.' *Medicine and Science in Sports and Exercise* 36 (10), 1776–1780

Vaitkevicius, P. V, Fleg, J.L., Engel, J.H., O'Connor, F.C., Wright, J.G., Lakatta, L.E., Yin, F.C., and Lakatta, E.G. (1993) 'Effects of Age and Aerobic Capacity on Arterial Stiffness in Healthy Adults.' *Circulation* 88 (4 Pt 1), 1456–1462

De Vente, W., Olff, M., Van Amsterdam, J.G.C., Kamphuis, J.H., and Emmelkamp, P.M.G. (2003) 'Physiological Differences between Burnout Patients and Healthy Controls: Blood Pressure, Heart Rate, and Cortisol Responses.' *Occupational and Environmental Medicine* 60 (Suppl 1), i54–i61

Verdecchia, P. (2000) 'Prognostic Value of Ambulatory Blood Pressure : Current Evidence and Clinical Implications.' *Hypertension* 35 (3), 844–851

Vinik, A.I., Maser, R.E., and Ziegler, D. (2011) 'Autonomic Imbalance: Prophet of Doom or Scope for Hope?' *Diabetic Medicine* 28 (6), 643–651

Volpe, M., Rubattu, S., and Burnett, J. (2014) 'Natriuretic Peptides in Cardiovascular Diseases: Current Use and Perspectives'. *European Heart Journal* 35 (7), 419–425

Vongpatanasin, W., Wang, Z., Arbique, D., Arbique, G., Adams-Huet, B., Mitchell, J.H., Victor, R.G., and Thomas, G.D. (2011) 'Functional Sympatholysis Is Impaired in Hypertensive Humans.' *The Journal of Physiologyhysiology* 589 (Pt 5), 1209–1220

Wendelin-Saarenhovi, M., Isoaho, R., Hartiala, J., Helenius, H., Kivela, S.L., and Hietanen, E. (2001) 'Long-Term Reproducibility of Ambulatory Blood Pressure in Unselected Elderly Subjects.' *Clinical Physiology (Oxford, England)* 21 (3), 316–322

Wesseling, K.H., de Wit, B., van der Hoeven, A., van Goudoever, J., and Settels, J.J. (1995) 'Physiocal, Calibrating Finger Vascular Physiology for Finapres'. *Homeostasis* 36 (2–3), 67–82

Wiles, J.D., Allum, S.R., Coleman, D. a, and Swaine, I.L. (2008) 'The Relationships between Exercise Intensity, Heart Rate, and Blood Pressure during an Incremental Isometric Exercise Test.' *Journal of Sports Sciences* 26

(2), 155–162

Wiles, J.D., Coleman, D. a., and Swaine, I.L. (2010) 'The Effects of Performing Isometric Training at Two Exercise Intensities in Healthy Young Males'. *European Journal of Applied Physiology* 108 (3), 419–428

Wiley, R., Dunn, C., Cox, R., Hueppchen, N., and Scott, M. (1992) 'Isometric Exercise Training Lowers Resting Blood Pressure'. *Medicine and Science in Sports and Exercise* 24 (7), 749–754

Williamson, J.W. (2010) 'The Relevance of Central Command for the Neural Cardiovascular Control of Exercise.' *Experimental Physiology* 95 (11), 1043–1048

Williamson, J.W., McColl, R., Mathews, D., Mitchell, J.H., Raven, P.B., and Morgan, W.P. (2002) 'Brain Activation by Central Command during Actual and Imagined Handgrip under Hypnosis'. *Journal of Applied Physiology* [online] 92 (3), 1317–1324. available from <http://jap.physiology.org/lookup/doi/10.1152/japplphysiol.00939.2001>

Willie, C.K., Ainslie, P.N., Taylor, C.E., Jones, H., Sin, P.Y.W., and Tzeng, Y.-C. (2011) 'Neuromechanical Features of the Cardiac Baroreflex after Exercise.' *Hypertension (Dallas, Tex. : 1979)* 57 (5), 927–933

Winter, E.M., Jones, A.M., Davison, R.R.., Bromley, P.D., and Mercer, T.H. (2007) *Sport and Exercise Physiology Testing Guidelines* [online] available from <http://books.google.com/books>

Wonisch, M., Hofmann, P., Fruhwald, F.M., Kraxner, W., Hodl, R., Pokan, R., and Klein, W. (2003) 'Influence of Beta-Blocker Use on Percentage of Target Heart Rate Exercise Prescription.' *European Journal of Cardiovascular Prevention and Rehabilitation* 10 (4), 296–301

Wu, J., Xia, S., Kalionis, B., Wan, W., and Sun, T. (2014) 'The Role of Oxidative Stress and Inflammation in Cardiovascular Aging'. *BioMed Research International* 2014 (615312), 1–13

Yamada, Y., Miyajima, E., Tochikubo, O., Matsukawa, T., and Ishii, M. (1989) 'Age-Related Changes in Muscle Sympathetic Nerve Activity in Essential Hypertension.' *Hypertension.* 13 (6 Pt 2), 870–877

Yanagisawa, M., Kurihara, H., Kimura, S., Goto, K., and Masaki, T. (1988) 'A Novel Peptide Vasoconstrictor, Endothelin, Is Produced by Vascular Endothelium and Modulates Smooth Muscle Ca2+ Channels.' *Journal of Hypertension. Supplement : Official Journal of the International Society of Hypertension* 6 (4), S188-91

Young, D.R. and Stewart, K.J. (2006) 'A Church-Based Physical Activity Intervention for African American Women.' *Family & Community Health* 29 (2), 103–117

Zimmer, H.-G. (2004) 'Heinrich Ewald Hering and the Carotid Sinus Reflex.' *Clinical Cardiology* 27 (8), 485–486

Zöllei, É., Csillik, A., Rabi, S., Gingl, Z., and Rudas, L. (2007) 'Respiratory Effects on the Reproducibility of

Cardiovascular Autonomic Parameters'. *Clinical Physiology and Functional Imaging* 27 (4), 205–210

Appendix 1

CSEP approved Sept 12 2011 version

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

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

SECTION 1 - GENERAL HEALTH

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

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Section 3 to sign the form. You do not need to complete Section 2.

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

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.

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SECTION 2 - CHRONIC MEDICAL CONDITIONS

		Please read the questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1.		Do you have Arthritis, Osteoporosis, or Back Problems?	☐ If yes, answer questions 1a-1c	☐ If no, go to question 2
	1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/ or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	☐	☐
	1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	☐	☐
2.		Do you have Cancer of any kind?	☐ If yes, answer questions 2a-2b	☐ If no, go to question 3
	2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	☐	☐
	2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	☐	☐
3.		Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm	☐ If yes, answer questions 3a-3e	☐ If no, go to question 4
	3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	3b.	Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	☐	☐
	3c.	Do you have chronic heart failure?	☐	☐
	3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)	☐	☐
	3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	☐	☐
4.		Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes	☐ If yes, answer questions 4a-4c	☐ If no, go to question 5
	4a.	Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)	☐	☐
	4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	☐	☐
	4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	☐	☐
5.		Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)	☐ If yes, answer questions 5a-5b	☐ If no, go to question 6
	5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	5b.	Do you also have back problems affecting nerves or muscles?	☐	☐

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Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure		☐ If yes, answer questions 6a-6d	☐ If no, go to question 7
	6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	☐	☐
	6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	☐	☐
	6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	☐	☐
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia		☐ If yes, answer questions 7a-7c	☐ If no, go to question 8
	7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	☐	☐
	7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	☐	☐
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event		☐ If yes, answer questions 8a-c	☐ If no, go to question 9
	8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	8b.	Do you have any impairment in walking or mobility?	☐	☐
	8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	☐	☐
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?		☐ If yes, answer questions 9a-c	☐ If no, read the advice on page 4
	9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	☐	☐
	9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	☐	☐
	9c.	Do you currently live with two chronic conditions?	☐	☐

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

PAR-Q+

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

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

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

- You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise profesional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
- Please read and sign the declaration below:

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

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES
1. Jamnik VJ, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the cectiveness of clearance for physical activity participation: background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document. APNM 36(S1):S266-s298, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.

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Appendix 2

Can the rating of perceived exertion scale be used to regulate the sympathetic response in pre-hypertensive and hypertensive adults (≥55years) during an isometric handgrip task?

Information Sheet for Participants

Invitation

We would like to invite you to take part in our research study. Before you decide on whether you would like to participate we would like you to understand the purpose of our research and what it would involve for you. We are very happy to answer any questions that you might have.

Purpose of the research

Research has previously shown that isometric exercise (similar to holding a moderately heavy shopping bag) has positive effects on lowering blood pressure – however, some findings demonstrate that some people do not respond to the exercise programme. It has been shown that your bodies' immediate response (i.e. change in blood pressure) to the exercise could predict how you will respond to the exercise. Using this information we would like to find out if there is a different way in which we can prescribe exercise to you – the exercise will be individualised and become your own personal exercise programme. This will hopefully give you the best chance of lowering your blood pressure.

We therefore need to test a new method of monitoring the exercise intensity. This method is called the Rate of Perceived Exertion – this is a simple chart that asks you to express feelings of how hard you are working in a numerical format.

What is involved in participating?

You will be required to visit the lab on 5 separate days.

Visit 1, part i) We will firstly need to confirm that you have high blood pressure. For this part of the research we will need you to visit the Human Performance Laboratory (High Wycombe Campus, Buckinghamshire New University) for a blood pressure measurement. You will be requested to avoid food (2 hours), caffeine (12 hours) and alcohol (24 hours) prior to the visit. You will also be asked to void your bladder in advance of the testing session.

Following 10 minutes of seated rest you will have your blood pressure taken between 2 and 4 times.

Visit 1, part ii) If you do have high blood pressure and are eligible for study participation we will introduce you to the perceived exertion scale (Category-ratio scale). We will take some resting measures (see below) and determine your maximal handgrip strength – this will involve 3 x maximal handgrip exercises with your

non-dominant hand. Following this you will be asked to carry out 3 x 2minte handgrip exercises (between 20-60% of your maximal strength). A 5 minute rest will be given following each exercise.

Resting measures

- The finger cuff will be attached onto the middle finger of your dominant (writing) hand.
- Once the device have been attached, you will be given time to relax. A resting reading of blood pressure, heart rate will be measured.

Isometric exercise

- Remaining seated you will perform 3 maximal handgrip exercises for 5 seconds. This will be followed by 3 x 2 minute handgrip contractions followed by 5 minutes rest.

Preparation for your appointment

- Wear a t-shirt/short sleeved shirt
- Avoid food for (2 hours), caffeine (12 hours) and alcohol (24 hours) prior to the visit.

Visit 2) You will return to the lab and following resting blood pressure and heart rate measurements you will be requested to perform 8 x 2 minute isometric handgrip contractions of varying intensity – your intensity will be displayed on a screen. Each contraction will be followed with a 5 minute rest

Preparation for your appointment

- Avoid food for (2 hours), caffeine (12 hours) and alcohol (24 hours) prior to the visit.

Visit 3, 4, 5) During this visit you will be asked to repeat 4 x 2 minute handgrips whilst controlling the intensity using the perceived exertion scale instead of the on screen intensity regulator. You will receive a 4 minute rest in between each contraction.

Benefits and risks

As a participant of this research you will contribute to new ways of potentially prescribing isometric exercise to those with high blood pressure.

Your safety is our upmost priority. Although participating in exercise is safe for most individuals, we will ensure that you are appropriately screened prior to participation (questionnaire). You will be asked to indicate to the researcher of any adverse signs associated with the exercise – for example, new onset or recurring anginal pain (chest pain or pressure, an ache in the jaw or neck, discomfort down the left or right arms (not associated with the exercise), pain across the shoulders and back); unaccustomed or unusual shortness of breath; dizziness or light-headedness. The researcher will also be monitoring blood pressure throughout the exercise.

In the unlikely event of you experiencing adverse reactions the exercise will be stopped immediately. The researcher working with you is first aid qualified.

Terms for withdrawal

You have the right to withdraw at any time without prejudice and without providing a reason. Withdrawal must be before 31st March 2016. Any data collected up until the point of withdrawal will be used in the analysis.

Usage of the data

Collected data will be analysed and used for publication within a PhD thesis document and a peer-reviewed journal. Data will remain stored on the researcher's computer – data may be used/shared with other researchers for publication in journals, reports, webpages and other research outputs.

Strategies for assuring ethical use of the data

Your identity as a participant will be protected throughout the research. All data from each participant will be anonymised using a unique reference code for each individual. The computer programme where your data is stored will be password protected and accessible only by Niamh Morrin (PhD student) and Dr Mark Stone (1st research supervisor)

Researcher contact

If you have any questions about the research throughout your participation please do not hesitate to contact Niamh Morrin.

- Niamh.morrin@bucks.ac.uk
- +447842902909

Appendix 3

Activity Diary

	0-15	15-30	30-45	45-60
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11				
12				
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14				
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Write in every space provided the categorical value which corresponds best to the dominant activity of each 15-minute period. Please consult the activity table to establish the proper coding.

Activity Description	Value
Sleeping or Resting in bed	1
Sitting: eating, listening, writing, etc	2
Light activity standing: washing, shaving, combing, cooking, etc	3
Slow walk (<4 km/h), driving, to dress, to shower, etc	4
Light manual work: floor sweeping, window washing, driving a truck, painting, waiting on tables, nursing chores, several house chores, electrician, barman, walking at 4 to 6 km/h	5
Leisure activities and sports in a recreational environment: baseball, golf, volleyball, canoeing or rowing, archery, bowling, cycling (<10 km/h), table tennis, etc	6
Manual work at moderate pace: mining, carpentry, house building, lumbering and wood cutting, snow shoveling, loading and unloading goods, etc	7
Leisure and sport activities of higher intensity (not competitive): canoeing (5 to 8 km/h), bicycling (>15 km/h), dancing, skiing, badminton, gymnastic, swimming, tennis, horse riding, walking, (>6 km/h), etc	8
Intense manual work, high intensity sport activities or sport competition: tree cutting, carrying heavy loads, jogging and running (>9 km/h), racquetball, badminton, swimming, tennis, cross country skiing (>8 km/ h), hiking and mountain climbing, etc	9

Evidence of Ethical Approval

bucks new university

7th May 2015

Niamh Morrin
Research Student Office
Bucks New University
Queen Alexandra Road
High Wycombe
HP11 2JZ

Dear Niamh

Ethical approval: Ref UEP2015May01

I am writing to confirm that Ethical approval was granted by the University Ethics Panel of Buckinghamshire New University on 7th May 2015 for your project:

"Consistency of 24-hr hemodynamic and autonomic variables in hypertensive adults."

between 7th May and 1st September 2015.

I hope that your research project goes well.

Yours sincerely,

Dr M. Nakisa
Secretary to the University Ethics Panel
Research Unit
Academic Quality Directorate

9 May 2016

Ms Niamh Morris
Bucks New University
Queen Alexandra Road
High Wycombe
HP11 2JZ

Dear Niamh

Ethical approval: Ref UEP2016Apr02

I am writing to confirm that ethical approval was granted by the University Research Ethics Panel of Buckinghamshire New University on 9 May 2016 for your project:

"The effects of isometric training on cardiovascular function in pre-hypertensive and hypertensive adults (≥55years)."

This approval is valid for data collection between 9 May 2016 and 7 July 2017.

Please ensure that you quote the above reference number as evidence of ethical approval and in all materials used to recruit participants.

The Research Unit must be notified of any amendments to the proposed research or any extension to the period of data collection.

I hope that your research project goes well.

Yours sincerely,

Dr M. Nakisa
Secretary to the University Research Ethics Panel
Research Unit
Academic Quality Directorate

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bucks new university

7th December 2015

Niamh Morrin
Department of Sports Management
Bucks New University
Queen Alexandra Road
High Wycombe
HP11 2JZ

Dear Niamh

Ethical approval: Ref UEP2015Nov02

I am writing to confirm that Ethical approval was granted by the University Research Ethics Panel of Buckinghamshire New University on 2nd December 2015 for your project:

"Can the rating of perceived exertion scale be used to regulate the sympathetic response in pre-hypertensive and hypertensive adults (≥55years) during an isometric handgrip task?"

This approval is for data collection between 2nd December 2015 and 31st March 2016.

Please ensure that you quote the above reference number as evidence of ethical approval and in all materials used to recruit participants.

I hope that your research project goes well.

Yours sincerely,

Dr M. Nakisa
Secretary to the University Research Ethics Panel
Research Unit
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