THE EFFECTS OF ISOMETRIC EXERCISE TRAINING AND DETRAINING ON CARDIOVASCULAR ADAPTATION, WITH SPECIAL REFERENCE TO RESTING BLOOD PRESSURE

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ABSTRACT

Isometric wall squat (IWS) training is now well established as an effective exercise training intervention for the reduction of resting blood pressure (BP). However, there remains limited research to support its widespread adoption and acknowledgement within healthcare guidelines. As a result, this thesis set out to investigate some key areas that were identified as gaps in the current literature to progress the clinical utility of IWS training. Study 1 explored the BP reductions and associated physiological mechanisms following 4 weeks of IWS training using a large sample size. The study also attempted to identify whether there were sex-based differences in any BP reductions observed. It was found that IWS training is effective at reducing resting BP in both males and females, and that the observed BP reductions were likely driven by decreases in total peripheral resistance and adaptations to cardiac autonomic function rather than centrally mediated changes in cardiac output. Study 2 then compared the BP reductions and cardiovascular adaptation between 4 and 8 weeks of IWS training period to ascertain the influence of training duration on resting BP reductions. The study found that extending IWS training to 8 weeks resulted in significantly greater sBP reductions (but not dBP or MAP), though the rate of reduction plateaued after 4 weeks. Study 3 then investigated the effects of detraining on resting BP reductions following the cessation of IWS training. Results from this study indicate that a complete cessation of IWS training results in a reversal of both resting BP reductions and all associated cardiovascular adaptations. Lastly, Study 4 sought to identify the minimum frequency of IWS sessions required to maintain resting BP reductions during a follow-up training period. It was demonstrated that significant reductions in resting sBP and MAP can be maintained with just one training session per week, although greater overall cardiovascular benefits can be achieved with three sessions per week. Collectively, the findings from this thesis have provided further evidence for the effectiveness of IWS training in reducing resting BP. The findings also elucidate the cardiovascular mechanisms involved in any BP reductions and offer practical guidelines for the maintenance of BP reductions with implications for improving the adherence and long-term efficacy of IWS training.

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ABBREVIATIONS

AIx - Augmentation Index

BP - Blood Pressure

BRS - Baroreceptor Reflex Sensitivity

BRS - Baroreflex Sensitivity

BSA - Body Surface Area

CID - Clinically Important Difference

CV - Coefficient of Variation

dBP - Diastolic Blood Pressure

ESH - European Society of Hypertension

HBPM - Home-Based Blood Pressure Monitoring

HF - High Frequency

HFnu - High Frequency Normalised Units

HR - Heart Rate

HRV - Heart Rate Variability

ICG - Impedance Cardiography

IWS - Isometric Wall Squat

LF - Low Frequency

LF:HF - Low Frequency to High Frequency Ratio

LFnu - Low Frequency Normalised Units

LoA - Limits of Agreement

MAP - Mean Arterial Pressure

NO - Nitric Oxide

PSD-RRI – Power Spectral Density of R-R Intervals

$\dot{Q}$ - Cardiac Output

Q̇i - Cardiac Output Index

ROS - Reactive Oxygen Species

RPE - Rate of Perceived Effort

sBP – Systolic Blood Pressure

Si - Stroke Volume Index

SV - Stroke Volume

TFM - Task Force Monitor

THRR - Target Heart Rate Range

TPR - Total Peripheral Resistance

TPRi - Total Peripheral Resistance Index

CHAPTER 1 – INTRODUCTION AND LITERATURE REVIEW

1.1. Hypertension

Blood pressure (BP) can be seen as the hydrostatic pressure exerted by the blood on the body's vasculature as it is transported through circulation. Arterial BP relates to the force applied by the blood on the arterial wall and is the most commonly used index to guide therapeutic interventions, particularly in clinical settings, with virtually all BP-related research in humans based on measurements in the brachial artery (upper arm) (Bos *et al*., 2007). Systolic BP (sBP) relates to the pressure exerted on the vasculature during myocardial contraction, and diastolic BP (dBP) refers to the pressure exerted during the relaxation of the myocardium (Saghiv and Sagiv, 2020). Systolic BP is primarily affected by stroke volume (SV), left ventricular ejection velocity, the elasticity of aortic and arterial walls, blood viscosity, and left ventricular preload and afterload. Diastolic BP is influenced by blood viscosity, the elasticity of arterial walls, vascular resistance, and the duration of the cardiac cycle (McGhee and Bridges, 2002). Systemic mean arterial pressure (MAP) relates to the mean perfusion pressure throughout the cardiac cycle and is the sum of cardiac output ($\dot{Q}$) and total peripheral resistance (TPR) (McGhee and Bridges, 2002). Many devices use an online calculation for MAP, but it can also be calculated offline as MAP = dBP + 1/3 (sBP-dBP) (DeMers and Wachs, 2019). Using MAP can provide an alternative index that may capture the person's overall exposure to a heightened pressure. Moreover, some evidence has shown MAP to be more accurate in the detection of hypertension, with a recent study showing a detection accuracy of 95.2% with MAP, compared to 89.3% and 88.9% with sBP and dBP, respectively (Kandil *et al*., 2023).

Raised or high resting BP is referred to as hypertension and is typically categorised based on clinical significance. The 2023 European Society of Hypertension (ESH) guidelines define hypertension as sBP ≥140 mmHg or a dBP ≥90 mmHg. Optimal sBP is classified as <120 mmHg, and optimal dBP as <80 mmHg (Mancia *et al*., 2023). Other guidelines, such as those presented by the American College of Cardiology and American Heart Association (ACC/AHA), have a higher threshold for each BP category (Table 1.1) (Mancia *et al.*, 2023). These higher thresholds are based on linear increases in cardiovascular risk corresponding with elevations in BP (Flack and Adekola, 2020). However, the ACC/AHA guidelines have yet to be recommended and utilised by health treatment guidelines in the UK or Europe, most likely because these guidelines would dramatically increase the number of individuals needing antihypertensive treatment, which could result in substantial socioeconomic and

also psychological consequences (Chrysant and Chrysant, 2019). As such, the 2023 ESH guidelines will be the default terminology used throughout this thesis (Mancia *et al.*, 2023).

Hypertension is one of the leading risks for mortality, morbidity and disability worldwide, affecting around 31.1% of the global adult population (Mills, Stefanescu and He, 2020). Hypertension can be influenced by several factors, including genetics, ethnicity, age, and sex (Sharman and Stowasser, 2009), as well as modifiable behavioural risk factors, such as an unhealthy diet, tobacco use, harmful use of alcohol, and physical inactivity (Wong *et al*., 2001). Over the past decade, the number of deaths related to hypertension has increased by 56.1%. Despite marked improvements in modern medicine and pharmacological treatments, it remains a major cause of premature death worldwide (Virani *et al.*, 2020). A global pooled analysis of 1201 population-based studies from 1990 to 2019 discovered that the number of people living with hypertension between the age of 30–79 years has doubled, from 331 million females and 317 million males in 1990 to 626 million females and 652 million males in 2019, with the majority of the rise in low and middle-income regions (Zhou *et al.*, 2021). The latest figures from the Office of National Statistics (2023) show that around 1/3 of adults in the United Kingdom (U.K.) have hypertension, with around 29%, or around 4.2 million, having undiagnosed hypertension. The data also highlighted that it is the younger, healthier adult population, with the lowest risk for high BP, that is most likely to include those with undiagnosed hypertension (Iacobucci, 2023).

Research has suggested that the total number of people living with hypertension worldwide is predicted to increase to 1.56 billion by 2025 (Forouzanfar *et al.*, 2017). In 2023, the WHO stated that the number was 1.3 billion adults worldwide, showing that these forecasts are increasingly likely (WHO, 2023). The prevalence of hypertension increases with age, and it is estimated that 65% of >65-year-olds in the United States (U.S.) are adversely affected by elevations in BP (Hajjar and Kotchen, 2003). Globally, the population is also ageing, with the proportion of people aged 65 or older reaching 9.3% in 2020, compared to 6.9% in 2000 and 5.1% in 1950. With the current trajectory, this is set to reach 15.9% in 2050 and 22.4% in 2100 (Gu, Andreev and Dupre, 2021). In the U.K., over 11 million people (18.6% of the population) are 65 years or older, compared with 16.4% at the time of the previous census in 2011 (Office for National Statistics, 2021). These data suggest that the impact of hypertension on the general population is likely to increase further over the coming decades.

Table 1:1 Comparison of ACC/AHA and ESH BP classifications

	ACC/AHA	ESH
Definition of hypertension (mmHg)	≥130/80	≥140/90
Normal BP ranges (mmHg)	Normal: <120/80 Elevated: 120-129/<80	Optimal: <120/80 Normal: 120-129/80-84 High normal: 130-139/85-89
Hypertension ranges (mmHg)	Stage 1: 130-139/80-89 Stage 2: ≥140/90	Grade 1: 140-159/90-99 Grade 2: 160-179/100-109 Grade 3: ≥180/110
Age-specific BP targets (mmHg)	<65 years: <130/80 ≥65 years: <130/80	<65 years: <120-129/70-79 ≥65 years: <130-139/70-79

1.1.1. Hypertension and cardiovascular disease

The association between cardiovascular disease and hypertension is well-established (Lackland and Weber, 2015). Large cohort studies have now demonstrated that hypertension is one of the strongest risk factors for numerous cardiovascular diseases, including heart failure, atrial fibrillation, valvular heart diseases, aortic syndromes, dementia, coronary heart disease and stroke (Kjeldsen, 2018; Fuchs and Whelton, 2020). Blood pressure values in hypertensive categories (sBP ≥140 mmHg or a dBP ≥90 mmHg) significantly increase the risk of cardiovascular disease, with the mortality risk increasing two-fold for each 20-mmHg and 10-mmHg elevation in sBP and dBP, respectively, over 115/75 mmHg (Jones and Hall, 2004). About two-thirds of strokes and almost half of cases of ischaemic heart disease can be attributed to elevated sBP greater than 115 mmHg (Murray et al., 2003). The annual rate of death associated with a sBP of 140 mmHg or more increased from approximately 97.9 per 100,000 persons in 1990 to 106.3 per 100,000 persons in 2015, as well as the number of disability-adjusted life-years rising from 5.2 million to 7.8 million (Forouzanfar *et al.*, 2017). Although other factors such as obesity or diabetes mellitus may adversely affect the incidence of hypertension and cardiovascular disease, it is unlikely this type of confounding effect can explain the observed relationship found between BP and cardiovascular disease (McLnnes, 1995).

1.1.2. Aetiology of hypertension

Hypertension must be related to either changes in Q̇ or TPR, the two determining factors of arterial BP (Wiles *et al.*, 2010). However, the aetiology of hypertension includes a range of interrelated disorders, such as excess sympathetic activity, an overactive renin-angiotensin-aldosterone system (RAAS), altered neurohormonal control, metabolic dysfunction and vascular impairment (Messerli *et al*., 2007). The autonomic nervous system (ANS) responds to efferent (mechanoreceptors) or afferent (adrenal medulla) inputs and signals to the vascular smooth muscle to maintain tissue perfusion (directly related to vasoconstriction or vasodilation) and is also responsible for alterations in Q̇. An overstimulated ANS can result in excessive sympathetic output and subsequent vasoconstriction, or elevated HR and Q̇, both of which can cause elevated BP. The RAAS is a regulatory mechanism involving hormonal signals that control BP, fluid balance, and electrolyte homeostasis. Excessive release of angiotensin II from the RAAS promotes increased vasoconstriction and sodium and water retention, thus increasing blood volume and BP. Angiotensin II can also enhance sympathetic outflow from the ANS, which modifies the release of hormones such as aldosterone, affecting blood volume, sodium levels, vascular, renal and cardiac regulation, and inflammatory processes (Young and Davisson, 2015). Synthesis of angiotensin II by angiotensin-converting-enzyme has also been shown to decrease nitric oxide (NO) and prostaglandin levels and stimulate the release of endothelin, both of which elevate BP (Klabunde, 2012). Dysregulation of neurohormonal compounds, including atrial natriuretic peptide, brain natriuretic peptide and adrenomedullin, inhibits sodium excretion vasodilation in response to changes in BP, which can result in sustained hypertension (Messerli *et al*., 2007). Metabolic syndrome (including obesity and insulin resistance) is also related to increased sympathetic tone, elevated angiotensin II activity, reduced endothelial cell-mediated vasodilation and altered renal function, all of which can result in hypertension (Messerli *et al*., 2007).

Vascular dysfunction also plays a crucial role in the development of hypertension. Endothelial dysfunction, typically related to a reduced ability to produce NO and an increased production of reactive oxygen species, can impair vasodilation and increase vascular resistance, both of which can contribute to elevated BP (Ghiadoni, Taddei and Virdis, 2011). Moreover, chronic inflammation has been shown to promote hypertension through the release of pro-inflammatory cytokines such as interleukin-6 and Tumor Necrosis Factor-α, which can also induce endothelial dysfunction, increase arterial stiffness, and impair normal BP regulation (Rodríguez-Iturbe *et al.*, 2004; Harrison *et al.*, 2011). The activation of immune cells, such as T-cells and macrophages, can also promote vascular inflammation and lead to a persistent elevation of BP (Guzik *et al.*, 2007).

1.1.3. Pathophysiology of hypertension

Prolonged hypertension results in sustained tangential tension on the myocardial and arterial walls. If left untreated, adverse cardiac and vascular adaptations will likely manifest (Nwabuo and Vasan, 2020). Previous research investigating cardiovascular complications arising from hypertension has predominately focused on a pathological form of left ventricular hypertrophy (Verdecchia *et al*., 1990). Amongst a large cohort of 37,700 untreated and high-risk hypertensive individuals, echocardiographic data revealed that this specific form of left ventricular hypertrophy was prevalent in 19%-48% of the untreated hypertensive individuals and 58%-77% in high-risk hypertensive individuals (Cuspidi *et al.*, 2012). Sustained pressure from arterial hypertension leads to concentric hypertrophy of the left ventricle, which is thought to increase proportionally to BP levels to maintain wall stress (Ganau *et al.*, 1992). The most common cause of concentric left ventricular hypertrophy is a chronic increase in workload on the myocardium, arising from haemodynamic pressure or volumetric burden amongst hypertensive individuals (Peguero *et al.*, 2017). Initially, the increased muscle mass or wall thickness that arises from concentric hypertrophy acts as a compensatory mechanism that helps to maintain contractile forces and counteract any increases in ventricular wall stress. However, over time, these effects soon dissipate, and the hypertrophied ventricular walls increase in stiffness due to the disproportionate increase in fibrous tissue, subsequently reducing left ventricular compliance (Kahan and Bergfeldt, 2005).

Pathological left ventricular hypertrophy puts individuals at significant risk for the development of heart failure, dysrhythmias, and sudden death (Shenasa and Shenasa, 2017). Diastolic dysfunction is commonly seen due to the inhibition of ventricular relaxation during diastole (Nadruz, Shah and Solomon, 2017). Diastolic dysfunction and ventricular hypertrophy can result in heart failure with preserved ejection fraction (Del Buono *et al*., 2018). Meta-analytic data has shown that ventricular hypertrophy is associated with a 5.5% increase in the risk of ventricular arrhythmias compared to 1.2% in patients with normal ventricular function (Chatterjee *et al*., 2014). Specifically, the study found the occurrence of ventricular tachycardia and ventricular fibrillation was 2.8-fold greater in the presence of left ventricular hypertrophy (Chatterjee *et al*., 2014). The increased risk of sudden death is most likely connected to myocardial ischemia, which is common among those with this type of left ventricular hypertrophy (Yildiz *et al.*, 2020) and also myocardial fibrosis (Shenasa and Shenasa, 2017). It should be highlighted that these conditions should be clearly distinguished from left ventricular hypertrophy commonly seen amongst athletes as there are clear, distinct differences that exist between athletes and patients with hypertension. For example, in athletes, there is an increase

in active muscular mass, while pathological conditions are characterised by myocardial fibrosis, even before left ventricular hypertrophy develops (Mandoli *et al.*, 2021).

Hypertension can also affect a range of target-organ damage beyond the left ventricle, such as micro- and macroscopic myocardial alterations and remodelling of the atria and ventricles (Nwabuo and Vasan, 2020). Arterial remodelling is also commonly observed amongst those with hypertension, with both large and small arteries affected by the high levels of shear stress. Noted alterations with large arteries include artery enlargement, increased artery wall thickness and stiffness, and aortic unfolding. Other changes that are more prevalent in small arteries include eutrophic remodelling and microvascular rarefaction (Kario *et al.*, 2019; Nwabuo and Vasan, 2020). Eutrophic remodelling is characterised by an increase in the wall thickness of small arteries, resulting in a reduction of lumen diameter. This has been shown to impair organ flow reserve and contribute to the development of hypertension-mediated organ damage. Microvascular rarefaction refers to a reduction in the density of small blood vessels, which can lead to tissue hypoxia and organ dysfunction (Greenstein *et al.*, 2007). Such changes are strongly correlated with an increased incidence of cardiovascular events (Schiffrin *et al.*, 2000).

Over time, prolonged physical stress of elevated BP also affects the endothelial cell's ability to maintain the local vasodilation-vasoconstriction balance of the blood vessels (Messerli *et al*., 2007). The vasodilatory compounds of NO, adenosine and prostaglandins are released by endothelial cells to increase local blood flow when required (Messerli *et al*., 2007). A reduction in NO secretion from endothelial cells increases vascular tone causing vascular smooth muscles to constrict, promoting elevated shear stress and raised BP (Li, Youn and Cai, 2015). Persistent mechanical stress on the endothelial lining leads to endothelial dysfunction and the accumulation of lipids and inflammatory cells which increases the risk of atherosclerotic plaque formation, especially of the coronary and cerebral vessels (Alnasir, 2008). It has been suggested that the underlying pathogenesis and progression linked with nearly all cardiovascular diseases are primarily of atherosclerotic origin (Flora and Nayak, 2019). Atherosclerosis is an inflammatory disease of the large arteries and is characterised by the build-up of fatty plaques and fibrous tissue that narrows and hardens the arteries (Björkegren and Lusis, 2022). The development of hypertension can also be a risk factor for the development of early-stage atherosclerosis (Alexander, 1995).

1.1.4. Treatment of hypertension

In 2013, the World Health Organisation (WHO) set a global target of a 25% relative reduction in the prevalence of raised BP by 2025 (WHO, 2013). However, most countries are not on course to meet

these targets (Zhou *et al.*, 2021), with estimates indicating the total number of people living with hypertension worldwide could increase to 1.56 billion by 2025 (Forouzanfar *et al.*, 2017). As previously outlined, the WHO have indicated that number was close to 1.3 billion adults worldwide in 2023, showing that these forecasts are potentially within reach (WHO, 2023). Interestingly, there are data to show that the prevalence of hypertension amongst high-income regions is in a decreasing trend, with healthcare systems achieving treatment rates of up to 80% and control rates of up to 60%, potentially highlighting an educational and/or resource issue in low and middle-income regions (Zhou *et al.*, 2021). However, overall the treatment and control of hypertension remains suboptimal on a population level (Yoon *et al.*, 2015; Zhou *et al.*, 2017, 2019, 2021).

The goal of any hypertensive treatment is to reduce resting BP below clinical levels (sBP <140 mmHg; dBP <90 mmHg) to mitigate as much clinical risk as possible. Reducing BP below these levels can reduce the prevalence of cardiovascular disease and mortality in various demographics. Data has shown that a reduction in sBP of 10 mmHg can reduce the risk of coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13% (Neal *et al.*, 2000; Ettehad *et al.*, 2016). The SPRINT (Systolic Blood Pressure Intervention Trial) trial showed that an aggressive reduction of sBP to below 120 mmHg, compared to a standard reduction of sBP to below 140 mmHg, gave greater reductions in cardiovascular morbidity and mortality (Wright *et al.*, 2021). The trial enrolled 9,361 high-risk hypertensive adults to compare intensive (using multiple drugs like diuretics, ACE inhibitors, with monthly visits and frequent dose adjustments) versus standard (less aggressive drug adjustments, quarterly visits) BP management. The study found that the intensive group had a 25% lower cardiovascular event rate and 27% reduced mortality after 3.26 years, leading to early termination of the trial (Wright *et al.*, 2021).

Treatment of hypertension includes pharmacologic and nonpharmacologic (also referred to as lifestyle modification) approaches. Numerous factors, particularly where there are pre-existing comorbidities (cardiovascular disease, diabetes mellitus, or chronic kidney disease), can influence the type of treatment given (Taler, 2018). Previous 2013 ESH guidelines recommended that patients with grade 1 hypertension and low cardiovascular risk should implement non-pharmacologic treatments, such as lifestyle modification, before utilising drug treatment (Mancia *et al.*, 2013). However, based on new data showing significant treatment-induced reductions in cardiovascular events, the 2023 ESH guidelines suggest that those individuals should now receive BP-lowering drugs at the onset of treatment alongside lifestyle modification (Mancia *et al.*, 2023). The guidelines are still the same for individuals with grade 1 hypertension and high cardiovascular risk and those with grade 2 or 3 hypertension, in that both lifestyle change and BP-lowering drug treatment should be utilised at the onset of treatment (Mancia *et al.*, 2023).

1.1.5. Traditional hypertensive treatment

The traditional treatment for hypertension involves the use of pharmacological agents, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and thiazide-like diuretics (Suchard *et al.*, 2019). In the U.S. there are a total of 69 drugs in 15 separate classes that have been approved for the treatment of hypertension, many of which are available in a single pill form (Oparil and Schmieder, 2015). Due to financial constraints within the NHS (NHS, 2023), the number of available drugs is likely to be less in the U.K., although there are no official figures to demonstrate this. Such treatments have shown promising results, with angiotensin receptor blockers and calcium channel blockers having the highest treatment ranking (Noone *et al.*, 2020).

Although numerous pharmacological treatments have been shown to reduce BP to optimal ranges effectively, they often come with unwanted side effects and involve lifelong adherence (Heidenreich *et al.*, 2011). Drug monitoring studies have revealed that between 25% to 65% of patients with hypertension do not adhere to their treatment (Ceral *et al.*, 2011; Jung *et al.*, 2013; Štrauch *et al.*, 2013; Brinker *et al.*, 2014; Tomaszewski *et al.*, 2014). This lack of adherence may be related to the adverse side effects typically seen with antihypertensive medication (Benson and Britten, 2006). Data from Public Health England (PHE) shows that pharmacological treatment for hypertension costs the NHS over £2.1 billion every year (Public Health England, 2014), and the total cost for BP and cardiovascular disease related issues is estimated the cost £7.4 billion annually (NHS, 2023). Moreover, the worldwide economic cost of hypertensive treatments comes in at approximately £300 billion annually (Valenzuela *et al.*, 2021). Therefore, it is no surprise that alternative treatment methods, such as lifestyle modification, have gained popularity in recent guidance (Fisher and Curfman, 2018).

1.2. Lifestyle modification

There are a wide range of lifestyle modifications that are effective in lowering resting sBP, including a reduction in alcohol consumption (2-4-mmHg reduction) (Rehm *et al.*, 2017), weight loss (1-mmHg reduction per kg of weight loss) (Neter *et al.*, 2003), nutritional alterations, including a reduction of dietary salt (-8.7-mmHg reduction) and increased fruit and vegetable intake (-5-mmHg reduction at seven portions/day) (Samadian, Dalili and Jamalian, 2016), stress management (-10.6-mmHg reduction) (Dickinson *et al.*, 2006), quitting smoking (-8-mmHg reduction) (Farsalinos *et al.*, 2016), and physical activity (-4-9-mmHg reduction) (Samadian *et al*., 2016; Williams *et al*., 2004). As

previously discussed, lifestyle modification, also referred to as non-pharmacological treatment, has been recommended as adjunctive treatment for individuals who are currently using antihypertensive medication or as part of the initial treatment for individuals with grade 1, 2 or 3 hypertension (Mancia *et al.*, 2023). One of the main benefits of lifestyle modification is the low financial cost (Pescatello *et al.*, 2015), far cheaper than the billions spent by economies on pharmacological treatments every year (Valenzuela *et al.*, 2021). However, such modifications can also be utilised to avert the onset of clinical hypertension (Appel, 2003) and minimise the long-term risks associated with suboptimal BP. As previously mentioned, the risk of cardiovascular complications increases from as low as 115/75 mmHg, sBP/dBP, respectively (Jones and Hall, 2004). There is also a 90% residual lifetime risk of a 55-year-old individual developing hypertension (Vasan *et al.*, 2002). As such, rather than simply waiting for hypertension to develop and then treating the issue once it becomes a health threat, lifestyle modification may also be used amongst normotensive demographics as a preventative measure.

1.2.1. Physical activity

One lifestyle modification that has received growing interest in recent recommendations is physical activity. Physical activity is an umbrella phrase commonly used throughout the literature. However, it is important to define related terms such as 'exercise' separately due to their unique characteristics and application. Physical activity relates to any bodily movement that expends energy above resting levels, which can comprise daily routine tasks such as commuting, occupational tasks, or household activities, as well as purposeful health-enhancing movements and activities (Caspersen *et al*., 1985). Exercise is a component of physical activity that entails a more planned, structured, and repetitive element, with the primary intention of improving or maintaining health. Unlike physical activity, the acute programme variables of an exercise programme are often deliberately manipulated to enhance training adaptations (Diaz and Shimbo, 2013).

The association between physical activity and the development of hypertension is now well established, with substantial evidence supporting acute, chronic and dose-dependent inverse relationships (Prasad and Das, 2009). Data has shown that physical inactivity may account for 5–13% of the risk in the development of hypertension (Geleijnse, Kok and Grobbee, 2004). Participation in regular physical activity has been shown to both prevent hypertension and also act as a method of treatment for hypertension (Borjesson *et al.*, 2016). The favourable effects of physical activity on BP reduction have been consistently yielded over the past four to five decades (Diaz and Shimbo, 2013; Edwards *et al*., 2023) and there is now an overriding consensus that those who are physically active throughout their life are less likely to have raised BP (Parker *et al.*, 2007; Carnethon *et al.*, 2010), as

well as a range of broader diseases and associated morbidities, such as cancer, recurrent falls, dementia, Alzheimer's disease, and depression (Cunningham *et al.*, 2020).

One of the key priority actions set out by the WHO is the implementation of public health policies that aim to reduce the number of physically inactive individuals (WHO, 2019). The WHO Global Action Plan (GAP) for the Prevention and Control of NCDs (non-communicable diseases) (2018–2030) set a global target of a 15% relative reduction in physical inactivity by 2030 (WHO, 2019). However, with the growing prevalence of decreased physical activity levels in the modern lifestyle, the situation can potentially worsen (Ng and Popkin, 2012). Indeed, estimates show that approximately 31% of adults are physically inactive (i.e. do not achieve 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity, or an equivalent combination per week), indicating a lack of progress towards reaching the WHO target (Cunningham *et al*., 2020). Globally, there was a 5% increase in physical inactivity levels between 2010 (26%) and 2022 (31%). If this trend continues, physical inactivity levels around the world are projected to rise to 35% by 2030 (38% in females and 32% in males) (WHO, 2024). These data reveal the world is off track to meet the global target of a 15% relative reduction in physical inactivity by 2030.

Reporting levels of physical inactivity is also problematic by itself. Research has shown that although approximately 60% of U.S. adults report meeting the recommended physical activity guidelines, the actual numbers may be less than 5% when physical activity is accurately measured using an accelerometer (Miller *et al.*, 2014). The recent coronavirus disease 2019 (COVID-19) has also exemplified the issue, with studies showing physical activity decreased by over 25% during the pandemic (Meyer *et al.*, 2020; Tison *et al.*, 2020; Bu *et al.*, 2021; Meiring *et al.*, 2021). Aside from the increased risk of hospitalisation and mortality (Sallis *et al.*, 2021), decreased physical activity during the COVID-19 pandemic was also linked to poorer mental health outcomes, highlighting the range of negative implications linked to physical inactivity (Faulkner *et al.*, 2021).

1.2.2. Details of current physical activity recommendations

The latest physical guidelines set by the WHO state that adults should aim for between 150 to 300 minutes of moderate-intensity physical activity or 75 to 150 minutes of vigorous-intensity physical activity each week. This equates to a minimum of 30 minutes of moderate-intensity activity 5 days per week, which has been shown to provide substantial benefits across a broad range of health outcomes for sedentary adults (WHO, 2021). The guidelines now also state that individuals should engage in resistance and flexibility training at least twice a week, promoting improvements in muscular strength and endurance, the maintenance of lean body mass, and the overall preservation

of functionality (WHO, 2021). However, it should be noted that this dose of exercise may not be satisfactory in preventing unhealthful weight gain for those individuals who require either a restriction of caloric intake or additional physical activity (Blair, LaMonte and Nichaman, 2004).

1.2.3. Aerobic and high-intensity interval training

Aerobic training protocols are historically accepted as the primary foundation of any health-related exercise programme (Murray *et al*., 2023). The American College of Sports Medicine (ACSM) defines aerobic exercise as 'any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature' (ACSM, 2013, p177). Many European and American hypertension organisations, such as the AHA, emphasise continuous forms of aerobic exercise (Costa *et al.*, 2018). A large amount of research now shows the effective hypotensive effects of aerobic exercise on resting (Halbert *et al.*, 1997; Kelley, Kelley and Vu Tran, 2001; Whelton *et al.*, 2002; Cornelissen and Smart, 2013; Johnson *et al.*, 2014) and ambulatory BP (Cornelissen *et al*., 2013; Sosner *et al*., 2017). A recent systematic review and meta-analysis demonstrated that aerobic exercise training produced reductions in both sBP (-5.11 mmHg [95% confidence intervals [CI] -7.36, -2.85) and dBP (-2.97 mmHg [CI -4.99, -0.94) (Lemes *et al.*, 2018).

There are numerous aerobic protocols that have been shown to be effective at reducing resting BP, including walking (Park, Rink and Wallace, 2008), running (Fagard, 2006), cycling (Zeigler *et al.*, 2018), swimming (Wong *et al*., 2019), high-intensity interval training (HIIT) (Clark *et al.*, 2020) and sprint interval training (SIT) (Adamson *et al.*, 2019) – both HIIT and SIT, particularly SIT, also stress the anaerobic metabolic pathways due to their inherent short duration and high-intensity (Hebisz and Hebisz, 2021). Interestingly, comparisons between low or moderate-intensity continuous aerobic training and HIIT have shown similar BP-reducing effects (Costa *et al.*, 2018; Carpes *et al.*, 2022; Edwards *et al.*, 2023). In a systematic review and meta-analysis by Edwards *et al.,* (2023), mean sBP and dBP reductions were -4.49 (CI -3.5, -5.5) and -2.53 (CI -1.8, -3.2) mmHg, respectively, following aerobic exercise training (walking, cycling and running), and -4.08 (CI -2.6, -5.5) and -2.5 (CI -1.2, -3.8) mmHg following HIIT and SIT. Although HIIT is prescribed with a smaller time commitment and overall training volume than aerobic exercise training (Gibala *et al.*, 2012), adherence rates and attendance to exercise sessions have been shown to be similar between both modes of exercise (Costa *et al.*, 2018).

1.2.4. Dynamic resistance training

Dynamic resistance exercise training involves concentric and/or eccentric muscular contractions that alter both the length and tension of the muscle (Cornelissen & Smart, 2013) and may consist of either constant or variable resistance by using either weight machines or free weights (Vanhees *et al.*, 2012). Typically, dynamic resistance exercise training has been known for its ability to improve muscular strength and functional capacity (Fragala *et al.*, 2019), as well as the prevention of sarcopenia and osteoporosis (Rodrigues *et al.*, 2022). However, a growing amount of research now shows that dynamic resistance training can help improve metabolic and cardiovascular health (Cornelissen *et al*., 2011; Hansen *et al*., 2019; Vanhees *et al*., 2012; Williams *et al*., 2007). The 2023 ESH guidelines has also highlight how dynamic resistance exercise training can improve BP and prevent cardiovascular disease (Mancia *et al.*, 2023). In terms of its BP-lowering effects, a systematic review and meta-analysis found that both medium-term and long-term resistance training produced significant reductions in both sBP (-4.02 [CI −5.92, −2.11] mmHg and -5.08 [−10.04, –0.13] mmHg, respectively) and dBP (-1.73 [−2.88, –0.57] mmHg and -4.93 [−8.58, –1.28] mmHg, respectively) versus control (Ashton *et al.*, 2020). More recently, Edwards *et al*., (2023) also found significant reductions in both sBP (-4.55 [CI -3.2, -5.9] mmHg) and dBP (-3.04 [CI -2.2, -3.9] mmHg) following dynamic resistance training. Other meta-analytic findings have also shown similar moderate reductions in resting BP following dynamic resistance training (Cornelissen *et al*., 2011; Cornelissen & Smart, 2013; Kelley *et al*., 2001).

1.3. Adherence to lifestyle modifications

Despite the benefits of lifestyle modifications, adherence rates are low (Iloh, 2014; Fang *et al.*, 2016; Selçuk *et al.*, 2017; Tibebu, Mengistu and Negesa, 2017; Dhakal, Takma and Neupane, 2021). Data from an American national survey stated that only 1.7% of hypertensive patients engaged with all five of the key lifestyle modifications - healthy diet, increased physical activity, weight control, smoking cessation, and limited alcohol consumption (Fang *et al.*, 2016). Research has also shown that adherence to lifestyle modification can sometimes be less than to hypertensive medication. Selçuk *et al.,* (2017) found that among hypertensive patients, 78% adhered to their prescribed anti-hypertensive medication, but just 42% adhered to lifestyle modifications. Another study looking at adherence rates amongst hypertensive patients found that just 23% of patients adhered to lifestyle modifications (Tibebu, Mengistu and Negesa, 2017). It has been reported that socio-demographic factors, such as education, marital status, and duration of disease, can influence the degree of

adherence to lifestyle modification treatments, highlighting the complexity and nuance of this issue (Obirikorang *et al.*, 2018).

1.3.1. Exercise adherence and attrition

Despite the recognised benefits of exercise, in most cases, the positive effects are only achieved if the recommended exercise programme is strictly adhered to (Collado-Mateo *et al.*, 2021). The current physical activity guidelines set by the WHO are a minimum of 150 minutes (30 minutes x 5 days per week) of moderate-intensity physical activity, with the potential for additional health benefits when performing 300 minutes per week (WHO, 2021). Nonetheless, the guidelines do state that any physical activity is better than none and that adults should aim to be active every day (WHO, 2021). However, as previously outlined, data has also shown that approximately 31% of the global population are not adhering to the recommended WHO physical activity guidelines (Cunningham *et al.*, 2020), although the actual numbers may be less than 5% when physical activity is accurately measured using an accelerometer (Miller *et al.*, 2014). Low adherence is also an issue within research studies aimed at sedentary individuals, with data suggesting that only 66% of individuals comply with the study design in its entirety (Linke, Gallo and Norman, 2011). However, adherence rates are not always reported in research studies and so the actual number may be higher (Linke, Gallo and Norman, 2011). There are some strategies, such as the use of consumer-based wearable activity, that have been shown to improve adherence rates to exercise training. However, these strategies normally involve high human or economic resource (i.e. wearable technology, or human interaction/coaching), which limit their impact and widespread adoption (Brickwood *et al.,* 2019).

Poor adherence rates or non-compliance (i.e. failure to completely meet exercise prescriptions) should not be confused with attrition rates (i.e. the drop-out rate from an exercise programme) (Mullen *et al.*, 2013). Rather than individuals not complying with the training instructions, either by missing sessions or not completing each session in its entirety, many individuals drop out of training programmes altogether. In previous studies amongst sedentary older age groups (>60 years), approximately 50% of participants dropped out of the training programme within the first 6 months of participation, and a mere 20% were still participating after 24 months (Dishman, 1988; Ettinger *et al.*, 1997; Resnick & Spellbring, 2000). Moreover, data from a study observing a community fitness centre demonstrated that approximately 63% of new members left the centre and dropped out of their gym programme before the third month, and less than 4% were still participating after 12 months of activity (Sperandei, Carvalho Vieira and Reis, 2019). Attrition rates are also high in research studies aimed at sedentary individuals (25– 50%), although there are concerns with a lack

of data reported on attrition, so these numbers may be much higher (Linke, Gallo and Norman, 2011).

1.3.2. Factors affecting physical activity adherence and attrition

The most commonly cited sociodemographic factor that can decrease adherence to physical activity is a lack of time (Alsobayel *et al*., 2020; Zunft *et al*., 1999). Many individuals struggle to commit to 30 minutes of physical activity daily and either skip out on training sessions or refrain from any physical activity altogether. There has also been criticism of the current guidelines in terms of their practicability and accessibility to the general population (Weed, 2016). High economic costs, such as gym memberships and expensive equipment, as well as self-confidence issues related to certain demographics feeling judged within a fitness setting, are some of the other common barriers cited (Salmon, 2001).

When designing exercise programmes, King *et al*., (1992) states there are three main categories to consider when trying to reduce attrition and improve adherence: environmental factors, personal factors and programme factors. Environmental factors comprise the physical (such as programme location) and social environment (such as social support). Easy access to the exercise programme, along with no significant financial obligations, should be a high priority. Personal factors include the demographic involved and also the beliefs and perception of the individual towards exercise training (King *et al.*, 1992). Indeed, the relationship between the participants and the programme organisers should be a primary concern (Dishman & Sallis, 1994). A close connection should be maintained throughout the training programme, with the participants fully engaged and aware of the methods and details of the programme. Likewise, the organisers need to appreciate the commitments and constraints of participants, with friendly support, consistent instruction, and peer support provided (Dishman & Sallis, 1994; Warren-Findlow *et al*., 2003). And lastly, and perhaps most pertinent for this thesis, are programme factors, such as the specific design and acute programme variables, (King *et al.*, 1992). The sets, reps, intensity and volume, as well as the physical training environment, are often controlled and manipulated by practitioners and researchers, and thoughtful considerations must take place when planning the intervention in order to minimise the risk of dropouts (Preloran, Browner and Lieber, 2001). From an adherence and attrition perspective, interventions that produce the greatest reductions in BP, and are also the most user-friendly, accessible and time-efficient, are arguably more desirable (Bickel, Cross and Bamman, 2011). One such exercise mode which may fit these criteria is isometric exercise training (IET).

1.4. Isometric exercise and resting blood pressure

Isometric exercise training is a form of resistance training involving a constant muscular contraction with little to no change in the muscle length or joint angle (Cornelissen & Smart, 2013). This typically occurs when the muscular force produced equals the resistance force, or the opposing load/resistance is greater than the muscular force (e.g. pushing against a brick wall) (Baffour-Awuah *et al.*, 2023). Many daily activities, such as lifting and holding items (e.g. carrying a shopping bag at arm's length), involve isometric contractions (Lind, 1983). Pure static contractions are only observed in vitro models as human cognition will always permit some movement (Millar *et al*., 2013). Therefore, within this thesis an isometric contraction will be regarded as a sustained contraction with no discernible change in muscle length.

Healthcare advisors have not traditionally recommended IET as a suitable mode of exercise training for the treatment of hypertension (Cornelissen & Smart, 2013). It was thought that the exaggerated pressor response that occurred during acute bouts of IET was evidence that it should not be permitted, or extra care should be taken, amongst clinical populations, such as those with hypertension or cardiovascular disease (Franklin, Gordon and Timmis, 1991). However, many early studies did not consider the relationship between % of maximal voluntary contraction (MVC) – a common method of prescribing isometric exercise – and the magnitude of pressor response, often using intensities as high as 100% MVC (Kiveloff and Huber, 1971). Over the past several decades, IET has been performed mainly in the range of 30% of maximal capacity (Smart *et al*., 2019), and has shown it can be performed within safe limits without extreme pressor responses (Wiles *et al*., 2018), whilst still producing antihypertensive effects (Edwards *et al*., 2023). Research from Carlson *et al*., (2017) demonstrated that IET produces a less pronounced rate pressure product (RPP) than both aerobic and dynamic resistance training. Rate pressure product is the product of sBP and HR and is often used by cardiologists to predict myocardial oxygen uptake and is a reliable marker of cardiac function and stress (Baffour-Awuah *et al.*, 2023). The muscular contractions during isometric exercise often produce a small increase in HR, and subsequently the pressor responses are smaller than typically seen with aerobic and dynamic resistance training, resulting in a lower RPP during isometric exercise (Carlson *et al.*, 2017). As such, this may suggest that IET may be less likely to elicit cardiac complications and exertional stress than aerobic or dynamic resistance training. Indeed, research from Hansford *et al*., (2021) has shown that there is only one adverse event per 38,444 bouts of IET amongst adults with elevated BP (sBP ≥130 mmHg/dBP ≥85 mmHg).

It is now well established that IET is effective at reducing resting BP. These BP lowering effects have been demonstrated in normal (Devereux, Wiles and Swaine, 2010; Wiles, Coleman and Swaine,

2010; Badrov, Bartol, *et al.*, 2013; Hess *et al.*, 2016; Wiles, Goldring and Coleman, 2017; Baddeley-White *et al.*, 2019; Baross *et al.*, 2022), high-normal (Baross, Wiles and Swaine, 2012, 2013; Carlson *et al.*, 2016; Gordon *et al.*, 2018, 2023; Ogbutor, Nwangwa and Uyagu, 2019; Rodrigues Souza *et al.*, 2019; Taylor *et al.*, 2019; Farah *et al.*, 2020; Decaux *et al.*, 2022) and hypertensive individuals (Taylor *et al.*, 2003; Okamoto *et al*., 2020; Punia and Kulandaivelan, 2020; Javidi *et al.*, 2022; Cohen *et al.*, 2023). There have also been numerous systematic reviews and meta-analyses that have demonstrated the BP-lowering effects (Owen, Wiles and Swaine, 2010; Cornelissen and Smart, 2013; Carlson *et al.*, 2014; Inder *et al.*, 2016; Edwards, Wiles and O'Driscoll, 2022). Moreover, recent meta-analytic work has demonstrated significant sBP and dBP reductions of -8.24 (CI -6.5, -10) and -4 (-2.7, -5.3) mmHg, respectively, following IET, which are greater than the reductions seen following aerobic (sBP -4.49 [CI -3.5, -5.5] and dBP -2.53 [CI -1.8, -3.2] mmHg), HIIT (sBP -4.08 [CI -2.6, -5.5] and dBP -2.5 [CI -1.2, -3.8] mmHg), and dynamic resistance training (sBP -4.55 [CI -3.2, -5.9] and dBP -3.04 [CI -2.2, -3.9] mmHg) (Edwards *et al*., 2023). Not only are these reductions clinically significant and greater than other forms of exercise training, but they are also comparable, or potentially greater, to the reductions commonly observed following standard pharmacological therapies (Law, Morris and Wald, 2009; Paz *et al.*, 2016). Moreover, short-term (<12 weeks) IET studies that have reported good adherence to training (Carlson *et al.*, 2016; Gordon *et al.*, 2018; Baddeley-White *et al.*, 2019; Ogbutor, Nwangwa and Uyagu, 2019; Nemoto *et al.*, 2021; Javidi *et al.*, 2022; Fecchio *et al.*, 2023) potentially owing to the small time commitment and increased accessibility.

The original interest in IET as a potential mode of exercise to lower resting BP was spurred by several landmark studies. The first study by Kiveloff & Huber (1971) investigated the effects of maximal short-duration isometric contractions over 5 to 8 weeks utilising whole-body muscle groups, including the neck, buttocks and abdomen. The study found that IET reduced resting BP in hypertensive individuals, but found no such reductions amongst normotensive participants. Another early study by Buck & Donner (1985) studied the effects of isometric occupational exercise and the incidence of hypertension. The study found that those workers who were regularly exposed to moderate or heavy occupational isometric exercise had a reduced rate of hypertension despite confounding variables such as age, obesity and alcohol intake.

Subsequent to this, Wiley *et al*., (1992) studied the effects of isometric handgrip (IHG) training on resting BP. The study utilised a novel protocol involving brief handgrip contractions separated by rest periods to avoid any dangerous pressor responses that may occur with prolonged fatiguing isometric contractions. As such, only moderate recurrent rises in sBP and dBP pressures acted as the stimuli for training adaptations in resting BP rather than a long continual elevation in BP. Two different protocols were studied by Wiley *et al*., (1992). One comprised 4 x 2-minute bouts of IHG exercise at

30% of their maximum effort for the day, separated by a 3-minute rest period. This was performed three times per week over 8 weeks. The second protocol involved 4 x 45-second bouts of IHG at 50% of their maximal effort for the day, separated by only 1 minute of rest. This was performed five times per week over a 5-week period. Both protocols produced significant reductions in resting BP. However, the first protocol, involving 4 x 2-minute bouts of isometric exercise, produced greater reductions in sBP and dBP, with group averages of -12.5 and -14.9 mmHg, respectively.

The results from this study (Wiley *et al.*, 1992) paved the way for the now widely adopted 4 x 2-minute IET protocol utilised in many research articles (Edwards *et al*., 2024). Although many studies have attempted to manipulate acute programme variables within IET studies, such as the intensity, frequency, duration and rest periods, the 4 x 2-minute protocol has stayed somewhat consistent. One key benefit of utilising a 4 x 2-minute protocol is the reduced time commitment, with only 8 minutes of active exercise time. Depending on the rest periods used, each session has a total time commitment between 11 and 20 minutes per session (Millar *et al*., 2013). When compared to the guidelines for aerobic exercise training (≥30 minutes/day), the time commitment with IET is considerably shorter (Pescatello *et al.*, 2015). This reduced time commitment, as well as the greater BP reductions compared to other forms of exercise training (Edwards *et al*., 2023), may help to break down some of the barriers to exercise and increase adherence to exercise programmes.

1.4.1. Mode of isometric exercise training

Various modes of IET have been utilised within research studies. One of the more commonly used modes is IHG training which can be prescribed either unilaterally (Wiley *et al.*, 1992; Ray and Carrasco, 2000; Peters *et al.*, 2006; McGowan, Visocchi, *et al.*, 2006, 2007; Millar *et al.*, 2007, 2013; Badrov, Horton, *et al.*, 2013; Garg *et al.*, 2014; Badrov, Dylan Olver and Kevin Sh Oemaker, 2016; Carlson *et al.*, 2016; Hess *et al.*, 2016; Cohen *et al.*, 2023) or bilaterally (Wiley *et al.*, 1992; Taylor *et al.*, 2003; McGowan, Levy, *et al.*, 2006; Millar *et al.*, 2007, 2008; Stiller-Moldovan, Kenno and McGowan, 2012; Badrov, Horton, *et al.*, 2013; Pagonas *et al.*, 2017; Goessler *et al.*, 2018; Somani *et al.*, 2018). During unilateral IHG, contractions are either performed with the dominant or non-dominant arm, while bilateral contractions are typically performed using alternate hands rather than both simultaneously. Other modes of IET that have been used to reduce resting BP include arm flexion (Howden *et al.*, 2002) and double-leg extension (Howden *et al.*, 2002; Devereux, Wiles and Swaine, 2010; Wiles, Coleman and Swaine, 2010; Baross, Wiles and Swaine, 2013).

Notwithstanding the aforementioned benefits, the vast amount of IET research has focused on protocols involving the use of costly and/or laboratory-based equipment. For example, the Zona Plus

Series 3 handgrip device, which is priced at around £549 (Baddeley-White *et al.*, 2019), presents a significant economic commitment. Modes such as the arm flexion and double-leg extension also involve the use of expensive laboratory-based equipment (Howden *et al.*, 2002; Devereux, Wiles and Swaine, 2010; Wiles, Coleman and Swaine, 2010; Baross, Wiles and Swaine, 2013) presenting both an economical and accessibility issue. Any travel commitments, such as to and from a laboratory, are also counterintuitive to the advantageous short duration of IET itself. Although Millar *et al*., (2008) proposed an inexpensive spring IHG device that could be used in the home, there were issues with the accuracy and monitoring of intensity, which as previously discussed, is important for safety and clinical application (Baffour-Awuah *et al.*, 2023). As such, it could be said that the associated financial expenses and/or specialised laboratory equipment accompanying these modes of IET may hinder the effectiveness of IET as a viable treatment for hypertension (Goldring, Wiles and Coleman, 2014).

1.4.2. Isometric wall squat training

Alternative protocols have recently been introduced into the field in an effort to develop and advance the real-world and clinical application of IET. As previously discussed, sedentary individuals have a high proclivity to abstain from, or not adhere to, physical activity guidelines. This highlights the importance of addressing any potential limitations to the prescription of IET and finding methods to circumvent the factors that may inhibit participation, such as the economic costs and accessibility (Zunft *et al.*, 1999; Alsobayel *et al.*, 2020). Isometric wall squat (IWS) training is a newly developed form of IET that has shown to be effective at reducing resting BP (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; O'Driscoll, Edwards, Coleman, *et al.*, 2022; Cohen *et al.*, 2023; Lea, O'Driscoll and Wiles, 2023). The IWS protocol involves maintaining a static wall squat position – sometimes referred to as a 'wall sit' (Gillingham, 1970). The knee angle during the IWS is commonly prescribed relative to an individualised target heart rate (HR) which is established during an incremental wall squat test (this will be explained further in Chapter 2, section 2:10:3) (Wiles, Goldring and Coleman, 2017). Other methods of prescribing the knee angle have also been recently introduced, but are not as well researched and recognised as the HR-based protocol outlined above (this will be explored further in Chapter 7, section 7:1).

Similar to previous forms of IET, the protocol used for IWS training involves a minimal time commitment, with only three sessions of 4 x 2-minute bouts of exercise, interspersed with 2 minutes of rest, bringing the total weekly volume to 24 minutes (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; O'Driscoll *et al.*, 2022; Cohen *et al.*, 2023). However, unlike some previous modes of IET, IWS training requires minimal equipment or supervision to execute, making it

highly accessible and user-friendly (Goldring, Wiles and Coleman, 2014). Furthermore, the total cost for the equipment used during IWS training when prescribed by a health professional also comes in at <£30 (Wiles, Goldring and Coleman, 2017), which is somewhat less costly than the Zona Plus Series 3 handgrip device (Baddeley-White *et al.*, 2019). Exercise that has minimal financial obligations and requires no specialised equipment or supervision could assist with the implementation and sustainability of regular exercise into an individual's lifestyle (Jette *et al.*, 1999). Furthermore, accessible home-based protocols, such as with IWS training, allow individuals to complete the exercise programme in the comfort and privacy of their own home, allowing easy integration into daily routines and eliminating the burden of travel (Steele *et al.*, 2008).

Not only does IWS training have numerous accessibility and financial benefits, but data has shown that the BP reductions are comparable to, or even greater than, all other modes of exercise training (Edwards *et al.*, 2023). The reductions seen following IWS training amongst normal and high-normal participants range between -4/-3 and -15/-6 mmHg (sBP/dBP) following just 4 weeks of training (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023) (see Table 1:2). Taylor *et al*., (2019) also demonstrated reductions in ambulatory BP over a 24-hour period of -11.8 and -5.6 mmHg in sBP/dBP, respectively, which is important as research has shown that ambulatory BP can be more predictive of target organ damage (Mancia *et al.*, 2013). It is noteworthy that the resting BP reductions found following IWS training are also similar or greater to the typical reductions seen following antihypertensive medication (Law, Morris and Wald, 2009; Paz *et al.*, 2016). In contrast, data from a recent meta-analysis showed that mean reductions following IHG training were -7.1 (CI -4.7, -9.5) mmHg and -3.46 (CI -1.7, -5.2) mmHg for sBP and dBP, respectively (Edwards *et al.*, 2023). Although some studies (Cohen *et al.*, 2023), have shown greater BP reductions following IHG training (-11.2 and -4 mmHg for sBP/dBP, respectively), pooled data from meta-analysis and systematic reviews have consistently demonstrated smaller BP reductions following IHG training (Bentley, Nguyen and Thomas, 2018; Smart *et al.*, 2019; Loaiza-Betancur and Chulvi-Medrano, 2020; Oliveira *et al.*, 2022). Research has also shown that compared to other forms of IET, such as IHG exercise, individuals perceive IWS exercise to be less strenuous (interpreted through rate of perceived exertion (RPE) data), even though it has been shown to produce more pronounced cardiovascular responses, a likely physiological stimulus for BP adaptation (Swift *et al.*, 2022).

Table 1:2 Previous IWS training studies

Study	Duration	Participants	Mean baseline BP (SBP/DBP) mmHg	Reductions (SBP/DBP) mmHg
Wiles et al., 2017	4 weeks	Normotensive	126/79	-4/3
Taylor et al., 2019	4 weeks	High-normal	132.4/81.4	-12.4/6.2
Decaux et al., 2022	4 weeks	Normotensive and high-normal	131/80	-15/5
O'Driscoll et al., 2022	1 year	High-normal	132.3/82	-10.5/8
Cohen et al., 2022	12 weeks	Unmedicated hypertensives	141.2/87	-12.9/4.1
Lea et al., 2023	4 weeks	Normotensive and high-normal	134/82.6	-14.2/6.4

First author, duration of training, participant demographic, mean baseline BP and magnitude of reduction in BP for all previous IWS training studies.

1.4.3. Mechanisms for blood pressure reduction following isometric exercise training

Isometric exercises produce a unique stimulus compared to other dynamic forms of exercise due to the static nature of the contraction (Baffour-Awuah *et al.*, 2023). The sustained nature of isometric contractions occludes blood flow within the active muscle (ischemia) and increases vascular resistance, resulting in a transient rise in BP known as the pressor response (Badrov et al., 2016). Previous work has demonstrated that the pressor response is greater during IWS exercise than IHG exercise, which is likely due to the larger muscle mass recruitment and subsequent greater area of occlusion (Swift et al., 2022). Isometric contractions affect group III/IV afferents sensitive to mechanical and metabolic stimuli which activate centrally mediated cardiovascular responses related to sympathetic activation and decreased parasympathetic activity. The transient increase in vascular resistance also increases cardiac afterload and $\dot{Q}$, which places a unique stress on the myocardium (Edwards et al., 2023). Following the cessation of the contraction and release of the pressor response there is reperfusion of the muscle with reactive hyperaemia. This increased blood flow and subsequent pattern of shear stress acts upon the endothelial cells lining of the vasculature to stimulate the secretion of flow-induced vasoactive substances, such as NO, prostaglandins, potassium, adenosine triphosphate and other important vasodilatory mechanisms (Dillon, Shepherd,

et al., 2020; Petterson et al., 2021). There are also changes in autonomic and baroreflex function post-isometric exercise, with a greater dominance of parasympathetic modulation, which may be related to the decreased TPR commonly seen post-isometric exercise (Taylor et al., 2017; Swift et al., 2022). Accompanying the increased vagal action, there is an increase in BRS during recovery which suggests a post-exercise resetting of the baroreceptors as HR and BP begin to reduce (Iellamo et al., 1999; 1999a).

When looking at the specific mechanisms responsible for any BP reductions following IET, fundamentally, they must be related to alterations in $\dot{Q}$ and/or TPR; the two determining factors of arterial BP. Data from a recent meta-analysis has shown that as well as significant reductions in sBP, dBP, and MAP, IET produces statistically significant reductions in HR, significant increases in SV, with no change in $\dot{Q}$ (Edwards, Wiles and O'Driscoll, 2022). Despite the reported reductions in HR, it should be acknowledged that the majority of IET literature has not supported any reductions in resting HR (Millar *et al*., 2014). Nonetheless, the decrease in resting HR reported by Edwards, Wiles and O'Driscoll (2022) is likely related to cardiac autonomic and baroreflex adaptations (Tank *et al.*, 2005). Indeed, significant improvements in the heart rate variability (HRV) measures and baroreceptor sensitivity (BRS) have been widely reported providing a strong argument for large autonomic contribution to any BP and HR reductions following IET (Millar *et al.*, 2014; Lawrence *et al.*, 2015; Rickson, Maris and Headley, 2021; Edwards, Wiles and O'Driscoll, 2022; Baffour-Awuah *et al.*, 2023). The increase in SV reported may be related to improvements in cardiac mechanics (evidenced by an increase in global work efficiency) and cardiac function (reduced myocardial performance index) as by-products of a reduction in cardiac afterload (O'Driscoll *et al.*, 2022).

The improvements in cardiac autonomic balance are potentially mediated through an increase in vagal activity and/or a decrease in sympathetic activity (Edwards, Wiles and O'Driscoll, 2022). Autonomic regulation is moderated through a coordinated system of reflexes involving feed-forward signals originating from either central command (i.e. higher brain centres), as well as peripheral feedback from muscle sensory afferents within the active muscle (i.e. exercise pressor reflex) (Badrov, Dylan Olver and Kevin Sh Oemaker, 2016). Heart rate variability is used to measure cardiac autonomic modulation (Millar *et al*., 2013). The frequency domain method of establishing HRV, measures overall power spectral density (PSD-RRI) to interpret the power variance distribution as a function of frequency (Taylor *et al*., 2017). Low-frequency (LF) parameters of PSD-RRI are associated with sympathetic activity, while high-frequency (HF) parameters are associated with parasympathetic activity (Pomeranz *et al*., 1985). An increase in HRV and HF parameters is indicative of an increase in cardiac vagal tone (Bonaz, Sinniger and Pellissier, 2016; Kim *et al.*, 2018; Honkalampi *et al.*, 2021). The ratio of low and high frequencies (LF:HF ratio) is considered a

representation of sympathovagal balance (Malliani, 1999). Improvements in the LF:HF ratio has been frequently observed following IET (Taylor *et al.*, 2003, Taylor *et al.*, 2019; Carlson *et al.*, 2014). Following 4-weeks of IWS training, Taylor *et al*., (2019) found significant increases in total PSD-RRI of HRV, as well as an increase in the HF component, with no change in the LF component. This resulted in a reduction in the overall LF:HF, which signifies a decrease in sympathetic and an increase in parasympathetic activity. Taylor *et al*., (2003) also found similar results following 4 weeks of IHG training.

The autonomic modulation may be related to the decreased BRS previously discussed. Decreased BRS would decrease sympathetic outflow and inhibit vascular tone, resulting in vasodilation (Edwards, Wiles and O'Driscoll, 2022). Research has also shown alterations in the peripheral afferent pathways modulating the autonomic response (Badrov, Olver and Oemaker, 2016). Acute bouts of isometric exercise result in muscle ischemia, intramuscular pressure, and metabolite release (including ATP, hydrogen ions, and lactate). Mechanoreceptors and metaboreceptors within the muscle are then activated, both of which control muscle sympathetic nerve activity traffic to the central nervous system (Rickson, Maris and Headley, 2021). This response, known as the exercise pressor reflex, leads to a transient increase in BP during exercise. With IET training, this reflexive response is attenuated (even in a rested state), therefore lowering the BP response at rest (Rondon *et al.*, 2006; Secher and Amann, 2012).

Reductions in TPR have also been frequently reported following IET (Millar *et al.*, 2014; Lawrence *et al.*, 2015; Rickson, Maris and Headley, 2021; Edwards, Wiles and O'Driscoll, 2022). Several vascular adaptations that may be linked to reductions in TPR have been reported following IET, both systemically and locally within the active muscle. Previous research has demonstrated an increase in endothelial-dependent vasodilation and an increase in NO production (Olher *et al.*, 2020). The increase in NO is associated with 1) improved endothelial function, 2) increased vasodilation in active blood vessels, and 3) reduction in arterial stiffness and improved haemodynamics (Rickson, Maris and Headley, 2021). The mechanistic pathways by which the vascular adaptations and NO release occur may be related to reactive hyperaemia, which is a result of the increased demand of muscular tissue during the isometric contraction. An isometric contraction differs somewhat from aerobic or dynamic resistance training due to the static nature and altered length-tension relation (Rickson, Maris and Headley, 2021). At the cessation of an isometric contraction, there is an influx of blood to the active muscle, stimulating the local release of NO and other vasodilators, which is thought to be one of the primary mechanisms contributing to the improved BP observed following IET (Hess & Smart, 2017; Souza *et al*., 2019). Another possible mechanistic pathway is the increase in BP and $\dot{Q}$ seen during isometric contractions (Swift *et al.*, 2022) which would result in systemic shear

stress (Tinken *et al.*, 2009). This may activate systemic endothelial NO release and promote vasorelaxation, although some research suggests vascular adaptations following IET occur locally in the muscle rather than systemically (McGowan, Visocchi, *et al.*, 2007; Badrov, Dylan Olver and Kevin Sh Oemaker, 2016; Inder *et al.*, 2016).

Improvements in the redox status have also been shown following IET, demonstrated by the upregulation of systemic antioxidants and a decreased production of reactive oxygen species (ROS) (Peters *et al.*, 2006). The ischemia-reperfusion seen within the active muscle following isometric exercise may mediate oxidative stress related to the dramatic change from low oxygen levels during ischemia to high oxygen levels during reperfusion. This results in increased antioxidant activity to avert or reduce damage to the vasculature arising from the combined pressure changes and oxygen exposure (Santangelo *et al.*, 2003). Low concentrations of intracellular ROS have an important role in the normal redox signalling maintaining vascular function and integrity. The bioavailability of NO is also highly dependent on the redox status through a reduction in endogenous inhibitors of NO synthases (Rodrigo, González and Paoletto, 2011).

Evidence suggests that the functional or structural nature of any vascular adaptations differs depending on the time course and duration of training (Tinken *et al*., 2008; 2010). Tinken *et al*., (2010) found that NO-dependent functional adaptations, such as improved endothelial function, initially increased following 2 weeks of IHG training but then returned close to resting values after 8 weeks of training. The attenuation of these functional adaptations was surpassed by an increase in peak reactive hyperaemia across the 8 weeks of training (peak reactive hyperaemia is a commonly used method for determining structural vessel remodelling). Similar results were also found by Badrov *et al.*, (2013) who observed an increase in peak reactive hyperaemia following 8 weeks of IHG training. Baross, Wiles and Swaine (2012) also found that potential structural vascular adaptations, such as increased artery diameter, only occur after longer periods of IET, between 4-8 weeks. The BP status of participants used has also been shown to affect vascular adaptations. Wiles, Goldring and Coleman (2017) found no changes in TPR following 4 weeks of IWS exercise training and suggested this was due to the normotensive status of the cohort used. On the contrary, Taylor *et al*., (2019) did find reductions in TPR following 4-weeks of IWS amongst a cohort of high-normal participants. However, Wiles, Goldring and Coleman (2017) did suggest that as the calculation of TPR utilised in the study reflected systemic vascular resistance, localised improvements in vascular function could not be ruled out.

Notwithstanding the above, Edwards, Wiles and O'Driscoll (2022) suggest there is still a lack of conclusive literature relating to whether the vascular changes following IET are locally regulated via

endothelial-dependent mechanisms or systemically modulated via structural remodelling and/or functional adaptations in autonomic vasomotor control. Indeed, BP adaptations resulting from IET are likely multifactorial and come from small changes in the multiple regulatory pathways (Rickson, Maris and Headley, 2021). However, due to variations in study designs and the BP status of participants used in each study (medicated/unmedicated, normotensive/hypertensive), the precise mechanisms for these physiological alterations are still somewhat speculative. Furthermore, the majority of studies are only powered to detect changes in BP rather than the mechanistic parameters previously discussed. As such, IET studies with larger sample sizes are required to enhance current understanding about the related mechanisms for BP reductions following IET. Larger sample-sized studies can also help with sub-group analysis, such as comparisons between males and females. Indeed, many studies that analyse the main effects stratified by sex are often underpowered, thus increasing the risk of type-2 error or false-negative results (Ferreira and Patino, 2017; Rich-Edwards *et al.*, 2018).

1.4.4. Rate and magnitude of BP reductions

As previously discussed, the magnitude of BP reductions following IWS training is greater than other forms of IET (IHG and bilateral-leg IET) (Edwards *et al.*, 2023). Another important aspect of IWS training is the rate at which resting BP reductions occur. The reductions in resting BP found by Wiles, Goldring and Coleman (2017) following IWS training (-4 and -3 mmHg for sBP and dBP, respectively) occurred at either a faster (Wiles, Coleman and Swaine, 2010) or equivalent rate (Devereux, Wiles and Swaine, 2010) in comparison to bilateral-leg IET (although it must be noted there were inherent differences in the prescription of intensity - EMG%, MVC%, and wall squat knee angle). Wiles, Goldring and Coleman (2017) suggested this may be a result of a larger muscle mass recruitment during IWS exercise, as leg extensions isolate the quadriceps (Delavier, 2002) and use a smaller muscle mass in comparison to the IWS exercise, which recruits a wider range of synergistic muscle groups (Contreras, 2014).

Previous research has shown that isometric contractions utilising larger muscle mass require increased central and peripheral drive (Gálvez *et al.*, 2000), and as such the cardiovascular control centres will be stimulated, resulting in a larger cardiovascular response (Swift *et al.*, 2022), which is a likely stimulus for resting BP adaptations (Taylor *et al*., 2017). Increased motor unit recruitment has also been shown to enhance the pressor response during exercise (Seals, 1989) due to either greater stimulation of the mechanoreceptors arising from a higher magnitude of physical deformation (Gálvez *et al.*, 2000) and/or increased stimulation of the metaboreceptors due to a rise in metabolites (Iellamo *et al.*, 1999). Recent research from Swift *et al*., (2022) that found a significantly

greater cardiovascular response (represented by HR and $\dot{Q}$) and a significantly greater post-exercise hypotensive response following IWS exercise compared to IHG exercise supports this notion. Swift *et al.*, (2022) also found the RPE was significantly less during IWS exercise compared to IHG, demonstrating that greater physiological responses can be achieved with less perceived exertion. It has also been suggested that squat-based exercises, such as the IWS, place less pressure on the knee joint in comparison to other lower-limb movements, such as the leg extension (Signorile *et al.*, 1994), which may have implications for those with lower-limb injuries.

1.5. The detraining effect and minimum session stimulus

Although IWS training seems to mitigate many of the barriers to exercise participation and adherence to short term IET is generally high (Carlson *et al.*, 2016; Gordon *et al.*, 2018; Baddeley-White *et al.*, 2019; Ogbutor, Nwangwa and Uyagu, 2019; Nemoto *et al.*, 2021; Javidi *et al.*, 2022; Fecchio *et al.*, 2023), it should still be expected (pragmatically anticipated) that some individuals will drop out of training after longer periods of training (Cunningham *et al.*, 2020). Indeed, recent work from Wiles *et al.,* (2024) found that 34% of participants withdrew from a home-based IWS training programme after 6 months, which may be related to the longer period of training. However, it may also be related to participants being clinically hypertensive and less motivated to partake in physical activity (Churilla and Ford, 2010). Research has shown that dropout rates are significantly higher in hypertensive individuals, often due to the physical and psychological burdens of hypertension management (Lopes *et al.*, 2021). However, despite the likelihood of dropouts from longer periods of training, there are currently a lack of data around the behaviour of resting BP levels following the cessation of IWS training. In order to progress and optimise the clinical value of IWS training within a healthcare setting, the magnitude and rate at which any BP reductions regress if training stops (detraining), as well as the mechanisms involved in any such changes, should be well understood (Murray, Delaney and Bell, 2006). Having an understanding of detraining periods will allow practitioners to design more effective training programmes, either to optimise and reduce any loss of adaptation, or to better understand how to manipulate training variables or potentially utilise periodisation models or maintenance periods within a training programme to reduce attrition and/or increase adherence rates (Issurin, 2010).

1.5.1. Defining key terms

Throughout the following review of literature, there are some key terms that should first be defined in the context of exercise training prescription. These key terms relate to the programme variables

(i.e. volume and frequency) that are commonly used within exercise training programmes. These variables can be manipulated and structured, and are normally organised to facilitate a desired training outcome (e.g. strength, power, hypertrophy) and generally aligned with the overall training goal (i.e. improvement in health or performance) (Bompa and Haff, 2009). The following terms will be defined: 'frequency' refers to the number of training sessions performed each week (e.g. three sessions per week), 'intensity' refers to the percentage of maximal capacity utilised during each exercise - such as % of peak HR (HR_{peak}) (e.g. 95% of HR_{peak}), and 'volume' refers to the amount of time spent exercising (e.g. 14 minutes per session). 'Total contraction volume' will also be used, which refers to the total amount of time spent exercising (i.e. total time spent contracting isometrically) over the full training programme.

1.5.2. The detraining effect

Acute responses to exercise, such as alterations in blood flow and cardiovascular drive, elicit biological stress and alter homeostasis, but are short-term and transient, normally returning to baseline within a short period of time (minutes-hours) following exercise (Rivera-Brown and Frontera 2012). Adaptations from exercise training are the result of repetitive challenges to homeostasis over time. Repeated bouts of stress from the accumulation of exercise bouts into a training period result in functional and structural adaptations to biological systems which are more chronic in nature (Lambert, 2016). The distinction between acute responses and training adaptations is an important one, where acute responses are more akin to 'exercise', and adaptations are the result of 'training'. This will be the default terminology throughout this thesis.

Following the cessation of exercise training, it is generally accepted that most physiological adaptations are progressively lost (Toraman and Ayceman, 2005). This is referred to as a 'detraining' effect and is based upon the simple principle of reversibility, i.e. 'use it or lose it' (Hart, 2021). As such, detraining may be defined more accurately as 'the loss of any adaptations achieved through exercise or physical training'. This occurs due to an insufficient training stimulus and can result in either a complete or partial loss of adaptations, depending on the degree to which the training stimulus has been reduced (Mujika and Padilla, 2000). As indicated, the term detraining is also closely aligned with the principle of reversibility. Reversibility states that whereas regular exercise or physical training leads to numerous physiological adaptations that can be beneficial for health or enhance certain performance markers, the cessation of training or a marked reduction in training causes a reversal of these adaptations, which can negate any such benefits (Mujika and Padilla, 2000; McMaster *et al.*, 2013). The detraining effect, or reversibility, affects many biological systems throughout the human body. Both acute and chronic under-use of these biological systems,

including the musculoskeletal and cardiovascular systems, can lead to a state of deconditioning, with symptoms such as atrophy and cardiac dysfunction (Hart, 2021). Thus, all humans need to uphold continuous physical activity levels within an appropriate physiological window in order to function and perform effectively across the lifespan, which Hart (2021) refers to as 'continual conditioning of the integrated systems'. On the other hand, the disuse of these biological systems can result in adverse physiological alterations, defined as 'deconditioning' (Hart, 2021). Certain factors, such as the length of the exercise training programme, duration of the detraining period, exercise intensity, and the training level of the individual, may all affect both the residual duration in which an individual can retain said physiological adaptations, and also the rate at which any adaptations are reversed (rate of reversibility, decay rate) (Mujika and Padilla 2000; Joo 2018; Sousa *et al*., 2019). However, as previously outlined, the specificity of the detraining effect in relation to BP reductions following IET is currently not well explored.

1.5.3. Antihypertensive medication withdrawal

Antihypertensive medication is commonly used by healthcare services in the treatment of hypertension (Birudaraju, Cherukuri and Budoff, 2020). Despite its effectiveness in reducing BP, adherence to treatment is poor (Abegaz *et al.*, 2017) and as such, it is likely that there will be periods of time in which BP is not controlled via medication. Interestingly, a recent review found that approximately 1 in 4 patients on antihypertensive therapy can withdraw from their treatment without hypertension returning for 2 or more years (Van Der Wardt *et al.*, 2017). However, authors did state that their findings may not apply to all antihypertensive agents, and that there is limited evidence for the withdrawal of medications such as renin inhibitors, calcium antagonists, vasodilators or hydrochloride. Indeed, Sasamura *et al*., (2013) found that both candesartan (angiotensin-II receptor antagonist) and nifedipine (calcium antagonist) were ineffective at maintaining BP reductions following a 1-year withdrawal period, although the study did find that nifedipine maintained the BP reductions longer than candesartan, demonstrating a potential difference in their mechanisms. Sheppard *et al.,* (2021) also found that the withdrawal of higher dose calcium channel blockers resulted in a reversal of BP reductions over a 12-week follow up period, but the withdrawal of low dose betablockers had little impact on BP over the follow-up period. This suggests that some forms of medication (and potentially doses) produce a more sustainable BP reduction, potentially due to the specific mechanisms of action (Birudaraju, Cherukuri and Budoff, 2020). However, it should be noted that in the previously discussed studies and reviews, there is variation in the period of initial drug treatment and the period of follow-up/withdrawal used, and thus, it can be difficult to compare findings accurately. As such, there is currently a lack of

consensus regarding the specific maintenance or withdrawal periods for antihypertensive medication. Nonetheless, it appears that for most individuals using antihypertensive medication, continued intervention will be required at some point to maintain reductions in BP (Paz *et al.*, 2016).

1.5.4. Effect of exercise detraining upon resting blood pressure

When looking at the broad exercise training literature in relation to the effects of detraining periods on resting BP there are difficulties comparing data due to the heterogeneous nature of acute programme variables and methodological differences amongst each study. This presents an issue when making informed decisions around the detraining effect of resting BP due to a wide variety of factors that may reverse or prolong any such resting BP reductions (Mujika and Padilla, 2000). There are also concerns with the consistency of data presentation, with some studies using shorter periods of detraining than others, or reporting data at opposing intervals throughout the detraining period (Mujika and Padilla, 2000). Therefore, it is important to approach findings cautiously and avoid over-speculating and generalising findings. The following review of the literature primarily includes randomised controlled trials. However, studies without control groups may be added to supplement findings where appropriate. For the purpose of this thesis and the subsequent review of literature, the term 'detraining period' will refer to the complete cessation of exercise training. Where there are periods of 'follow-up' training, this will refer to a 'maintenance period'. The maintenance period occurs after an initial period of training or when an intervention has been completed. During this period, certain training parameters (such as intensity, frequency, or volume) can be modified to maintain the physiological adaptations that were achieved during the initial programme, but without continuing the full training dose of the original training. All included detraining studies can be seen in Table 1:3.

1.5.5. Continuous aerobic exercise training

Following continuous aerobic training programmes, BP reductions appear to reverse after a short detraining period. A study by Murray, Delaney and Bell (2006) looked at the detraining effect following a 4-week aerobic cycle ergometry programme. Training consisted of 30 minutes cycling at 60% $VO2_{peak}$ 3–4 times per week. Both sBP and dBP were significantly reduced compared to the control group (121 ± 7 mmHg to 110 ± 5 mmHg and 66 ± 6 mmHg to 57 ± 7 mmHg, respectively), following the initial 4-week training period. Following 1 week of detraining, sBP reductions were no longer significantly different from the control group. However, reductions in dBP were sustained for slightly longer, with differences compared to the control group lasting for 2 weeks. In another study

from Wang *et al*., (1997), normotensive participants carried out an 8-week continuous aerobic training programming consisting of cycling at 50% HR_{max} for 30 minutes, five times per week. The study found significant reductions compared to a control group for both sBP (101 ± 3 to 93 ± 1 mmHg) and dBP (67 ± 3 to 58 ± 2 mmHg). The reductions in BP were not significantly different to the control group after a 4-week detraining period. However, the changes in BP were not reported throughout the detraining period, so the specific duration that BP reductions were maintained below baseline is unknown.

There is also a selection of studies without a control group that have found similar results to Wang *et al*., (1997) and Murray, Delaney and Bell (2006). Following a 4-week continuous aerobic training programme involving 40-minute bicycle exercises three times per week at 60-70% of VO_2max, Meredith *et al*., (1990) found significant reductions of -3.6 ± 0.5 mmHg in MAP (sBP and dBP were not reported). During the detraining period, MAP remained lower than baseline for 1-2 weeks after the cessation of exercise. Another study from Wang (2005) found significant reductions in both sBP (125 ± 4 to 114 ± 2 mmHg) and dBP (76 ± 2 to 65 ± 2 mmHg) following a slightly longer 8-week continuous aerobic training programme. Training consisted of cycling at 50% HRmax for 30 minutes, five times per week. Following an 8-week detraining period the BP reductions returned to baseline (sBP: 120 ± 3 mmHg and dBP: 72 ± 2 mmHg) – although BP changes were again not reported throughout the detraining period so may have been sustained for a shorter period than 8 weeks.

It appears that following short-term (<8 weeks) aerobic training, BP reductions will reverse within several weeks (1-2 weeks). It has been shown that longer periods of training (>8 weeks) elicit structural vascular adaptations (Tinken *et al.*, 2008; 2010), and it may well be that short-term functional adaptations are more reversible. Indeed, previous research has shown the longer the period of training, the longer any adaptations can be maintained through a period of detraining (Joo, 2018; Sousa *et al.*, 2019). It may also be related to the baseline BP levels, with all participants having optimal or normal BP values (sBP: 101-125 mmHg and dBP: 67-76 mmHg) in the latter studies. Lower starting BP may indicate BP is already near a homeostatic threshold, and the body may protect against an excessive hypotensive response by returning BP back to normal levels following the cessation of training BP (Halliwill *et al.*, 2013; Edwards *et al.*, 2021). However, it is difficult to ascertain the specific trends in BP during a detraining period following continuous aerobic training due to the heterogeneity in study designs and lack of data reporting through the detraining period. For example, an aerobic exercise training study from Boyce *et al*., (1997) that used 30-minute walking and 30-minute cycling thrice weekly, starting at 50-60% heart rate reserve (HRR) and progressing up to 70% HRR over 4 months found a reversal of BP reductions of BP reductions after a 2-month detraining period. However, the study used a higher baseline BP of 145/89 mmHg, utilised

a longer period of training (4 months), and achieved large significant reductions in both sBP (21 mmHg) and dBP (11 mmHg) and so it would be expected (based upon the findings from Meredith *et al.*, (1990) and Murray, Delaney and Bell (2006)), that the resting BP reductions would have been maintained for smaller period throughout the 2-month detraining period. However, Boyce et al. (1997) did not report BP levels throughout the detraining period and so comparisons between studies are difficult.

1.5.6. Dynamic resistance exercise training

The only dynamic resistance training study to explore the detraining effect whilst using a control group is from Tofas *et al*., (2021) who investigated the effects of a long-term 8-month upper and lower body dynamic resistance training programme. Participants trained thrice weekly, performing 2 sets of 12-15 reps at 60% 1RM. The study found significant reductions in resting sBP (139 ± 7 to 123 ± 3 mmHg) and dBP (81 ± 7 to 78 ± 8 mmHg) compared to a control group following the 8-month training period. Following 1 month of detraining, sBP, but not dBP, was maintained lower than the control group. Following 2 months of detraining, both sBP and dBP were not significantly different from the control group. The longer duration that BP reductions were sustained throughout the detraining period compared to the previously outlined aerobic training programmes may be related to the specific mode of exercise training, or potentially the extended period of training (8 months).

A selection of dynamic resistance training studies found similar results following longer training periods but without a comparative control group. A study by Nascimento *et al*., (2014) investigated the effect of a dynamic resistance training programme on resting BP during an extended detraining period amongst a group of pre-hypertensive medicated sedentary females. The training programme consisted of a mixture of upper and lower body resistance exercises, with 3 sets of 8 to 12 repetitions performed at a moderate intensity. Training was carried out two times per week over a 14-week period. The study found significant reductions compared to baseline in all resting BP variables following the initial intervention; sBP reduced from 130.60 ± 8.05 mmHg to 112.50 ± 9.66 mmHg, dBP from 80.60 ± 7.55 mmHg to 70.50 ± 9.51 mmHg, and MAP from 97.30 ± 6.62 mmHg to 84.50 ± 9.11 mmHg. The study then utilised a 14-week detraining period and found that sBP and MAP remained significantly lower than baseline after this period (116 ± 10 and 85 ± 7 mmHg for sBP and MAP, respectively). However, dBP was not significantly lower following the detraining period (69.70 ± 7 mmHg) – although it must be acknowledged that while not significant, dBP was lower than the post-training value and remained 13% lower when compared to baseline values. Moraes *et al*., (2012) also found sustained resting BP reductions following a dynamic resistance training programme amongst a group of hypertensive males. The study utilised a mixture of upper and lower

body resistance exercises, all performed for 3 sets of 12 repetitions at 60% 1RM. Although the programme was a slightly shorter 12-week period, the training frequency was higher at 3 times per week. Training produced significant reductions in sBP, dBP, and MAP compared to baseline (sBP 150 ± 3 to 134 ± 4 mmHg; dBP 93 ± 2 to 81 ± 1 mmHg; MAP 112 ± 2 to 99 ± 3 mmHg, respectively). These reductions remained significantly lower than baseline after a 4-week detraining period.

Following shorter dynamic resistance training programmes there are contrasting results. Elliot *et al*., (2002) explored the detraining effect following an 8-week programme consisting of upper and lower body resistance exercises, with 3 sets of 8 reps at 80% 10RM performed three times per week. The study found BP reductions were not significantly different compared to a control group, although there were still clinically relevant reductions in sBP (133 ± 20 to 118 ± 15 mmHg), dBP (72 ± 11 to 66 ± 10 mmHg), and MAP (92 ± 13 to 83 ± 10 mmHg). Following an 8-week detraining period, the clinically-relevant reductions had reversed and were not different from the control group. One reason that Moraes *et al.*, (2012), Nascimento *et al.*, (2014) and Tofas *et al.*, (2021) managed to maintain the reductions throughout a detraining period compared to Elliot *et al*., (2002) could be related to the longer period of training. However, it is difficult to compare studies due to variations in programme design. In particular, the duration of the detraining period, which, as noted above, differed somewhat between each study. For example, it may be that the reductions seen by Moraes *et al.,* (2012) lasted longer than the short 4-week detraining period. Likewise, the clinically relevant BP reductions seen by Elliot *et al*., (2002) may have remained lower than baseline for a shorter period than the prescribed 8-week detraining period. Despite the difficulties comparing studies, it can be seen that the dynamic resistance training studies that have demonstrated prolonged BP reductions throughout the detraining period all have longer periods of training as well as higher baseline BP. However, although direct comparisons between exercise modes are difficult, it may also be that the specific stimulus of resistance training (i.e. greater muscle mass recruitment) helps to promote a longer sustained BP reduction throughout the detraining period compared to continuous aerobic training (Tofas *et al.*, 2021). The specific adaptations seen following resistance training may also aid in improvements in vascular function and arterial compliance, which could help in the sustainability of BP reductions (Fagard, 2006).

1.5.7. Interval exercise training

The study from Tofas *et al*., (2021) also investigated an interval-style exercise training programme amongst a similar participant demographic. Training consisted of 4 x 10-minute high-intensity aerobic intervals at 75% HR_{max} on either a treadmill or bicycle (high-intensity aerobic training involves high 'aerobic efforts' aimed at stressing 'oxidative metabolic pathways' and should be

clearly differentiated from 'HIIT' which typically works 'anaerobic metabolic pathways' and has a higher relative intensity). The training was prescribed for 8 months and resulted in significant reductions in both sBP (140 ± 5 to 128 ± 4 mmHg) and dBP (84 ± 8 to 79 ± 5 mmHg) compared to the control group. Similar to the dynamic resistance training group in the study (section 1:5:6), sBP, but not dBP, was maintained lower than the control group following 1 month of detraining. Following 2 months of detraining, both sBP and dBP were not significantly different from the control group. These findings suggest that the sustainability of BP reductions throughout a detraining period is similar following both high-intensity aerobic intervals and dynamic resistance training.

Another study from Morales-Palamo *et al*., (2017) utilised a 4-month HIIT protocol, consisting of 4 x 4-minute intervals at 90% HR_{max} with 3-minute active recovery, performed three times per week. Participants were obese middle-aged individuals. The study used a repeated measures design over a 2-year period, with participants performing 4 months of HIIT followed by an 8-month detraining period (year 1), directly into a second 4-month period of HIIT, followed by another 8-month detraining period (year 2). During the first yearly cycle, there were significant reductions in sBP (139 ± 3 to 127 ± 3 mmHg) but not dBP (85 ± 3 to 77 ± 2 mmHg) compared to the control group. Following an 8-month detraining period the reductions in sBP had reversed and were not significantly different from the control group. Following a second 4-month HIIT training period, although there were clinically relevant reductions in both sBP (131 ± 3 to 126 ± 3 mmHg) and dBP (80 ± 2 to 78 ± 2 mmHg), these were not significantly different from the control group. However, following the second 8-month detraining period, both sBP and dBP reductions significantly differed from the control group. Although the differences compared to the control group were not significantly different after the training period, it may be that there was a further reduction in the period after data collection. These data potentially demonstrate that BP reductions following HIIT have the potential to be sustained for up to 8 months post-training - although it should be noted that these differences may have also be related to the reductions in body mass and waist circumference reported in the study.

Mora-Rodríguez *et al*., (2014) also looked at the effects of a 1-month detraining period following 4 months of supervised HIIT amongst a group of pre-hypertensive individuals, but without a comparative control group. The training was performed thrice weekly and consisted of 4 x 4-minute intervals at 90% of HR_{max} interspersed with 3 minutes of active recovery. After the initial 4-month training period, sBP significantly reduced from 139 ± 2 to 121 ± 2 mmHg, and dBP reduced from 89 ± 1 to 78 ± 1 mmHg. Following 1 month of detraining, both sBP and dBP remained significantly lower than baseline (123 ± 2 and 79 ± 1 mmHg, respectively).

The greater sustainability of BP reductions throughout a detraining period seen following interval training and dynamic resistance training may be related to the specific training stimulus or the relative training intensity, although comparing intensity between studies is hard due to variations in prescription, e.g. %1RM, % VO_2max or %HR_{max}. However, it is worth noting that similar to the dynamic resistance training studies, all three interval-based studies (Mora-Rodriguez *et al.*, 2014; Morales-Palomo *et al.*, 2017; Tofas *et al.*, 2021) utilised long-term training interventions (between 4-8 months), and as previously discussed, research has shown the longer the period of training, the longer any adaptations can be maintained through a period of detraining (Joo, 2018; Sousa *et al.*, 2019). The baseline BP values are also higher in the interval training studies compared to the previous exercise modes discussed, which again highlights the influence this may have on the sustainability of BP reductions throughout a detraining period.

1.5.8. Combined exercise training

A selection of studies have looked at the detraining effect following combined exercise training. Combined training studies typically involve two or more modes of exercise combined into the same training programme. In the Tofas *et al*., (2021) study that has been discussed previously, authors also investigated the detraining effect with a combined exercise group. Like other groups within the study, the combined group utilised an 8-month training period and a 3-month detraining period. Training consisted of a mix of both the aerobic intervals and the resistance training described previously, carried out three times per week. Following training, there were significant reductions in sBP (152 ± 8 to 123 ± 3 mmHg) but not dBP (83 ± 8 to 80 ± 6 mmHg) compared to the control group. Following 1 month of detraining, both sBP and dBP were not significantly different from the control group, demonstrating the protective effect of exercise on reducing BP is lost within 4 weeks of stopping exercise. Another study from Leitão *et al*., (2022) explored the effects of a 9-month combined aerobic and resistance training programme performed at a moderate intensity with two weekly sessions. There were significant reductions compared to a control group in both sBP (144 to 137 mmHg) and dBP (87 to 83 mmHg) following training. Interestingly, unlike the combined study from Tofas *et al*., (2021), dBP, but not sBP reductions, remained significantly lower than the control group following 12 months of detraining. Although contrasting results were found, the studies were both similar, with moderate-intensity aerobic and resistance training performed for an extended period of time (8/9 months). Moreover, the Tofas *et al.,* (2021) study had a higher baseline BP and achieved greater BP reductions compared to the Leitão *et al.,* (2022) study, and so it would be expected (based on the findings outlined previously) that the Tofas et al., (2021) study should demonstrate a greater ability to sustain BP reductions. However, the contrasting outcomes suggest

that the differences observed cannot be solely attributed to participant characteristics or study design. A potential explanation for the sustained dBP reductions observed by Leitão *et al.,* (2022) is that structural vascular adaptations, such as arterial remodelling and a reduction in arterial stiffness (Tinken *et al.,* 2008; 2010), which are known to contribute to dBP reduction, may have persisted longer amongst participants in the study.

Studies without control groups have also found that BP reductions were not maintained throughout a detraining period when using a combined training approach. Oliveira *et al*., (2017) looked at the effects of two types of combined training on the reversibility of resting BP reductions: one land-based (L) and one aquatic-based (A). Land-based training consisted of a mixture of aerobic, strength, flexibility and balance training, and the A group consisted of components of the L group, but with added aquatic training. Both groups trained for 9 months, three times per week, at a moderate intensity (specific intensity not stated). Both groups saw a significant reduction in resting BP following training (L: sBP 138 ± 25 to 124 ± 17 mmHg and dBP 75 ± 10 to 67 ± 11 mmHg, A: sBP 138 ± 21 to 128 ± 13 mmHg and dBP 75 ± 12 to 66 ± 7 mmHg), but these reductions had returned to baseline after a 3-month detraining period (L: sBP 133 ± 17 and dBP 73 ± 12 mmHg, A: sBP 135 ± 16 and dBP 69 ± 10 mmHg) – although BP data was not reported throughout the detraining period and so it is not known whether the BP reductions were sustained for a shorter period than the prescribed 3 months of detraining.

Another study by Zanettini *et al*., (1997) used a 12-week combined training programme consisting of stretching, body-weight exercises (calisthenics), resistance and aerobic training. Exercise was performed at 70-85% HR_{max} three times per week. Following the training period, sBP was significantly reduced from 148 ± 10 to 133 ± 10 mmHg, and dBP was significantly reduced from 97 ± 5 to 85 ± 6 mmHg. Following an 8-week detraining period, both sBP (150 ± 10 mmHg) and dBP (95 ± 6 mmHg) returned to baseline. Another study by Okamoto *et al*., (2007) found similar results using 8 weeks of mixed aerobic and resistance training, carried out twice weekly. Aerobic training was performed at 60% HRR, and resistance training was conducted at 80% 1RM. The study had two intervention groups; one performed aerobic training first, followed by resistance training (group 1), and the other performed resistance training first, followed by aerobic training (group 2). Both groups had significant reductions following training (group 1: sBP 114 ± 3 to 111 ± 3 mmHg and dBP 63 ± 2 to 61 ± 2 mmHg, group 2: sBP 114 ± 4 to 110 ± 4 mmHg and dBP: 65 ± 2 to 60 ± 3 mmHg), but these reductions returned to baseline after a 4-week detraining period (group 1: sBP 109 ± 4 mmHg, and dBP 60 ± 2-mmHg, group 2: sBP 111 ± 4 mmHg and dBP: 60 ± 3 mmHg). The results from Okamoto *et al.,* (2007) potentially indicate that the order of exercise selection does not affect the detraining effect of resting BP. Furthermore, both the latter studies (Zanettini *et al.*, 1997; Okamoto *et al.,*

2007) utilised a shorter training period (8-12 weeks), which may have affected the BP detraining effect. Okamoto *et al.,* (2007) also used a demographic with a low baseline BP and experienced very small reductions in both sBP (3 mmHg) and dBP (3 mmHg) following training, which may have affected the reversal of BP during the detraining period.

1.5.9. Detraining following isometric exercise training

As previously mentioned, there are currently no published studies specifically investigating detraining periods following IWS training. The only available data is from Wiles, Goldring and Coleman (2017) and Taylor *et al.,* (2019) who used a randomised cross-over design, with 4- and 3-week wash-out periods, respectively, between the intervention and control conditions. Baseline BP values were 126/79 mmHg and 132.4/81.4 mmHg, respectively. Both studies observed BP return back to baseline values following the short wash out periods. Although Wiles, Goldring and Coleman (2017) and Taylor *et al*., (2019) did not set out to investigate the detraining effect, these findings would suggest that BP reductions are reversed within several weeks following the cessation of IWS training.

Other IET studies that have used short training periods have found similar results. Howden *et al*., (2002) found significant reductions in sBP (120.7 to 110.7 mmHg) (but not dBP) compared to baseline, following 5 weeks of bilateral-leg extension IET involving 4 x 2-minute bouts of isometric leg exercise at 20% maximum voluntary contraction (MVC), performed 3 days per week for 5 weeks. Following training, reductions disappeared after a short 10-day detraining period. Following an 8-week washout period, participants then undertook a 5-week IHG training programme (4 x 2-minute, 30% MVC). Training produced significant reductions in BP, but similar to leg training, reductions were reduced within a 10-day detraining period (Howden *et al.*, 2002). Although the study did not compare BP reductions directly to the control group, the study did report no changes in the control group BP data over both training and detraining periods.

Like the exercise training modes discussed previously (aerobic, dynamic, interval), IET studies that have used longer training periods have found greater sustainability of BP reductions throughout a detraining period. Gordon *et al*., (2018) studied the detraining effect following 12 weeks of IHG training amongst a group of hypertensive participants performed in both the laboratory and in a home-based environment. The training prescribed was 4 x 2-minute bouts of IHG exercise at 30% MVC, 3 days per week. Although no significant reductions were found compared to the control group for sBP or dBP (due to a concurrent decrease in control sBP and dBP), the study did evidence significant reductions compared to baseline in sBP, but not dBP, following the 12-week training

period in both the laboratory (137.6 to 128.5 mmHg) and home-based group (137.7 to 128 mmHg). Following a 6-week detraining period, the study reported that in both home-based and laboratory-based groups, sBP remained significantly lower than baseline (129.31 and 132.2 mmHg, respectively). More recently, Gordon *et al*., (2023) employed a similar study design (12 weeks of IHG, 4 x 2-minute bouts at 30% MVC, 3 days per week) but amongst a cohort of elderly participants in a group setting. Interestingly, this study also found no significant differences in the BP reductions compared to the control group due to adjacent reductions in control BP levels. However, the study did find significant reductions in both sBP (131.4 to 121.2 mmHg) and dBP (75.3 to 70.6 mmHg) compared to baseline following training. The reductions in sBP, but not dBP, were also significantly lower than baseline (121.8 mmHg) following a 6-week detraining period. Nonetheless, due to the reductions in control BP in both the latter studies (Gordon *et al*., 2018; 2023), the conclusions made here are highly speculative and should be approached with caution.

There is also a selection of IET studies that have explored the detraining effect but without a control group altogether. A thesis from Devereux (2010) found BP reductions returned to baseline after just seven days. Training consisted of bilateral-leg extension IET for 4 weeks, thrice weekly. The intensity was set at an EMG relative to 95% HR_{peak} / 24% MVC. Baseline BP for the participants was 119.9/89.2 mmHg, sBP/dBP, respectively. Following the 4-week training programme, the study found significant reductions in sBP (-4.9 ± 5.8 mmHg) and dBP (-2.8 ± 3.2 mmHg), and these reductions were reversed to pre-baseline values within seven days of detraining. Wiley (1992) also looked at the detraining effect following a short 5-week period of IHG training. Training consisted of 4 x 45-second contractions at 50% of maximum effort separated by 1 minute of rest. These were performed five times per week for 5 weeks. The study found significant reductions in resting BP, with sBP declining from 127.0 ± 2.28 mmHg at baseline, to 117.5 ± 2.23 mmHg at week 5, and dBP also showing a similar pattern, significantly reducing from 86.2 ± 1.85 mmHg at baseline, to 77.4 ± 1.49 mmHg at week 5. Following a 5-week detraining period, both sBP (126.8 ± 1.84 mmHg) and dBP (86.6 ± 1.34 mmHg) returned to baseline values. However, it was not until the third week of the detraining period that BP values significantly differed from BP values following training, showing the BP reductions were sustained for 2 weeks. Another study from Baross *et al*., (2022) found resting BP reductions were maintained for 8 weeks following a more extended 8-week bilateral isometric leg-extension training programme amongst a group of normotensive participants (127/69 mmHg). Training consisted of 4 × 2-minute isometric contractions at 20% MVC, performed thrice weekly in a supervised environment. There were significant reductions in sBP (−6 ± 6 mmHg), but not dBP (−2 ± 8 mmHg) compared to baseline after 8 weeks of training. Following an 8-week detraining period, the significant reductions in sBP were maintained below baseline (−4 ± 6 mmHg). Likewise, in a thesis

from Carlson (2016), BP reductions were maintained for 12 weeks following a longer 12 weeks of IHG, with 4 x 2-minute bouts at 30% MVC, 3 days per week. However, although the differences were still significant compared to baseline at the 12-week mark, it should be acknowledged the reductions were only 3 mmHg lower than baseline.

These findings suggest that the more extended period of sustained BP reductions observed by Gordon *et al*., (2018; 2023), Baross *et al*., (2022) and Carlson (2016) may be due to the duration of training, which was over twice as long as that used by the other studies discussed (Wiley *et al*., 1992; Howden *et al*., 2002; Devereux 2010). Interestingly, one of the studies that managed to maintain BP reductions for the longest was Baross *et al*., (2022) who also recruited normotensive participants (123/69 mmHg), and only managed to achieve a modest −6 ± 6-mmHg reduction in sBP, comparatively lower than the studies that only maintained BP below baseline for several weeks into a detraining period (Wiley *et al.*, 1992; Howden *et al*., 2002). These findings may indicate that the length of the initial training period has the most impact on the sustainability of BP reductions during a detraining period. However, it should also be acknowledged that the study with the smallest magnitude of BP reductions after the initial intervention, the smallest duration exercise training period (4 weeks), and the lowest resting BP at baseline, experienced the shortest period of sustained reductions, evidencing a full return to baseline BP values after seven days of detraining (Devereux 2010).

1.5.10. Summary of findings

Based upon the findings from all exercise modes described above (see Table 1:3), it is likely that any resting BP reductions elicited following a short period of exercise training (≤4 weeks) will reverse within a short period following the cessation of training (1-2 weeks). Although multiple factors, including the magnitude of resting BP reduction, baseline BP values, training mode, and training intensity, may also contribute to the sustainability of resting BP reductions during a detraining period, it seems the most consistent variable from the available literature previously discussed is the length of the initial training period. This finding is consistent with previous suggestions that claim the longer the period of training, the longer any physiological adaptations can be maintained through a period of detraining (Joo, 2018; Sousa *et al.*, 2019), which may be linked to the functional and reversible nature of short-term cardiovascular adaptations (Tinken *et al.*, 2008; 2010). However, as previously discussed, there is limited reporting of BP levels through the detraining periods in the studies previously outlined, so it is not known if BP reductions were sustained for a shorter duration of time. This can be an issue when looking at the trend of BP during a detraining period, and

something this thesis will look to address by implementing BP monitoring throughout the detraining period.

Table 0:3 Prospective studies that have investigated the detraining effect on resting BP reductions following exercise training

Study	Mode	Study design	Intensity	Frequency	Baseline sBP/dBP (mmHg)	Length of training	sBP/dBP post-training (mmHg)	Detraining period	sBP/dBP post-detraining (mmHg)
Wiley et al., 1992	IHG	4 x 45 sec, 1 min rest, alternating arms	50% MVC	5 x per week	127/86	5 weeks	118/77	4 weeks	127/87
Gordon et al., 2018 (LAB)	IHG	4 x 2 min, 1 min rest, dominant arm	30% MVC	3 x per week	138/87	12 weeks	129/84	6 weeks	129/83
Gordon et al., 2018 (HOME)	IHG	4 x 2 min, 1 min rest, dominant arm	30% MVC	3 x per week	138/88	12 weeks	128/82	6 weeks	132/84
Gordon et al., 2023	IHG	4 x 2 min, 1 min rest, dominant arm	30% MVC	3 x per week	131/75	12 weeks	121/71	6 weeks	122/71
Howden et al., 2002	IHG	4 x 2 min, 3 min rest, dominant arm	30% MVC	3 x per week	121/70	5 weeks	111/67	10 days	116/67
Carlson 2017	IHG	4 x 2 min, 3 min rest, dominant arm	30% MVC	3 x per week	154/89	12 weeks	147/84	12 weeks	151/86

Howden et al., 2002	Bi-leg extension IET	4 x 2 min, 3 min rest	20% MVC	3 x per week	114/65	5 weeks	102/59	10 days	117/58
Devereux, 2010	Bi-leg extension IET	4 x 2 min, 3 min rest	24% MVC	3 x per week	120/69	4 weeks	115/66	1 week	119/68
Baross, 2022	Bi-leg extension IET	4 x 2 min, 3 min rest	20% MVC	3 x per week	123/70	8 weeks	117/68	8 weeks	119/68
Nascimento et al., 2014	Dynamic RT	6 upper/lower body exercises, 3 x 8-12 reps	Moderate	2 x per week	131/81	14 weeks	113/71	14 weeks	116/70
Moraes et al., 2012	Dynamic RT	8 upper/lower body exercises, 3 x 12 reps	60% 1RM	3 x per week	150/93	12 weeks	134/81	4 weeks	139/88
Elliot et al., 2002	Dynamic RT	5 upper/lower body exercises, 3 x 8 reps	80% 10RM	3 x per week	133/72	8 weeks	118/66	8 weeks	129/67
Tofas et al., 2021	Dynamic RT	8 upper/lower body exercises, 2 x 12-15 reps	60% 1RM	3 x per week	139/81	8 months	123/78	3 months	135/80
Wang et al., 1997	Continuous aerobic	Cycling 30min per day	50% HRmax	5 x per week	101/67	8 weeks	93/58	4 weeks	100/66

Murray et al., 2006	Continuous aerobic	Cycling 30 min per day	60% VO_2max	3 x per week	121/66	4 weeks	107/53	4 weeks	115/61
Wang et al., 2005	Continuous aerobic	Cycling 30 min per day	50% VO_2max	5 x per week	125/76	8 weeks	114/65	8 weeks	120/72
Meredith et al., 1990	Continuous aerobic	Cycling 40 min per day	60-70% HRmax	3 x per week	114/70	4 weeks	106/65	4 weeks	114/75
Boyce et al., 1997	Continuous aerobic	30 min walking, 30 min cycling	70% HRmax	3 x per week	145/89	4 months	124/78	2 months	140/87
Tofas et al., 2021	Aerobic intervals	4 x 10 min cycle/treadmill intervals	60-75% HRmax	3 x per week	140/84	8 months	128/79	3 months	131/80
Mora-Rodriguez et al., 2014	HIIT	4 x 4 min cycle intervals, 3 min recovery	90% HRmax	3 x per week	139/89	16 weeks	121/78	4 weeks	123/79
Morales-Palamo et al., 2017 (year 1)	HIIT	4 x 4 min cycle intervals, 3 min recovery	90% HRmax	3 x per week	139/85	4 months	127/77	8 months	131/80
Morales-Palamo et al., 2017 (year 2)	HIIT	4 x 4 min cycle intervals, 3 min recovery	90% HRmax	3 x per week	131/80	4 months	126/78	8 months	128/76
Oliveira et al., 2017 (land)	Combined	Walking and strength exercises	Moderate	2 x per week	138/75	9 months	124/67	3 months	133/73

Oliveira et al., 2017 (aquatic)	Combined	Same as land + aquatic exercises	Moderate	2 x per week	138/75	9 months	128/66	3 months	135/69
Leitao et al., 2022	Combined	Aerobic and RT	Moderate	2 x per week	144/87	9 months	137/83	12 months	147/80
Zanettini et al., 1997	Combined	Calisthenic, RT, aerobic	75-85% HRmax	3 x per week	148/97	12 weeks	133/85	8 weeks	150/95
Okamoto et al., 2007 (group 1)	Combined	Aerobic into RT	60% HRR and 80% 1RM	2 x per week	114/63	8 weeks	111/61	4 weeks	109/60
Okamoto et al., 2007 (group 2)	Combined	RT into aerobic	80% 1RM and 60% HRR	2 x per week	114/65	8 weeks	110/60	4 weeks	111/60
Tofas et al., 2021	Combined	Combination of aerobic and RT	60-75% HRmax and 60% 1RM	3 x per week	152/83	8 months	123/80	3 months	129/81

1.6. Physiological mechanisms and associative variables

The following section will explore the associative variables and potential physiological mechanisms of BP reduction that may also be involved during a detraining period in order to further understand BP changes following the cessation of exercise training. Although there is some consensus in the literature that various health indicators decline with the cessation of exercise training, there is substantial variability reported on which parameters change during detraining periods (Nolan *et al.*, 2018).

In the thesis by Devereux (2010), BP reductions returned to baseline within 7 days following 4-weeks of IHG training amongst a group of normotensive participants. Devereux (2010) argued that it is doubtful any central adaptations and structural changes could be reversed after such a short period of time. However, functional adaptations following IET, such as reductions in TPR (potentially related to a transient release of NO), may be more prone to reversibility following the cessation of training. Findings from Murray, Delaney and Bell (2006) may support this idea. Authors found significant reductions in resting BP following a 4-week aerobic training programme, as well as a significant rise in resting forearm conductance (potentially related to a decrease in TPR). Following the cessation of training, sBP and vascular conductance returned to baseline within 1 week, which highlights the temporal nature of functional responses following exercise training (Murray, Delaney and Bell, 2006).

It has been suggested that one of the main mechanisms responsible for functional changes in TPR following exercise is an endothelial reaction to vasodilator chemicals, especially NO, which can be stimulated via the shear stress exerted on the endothelium during exercise (Green *et al.*, 2004; Tinken *et al.*, 2009). This is supported by Wang (2005), who explored the effects that both training and detraining can have on microvascular function and the regulatory role of endothelium-dependent dilation in skin vasculature. The study involved continuous aerobic exercise on a cycle ergometer at 50% VO_2max. Exercise was carried out for 30 minutes per day, 5 days per week, for a period of 8 weeks. Participants then went on to an 8-week detraining period in which they were instructed to abstain from any exercise training. Following the initial period of aerobic exercise training, there was an increase of plasma NO metabolites, which corresponded with a reduction in resting sBP (125 ± 4 to 114 ± 2 mmHg) and dBP (76 ± 2 to 65 ± 2 mmHg). The study also found that skin blood flow and cutaneous microvascular function were enhanced following training. Following the 8-week detraining period, both sBP (120 ± 3 mmHg) and dBP (72 ± 2 mmHg) were no longer significantly lower than baseline, and the changes in cutaneous microvascular function and plasma NO metabolite levels were reversed. These findings potentially suggest that endothelium-dependent

vasodilation is improved by aerobic exercise (related to increased NO metabolites), but also reversed back to baseline levels following a short period of detraining, demonstrating the functional nature of these responses. Unfortunately, the study did not report any data on the trend of reversal for NO metabolites or resting BP, so it is not clear how quickly these variables were returned to baseline values during the 8-week period.

Another study from Madhura and Sandhya (2012) found a significant increase in arterial compliance following 8 weeks of endurance training weeks. Although the study did not measure BP, improvements in arterial compliance have been associated with reductions in BP and can be linked to both functional and structural vascular adaptations. Arterial compliance refers to the elasticity of arteries, enabling them to expand and contract effectively during the cardiac cycle. It can be measured using pulse wave velocity (PWV), which is a measure of the speed at which the pressure wave travels through the arteries, with higher values indicating stiffer vessels and lower values reflecting greater elasticity and improved vascular health (Raij and Gonzalez-Ochoa, 2011). In the study from Madhura and Sandhya (2012), arterial compliance was reflected by the decrease in brachial finger pulse wave velocity. Following the cessation of training, the increase in arterial compliance showed a trend to reverse after just 1 month of detraining. The authors suggested that as structural adaptations in arterial compliance (e.g. changes to the elastin collagen composition of the arterial wall) are believed to occur over long periods (years), it may be that increased pulse pressures and mechanical distension during the exercise sessions stretched collagen fibres, resulting in functional changes to arterial compliance. Furthermore they indicated that the exercise training may have also increased arterial compliance by enhancing the sympathoinhibitory effect of NO, which was easily reversed within the short detraining period (Madhura and Sandhya, 2012).

There is also some evidence to suggest that the sustainability of BP reductions is related to autonomic factors. In the study by Meredith *et al*., (1990), plasma noradrenaline and TPR were also measured alongside BP following the 4-week aerobic training programme. Authors argued that the release of noradrenaline was a marker of autonomic activity, with higher concentrations representing greater sympathetic activity. The study found that during exercise training, there were significant reductions in BP and TPR by the start of the second week that remained significantly lower than baseline through the rest of training. However, reductions of noradrenaline were confined to the third and fourth week, lagging behind reductions in BP. On the contrary, during the detraining period, BP, TPR and plasma noradrenaline were sustained below baseline values for 1-2 weeks following the cessation of training, before simultaneously rising back towards initial sedentary levels in week 3. Meredith *et al*., (1990) concluded that as BP and TPR fell before noradrenaline during training, it is likely that non-autonomic factors, potentially connected to the fall in TPR, are

important in the initial lowering of BP. However, as plasma noradrenaline and BP levels were more closely aligned during the detraining period, it was concluded that the maintenance of lower BP is closely associated with autonomic factors (Meredith *et al*., 1990).

Based on this research, it could be suggested that the sustainability of resting BP reductions following short periods of exercise training is related to functional mechanisms, such as the release of vasodilator chemicals and autonomic regulation. As outlined above, it appears that the longer the initial training period, the longer any BP reductions can be sustained during a detraining period. This may indicate that there are unique cardiovascular adaptations following longer training periods that help to prolong any BP reductions during detraining. However, there are currently limited data focused on the mechanisms involved in any BP changes following long training periods. Nonetheless, as previously discussed, research has demonstrated that structural vascular adaptations following longer training periods differ from functional adaptations brought about following shorter periods of training (Tinken *et al.*, 2008; 2010; Baross, Wiles and Swaine, 2012; Badrov *et al.*, 2013). As such, although only speculative, it could be argued that structural vascular changes which are more stable and long lasting, such as resistance vessel structural remodelling, may be responsible for the prolonged BP reductions seen following longer periods of exercise training (Tinken *et al.,* 2008; 2010).

1.7. Maintenance of BP reductions

As previously discussed, evidence suggests that resting BP reductions are reversed within several weeks following the cessation of short IET programmes (<4 weeks) (section 1:5:10). Although the sustainability of BP reductions seems to be improved following longer training programmes, continued intervention is likely required to sustain BP reductions over the long term. However, long term commitment to exercise training programmes is a global issue, with data showing that approximately 31% of the population are not adhering to the recommended WHO physical activity guidelines (Cunningham *et al.*, 2020). As the most commonly cited barrier to participation is a lack of time (Alsobayel *et al*., 2020; Zunft *et al*., 1999), it is suggested that research should focus on promoting time-efficient exercise interventions and making such interventions accessible and sustainable to encourage long-term participation and health benefits. Indeed, the application of exercise training programmes without sufficient effort to understand the relationship between dose and response could result in unrealistic expectations and inefficient therapy. As Nolan (2018) highlights, determining the minimum frequency, intensity, duration, and volume of exercise to maintain any health benefits following exercise training remains to be determined and represents

important future work in the area of exercise and health. However, there are currently limited data to inform whether it is possible to maintain BP reductions with a reduced training dose following IWS training.

Before investigating the minimal IWS dose needed to maintain BP, it is important to investigate the dose response needed for BP reductions during the initial training period. Although there is now strong evidence that IET has clinically relevant and statistically significant anti-hypertensive effects, the optimal/minimal exercise dose needed to produce the most clinically meaningful/maximal reductions in BP is still under researched (Alves *et al.*, 2022). Although attempts, such as from Rickson *et al.,* (2021), have been made to produce guidelines for the optimal prescription and implementation of IET, only a limited number of studies were included, with no reference to IWS training in the analysis.

1.8. Intensity during isometric exercise

Exercise adherence literature indicates that activities of lower intensities are more tolerable to the average individual than exercise at higher intensities (Dishman & Ickes, 1981). Although increased exercise intensity has been connected to larger improvements in health, fitness and increased longevity (Lee and Paffenbarger, 2000; Duncan *et al.*, 2005; Schnohr, Scharling and Jensen, 2007), research has shown that higher intensities are also potentially related to poorer adherence (Dishman, 2020; Sallis & Owen, 1999). Whilst current evidence suggests that IET intensity is strongly related to the degree and rate of resting BP reductions following IET, with higher intensities evoking a faster rate and greater degree of BP reductions (Wiles *et al*., 2010, Baross *et al*., 2012), few studies have explored this occurrence, and comparisons between studies can be difficult due to differences in programme variables (Millar *et al*., 2014).

Previous IWS training studies have utilised 4 x 2-minute bouts performed three times per week, all producing significant reductions in resting BP (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; O'Driscoll *et al.*, 2022). The intensity prescribed in these studies was 95% HR_{peak}. The rationale for the intensity was based on previous research that compared high and low-intensity isometric leg exercises (Wiles, Coleman and Swaine, 2010; Baross, Wiles and Swaine, 2012). Wiles, Coleman and Swaine (2010) compared the effects between isometric double-leg extension at 75% HR_{peak} (~10% MVC) and 95% HR_{peak} (~21% MVC). The study showed that both high and low-intensity interventions produced significant reductions in resting BP compared to a control group, although the reductions in sBP were less in the low-intensity group (-3.7 mmHg) compared to the

higher-intensity group (-5.2 mmHg) (there were no noticeable differences in the dBP and MAP between groups) (Wiles, Coleman and Swaine, 2010). The rate of reduction for sBP was also different between groups, with reductions found after 4 weeks in the high-intensity group, but the low-intensity group taking the full 8 weeks (although this finding was not statistically significant) (Wiles, Coleman and Swaine, 2010). Baross, Wiles and Swaine (2012) also compared the effects between isometric double-leg extension performed at a high (85% HR_{peak}; ~14% MVC) and low (70% HR_{peak}; ~8% MVC) intensity. Following 8 weeks of training, there were no significant BP reductions in the low-intensity group. However, the high-intensity group found significant reductions in sBP (-10.8 mmHg) and MAP (-4.7 mmHg). These findings demonstrate that higher intensities are more optimal for BP reductions following IET. As such, Wiles, Goldring and Coleman, (2017) argued that a higher intensity should be used during home-based IWS exercise training, such as 95% HR_{peak}. The rationale for prescribing IWS training intensity at 95% HR_{peak} is supported by the findings from Decaux *et al.,* (2022), who compared the BP lowering effects from the established 95% HR_{peak} intensity with IWS training, and a lower 75% HR_{peak} intensity for a comparative sham group. The study found that participants in the 95% HR_{peak} group achieved significant reductions in resting sBP (−15 ± 9 mmHg), mBP (−7 ± 4 mmHg), and dBP (−5 ± 5 mmHg) with no significant changes in the lower intensity 75% HR_{peak} sham group (sBP −1 ± 5 mmHg; mBP 0 ± 4 mmHg; and dBP 0 ± 2 mmHg).

The mechanistic pathways between higher training intensities with IET and greater reductions in resting BP are likely to be related to the proportional increases in cardiovascular drive and the subsequent exercise pressor response (Wiles, Goldring and Coleman, 2017). Research has shown that BP and HR responses increase linearly with exercise intensity (Fisher *et al.*, 2007; Devereux *et al.*, 2012; Goldring, Wiles and Coleman, 2014). The cardiovascular response to isometric exercise is the outcome of the interplay of various central and peripheral factors (Bakke *et al.*, 2007). Greater contraction intensities have been shown to recruit more muscle fibres, which subsequently promotes greater occlusion of the vasculature (Folland and Williams, 2007). This results in the targeted muscles working ischaemically, which in turn enhances the magnitude of metaboreceptor stimulation, a key stimulus for alterations in cardiovascular drive (Fisher and White, 2004). It has also been suggested that there is an intensity-dependent accumulation of exercising metabolites which has a substantial influence on the stimulation of metaboreceptors (Baross, Wiles and Swaine, 2012; Devereux *et al.*, 2012). Devereux *et al.*, (2012) found a significant relationship between higher rates of lactate concentration and the magnitude of resting BP reductions and suggested that the intensity during isometric exercise needs to be high enough for the muscle to build up localised fatigue. This results in the accumulation of metabolites, such as lactate and H^+ ions, which affects the pressor response via metaboreceptor stimulation (Fisher and White, 2004). Higher contraction intensities

are also related to an increase in sympathetic nerve activity and a greater reflex inhibition of cardiac vagal tone (Iellamo *et al*., 1999), which may be related to increased muscle mechanoreceptor activation (Fisher and White, 2004). Some degree of central command (Baross, Wiles and Swaine, 2012), and input from arterial and cardiopulmonary baroreceptors, are also likely to be involved in the degree of pressor response during isometric exercise (Fisher *et al.*, 2007).

Baross, Wiles and Swaine (2012) proposed that a strong pressor response and increased occlusion observed during higher-intensity isometric exercise is one of the primary factors influencing blood flow and, subsequently, rates of vascular shear stress. Shear stress is a likely mechanistic link for vascular adaptations due to its effect on endothelium-dependent function. This works by stimulating the release of the potent vasodilator endothelium-derived NO, which works to reduce TPR and resting BP (Peters *et al.*, 2006; McGowan *et al.*, 2007). As such, at intensities where the pressor response is weak and the occlusion is inadequate, there is a reduced stimulus for vascular adaptations and thus any subsequent reductions in resting BP following IET may be attenuated (Baross, Wiles and Swaine, 2012).

1.8.1. Intensity during other forms of exercise training

An intensity-dependent magnitude of BP reduction has also been seen following aerobic exercise training. Meta-analytic data from Cornelissen and Smart (2013) showed that moderate or high-intensity aerobic training produced greater BP reductions compared to low-intensity training. Conversely, some studies have found no differences in the BP reductions with differing intensities. A review from Fagard (2001) found no differences in resting BP reductions between moderate-intensity aerobic exercise (40–50% of net maximal exercise performance) and high-intensity exercise (70% of net maximal exercise performance). Fagard (2001) proposed that this finding has good practical value as moderate-intensity exercise is generally more appealable than high-intensity exercise, especially amongst hypertensive individuals (Lopes *et al.*, 2021). Similar results have also been found in dynamic resistance training studies. Cornelissen and Smart (2013) reported no differences in BP responses between low, moderate, and high intensity (% of 1RM and specific intensities for each descriptor not stated) dynamic resistance training. This may suggest that with other more dynamic forms of training, such as aerobic or dynamic exercise training, intensity does not have as much of an influence on resting BP reductions as seen with IET.

1.8.2. Manipulation of exercise intensity during a follow-up period of training

There is currently no research that has explored the levels of intensity needed during a follow-up period of IET to maintain resting BP reductions. However, there is data to show that reducing the intensity of training following the initial period of training has adverse effects on the sustainability of other physiological adaptations. A study by Hickson *et al*., (1985) explored the effects of a reduction in intensity after a group of moderately trained subjects conducted aerobic exercise training at ∼90–100% of HR_{max} for ten weeks. Following the initial training period, one group reduced the intensity of training down to 82-87% HR_{max} (high) and the other down even lower to 61-67% HR_{max} (low). Both groups continued training for 15 weeks at these intensities, whilst the frequency and volume of training remained the same (6 sessions per week, 40 minutes per session). Following this period of reduced intensity, short-term endurance (max effort cycle or run for 4 to 8 minutes) was maintained in the high-intensity group. However, both high and low-intensity groups found that $\dot{V}02_{max}$ and long-term endurance (max effort cycle or run for >1 hour) were not maintained to levels seen at the end of the initial training period. The poor maintenance of endurance adaptations and VO_2max despite the continuation of a high frequency and volume of training highlights the importance of intensity to maintain adaptations during a follow-up period of training.

Another study from Morehouse (1967) looked at the maintenance of muscular strength in a follow-up training period with a reduced intensity. Participants in the study trained isometrically for a 9-week period at an intensity of 100% MVC. Following the initial period of training, participants in the study were required to either reduce training frequency, volume, or intensity for a further 8-week period. Results from the study found that participants who maintained isometric intensity at 100% MVC were able to maintain levels of muscular strength. However, those participants who reduced intensity to 50% MVC were not able to maintain their strength levels. The study concluded that intensity must remain at near-maximal levels to maintain maximal isometric muscle strength.

1.9. Volume, duration and frequency during isometric exercise

The only IET study to investigate the effect of training frequency on the magnitude of BP reductions is from Badrov *et al.*, (2013). The study found no significant differences in resting BP reductions after performing IHG training either 5 days per week or 3 days per week at 30% MVC over an 8-week period among normotensive female participants. However, it should be noted that sBP reductions were more prominent at week 4 in the group training 5 days per week (3 days per week: 94 ± 6 to 91 ± 6 mmHg, 5 days per week: 97 ± 11 to 90 ± 9 mmHg), and the reductions were also greater at the 4-

week period than the 3 days per week groups reductions were at the end of the full 8 weeks of training. However, Badrov *et al*., (2013) also found the BP reductions plateaued at the 4-week mark in the 5 days a week group, with no further reductions during the latter half of the training programme (91 ± 9 mmHg). Another study from Okamoto *et al*., (2020) also observed significant reductions in BP after 8 weeks of IHG training when training 5 days per week, but with a plateau in reductions past the 4-week mark (156 ± 12 to 142 ± 11 to 139 ± 13 mmHg, pre-, mid and post-training). Conversely, a multi-level analysis by Millar *et al.,* (2007) that used an 8-week training period but a frequency of three times per week found a negative linear trend in resting sBP reductions which continued to decline all the way up until the end of the 8-week mark (139 ± 2.5 to 135 ± 1.53 mmHg) – albeit with a small magnitude of reduction. This finding potentially demonstrates a dose-response relationship between training frequency and rate of adaptation, and that higher training frequencies may bring about BP reductions at a faster rate than lower training frequencies. However, although all studies used the same intensity (30% MVC), and intra-session volume (4 x 2-minute bouts), Okamoto *et al*., (2020) used an unmedicated hypertensive cohort (156/94 mmHg), Badrov *et al*., (2013) used normotensive females with low BP (97/57 mmHg), and Millar *et al.,* (2007) used a medicated hypertensive cohort (139/79 mmHg), which makes comparisons between the studies difficult.

Although the appropriate training frequency is vital in the prescription of exercise training, it is also important to look at the overall contraction volume. Total contraction volume is related to the total length of time performing isometric contractions (either during a session, week or during an entire IET programme) and can be manipulated by either the training frequency (how many times IET is performed per week), intra-session volume (the number of sets and reps during in each session), or the duration of the training programme (how many weeks of training) (Lum and Barbosa, 2019). The current session volume that has been adopted within IWS studies is comprised of 4 x 2-minute bouts of exercise with 2 minutes of rest between each bout (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; O'Driscoll *et al.*, 2022; Cohen *et al.*, 2023; Lea, O'Driscoll and Wiles, 2023). This equates to a total of 14 minutes of work, with only 8 minutes of actual exercise completed. When performed over a 4-week period, with exercise carried out 3 days per week, this equates to an overall contraction volume of 96 minutes (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023). As discussed in the preceding section, these studies observed significant reductions in resting BP.

Increasing the duration of IET to 8 weeks while maintaining training frequency at three sessions per week with 8 minutes of exercise per session results in an overall contraction volume of 192 minutes. Some IET studies that have used this increased volume of training have shown improvements in

resting BP (Millar *et al.*, 2007; Owen, Wiles and Swaine, 2010; Wiles, Coleman and Swaine, 2010), although some have not (McGowan, Levy, *et al.*, 2006; Bartol, Kenno and McGowan, 2012; Stiller-Moldovan, Kenno and McGowan, 2012). However, it should be noted that the latter studies used normotensive participants who had a lower baseline resting BP and/or were on antihypertensive medication. It is well-established that antihypertensive medication and low baseline BP can hinder the magnitude of BP reductions (Ishikawa-Takata, Ohta and Tanaka, 2003; Inder *et al.*, 2016; Smart *et al.*, 2019). Hypertension medications, such as ACE inhibitors and beta-blockers, may hinder BP reductions following exercise by altering vascular responsiveness and sympathetic nervous system activity, potentially blunting the specific adaptations that lower BP (Smart *et al*., 2019). Interestingly, Ray and Carrasco (2000) managed to produce significant reductions in resting dBP (67 ± 1 to 62 ± 1 mmHg) and MAP (86 ± 1 to 82 ± 1 mmHg) among a group of normotensive participants when using an even greater total training volume of 240 minutes. The greater overall training volume was achieved by increasing both the contraction time (4 x 3-minute IHG contraction) and the weekly frequency (4 days per week for 5 weeks) with a 50% MVC intensity - although it should be noted that sBP was not reduced. While this may suggest there is a need for a greater overall contraction volume with cohorts that have lower baseline BP, the IWS study from Wiles, Goldring and Coleman (2017) achieved significant reductions in sBP (-4 ± 5 mmHg), dBP (-3 ± 3 mmHg), and MAP (-3 ± 3 mmHg) amongst a group of heathy normotensive participants with only 96 minutes of total training volume over 4 weeks. The reductions in all BP parameters from Wiles, Goldring and Coleman (2017) amongst normotensive participants may be related to the higher comparable cardiovascular responses and greater post-exercise hypotension seen with IWS exercise compared to IHG exercise, potentially associated with larger muscle mass recruitment (Swift *et al*., 2022).

A study from Pagonas *et al*., (2017) that used five sessions of IHG exercise (4 x 2 minutes at 30% MVC) per week over a 12-week period (total contraction volume of 480 minutes) found no significant reductions in any resting BP parameters amongst a group of medicated hypertensive participants (135/78 mmHg). Conversely, a study from Cohen *et al.,* (2023) with same intensity as Pagonas *et al*., (2017) (4 x 2 minutes at 30% MVC), but with a reduced training frequency (three sessions per week), did find significant reductions in resting sBP amongst a group of unmedicated hypertensive participants following a 12-week IHG training programme (140/86.7 to 128.8/82.7 mmHg). This may suggest that the level of overload (intensity and volume/frequency) used was inappropriate and promoted a stimulus that is not conducive towards resting BP reductions. However, it should be noted that Pagonas *et al*., (2017) was not powered to detect changes in sBP, and participants were also medicated, and as such inferences from this data should be approached with caution (Smart *et al.*, 2019).

In relation to the optimal duration of IET for reducing resting BP, several meta-analyses have reported contrasting findings. Baffour-Awuah *et al*., (2023) found that IET programmes >8 weeks did not significantly reduce dBP amongst hypertensive individuals. On the other hand, Inder *et al.,* (2016) found that IET programmes >8 weeks were required for optimal BP reductions and also found no significant differences in the magnitude of dBP reductions between normotensive and hypertensive individuals. Baffour-Awuah *et al.,* (2023) did suggest that the lack of dBP reductions past the 8-week mark may be due to poor adherence to longer training programmes. However, O'Driscoll *et al.,* (2022) found significant reductions in both sBP (-8.5 ± 5 mmHg) and dBP (-7.3 ± 5.8 mmHg) compared to a control group following 1-year of home-based IWS exercise training. Participants performed IWS exercise three times per week at 95% HR_{peak}. Adherence to training across all participants was 77%, with no participant withdrawals throughout the entire programme. The findings from Inder *et al.,* (2016) and O'Driscoll *et al.,* (2022) contrast those of Baffour-Awuah *et al.,* (2023) and suggest that longer periods of training are conducive towards resting BP reductions. Mechanistically this makes sense, as structural vascular adaptations, such as increased artery diameter, typically occur after long periods of training (>8 weeks) (Tinken *et al.*, 2008; 2010; Baross, Wiles and Swaine, 2012) – although there is still limited evidence to show a correlation between structural vascular adaptations and further reductions in resting BP.

Interestingly, several studies have utilised much smaller overall training volumes but with a greater intensity and still found significant reductions in resting BP. Wiley *et al.,* (1992) utilised a protocol consisting of 4 x 45-second IHG contraction contractions at 50% MVC, 5 days per week for 5 weeks resulting in a much smaller contraction volume of 75 minutes, but still found significant reductions in sBP (127 ± 2.28 (SE) to 117.5 ± 2.23 mmHg) and dBP (86.2 ± 1.85 to 77.4 ± 1.49 mmHg). Peters *et al*., (2006) also used a 4 x 45-second IHG contraction at 50% MVC amongst a group of unmedicated hypertensives but with an even smaller training frequency of 3 days per week for 6 weeks. Although this resulted in only 54 minutes of overall contraction volume, the study still reported significant reductions in sBP (146 ± 11 to 133 ± 14 mmHg). Taken collectively, these findings tend to support the idea that exercise intensity has a greater influence on resting BP reductions than training frequency or volume during IET. However, other factors, such as baseline BP values, will also play a large part in the magnitude of resting BP reductions.

1.9.1. Volume, duration and frequency during other forms of exercise training

There are also other exercise training studies from the broader literature that have investigated the dose-response for training frequency and volume. Foulds *et al.,* (2014) looked at the effect of a number of different training volumes on resting BP amongst a group of healthy, active participants.

The study found that as little as 30 minutes of moderate aerobic exercise 3 times per week for 13 weeks is enough to significantly reduce resting BP (BP levels were not reported). Another study from Moraes *et al.,* (2012) found that just 2 x 60-minute sessions of a multi-component exercise training (including aerobic, strength, flexibility and balance exercises) per week for 12 weeks is enough to significantly reduce both sBP and dBP (-3.6% and -1.2%, respectively) amongst a group of elderly (>60 years) hypertensive participants. Ishikawa-Takata *et al*., (2003) also found similar results but amongst a group of stage 1 or 2 essential hypertensive participants. The study used five experimental groups: sedentary control, 30 to 60 minutes per week, 61 to 90 minutes per week, 91 to 120 minutes per week, and >120 minutes per week. Results from the study show significant reductions in both sBP and dBP with as little as 30 to 60 minutes of moderate aerobic exercise per week over an 8-week period. Although greater reductions in resting BP were found in the 61 to 90 minutes per week group, no further reductions were found in sBP with further increases in weekly training volume, and the rate of reductions in dBP did not differ between all four of the exercise groups. This suggests again that BP reductions can be achieved with as little as 30-60 minutes per week of aerobic exercise, and that there may be a volume limit where the optimal stimulus starts to plateau. Indeed, meta-analytic data from Cornelissen and Smart (2013) found that the smallest reductions in BP were found with >210 minutes of weekly exercise (>210 being the comparative group with the highest training volume), supporting the idea that there may be a ceiling to the antihypertensive benefits of exercise volume (however, authors did speculate that the lower BP reductions seen with >210 minutes of weekly exercise may be related to the lower corresponding intensities used).

The meta-analytic findings from Cornelissen and Smart (2013) also demonstrated that with aerobic exercise training, longer programmes lasting over 6 months result in smaller BP reductions compared with shorter programmes (<6 months) – although it was suggested that this may be partly due to a lack of adherence due to unsupervised exercise sessions. On the contrary, data from dynamic resistance training studies showed no difference between programmes of shorter and longer durations (Cornelissen and Smart, 2013). Cornelissen and Smart (2013) concluded that this may due to the supervised nature of many resistance training studies. Indeed, research has shown that studies carried out in a facility-based environment typically demonstrate the highest adherence rates (Garber *et al.*, 2011).

Overall, when looking at resting BP reductions following exercise training, it appears that greater BP reductions are not always obtained with a higher training frequency and/or volume. Although some studies have shown that greater BP reductions are demonstrated through increasing training frequency (Badrov *et al.*, 2013), others have shown that there is an upper limit to training frequency

and total training volume before the BP lowering effects are attenuated (Cornelissen and Smart, 2013; Pagonas *et al.*, 2017). On the other hand, some studies have shown that BP can be reduced with much smaller training volumes, but with a higher training intensity (Wiley *et al.*, 1992; Peters *et al.*, 2006). However, there are limitations to these findings due to a lack of data reporting in areas and contrasting study designs. As such, more research is needed to explore the relationship between training frequency, volume, intensity and BP reductions.

1.9.2. Manipulation of training volume, frequency and duration during a follow-up period of training

As previously discussed, due to a reduced cardiovascular stimulus/sub-threshold stimulus during isometric exercise when intensity is reduced to below a certain level, it would appear logical to investigate alterations of other programme variables, such as volume and frequency, during a follow-up period of training. As resting BP reductions have been achieved with training frequencies as low as twice per week (Moraes *et al*., 2012), there may be scope to reduce the frequency or total training volume and still maintain the resting BP reductions. Indeed, training strategies that have maintained intensity during a follow-up period of training, but utilised a reduced training volume or frequency, have been shown to delay reversibility in cardiorespiratory, metabolic, muscular and hormonal functions (Mujika and Padilla, 2000). It has been shown that during a follow-up period of training, training volume (total work performed per session) can be reduced by up to 60% to 90% without hindering training-induced physiological and performance adaptations, and training frequency can be reduced by 20% to 30% in athletes, or up to 50% in less trained individuals (Mujika and Padilla, 2000).

The only IET study that has explored the effects of maintaining resting BP reductions with a reduced training frequency is from Cohen *et al.,* (2023) who looked at the maintenance of BP reductions following 12 weeks of IWS and IHG training. During the initial 12-week period of IWS training, the intensity was set based on each participant's ability to perform a wall squat position at 95° for 2 minutes, rather than the incremental wall squat test utilised by previous IWS training studies (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019). Participants who managed to complete the 2 minute period at 95° performed 4 x 2-minute wall squats at decreasing knee angles, starting at 125° and progressing to 95° by week 12, while those unable to hold the 95° angle began at 135° and progressed to 95° by week 12 (Cohen *et al.*, 2023). Although this method of prescribing exercise intensity may be a pragmatic and accessible alternative to the incremental wall squat test (Chapter 2, section 2:10:3), it must be noted that there is no way of knowing whether the exercise stimulus

was at a sufficient level during the early stages of training. However, it does allow for progressive overload throughout the training period, a key principle of training (Khushhal *et al.*, 2020), and may also be more suited towards those who potentially struggle with the squat position initially. In the IHG group, participants performed 4 x 2-minute contractions at 30% MVC. The MVC was re-established every 4 weeks throughout the 12-week programme. All training in both intervention groups was performed under supervision by qualified physiotherapists who contacted the participants and met them in their office or work area at scheduled times. Following the initial 12-week period of training there were significant reductions in sBP and dBP compared to baseline in both IWS (141/87 to 128/83 mmHg, respectively) and IHG groups (140/87 to 129/83 mmHg, respectively). However, only sBP was significantly different from the control group at 12 weeks for both the IWS and IHG training groups. In the follow-up maintenance period of training, participants were required to perform IWS or IHG exercise once per week. The single weekly session was performed at the same intensity used during the initial period of training (95° in the IWS group, and 30% MVC in the IHG group). Following this maintenance training period, sBP, but not dBP, in both groups was significantly different from the control group. These data show that resting sBP reductions can be maintained with just a single training session per week following a 12-week IWS or IHG training programme. Nonetheless, it should be noted that the intensity was slightly increased (95° knee angle) during the follow-up period of IWS training relative to the intensity that was utilised at the start of the initial training period, even though participants were only exposed to this angle for the last 2 weeks of training. Therefore, it could be suggested that the maintenance of BP reductions during the follow-up period of training was influenced by the exposure to a higher relative exercise intensity. Furthermore, the study does not outline the physical activity level of the participants prior to testing (inclusion/exclusion criteria) or during the detraining period (continuation of pre-testing physical activity levels). If participants began new activities (e.g. walking, running) during the maintenance period, this might have contributed to the sustained or improved BP reductions, confounding the conclusion that a single weekly session alone maintains benefits.

1.9.3. Examples from performance studies

It is common practice amongst athletic training programmes to manipulate the programme variables, such as intensity, frequency, and volume of exercise (Morton, Colenso-Semple and Phillips, 2019). One well-known coaching practice used to achieve peak performance is the taper period, which generally involves a period of short-term reduction in training volume while the intensity is maintained. The goal of the taper period is to reduce accumulated fatigue, which subsequently enhances performance through greater recovery. However, when both intensity and

volume are reduced, or there is a complete cessation of training, the likelihood of a partial or complete loss of the training adaptations increases (Morton, Colenso-Semple and Phillips, 2019).

There are several performance orientated research studies that have shown a reduction in volume and/or training frequency can be utilised during a maintenance period. A study from Hickson and Rosenkoetter (1981) investigated the effects of reducing training frequency amongst a group of moderately trained participants following a 10-week aerobic training programme. The initial training programme consisted of six sessions per week. In the follow-up period of training, training frequency was reduced to either four sessions or two sessions per week for 15 weeks, while the intra-session volume (40 minutes per session) and training intensity (~90–100% of HR_{max}) were maintained. Results from the study show that both training frequencies were able to maintain short-term endurance (max effort cycle or run for 4 to 8 minutes) and $\dot{V}02_{max}$. However, due to the study design, it was not clear whether reducing the frequency to less than two sessions per week would have been effective at maintaining adaptations. The study also investigated the effects of reducing exercise volume from 40 minutes per session down to either 26 or 13 minutes per session for the follow-up 15-week period but kept frequency and intensity the same. Similar to the effects seen with a reduced frequency, the study found short-term endurance and $\dot{V}02_{max}$ were fully maintained, regardless of the exercise volume.

Another study from Brynteson and Sinning (1973) looked at the effects of reducing training frequency following a 5-week aerobic training programme. Training was carried out five times per week, for 30 minutes each session, with an intensity of 80% of HR_{max}. Following the initial period of training, participants were required to continue training for a further 5-week period, but randomly assigned a new training frequency of between one and four sessions per week. Results from the study show that irrespective of training frequency, all groups were able to maintain VO_2max. However, when looking at the data across groups, those participants who reduced their training frequency to one or two sessions per week were slightly less effective in maintaining their VO_2max (−3% compared with post-training values) compared to the groups using three to four sessions per week (+1% compared with post-training values).

The investigation of reduced exercise frequency has also been explored within strength training research. Tucci *et al*., (1992) found that if intensity and session volume were maintained, one session of isometric strength exercise performed every 4 weeks is enough to maintain maximal isometric strength for up to 12 weeks. On the other hand, studies that have looked at the maintenance of one repetition max (1RM) strength found that during a follow-up period of training, one session per week was needed to sustain, or in some instances increase, strength levels, as long as session

volume and intensity was maintained (Bickel, Cross and Bamman, 2011; Rønnestad, Nymark and Raastad, 2011; Tavares *et al.*, 2017; Walker, Serrano and van Roie, 2018). Another study Rønnestad *et al*., (2011) looked at the maintenance of 1RM squat strength and sprint speed amongst a group of professional soccer players. The study found that those players who received one session of strength training per week were more effective in maintaining strength and sprint speed than those athletes who received one session every two weeks, with the latter experiencing a significant decline in strength and sprint speed after a 12-week period, thus supporting the concept of a minimum threshold stimulus for exercise frequency during a follow-up period of training.

Several studies have also investigated the effects of a reduced training frequency period on muscular size. For younger individuals between the ages of 20-35, it seems that just one session of strength training per week is enough to maintain muscular size (muscle cross-sectional area measured by imaging techniques) following an initial period of training (Bickel, Cross and Bamman, 2011; Tavares *et al.*, 2017). However, for older individuals between the ages of 60-75, it seems one session per week is not always enough to maintain muscular size (Trappe, Williamson and Godard, 2002) and therefore may need upwards of two sessions per week (Tavares *et al.*, 2017). Mechanistically this makes sense, as older individuals are prone to conditions such as sarcopenia and have a greater rate of decline in muscular size and strength (Montero-Fernández and Serra-Rexach, 2013).

Research has also shown that strength levels can be maintained when reducing frequency and volume simultaneously (total contraction volume) while exercise intensity remains continuous. Bickel *et al*., (2011) reduced training frequency from three sessions per week to one session per week and exercise volume from three sets per exercise to one set per exercise during a follow-up initial period of training, keeping the intensity at 8-12RM. The study found that 1RM strength levels were improved during the follow-up period of training when reducing the frequency and volume together. Muscle size as well as strength was also maintained amongst the younger participants (20–35-year-olds). Another study from Tavares *et al*., (2017) found that muscle strength and size can be maintained with a reduction in training frequency and volume. The study reported that if exercise intensity is maintained during an 8-week follow-up period of training, the frequency could be reduced from three sessions per week to two sessions per week, and the volume could be reduced from three sets to two sets per exercise, without affecting any muscular adaptations.

Overall, the findings presented in this review highlight the influence intensity has on physiological adaptations produced through exercise training. The evidence suggests that exercise intensity must be kept constant during any follow-up training period to ensure physiological adaptations are maintained. If the intensity remains the same, it is likely that a reduction in training frequency,

potentially down to one session per week, may be sufficient to maintain physiological adaptations achieved through exercise training. However, due to a lack of research, it is currently unknown whether the same dose-response relationship would apply to resting BP reductions following IWS training. Although Cohen *et al.,* (2023) demonstrated the maintenance of BP with one session per week, there were some potential issues with the study's design, including a lack of a comparative detraining group, an increase in relative intensity during the follow-up period of training, and no detail on the physical activity status of the participants. Furthermore, there are no studies that have explored the associated physiological mechanisms during a maintenance period following IET or IWS training, which presents an important gap in the research.

1.10. Executive summary

Although IWS training has shown promising results, both for the health efficacy of physiological adaptations, and for the economic and accessibility benefits, there are currently only a small selection of studies that have explored the effects of IWS training on resting BP, all of which have used sample sizes (n<41) primarily aimed at exploring differences in BP (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; O'Driscoll *et al.*, 2022; Cohen *et al.*, 2023). As previously discussed, most studies are underpowered to detect changes in associative mechanistic variables or to conduct sub-group analysis (such as between males and females). Therefore, large randomised controlled trials are needed to further support the efficacy of IWS training as an effective anti-hypertensive strategy.

Additionally, only two studies have looked at IWS training past the 4-week mark. The first, from Cohen *et al*., (2023), found significant BP reductions after 12 weeks of IWS training with three training sessions per week. These reductions were also maintained with only one session per week during a 12-week follow-up period. However, as previously discussed, there were some potential issues with the study design from Cohen *et al*., (2023). Another study from O'Driscoll *et al*., (2022) found significant reductions in sBP and dBP by -10.5 and -8 mmHg, respectively, following 1 year of IWS training. However, it is difficult to compare data from this study to short-term interventions (4-12 weeks), and so inferences are difficult. Furthermore, there are limited mechanistic data past the 4-week time point. Although O'Driscoll *et al*., (2022) explored a selection of haemodynamic variables following 1 year of IWS, further mechanistic insights from longer-duration studies are warranted.

Moreover, aside from the 3-week and 4-week washout periods from Taylor *et al*., (2019) and Wiles, Goldring and Coleman (2017), and the 12-week maintenance period from Cohen *et al*., (2023), there

are no other studies that have explored the detraining effect or the sustainability/maintenance of BP reductions following IWS training. Although IWS training attempts to mitigate many of the barriers to exercise previously discussed (resulting in good adherence to short-term IET), it is still likely that there will still be some attrition and adherence issues with longer training programmes. Indeed, recent work from Wiles *et al*., (2024) found that 34% of participants withdrew from a home-based IWS training programme after 6 months. Therefore, it would seem pragmatic to understand the detraining effect following the cessation of IWS training and to explore the minimum training dose that is needed to maintain reductions in BP during a maintenance period of training.

1.10.1. Research aims and objectives

Therefore, the overall aim of this thesis is to further explore the BP lowering effects and associated physiological mechanisms of IWS training, and also to investigate the detraining effect and the maintenance of BP reductions during a follow-up training period.

As such, the objectives of this thesis are:

1. To investigate the BP reductions and associated haemodynamic and cardiac autonomic adaptations following IWS training (Study 1, Chapter 3).
2. To compare differences in the BP adaptations between male and female participants following IWS training (Study 1, Chapter 3).
3. To determine the magnitude and trend of resting BP reductions, and changes in associated haemodynamic and cardiac autonomic variables, following 8 weeks of IWS training (Study 2, Chapter 4).
4. To understand the effects of detraining on resting BP reductions and cardiovascular adaptation following the cessation of IWS training (Study 3, Chapter 5).
5. To identify the minimum frequency of IWS sessions required to maintain resting BP reductions and cardiovascular adaptations (Study 4, Chapter 6).

1.10.2. Hypotheses

Study 1*:*

1. There will be statistically significant and clinically significant resting BP reductions following 4 weeks of IWS training.
2. There will be a reduction in TPR, increased SV, and increased parasympathetic modulation/decreased sympathetic modulation following IWS training.

3. There will be no statistically significant differences in the BP reductions between male and female participants.

Study 2*:*

1. Eight weeks of IWS training will result in greater resting BP reductions than following 4 weeks of IWS training.
2. Eight weeks of IWS training will produce further associated cardiovascular adaptations.
3. There will be a reduction in the trend of BP reduction following 4 weeks of IWS training.

Study 3*:*

1. All reductions in resting BP achieved through 4 weeks of IWS training will be fully reversed following the complete cessation of training.
2. Any associated physiological adaptations following the short 4-week training period will also be reversed.

Study 4*:*

1. Resting BP reductions will be maintained with one or two IWS session per week.
2. Greater maintenance of BP reductions will be achieved with two IWS sessions per week.
3. Adaptations in TPR and HRV will facilitate the maintenance of BP reductions during the follow-up period of training.

CHAPTER 2 – GENERAL METHODS

2.1. Overview

This chapter aims to provide a comprehensive outline of the methodology used in relation to the proposed research approach, the participants studied, common procedures, and the variables measured. Details of measurements and recordings will be provided in relation to the following cardiovascular variables: BP, HR, TPR, $\dot{Q}$, SV, and cardiac autonomic variables, including HRV and BRS. The acute programme variables for the IWS protocol and subsequent home-based prescription will also be outlined. A collated data set was used within this thesis, so the main methodological protocols outlined within the general methods will be applicable to all studies within this thesis, unless stated otherwise.

2.1.1. The research approach

The research approach within this thesis adopted a quantitative and experimental design. It will be based in a post-positivist paradigm, emphasising objective measurement while acknowledging the influence of context and potential limitations in establishing absolute truths. The approach was focused on one main collated data set, which was broken down into four distinct studies, each with its own specific aims and objectives (Figure 2.1). The first study (Chapter 3, p.112) examined the effects of 4-weeks of home-based IWS training on resting BP using a large participant sample size. The second study (Chapter 4, p.137) explored the differences between 4 and 8 weeks of home-based IWS training on resting BP. For both these studies, laboratory-based haemodynamic variables, including resting BP, HR, TPR, $\dot{Q}$, and SV, and cardiac autonomic variables, including HRV and BRS, were measured. Within the first study, these measures were taken pre and post the 4-week training programme. For the second study, these measures were taken pre, during (following 4 weeks of training), and post-training (following 8 weeks of training). Participants were also required to self-measure resting BP twice a day at home during the second 4-weeks, once in the morning (within 1 hour of waking) and once in the evening (within 1 hour of sleeping) with the use of an automated home-based BP device. Results from these studies are presented in Chapter*s* 3 and 4, respectively.

Studies 3 (Chapter 5, p.159) and 4 (Chapter 6, p.176) examined the detraining effects of resting BP following 4-weeks of IWS training. The detraining effect was analysed either with a total cessation of exercise training (Study 3), or with a reduced training frequency in order to understand the

minimum stimulus needed to maintain BP reductions (Study 4). To analyse the detraining effect upon resting BP in Study 3, resting BP was analysed following a 4-week detraining period which involved a complete absence from exercise. Additional home-based BP measures were also taken twice a day during the second half of the 8-week training study. To analyse the maintenance of resting BP reductions in Study 4, participants continued IWS training for a further 4 weeks but reduced the weekly frequency of exercise training down from three sessions per week in the first 4-week period to either one or two sessions per week. As with Study 2 and 3, participants self-measured BP twice a day at home using an automated home-based BP device. Haemodynamic variables, including resting BP, HR, TPR, $\dot{Q}$, and SV, and cardiac autonomic variables, including HRV and BRS, were measured in the laboratory at baseline, week 4, and after the additional training/detraining period was completed (week 8) in both Study 3 and 4. Results from these studies are presented in Chapter*s* 5 and 6.

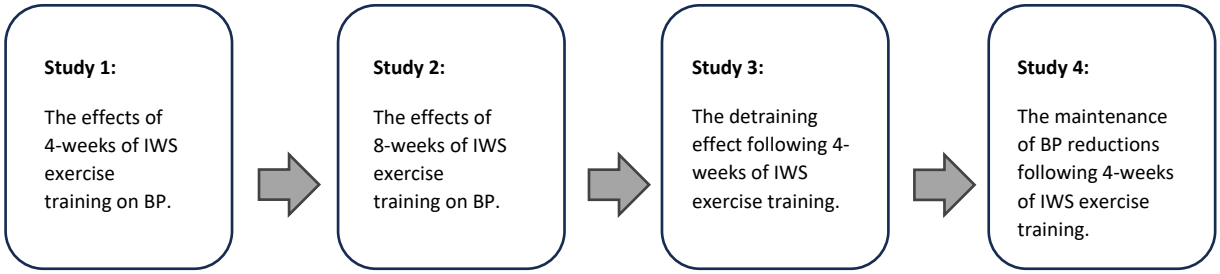


Figure 2:1 Schematic of the studies contained within this thesis

All testing within this thesis was carried out either within the Section of Sport and Exercise Sciences laboratories at Canterbury Christ Church University (CCCU), or in a home-based environment using the standardised portable equipment given. Each study was approved by the CCCU Ethics Committee and all processes were carried out according to the Declaration of Helsinki (2013). A copy of the letter of approval is presented in Appendix 1.

2.2. Participant information

Both males and females who had sBP in the normal to high normal category between 120-139 mmHg were recruited for this thesis (36 ± 11 years; 79 ± 14 kg; 173 ± 9 cm). Blood pressure categorisation was determined using the 2023 ESH guidelines (Mancia *et al.*, 2023). Three resting

sBP measurements were taken, with the average of the last two readings used for the purpose of BP classification (Mancia *et al.*, 2023). If participants had BP values outside of these ranges, they were excluded from the study. Participants who were hypertensive (sBP >140 mmHg) were given a second appointment to ensure they did not have a transient hypertensive effect, such as white-coat syndrome. If their BP was still elevated on the second visit, they were formally advised to speak to their GP. A current physical activity level below the public health recommendations of 150 minutes of moderate physical activity per week was also required for participation (Franklin, 2021). This included low-level physical activity, such as walking, light cycling and general household activities. If any participants were involved in any purposeful exercise regimes, such as running, HIIT, or dynamic resistance training, they were excluded from the study. Physical activity levels were self-reported by participants and also determined from information given on the physical activity and health questionnaire during initial screening (see Appendix 3).

All participants were free from any injuries or illnesses that may have affected the outcome variables of the study, specifically any cardiovascular conditions/disorders, and were not taking any medication. All participants were also non-smokers and consumed under the recommended alcohol drinking guidelines (no more than 14 units of alcohol a week) (Lovatt *et al.*, 2015). Female participants were either taking hormonal contraception at the time of testing, had regular menstruation (28-day cycle), or were post-menopausal. At the time of testing, 15 female participants were taking hormonal contraception, 23 had regular menstruation, and 6 were post-menopausal. Research has shown minimal influence on BP and HRV with oral contraceptives (Teixeira et al., 2015) and so this was not controlled within this thesis. For females who were eumenorrheic and had regular menstruation, the laboratory data collection was timed around their early follicular phase (days 1–7 of their menstrual cycle – this was not measured physiologically but was self-reported by participants and validated over historical cycle tracking). This early follicular phase is when the endometrium sheds, and follicle development begins. Blood pressure is relatively stable during this phase which is attributed to minimal hormonal influence on vascular tone and fluid retention (Harlow *et al*., 2012). Postmenopausal was defined as following 12 months of amenorrhea, reflecting a complete cessation of ovarian follicular function (Harlow *et al*., 2012). Hormone replacement therapy was not reported amongst any of the post-menopausal females. Although attempts were made to mitigate any influence of menstruation on resting BP reductions, previous research has noted no significant difference in BP changes between males and females following IET (Inder *et al.,* 2016; Somani *et al.*, 2017; Smart *et al.*, 2019; Baross *et al.*, 2022).

2.2.1. Sample size

Within this thesis, the sample size was determined using an a priori analysis on G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) (Faul *et al.*, 2009). G*Power calculations are determined by the following factors: type of statistical analysis, effect size, power (1-β), and significance level (α). The analysis used a power of 0.80 (equivalent to a Type II error rate of ≤ 20%), with 0.05 significance level (equivalent to a Type I error rate of 5%) (Hopkins, 2000). The measurement of sBP pre- and post-IWS training was the primary outcome variable utilised in this thesis for the effect size. The justification for using sBP rather than dBP is related to its prognostic value and its application within BP guidelines (Benetos *et al.*, 2002; Li *et al*., 2014). The study recruited normal and high-normal (sBP: 120–139 mmHg), sedentary participants. With this participant group, it was expected that the reduction in BP over a 4-week period would be in the region of 12 mmHg (Taylor *et al.*, 2019). The effect size statistics calculated indicate that the IWS training prescribed by Taylor *et al*., (2019) had a large effect on sBP and dBP reductions (*d* = 2.17 and 0.95, sBP and dBP, respectively), based on Cohen's (1988) criteria (large effect ≥ 0.8). However, the studies within this thesis will be over an 8-week period and there are currently no 8-week IWS training data to inform calculations. Furthermore, based on the set up of studies in this thesis, with five groups all using a different training stimulus over the 8-week period, it is likely that effect size differences between groups will be smaller. Using this information and taking a pragmatic approach to be able to detect small to moderate effect sizes, initial calculations using G*Power estimated that when using a 0.05 significance level, power of 0.80, with five groups and one covariate, a sample size of 100 participants would be able to detect an effect size (Cohen's f) of 0.35 (small-moderate effects (Cohen 1988). Previous research has shown dropout rates of around 20% during randomised clinical control trials (Wood, White and Thompson, 2004). Using the following formula: Nd = N/N(1 – d), where N: sample size before considering drop-out and d: expected drop-out rate, the sample size considering drop-out (Nd) was estimated at 125 participants (Kang, 2021).

2.2.2. Recruitment

Participants included within this thesis were predominately students and members of staff from CCCU, or close associates that heard about the study via word of mouth. Due to the constraints of collecting a large sample size, recruitment was staggered and carried out in batches of 10 participants. The study set out to recruit a 50:50 split of males and females, so in each batch, 5 male and 5 female participants were recruited. Once a batch of 10 participants were recruited, they were randomly allocated into either one of the four experimental groups or the control. To maintain sex-

based equity across groups, randomisation was conducted separately for males and females, ensuring that each of the five groups within a batch included one male and one female.

Whilst each study in this thesis is presented as an independent entity and organised sequentially for clarity, the data collection process was conducted concurrently across all five groups (3x per week, 2x per week, 1x per week, 0x per week, and the control) within each batch of 10 participants. Specifically, for every batch, data collection began simultaneously for all groups, with the objective of obtaining two complete data entries (one male and one female) for each experimental and control group per batch. This approach resulted in a single, collated dataset, which was subsequently analysed distinctly for each chapter, rather than collecting data sequentially for one study at a time (e.g. Chapter 1 followed by Chapter 2). This concurrent collection data method ensured consistency across groups within each batch, although the analyses were tailored to address the specific objectives of each study as presented. Regardless of any attrition imbalance (i.e. if more females dropped out of a batch than males), the 50:50 split for male/female recruitment was maintained within each subsequent batch to uphold consistency and avoid recruitment bias.

Recruitment was continued in a staggered formation until 100 participants had completed the study. Due to voluntary dropouts (n=6), COVID-19 related dropouts (n=7), and participants being excluded from the study due to not meeting the compliance criteria (n=5) (compliance for each study will be outlined in each prospective chapter), a total of 118 participants were recruited over the data collection period (from July 2020 – September 2023) (see Figure 2.2). If participants were withdrawn from the study due to non-compliance, they were still encouraged to continue IWS training for the remainder of the study duration, but the data was not included within the analysis.

Participants were systematically recruited through a randomised approach, either through face-to-face recruitment around campus or via email, and were given a participant information sheet which included a description of the requirements of testing, the protocols used, and a summary of the investigation purpose (see Appendix 2). If interest was shown, the individuals were invited to voluntarily attend the laboratory to check their resting BP levels fell within the required range. To assess BP levels, an automated BP monitor (Dinamap® Pro, GEMedical Systems, Slough, Berks, U.K.) was used (section 2.6). After 15 minutes of seated rest, three single measures were taken, separated by a 1-minute period of rest. The average of the last two readings was used for BP classification (Mancia *et al.*, 2023). All potential participants were also screened using a standard self-reported health questionnaire, which included questions relating to personal, family heredity health, and menstruation questions (if applicable) (see Appendix 3). If individuals were deemed suitable, they were formally invited to participate in the study and were asked to complete an informed consent

form (see Appendix 4) and book in for a familiarisation session. By signing the consent form, participants confirmed that they were willing to participate in the research and that they understood the information sheet. Participants were also informed that participation was voluntary, they could withdraw anytime, and no monetary or material rewards were given. Upon completion of the study, all participants were offered feedback and advice regarding the health and fitness benefits of exercise and given details of all cardiovascular assessments that were carried out during the research.

2.2.3. Familiarisation

During the familiarisation session participants were given a full overview of the study protocols and familiarised with all equipment used within the main testing sessions. The session was also carried out in the same temperature-controlled room as the data collection sessions. There was also an opportunity to ask questions if a participant so wished.

2.3. General laboratory proceedings

Once participants had opted into the study and given consent following their familiarisation visit, they were randomly allocated into 1 of 4 experimental groups, or the control group. Randomisation was carried out using the random function on Microsoft Excel. Each experimental group had 20 participants. Figure 2:2 provides a schematic diagram of the study design and group allocation. Experimental groups were required to attend the laboratory on four more occasions, while the control group was only needed for a further three occasions. For all participants, each visit occurred at the same time on each day (± 2 hours) in a temperature (16-20^{o}C) and noise-controlled room with dim lights. During the first visit, baseline haemodynamic and cardiac autonomic measurements were carried out on the Task Force® Monitor (TFM) (section 2:4). During the second visit, the incremental IWS test was carried out (used to establish IWS training intensity for the experimental groups (section 2.10.3). The participants allocated to the control group were only required to attend the laboratory for the baseline haemodynamic and cardiac autonomic measurements and were not required to attend the laboratory for the incremental IWS test. Following the incremental IWS test, participants in the experimental groups were given all the equipment needed to perform the IWS in a home-based environment. Participants were then given a full demonstration on how to use the equipment and were required to demonstrate compliance with the specific protocol which was observed and approved by the lead researcher. Detailed instructions on how to use the equipment

were also provided in the training manual. The last two laboratory visits were the week 4 and week 8 laboratory data collection visits for both the experimental and control participants (Figure 2:2).

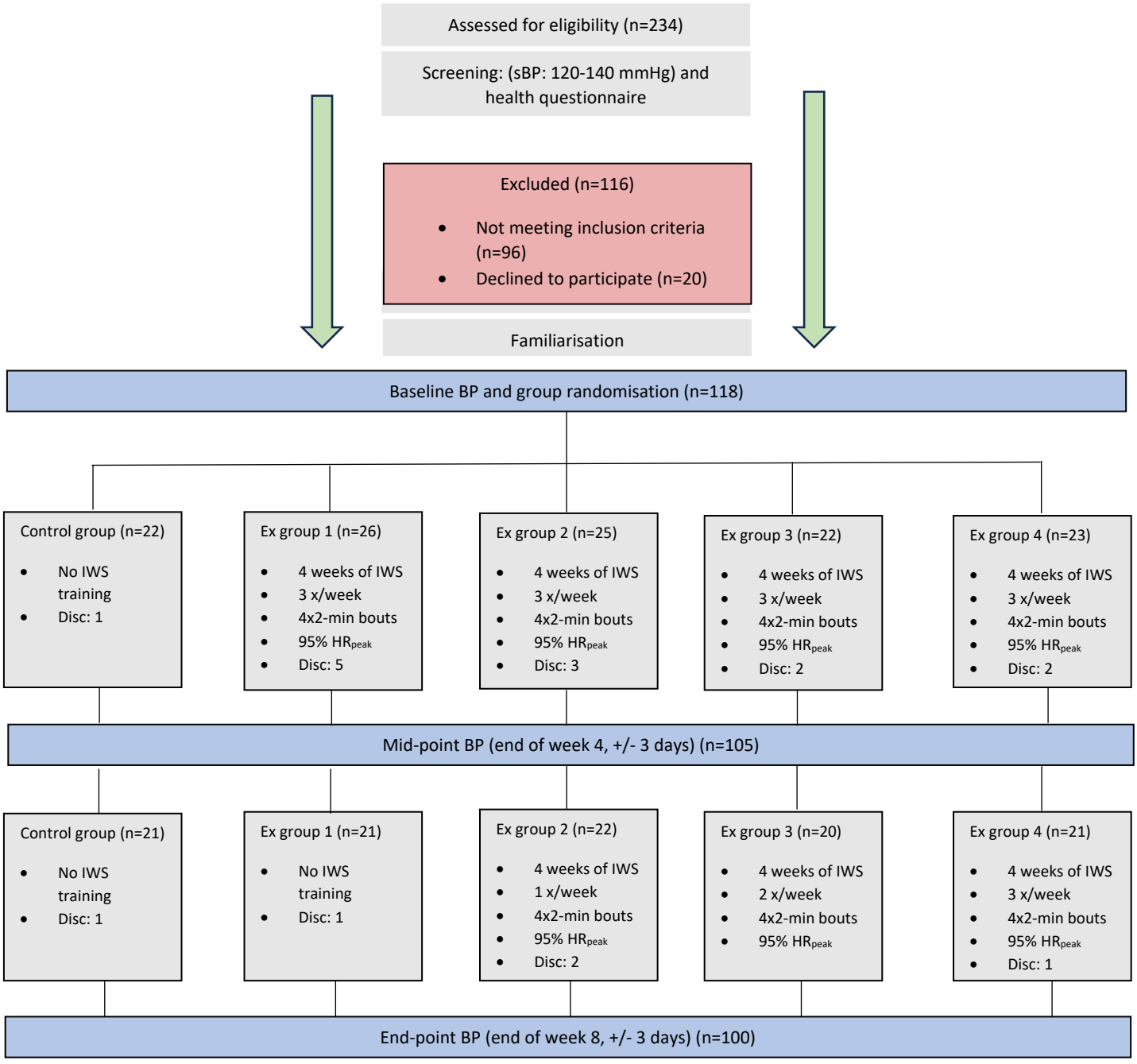


Figure 2:2 Consort Diagram showing the participant numbers for all studies during enrolment, allocation, follow-up, and analysis.

2.3.1. Testing requirements

Before attending the laboratory, participants were asked to avoid any food for 2 hours, caffeine for 4 hours, and alcohol for 12 hours pretesting. They were also asked not to carry out strenuous physical activity (including IWS exercise) 48 hours pretesting to avoid any interference with BP and HR measurements (James, Leidy Sievert and Flanagan, 2004; Forjaz *et al.*, 2004; Rezk *et al.*, 2006). Participants were asked to void their bladder before each testing session began to avoid a potential rise in BP arising from bladder distention (Fagius and Karhuvaara, 1989). Throughout the duration of the IWS training programmes, participants were required to continue their pre-participation nutritional habits and physical activity levels (not including the prescribed IWS training). The adherence to these conditions was confirmed verbally prior to each laboratory visit and tracked within an activity log that participants were given in the training manual.

2.4. Measurement of the variables studied

The following section will outline the methodological procedures utilised to measure the haemodynamic and cardiac autonomic variables measured within this thesis. Previous research that pertains to similar objectives to this thesis will be used to validate each measure.

2.4.1. Haemodynamic and cardiac autonomic assessment

To measure haemodynamic and cardiac autonomic variables within this thesis, the multi-use Task Force® Monitor (TFM) (CNSystems, Graz, Austria) was used. The TFM is shown in Figure 2.3. In clinical practises, resting BP measurements are commonly taken with the use of a sphygmomanometer (Whelton *et al.*, 2018). However, this method does not reliably account for acute alterations in BP. Observation of beat-to-beat changes in arterial BP provides a real-time evaluation that corresponds with any cardiovascular fluctuations (Fortin *et al.*, 2002). The continuous measurements on the TFM allow for simultaneous analysis of BP and other haemodynamic and cardiac autonomic variables. This allows a better understanding of any corresponding mechanisms that may be responsible for changes in an individual's BP. To measure continuous BP, the TFM uses a vascular unloading technique at the proximal limb of the index or middle finger to measure continuous BP (Parati *et al.*, 2003). Impedance cardiography (ICG) is recorded via the beat-to-beat SV (Gratze *et al.*, 1998). To measure R-R intervals, a 6-channel ECG is included, with the subsequent beat-to-beat values used to calculate real-time HRV via an

autoregressive model (Fortin *et al.*, 2001). The calculation of BRS is automatically calculated via the sequence method.

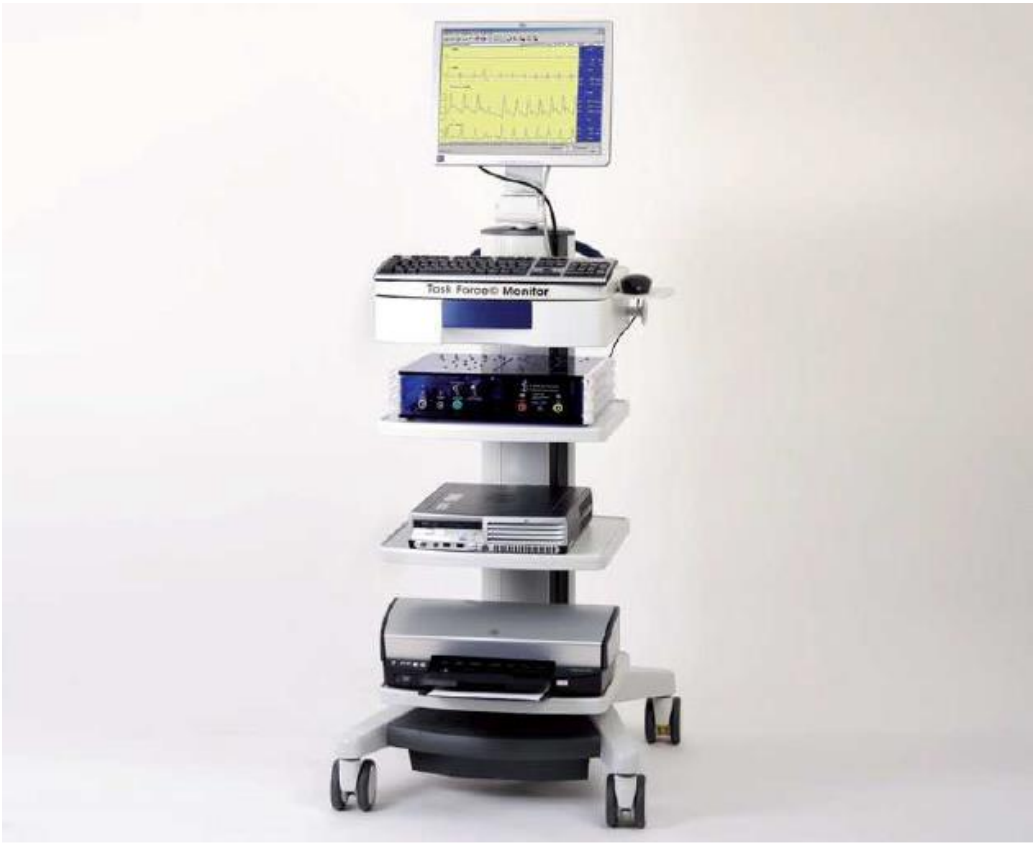


Figure 2:3 The Task Force® monitor

Before any resting measures were taken with the TFM, participants were required to remove any clothing from their left arm that may have produced a tourniquet effect. It has been previously demonstrated that there are significant differences in BP measures between arms. The left arm was therefore utilised for all resting measures to ensure consistency between conditions (Pickering *et al.*, 2005). Each participant had their arm circumference measured using an ergonomic circumference measuring tape (Seca 201, Seca GmbH & Co. KG., Hamberg, Germany) in order to select an appropriately sized arm cuff that covered the left brachial artery and was approximately 1.5 cm above the antecubital fossa and level with the heart. The finger cuff was placed on the proximal limb of the index or middle finger on the right hand. When seated, the finger cuff was positioned in line with the heart and the arm cuff on the left arm to ensure the continuous readings were closely correlated to the oscillometric BP values (Figure 2:4). Participants were also required to wear loosely fit clothing to allow the ECG and ICG electrodes to be positioned on the body (Figure 2:4). The

application of electrodes required the removal of any excess hair to ensure an accurate signal transmission. Each site was also cleaned with a non-alcoholic wipe and then dried vigorously to promote capillary blood flow.

Once all equipment was set up and attached to the participant, there was 15 minutes of seated rest in silence to encourage a fully rested state. This 15-minute period also allowed sufficient time for the continuous BP readings to adjust to the oscillometric BP values on the arm cuff. A continuous 5-minute seated measurement was then recorded (haemodynamic and cardiac autonomic), with three arm cuff measurements taken adjacently within the 5-minute period. To improve reliability of HRV data, participants were required to ensure they paced their breathing through regular and controlled breaths within this 5-minute period (Pinna *et al.*, 2007). All testing requirements previously outlined were sent to participants before every visit and verbal or written confirmation was given by each participant prior to any resting BP measurements. The same protocol was used each time resting measurements were taken on the TFM within this thesis.

The TFM system calculates all haemodynamic and cardiac autonomic parameters online using an automated system (Fortin *et al.*, 2001). A number of haemodynamic variables were indexed to participant body surface area (BSA). Mechanical column scales (Seca 710, Seca GmbH & Co. Kg, Hamburg, Germany) were used to measure body mass in kilograms (kg). A stadiometer (Seca 213, Seca GmbH & Co. Kg., Hamburg, Germany) was used to measure each participants stature in centimetres (cm). These anthropometric measurements were taken during the first laboratory visit but also during each ensuing laboratory visit. The TFM aligns with the EN60601-1 for class CF devices (Albert *et al.*, 2004) and has been deemed safe for research purposes by the International Electrotechnical Commission.

Figure 2:4 TFM electrode placement for both ECG and ICG

2.4.2. Continuous blood pressure monitoring

The TFM uses a vascular unloading technique at the proximal limb of the index or middle finger to measure continuous BP (Parati *et al.*, 2003). The continuous measurement of BP is then adjusted in accordance with oscillometric BP values from the brachial artery of the contralateral arm *(Fortin et al*., 2002). This technique detects blood volume changes in the finger and transforms plethysmographic signals into continuous BP information. The finger cuff uses an infrared light system to detect blood flow. Integrated pressure chambers are then inflated or deflated in order to exert pressure on the artery to neutralise the pulsation and keep blood flow constant. The subsequent pressure required to keep blood flow constant precipitates the beat-to-beat BP output. The TFM uses numerous feedback loops to exert system control and ensures artefact and vasomotor activity rejection (CNSystems, 2014). To ensure accurate correlations between the pressure found in the finger's arteries and that of the body's larger arteries, the beat-to-beat BP is automatically adjusted to oscillometric BP values taken contralaterally at the brachial artery (Gratze *et al.*, 1998). The TFM's beat-to-beat measurements have been tested against the Finapres ® NOVA and also intra-arterial BP devices, with all tests demonstrating similar results, both at rest and during autonomic function testing (Fortin *et al*., 2001).

The TFM offers several advantages over the Finapres ® NOVA, such as the TFM's ability to provide continuous non-interrupted continuous measurement compared to the Finapres ® NOVA which required recalibration during testing. Furthermore, the oscillometric BP device available with the TFM is well validated, including against the American national standard for electronic or automated sphygmomanometers (ANSI AAMI SP10-1992) and also against devices such as the Dinamap® BP monitor (Fortin *et al*., 2001).

2.4.3. Impedance cardiography

Impedance cardiography (ICG) is a measure of the mechanical activation in the heart. A number of cardiodynamic parameters such as SV and $\dot{Q}$ can be continuously processed non-invasively by measuring the cardiac cycle in relation to changes in thorax conductivity over time (Fortin *et al*., 2001; Ventura *et al*., 2000). Although invasive measures like the thermodilution technique are still recognised as the gold standard measure of $\dot{Q}$, they also present a serious of barriers for use within the research setting, such as high costs, user expertise, and possible risk of health complications (Harms *et al.*, 1999; Parrott *et al.*, 2004). As such, non-invasive techniques such as ICG are a more pragmatic and suitable option for use within this thesis.

The TFM produces non-invasive recordings of numerous haemodynamic parameters that are equivalent to those of the thermodilution technique (Fortin *et al*., 2006; Parrott *et al.*, 2004). It calculates the change of blood volume in the aorta and the change of fluid in the thorax (Fortin *et al*., 2006). It is well known that a person's anthropometrics can influence the shape of their thorax. As such, the TFM also integrates individual differences into its online calculations and uses each participant's BSA to allow more accurate measurements of SV. Continuous interpretation of the left ventricular SV is calculated using the maximum thoracic electrical impedance rate during the ejection period, divided by the base impedance, and multiplied by the volume constant of the chest and the LV ejection time. The volume constant of the chest is ascertained via each participant's weight, height, age, and BSA (Fortin *et al*., 2006; Valipour *et al*., 2005).

The ICG electrodes used by the TFM consist of two electrode bands fixed onto strips of adhesive, allowing for easy reproducibility of placement and thus proving beneficial over spot electrodes for use within research. There are three individual electrodes, one placed on the neck, and the remaining two on the left and right side of the thorax in line with the xiphoid process, creating the high frequency alternating current field necessary for ICG (Figure 2*:*4) (Fortin *et al*., 2006). Each electrode has a large surface area allowing very limited participant disruption. This allows high reproducibility, as previously cited by Fortin *et al*., (2001) ($r=0.963$, $N=42$, $p<0.001$) and Fortin *et al.,* (2006) ($r=0.971$, $N=20$, $p<0.001$). Total peripheral resistance and total peripheral resistance index (TPRi) are also calculated in accordance with Ohm's law (Fortin *et al.*, 2006).

2.4.4. Heart rate variability

Heart rate variability is reflective of autonomic nervous system dynamics and the heart to brain interactions (Blaber, Yamamoto and Hughson, 1995; Shaffer, McCraty and Zerr, 2014). It is recognised as an indicator of cardiac autonomic activity and can be explored through both power spectral analysis and ECG. Heart rate variability represents the end organ response of the SA node and is thought to reflect inputs from both sympathetic and parasympathetic branches of the autonomic nervous system (Sandercock, Bromley and Brodie, 2005).

There is a hierarchal neural interplay that elicits modifications in myocardial output, R-R intervals and vascular tone to maintain homeostasis (Lanfranchi and Somers, 2002). The fluctuations in R-R intervals result from alterations in sympathetic and vagal impulses. The sympathetically modulated output to the heart is associated with the low frequency (LF) component and the parasympathetic outflow via the vagus nerve with the high frequency (HF) component. The ratio of LF:HF can be used as a marker of cardiac sympathovagal balance (Kim *et al.*, 2018). It is widely accepted that the

greater the beat-to-beat variability, the greater the capacity to adapt to transient alterations in autonomic input. Therefore, a healthy heart will have high variability in R-R intervals (Pagani *et al.*, 1997).

Heart rate variability data on the TFM is measured via PSD analysis, which works by grouping each R-R interval into a sum of waves (sinusoidal) in relation to the frequency and amplitude. Derived data is then subsequently displayed along with the degree of variability, which reflects the amplitude of R-R interval oscillations at numerous frequencies, subsequently allowing specific oscillations to be examined (see Figure 2:5) (Akselrod *et al.*, 1981; Ditor *et al.*, 2005).

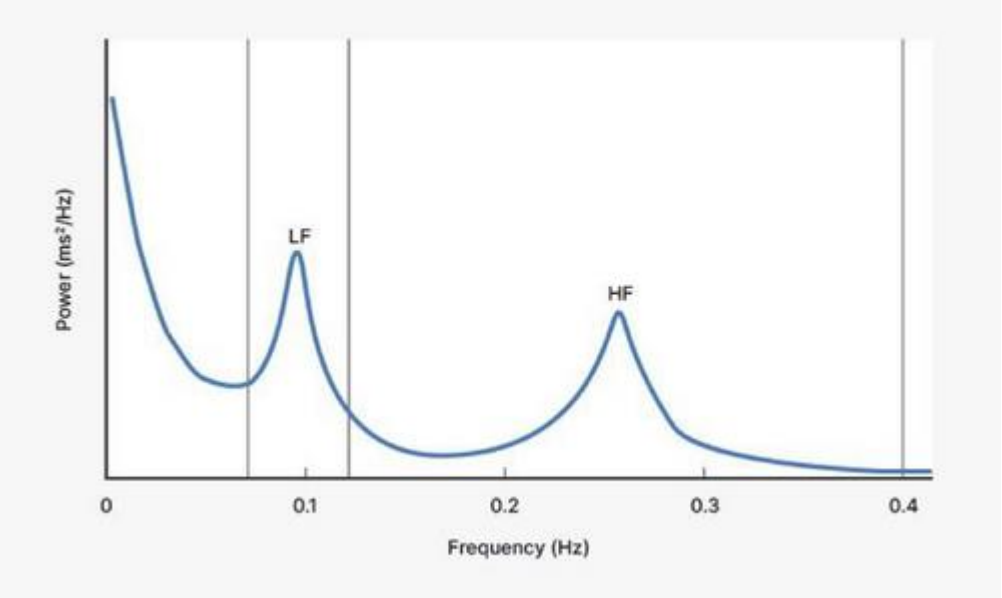


Figure 2:5 Two prominent frequency peaks in a frequency decomposition of HRV. Squared variation in ms at a particular frequency (power) is shown for all frequencies of variation from 0 to 0.4 Hz (Quigley et al., 2024)

The TFM uses several integrated detection algorithms. Prospective output data are analysed via an autoregressive model to calculate real-time HRV, which is displayed via a three-dimensional sliding power spectra (Li *et al*., 1995). The LF, HF and VLF band data are expressed in absolute values (ms^2). The utility of VLF components remains unknown, with no definitively drawn assertions (Kim *et al.*, 2018). Therefore, it is only expressed as noise when analysing PSD variance and is thus not used for analysis. The LF and HF measures are also conveyed as normalised units (LFnu and HFnu) by dividing the power of every LF and HF component by the total power and multiplying the ratio by 100 (Sharma *et al.*, 2015). The algorithms used by the TFM have achieved a detection rate of 98.97%,

proving the reliability of the device. This detection rate was evaluated against the MIT/BIH databases, of which 69 contained 24 hours of real-world ECG data (Fortin *et al*., 2001).

The measurement of HRV will be simultaneous to the continuous BP measurements taken on the TFM in a seated position. When measuring HRV, it is essential to use the appropriate body position to ensure accurate and consistent readings. Reports have found that HRV should ideally be measured in a seated position (Vila, Lado and Cuesta-Morales, 2019). However, more importantly, it is vital that the position is the same for repeated measurements to improve reliability. As such, the exact same equipment, chair, and seated position will be used for all HRV measurements.

2.4.5. Baroreceptor reflex sensitivity

The regulation of transient BP alterations is controlled via the baroreflex which acts as a homeostatic mechanism. The baroreflex works via a negative feedback loop in which short-term changes in BP stimulate a reflexive modification in HR, the contractibility of the myocardium, and alterations in vascular tone in order to maintain BP at almost constant levels (Valipour *et al.*, 2005). The degree of control the baroreflex has on the homeostatic regulation of BP is referred to as BRS. An individual's BRS is a marker of health and disease and has an inverse relationship with hypertension, CVD, and age (Gribbin *et al.*, 1971; Pinna *et al*., 2000).

Baroreceptor sensitivity can be measured invasively via arterial cannulation. Alpha-adrenoreceptor stimulant or vasoactive drugs are administered intravenously (Kardos *et al.*, 2001), and the linear regression line between reflex lengthening of the pulse interval (PI) and increases in sBP is used to indicate the degree of BRS (Pinna *et al*., 2000). However, such invasive techniques are only recommended for use with outpatients as the application is expensive, requires a highly skilled administrator and carries some risk. Therefore, non-invasive techniques are required for use within research.

The TFM utilises the sequence method to measure BRS. This technique is non-invasive and is commonly adopted within clinical settings (Robbe *et al.*, 1987). The degree of BRS is established by measuring the coupling between sBP and the R-R interval, which demonstrates the capability of the autonomic nervous system to respond by varying the R-R interval. When an acute adjustment in BP is identified, there is either a sympathetic or parasympathetic response which stimulates the HR to adjust accordingly, subsequently allowing the sensitivity of the baroreceptor reflex to be interpreted (CNSystems, 2014). The TFM detects a sequence of consecutive increases in sBP and lengthening of the PI (Valipour *et al.*, 2005). The slope of the regression line between the sBP and PI values within

each sequence represents a measure of BRS (Di Rienzo *et al.*, 2001). The consensus throughout most literature is that interactive sequences of sBP and PI are deemed as real physiological events and are not induced through coincidence (Valipour *et al.*, 2005).

2.5. Task Force® monitor reliability and validity

The most precise measurements of HRV can be ascertained through invasive practices. However, although invasive methods have proved superiorly efficacious, they pertain to several barriers, such as high costs and operating skill levels, and thus, such techniques are unfeasible within research settings. Non-invasive techniques, such as those employed by the TFM, can deliver similar results to invasive methods and have provided researchers with a more practical method of measuring HRV. Although some early non-invasive HRV techniques returned poor results, with coefficient of variation (CV) ranging from 1-235% (Sandercock, Bromley and Brodie, 2005), the TFM has demonstrated low intraindividual and moderate intra-individual CV when analysed over 4 separate trials at 2-week intervals (Goswami *et al.*, 2009).

The continuous BP (contBP) data from the TFM has been tested against intra-arterial BP methods and the continuous measurements from the Finapres. The results between devices were shown to be comparable at both rest and during autonomic function testing (Fortin *et al*., 2001). The oscillometric BP (oscBP) readings from the TFM have also been evaluated against the American national standard for electronic or automated sphygmomanometers and have also been validated against the Dinamap® BP monitor (Fortin *et al*., 2001). In addition, the oscBP of the TFM achieves the criteria for the quality mark of the German Hypertension League. To achieve this quality mark the device is compared against an Erkameter mercury sphygmomanometer device. The mean difference between the TFM and the mercury sphygmomanometer device was -1.82 ± 7.64 mmHg for sBP, and - 1.76 ± 6.36 mmHg for dBP (Fortin *et al*., 2001).

The reliability of the TFM as a measure of haemodynamic function has been shown in both clinical (O'Driscoll, 2009) and non-clinical (Taylor, 2017) cohorts. Taylor (2017) reported within-subject variation expressed as a CV with 95% confidence intervals (CI). Authors reported a sBP beat-to-beat (mmHg) CV of 3.08% (CI 2.34-4.50) and dBP beat-to-beat (mmHg) CV of 5.66% (CI 4.30-8.27) (Taylor, 2017). The TFM also meets the requirements of the CE mark (CE 0408, TUeV Austria, Vienna) and the Food and Drug Administration (FDA) clearance 510(k). These findings support the use of the TFM for research purposes within this thesis.

2.5.1. Oscillatory blood pressure monitoring

Automated oscillometric BP devices are comprised of a pneumatic upper arm cuff, a monitor, an air hose, and a transducer. The device's autonomic and manual activation both prompt a sequence of inflations and deflations within the arm cuff, controlled by a microprocessor. Each cycle lasts approximately 20-30 seconds. When the sequence begins, the cuff inflates to suprasystolic pressure which occludes the brachial artery. The transducer within the arm cuff monitors the amplitude of oscillations in the arterial wall. When these oscillations cannot be sensed, inflation of the arm cuff stops, followed by a subsequent deflation in 5 mmHg increments. The deflation occurs progressively every time two pressure pulsations of equal amplitude are detected, referred to a stepped deflation (GM Systems, 2002).

The detection of sBP occurs when oscillation amplitudes increase the quickest, as the artery is no longer occluded, and blood begins to pass again. On the contrary, the detection of dBP occurs when oscillation amplitudes decrease most rapidly. Full deflation of the cuff occurs when oscillation amplitudes are not detected below dBP. It is important to ensure a suitably sized cuff is used, as the margin of error increases when the cuff is not large enough (Bovet *et al.*, 1994). The ideal size for the cuff for optimal accuracy should be 46% of the participant's upper arm (Marks and Groch, 2000), with 2:1 ratio for the length and width (Pickering *et al.*, 2005). Several positional and postural factors should also be acknowledged when measuring oscillometric BP and consistency is also important. For example, if a person is seated, BP may be up to 5 mmHg higher than in the supine position (Privšek *et al.*, 2018). Moreover, to avoid any unwanted variability, it is essential that the back is supported (Cushman *et al.*, 1990), legs are un-crossed (Peters, Binder and Campbell, 1999), and the arm with the cuff on is level with the right atrium (Pickering *et al.*, 2005).

2.5.2. Office resting blood pressure measurement

Pre-testing resting BP measures were taken using the Dinamap® Pro automated BP monitor (Dinamap® Pro, GEMedical Systems, Slough, Berks, U.K.). These measures were used to screen participants during a preliminary testing session to ensure their BP values fell within the required range. The Dinamap was used as it is commonly used within clinical settings to screen for hypertension and is quick and easy to set up and use (Friedman, 1997; NHS, 2016). The device has also been shown to be valid and reliable in both clinical and laboratory settings (this will be discussed below).

The Dinamap® operates using the oscillometric technique (as previously outlined). Before any resting BP measures were taken the participants were required to remove clothing from their left arm that may have produced a tourniquet effect. It has been previously demonstrated that there are significant differences in BP measures between arms, and thus, the left arm was utilised for all resting measures to ensure consistency between conditions (Pickering *et al.*, 2005). Each participant had their arm circumference measured using an ergonomic circumference measuring tape (Seca 201, Seca GmbH & Co. KG., Hamberg, Germany) to select an appropriately sized arm cuff that covered the left brachial artery and was approximately 1.5 cm above the anticubital fossa and level with the heart.

The protocol began with 15 minutes of seated rest in silence to encourage a fully rested state. For the BP readings, participants were required to continue in a seated position, with legs uncrossed, feet flat on the floor, and with the left arm supported at heart level. The manual mode of the Dinamap® was utilised for BP measurement, and three single measures were taken, separated with a 1-minute period of rest. The average of the last two readings was used for analysis (Mancia *et al.*, 2023). All testing requirements previously discussed were sent to participants before every visit and verbal or written confirmation was given by each participant prior to any resting BP measurements.

2.6. Dinamap® pro validity and reliability

The Dinamap® Pro is listed by the BHS (2016) as a validated monitor for clinical use and has been tested in accordance with the European Society of Hypertension International Protocol (O'Brien *et al.*, 1993, 2010). These guidelines specify that all devices need to have a mean difference of ≤5 mmHg to a comparative mercury sphygmomanometer device and have a standard deviation of ≤8 mmHg for both sBP and dBP (O'Brien *et al.*, 2010). There is also a requirement that all devices reach an accuracy grade A or B for both sBP and dBP on the BHS grading system (2006) before clinical recommendation. The Dinamap® Pro monitors accuracy has also been validated by Reinders *et al*., (2006), who compared 9 single-arm BP measurements undertaken via a mercury sphygmomanometer device against the Dinamap® pro in 33 patient volunteers. This validation was carried out by two independent observers and found sBP accuracy to be -2.5 (±5.4) mmHg, and DBP to be 0.5 (±4.5) mmHg (Reinders, Reggiori and Shennan, 2006). The operation manual for the Dinamap® Pro Series (100-400) states that the device has also been validated against 75 intra-aortic values from invasive central aorta catheter measurements and the differences meet the American National Standards Institute/Association for the Advancement of Medical Instrumentation requirements for accuracy (GMSystems, 2002). Although there have been previous criticisms for the

Dinamap® series overestimating dBP (Beaubien *et al.*, 2002) and underestimating both sBP and dBP (O'Brien *et al.*, 1990), the device has been shown to produce similar outcomes to other semi-automated devices (Lewis *et al.*, 2002). Moreover, any inaccuracies are still understood to eliminate any bias from the investigator, as manual auscultatory reads are susceptible to subjectively amended adjustments based on pre-empted expectations (Coe and Houghton, 2002).

The only available reliability data for the Dinamap Pro 200 for the measurement of BP is within the PhD thesis of Wiles (2008), who took three separate BP measurements on the Dinamap over a 7-day period amongst a group of 10 healthy male participants. The measurements were taken in the seated position after 15 minutes of seated rest. Three readings were taken, each separated by 1 minute of rest, with the lowest reading used for analysis. The within-subject variation was expressed as a CV with 95% confidence intervals (CI). Data from the thesis showed that sBP had a CV of 3.54% (CI: 2.47-4.95%), DBP had a CV of 4.73% (CI: 3.29-6.62%), and MAP had a CV of 2.83% (CI: 1.97-3.96%) (Wiles, 2008).

2.7. Home-based blood pressure measurement

All home-based BP measurements within this thesis were taken using the A&D UA-1020-W (A&D, Tokyo, Japan) self-measurement BP monitor. The A&D UA-1020-W was used as it has been shown to be a valid home-based BP device by the BHS (2016) and is also relatively inexpensive (<£100). The wide range cuff version was also used as recruitment for the thesis targeted a variety of body sizes and compositions. The device is an automated electronic digital upper-arm BP monitor, supplied standard with a wide range adult 22-42cm cuff. The device also features A&D Medical's IHB/AFib technology to screen for an irregular rhythm during a measurement. Similar to the Dinamap ® Pro and other automated devices, the A&D UA-1020-W uses the oscillometric technique. It takes BP measurements through deflation only, and always reports the last readings of measurement. The device measures pressure values ranging from 0-299 mmHg, and pulse rates values from 40 to 180bpm (Zeng *et al.*, 2013).

When measuring resting BP in the home, participants were required to adhere to the 2023 ESH guidelines to ensure the data was as reliable as possible (Mancia *et al.*, 2023). Participants were required to rest for 5 minutes in silence before measuring BP and asked to abstain from caffeine, heavy foods, or any physical exercise (including IET) for 30 minutes before the measurement. Participants were required to be seated with legs uncrossed, feet flat on the floor, and the left arm supported at heart level. Each participant had their arm circumference measured prior to testing

using an ergonomic circumference measuring tape (Seca 201, Seca GmbH & Co. KG., Hamberg, Germany) to ensure they fit within the wide range 22-42cm cuff. A smaller or larger cuff was utilised if any participant's arms did not fit within the cuff. The cuff was required to cover the left brachial artery, be positioned approximately 1.5 cm above the anticubital fossa, and be level with the heart. Based on ESH guidelines, two BP readings were taken in the morning (within 2 hours of waking) and two in the evening (within 2 hours before sleep) for each day that home-based BP monitoring was required (Mancia *et al.*, 2023). If the first two readings were largely different (over 10 mmHg difference), a further reading was required. Each reading was separated by a 1-minute rest period, with the average of the last two readings used for analysis (Mancia *et al.*, 2023). Resting BP measures using the A&D device were also taken during each laboratory visit to give comparative data for analysis throughout the full training programme. All participants were given a full demonstration and explanation of how to use the self-administered device correctly. Each participant was required to perform three readings within the laboratory in front of the researcher to ensure correct practice, and support and guidance were given where needed. An information sheet was also given to each participant (see Appendix 5) that outlined all the procedural considerations for self-administering resting BP in the home.

2.7.1. A&D UA-1020-W reliability and validity

The A&D UA-1020 device has previously passed the requirements of the BHS Protocol for the D-ring cuff and is recommended for home use in adults. Zeng *et al.*, (2013) reported the mean (±SD) differences between the A&D UA-1020 device and a mercury sphygmomanometer (often regarded as the clinic gold standard measurement device (Pickering *et al.*, 2005)) were −0.2±7.3 mmHg ($P=0.64$) and 1.7±5.8 mmHg ($P<0.01$) for sBP and dBP, respectively. For an adult population, previous models of the BP monitor (A&D UA-767) have also satisfied the Association for the Advancement of Medical Instrumentation (AAMI) criteria, achieved a BHS grade of A/A (the highest grade achievable) and have subsequently been recommended for monitoring BP in home and clinical conditions by patients with mild-to-moderate arterial hypertension (Rogoza, Pavlova and Sergeeva, 2000). As previously discussed, the wide range D-ring cuff version (A&D UA-1020-W) will be used within this thesis due to the anticipation of a wide range of physiques and arm sizes.

Although the A&D UA-1020 has been shown to be valid, there is currently no reliability data available for the A&D UA-1020-W with the wide-range cuff. It is essential to quantify and understand the reliability of the A&D UA-1020-W within this thesis as HBMP measurements will be used to measure BP at home throughout the training period. Knowing the reliability data will also allow the

researcher to interpret participant individual data with appropriate caution when analysing collated data. Additionally, pilot testing also exposed high variability between HBPM readings measured using the A&D UA-1020-W and the BP readings taken within the laboratory on the Dinamap and TFM. As such, a preliminary study was conducted to establish the reliability of the A&D UA-1020-W and to explore the relationship between the A&D UA-1020-W and the laboratory-based equipment used within this thesis (Dinamap and TFM).

2.8. Preliminary study – Reliability of the A&D UA-1020-W

2.8.1. Introduction

The increased availability of electronic self-administered BP devices has led to widespread adoption of HBPM (Parati *et al.*, 2008). Furthermore, restrictions to medical services for all but life-threatening cases during the Covid-19 pandemic, along with a resource crisis in the NHS, has accelerated the shift from clinic-based to home-based initial assessment and monitoring of physiological parameters, such as resting BP (Citoni *et al.*, 2022). Many organisations now endorse the use of HBPM, including the ESH (Mancia *et al.*, 2023) and the ACC/AHA (Muntner *et al.*, 2019).

In addition to this recent accelerated requirement for HBPM, other arguments exist for making this resource more widely available and its utilisation in BP research studies. Although clinic BP measurements remain the more commonly used method for hypertension management and detection, there are some issues inherent to the accuracy of BP measurements taken within a clinical environment (Powers *et al.*, 2011). Some of these issues stem from the healthcare professional administering the BP measurement due to a lack of competence with the device or insufficient training (Zullig *et al.*, 2013). Other common mistakes that can lead to inaccurate readings include failing to allow for a rest period between multiple readings within a session, talking with the patient whilst taking the recording, and incorrect positioning of the patient positioning (Whelton and Williams, 2018). Aside from human error, complications also arise due to the natural variability in a person's BP depending on their physiological and psychological state, with white-coat syndrome (elevated BP due to anxiety over interaction with practitioners and healthcare professionals) one of the most evidenced phenomena shown to affect the reliability of clinic BP readings (Whelton and Williams 2018). Natural biological day-to-day variation in BP, as well as physiological responses linked to an individual's behavioural changes, such as sleep and diet, are also related to the potential variation (Mancia, 2012).

The harmful effects of hypertension are presumed to be due to prolonged and elevated BP and therefore, repeated and longitudinal measurements, such as the HBPM protocol, prescribed as an alternative or adjunctive method, would likely give a more accurate representation of BP values (Pickering, Gerin and Schwartz, 2002). It would also enhance the detection of different hypertension phenotypes, such as white-coat hypertension, true hypertension, and masked hypertension (Ruberti *et al.*, 2021). In fact, there are data to show that HBPM may be a better predictor of future cardiovascular prognosis (Bobrie *et al.*, 2004; Mallick, Kanthety and Rahman, 2009) and end-stage renal disease (Agarwal & Andersen, 2006) than office and clinic-based BP measurements. It has been observed that HBPM readings are regularly lower than office BP readings and closer to the BP recorded during 24-hour ABPM (McGowan and Padfield, 2010). As such, HBPM could obviate unnecessary medication or therapy that may be prescribed due to inaccurate readings (Mallick, Kanthety and Rahman, 2009). Furthermore, as opposed to clinic-based BP monitoring, HBPM may promote more suitable utilisation of allocated resources by curtailing unnecessary in-person laboratory or clinic visits (i.e. visits solely for a BP check). Meta-analytic data has also shown improvements in resting BP when clinical patients have adopted an HBPM protocol, potentially due to better adherence to antihypertensive therapy (Agarwal & Hemal, 2011).

Home-based BP monitoring uses the same technology as ambulatory BP monitors but gives patients the freedom to monitor BP as often as they need. While ABPM produces BP readings at numerous time points throughout a particular day - typically also during unrestricted routine daily activities - HBPM produces BP readings under fixed times and conditions over an extended period (Stergiou *et al.*, 2015). As such, HBPM readings are more reproducible and provide improved correlations with measures of target organ damage (Pickering and White, 2010). Some data has also shown the within-patient variability of HBPM is lower than that of office BP or ABPM. Warren *et al.,* (2010) measured office BP, ABPM and HBPM over a 6-week period and found CVs of 8.6%, 5.5% and 4.2%, respectively. However, it must be acknowledged that there are some limitations with HBPM (Zullig *et al.*, 2013). The most apparent limitation relates to the fact that individuals who are required to carry out HBPM generally receive very basic training or education regarding how and when to perform self-administered BP measurements effectively. The accuracy of HBPM readings may also vary unnecessarily due to variation in methodological procedures at home, either due to minimal training or a lack of consistency in the application of measurements. Indeed, despite clear, unambiguous procedures and instructions, it is challenging to ensure testing conditions are consistent and replicable over time due to a lack of supervision or guidance from a trained professional (Zullig *et al.*, 2013). Another limitation concerning this thesis is the lack of ability to measure additional cardiovascular variables. One of the overarching aims of this thesis was to

explore any corresponding changes in haemodynamic and cardiac autonomic variables that may be associated with reductions in BP following IWS training. As such, only laboratory-based equipment, such as the TFM, would be suitable to measure such variables.

In order to explore the effect of detraining following a period of IWS training, it would be useful to investigate the trends in BP alterations. One approach to do this is to ask participants to visit the laboratory every day, or multiple times every week, to measure BP. However, this is not a practical solution due to the required time and resource commitments. An alternative approach would be to use both laboratory and HBPM readings together simultaneously. This would not only produce a more comprehensive overview of resting BP over time but also mitigate any logistical and economic limitations of consecutive laboratory visits. Indeed, in both research and clinical settings, it would be advantageous to measure BP over an extended period of time due to the increased prognostic value of multiple readings (Millar *et al.*, 2007). However, to allow the BP measurements from HBPM equipment to be used interchangeably with laboratory or clinical-based equipment, the relationship between each device needs to be ascertained to ensure that readings can be reliably evaluated within the same analysis. Establishing any bias between devices within the same environment will allow more accurate comparisons of BP between equipment, thus increasing the certainty of any meaningful changes when measuring BP on alternate devices. There are currently no available data to inform whether the HBPM and laboratory-based devices used within this thesis can be used interchangeably.

Therefore, the primary aims of this study were to analyse the relationship between the A&D UA-1020-W and the laboratory and clinical BP equipment used within this thesis and also to produce reliability data for the A&D UA-1020-W device. Reliability data on the Dinamap Pro (Wiles, 2008) and the TFM (O'Driscoll 2009; Taylor, 2017) were conducted on a male cohort. However, as the recruitment for participants within this thesis will be a 50:50 split of males and females, data from an all-male cohort may not be suitable. As such, a secondary aim of this study was to assess the reliability data for each device contextualised to the specific environments, conditions and demographics used within this thesis. To the knowledge of the author, this is the first study to assess the reliability of these devices in a mixed-sex population.

2.8.2. Method

Participants

Eighteen healthy male and female (50:50) participants volunteered to participate in the preliminary study (33 ± 5 years, 171 ± 15 cm, 72 ± 18 kg). Height was measured in centimetres (cm) using a stadiometer (Seca 213, Seca GmbH & Co. Kg., Hamburg, Germany) and body mass was measured in kilograms (kg) using mechanical column scales (Seca 710, Seca GmbH & Co. Kg, Hamburg, Germany). All participants had previously participated in research trials in this laboratory and were familiar with general laboratory procedures. Written consent was given by each participant before taking part and ethical approval was granted from CCCU.

Equipment

The BP monitors used within this preliminary study are the same devices used to measure BP within the main studies of this thesis. As previously discussed, the TFM was used within the thesis due to its capacity to measure a wide range of haemodynamic and cardiac autonomic variables continuously, accounting for any fluctuations in cardiovascular parameters. It has also been used numerous times within previous IET studies to measure acute and chronic responses (Taylor *et al.*, 2017, 2019; O'Driscoll *et al.*, 2021). The Dinamap Pro was used as it is commonly utilised within clinical settings to assess BP levels and screen for hypertension (Unsworth, Tucker and Hindmarsh, 2015) and has also been utilised in previous IET studies (Devereux *et al*., 2010; Wiles *et al*., 2017). This made it the ideal screening tool to assess BP levels prior to testing. Both the TFM and Dinamap Pro have been previously assessed for reliability and validity (section 2.5 and 2.6, respectively). Although there is currently no reliability data for the A&D UA-1020-W model, the device (model UA-1020) has been shown to be a valid measuring tool for HBPM (Zeng *et al.*, 2013). The wide range D-ring cuff version (A&D UA-1020-W) was used in this thesis due to the anticipation of a wide range of physiques and arm sizes.

Procedure

All participants were familiarised with each BP device prior to data collection. The familiarisation session was designed to be almost identical to the experimental laboratory visits outlined below. Upon completion of a familiarisation session, participants returned to the laboratory on a further three occasions over a 4-week period for data collection. Each visit occurred at the same time on

each day (± 2 hours) in a temperature and noise-controlled room with dim lights (temperature, 16-20^{o}C). The visit protocol was precisely replicated on each occasion. Prior to each laboratory visit, each participant was requested to inform researchers if there had been any changes in diet, physical activity levels, sleep or stress which would require a rescheduled testing session. All measurements were taken within the laboratory at CCCU.

Readings taken on the each device were performed by a researcher and adhered to the guidelines set out previously in the main methods (see Chapter 2). There were three readings taken on both the A&D UA-1020-W and Dinamap, each separated with 1-minute of rest, with the mean of the last two readings used for data analysis (Mancia *et al.*, 2023). For the TFM, both continuous TFM (contTFM) and oscillometric TFM (oscTFM) measurements were taken simultaneously over a 5-minute period. Whilst continuous BP data was being collected, three oscillometric measurements were taken, each separated by 1 minute of rest, with the mean of the last two readings used for data analysis. For device comparisons, the mean scores of the three visits for each device were used in the analysis of sBP and dBP.

Data analysis

Prior to analysis, data was checked for parametric assumptions. For both sBP and dBP the mean values were calculated for each device during each session. Per the ESH guidelines, the mean of the last two readings was used for the analysis (Mancia *et al.*, 2023). A two-phased analysis (BP reading 1-2, and 2-3) was used to ascertain the reliability of each device. Where comparisons of data from trials 1-2 fell within the 95% confidence intervals of the subsequent 2-3 comparison, a single CV was calculated deriving the within-participant variation (CV) from log-transformed data via a two-way analysis of variance as described by Atkinson and Nevill (2001), together with the confidence intervals for a normal distribution (Tate and Klett, 1959).

Bias was calculated as the mean difference between each device. Any statistical differences between each measure and each device ($p<0.05$) were assessed using a t-test following checks for the homogeneity of variance. The upper and the lower limits of agreement (LoA) were calculated as bias–2 SD and defined the range in which 95% of the differences between the methods were expected to lay. Atkinson and Nevill (2001) report that the international standards organisation advocates using the 95% LoA to indicate the limits represented by measurement error. If changes are outside these parameters they are likely to be real (Atkinson and Nevill, 2001).

2.8.3. Results

In total, 54 data points were collected from the 18 subjects. The overall mean data was 109/70 (±10/8) mmHg for oscTFM reading for sBP and dBP respectively. These data were then compared to readings from the other devices of 110/71 (±12/9) mmHg for contTFM, 116/72 (±11/8) for Dinamap and 112/67 (±10/8) for the A&D device. There were no significant differences in BP parameters ($p>0.05$) between the three trials for the oscTFM, or the contTFM. There were significant differences in sBP for both the Dinamap (-4 ± 6 mmHg, $p=0.01$) and A&D device (-6 ± 10 mmHg, $p=0.03$) when trial 1 was compared to trial 3. For dBP there was a significant difference for trial 1-3 comparisons for the Dinamap device (-4 ± 4 mmHg, $p<0.01$).

Table 2:1 Coefficient of variation data for each device

Device	BP measure	Trial 1-2 CV (CI)	Trial 2-3 CV (CI)	Overall CV (CI)
oscTFM	sBP	3.64% (CI 2.77 - 5.60)	3.66% (CI 2.78 - 5.64)	3.72% (CI 3 - 4.9)
	dBP	7.82% (CI 6.05 - 12.44)	8.42% (CI 6.52 - 13.46).	7.55% (CI 6.1 - 9.9).
contTFM	sBP	4.84% (CI 3.70 to 7.53),	6.06% (CI 4.65 to 9.50)	5.66% (CI 4.60 – 7.40)
	dBP	10.83% (CI 8.47 – 17.63),	9.18% (CI 7.13 – 14.75).	9.82% (CI 7.9 - 13).
A&D	sBP	6.14% (CI 4.72 – 9.64),	5.94% (CI 4.56 – 9.31).	6% (CI 4.90 – 7.90)
	dBP	8.01% (CI 6.19 – 12.76),	8.34% (CI 6.46 – 13.32).	7.28% (CI 5.90 – 9.50).
Dinamap	sBP	4.86% (CI 3.71 – 7.56),	4.69% (CI 3.59 – 7.29).	4.46% (CI 3.60 – 5.80)
	dBP	6.23% (CI 4.79 – 9.79)	8.14% (CI 6.30 – 12.98).	N/A

Reliability (CV) data and confidence intervals (CI) are presented for each device. oscTFM: oscillometric TFM, contTFM: continous TFM, A&D: A&D UA-1020-W.

Comparison of readings from oscTFM and contTFM

There were no significant differences between devices for both sBP (-0.32 ± 3.62 mmHg, $p>0.05$) and dBP (-0.28 ± 3.08 mmHg, $p>0.05$). For sBP and dBP, the ratio 95% LoA were 1.002159 x/÷ 1.066427 and 1.002683 x/÷ 1.08705, respectively. Using these LoA, with a sBP of 120 mmHg recorded on the oscTFM, it is likely (95% confidence) a score between 113 and 128 mmHg would be recorded using the contTFM. For a dBP of 80 mmHG recorded on the oscTFM it is likely (95% confidence) a score between 74 and 87 mmHg would be recorded using the contTFM. These data are presented in Table 2.2.

Comparison of readings from oscTFM and Dinamap

There was a significant difference in dBP between the oscTFM and the Dinamap devices (3.5 ± 4.98 mmHg, P<0.01) There were no significant differences for sBP (-2.93 ± 6.2 mmHg p>0.05). LoA data are presented in Table 2.2.

Comparison of readings from oscTFM and the A&D device

The data from the oscTFM and the A&D device demonstrated significant differences between sBP readings (-6.28 ± 6.11 mmHg, p<0.01), but not for dBP (-1.33 ± 6.1 mmHg, p>0.05). LoA data are presented in Table 2.2.

Comparison of readings from contTFM and the A&D device

Between the contTFM and the A&D device there were significant differences between sBP readings (-5.95 ± 8.29 mmHg, <0.01), but not for dBP (-1.06 ± 6.74 mmHg, >0.05). LoA data are presented in Table 2.2.

Comparison of readings from the contTFM and the Dinamap

Between contTFM and the Dinamap there were significant differences between dBP readings (3.78 ± 5.43 mmHg, <0.05), but not for sBP (-2.6 ± 8.27 mmHg, >0.05). LoA data are presented in Table 2.2.

Comparison of readings from the A&D device and the Dinamap

Between the A&D device and the Dinamap there were no significant differences between sBP (3.35 ± 2.67 mmHg, >0.05) or dBP readings (4.83 ± 3.98 mmHg, >0.05). LoA data are presented in Table 2.2.

Table 2:2 Limits of agreement and bias between each device

Equipment	BP	Bias	Error	Lower limit	Upper limit
oscTFM vs contTFM	SBP	1.002159	1.066427	113	128
	DBP	1.002683	1.08705	74	87
oscTFM vs DM	SBP	1.027692	1.118779	110	138
	DBP	0.950212*	1.15727	66	88
oscTFM vs A&D	SBP	1.058763*	1.116801	114	142
	DBP	1.019236	1.189823	69	97
contTFM vs A&D	SBP	1.056482*	1.161335	109	147
	DBP	1.016509	1.211625	67	99
contTFM vs DM	SBP	1.025478	1.60472	106	143
	DBP	0.947669*	1.173543	65	89
A&D vs DM	SBP	0.970653693	1.047665903	111	122
	DBP	0.932278475	1.119767514	67	84

Data are presented as absolute values. The upper and lower limits are presented as an example with a sBP of 120 mmHg and dBP of 80 mmHg for the first comparable device in each row.

2.8.4. Discussion

The aims of this study were to assess the reliability of the A&D UA-1020-W, Dinamap, and TFM in the context of the specific testing conditions used within this thesis. The study also sought analyse the relationship between the A&D UA-1020-W and the laboratory and clinical BP equipment used within this thesis. The study demonstrated that measurements from these devices cannot be used interchangeably. It was also found that the data for sBP in both laboratory-based devices (Dinamap Pro and TFM) was more reliable than the HBPM device (A&D UA-1020-W) when measured using the protocols described above.

Findings from this study have shown that the CV for sBP in both the Dinamap Pro and TFM is lower than the A&D UA-1020-W, signifying greater reliability with the laboratory-based equipment. Interestingly, for dBP, the lowest reliability came from the laboratory-based contTFM readings. Although these data may suggest that the reproducibility of the contTFM is worse than the oscillometric equipment used for dBP, continuous BP accounts for acute alterations in BP and provides real-time evaluation that corresponds with any cardiovascular fluctuations, and so is more responsive to any transient changes in BP (Fortin *et al*., 2002). It should also be noted that all CV values for the devices used within this study were under 10%. Scott, Randolph and Leier (1989) argue that a CV under 10% is considered good, and a CV under 20% is considered acceptable. Although arbitrary cut of points such as a 10% for CVs have been discouraged due to a lack of

association between the error detailed and the use of the measurement tool (Atkinson and Nevill, 2001), the reliability data reported in the present study appears to be sufficient for the detection of meaningful changes in BP when a moderate sample size is used.

Despite the sBP readings from the HBPM equipment demonstrating greater variance than the laboratory-based devices in the present study, in a real-world scenario, HBPM readings would be taken within a home-based environment. This would allow for a far greater number of measurements to be taken without travelling to and from the laboratory, which would likely increase the reliability of the data. This has been previously reported by Warren *et al*., (2010) who found a lower CV with HBPM (4.2%), compared with office-based BP (8.6%) and ABPM (5.5%), respectively. The office and ABPM readings were conducted pre- and post-a 6-week period, whereas the HBPM readings were taken every day for 6 weeks, resulting in a much larger data set. Schwartz *et al.,* (2020) also found that 1 week of HBPM was more reliable than three office visits with mercury sphygmomanometry and 24-h ABPM for both sBP and dBP. Indeed, using a greater amount of data collected over time may provide a more accurate picture of BP changes, including trend analysis, rather than a simple pre-post comparison (Schwartz *et al.*, 2020). As previously discussed, there are concerns when taking a single 'snapshot' of BP, and potential errors in pre- and post-training BP measurements could make it difficult to ascertain training effects and may lead to false negative and positive results (Millar *et al.*, 2007).

Similar to previous research, the CV for sBP was lower than for dBP on all devices (Shepard, 1981; McKinney *et al.*, 1985; Llabre *et al.*, 1988). This is important, as sBP has been shown to be a better prognostic tool for diagnosing hypertension than dBP (Benetos *et al.*, 2002; Li *et al*., 2014). This finding confirms the use of sBP as the primary outcome variable within this thesis. However, the CVs in the current study do differ from previous findings. For contTFM readings, Taylor (2017) reported 3.08% (CI 2.34-4.50) for sBP and 5.66% (CI 4.30-8.27) for dBP. The current data falls outside by ~1% of the 95% confidence intervals presented in their study. With the Dinamap, thesis data from Wiles (2008) reported 3.54% (CI: 2.47-4.95%) for sBP, and 4.73% (CI: 3.29-6.62%) for dBP. The current data fall within these 95% confidence limits for sBP, but not for dBP. These previous CV data are lower than that in the current study and do not fall within the 95% confidence intervals generated from current findings. One potential explanation for the discrepancy between the data is due to the participants used in the studies. The participants in the Taylor (2017) and Wiles (2008) studies were all males. In contrast, the current study used a 50:50 split of males and females, and there may be a sex-related influence on the reliability of BP obtained from the TFM and Dinamap. To the knowledge

of the author, this is the first study to assess the reliability of these devices in a mixed-sex population.

When looking at the agreement between the BP devices, the interpretation of data using the 95% LoA demonstrates the difficulties of using these devices interchangeably. Where data crosses decision-making boundaries, this is problematic for the practitioner, researcher, and ultimately the patient in a clinical setting. This could be seen for all device comparisons, with the Dinamap/A&D comparison for sBP (11 mmHg) having the lowest interval of comparison. Even the 'within device' TFM comparisons were reasonably large (15 mmHg for sBP). The oscTFM/contTFM comparison demonstrated the smallest interval for dBP (13 mmHg). The pragmatics of the LoA data suggest that without the possibility of using devices interchangeably, there is a need to ensure that devices are consistent and well-maintained to ensure that the risk of devices failing is minimal. The loss of any device for a period due to a technical or accessibility issue would be problematic and would limit interpretation, so again, clearly identifying the importance of this study. These findings also strengthen the justification for using a staggered batch recruitment protocol for testing within this thesis, as this limits the risk of losing large amounts of data mid-testing if any of the devices were to fail.

Overall, the results from this study indicate that the A&D UA-1020-W has acceptable reliability within laboratory conditions. Along with the previously established validity data (Zeng *et al.*, 2013), these findings suggest the A&D UA-1020-W can be used as a HBPM tool within this thesis. Data from this study also indicates that CV values within the conditions of this study are slightly higher than previously established data. Finally, LoA data has demonstrated that the devices used within this thesis cannot be used interchangeably due to the large intervals of comparison between each device.

End of study

2.9. Home-based measurement of exercising heart rate using a heart rate monitor

In order to measure HR during home-based IWS training, subjects wore a wrist-worn HR monitor (Polar M200, Warminster, PA) and a Polar H10 HR chest strap (Polar Electro Oy). The Polar M200 has previously been used in research settings to monitor HR (Farris *et al.*, 2020; Harper *et al.*, 2020; D'Agata *et al.*, 2023). This latest M200 version of the Polar HR watch allows synchronisation to a mobile device and the Polar Flow App, allowing data to be easily downloaded onto a phone and/or

computer. The Polar H10 chest strap is a cardiac belt device embedding high-quality electrodes. The strap comes with a soft adjustable sensor touching the skin of the chest to capture the HR in real-time (Chattopadhyay and Das, 2021). The Polar H10 was used as HR straps have been shown to be more accurate as opposed to wrist-based devices (Hernando *et al.*, 2018; Giggins *et al.*, 2021), partly due to the different sensing principle, which is based on electrodes as opposed to photoplethysmogram (optical signal), and also because they are placed on the thoracic area, in correspondence to the heart (Wang *et al.*, 2017).

2.9.1. The validity and reliability of using a heart rate monitor to measure heart rate

There are currently no validity or reliability data for the Polar M200's HR measurement. As such, the Polar H10 was used to provide an accurate measurement of HR when performing IWS in the home. The Polar H10 HR sensor is a widely used biofeedback instrument and is often referred to as the gold standard when used during physical exercise and worn on the chest with a belt (Cosoli *et al.*, 2022). Several studies have shown the H10 chest strap to be valid and reliable during rest and exercise (Cheatham, Kolber and Ernst, 2015; Gilgen-Ammann, Schweizer and Wyss, 2019; Speer *et al.*, 2020)., 2020). Gilgen-Ammann, Schweizer and Wyss (2019) found that the Polar H10 was a valid measurement of HR, with a correlation of r=0.997 compared with ECG readings. Polar reported data showing an error in HR of <4% in all the tested activities (running, cycling, weight training, and a combination of them), proving that its performance in measuring RR intervals is excellent (Polar, 2022). The Polar H10 strap is also commonly used as the criterion device to compare resting and moving HR data against other wrist-based HR devices (Hernando *et al.*, 2018; Müller *et al.*, 2019; Hinde, White and Armstrong, 2021).

2.10. Isometric exercise training

2.10.1. Isometric wall squat

The IET protocol used within this thesis was the isometric wall squat (IWS). For the purpose of this thesis, 'IWS exercise' refers to a single bout, or session, of IWS exercise, whereas 'IWS training' refers to a set period of consecutive IWS exercise sessions within an IWS training programme. All IWS training performed within this thesis pertained to a 'training' set-up. For Study 1, IWS training was performed over a 4-week period, 3x per week. For Study 2, IWS training was performed over an 8-week period, 3x per week. Study 3 involved 4 weeks of IWS training performed 3x per week, and then a second 4-week period involving a complete absence of IWS training (0x per week). Study 4

involved 4 weeks of IWS training performed 3x per week, and then a second 4-week period involving IWS training performed either 1x or 2x per week (Figure 2:2).

2.10.2. Establishing an individualised knee angle during isometric wall squat training

It has been established that a greater cardiovascular response can be elicited through adjustments of the knee angle during IWS exercise by means of increasing the degree of knee flexion (Goldring, Wiles and Coleman, 2014). The premise for this finding is based upon the linear relationship between EMG activity in the vastus lateralis and HR and BP responses shown during incremental isometric leg extension exercise (Wiles, 2008). Since the EMG activity of the quadriceps increases in similar manner when there is an increase in flexion at the knee (Escamilla, 2001; Kvist and Gillquist, 2001; Coqueiro *et al.*, 2005), the manipulation of knee joint angle is an effective method to control/alter training intensity in IWS exercise (Goldring, Wiles and Coleman, 2014).

Participants in all studies received an individually prescribed knee joint angle for IWS exercise training. The individualised knee joint angle was ascertained through a previously validated incremental IWS test (outlined below). During the incremental IWS test, a goniometer was used to measure the participants' knee joint angle (MIE Clinical Goniometer, MIE Medical Research Ltd., Leeds, U.K). This device has been used in previous research to calculate the knee joint angle during a series of squat exercises (Youdas *et al.*, 2007), as well as in previous IWS studies (Wiles *et al*., 2017; Taylor *et al*., 2019). The device was made from see-through plastic, with 1° increments marked around a 360% axis in which two mounted arms were attached.

The goniometer was fitted to each participant while seated with their left knee at 90°. All participants were requested to wear shorts or leggings so that the applicable bony landmarks, specifically at the knee, hip, and ankle, were exposed or clearly identifiable. This allowed precise fitment of the goniometer to ensure high accuracy and reproducibility. The goniometer consisted of a stationary arm and a moving arm. The stationary arm was aligned with the lateral midline of the fibula (lower leg), using the malleolus and fibular head as reference points. The moving arm was aligned with the midline of the femur (upper leg) with the greater trochanter used as a reference point. The lateral epicondyle of the femur was used as the axis of rotation in the sagittal plane, which was aligned with the fulcrum of the goniometer. A spirit level was attached to the goniometer to ensure the lower leg remained vertical during the test. The device also had four 25mm elastic Velcro straps – two on the upper and two on the lower leg. These straps passed around the participant's leg to ensure the device did not move during the test whilst ensuring no muscle

compression. The lead researcher assessed the alignment of the device during exercise to ensure correct fitment.

2.10.3. The incremental isometric wall squat test protocol

Following correct fitment of the goniometer, participants positioned themselves upright with their back flush and rested on a fixed wall and their feet flat on the floor, roughly shoulder width apart with toes pointing forward. The experimenter would then start the test and instruct the participant to subtly raise and lower their back and slowly shuffle their feet forwards and backwards until the knee angle was at 135°. The internal angle between the femur and fibula was measured as the knee joint angle. The spirit level attached to the goniometer was observed to ensure the participant's lower leg remained vertical throughout the test.

The incremental IWS test consisted of five stages, each held for 2 minutes. The five stages were continuous with no rest, moving from one stage to the next with no contraction release. Stage 1 began at 135°. At the end of each stage the knee angle was reduced by 10° and participants were requested to slide their back down the wall, while simultaneously moving by shuffling their feet outwards to reduce the knee joint angle. This alteration of position took approximately 2-5 seconds on average. The five angles involved within the incremental test were 135°, 125°, 115°, 105°, 95° (Wiles, Goldring and Coleman, 2017).

Throughout each stage, participants were informed of the elapsed time and were given verbal support and encouraged to finish the test or to maintain the contraction for as long as they could manage. All participants were instructed to breathe normally during the test to avoid a Valsalva manoeuvre. Continuous HR data and RPE were recorded throughout the test (Borg CR10) (Borg, 1982). The test finished either at the completion of all 5 stages (10 minutes) or once volitional exhaustion was reached (9-10 RPE).

Each participant had their feet and back position measured at each stage using a standard metre rule. The position of the feet was measured using the direct distance from the wall to the back of the left heel, and the back position was calculated using the distance from the floor to the lower back (coccyx). These measurements were taken in order to replicate specific positions that were relative to the knee joint angles without the use of laboratory equipment.

2.10.4. Establishing isometric exercise training intensity

The HR data obtained during the incremental IWS test was used to determine a participant specific training angle. Previous research has demonstrated that prescribing a knee joint angle that is relative to 95% of the peak HR elicited during an incremental IWS squat test produces significant reductions in resting BP (Wiles *et al*., 2017; Taylor *et al*., 2019).

It has been previously shown that there is an inverse curvilinear relationship between the knee joint angle and HR during IWS exercise (Goldring, Wiles and Coleman, 2014). It has also been found that a 'steady-state' HR occurs during the final 30 seconds of a 2-minute bout of IET when using a constant EMG to determine the intensity (Wiles *et al.*, 2008) and also when using the constant positions during an incremental IWS test (Goldring, Wiles and Coleman, 2014). Achieving a 'steady state' during the last 30 seconds is crucial in order to establish the required intensity from an incremental test (Kraemer, Fleck and Deschenes, 2012). Therefore, the knee joint angle was plotted against the mean HR for the last 30 seconds of each stage of the incremental IWS test. If the relationship between HR and knee joint angle was non-linear, a one-phase exponential decay model was utilised using GraphPad Prism (GraphPad Prism version 5.01 for Windows, GraphPad Software, San Diego, CA). If any relationship was linear, the relationship was investigated using Pearson's product-moment correlation coefficient with Microsoft Excel software (Microsoft Excel 10, Microsoft Corporation, Redmond, WA). For each participant, the relationship generated was then used to determine the knee joint angle that would elicit a target of 95% HR_{peak} (HR_{peak} relates to the mean HR during the final 30 seconds of the incremental test), as seen in prior studies (Wiles, Goldring and Coleman, 2017; Taylor *et al*., 2019).

Once the appropriate knee angle had been established, the floor and wall positions that were previously calculated during each stage of the incremental test were also correlated against the knee angle. A specific measurement for both the foot and back placement could then be given to the participant that would reproduce their prescribed knee angle using a bend and squat device (this will be outlined below). Following the incremental IWS test, the participant-specific knee angle was verified using a goniometer to ensure that prospective home-based exercise sessions were performed at the required knee angle.

2.10.5. Bend and squat device

The IWS training within this thesis utilised a home-based approach with no technical support from a skilled researcher. Therefore, equipment to establish the required knee angle, such as the clinical

goniometer used during the laboratory testing, was not suitable due to its inherent high skill level requirement for accurate fitment. The goniometer is also susceptible to movement and misalignment which would lead to IWS training being undertaken at an inaccurately determined knee angle.

Previous research has demonstrated that a simple 'bend and squat device' can be used to recreate a target knee-joint angle (Figure 2:6) (Wiles, Goldring and Coleman, 2017). The device can be precisely adjusted so each participant can easily position their foot and back placement in order to reproduce the desired knee angle. The device is easily adjusted and does not require any operative skill.

The bend and squat device is comprised of two arms that are joined by a hinge in the middle – one labelled 'floor' and one labelled 'wall'. The length of each arm can be easily adjusted with a specific measurement in cm. The measurements on the wall arm ranged from 50-83cm, and the floor arm ranged from 32-54cm, both of which were established in previous research by Wiles, Goldring and Coleman, (2017). Both arms were adjusted to each participant's specific wall and floor measurements and held in place with a nut and bolt mechanism. Once the arms were at the desired length, the respective arms were placed on the floor and wall, subsequently positioning the device at a right angle. The device also had a detachable plastic arm that could be attached through the floor arm parallel to the wall, which allowed the back of the heel to rest against to help the participants sustain the exact foot placement. There was also a plastic lip on the wall arm to provide a tactile reference point for the participant to help reduce unwanted movement down the wall. However, the lip was a reference point and not used to support the participant's weight.

Figure 2:6 Bend and squat device used for home-based isometric wall squat training

2.10.6. Isometric exercise training prescription

All experimental participants in all studies (n=80) undertook the same initial 4 weeks of IWS training, consisting of 4 x 2-minute bouts of IWS at 95% HR_{peak}, with 2 minutes of rest between each bout (Figure 2*:*7). Each session lasted 14 minutes in total, including recovery periods, and was based upon previous research showing significant reductions in resting BP following 4 weeks of IWS training (Wiles *et al*., 2017; Taylor *et al*., 2019). During the second 4-week period, participants were randomly allocated to 1 of 4 groups with varying training frequencies (randomisation was carried out prior to the initial 4-week training period) (Figure 2*:*2). Within this thesis, training frequency was defined as the number of IWS sessions carried out per week. The prescribed training frequencies during the second period were 3x per week (continuation of frequency during the first 4-week period), 2x per week, 1x per week, and 0x per week. Each group continued the established intensity of 4 x 2 minutes at 95% HR_{peak}, with 2-minute rest periods, but were assigned differing training frequencies.

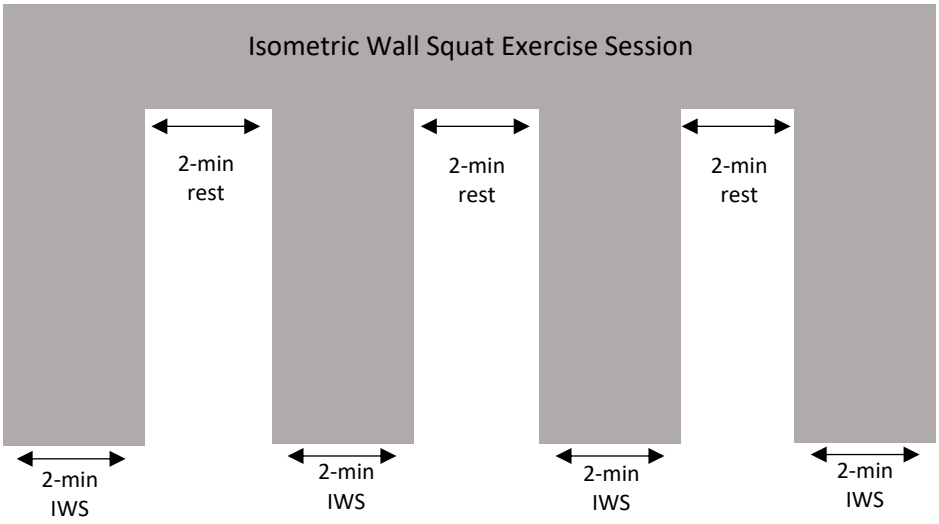


Figure 2:7 Overview of an isometric wall squat exercise session

2.10.7. Home-based isometric exercise training

All home-based IWS training complied with the standard protocol used in previous peer-reviewed research (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023). Following the incremental IWS test, participants were given all equipment needed to perform IWS training in the home: wrist-worn HR monitor and a Polar H10 HR chest strap, and a bend-and-squat device. Participants were then shown how to set up and operate the bend and squat device and HR monitor. Each participant was then required to demonstrate compliance with the home-based protocol. This allowed the participants to get familiarised with the protocol under the guidance of the researchers. The knee angle produced through the bend and squat device was also verified using a goniometer.

Participants also received a training manual (see Appendix 6) outlining the specific protocol for home-based IWS training and guidelines on how to use the equipment given. The training manual also included an RPE Borg CR10 scale and data sheets for recording HR and RPE data during each session, as well as a session timetable to track each training session, and an outline of the pre-training session requirements. A disclaimer was also included that gave recommendations on what to do in the unlikely event of any adverse reactions to IWS exercise (e.g. shortness of breath, chest pain or dizziness). Throughout the duration of IWS training, participants were required to continue their pre-participation nutritional habits and physical activity levels (not including the prescribed IWS training).

2.10.8. Heart rate data

During home-based IWS training, the participants were required to send HR data to the researchers following each IWS exercise session. Data was sent via email or WhatsApp messenger. The HR data was used to establish if IWS exercise was being performed in the target heart rate range (THRR) (this will be outlined below). As previously discussed, a Polar M200 HR monitor and Polar H10 chest strap were used to record the HR data. This was recorded continuously through each training session. To record the data, participants were required to note the last HR value seen on the screen of their HR watch following each bout of IWS exercise and record this in the training manual (Appendix 6) during the rest period. This method of observing and recording HR has been established in previous research from Goldring, Wiles and Coleman, (2014) who found a 'steady-state' HR during the last 30 seconds of each bout. Using the last 30 seconds from each bout was shown to more accurately reflect the target HR (95% HR_{peak}), which relates to the final 30 seconds of the incremental IWS test rather than the average of the final 2-minute period. The participant's RPE data was also recorded after each bout of IWS exercise. This data was only accessible to the participant and lead researcher. The researcher regularly reviewed the training data to confirm that each participant's HR stayed within the specified target zone. Heart rate data was downloaded from the HR watch at the end of the study to check compliance with exercise over the training period.

2.10.9. Target heart rate range

Due to the inherently volatile nature of HR, a THRR was adopted. The range utilises modified limits of agreement equation (Hopkins, 2000) in order to monitor the training intensity rather than using a single value. If the mean training HR value from all four IWS exercise bouts (HR data recorded by participants following each bout of IWS exercise as outlined above) fluctuated within this range, it was considered natural variability. However, if the HR value were to deviate from the THRR than it could be construed as a real change (Eliasziw *et al*., 1994), possibly arising from training adaptations, or conversely, the training stimulus being too great. Nonetheless, this real change was only assumed if the participant's mean self-reported HR fell outside the target HR range for two consecutive training sessions, in which case the individual's training angle would be adjusted for the following IWS session to ensure the mean HR value fell back within the THRR. This would confirm a sufficient cardiovascular stimulus was being elicited.

Previous studies have requested participants to re-attend the laboratory to repeat the incremental IWS test and re-establish the required training intensity if their HR fell outside of the THRR *(*Wiles *et al*., 2017). However, based on findings from Goldring, Wiles and Coleman, (2014), it was deemed

that small calculated changes in knee angle could manipulate the training intensity without the need to visit the laboratory. Goldring, Wiles and Coleman, (2014) found small but significant changes in HR and BP with only a 5° change in some participants. Therefore, for this thesis, it was deemed a 5° change in the wall squat knee angle was suitable. Although this may only be a small change in intensity, it was considered pragmatic to start with a smaller increase with the potential for further increases, rather than a large increase which may have to be reversed again if the new angle is unachievable for the participant.

2.10.10. Rate of perceived exertion measurement

In this thesis, subjective markers of somatic symptoms were analysed using the Borg CR10 scale (1998). The scale ranges from 0 to 10 to help to quantify the perceived level of effort, exertion, fatigue and pain. Descriptive verbal anchors were used to describe the level of local discomfort within the quadriceps muscle. These anchors were on a scale where 0 equals 'nothing at all', and 10 equals 'extremely strong' (see Appendix 6). The CR10 is a non-linear scale, and as such, the 'moderate' anchor does not signify the middle of the scale but instead is arranged more towards the bottom end of the scale at number 3. Wiles *et al*., (2005) has previously used the CR10 scale during isometric leg exercise to assess both discomfort and perceived exertion. Due to the occlusion of muscle blood flow and an increase in local metabolic by-products, localised pain or discomfort within the contracted muscle is expected during IET, more so during fatiguing contractions (Broxterman *et al.*, 2015). If there is too much discomfort during exercise, an individual's capacity to continue exercising may be affected, thus resulting in either a reduced intensity or the voluntary cessation of exercise.

The CR10 scale was utilised during the incremental IWS test to determine each participant's capacity to finish the test or as a warning of when they were close to volitional exhaustion. During the home-based training, participants recorded RPE values using the CR10 scale, along with HR values at the end of each bout of IWS. This allowed the researchers to ascertain if the perceived training intensity was consistent throughout the programme. It should be noted that RPE data provided an additional subjective means of monitoring safe levels of physical exertion and was not used to guide or amend the prescription of exercise intensity.

CHAPTER 3 – STUDY 1

The effects of IWS training on haemodynamic and cardiac autonomic variables amongst a large participant cohort

3.1. Introduction

As discussed in Chapter 1, there is a growing consensus around the physiological mechanisms associated with BP reductions following IET. Fundamentally, a decrease in resting BP must be mediated by changes to $\dot{Q}$ and/or TPR. Recent findings in a meta-analysis from Edwards, Wiles and O'Driscoll, (2022) indicate reductions are most likely due to significant reductions in TPR since no changes in $\dot{Q}$ were found in the analysis. However, when looking at IWS training specifically, there are some noticeable differences. Amongst a high-normal demographic (sBP >130 mmHg) Taylor *et al*., (2019) found significant reductions compared to a control group in sBP (-12.4 ± 3.9 mmHg), dBP (-8 ± 4.3 mmHg), and MAP (-6.2 ± 3.8 mmHg), which were accompanied by significant reductions in TPR (-176 dyne·s·cm^5), as well a significant increase in SV (6.46 mL). The study also found significant improvements in cardiac autonomic variables, including an increase in the total power spectrum of HRV expressed as PSD-RRI (ms2) (1031 ± 975) and HF components (ms2) (540 ± 357), a decrease in the LF:HF ratio (-1.86 ± 2.85), an increase and decrease in HFnu and LFnu (11.9 ± 17.5% and -11.9 ± 17.5%) respectively, and a significant increase in BRS (8.2 ± 5.2). The only variable that differs from the findings reported by Edwards, Wiles and O'Driscoll, (2022) was a significant increase in $\dot{Q}$ (0.37 L·min^{-1}), which was likely due to the significant increase in SV. Interestingly, Wiles, Goldring and Coleman (2017) found that as well as significant reductions in sBP (-4 ± 5 mmHg), dBP (−3 ± 3 mmHg) and MAP (−3 ± 3 mmHg), there was a significant decrease in $\dot{Q}$ (−0.54 ± 0.66 L·min^{-1}) compared to a control group following IWS training, which was likely a result of the significant decrease in HR (−5 ± 7 beats·min^{-1}). However, unlike Taylor *et al*., (2019) there were no significant changes in SV or reductions in TPR compared to the control group, which the authors suggested may be due to the normotensive population studied. Normotensive participants have a limited capacity for vascular improvements due the baseline status of vascular function (Green et al., 2004). However, Wiles, Goldring and Coleman (2017) also suggested the lack of TPR response may be due to the time course needed for structural vascular adaptations (>4 weeks) (Tinken *et al*., 2008, 2010).

On the other hand, a study from O'Driscoll *et al.*, (2022) that explored associative haemodynamic variables following 1 year of IWS training found as well as significant reductions in sBP (-8.5 ± 5

mmHg) and dBP (-7.3 ± 5.8 mmHg), there was a significant increase in SV (11.2 ± 2.8 mL) and a significant decrease in TPR (-246 dyne·s·cm^{5}). The magnitude of change for TPR and SV was also greater than the 4-week study from Taylor *et al*., (2019), potentially highlighting the influence training duration has on vascular and myocardial adaptations. Interestingly the study found no changes in Q̇, which was likely a result of the concurrent decrease in HR, and authors therefore argued that TPR reductions were the main driver for the BP reductions seen. More recently, following 4 weeks of IWS training Decaux *et al*., (2022) found significant reductions in sBP (-15 ± 9 mmHg), dBP (-5 ± 5 mmHg), and MAP (-7 ± 4 mmHg), compared to a control group in healthy participants with normal or high-normal BP. Although the study did not report changes in TPR, Q̇ or SV, the study reported no significant changes in PSD-RRI, HF components, HR, or BRS compared to a control group, contrasting the findings from Taylor *et al*., (2019), Wiles, Goldring and Coleman (2017) and O'Driscoll *et al.*, (2022).

Although some general trends could be delineated from the IWS studies previously discussed, some of the training adaptations (changes in Q̇) differ from the meta-analytic findings previously discussed (Edwards, Wiles and O'Driscoll, 2022). Furthermore, there are inconsistent findings (TPR, HR and HRV adaptations) between studies, which highlights the need for further exploration of the physiological mechanisms responsible for BP reductions following IWS training. In fact, it is generally suggested that there is a lack of consistency in the wider field and that more research is needed to understand the mechanistic pathways involved with any BP reductions following IET (Rickson, Maris and Headley, 2021; Edwards, Wiles and O'Driscoll, 2022; Baffour-Awuah *et al.*, 2023). Moreover, the BP adaptations resulting from IET are multifactorial and come from small changes in multiple regulatory pathways (Rickson, Maris and Headley, 2021). Due to variations in study designs and the pathological profiles of participants used in each study (medicated/unmedicated, normotensive/hypertensive), the precise mechanisms for these physiological alterations remain somewhat speculative. However, perhaps more importantly, the majority of studies are only powered to detect changes in BP rather than the mechanistic parameters previously discussed (Edwards, Wiles and O'Driscoll, 2022), meaning that accepting the null hypothesis and subsequent interpretation becomes problematic.

There are currently very few studies with large sample sizes that have investigated the effects of IET training on haemodynamic and cardiac autonomic variables (Edwards, Wiles and O'Driscoll, 2022). The largest study to date is from Correia *et al.,* (2020) who recently investigated the effects of a 4-week IHG training programme on resting BP, arterial stiffness parameters, vascular function and cardiac autonomics, using a sample size of 102 participants (50 experimental: 52 control). Interestingly, the study found no significant reductions in sBP and no changes in markers of arterial

stiffness or cardiac autonomics – although it should be noted that participants all had peripheral artery disease and were taking antihypertensive medication, which may have affected the results. The lack of studies with appropriate sample sizes presents an issue when investigating any corresponding mechanistic variables, as most studies are only statistically powered to detect changes in resting BP. It has been argued that the power of a study can be adequate with a smaller sample size if the effect size is large (Algina and Olejnik, 2003) and that smaller studies are more accurate when reporting effects as they are less likely to show small and trivial effect sizes (Ingre, 2013). However, smaller sample sizes have been shown to increase the bias in reported (inflated) effect sizes as they are more likely to be affected by chance variation (Schweizer and Furley, 2016). Furthermore, when sample size calculations and confidence intervals are used, larger samples are effective at protecting against trivial effect sizes and more accurate in detecting small-moderate effects (Cohen, 1962). In addition to the above points, studies that use small sample sizes are also susceptible to biasing influences from the researcher (Schweizer and Furley, 2016). Nonetheless, it should be stated that from an economic point of view, studies with an overly large sample size may lead to a waste of time, money, effort, and resources, especially if availability is limited. From an ethical point of view, overly large sample sizes may cause the participants to waste their effort and time (if their participation was not required for adequate statistical power) and may also expose the participants to more risks and inconveniences (Kang, 2021). As such, sample size calculations should still be used as it is important to ensure that the large sample size used is still appropriate and proportionate to the research aims and objectives.

Small sample sizes may have limited the ability to detect changes in cardiovascular variables in previous IWS studies. For instance, Decaux *et al*., (2022) found no significant changes in PSD-RRI, HF components, HR, or BRS following 4 weeks of IWS training. However, the study included 30 participants, which, based on G*Power calculations, would have only been able to detect a medium effect size (d = 0.54). This meant that the study was underpowered to detect smaller effect sizes in PSD-RRI (d = 0.26), HF components (d = 0.44), HR (d = 0.09), and BRS (d = 0.24). Similarly, the study by Wiles, Goldring, and Coleman (2017) did not observe significant reductions in TPR following IWS training. With a sample size of 28, the study was also underpowered to detect a smaller effect size in TPR (d = 0.37). A-priori G*Power calculations suggest that a sample size of 100 participants (as used in this thesis) would be required to detect a small to medium effect size (d=0.3). As such, a larger sample size enhances the statistical power of the study, increasing the likelihood of detecting meaningful changes in cardiovascular variables that may have been missed in previous research with smaller cohorts.

Another benefit of large sample sizes relates to sub-group analysis within a data set. A key comparison relevant to this thesis is the difference in BP reductions between male and female participants following IWS training. Current ESH guidelines state that there are likely to be differences between males and females in terms of the magnitude of BP reductions when following the exercise recommendations presented (aerobic and dynamic resistance training) (Mancia *et al*., 2023). However, this statement is based on a single meta-analysis conducted over a decade ago that found a greater BP-lowering effect following exercise training in males (Cornelissen and Smart, 2013). Conversely, when looking at the sex-based differences following IET, pooled data in a meta-analysis from Inder *et al.*, (2016) and an individual participant data meta-analysis from Smart *et al.*, (2019) found that there are no differences in BP responses between males and females. However, most studies that have directly compared the sex differences to IET have used small sample sizes (n=20-24) (Hanik *et al.*, 2012; Somani *et al.*, 2017; Baross *et al.*, 2022) or with an unbalanced ratio of males and females (Gill *et al*., 2015; Millar *et al*., 2007) and may not be powered to detect differences between males and females with a sub-group analysis (Ferreira and Patino, 2017; Rich-Edwards *et al.*, 2018). When looking at IWS studies specifically, there have been either solely males recruited (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019), or very few females (Lea, O'Driscoll and Wiles, 2023). While Decaux *et al*., (2022) recently used a split of males and females, the sample size was small and so sex-based comparisons are difficult. Overall, there is currently a dearth of research to support purported sex-based differences in BP adaptation following IWS training and further research in this area is warranted.

Therefore, the primary aim of this study was to investigate the effects of a 4-week IWS training programme on BP and associated haemodynamic and cardiac autonomic parameters using a large sample size. The participant cohort was based on the collated data set of 100 participants (80 experimental, 20 control). A secondary aim of the study was to compare differences in the BP reductions between male and female participants following the 4-week IWS training period.

3.2. Method

3.2.1. Participants

One hundred and thirteen healthy males and females with a resting sBP between 120-140 mmHg were recruited for the study. The determination of BP categorisation was ascertained following the ESH guidelines: three resting sBP measurements of ≥120 mmHg and <140 mmHg (Mancia *et al.*, 2023). A current physical activity level below the public health recommendations of 150 minutes of

moderate physical activity per week was also required for participation (Franklin, 2021). This included low-level physical activity, such as walking, light cycling and general household activities. If any participants were involved in any purposeful exercise regimes, such as running, HIIT, or dynamic resistance training they were excluded from the study. Full details of the participant cohort can be seen in Chapter 2 (section 2.2).

3.2.2. Sample size estimation

The sample size for the current study was based on the collated data set of 100 participants. Using G*Power calculations, based upon a significance level of 0.05, a power of 0.80, 2 groups (uneven groups, 80:20) and 1 covariate (baseline BP), the current study was powered to detect a small to moderate effect size (Cohen's *d* = 0.3). This will allow a sufficiently powered detection of changes of additional variables with a small to medium effect size. Although the ratio between experimental and control groups is large (4:1), based on previous effect sizes seen for sBP following IWS training (*d* = 2.17), an equal control group was not deemed necessary. Full details of the sample size calculations can be seen in Chapter 2 (section 2.2.1).

3.2.3. Recruitment

Recruitment was staggered in groups of 10 participants from July 2020 – September 2023. Although the predicted sample size with dropouts was 125, the target for statistical analysis was 100 participants. As such, staggered recruitment continued until 100 participants completed the full study. There were 13 dropouts in total (seven of these were COVID-19 related, three were not compliant with the protocol and so were withdrawn, and three voluntarily dropped out), so 113 participants were recruited for this study. Volunteers who participated in all studies included within this thesis were predominately students and members of staff from CCCU, or close associates that heard about the study via word of mouth. If an interest was shown, the individuals were invited to attend the laboratory to check their resting BP levels fell within the required range. To assess BP levels, an automated BP monitor was used. All potential participants were also screened with a physical activity and health questionnaire to ensure they fit the eligibility criteria. If individuals were deemed suitable, they were formally invited to participate in the study and were asked to fill out an informed consent and book in for a familiarisation session. The recruitment process for the collated data set is described in detail in Chapter 2 (section 2.2.2).

3.2.4. Equipment

Laboratory-based equipment

Haemodynamic and cardiac autonomic assessment: All haemodynamic and cardiac autonomic variables in this study were measured using the TFM. The TFM allows for observation of beat-to-beat changes in arterial BP, providing real time evaluation that corresponds with any cardiovascular fluctuations (Fortin *et al*., 2002). The continuous measurements on the TFM also allow for simultaneous analysis of BP along with other haemodynamic and cardiac autonomic variables. Full details of the TFM can be found in Chapter 2 (section 2.4.1)

Wall squat knee joint angle: Knee joint angle was measured during exercise using a clinical goniometer. For further details see Chapter 2 (section 2.10.4).

Rate of perceived effort (RPE): The Borg CR10 scale was used to measure and rate effort felt in the participant's upper legs during exercise in the laboratory and at home. For further details see Chapter 2 (section 2.10.10).

Home-based equipment

Heart rate: In order to measure HR during home-based IWS training, participants wore a wrist-mounted HR monitor and a Polar H10 HR chest strap. Full details of the home-based HR equipment can be seen in Chapter 2 (section 2.10.8).

Wall squat knee joint angle: During home-based IWS exercise sessions, the knee joint angle was established by using a Bend and Squat device which can be used to recreate a target knee-joint angle. The device can be precisely adjusted so each participant can easily position their foot and back placement in order to reproduce the desired knee angle. Full detail on the knee joint angle can be seen in Chapter 2 (section 2.10.5).

Training manual: During home-based IWS training, participants also received a training manual which outlined the specific protocol for home-based IWS training, as well as guidance on how to use the equipment given. The training manual also included data sheets to input HR and RPE data on from their training sessions. The purpose of each participant recording their own data was to

monitor physiological responses and also to ascertain compliance to training. Compliance was validated by downloading HR data from the participant's watch at the end of the 4-week period.

3.2.5. Procedures

Familiarisation

During the familiarisation session participants were given a full overview of the study protocols and familiarised with all equipment used within the study. Full details of the familiarisation session can be seen in Chapter 2 (section 2.2.3).

Overall study design

Once participants were familiarised with the study and enrolled, they were randomised into either the experimental group (n=92) or the control group (n=21). Randomisation was conducted using the random function on Microsoft Excel and was carried out before baseline BP measures were taken to avoid any recruitment bias. Following the familiarisation session there were three more visits to the laboratory. Visit 1 was to carry out the incremental wall squat test (section 2.10.3). Visit 2 and visit 3 were to measure baseline and week-4 cardiovascular parameters, respectively (Figure 3:1).

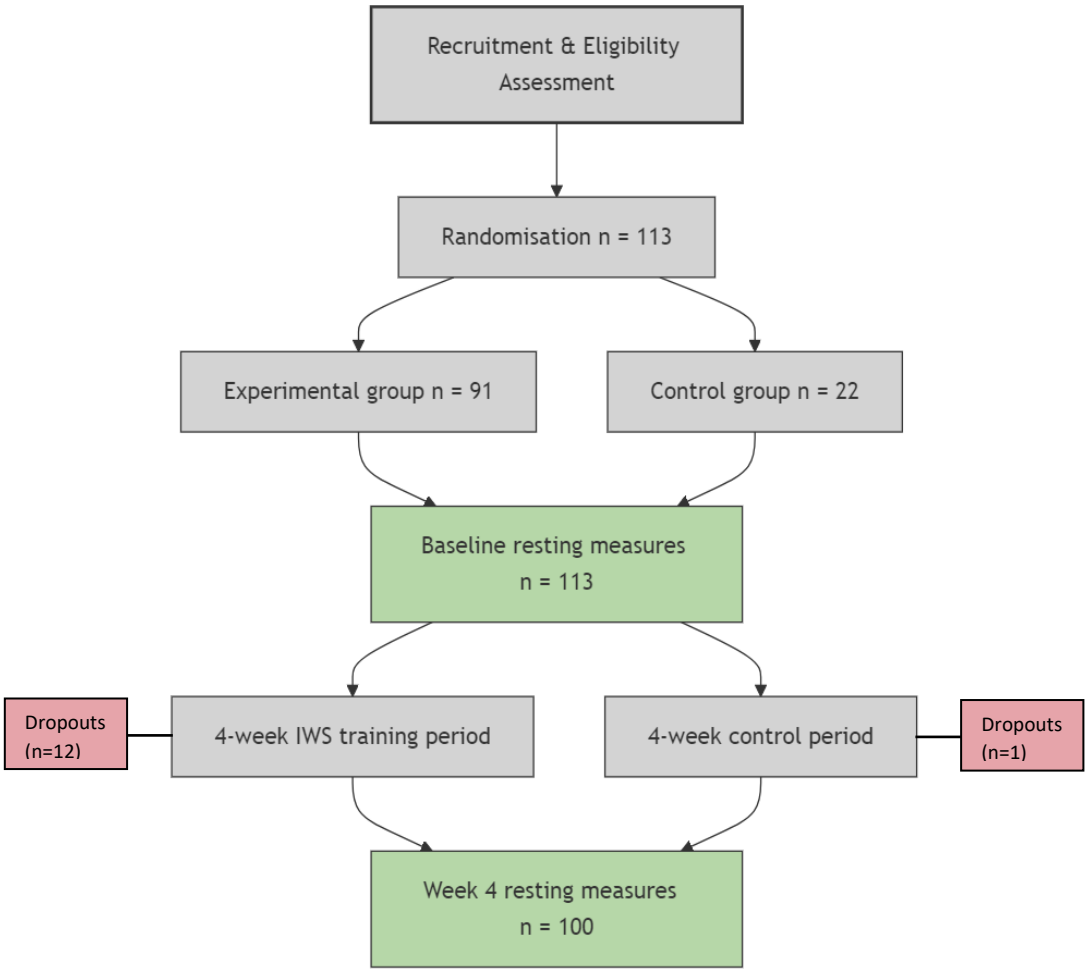


Figure 3:1 Data collection timeline and sample sizes used

Training condition

During the first laboratory visit, all experimental participants were required to undertake an incremental IWS test to determine the knee joint angle used during training (see Chapter 2, section 2.10.3). The knee joint angle was established to elicit a training intensity of 95% HR_{peak} during home-based sessions. The accuracy of the bend and squat to elicit the specific individual knee angle was then checked using the goniometer and adjusted where necessary. Before beginning training, all participants were given full demonstrations on how to use all equipment. They were then invited to demonstrate to the researcher that they could set up and use all equipment as per the protocol and instructions given with further guidance provided if required. Following baseline resting measurements, all experimental participants then carried out a 4-week home-based IWS training programme. Training was carried out three times per week over the 4-week period (n=12), with 48

hours between each session. Each training session comprised of 4 x 2 minutes of IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest.

To monitor the home-based training, participants were required to self-report their HR (last 30 seconds of each bout) during the IWS exercise sessions. This data was then sent via email or WhatsApp messenger to the research team after each session and subsequently examined to check if it fell within the THRR (section 2.10.9). If the HR fell outside the THRR for more than two sessions, the knee angle was reduced or increased by 5° to ensure the HR fell back within the correct range (Goldring, Wiles and Coleman, 2014). Participants were also required to report their RPE during each IWS exercise session. Following the 4-week training period, participants were required to attend the laboratory for post-training resting measures. To check compliance with exercise protocol and individualised training zone prescribed over the training period, HR data was downloaded from the HR watch at the end of the study. The completion of at least 10 out of 12 sessions was required for inclusion in the study. If participants were withdrawn, they were encouraged to carry on with the IWS training, although their data was not used for analysis. Full details of the IWS training protocol can be found in Chapter 2 (section 2.10).

Control condition

During the control condition, participants were requested to maintain their habitual dietary and physical activity daily routines for the 4-week period. During this period, participants did not visit the laboratory (aside from baseline and week-4 BP measurements), and no additional measures were taken. Adherence to these conditions was verbally confirmed during the subsequent laboratory session.

3.2.6. Resting measures

Laboratory-based measures

Both experimental and control participants were required to attend the laboratory for resting haemodynamic and cardiac autonomic measures. Before attending the laboratory, participants were asked to avoid any food for 2 hours, caffeine for 4 hours, and alcohol for 12 hours pretesting (James, Leidy Sievert and Flanagan, 2004; Rezk *et al.*, 2006). Upon arrival to the laboratory, participants rested in a seated position for 15 minutes to ensure they were fully rested. Following the seated rest, sBP, dBP, MAP, $\dot{Q}$, SV, TPR, BRS, LF, HF, LFnu, HFnu, and PSD-RRI were measured continuously in the seated position for 5 minutes using the TFM. After this time, the mean for each variable were calculated offline for the 5-minute period. A number of measures were indexed to BSA. Resting

measures were taken at baseline and post-training (4 weeks). Post-training resting measures were taken 72 hours after the final bout exercise at week 4 (Wiles *et al.*, 2008) to avoid any transient effects which may persist post-exercise (Kenney and Seals 1993). Full details of the protocol to obtain resting measures can be seen in Chapter 2 (section 2.4).

3.2.7. Data analysis

All data were checked for normality and homogeneity of variances (Field, 2013). Where the parametric assumptions were met, a one-way analysis of covariance (ANCOVA) was carried out to explore the possible differences in each dependent variable (week 4 resting measures) compared to the control group, using baseline measures as the covariate. An ANCOVA was also used for the sub-group analysis of males and females. Using an ANCOVA increases the statistical power by reducing error variance typically seen when using multiple data sets within the same analysis. This test was selected to maintain statistical power and reduce the probability of a type II error. Where data were not normally distributed, a Quade non-parametric ANCOVA was used. The Quade test rank transforms the data to achieve a normal distribution pattern. Effect sizes were calculated according to Cohen's criteria (Cohen's *d*), where values were classified as trivial (< 0.2), small (0.2–0.5), moderate (0.5–0.8), large (0.8–1.2), and very large (> 1.2) to assess the magnitude of differences in BP outcomes between the intervention and control group (Cohen 1988). For all tests, an alpha level of <0.05 was set as the threshold for statistical significance. Data analysis was performed with IBM SPSS (BM SPSS Statistics for Windows, version 19.0, Armonk, NY: IBM Corporation).

3.3. Results

One hundred participants (M=55: F=45) completed the study (36 ± 11 years; 79 ± 14 kg; 173 ± 9 cm). The allocation of male and female participants was 44:36 in the experimental, and 12:8 in the control group. Out of the total 80 experimental participants who were compliant with the inclusion criteria, 77 completed all 12 training sessions during the 4-week training period. Of the remaining three, each missed one session, and so totalled 11 training sessions over the 4-week period. Resting haemodynamic and cardiac autonomic data were obtained from all participants during the laboratory visits at baseline and week 4.

3.3.1. Resting blood pressure

As shown in Figure 3:2, resting sBP decreased post-IWS training (-9.45 ± 6.69 mmHg) and was significantly different to the control group ($F(1,97) = 27.338$, $p<0.001$). Resting dBP reduced following IWS training (-5.62 ± 9.92 mmHg) and was also significantly different to the control group ($F(1,98) = 7.719$, $p=0.007$). Reductions in MAP (-6.90 ± 7.77 mmHg) were also significantly different from the control group following IWS training ($F(1,98) = 14.935$, $p<0.001$). Mean values for sBP, dBP and MAP can be seen in Table 3:1. There were no significant differences between males and females for sBP ($F(1,77) = 2.049$, $p=0.156$), dBP ($F(1,77) = 3.199$, $p=0.78$), or MAP ($F(1,77) = 3.869$, $p=0.53$) (Table 3:2).

Table 3:1 Mean values for systolic, diastolic and mean blood pressure

Variable	IWS Pre	IWS Post	Control Pre	Control Post
sBP (mmHg)	130.52 ± 5.78	121.07 ± 7.24**	127.77 ± 5.99	126.98 ± 6.0
dBP (mmHg)	84.15 ± 9.23	78.53 ± 8.46*	80.91 ± 10.08	83.10 ± 8.25
MAP (mmHg)	99.61 ± 7.06	92.71 ± 7.30 **	96.53 ± 7.56	97.73 ± 5.60

Mean values and SD for resting systolic (sBP), diastolic (dBP) and mean arterial (MAP) pressure before and after the training and control conditions. ** $p<0.001$ and * $P<0.05$ for difference between experimental and control conditions.

Table 3:2 Mean systolic, diastolic and mean arterial pressure for males and females

Variable	Male Pre	Male Post	Female Pre	Female Post
sBP (mmHg)	130.88 ± 6.19	122.09 ± 6.94	130.08 ± 5.27	119.61 ± 7.19
dBP (mmHg)	83.38 ± 9.48	80.02 ± 8.33	85.09 ± 8.95	77.43 ± 8.62
MAP (mmHg)	99.22 ± 7.36	94.04 ± 7.13	100.08 ± 6.76	91.49 ± 7.42

Mean values and SD for resting systolic (sBP), diastolic (dBP) and mean arterial (MAP) pressure before and after the training condition for males and females. ** $p<0.001$ and * $P<0.05$ for difference between males and females.

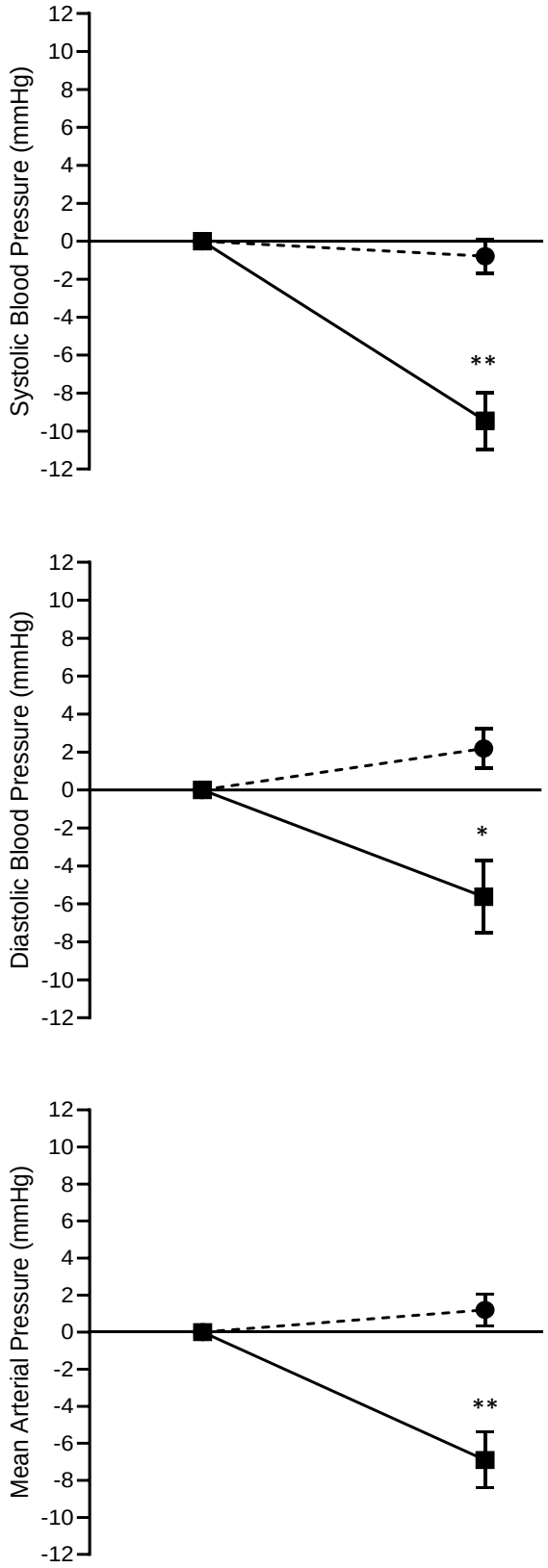


Figure 3:2 The mean systolic (a), diastolic (b) and mean arterial (c) pressure changes for the control (●) and training (■) conditions. Error bars indicate standard error of the mean. ** p<0.001 and * P<0.05 for difference between experimental and control conditions.

3.3.2. Resting cardiac output, total peripheral resistance, heart rate and stroke volume

Following IWS training there were reductions in TPR (-168.93 ± 372.8 dyne·s·cm^5) and TPRi (-87.73 ± 191.50 dyne·s·m^2·cm^5) which were significantly different to the control group ($F(1,97) = 7.475$, $p=0.007$, $F(1,97) = 9.649$, $p=0.002$, respectively). However, following training there were no significant differences in resting HR (-2.59 ± 10.59 beats·min^{-1}, $F(1,98) = 0.22$, $p=0.64$)) Q̇ (0.29 ± 1.59 L·min^{-1}, $F(1,98) = 2.65$, $p=0.11$), Q̇i (-0.15 ± 0.83 L·min^{-1}·m^2, $F(1,98) = 2.65$, $p=0.11$), SV (-0.41 ± 21.89 mL, $F(1,98) = 3.26$, $p=0.57$) or Si (-0.24 ± 11.29 mL·m^2, $F(1,97) = 1.01$, $p=0.32$) compared to the control group. Mean values for TPR, HR, CO, and SV can be seen in Table 3.3.

Table 3:3 Mean values for total peripheral resistance, heart rate, cardiac output, and stroke volume

Variable	IWS Pre	IWS Post	Control Pre	Control Post
HR (bpm)	73.25 ± 9.90	70.54 ± 10.45	68.28 ± 10.83	67.93 ± 6.76
TPR (dyne·s·cm^5)	1443.12 ± 449.88	1274.18 ± 382.76*	1420.38 ± 533.74	1475.98 ± 439.61
TPRi (dyne·s·m^2.cm^5)	748.26 ± 240.13	660.54 ± 203.74*	771.69 ± 330.44	803.46 ± 283.72
Q̇ (L.min)	5.90 ± 1.67	5.62 ± 1.23	5.50 ± 1.36	5.69 ± 1.69
Q̇I (L.min.m^2)	3.06 ± 0.89	2.92 ± 0.69	2.94 ± 0.77	3.03 ± 0.86
SV (mL)	81.00 ± 21.27	80.59 ± 18.36	81.22 ± 18.91	84.15 ± 23.93
SI (mL^2)	42.09 ± 11.62	41.85 ± 10.08	43.30 ± 9.88	44.69 ± 11.81

Mean values and SD for resting heart rate (HR), total peripheral resistance (TPR), TPR index (TPRi), cardiac ouput (Q̇), cardiac output index (Q̇I), stroke volume (SV) and SV index (SI) before and after the training and control conditions.** p<0.001 and * P<0.05 for difference between experimental and control conditions.

3.3.3. Resting heart rate variability and baroreceptor sensitivity

Following IWS training there was an increase in PSD-RRI (917.19 ± 1645.28 ms^2), which was significantly different to the control group (F(1,98) = 5.19, p= 0.025). There was also an increase in HFnu (10.65 ± 20.38%) accompanied by a reciprocal decrease in LFnu (-10.65 ± 20.38%) which were both significantly different to the control group following IWS training (F(1,97) = 4.68, p=0.03 and F(1,97) = 4.68, p=0.03, respectively). There was an increase in HF components (576.13 ± 1115.38 ms^2) following IWS training which was significantly different to the control group (F(1,98) = 8.04, p=0.01). Although there was a slight increase in LF components (233.28 ± 1093.94 ms^2), it was not significantly different from the control group (F(1,98) = 0.53, p=0.47). As a consequence of these cardiac autonomic responses, there was a reduction in the LF:HF (-1.11 ± 2.21), which was significantly lower than the control group following training (F(1,98) = 11.99, p<0.001). In addition, there was an increase in BRS (9.38 ± 12.19 ms·mmHg) which was significantly different from the control group following training (F(1,98) = 4.96, p=0.028). Mean values for LF, HF, LF:HF, PSD, LFnu, HFnu and BRS can be seen in Table 3:4.

Table 3:4 Mean values for heart rate variability and baroreceptor sensitivity

Variable	IWS Pre	IWS Post	Control Pre	Control Post
LF (ms^2)	1034.88 ± 937.09	1268.17 ± 1196.0	944.40 ± 700.55	1040.12 ± 800.78
HF (ms^2)	520.43 ± 484.92	1096.56 ± 1192.04*	597.77 ± 662.89	537.82 ± 605.90
LF:HF (ratio)	2.85 ± 2.0	1.74 ± 3.35**	2.84 ± 2.35	3.17 ± 2.37
PSD-RRI (ms^2)	2069.98 ± 1317.65	2987.17 ± 1708.29*	2080.82 ± 1674.91	2049.28 ± 1296.02
LFnu (%)	66.77 ± 16.33	56.12 ± 17.33*	71.15 ± 14.11	66.84 ± 17.29
HFnu (%)	33.23 ± 16.33	43.88 ± 17.33*	28.85 ± 14.11	33.16 ± 17.29
BRS (ms.mmHg)	12.66 ± 6.19	22.05 ± 12.56*	13.48 ± 8.83	15.74 ± 5.71

Mean values and SD for low frequency (LF), high frequency (HF), low/high frequency ratio (LF:HF), power spectral density (PSD–RRI), low frequency normalised units (LFnu), high frequency normalised units (HFnu), baroreceptor reflex sensitivity (BRS). ** p<0.001 and * P<0.05 for difference between experimental and control conditions.

Table 3:5 BP reductions and cardiovascular adaptations from previous IWS studies

Study	Baseline mmHg	sBP/dBP mmHg	HR b·min-1	TPR d·s·cm^5	CO L·min-^{1}	SV mL	PSD-RRI ms^2	HF ms^2	LF ms^2	LF/HF ratio	HFnu %	LFnu %	BRS ms·mmHg
Wiles et al., 2017	126/79	-4*/3*	-5*	88	-0.5*	-1.6	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Taylor et al., 2019	132/81	-12.4*/6.2*	-0.51	-176*	0.37*	6.46*	1031*	540*	310	-1.86*	11.9*	-11.9*	8.2*
Decaux et al., 2022	131/80	-15*/5*	-1	n/a	n/a	n/a	642	769	-191	-0.41	12*	-12*	3.4
O'Driscoll et al., 2022	132/82	-8.5*/7.3*	-4.2*	-246*	-0.12	11.2*	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Current study	130/84	-9.5*/5.3*	-2.71	-185*	-0.29	0.23	1087*	576*	233	-1.18*	10.64*	-10.64*	9.5*

Change scores (Δ) for each variable from Wiles et al., (2017), Taylor et al., (2019), Decaux et al., (2022), O'Driscoll et al., (2022) and the current study. * = significant difference to control group within the individual study. Resting systolic (SBP) and diastolic (DBP) pressure, heart rate (HR), total peripheral resistance (TPR), cardiac ouput (CO), stroke volume (SV), power spectral density (PSD–RRI), high frequency (HF), low frequency (LF), low:high frequency ratio (LF:HF), high frequency normalised units (HFnu), low frequency normalised units (LFnu),and baroreceptor reflex sensitivity (BRS).

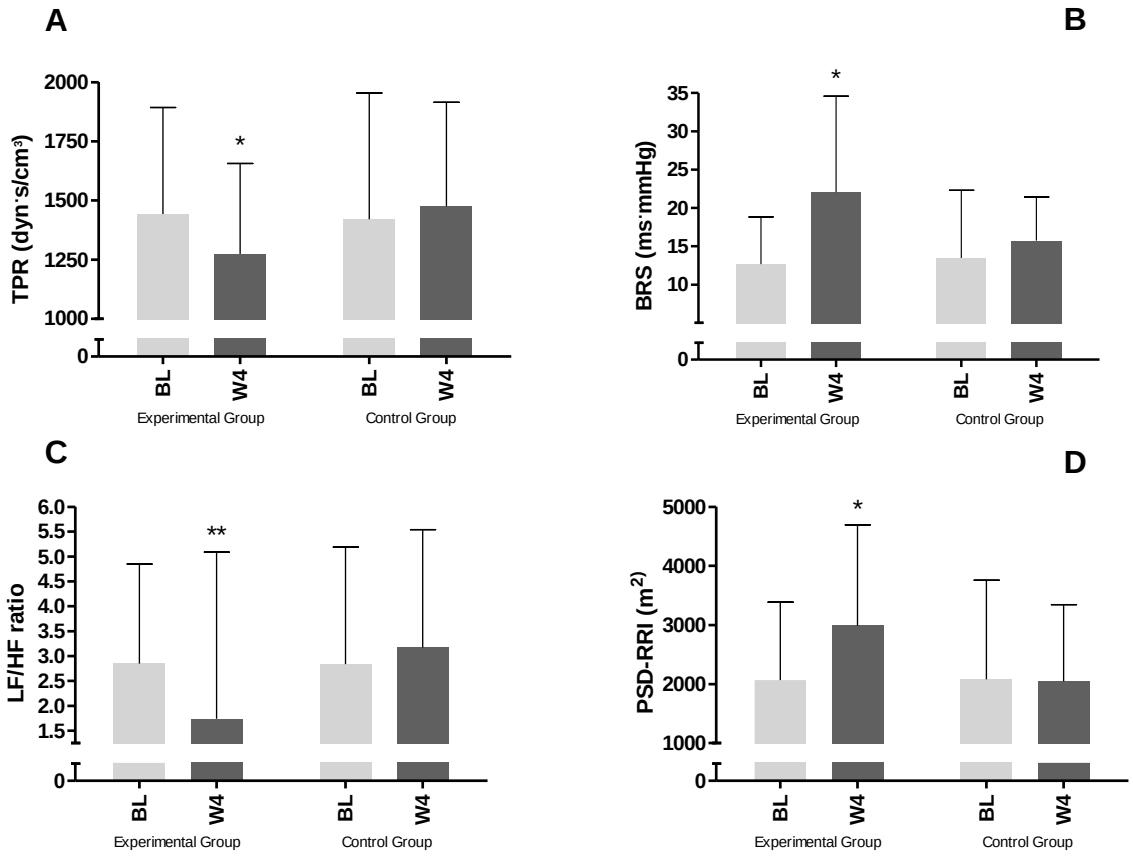


Figure 3:3 The mean TPR (A), BRS (B) LF:HF ratio (C) and PSD-RRI (D) at baseline and week 4 for the experimental and control conditions. Error bars indicate standard deviation of the mean. ** p<0.001 and * P<0.05 for difference between experimental and control conditions.

Table 3:6 Cohen's effect statistics

Variable	Difference in week-4 data compared to control	Cohen's effect size (between-group)
HR	2.62	0.30 *
sBP	-5.91	0.90 ***
dBP	-4.42	0.53 **
MAP	-4.91	0.76 **
SV	-3.56	0.17
CO	-0.07	0.05
TPR	-201.80	0.49 *
LFnu	-10.72	0.71 **
HFnu	10.72	0.71 **
LF	228.04	0.22 *
HF	558.74	0.59 **
LF/HF ratio	-1.43	0.49*
PSD-RRI	937.89	0.62**
BRS	6.31	0.65**

Mean differences compared to the control group for each variable at week 4 within this study, plus Cohen's effect size for between-group analysis. * = small effect, ** = medium effect, *** = large effect.

3.4. Discussion

The main aim of the current study was to further elucidate the haemodynamic and cardiac autonomic adaptations following 4 weeks of IWS training using a large participant sample size. Although previous interventions have explored the BP lowering effects and associated mechanisms following IWS training, to the authors knowledge, all have utilised sample size calculations only suitable to investigate changes in BP variables. As such, some variables may not have been detected due to a lack of statistical power.

3.4.1. Blood pressure

The current study has shown that 4 weeks of IWS training produces significant reductions in sBP, dBP, and MAP compared to a control group (Figure 3.2). The magnitude of these reductions is similar to previous 4-week IWS studies that have used a similar demographic of normal to high-normal

participants (Table 3:5). The reductions are also greater than those seen following other forms of exercise training, including aerobic (sBP= -4.49 mmHg), high-intensity interval training (sBP = -4.08 mmHg) and dynamic resistance training (sBP= -4.55 mmHg) (Edwards *et al.*, 2023), and also similar to the reductions reported following antihypertensive medication (Law, Morris and Wald, 2009; Paz *et al.*, 2016). These reductions seen are particularly pertinent for the normal and high-normal participants studied with this thesis as the associated risk of CVD begins to develop from BP levels as low as 115/75 mmHg (Lewington *et al.*, 2002). These findings are important as they strengthen the growing consensus supporting the highly effective BP-lowering effects of IET, and more specifically, IWS training (Edwards *et al.*, 2023). Moreover, when using a larger sample size, there is a reduced chance of making a type 1 error, which improves the statistical confidence in the output of the data (i.e. IWS training is effective at reducing resting BP and that the reductions did not happen by chance), subsequently providing more reliable and precise estimates, and adding further confidence to the clinical utility of IWS training for the treatment of elevated BP.

It has been previously argued that larger effect sizes have more clinical utility (Jacobson and Truax, 1991). Effect size calculations for the current study demonstrate that the IWS training protocol had a large effect for sBP (d = 0.88), and a medium effect for dBP (d = 0.55) and MAP (d = 0.77), based on Cohen's (1988) criteria (see Table 3:6). While these effect sizes are different from those previously reported by Wiles, Goldring and Coleman (2017) (d = 1.10 and 1.00, respectively) and Taylor et al., (2019) (d = 2.17 and 0.95, respectively), who found large effects for both sBP and dBP, it should be noted that effect statistics reported in the current study are compared to the control group as opposed to within-group effect sizes reported from the latter studies, and so direct comparisons are difficult. Moreover, although the magnitude of the effect size (moderate effect) for dBP is less than Taylor *et al*., (2019) and Wiles, Goldring and Coleman (2017), the smaller relative effect size for dBP in comparison to sBP is consistent with their findings. In fact, when looking at the broader IET literature, many studies have found smaller effect sizes for dBP, or have found no significant reductions at all in dBP (Howden *et al.*, 2002; Taylor *et al.*, 2003; Peters *et al.*, 2006; McGowan, Levy, *et al.*, 2007; McGowan, Visocchi, *et al.*, 2007; Stiller-Moldovan, Kenno and McGowan, 2012; Baross, Wiles and Swaine, 2012; Badrov, Bartol, *et al.*, 2013, 2013; Millar *et al.*, 2013; Loaiza-Betancur and Chulvi-Medrano, 2020; Palmeira *et al.*, 2021; Kelley, Kelley and Stauffer, 2021; Cohen *et al.*, 2023). Despite the smaller effect sizes seen with dBP, when looking at the prognostic value of sBP and dBP reductions, it is reductions in sBP after exercise training that have a greater association with decreased cardiovascular risk and improved mortality outcomes (Schillaci and Pucci, 2011; Xie *et al.*, 2021; Muntner and Rahimi, 2022).

The current study also found no significant differences in the BP reductions between males and females following the 4-week intervention period. These findings support previous meta-analytic data from Inder *et al*., (2016) and Smart *et al.,* (2019) who also found no differences in the BP responses between males and females following IET. However, despite the lack of statistical difference, it should be acknowledged that the BP data did reveal a trend for greater reductions amongst female participants. When looking at the dBP and MAP reductions, the magnitude of reductions were 4.3 and 3.4 mmHg greater, respectively. The p values were also 0.078 and 0.053, respectively, showing although the reductions were not significant ($p<0.05$), they were close to the alpha value threshold. As previously outlined, there are physiological differences in cardiovascular regulation between males and females which may help to explain why there was a trend for greater BP reductions in females. Males have also been shown to have higher levels of epinephrine at rest and reduced HRV compared to females (Evans *et al.*, 2001). Conversely, females have increased oestrogen levels and typically show greater parasympathetic activity affecting the heart, and less sympathetic input in vascular tone compared to men (Fisher *et al.*, 2013). Although oestrogen levels were not measured in the current study, it is feasible to consider that the oestrogenic cardioprotective effects may have influenced the BP reductions seen following the 4-week training period. However, these inferences are purely speculative as there were no statistical differences found, and further research is needed to fully elucidate any differences in the BP reductions and cardiovascular adaptations between males and females following IWS training.

3.4.2. Physiological mechanisms underpinning BP reduction

Haemodynamic variables

As well as significant reductions in sBP, dBP and MAP, the current study found significant changes in wider haemodynamic variables compared to the control group. Following the 4-week intervention period, there were significant reductions in TPR. The magnitude of the TPR reductions was similar to those seen by Taylor *et al*., (2019) who recruited similar participants to those involved in the current study. Reductions in TPR following IET were also reported in the recent review from Edwards, Wiles and O'Driscoll (2022) who proposed that BP reductions are likely related to vascular adaptations since no changes in $\dot{Q}$ were found in their analysis. While current evidence surrounding the specifics of vascular adaptation to IET is rather conflicted (Edwards, Wiles and O'Driscoll, 2022), there are several adaptations that have been reported, including local endothelial-dependant mechanisms, structural remodelling, and/or functional adaptations in autonomic vasomotor control (Edwards, Wiles and O'Driscoll, 2022). Increases in NO are associated with improved endothelial function,

increased vasodilation in active blood vessels, and a reduction in arterial stiffness (Rickson et al., 2021). These findings are supported by Edwards *et al.,* (2023) - a sub-study of Taylor *et al*., (2019) - who found significant reductions in the augmentation index (AIx), (an index of systemic arterial stiffness) following 4-weeks of IWS training. From a clinical perspective these findings are important, as for every 10% reduction in AIx, there is a 32% decreased risk of an adverse cardiovascular event. As Edwards *et al*., (2023) found a 6.6% reduction in AIx, there may be a 21% reduced cardiovascular disease risk (Vlachopoulos *et al*., 2010). Taylor *et al*., (2019) also demonstrated that the reductions in TPR improvements occurred concurrently with changes in biomarkers associated with anti-inflammatory and improved endothelial function, measured through serum interleukin-6 and asymmetric dimethylarginine. Nonetheless, it should be acknowledged that the mechanistic review from Edwards, Wiles and O'Driscoll (2022) did not find any significant changes in flow-mediated dilation, pulse wave velocity, brachial artery blood flow, or brachial artery diameter, as localised measures of vascular function and structure following IET – although authors did state that these findings may be subject to statistically underpowered analyses with insufficient data to draw definitive conclusions.

The mechanistic pathways by which any potential vascular adaptations and NO release occur may be related to several haemodynamic processes, such as reactive hyperaemia, which is a result of the increased demand of muscular tissue during the isometric contraction (Rickson, Maris and Headley, 2021). On cessation of an isometric contraction, there is rapid reperfusion of blood to the previously compressed vasculature which results in an elevated shear rate against the localised endothelial lining to stimulate the secretion of flow-induced vasoactive substances (Dillon, Lichter, *et al.*, 2020). Another possible pathway is the increase in BP and $\dot{Q}$ and subsequent pressor response seen during isometric contractions (Swift *et al*., 2022) which may cause systemic shear stress and activate endothelial NO release, causing vasorelaxation and acute post-exercise hypotension (Peters *et al.*, 2006). However, previous studies have found that vascular adaptations following IHG (McGowan *et al.*, 2007) and double-leg extension IET (Baross, Wiles and Swaine, 2012) are localised in the trained limb. McGowan *et al.,* (2007) did not find any systemic endothelium-dependent vasodilation following IHG training and argued that shear stress related mechanisms likely only occur in the active musculature. Nonetheless, due to large muscle mass recruitment, IWS training may benefit more from systemic shear stress related mechanisms. Indeed, Swift *et al*., (2022) found that during an acute bout of IWS exercise (4 x 2 minute @95% HRpeak) there was a significantly greater increase in BP, HR, and $\dot{Q}$ than during an acute bout of IHG exercise (4 x 2 minute @30% MVC), suggesting a greater pressor response. The authors argued this was a result of greater muscle mass activation during the wall squat and subsequent increase in muscle sympathetic nerve activity, which is known

to contribute to increases in exercise pressor response (Rowell & O'Leary, 1990; Seals, 1989). The findings from Edwards *et al*., (2023) support this idea, as the improvements in AIx were measured at the index or middle finger and brachial artery, and therefore must reflect some degree of systematic change in vascular resistance rather than localised adaptations within the muscles used during IWS exercise.

Nonetheless, there is limited research available to make an informed decision regarding the degree to which any vascular changes following IET are locally regulated via endothelial-dependant mechanisms, or systemically modulated via structural remodelling, and/or functional adaptations in autonomic vasomotor control (Edwards, Wiles and O'Driscoll, 2022). However, due to the short 4-week period of training, it is likely that any potential vascular adaptations related to the reductions in TPR were more functional than structural. This argument is based on the findings of Tinken *et al*., (2010) who found that NO-dependent functional adaptations were superseded by structural adaptations after 8 weeks of training. However, assumptions around the nature of vascular adaptations are beyond the scope of this study, and more research is needed to investigate the functional and/or structural nature of any such adaptations following IWS training.

The current study found no change in $\dot{Q}$ following the 4-week training period, which suggests that the BP reductions were primarily driven by reductions in TPR (BP= $\dot{Q}$*TPR). Although Edwards, Wiles and O'Driscoll (2022) also found no changes in $\dot{Q}$, the study did find a concurrent increase in SV and reduction in HR, which likely explains the lack of change in $\dot{Q}$ ($\dot{Q}$ = HR*SV). In the current study there were no significant changes in HR or SV which opposes the findings from Edwards, Wiles and O'Driscoll (2022). However, when looking at previous IWS studies, there seems to be inconsistent outcomes for SV, HR and $\dot{Q}$, with Taylor *et al*., (2019) finding significant increases in SV and $\dot{Q}$, but no significant reductions in HR, and Wiles, Goldring and Coleman (2017) finding significant reductions in HR and $\dot{Q}$, but no changes SV. There is also a large majority of IET literature that has not supported any reductions in resting HR (Millar *et al.*, 2014) and other studies that have not found a change in SV following IET (Devereux, Wiles and Swaine, 2010; Wiles *et al.*, 2010). Furthermore, in the review from Edwards, Wiles and O'Driscoll (2022), the confidence intervals for the reported SV data were large (0.35 – 12.60), which introduces substantial uncertainty and makes precise estimates difficult.

Recent work from O'Driscoll *et al.,* (2022) found that following IET there were improvements in cardiac function, mechanics and global myocardial work efficiency as by-products of a reduction in cardiac afterload. Edwards, Wiles and O'Driscoll (2022) used these findings to explain the mechanistic underpinning for an increase in SV following IET. The reduction in afterload following IWS training reported by O'Driscoll *et al*., (2022) was suggested to be a consequence of the

reduction in TPR. Levinger *et al*., (2005) suggested that a reduction in TPR following resistance training elicits a reduction in afterload, subsequently improving LV function and contractile efficiency. However, the current study, as well as Wiles, Goldring and Coleman (2017), found no change in SV following 4 weeks of IWS training. This is an interesting finding, as the current study also found reductions in TPR, and so it would be expected that SV should also have changed based on the principles outlined above. There are several potential reasons for the lack of change in SV despite the reductions in TPR. Firstly, it has been argued that TPR is an unreliable index of left ventricular afterload, reflecting only peripheral arteriolar tone rather than left ventricular systolic wall force, and so the reduction in TPR in the current study may not have induced reductions in afterload (Lang *et al.*, 1986). Secondly, there were differences in the methods of data collection. Both the current study and Wiles, Goldring and Coleman (2017) utilised a seated position for the resting measures, whereas O'Driscoll *et al*., (2022) collected data in the supine position. Previous research has demonstrated that left ventricular SV diminishes in the upright position, presumably via a reduction in preload (Sundblad & Wranne, 2002). The reduction in preload may be linked to a reduction in venous return as a result of gravitational forces and has been shown to reduce ventricular filling and end-diastolic volume, both of which are known to be related to improvements in SV (Frank-Starling mechanism) (Kounoupis *et al.*, 2020). Previous research has also demonstrated no change in SV immediately following an acute bout of IWS exercise when measured in the seated position (Swift *et al.*, 2022).

However, another possible reason for the lack of change in SV is there was insufficient time for the myocardium to adapt to the reduced TPR and afterload. The greatest reductions in TPR and increases in SV seen following IWS training were after the 1-year training study from O'Driscoll *et al*., (2022) (see Table 3.5) potentially suggesting there is a greater myocardial response following extended periods of training. As previously discussed, research has shown that adaptations following longer periods of training (>8 weeks) are different to those brought about by shorter periods of training (Tinken *et al.*, 2008; 2010; Baross, Wiles and Swaine, 2012; Badrov *et al.*, 2013). Although these results are related to vascular adaptations, it may be that a similar delayed response could be seen with the myocardium and that more time is sometimes needed for myocardium to adapt to the reduced afterload and/or increase preload following the cessation of training (O'Driscoll *et al.*, 2017; Taylor *et al.*, 2017). Furthermore, it is also not known when the reductions in TPR occurred in current study, but if they were confined to the latter part of the 4-week period, then this would give the myocardium even less time to adapt. As such, it could be suggested that performing IWS training for longer than 4 weeks might elicit further adaptations to the myocardium, such as an increase in SV.

Cardiac autonomic variables

The assessment of HRV provides additional insight into the relative changes in cardiac sympathetic and vagal modulations following exercise training (Millar *et al*., 2014). The beneficial effect of exercise training on cardiac autonomic modulation, with a tonic decrease in sympathetic activity and augmented vagal modulation, has been well documented in clinical and experimental studies, as well as in the recent meta-analytic study from Edwards, Wiles and O'Driscoll (2022). In the current study, there were significant changes in cardiac autonomic variables compared to a control group, including a significant increase in PSD-RRI and the HF component, with no significant change in the LF component. An increase in HRV and HF parameters is indicative of an increase in cardiac vagal tone and parasympathetic modulation (Bonaz, Sinniger and Pellissier, 2016; Kim *et al.*, 2018; Honkalampi *et al.*, 2021). There was also a significant reduction in the LF:HF ratio which is considered a representation of sympathovagal balance (Pagani *et al.*, 1997). Normalised units of HFnu and LFnu also significant increased and decreased, respectively. The magnitude of these reductions are similar to those previously reported by Taylor *et al.,* (2019), who found significant increases in PSD-RRI, as well as a an increase in the HF component, with no change in the LF component, and a reduction in the overall LF:HF. Changes in the normalised units and BRS were also in agreement with Taylor *et al*., (2019).

The link between the autonomic adaptations seen following IET and reductions in BP is related to the complex interacting effects of several BP-modulating influences. As the current study found no changes in HR, SV or $\dot{Q}$, the reductions in TPR seen in the current study suggest there may have been vasodilatory effects, potentially facilitated through autonomic modulation. As previously discussed, following 4 weeks of IWS training, Edwards *et al.*, (2023) found significant reductions in the AIx (an index of systemic arterial stiffness) and argued this may be due to functional adaptations in autonomic vasomotor control (e.g. increased vasodilation). Autonomic responses are regulated through coordinated reflexive systems, integrating both feed-forward (e.g. central command) and feedback (e.g. sensory receptors) mechanisms to maintain cardiovascular stability (Badrov *et al*., 2016). The baroreflex serves as a key regulatory mechanism for both short- and long-term BP control, responding to fluctuations in arterial pressure by modulating autonomic output. When BP rises, baroreceptors in the carotid sinus and aortic arch detect arterial stretch, triggering inhibition of sympathetic activity and activation of parasympathetic pathways. This results in vasodilation and/or a reduction in $\dot{Q}$ to restore BP homeostasis. Conversely, when BP drops, sympathetic activation increases to promote vasoconstriction and increase $\dot{Q}$ (Hesse *et al.*, 2007; Taylor *et al.*, 2019). In the present study, the increase in BRS following training suggests enhanced autonomic

regulation. Since BRS is positively correlated with HRV and inversely related to MAP (Hesse *et al*., 2007; Taylor *et al*., 2019), these findings indicate a more efficient autonomic response to BP fluctuations, allowing for faster and more precise cardiovascular adjustments. This enhanced baroreflex function may reflect adaptations in both neural control (e.g. increased sensitivity of brainstem autonomic centres) and vascular compliance (e.g. improved arterial distensibility and mechanoelastic properties of vessels), supporting long-term improvements in BP regulation.

Feedback signals also originate peripherally from muscle sensory afferents within the active muscle (i.e. exercise pressor reflex) (Badrov *et al*., 2016). Muscle ischemia, intramuscular pressure, and metabolite release (including ATP, hydrogen ions, and lactate) all occur during acute bouts of IET. Mechanoreceptors and metaboreceptors within the muscle are then activated, both of which control muscle sympathetic nerve activity traffic to the central nervous system (Rickson, Maris and Headley, 2021). This response elicits a transient increase in BP (pressor reflex), which has been previously demonstrated during acute bouts of IWS training (Swift *et al.*, 2022). Following IET training, this reflexive response is attenuated (heightened antagonism of cardiac sympathetic activity) which aids in the reduction of resting BP (Rondon *et al.*, 2006; Secher and Amann, 2012).

3.4.3. Effect sizes and statistical power

One of the unique advantages of the current study is the larger sample size used. This was to allow greater exploration of physiological data where there can be relatively large day-to-day variation. Initial (a-priori) G*Power calculations estimated that a sample size of 100 participants (with two uneven groups 80:20) would be able to detect an effect size of 0.3 (Cohen, 1988). Alongside BP, this study detected changes in TPR, LFnu and HFnu, LF:HF ratio, PSD-RRI, HF, and BRS. However, even with the larger sample size there were physiological markers that were not significantly different between the intervention and control conditions, with the effect statistics for differences which were below 0.3 for these parameters ($\dot{Q}$ and SV). This is an important finding as although these markers have been postulated to play a role in the reductions in BP seen with IET, this is the largest study that indicates there are no changes evident. A parameter with a small change (small effect statistic) could still be physiologically meaningful, though this study may not have had the statistical power to detect the changes. Thus, presentation of the data will allow future researchers to estimate sample sizes required if they are to ascertain if the small changes seen here are in fact linked to the reductions in BP.

3.4.4. Conclusion

Results from the current study have confirmed that 4 weeks of IWS training can produce statistically significant reductions in resting BP. These results are important as they increase the clinical utility of IWS training as an effective intervention to reduce the prevalence of elevated BP and the concomitant risk of cardiovascular disease. The study also provided further detail about the mechanisms responsible for any BP reductions following IWS training. Results demonstrated that IWS training promotes adaptations in TPR and HRV, including an increase in HF parameters and BRS. These findings have been demonstrated on a large participant sample size, adding confidence to the statistical output. However, the study was still technically underpowered to detect changes in $\dot{Q}$ and SV, and further research with larger sample sizes and longer training periods may be needed. Further research is also warranted to fully ascertain the sex-based responses following IWS training.

CHAPTER 4 – STUDY 2

A comparison of 4 and 8 weeks of isometric wall squat training on haemodynamic and cardiac autonomic adaptation

4.1. Introduction

The results from Chapter 3 have demonstrated that 4 weeks of IWS training produces significant reductions in resting BP amongst participants with normal to high-normal BP classification. Whilst this is not a new finding per se, the study was novel due to its large sample size, which not only improves the statistical confidence in the BP reductions seen (less chance of type-1 error) but also means, unlike much of the previous work in this area, the study was adequately powered to detect changes in a greater number of haemodynamic and cardiac autonomic variables (less chance of type-2 error). Therefore, the findings provide further evidence for the efficacy of IWS training in reducing resting BP and also improve the current understanding of the associated physiological mechanisms underpinning this adaptation. Nonetheless, while the findings from Chapter 3 are useful and may help shape future clinical guidelines, it should be acknowledged that the results are restricted to a short 4-week period. In fact, the majority of IWS training studies to date have used 4-week training periods (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023). Although longer IWS training studies have been published (O'Driscoll *et al.*, 2022; Cohen *et al.*, 2023), direct comparisons are difficult as these studies failed to report BP changes throughout the training period, and it is therefore not known when BP reductions reached their peak. Ideally, steps should be taken to explore the trend of BP throughout longer periods of training to gain a better understanding of the optimal dose response for BP reductions following IWS training. Furthermore, the majority of IWS training studies that have explored the physiological mechanisms are also limited to 4 weeks (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023) and further mechanistic insights may be elucidated over longer periods of training. Although O'Driscoll *et al.*, (2022) examined the haemodynamic mechanistic adaptations following a longer 1-year period, no data were reported at interim points throughout the training period, and direct comparisons to shorter periods of training are therefore difficult.

As previously outlined, the majority of current IWS training studies have used 4-week training periods (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll

and Wiles, 2023) - all of which found statistically significant reductions in resting BP (see Chapter 1, Table 1:2). The two longer-duration studies from Cohen *et al.,* (2023) and O'Driscoll *et al*., (2022) also found significant reductions in BP following 12 weeks and 1 year of IWS training, respectively. However, the greatest sBP reductions currently seen from all IWS training studies are from Decaux *et al*., (2022) and Lea, O'Driscoll and Wiles (2023), who found significant reductions of 15/5 mmHg and 14.2/6.4 mmHg in sBP and dBP, respectively, following 4-week training periods. These reductions are greater than those reported by O'Driscoll *et al*., (2022) following a longer 1-year training period. As O'Driscoll *et al*., (2022) did not report BP throughout the training period, it is unknown whether reductions reached a zenith at any point during the training period. Based on the reductions seen from Decaux *et al.,* (2022) and Lea, O'Driscoll and Wiles (2023), it may be that BP reductions plateau following the 4-week timepoint. Indeed, BP reductions cannot keep their trajectory indefinitely as a functional body (through homeostasis) will eventually regulate the rate of reduction to avoid hypotension (Halliwill *et al.*, 2013; Edwards *et al.*, 2021). Moreover, the training principle of 'accommodation' states that if the applied stress remains at the same magnitude (intensity, volume and frequency) for a prolonged period, the system will accommodate to this stress and no further improvements in physical fitness will occur (Harries, Lubans and Callister, 2015). As no progressive overload in either intensity or volume was given to the participants in the 1-year study from O'Driscoll *et al*., (2022), it may also be (based upon the reduced BP reductions compared to shorter studies) that the participants accommodated to the training stimulus over the 1-year period. However, it should be noted that O'Driscoll *et al*., (2022) experienced the greatest magnitude of dBP and TPR reduction compared to other IWS studies, which may be related to structural vascular adaptations that are commonly reported following longer periods of training (Tinken *et al.,* 2008; 2010).

When looking at the broader IET literature, comparisons between studies are difficult due to heterogenous methodological protocols. Meta-analytic findings from Inder et al., (2016) found that the optimal IET protocol for BP reductions was >8 weeks of unilateral IHG training. Conversely, Baffour-Awuah *et al.,* (2023) reported that IET interventions >8 weeks did not significantly reduce dBP; although the authors did mention that this may be due to adherence issues with longer training programmes. When looking at individual studies, the magnitude of BP reduction following 4 weeks (Devereux, Wiles and Swaine, 2010; Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023), 5 weeks (Wiley *et al.*, 1992; Ray and Carrasco, 2000; Howden *et al.*, 2002), 6 weeks (Peters *et al.*, 2006), and 8-week IET studies (Wiley *et al.*, 1992; McGowan *et al.*, 2006, 2007; Millar *et al.*, 2007, 2008, 2013; Wiles *et al.*, 2010; Baross, Wiles and Swaine, 2012; Badrov *et al.*, 2013; Carlson *et al.*, 2016; Correia *et al.*, 2020; Okamoto *et al.,* 2020;

Punia and Kulandaivelan, 2020; Cohen *et al.*, 2023) varies considerably with any interpretation confounded by, as indicated above, a lack of consistency between study designs (intensity, volume, participants, mode of IET).

It should also be noted that many studies fail to report trends of BP reductions throughout the training period, and so it is not known when/if BP reductions have reached their peak. Ideally, steps should be taken to investigate the trend of BP reductions throughout training periods to improve the current understanding of the dose-response relationship. Such an approach is possible with regular monitoring/tracking of BP using a home-based blood pressure monitoring (HBPM) protocol (as outlined in Chapter 2, section 2.7). Using a HBPM approach allows greater insights into changes in BP as they may occur over time (Millar *et al.*, 2007).

There are only a small selection of studies that have directly compared the effects of training durations on BP reductions. Some have shown that significant reductions in resting BP parameters were only found after 8 weeks, with no significant reductions evident at the 4-week mark (Wiles *et al.*, 2010; Baross, Wiles and Swaine, 2012; Badrov *et al.*, 2013). However, in the study by Wiles et al., (2010) a large proportion of the reduction in resting sBP, dBP and MAP occurred in the first 4 weeks, but was not statistically significant until week 8. Other studies that have utilised longer periods of training (8-10 weeks) found significant reductions in resting BP after only 4-6 weeks, but with greater reductions found after 8-10 weeks (Wiley *et al.*, 1992; Taylor *et al.*, 2003). However, there are some contrasting findings and disparities between studies that make any definitive interpretation difficult. For example, Stiller-Moldovan, Kenno and McGowan (2012) found no significant reductions in resting BP following 8 weeks of IHG training, whilst Millar *et al*., (2007) found a significant negative linear trend in resting BP, which continued to decline until the end of the 8-week IHG training study. Both these latter studies used similar participants (medicated hypertensives) and training variables (IHG, 3x per week, 4 x 2 minutes, 30% MVC).

There is evidence from IET studies that the dose-response needs to be carefully considered in relation to the duration of training to produce a sufficient training stimulus. As previously discussed, the training principle of 'accommodation' states that if the applied stress remains at the same magnitude (intensity, volume and frequency) for a prolonged period, the system will accommodate to this stress and no further improvements in physical fitness will occur (Harries, Lubans and Callister, 2015). Based on the comparatively smaller sBP reductions seen following the 1-year IWS study with no progression in intensity or volume (O'Driscoll *et al.*, 2022), compared to shorter 4-week IWS training studies from Decaux *et al.,* (2022) and Lea, O'Driscoll and Wiles (2023), it is likely that the accommodation principles apply to BP reductions following IET. On the other hand, if a

training stressor is too high for too long without sufficient recovery, then an inappropriate level of overload may occur, which could hinder any adaptations from training (Carter, Potter and Brooks, 2014). A study by Pagonas *et al.*, (2017) utilised a 12-week IHG training period and did not observe any significant reductions in resting BP. Along with the extended 12-week training period, the study also utilised an increased training frequency (five times per week) with the intensity set at 30% MVC. A possible explanation for this outcome might be that participants were overloaded too soon due to the higher training frequency, resulting in them being overworked throughout the 12 weeks, and therefore exposed to a stimulus that was not conducive towards resting BP adaptations. As such, there could be a ceiling to total training volume in respect to the duration of training and longer training programmes may need to consider manipulating the volume to ensure an appropriate level of overload is utilised (Carter, Potter and Brooks, 2014; Harries, Lubans and Callister, 2015). However, another study from Badrov *et al.,* (2013) found a plateau in sBP reductions after just 4 weeks when IHG training was carried out five times per week, suggesting it is not just longer duration training programmes that may need to consider the consequences of utilising a high training frequency. Indeed, it has been suggested that there is a sigmoidal effect between physical activity levels and resting BP reductions, in that the dose-response relationship is the steepest when exercise volume is increased from sedentary to moderately active levels (Jennings *et al.*, 1991).

Research has shown that there is also a relationship between training duration and intensity (Lawrence *et al.*, 2015). The majority of studies that have found significant reductions in resting BP after 4 weeks of IET have used a training intensity of 30% MVC or higher (Wiley *et al.*, 1992; Devereux, Wiles and Swaine, 2010; Badrov *et al.*, 2013), or an approximate equivalent, such as 95% HR_{peak} (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023). However, when using a lower relative intensity of between 14 – 24% MVC, some studies found it took 8 weeks of isometric bilateral leg training to bring about any reductions in resting BP parameters (Wiles *et al.*, 2010; Baross, Wiles and Swaine, 2012). Wiley *et al*., (1992) also observed comparable resting BP reductions following IHG training at 30% MVC for 8 weeks, and 50% MVC for 5 weeks, demonstrating that shorter periods of training can be effective at reducing BP if the intensity is increased.

Overall, there is a lack of consistent evidence to indicate the optimal period of IWS training needed to elicit the greatest magnitude of BP reduction and cardiovascular adaptation. There are also limited data available to outline the trend of BP reduction throughout longer periods of training. Therefore, the aim of this study was to determine the magnitude and trend of resting BP reductions, as well as changes in associated haemodynamic and cardiac autonomic variables, following 8 weeks of IWS training.

4.2. Methods

4.2.1. Participants

Forty-five sedentary males and females with a resting sBP value between 120-140mmHg were recruited for the study. The determination of BP categorisation was ascertained following the ESH guidelines: three resting sBP measurements of ≥120 mmHg and <140 mmHg (Mancia *et al.*, 2023). A current physical activity level below the public health recommendations of 150 minutes of moderate physical activity per week was also required for participation (Franklin 2021). This included low-level physical activity, such as walking, light cycling and general household activities. If any participants were involved in any purposeful exercise regimes, such as running, HIIT, or dynamic resistance training they were excluded from the study. Full details of the participant cohort can be seen in Chapter 2 (section 2.2).

4.2.2. Sample size estimation

Sample size estimates for this study were based upon the collated data set. Using a sample size of 40, with 2 groups, 1 covariate (baseline BP), a significance level of 0.05 and power of 0.80, the current study was powered to detect a moderate effect size (d=0.46). Full details of sample size calculations can be seen in Chapter 2 (section 2.2.1).

4.2.3. Recruitment

Participants were from the collated data set of 100 participants. From the two groups used within this study (3x per-week group and the control group) there were five dropouts (two related to COVID-19, one voluntary drop out, and two non-compliant), so 45 participants were recruited in total (Figure 4:1). Data were collected from July 2020 – September 2023. Once participants showed an interest in the study, they were invited to attend the laboratory to check their resting BP levels fell within the required range using an automated BP monitor was used. All potential participants were also screened with a physical activity and health questionnaire to ensure they complied with the eligibility criteria. If individuals were deemed suitable, they were formally invited to participate in the study and were required to sign an informed consent form and book in for a familiarisation session. The recruitment process for the collated data set is described in detail in Chapter 2 (section 2.2.2).

4.2.4. Equipment

Laboratory-based equipment

Haemodynamic and cardiac autonomic assessment: All haemodynamic and cardiac autonomic variables in this study were measured using the TFM. Full details of the TFM can be found in Chapter 2 (section 2.4.1).

Wall squat knee joint angle: Knee joint angle was measured during exercise using a clinical goniometer. For further details see Chapter 2 (section 2.10.4).

Rate of perceived effort (RPE): The Borg CR10 scale was used to measure and rate effort felt in the participant's upper legs during exercise in the laboratory and at home. For further details see Chapter 2 (section 2.10.10).

Home-based equipment

Home-based BP device: During the second 4-week period of training, participants were required to self-measure BP in the home using the A&D UA-1020-W HBPM device. Full details of the A&D device can be seen in Chapter 2 (section 2.7).

Heart rate: In order to measure HR during home-based IWS training, participants wore a wrist-worn HR monitor and a Polar H10 HR chest strap. Full details of the home-based HR equipment can be seen in Chapter 2 (section 2.10.8).

Wall squat knee joint angle: During home-based IWS exercise sessions, the knee joint angle was established by using a Bend and Squat devise which can be used to recreate a target knee-joint angle. The device can be precisely adjusted so each participant can easily position their foot and back placement in order to reproduce the desired knee angle. For further details see Chapter 2 (section 2.10.4).

Training manual: During home-based IWS training, participants also received a training manual which outlined the specific protocol for home-based IWS training, as well as guidance on how to use the equipment given. The training manual also included data sheets to input HR and RPE data on

from their training sessions, as well as data sheets for the HBPM readings taken during the second 4-week period.

4.2.5. Procedures

Familiarisation

During the familiarisation session participants were given a full overview of the study protocols and familiarised with all equipment used within the study. Full details of the familiarisation session can be seen in Chapter 2 (section 2.2.3).

Overall study design

Once participants were enrolled to the study, they were randomised into either the 8-week IWS experimental group (n=23), or the control group (n=22). Randomisation was carried out using the random function on Microsoft Excel and was carried out before baseline BP measures were taken to avoid any recruitment bias.

Training condition

All experimental participants (n=20) were required to undertake an incremental IWS test to determine the knee joint angle used during training (see Chapter 2, section 2.10.3). The knee joint angle was established to elicit a training intensity of 95% HR_{peak} previously shown to effectively lower resting BP during home-based sessions (Wiles, Goldring and Coleman, 2017). Participants then carried out an 8-week home-based IWS training programme. Training was carried out three times per week over the 8-week period with 48 hours between each session. Each training session comprised of 4 x 2 minutes of IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest (Wiles, Goldring and Coleman, 2017). Following the first 4-week training period, participants were required to attend the laboratory for mid-training resting measures.

The participants then began their second 4-week period of training the day directly following their mid-point laboratory visit. During the second 4-week period, each training session still comprised of 4 x 2 minutes of IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest. Participants were also required to self-monitor their BP at home using an HBPM device. Following the full 8-week period, participants were again required to attend the laboratory for post-training resting measures. To monitor the home-based training, participants were required to self-report their HR during each IWS exercise session. To check compliance with exercise protocol and individualised training zone prescribed over the training period, HR data was downloaded from the HR watch at the end of the

study. The threshold for minimum adherence was 10 out of 12 sessions within each 4-week period. If participants were withdrawn, they were encouraged to carry on with the IWS training, although their data was not used for analysis. Full details of the IWS training protocol can be found in Chapter 2 (section 2.10).

Control condition

During the control condition, participants were requested to maintain their habitual dietary and physical activity daily routines for an 8-week period. Adherence to these conditions was verbally confirmed during the subsequent laboratory session. During the first 4-week period, participants did not visit the laboratory, and no additional measures were taken until they visited the laboratory at week 4. During the second 4-week period, participants were required to self-monitor their BP at home using the same protocol and HBPM device as the experimental group.

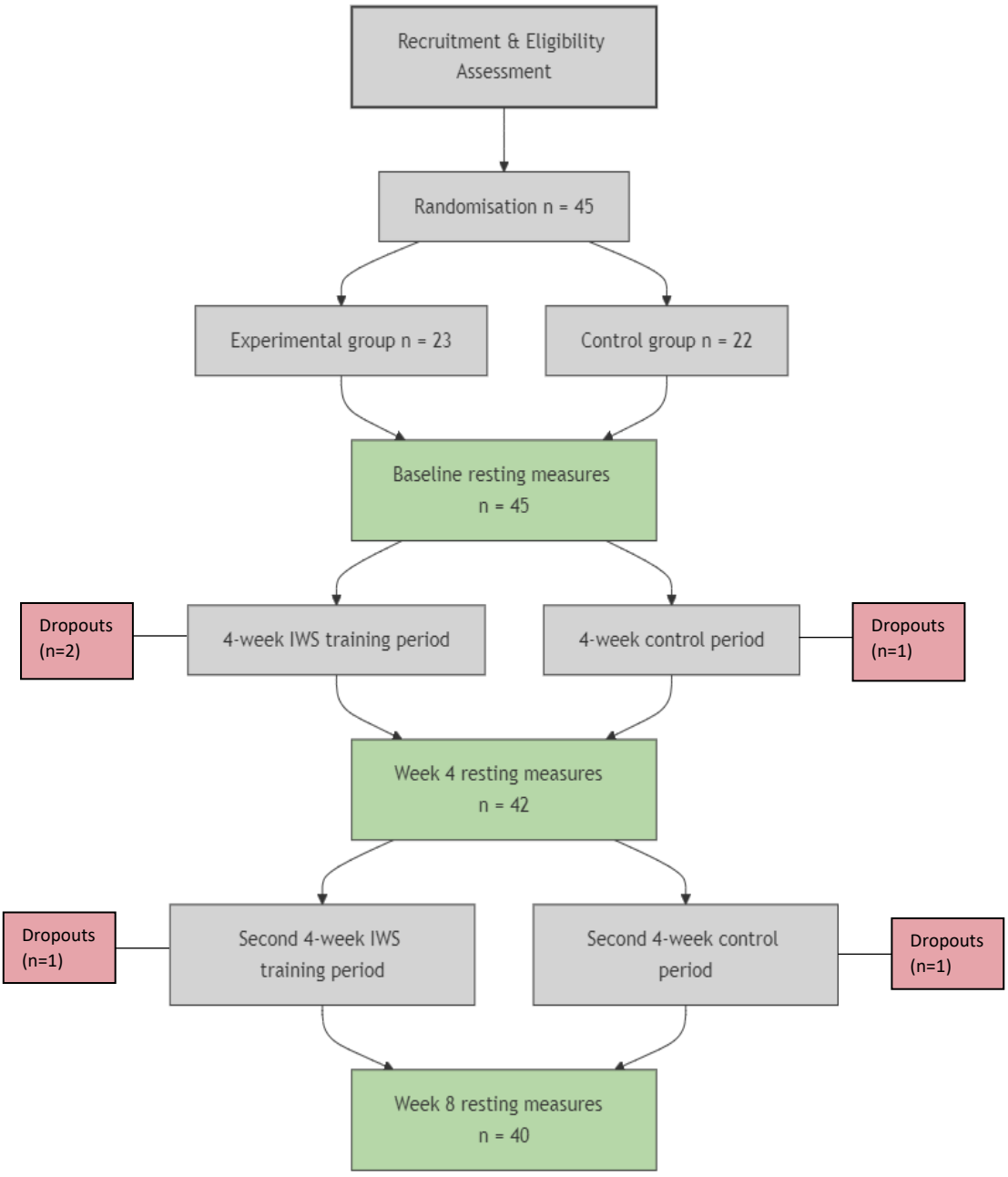


Figure 4:1 Data collection timeline and sample sizes used

4.2.6. Resting measures

Laboratory-based measures

Both experimental and control participants were required to attend the laboratory for resting cardiovascular measures. Resting haemodynamic and cardiac autonomic measures were taken at baseline, mid-training (4 weeks) and post-training (8 weeks). Mid- and post-training measures were

taken 72 hours after the final bout exercise at week 4 and at week 8 to avoid any transient effects which may persist post-exercise (Kenney and Seals 1993). Before attending the laboratory, participants were asked to avoid any food for 2 hours, caffeine for 4 hours, and alcohol for 12 hours pretesting (James, Leidy Sievert and Flanagan, 2004; Rezk *et al.*, 2006). Upon arrival at the laboratory, participants rested in a seated position for 15 minutes. Following the seated rest, sBP, dBP, MAP, Q̇, SV, TPR, BRS, LF, HF, LFnu, HFnu, and PSD-RRI were measured continuously for 5 minutes in the seated position using the TFM. After this time, the mean values for each variable were calculated offline for the 5-minute period. A number of measures were indexed to BSA. Full details of the protocol to obtain resting measures can be seen in Chapter 2 (section 2.4).

Home-based blood pressure monitoring

Home-based blood pressure monitoring was also used to explore the trend of BP alterations throughout second 4-week training period. Based on ESH guidelines (Mancia *et al.*, 2023) two BP readings were taken in the morning (within 2 hours of waking) and two in the evening (within 2 hours of sleeping) for each day that home-based BP monitoring was required. If the first two readings were largely different (over 10-mmHg difference) a further reading was required. Each reading was separated by 1 minute of rest, with the average of the last two readings used for analysis. The mean BP values for each week were used for analysis. Resting BP measures using the A&D device were also taken during each laboratory visit to give comparative data for analysis throughout the full training programme. Full details of the HBPM protocol can be found in Chapter 2 (section 2.7).

4.2.7. Data analysis

All data were checked for normality and homogeneity of variances (Field, 2013). Where the parametric assumptions were met, a two-way repeated measures analysis of covariance (RMANCOVA) was used, with baseline measures as the covariate, and week 4 and week 8 data as the within subject variables. If the RMANCOVA was statistically significant, a least significant difference (LSD) post-hoc test was used to explore any pairwise comparisons. This test was selected to maintain statistical power and decrease the risk of incurring a type II error. If sphericity assumptions were violated, the degrees of freedom (DoF) were corrected using either the Greenhouse–Geisser or the Huynh–Feldt. If the Greenhouse–Geisser estimate of sphericity (ε) was >0.75 then the Huynh–Feldt correction was used, and if ε was <0.75 then the Greenhouse-Geisser was used (Field 2013). Corrected DoF are reported throughout. For non-parametric data, a generalised estimating equation was used. The non-parametric RPE data from the home-based training was also analysed using the

non-parametric Wilcoxon signed ranks test. For all tests, an alpha level of <0.05 was set as the threshold for statistical significance. Data analysis was performed with IBM SPSS (BM SPSS Statistics for Windows, version 19.0, Armonk, NY: IBM Corporation).

4.3. Results

Forty participants (M=23: F=17) completed the study (35 ± 13 years; 83 ± 15 kg; 175 ± 10 cm). The allocation of male and female participants was 11:9 in the experimental, and 12:8 in the control group. Out of the total 20 experimental participants that were compliant with the inclusion criteria, 18 completed all 24 training sessions during the 8-week training period. Of the remaining two, each missed one session (both in the first 4-week period), and so completed 23 training sessions over the 8 weeks. Resting haemodynamic and cardiac autonomic data were obtained from all participants during the laboratory visits at baseline, week 4 and week 8.

4.3.1. Resting blood pressure

There was a significant group main effect for each BP parameter: sBP (Wald $\chi^2(1) = 18.957$, $p < 0.001$), dBP (Wald $\chi^2(1) = 4.199$, $p=0.04$), and MAP ($F(1,37)=27.873$, $p < 0.001$). There were significant reductions in sBP, dBP and MAP and both week 4 (-8.84 ± 6.66 mmHg, p<0.001; -4.75 ± 8.80 mmHg, p=0.005; -6.11 ± 6.89 mmHg, p<0.001, respectively) and week 8 (-13.73 ± 5.72 mmHg, p<0.001; -8.22 ± 9.40 mmHg, p=0.003; -10.06 ± 7.39 mmHg, p<0.001, respectively) (Figure 4:2). Mean values for sBP, dBP and MAP can be seen in Table 4:2.

Table 4:1 Mean values for systolic, diastolic and mean blood pressure

Variable	IWS Pre	IWS Mid	IWS Post	Control Pre	Control Mid	Control Post
sBP (mmHg)	131.20 ± 5.74	122.37 ± 7.77**	117.47 ± 6.39**	127.77 ± 5.99	126.98 ± 6.0**	128.59 ± 6.27**
dBP (mmHg)	84.39 ± 8.45	79.64 ± 6.71*	76.17 ± 10.04*	80.91 ± 10.08	83.10 ± 8.25*	82.80 ± 9.91*
MAP (mmHg)	100 ± 6.61	93.88 ± 6.57**	89.94 ± 8.25**	96.53 ± 7.56	97.73 ± 5.60**	98.06 ± 6.89**

Mean values and SD for resting systolic (SBP), diastolic (DBP) and mean arterial (MAP) pressure before and after the training and control conditions.** p<0.001 and * p<0.05 for difference between experimental and control conditions.

4.3.2. Resting cardiac output, total peripheral resistance, heart rate and stroke volume

Significant group main effects were only found for TPRi (Wald $\chi^2(1) = 18.957$, $p<0.001$). There were significant differences in TPRi compared to the control group at both week 4 (-47.79 ± 169.92 dyne·s·m^2·cm^5, p=0.04) and week 8 (99.48 ± 156.15 dyne·s·m^2·cm^5 ,p<0.001). There were no significant group main effects for resting HR (-2.82 ± 7.32 beats·min^{-1}, F(1,37) = 0.410, p=0.526)) Q̇ (0.05 ± 1.47 L·min^{-1}, F(1,37) = 0.077, p=0.783), Q̇i (0.08 ± 0.75 L·min^{-1}·m2, F(1,37) = 0.012, p= 0.912), SV (3.83 ± 18.83 mL, F(1,37) = 0.395, p=0.533) or Si (1.71 ± 9.48 mL·m^2, F(1,37) = 0.022, p=0.882). Mean values for TPR, HR, CO, and SV can be seen in Table 4:3.

Table 4:2 Mean values for total peripheral resistance, heart rate, cardiac output, and stroke volume

Variable	IWS Pre	IWS Mid	IWS Post	Control Pre	Control Mid	Control Post
HR (bpm)	72.47 ± 6.15	70.02 ± 9.73	69.65 ± 10.30	68.28 ± 10.98	67.92 ± 6.76	69.50 ± 9.03
TPR (dyne·s·cm^5)	1462.82 ± 428.99	1356.57 ± 386.75*	1262.78 ± 362.79	1420.38 ± 533.74	1475.98 ± 439.61*	1546.68 ± 428.31
TPRi (dyne·s·m^2.cm^5)	741.63 ± 216.98	693.84 ± 210.83*	642.16 ± 196.10**	771.69 ± 330.44	803.46 ± 283.72*	827.80 ± 244.60
Q̇ (L.min)	5.98 ± 1.48	5.79 ± 1.0	6.03 ± 1.12	5.50 ± 1.36	5.69 ± 1.69	5.50 ± 1.87
Q̇I (L.min.m^2)	3.07 ± 0.92	2.95 ± 0.63	3.16 ± 1.01	2.94 ± 0.77	3.03 ± 0.86	2.96 ± 1.12
SV (mL)	83.25 ± 22.46	83.52 ± 14.77	87.07 ± 13.76	81.22 ± 18.91	84.15 ± 23.93	78.73 ± 22.48
SI (mL^2)	42.86 ± 13.81	42.74 ± 10.02	44.56 ± 9.58	43.30 ± 9.88	44.69 ± 11.81	42.32 ± 13.59

Mean values and SD for resting heart rate (HR), total peripheral resistance (TPR), TPR index (TPRi), cardiac ouput (CO), cardiac output index (CI), stroke volume (SV) and SV index (SI) before and after the training and control conditions.** p<0.001 and * p<0.05 for difference between experimental and control conditions.

4.3.3. Resting heart rate variability and baroreceptor sensitivity

There were significant main group effects for HF (Wald $\chi^2(1) = 6.235$, $p<0.013$), LF:HF ratio (Wald $\chi^2(1) = 8$, $p =0.005$), PSD-RRI (Wald $\chi^2(1) = 6.585$, $p=0.01$), LFnu and HFnu (Wald $\chi^2(1) = 5.706$, $p =0.017$), and BRS (Wald $\chi^2(1) = 5.672$, $p=0.017$). There was a significant increase in HF parameters following 4 (368.64 ± 632.12 ms^2, $p=0.003$) and 8 weeks (747.48 ± 704.58 ms^2, $p<0.001$) of IWS training. The low-frequency/high-frequency ratio also significantly decreased at both week 4 (-1.37 ± 2.34, $p<0.001$) and week 8 (-1.49 ± 2.17, $p<0.001$). A similar finding was also seen with PSD-RRI, which significantly increased at both week 4 (1035.54 ± 752.13 ms^2, $p<0.001$) and week 8 (1244.81 ± 2007.31 ms^2, $p=0.003$). Both HFnu and LFnu significantly increased and decreased, respectively, and week 4 (13.64 ± 17.37%, $p=0.04$; -13.64 ± 17.37%, $p=0.04$) and week 8 (16.59 ± 19.75%, $p<0.001$; -16.59 ± 19.75%, $p<0.001$). There was a significant increase in BRS at week 8 (9.54 ± 9.44 ms·mmHg, $p<0.001$), but not at week 4 ($p>0.05$). There were no significant differences compared to the control group for LF parameters at both week 4 and week 8 ($p>0.05$). Mean values for cardiac autonomic variables can be found in Table 4*:*4*.*

Table 4:3 Mean values for heart rate variability and baroreceptor sensitivity

Variable	IWS Pre	IWS Mid	IWS Post	Control Pre	Control Mid	Control Post
LF (ms^2)	811.05 ± 462.45	1111.31 ± 749.41	1310.99 ± 760.66	944.40 ± 700.55	1040.12 ± 800.78	1196.18 ± 1190.88
HF (ms^2)	452.28 ± 450.49	820.92 ± 541.10*	1199.76 ± 711.93**	597.77 ± 662.89	537.82 ± 605.90*	571.42 ± 756.40
LF:HF (ratio)	3.11 ± 2.48	1.73 ± 1.52**	1.61 ± 1.62**	2.84 ± 2.35	3.17 ± 2.37**	3.23 ± 2.11
PSD-RRI (ms^2)	1840.56 ± 820.60	2876.11 ± 816.75**	3085.37 ± 1895.59*	2080.82 ± 1674.91	2049.28 ± 1296.02**	1909.39 ± 1527.04
LFnu (%)	71.70 ± 13.95	58.07 ± 17.32*	55.12 ± 15.97*	71.15 ± 14.11	66.84 ± 17.29*	68.74 ± 16.75
HFnu (%)	28.30 ± 13.95	41.93 ± 17.32*	44.88 ± 15.97*	28.85 ± 14.11	33.16 ± 17.29*	31.26 ± 16.75
BRS (ms.mmHg)	11.84 ± 5.57	19.04 ± 14.17	21.39 ± 11.42**	13.48 ± 8.83	15.74 ± 5.71	13.12 ± 3.38**

Mean values and SD for low frequency (LF), high frequency (HF), low:high frequency ratio (LF:HF), power spectral density (PSD–RRI), low frequency normalised units (LFnu), high frequency normalised units (HFnu), baroreceptor reflex sensitivity (BRS). ** $p<0.001$ and * $p<0.05$ for difference between experimental and control conditions.

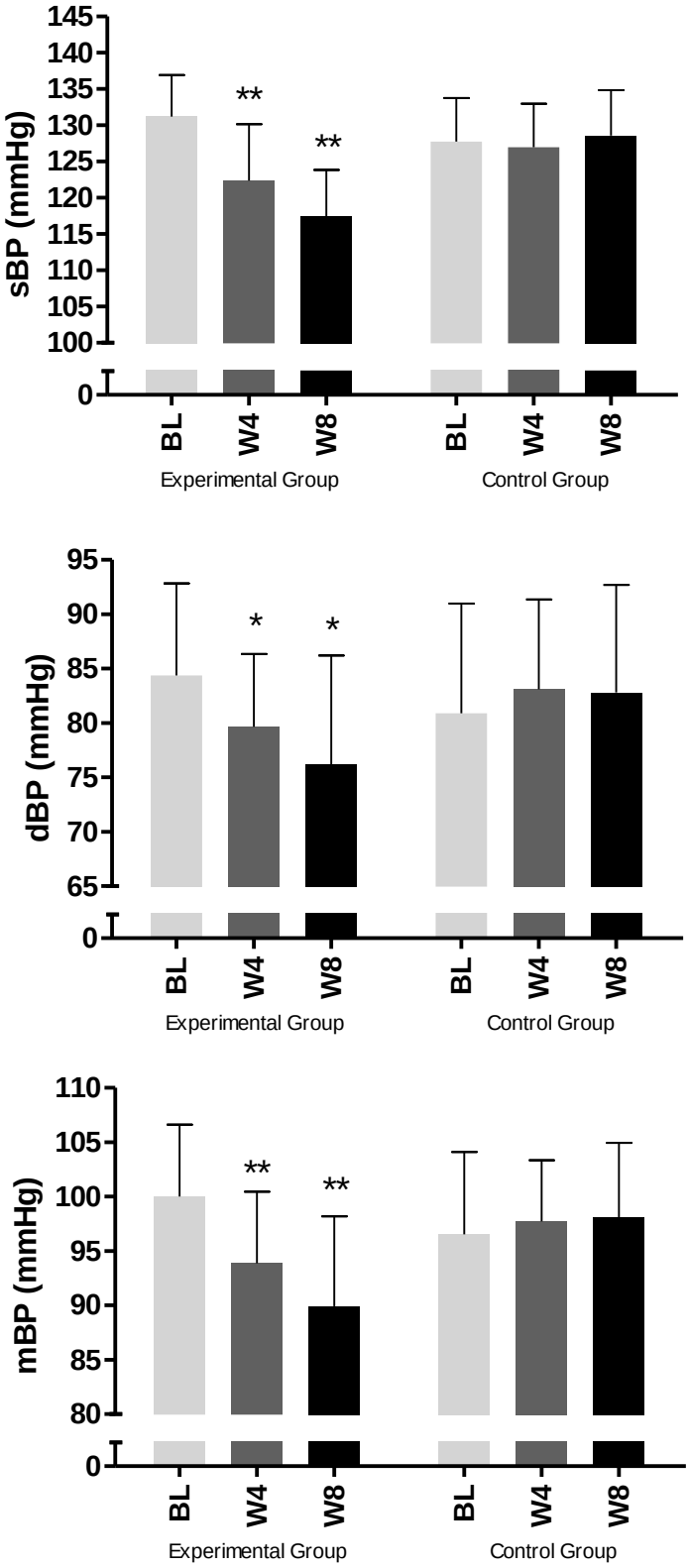


Figure 4:2 The mean sBP, dBP and MAP values at baseline, week 4 and week 8 for the experimental and control conditions. Error bars indicate standard deviation of the mean. ** $p<0.001$ and * $p<0.05$ for difference between experimental and control conditions.

4.3.4. Home-based blood pressure

Table 4:4 Laboratory and home-based BP values obtained from the A&D UA-1020-W device

Variable	Baseline Lab	Week 4 Lab	Week 5 Home	Week 6 Home	Week 7 Home	Week 8 Home	Week 8 Lab
sBP	131.80 ± 7.07	120.60 ± 6.18	120.86 ± 7.14	121.20 ± 8.37	119.32 ± 7.22	117.26 ± 6.0	118.05 ± 4.48
dBP	83.25 ± 7.39	76.80 ± 5.51	75.15 ± 6.26	73.91 ± 7.13	73.78 ± 7.48	72.36 ± 6.84	75.65 ± 6.73
Con sBP	128.30 ± 7.26	128.90 ± 7.66	130.09 ± 7.60	131.08 ± 8.27	130.61 ± 8.50	131.63 ± 7.81	130.35 ± 6.87
Con dBP	81.20 ± 7.54	82.45 ± 8.43	83.72 ± 8.11	81.20 ± 8.65	79.72 ± 9.12	80.50 ± 8.31	82.25 ± 7.48

Mean values and SD for resting sBP and dBP during all laboratory visits (baseline, week 4 and week 8) and each week at home (week 5, 6, 7 and 8).

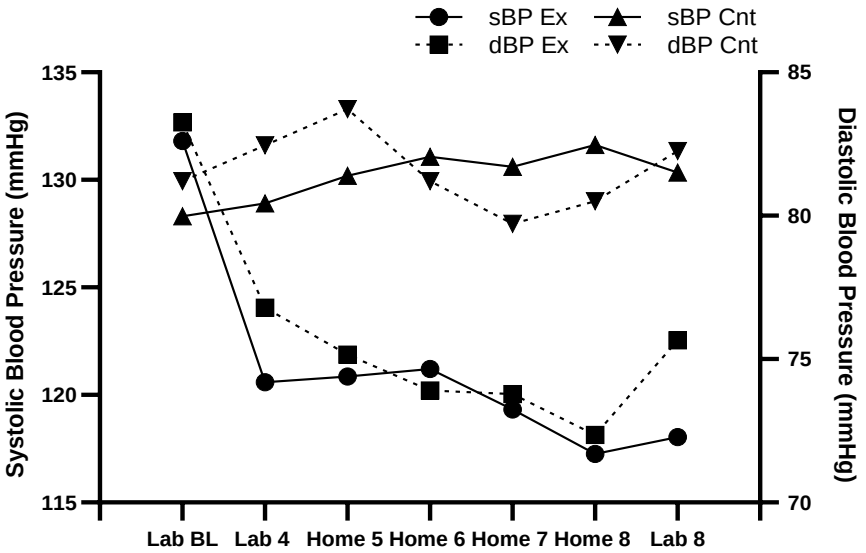


Figure 4:3 Mean home and laboratory sBP and dBP values over the 8-week period for both the experimental and control groups taken with the A&D UA-1020-W

4.3.5. Rate of perceived exertion

There was a significant difference between the RPE data at baseline and week 8 ($p<0.001$). Mean RPE values can be seen in Table 4:6.

Table 4:5 RPE data throughout the 8-week training period

Variable	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
RPE	7.85 ± 0.81	7.35 ± 0.75	6.85 ± 0.93	7.1 ± 1.17	6.91 ± 0.36	6.47 ± 0.72	6.35 ± 0.49	5.95 ± 0.61**

Mean values and SD for rate of perceived exertion data from week 1 through to week 8. Data are reported as the mean of the 3 IWS sessions during each week for all experimental participants (n=20) ** $p<0.001$ for difference between week 8 and week 1 data.

4.3.6. Week 4 to week 8 differences

There was a significant group*time interaction for sBP (Wald $\chi^2(1) = 11.385$, $p<0.001$). There were no group*time interactions for any other variable ($p<0.05$). Change scores for all variables can be seen in Table 4:7.

Table 4:6 Delta scores from week 4 and week 8 variables

Variable	Change scores 4- 8 (Δ)
sBP	-4.90 ± 6.05*
dBP	-3.47 ± 9.39
MAP	-3.94 ± 7.55
HR	0.38 ± 11.20
CO	0.24 ± 1.06
CI	0.20 ± 0.89
SV	3.56 ± 12.52
SI	1.82 ± 6.83
TPR	-93.78 ± 377.33
TPRi	-51.69 ± 196.10
LF	199.68 ± 939.32
HF	378.84 ± 740.23
LF:HF ratio	-0.12 ± 1.30
PSD-RRI	209.27 ± 1730.34
LFnu	-2.95 ± 18.68
HFnu	2.95 ± 18.68
BRS	2.35 ± 14.96

Change scores for all haemodynamic and cardiac autonomic variables measured. * $p<0.05$ for difference between week 4 and week 8 experimental data.

4.4. Discussion

The aim of the current study was to explore the BP reductions and mechanistic adaptations following 8 weeks of IWS training. The study found that sBP, dBP and MAP were significantly different from the control group at both week 4 and week 8 (Table 4:2). However, within-group analysis of the experimental data demonstrated that the reduction in sBP (but not dBP or MAP) at week 8 was significantly greater when compared to week 4 (Table 4:7). This is an important finding as it demonstrates that greater BP-lowering effects may be elicited over longer training periods. These data support previous work that has demonstrated greater BP reductions following longer (8-10 weeks) periods of IET (Wiley *et al.*, 1992; Taylor *et al.*, 2003; Wiles *et al.*, 2010; Baross, Wiles and Swaine, 2012; Badrov, Bartol, *et al.*, 2013) and Millar *et al.*, (2007) who reported a negative linear

trend in resting BP which continued to decline all the way up until the end of the 8-week IHG training study.

The larger sBP reduction seen at the 8-week time point is likely related to a greater overall training volume and longer exposure to the exercise stimulus. Although any further reductions in BP must be related to changes in either TPR or Q̇, the current study did not find any significant difference between the week 4 and week 8 data for any haemodynamic or cardiac autonomic variables. However, there were some trends in the data that may help to explain the further reductions in sBP. For example, although TPRi was significantly different to the control group at both week 4 and week 8 (Table 2), the magnitude of reduction was greater at week 8, with a lower p-value at week 8 (<0.001) compared to week 4 (0.037). This may suggest there was a trend for further reductions in TPRi which may indicate further adaptations to the vasculature. The effects of shear stress on the local vasculature follow a biphasic pattern, with early alterations in vascular function induced through the release of NO (<4 weeks), but long-term changes (>4 weeks) are associated with vascular remodelling and structural adaptations to normalise shear stress (Tinken *et al.,* 2008; 2010). Nonetheless, the functional and/or structural nature of any vascular adaptation was not measured and is therefore beyond the scope of this study. There is also limited data to suggest whether structural adaptations would equate to greater reductions in sBP. Furthermore, other factors such as altered autonomic and baroreflex vasomotor control may also be responsible (Taylor *et al*., 2019).

The current study found that measures of BRS were not significantly different from the control group until week 8, which may suggest that the further decreases in sBP at the 8-week mark were facilitated through an increase in the sensitivity of the baroreceptor. As previously discussed, the baroreceptor functions to inhibit sympathetic tone when BP is high, which produces a vasodilatory effect. The sensitivity of the baroreceptor is positively correlated with HRV and inversely related to BP (i.e. when BRS is high, the reflex can quickly adjust sympathetic and parasympathetic activity to maintain BP stability) (Hesse *et al.*, 2007; Taylor *et al.*, 2019). In accordance, although the current study did not find significant differences in measures of HRV between weeks 4 and 8, it should be noted that the increase in HF components was very close to the alpha threshold level (p=0.053). As such, these findings may suggest that the further increases in BRS augmented HRV and vascular tone, subsequently reducing TPR and BP. However, these findings should be viewed with caution since both HF and TPR were not significantly different between weeks 4 and 8. Furthermore, it should be noted that when observing the trend of BRS throughout the 8-week period (Table 4:4), most of the increase occurred during the first 4-week period.

In Chapter 3 it was speculated that SV may not have changed following 4 weeks of IWS training despite a reduction in TPR (and thus presumably afterload) due to a lack of time for the myocardium to adapt. It was argued that performing IWS training for longer than 4 weeks could potentially elicit further adaptations to the myocardium, such as an increase in SV, as seen by O'Driscoll *et al.,* (2022) following 1 year of IWS training. However, the current study found no changes in HR, SV or $\dot{Q}$ following 8 weeks of IWS training compared to the control group. It is therefore likely, as discussed above, that the BP reductions seen in the current study were primarily driven by TPR reductions (potentially related to vascular vasomotor activity mediated through HF and BRS alterations) rather than centrally mediated changes in $\dot{Q}$. Nonetheless, it should be acknowledged that the current study was not powered to detect changes in HR, SV, or $\dot{Q}$ due to a reduced sample size and smaller effect sizes for these variables (d=0.33, 0.21, and 0.038, respectively), so inferences should be approached with caution.

4.4.1. Adherence and clinical impact

Although five participants dropped out from this study, it should be noted that two were from the control group, and the remaining three in the experimental were all COVID-19 related. Of the participants that completed the study, only two missed one session each, resulting in 99% adherence to the study. The validation of this adherence data was confirmed by downloading HR data from each participant's watch at the end of the 8-week period and comparing it to the data that was manually input into their training manual. This adherence data is in alignment with previous short-term (<12 weeks) studies that have reported good adherence to IET (Carlson *et al.*, 2016; Gordon *et al.*, 2018; Baddeley-White *et al.*, 2019; Ogbutor, Nwangwa and Uyagu, 2019; Nemoto *et al.*, 2021; Javidi *et al.*, 2022; Fecchio *et al.*, 2023). These findings are important as many individuals struggle to commit to the current physical activity guidelines (Ussery *et al.*, 2021). Adherence to anti-hypertensive medication has also been reported at <50% (Vrijens *et al.*, 2008). As such, effective and adherable non-pharmacological approaches, such as IWS training, may have great utility in front-line care. However, it should be noted that participants in this study may have been more motivated than the general population due to being recruited within a university environment and so the results may not be applicable to a real-world scenario. There is also still limited data on longitudinal adherence to IET over extended periods of training (>12 weeks), which remains an essential gap in the present literature.

4.4.2. Rate of reduction in blood pressure

As previously outlined, many IET studies fail to report BP trends throughout the training period. It is therefore difficult to ascertain when BP reductions were at their greatest. Although the current study found greater reductions in sBP following 8 weeks of IWS training, it should be acknowledged that the reductions in sBP were significantly different from the control group at both week 4 and week 8. Furthermore, when looking at the trend of BP reductions taken from the HBPM equipment, the majority of the BP reduction seemed to occur between baseline and week 4. Figure 4:3 demonstrates a steep drop from baseline to week 4, which appears to taper off in the second 4-week period. It should also be noted that the greatest BP reductions seen following IWS training have come from Decaux *et al.,* (2022) and Lea, O'Driscoll and Wiles (2023) who used a 4-week training period. Both studies found reductions greater than those found in the current study (8 weeks), and from Cohen *et al.,* (2023) (12 weeks) and O'Driscoll *et al.,* (2022) (1 year). This may indicate a potential plateau in the rate of BP reduction past the 4-week mark, which could be interpreted in several ways.

Firstly, it is likely that BP reductions (in people with regular cardiovascular function) are constrained by homeostatic regulation that prohibits reductions past a certain threshold to avoid hypotensive responses (Halliwill *et al.*, 2013). It is well known that the BP lowering response following exercise training is reduced in normotensive individuals (Ishikawa-Takata *et al*., 2003; Inder *et al*., 2016). As the mean BP for all participants was in the normotensive range at the 4-week mark (sBP 122.37 ± 7.77 mmHg), any further BP reductions may have been constrained. The same may be true when looking at the associative physiological mechanisms, as there were no further changes in any variable from week 4 to 8, potentially demonstrating limited physiological adaptation in the latter half of the training period, which may also help to explain why there were no further reductions in dBP or MAP. However, interestingly, participants in the 12-week Cohen *et al*., (2023) study were unmedicated hypertensives with a higher baseline BP (141.2/87 mmHg), yet experienced smaller reductions when compared to Decaux *et al*., (2022), Lea, O'Driscoll and Wiles (2023) and the current study, who all used normal and high-normal participants. Nonetheless, this may be related to the methods used by Cohen et al., (2023) who (as previously explained) potentially exposed participants to a reduced exercise intensity during the early stages of the training period.

The second possible interpretation from the trend of BP reduction found in the current study is that participants potentially accommodated to the training stimulus (95% HR_{peak}) over the 8-week training period. As previously discussed, the training principle of accommodation states that if the applied stress remains at the same magnitude (intensity, volume and frequency) for a prolonged

period of time, the system will accommodate to this stress and no further improvements in physical fitness will occur (Harries, Lubans and Callister, 2015). When looking at the RPE data in the current study (Table 4:6), there was a significant difference between the mean data from week 1 and week 8 (-1.9, $p<0.001$). This may suggest that participants adapted to the training stimulus over the 8-week period. However, HR data remained within the THRR to elicit the desired exercise stimulus (relative to 95% HRpeak) throughout the entire training programme (knee angle was adjusted if HR data fell outside the THRR, as outlined in Chapter 2, section 2:10:9). As such, it is likely that other factors, such as neuromuscular fatigue, also contribute to RPE as a marker of internal load, without directly affecting the cardiovascular stimulus (95% HR_{peak}) (Raeder *et al.,* 2016).

The last feasible interpretation of these findings is that the exercise stimulus from IWS training produces a more pronounced and steeper rate of reduction in BP than other forms of IET. When looking at previous IHG (Badrov *et al.*, 2013) and isometric double-leg extension studies (Wiles *et al.*, 2010; Baross, Wiles and Swaine, 2012) that have explored the trend of BP reductions throughout the training period, significant reductions in resting BP parameters were only found after 8 weeks, with no significant reductions evident at the 4-week mark. The greater rate of reduction seen following IWS training (Wiles *et al.,* 2017) is suggested to be related to the increased muscle mass recruitment during IWS exercise and wider range of synergistic muscle groups (Contreras, 2014), which has been shown to augment the cardiovascular response and post-exercise hypotension (a likely predictor of chronic adaptations (Farah *et al.*, 2017)), compared to other forms of IET (Swift *et al.*, 2022).

4.4.3. Conclusion

Findings from the current study have demonstrated that greater sBP, but not dBP or MAP, reductions can be achieved over a longer 8-week period of IWS training. The greater reductions in sBP are likely related to an increase in BRS, which was not significantly different from the control group until week 8. Although there were no statistically significant differences found in any other variables from weeks 4 to 8, there were some trends in the data that may help explain the greater reduction in sBP, such as further reductions in TPRi, and increased HF at week 8. Overall, the findings presented can help inform practitioners of the increased benefits that can be seen over longer periods of IWS training, particularly in light of the high adherence to the 8-week training period. Nonetheless, when observing the rate of reduction in the current study, a trend was identified highlighting a plateau in BP reductions past the 4-week mark, which may be related to homeostatic regulation, or participants accommodating to the training stressor.

CHAPTER 5 - STUDY 3

The detraining effect following isometric wall squat exercise training

5.1. Introduction

As outlined in Chapter 2, it is likely that any reductions in resting BP following a short period of exercise training (≤4 weeks) will reverse within a relatively short period following the cessation of training (1-2 weeks) (Wiley *et al.*, 1992; Howden *et al.*, 2002; Williams, 2006; Devereux, 2010). Conversely, following longer periods of IET (>8 weeks), BP reductions appear to be sustained for longer durations (Carlson *et al.*, 2016; Gordon *et al.*, 2018, 2023; Baross *et al.*, 2022). While several factors, including the magnitude of resting BP reduction, baseline BP values, training mode and training intensity may contribute to the sustainability of resting BP reductions during a detraining period, it seems the most consistent variable from the available literature is the length of the initial training period. Based upon the quick reversal of BP reductions seen during the short wash-out periods following IWS used by Wiles, Goldring and Coleman (2017) (4 weeks) and Taylor *et al*., (2019) (3 weeks), it is likely that BP reductions are also reversed in a relatively small timeframe following short periods of IWS training. Nevertheless, a gap remains in the research, as no studies have specifically investigated the detraining effect upon the cessation of IWS training. This is an important area of study due to the likelihood of dropouts and higher attrition following longer periods of training. Research indicates that approximately 50% of individuals discontinue exercise programs within the first six months, and only 20% remain committed after 24 months (Dishman, 1988; Ettinger *et al.*, 1997; Resnick and Spellbring, 2000). Moreover, despite the benefits of IWS training (low financial costs, accessibility, home-based), a recent real-world IWS training study that has been conducted within front-line NHS care amongst hypertensive individuals also demonstrated attrition issues (34% after 6 months) (Wiles *et al*., 2024). Therefore, for IWS training to be successfully implemented as an antihypertensive intervention, it is important to understand the effects of detraining following the cessation of training. This information is key to anticipating the changes in BP that may occur once training stops.

When looking at the wider exercise detraining literature, it is noted that many studies do not report the trend of BP reversal during a detraining period. This presents an issue when it comes to understanding the detraining effect, as the length of time BP remains significantly reduced is not always reflected in the reported data. For example, a study may use a 4-week detraining period, and

report that BP reductions returned to baseline following the 4 weeks, but it is not known whether the reductions stayed significantly reduced for a period within the 4-week period (e.g. 2 weeks). An understanding of specific detraining periods is important to be able to compare responses between interventions and to allow practitioners to better understand the risks if individuals do not adhere to or withdraw from training. As demonstrated in Chapter 3, an effective way to measure BP levels during a detraining period is using a HBPM approach. This approach to monitoring BP allows data to be recorded continuously and will give a clearer understanding of the trend in BP changes throughout the detraining period.

Therefore, the aim of this study was to investigate the detraining effect and trend of resting BP, as well as the changes in associated haemodynamic and cardiac autonomic variables, following the cessation of IWS training.

5.2. Method

5.2.1. Participants

Forty-eight healthy males and females with a resting sBP value between 120-140mmHg were recruited for the study. The determination of BP categorisation was ascertained following the ESH (2023) guidelines: three resting sBP measurements of ≥120 mmHg and <140 mmHg (Mancia *et al.*, 2023). A current physical activity level below the public health recommendations of 150 minutes of moderate-intensity physical activity per week was also required for participation (Franklin 2021). This included low-level physical activity, such as walking, light cycling and general household activities. If any participants were involved in any purposeful exercise regimes, such as running, HIIT, or dynamic resistance training, they were excluded from the study. Full details of the participant cohort can be seen in Chapter 2 (section 2.2).

5.2.2. Sample size estimation

Sample size estimates for this study were based on the collated data set. Using a sample size of 40, with 2 groups, 1 covariate (baseline BP), a significance level of 0.05 and power of 0.80, the current study was powered to detect a moderate effect size (d=0.46). Full details of sample size calculations can be seen in Chapter 2 (section 2.2.1).

5.2.3. Recruitment

Participants were from the collated data set of 100 participants. From the two groups used within this study (0x per-week group and the control group) there were 8 dropouts (three related to COVID-19, three voluntary dropouts, and two non-compliant), so 48 participants were recruited in total (Figure 5:1). The recruitment process for the collated data set is described in detail in Chapter 2 (section 2.2.2).

5.2.4. Equipment

Laboratory-based equipment

Haemodynamic and cardiac autonomic assessment: All haemodynamic and cardiac autonomic variables in this study were measured using the TFM. Full details of the TFM can be found in Chapter 2 (section 2.4.1).

Wall squat knee joint angle: Knee joint angle was measured during exercise using a clinical goniometer. For further details see Chapter 2 (section 2.10.4).

Rate of perceived effort (RPE): The Borg CR10 scale was used to measure and rate effort felt in the participant's upper legs during exercise in the laboratory and at home. For further details see Chapter 2 (section 2.10.10).

Home-based equipment

Home-based BP device: During the second 4-week period of training, participants were required to self-measure BP in the home using the A&D UA-1020-W HBPM device. Full details of the A&D device can be seen in Chapter 2 (section 2.7).

Heart rate: In order to measure HR during home-based IWS training, participants wore a wrist-worn HR monitor and a Polar H10 HR chest strap. Full details of the home-based HR equipment can be seen in Chapter 2 (section 2.10.8).

Wall squat knee joint angle: During home-based IWS exercise sessions, the knee joint angle was established by using a Bend and Squat devise which can be used to recreate a target knee-joint

angle. The device can be precisely adjusted so each participant can easily position their foot and back placement in order to reproduce the desired knee angle. Full details can be seen in Chapter 2 (section 2.10.4).

Training manual: During home-based IWS training, participants also received a training manual which outlined the specific protocol for home-based IWS training, as well as guidance on how to use the equipment given. The training manual also included data sheets to input HR and RPE data on from their training sessions, as well as data sheets for the HBPM readings taken during the second 4-week period.

5.2.5. Procedures

Familiarisation

During the familiarisation session participants were given a full overview of the study protocols and familiarised with all equipment used within the study. Full details of the familiarisation session can be seen in Chapter 2 (section 2.2.3).

Overall study design

Once participants were enrolled in the study, they were randomly assigned to either the 8-week IWS experimental group (n=22) or the control group (n=26). Randomisation was carried out using the random function on Microsoft Excel and before baseline BP measures were taken to avoid any recruitment bias.

Training condition

All experimental participants were required to undertake an incremental IWS test to determine the knee joint angle used during training (see Chapter 2, section 2.10.3). The knee joint angle was established to elicit a training intensity of 95% HR_{peak} during home-based sessions. Participants then carried out a 4-week home-based IWS training programme. Training was carried out three times per week over the 4 weeks (n=12), with 48 hours between each session. Each training session comprised of 4 x 2 minutes of IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest (Wiles, Goldring and Coleman, 2017). Following the first 4-week training period, participants were required to attend the laboratory for mid-training resting measures.

Participants then began their detraining period the day directly following their mid-point laboratory visit. The 4-week detraining period involved a complete cessation of IWS training. Participants were

required to continue their usual dietary and physical activity levels (any physical activity - including walking - that was also carried out during the initial 4-week training period) which was verbally confirmed during the subsequent laboratory visit. Participants were also required to self-monitor their BP in the home using a HBPM device. Following the full 8-week period, participants were again required to attend the laboratory for post-detraining resting measures. To check compliance with exercise protocol and individualised training zone prescribed over the training period, HR data was downloaded from the HR watch at the end of the study. The threshold for compliance to the full 8-week period was 10 out of 12 sessions during the training period, and verbal confirmation of compliance to the detraining period. If participants were withdrawn, they were encouraged to carry on with the IWS training, although their data was not used for analysis. Full details of the IWS training protocol can be found in Chapter 2 (section 2.10).

Control condition

During the control condition, participants were requested to maintain their habitual dietary and physical activity daily routines for 8 weeks. Adherence to these conditions was verbally confirmed during the subsequent laboratory session. During the first 4-week period participants did not visit the laboratory, and no additional measures were taken until they visited the laboratory at week 4. During the second 4-week period, participants were required to self-monitor their BP in the home using a HBPM device.

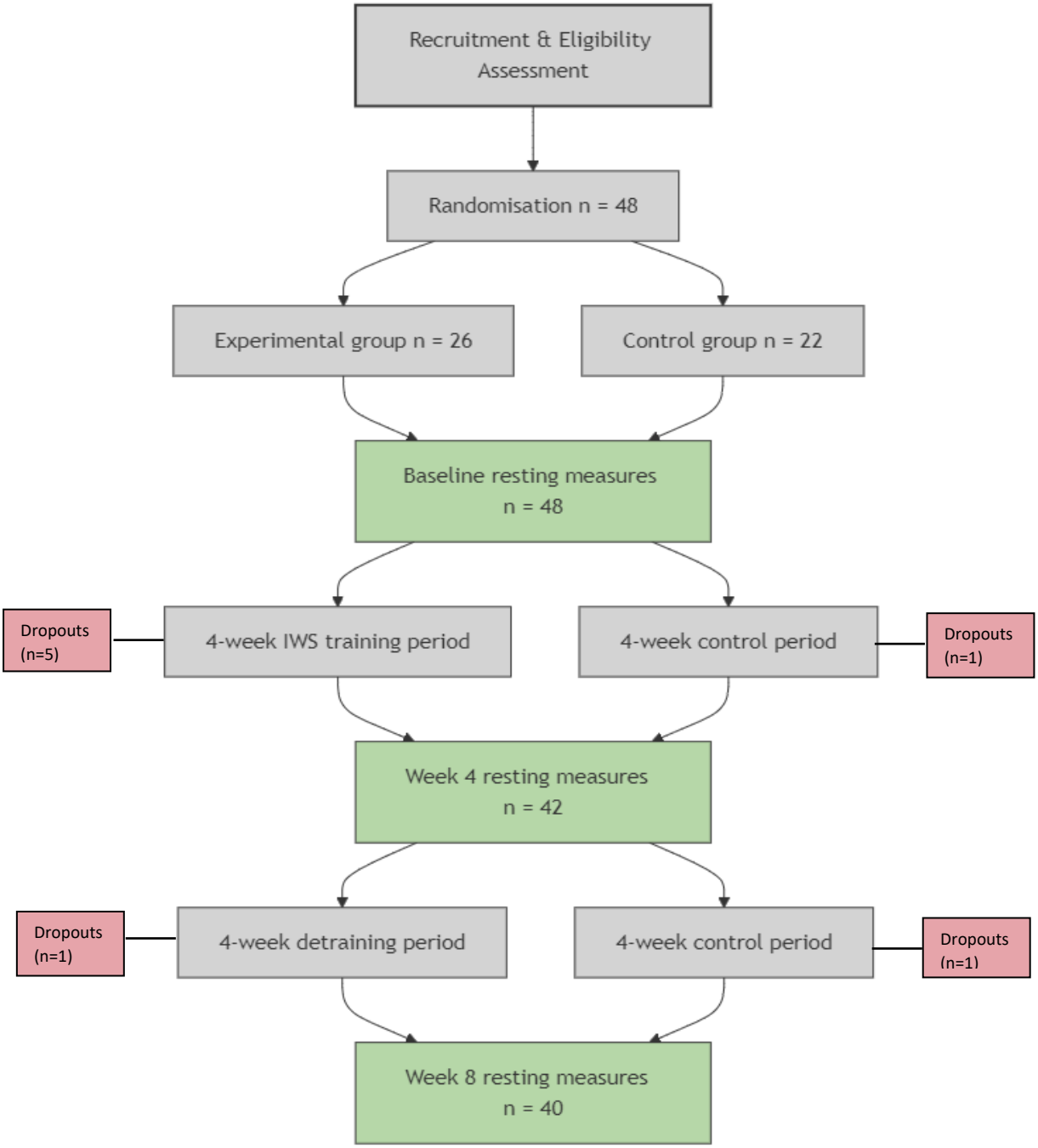


Figure 5:1 Data collection timeline and sample sizes used

5.2.6. Resting measures

Laboratory-based measures

Both experimental and control participants were required to attend the laboratory for resting cardiovascular measures. Resting haemodynamic and cardiac autonomic measures were taken at

baseline, mid-training (4 weeks) and post-training (8 weeks). The mid- and post-training measures were taken 72 hours after the final bout exercise at week 4 and at week 8 to avoid any transient effects which may persist post-exercise (Kenney and Seals 1993). Before attending the laboratory, participants were asked to avoid any food for 2 hours, caffeine for 4 hours, and alcohol for 12 hours pretesting. They were also asked not to carry out strenuous physical activity (including IWS exercise) 48 hours pretesting to avoid any interference with BP and HR measurements (James, Leidy Sievert and Flanagan, 2004; Rezk *et al.*, 2006). Upon arrival at the laboratory, participants rested seated for 15 minutes. Following the seated rest, sBP, dBP, MAP, Q̇, SV, TPR, BRS, LF, HF, LFnu, HFnu, and PSD-RRI were measured continuously for 5 minutes in the seated position using the TFM. After this time, the mean values for each variable were calculated offline for the 5-minute period. A number of measures were indexed to BSA. Full details of the protocol to obtain resting measures can be seen in Chapter 2 (section 2.4).

Home-based blood pressure monitoring

Home-based blood pressure monitoring was also used to explore the trend of BP alterations throughout the second 4-week training period. Based on ESH guidelines (Mancia *et al.*, 2023) two BP readings were taken in the morning (within 2 hours of waking) and two in the evening (within 2 hours of sleeping) for each day that home-based BP monitoring was required. If the first two readings were largely different (over 10-mmHg difference) a further reading was required. Each reading was separated by 1 minute of rest, with the average of the last two readings used for analysis. The mean BP values for each week were used for analysis. Resting BP measures using the A&D device were also taken during each laboratory visit to give comparative data for analysis throughout the full training programme. Full details of the HBPM protocol can be found in Chapter 2 (section 2.7).

5.2.7. Data analysis

All data were checked for normality and homogeneity of variances (Field, 2013). Where the parametric assumptions were met, a one-way analysis of covariance (ANCOVA) was carried out to explore the possible differences in each dependent variable, using baseline measures as the covariate with either the week 4 or week 8 data. This test was selected to maintain statistical power and reduce the probability of a type II error. Where data were not normally distributed, a Quade non-parametric ANCOVA was used which rank transforms the data to achieve a normal distribution pattern. A two-way repeated measures analysis of covariance (RMANCOVA) was also used to analyse the HBPM data (both laboratory and home-based readings) with baseline measures as the covariate.

If the RMANCOVA was statistically significant, a least significant difference (LSD) post-hoc test was used to explore any pairwise comparisons. For non-parametric data, a generalised estimating equation was used. For all tests, an alpha level of <0.05 was set as the threshold for statistical significance. Data analysis was performed with IBM SPSS (BM SPSS Statistics for Windows, version 19.0, Armonk, NY: IBM Corporation).

5.3. Results

Forty participants (M=23: F=17) completed the study (39 ± 10 years; 78 ± 10 kg; 171 ± 9 cm). The allocation of male and female participants was 11:9 in the experimental, and 12:8 in the control group. Of the 20 experimental participants who were compliant with the study inclusion criteria, all 20 completed the 12 training sessions during the initial 4-week training period and then also complied with the detraining conditions during the detraining period. Resting haemodynamic and cardiac autonomic data were obtained from all experimental and control participants during the laboratory visits at baseline and week 4.

5.3.1. Resting blood pressure

Following 4 weeks of IWS training there was a reduction in sBP (-7.40 ± 6.72 mmHg) which was significantly different to the control group ($F(1,37) = 9.725$, $p=0.004$). Following the 4-week detraining period, sBP reductions had reversed and were no longer significantly different from the control group ($F(1,37) = 1.337$, $p=0.255$). Resting dBP (-3.81 ± 8.55 mmHg, $F(1,38) = 8.216$, $p=0.007$). and MAP (-5.01 ± 6.76 mmHg, $F(1,38) = 7.603$, $p=0.009$) followed a similar trend, reducing compared to the control group following the 4-week training period, but reversing following the 4-week detraining period ($F(1,38) = 0.735$, $p=0.397$; $F(1,38) = 0.622$, $p=0.435$) (Figure 5:2). Mean values for sBP, dBP and MAP can be seen in Table 5:1.

Table 5:1 Mean values for systolic, diastolic and mean blood pressure

Variable	IWS Baseline	IWS Week 4	IWS Detrain	Con Baseline	Con Week 4	Con Week 8
sBP (mmHg)	131.53 ± 5.70	124.13 ± 7.35*	127.67 ± 4.40	127.77 ± 5.99	126.98 ± 6.0*	128.59 ± 6.27
dBP (mmHg)	83.23 ± 8.75	79.42 ± 8.10*	82.74 ± 7.53	80.91 ± 10.08	83.10 ± 8.25*	82.80 ± 9.91
MAP (mmHg)	99.33 ± 6.37	94.32 ± 6.62*	97.72 ± 4.44	96.53 ± 7.56	97.73 ± 5.60*	98.06 ± 6.89

Mean values and SD for resting systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressure before and after the training and control conditions.* P<0.05 for difference between experimental and control conditions.

5.3.2. Resting cardiac output, total peripheral resistance, heart rate and stroke volume

Following 4-weeks of IWS training there were reductions in TPR (-297.21 ± 278.97 dyne·s·cm^5) and TPRi (159.66 ± 147.24 dyne·s·m2·cm^5) which were significantly different to the control group (TPR F(1,38) = 10.306, p=0.003, TPRi F(1,38) = 12.216, p=0.001). Following the 4-week detraining period, the reductions in TPR and TPRi had reversed and were no longer significantly different from the control group (TPR F(1,38) = 0.133, p=0.717, TPRi F(1,38) = 0.034, p=0.855).

There were no significant differences compared to the control group following the 4-week training period in resting HR (-2.34 ± 9.13 beats·min^{-1}, F(1,37) = 0.005, p=0.944)) $\dot{Q}$ (-0.17 ± 1.84 L·min^{-1}, F(1,38) = 0.21, p= 0.887), $\dot{Q}$i (-0.09 ± 0.95 L·min^{-1}·m2, F(1,38) = 0.077, p=0.782), SV (-0.74 ± 27.94 mL, F(1,38) = 0.097, p=0.757) or Si (-0.29 ± 14.47 mL·m2, F(1,38) = 0.076, p=0.784). Following the 4-week detraining period, there remained no statistical difference compared to the control group for these variables (p>0.05). Mean values for TPR, HR, $\dot{Q}$, and SV can be seen in Table 5:2.

Table 5:2 Mean values for total peripheral resistance, heart rate, cardiac output, and stroke volume

Variable	IWS Baseline	IWS Week 4	IWS Detrain	Con Baseline	Con Week 4	Con Week 8
HR (bpm)	71.79 ± 10.92	69.45 ± 9.86	70.19 ± 8.10	68.28 ± 10.98	67.92 ± 6.76	69.50 ± 9.03
TPR ($dyne \cdot s \cdot cm^5$)	1519.87 ± 370.36	1222.63 ± 393.70*	1709.36 ± 468.66	1420.38 ± 533.74	1475.98 ± 439.61*	1546.68 ± 428.31
TPRi ($dyne \cdot s \cdot m^2.cm^5$)	808.68 ± 276.49	649.02 ± 256.14*	905.14 ± 316.23	771.69 ± 330.44	803.46 ± 283.72*	827.80 ± 244.60
Q̇ (L.min)	5.63 ± 1.62	5.46 ± 1.12	5.54 ± 1.53	5.50 ± 1.36	5.69 ± 1.69	5.50 ± 1.87
Q̇I ($L.min.m^2$)	2.97 ± 0.96	2.89 ± 0.80	2.93 ± 0.97	2.94 ± 0.77	3.03 ± 0.86	2.96 ± 1.12
SV (mL)	79.69 ± 25.74	78.96 ± 13.78	79.52 ± 22.23	81.22 ± 18.91	84.15 ± 23.93	78.73 ± 22.48
SI (mL^2)	42.20 ± 15.85	41.91 ± 11.95	42.11 ± 14.83	43.30 ± 9.88	44.69 ± 11.81	42.32 ± 13.59

Mean values and SD for resting heart rate (HR), total peripheral resistance (TPR), TPR index (TPRi), cardiac ouput (Q̇), cardiac output index (Q̇i), stroke volume (SV) and SV index (SI) before and after the training and control conditions.* P<0.05 for difference between experimental and control conditions.

5.3.3. Resting heart rate variability and baroreceptor sensitivity

Following IWS training there were increases in HRV expressed as PSD-RRI (1431.02 ± 1915.92 ms^2), and HF (872.53 ± 1489.90 ms^2), which were both significantly different from the control group ($F(1,38) = 7.332$, $p=0.01$, $F(1,38) = 7.611$, $p=0.009$, respectively). There was also a decrease in the LF:HF ratio (-1.68 ± 2.30) which was significantly different from the control group ($F(1,38) = 6.207$, $p=0.017$). Following the detraining period these changes had reversed and there were no significant differences in PSD-RRI ($F(1,38) = 0.005$, $p=0.942$), HF ($F(1,38) = 0.00$, $p=0.984$) or LF:HF ($F(1,38) = 0.769$, $p=0.386$) compared to the control group. Following the initial 4-week training period, low frequency ($F(1,38) = 1.514$, $p=0.226$), LFnu ($F(1,38) = 1.996$, $p=0.166$), HFnu ($F(1,38) = 1.996$, $p=0.166$) or BRS ($F(1,38) = 1.027$, $p=0.317$) were not significantly different from the control group. These variables were also not significantly different from the control group after the detraining period ($p>0.05$). Mean cardiac autonomic variables can be seen in Table 5:3.

Table 5:3 Mean values for heart rate variability and baroreceptor sensitivity

Variable	IWS Baseline	IWS Week 4	IWS Detrain	Con Baseline	Con Week 4	Con Week 8
LF	1123.34 ± 771.58	1458.70 ± 961.24	893.61 ± 643.33	944.40 ± 700.55	1040.12 ± 800.78	1196.18 ± 1190.88
HF	533.97 ± 526.40	1406.50 ± 1486.90*	396.76 ± 325.38	597.77 ± 662.89	537.82 ± 605.90*	571.42 ± 756.40
LF:HF ratio	3.35 ± 2.28	1.68 ± 0.99*	2.88 ± 1.89	2.84 ± 2.35	3.17 ± 2.37*	3.23 ± 2.11
PSD-RRI	2122.70 ± 1392.00	3553.72 ± 2153.31*	1839.13 ± 1138.11	2080.82 ± 1674.91	2049.28 ± 1296.02*	1909.39 ± 1527.04
LFnu	68.96 ± 15.78	59.08 ± 16.16	66.37 ± 14.00	71.15 ± 14.11	66.84 ± 17.29	68.74 ± 16.75
HFnu	31.04 ± 15.78	40.92 ± 16.16	33.63 ± 14.00	28.85 ± 14.11	33.16 ± 17.29	31.26 ± 16.75
BRS	13.07 ± 7.64	21.50 ± 13.07	11.77 ± 7.49	13.48 ± 8.83	15.74 ± 5.71	13.12 ± 3.38

Mean values and SD for low frequency (LF), high frequency (HF), low:high frequency ratio (LF:HF), power spectral density (PSD–RRI), low frequency normalised units (LFnu), high frequency normalised units (HFnu), baroreceptor reflex sensitivity (BRS).* $P<0.05$ for difference between experimental and control conditions.

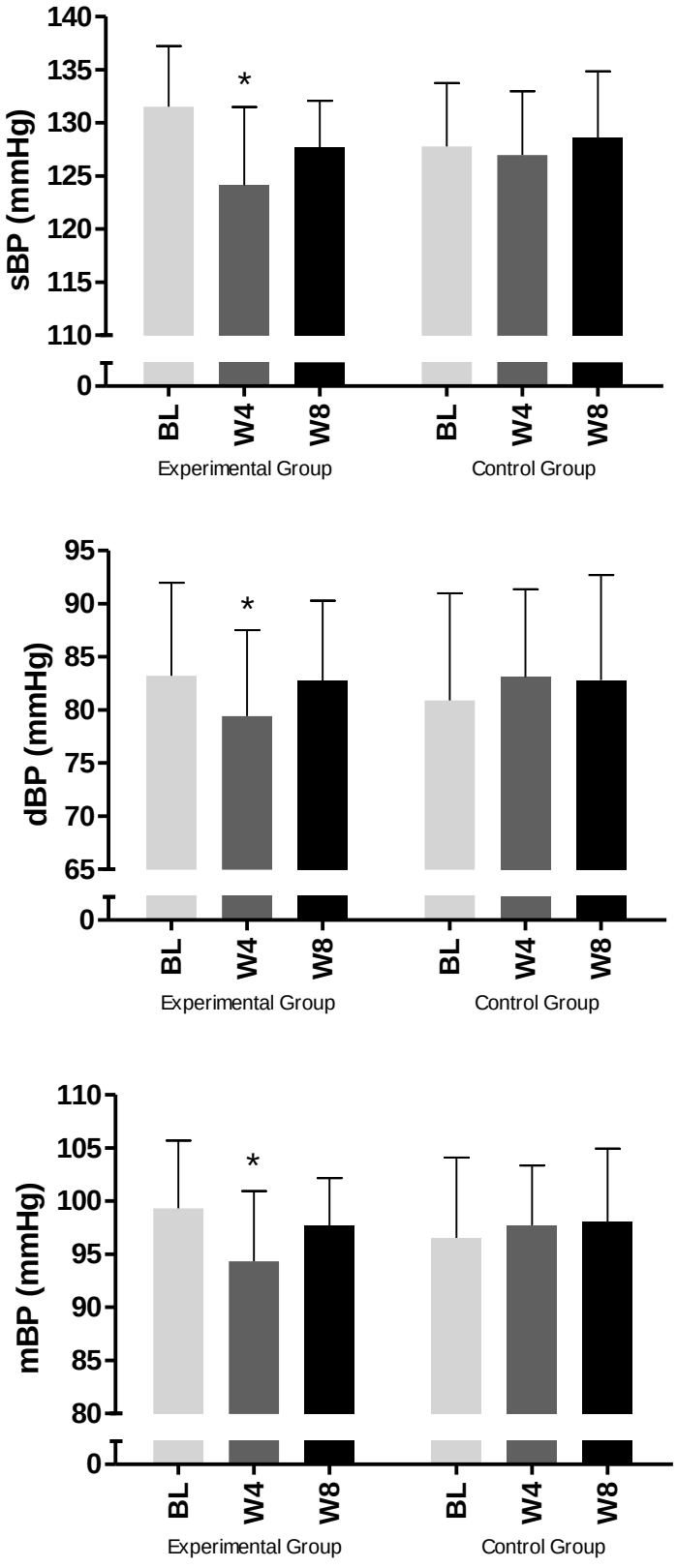


Figure 5:2 The mean sBP, dBP and MAP values at baseline, week 4 and week 8 for the experimental and control conditions. Error bars indicate standard deviation of the mean. ** $p<0.001$ and * $p<0.05$ for difference between experimental and control conditions.

5.3.4. Home-based blood pressure

Laboratory and home-based BP values obtained from the A&D UA-1020-W device demonstrated significant differences compared to the control group at week 4, 5, 6, 7 ($p<0.001$) and week 8 ($p=0.032$) for sBP, and at week 5 ($p<0.001$), 6 ($p=0.021$), 7 ($p=0.016$) and 8 ($p=0.03$) for dBP. Mean values can be seen in Table 5:4.

Table 5:4 Laboratory and home-based BP values obtained from the A&D UA-1020-W device for both the experimental and control groups

Variable	Baseline Lab	Week 4 Lab	Week 5 Home	Week 6 Home	Week 7 Home	Week 8 Home	Week 8 Lab
IWS sBP	132.40 ± 7.28	122.05 ± 6.12**	121.20 ± 5.85**	122.75 ± 7.40**	122.50 ± 7.46**	126.90 ± 8.64*	131.25 ± 7.09
IWS dBP	81.80 ± 8.15	79.95 ± 6.80	74.65 ± 8.40**	73.62 ± 9.30*	73.04 ± 9.68*	73.73 ± 9.97*	83.05 ± 4.98
Con sBP	128.30 ± 7.26	128.90 ± 7.66	130.09 ± 7.60	131.08 ± 8.27	130.61 ± 8.50	131.63 ± 7.81	130.35 ± 6.87
Con dBP	81.20 ± 7.54	82.45 ± 8.43	83.72 ± 8.11	81.20 ± 8.65	79.72 ± 9.12	80.50 ± 8.31	82.25 ± 7.48

Mean values and SD for resting sBP and dBP during all laboratory visits (baseline, week 4 and week 8) and each week at home (week 5, 6, 7 and 8). * $p<0.05$ and ** $p<0.001$, for difference between experimental and control conditions.

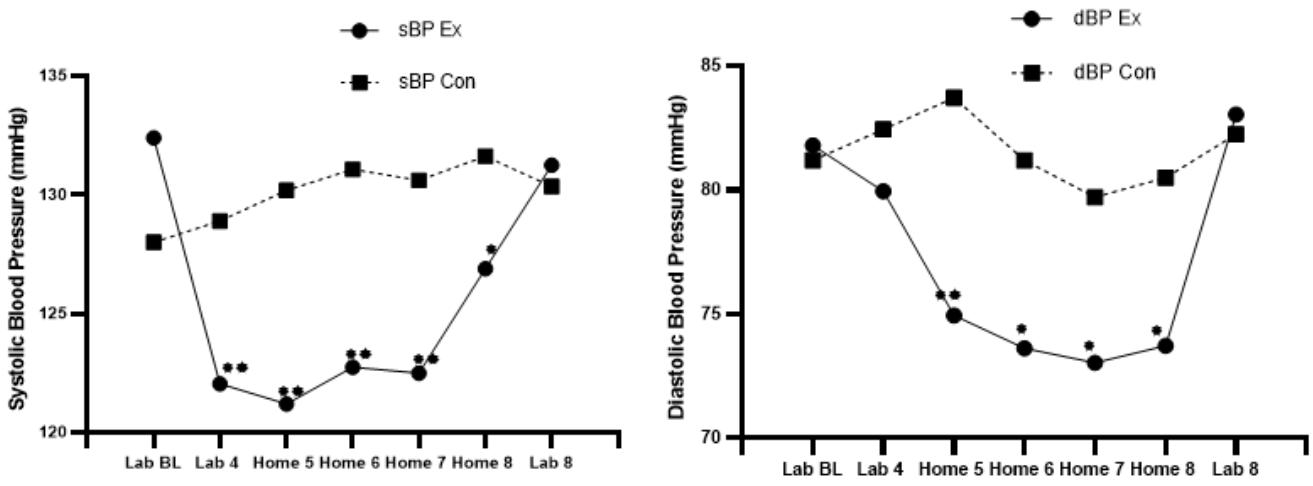


Figure 5:3 Mean home and laboratory sBP and dBP values over the 8-week period for both the experimental and control groups taken with the A&D UA-1020-W. * $p<0.05$ and ** $p<0.001$, for difference between experimental and control conditions.

5.4. Discussion

The current study aimed to explore the effect of detraining on resting BP reductions following the complete cessation of IWS training. It was found that sBP, dBP and MAP were all significantly reduced following the initial 4-week training period, but reversed after 4 weeks of detraining. The reversal of BP reductions within the 4 weeks highlights the temporal nature of BP reductions following short training periods. This temporal effect is likely related to the functional nature of any associated physiological adaptations that are responsible for BP regulation. Indeed, the current study found that significant reductions in TPR compared to the control group following the 4-week training period were reversed after the 4-week detraining period. Although only speculative, this finding may suggest the TPR reductions were facilitated through short-term functional changes (Murray, Delaney and Bell, 2006; Tinken *et al.*, 2008; 2010), such as increased NO production and endothelium-dependent vasodilation (Wang, 2005), or increased arterial compliance (Madhura and Sandhya, 2012), all of which have been shown to reverse within several weeks upon the cessation of a variety of types of exercise training.

Improvements in HRV parameters, including a reduction in the LF:HF ratio and increases in HF and PSD-RRI, were also significantly different from the control group at week 4, but not following the 4-week detraining period. These data highlight the temporal nature of cardiac autonomic adaptations following short-term IWS training. This finding is in agreement with Meredith *et al*., (1990) who found plasma noradrenaline levels (a marker of sympathetic activity) and BP levels were closely aligned during the detraining period, and suggested the maintenance of lower BP is closely associated with autonomic factors. The reversal of the HRV parameters in the current study may also be related to the reversal of TPR during the detraining period. Increased parasympathetic activity and improvements in HRV are well known to influence TPR reductions via vasomotor modulation (vasodilation) (Taylor *et al*., 2019). As HRV and TPR both reversed simultaneously following training, this may suggest that the changes in TPR seen following training and detraining were mediated through alterations in HRV and vascular tone.

A secondary aim of the current study was to explore the trend of BP alterations during the detraining period using a HBPM approach. Both sBP and dBP values that were obtained using the HBPM equipment were significantly lower in the experimental group compared to the control until the laboratory visit at the end of week 8 (Figure 5.3). The reductions show a gradual return to the levels at baseline, demonstrating a progressive reversal of BP reductions. As the reductions (predominately for sBP) were reversed during the 4th week, this demonstrates that BP reductions are sustained for at least 3 weeks upon the cessation of IWS training. This is longer than the 3-week

wash-out period previously used by Taylor *et al.,* (2019). However, Taylor *et al*. (2019) only used male participants, and there are well-known sex-based differences in cardiovascular regulation between males and females (such as increased parasympathetic modulation post-exercise in females (Fisher *et al.*, 2013)) that may influence the detraining effect (Gerdts *et al.*, 2022). The period that BP reductions were sustained in the current study is also longer than previous 4-week studies that have explored the detraining effect following IHG training (Wiley *et al.*, 1992; Howden *et al.*, 2002) and double leg IET (Devereux, 2010), potentially indicating a greater ability of IWS training to sustain BP reductions. Nonetheless, the period of sustained reductions is less than those seen following longer periods of IET (>8 weeks) (Carlson *et al.*, 2016; Gordon *et al.*, 2018, 2023; Baross *et al.*, 2022) which may reiterate the likely differences in the adaptations (functional/ structural) and subsequent rate of BP reversal seen between shorter and longer studies.

Another important consideration of this data is that it demonstrated the BP reductions are not the result an acute post-exercise response. Adaptations from exercise are the result of repetitive challenges to homeostasis over time (Lambert 2016). Acute responses to exercise, such as alterations in blood flow and cardiovascular drive, elicit biological stress and alter homeostasis, but are short-term and transient, normally returning to baseline within a short period of time (minutes-hours) following exercise (Rivera-Brown and Frontera 2012). Adaptations are the result of repeated bouts of stress from the accumulation of exercise bouts into a training period, resulting in functional and structural alterations to biological systems, which are more chronic and long-term in nature (Lambert 2016). Although the week-4 laboratory BP readings were taken 72 hours following the last IWS exercise session to avoid any acute interference (post-exercise hypotension), the duration of BP reductions seen throughout the detraining period improves the confidence that the BP reductions seen were caused by chronic adaptation rather than being a short-term acute response. From a practical perspective, these data also demonstrate that if there are periods of time where individuals abstain from training (holidays, low motivation, busy work periods), they can be assured that BP reductions may be maintained for at least 3 weeks following the cessation of training. This information is also relevant for future IET studies with both male and female participants that need to use washout periods, and it should be recommended that a 4-week period is utilised to ensure BP reductions are fully reversed. However, it should also be acknowledged that despite the complete group reversal of BP reductions at week 8, 45% of the participants still had a 5-mmHg CID (Rahimi *et al.,* 2021) after the detraining period. This finding may indicate high inter-individual differences in the BP detraining effect, and that for some, the cardioprotective effects can be sustained for longer periods. This may also have implications for crossover training studies using washout periods, as it is

likely that some participants may still have an augmented BP status even after a 4-week washout period.

5.4.1. Future research directions

As BP reductions are reversed within a short period of time (3-4 weeks) following 4 weeks of IWS training, it is likely that continued intervention will be needed to maintain the benefits. Therefore, future research should investigate ways to reduce the risk of attrition over long-term IWS training periods, as seen by Wiles *et al*., (2024) (e.g. investigating minimal training dose to maintain resting BP reductions). Moreover, exploring further physiological mechanistic differences (e.g. vascular adaptations such as flow-mediated dilation or arterial compliance) between short-term and long-term training could also provide deeper insights into how exercise duration influences the detraining effect. Additionally, assessing the impact of intermittent IWS training cessation and resumption on BP could offer practical guidance for exercise prescription and may also have important implications for IET studies using crossover washout periods.

5.4.2. Conclusion

The current study found that BP reductions are reversed within a 4-week period following the cessation of a 4-week IWS training programme. The reversal of BP reductions in this short period suggests the adaptations may have been more functional than structural. These findings support the general view that, similar to other forms of exercise training, continuous engagement with IWS training is needed to sustain physiological adaptation (i.e. reductions in resting BP). As such, sustainable exercise programmes that address potential barriers to long-term adherence are important to ensure individuals can maintain BP reductions. Future research should explore strategies to enhance long-term adherence and focus on understanding the mechanisms underlying short and long-term sustained BP and cardiovascular adaptation.

CHAPTER 6 – STUDY 4

Minimum training dose and the maintenance of BP reductions following 4 weeks of IWS training

6.1. Introduction

The results from Chapter 5 have shown that BP reductions are reversed within 4 weeks following the complete cessation of a 4-week IWS training programme. These findings are important as they highlight the need for continued intervention for longer-term maintenance of BP reductions. As seen from Chapter 4, a continuation of IWS training over an 8-week period with the original training prescription produces significantly greater sBP reductions than following 4 weeks of IWS training. However, despite the advantages of the extended 8-week training period, it is currently not known if the BP reductions can be maintained, or even similarly improved, with a reduced training dose (i.e. reduced training frequency or intensity) during a follow-up period of training. The application of exercise training programmes without sufficient effort to understand the relationship between dose and response could result in unrealistic expectations and inefficient exercise therapy. As Nolan (2018) highlights, determining the minimum frequency, intensity, duration, and volume of exercise to maintain any health benefits following exercise training remains to be determined and represents important future work in the area of exercise and health. Millar *et al*., (2013) also suggested that the exploration of a minimum training dose is needed for IET to be considered a potential hypertension therapy.

The investigation of a minimum training dose is warranted for several reasons. Firstly, a large proportion (31%) of individuals are currently not meeting physical activity guidelines (Cunningham *et al.*, 2020). As the most commonly cited barrier to participation is a lack of time (Alsobayel *et al*., 2020; Zunft *et al*., 1999), research should focus on promoting time-efficient exercise interventions and making such interventions accessible and sustainable to encourage long-term participation and improve health outcomes. Although IWS training is a time-efficient mode of training and appears to mitigate a lot of the barriers to participation, a real-world study by Wiles *et al.,* (2024) found that 34% of participants withdrew from a home-based IWS training programme after 6 months, indicating that attrition issues are still pertinent within longer IWS training programmes. Indeed, for individuals who exercise or take part in physical activity, it is realistic to expect that at some point, periods of training cessation or inactivity will occur (Cunningham *et al.*, 2020). As such, investigating a minimum training dose to maintain BP reductions (once they have been observed) may help

mitigate this risk and make IWS training more sustainable over the long term. From an adherence and attrition perspective, more is not always better, and finding the 'sweet spot' that is needed to maintain BP reductions would likely have an impact on the long-term uptake of a training programme. Finding the minimum training dose required to maintain BP reductions can also be helpful during holidays or busy work periods, where time and/or motivation are even more limited.

Secondly, a continuation of the original training dose may not be appropriate, or needed, for all individuals. It has been suggested that an individualised approach suited to personal needs should be taken with IET prescription (Ash, Eicher and Pescatello, 2013). One way to individualise IET prescription is to focus on specific BP-lowering targets. Current ESH guidelines (Mancia *et al.*, 2023) define sBP <120 mmHg as 'optimal' and outline potential benefits for greater BP lowering in some high-risk populations, citing the SPRINT trial paper that found greater cardiovascular benefits below 120 mmHg (Wright *et al.*, 2021). However, the recommendations do state that for most individuals, an sBP target of between 120/129 mmHg is suitable (Mancia *et al.*, 2023). Authors also mention lower BP targets should be approached with caution and to individualise treatment goals based on patient-specific factors, considering the associated risks and the need to balance the benefits of intensive BP lowering with the potential for adverse effects (e.g. hypotension and syncope) (Mancia *et al.*, 2023). As seen in Chapter 5, further BP reductions can be achieved following 8 weeks of IWS training, lowering BP down into the optimal range, which may be beneficial for some individuals. However, the mean sBP at week 4 was 122 mmHg, which is at the lower end of the normotensive category. As such, for some individuals (potentially those who have a proclivity to drop out of exercise training programmes) a reduced training dose to maintain BP reductions may be more suitable, with the option to reinstate the original training dose at a future period if deemed necessary.

Lastly, from a training prescription perspective, periods of rest or reduced training volume, also known as 'de-load periods', or 'taper periods' are commonly used in performance settings, as they let athletes recover, and allow time for adaptations to occur before moving on to a subsequent phase of training (Turner, 2011; Le Meur, Hausswirth and Mujika, 2012). Optimal training adaptations occur from the manipulation of programme variables, including the intensity, frequency, and volume of exercise. Using a periodised approach to resistance training typically involves a period of reduced training stimulus (normally volume or intensity) to diminish any residual fatigue, allowing greater recovery, which ultimately improves performance via supercompensation (Bompa and Haff, 2009). In terms of IET and BP reductions, training programmes from within research studies, such as the 1-year study from O'Driscoll *et al.*, (2022), have typically utilised the same prescription for the entirety of the training programme rather than employing periodised approaches. Although only

speculative, over the long term, periods of reduced training volume may also optimise physiological adaptation by reducing any residual fatigue and allowing supercompensation (Turner, 2011). This may also help with the implementation of progressive overload models, as the body can successfully adapt and recover from the previous training period before an increase in load or volume is prescribed (Khushhal *et al.*, 2020).

In most cases, the positive effects of exercise are only achieved if the recommended prescription is strictly adhered to (i.e. sufficient exercise stimulus as a result of appropriate intensity and volume) (Collado-Mateo *et al.*, 2021). However, as outlined in Chapter 1, there is evidence to suggest the training dose can be reduced once adaptations have been achieved. Several studies that have utilised a reduced training volume or frequency during a follow-up period of training have been shown maintain VO_2max (Hickson and Rosenkoetter 1981; Brynteson and Sinning 1973), maximal isometric strength (Tucci *et al.*, 1992), maximal dynamic strength (Bickel, Cross and Bamman, 2011; Rønnestad, Nymark and Raastad, 2011; Tavares *et al.*, 2017; Walker, Serrano and van Roie, 2018) and muscular size (Trappe, Williamson and Godard, 2002; Bickel, Cross and Bamman, 2011; Tavares *et al.*, 2017). However, there is limited research to establish if this is also relevant to BP reductions following IET. The only current study is from Cohen *et al.*, (2023) who found that BP reductions could be maintained with just one session per week, indicating that if the intensity of exercise is continued, BP reductions can be maintained with a reduced training frequency. However, as outlined in Chapter 1 (section 1:9:2), there are some inherent limitations with the study design. Furthermore, a comparative detraining control group was also not used, and no other cardiovascular variables were measured.

Therefore, the aim of this study was to investigate the minimal training dose needed to maintain BP reductions and cardiovascular adaptations following IWS training. Based on the findings outlined above, the study investigated the minimal training dose in relation to a reduced training frequency.

6.2. Method

6.2.1. Participants

One hundred and eighteen sedentary males and females with a resting sBP between 120-140 mmHg were recruited for the study. Full details of the participant cohort can be seen in Chapter 2 (section 2.2).

6.2.2. Sample size estimation

To ensure the research was adequately powered, G*Power sample size calculations were used. Using G*Power calculations, based upon a sample size of 100 participants, a significance level of 0.05, a power of 0.80, 5 groups and 1 covariate (baseline BP), the current study was powered to detect a small to moderate effect size (f = 0.35). Full details can be seen in Chapter 2 (section 2.2.1).

6.2.3. Recruitment

Recruitment was staggered in groups of 10 participants from July 2020 – September 2023. There were 18 dropouts (six due to voluntary dropouts, seven due to COVID-19, and five non-compliant), so a total of 118 participants were recruited in total (see Chapter 2*,* Figure 2*:*2). The recruitment process for the collated data set is described in detail in Chapter 2 (section 2.2.2).

6.2.4. Equipment

Laboratory-based equipment

Haemodynamic and cardiac autonomic assessment: All haemodynamic and cardiac autonomic variables in this study were measured using the TFM. Full details of the TFM can be found in Chapter 2 (section 2.4.1).

Wall squat knee joint angle: Knee joint angle was measured during exercise using a clinical goniometer. For further details see Chapter 2 (section 2.10.4).

Rate of perceived effort (RPE): The Borg CR10 scale was used to measure and rate effort felt in the participant's upper legs during exercise in the laboratory and at home. For further details see Chapter 2 (section 2.10.10).

Home-based equipment

Home-based BP device: During the second 4-week period of training, participants were required to self-measure BP in the home using the A&D UA-1020-W HBPM device. Full details of the A&D device can be seen in Chapter 2 (section 2.7).

Heart rate: In order to measure HR during home-based IWS training, participants wore a wrist-worn HR monitor and a Polar H10 HR chest strap. Full details of the home-based HR equipment can be seen in Chapter 2 (section 2.10.8).

Wall squat knee joint angle: During home-based IWS exercise sessions, the knee joint angle was established by using a Bend and Squat devise which can be used to recreate a target knee-joint angle. The device can be precisely adjusted so each participant can easily position their foot and back placement in order to reproduce the desired knee angle. Full detail on the knee joint angle can be seen in Chapter 2 (section 2.10.4).

Training manual: During home-based IWS training, participants also received a training manual which outlined the specific protocol for home-based IWS training, as well as guidance on how to use the equipment given. The training manual also included data sheets to input HR and RPE data from their training sessions and HBPM readings taken during the second 4-week period.

6.2.5. Procedures

Familiarisation

During the familiarisation session participants were given a full overview of the study protocols and familiarised with all equipment used within the study. Full details of the familiarisation session can be seen in Chapter 2 (section 2.2.3).

Overall study design

Once participants were enrolled to the study, they were randomised into 1 of 5 groups: 3x per-week group (n=23), 2x per-week group (n=22), 1x per-week group (n=25), 0x per-week/detraining group (n=26), or control (n=22) (see Chapter 2, section 2.3, Figure 2.2). Due to the high incidence and homogeneity of BP reductions typically seen following IWS training (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023) it was not deemed necessary to allocate groups based on the magnitude of BP reductions following the first 4 weeks of training. As such, the randomisation was carried out before baseline BP measures were taken to avoid any recruitment bias.

Training condition

All experimental participants were required to undertake an incremental IWS test to determine the knee joint angle used during training (see Chapter 2, section 2.10.3). The knee joint angle was

established to elicit a training intensity of 95% HR_{peak} during home-based sessions. Following baseline resting measurements, all experimental participants then carried out an initial 4-week home-based IWS training programme. Training was carried out three times per week over the 4-week period, with 48 hours between each session. Each training session comprised of 4 bouts of IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest. Following the first 4-week training period, participants were required to attend the laboratory for mid-training resting measures. The experimental participants were then informed of their new training frequency for the second 4-week period (3x per week, 2x per week, 1x per week or 0x per week/detraining). No information was given to the participants regarding any potential benefits or detrimental effects that may occur from their new training prescription (e.g. your BP may increase again if your training frequency decreases) to avoid any possible placebo or nocebo effects (Hurst *et al.*, 2020).

Participants began their second 4-week training period the day directly following their mid-point laboratory visit. Despite the changes in training frequency, all groups still performed IWS exercise at 95% HR_{peak}, separated by 2 minutes of seated rest, with 48 hours between each session. During the second 4-week training period, each participant was required to self-monitor their BP at home using a HBPM device. Readings were taken in the morning and evening for the full 4-week period. Following the full 8-week period, participants were again required to attend the laboratory for post-training resting measures. To monitor the home-based training, participants were required to self-report their HR during each IWS exercise session. To check compliance with exercise protocol and individualised training zone prescribed over the training period, HR data was downloaded from the HR watch at the end of the study. During the first 4-week period, the compliance threshold was 10 out of 12 sessions. During the second 4-week period, compliance to all IWS sessions in all groups was required due to the need for accurate comparisons between the training frequencies. If participants were withdrawn, they were encouraged to carry on with the IWS training, although their data was not used for analysis. Full details of the IWS training protocol can be found in Chapter 2 (section 2.10).

Control condition

During the control condition, participants were requested to maintain their habitual dietary and physical activity daily routines for an 8-week period. Adherence to these conditions was verbally confirmed during each laboratory session. During the first 4-week period participants did not visit the laboratory and no additional measures were taken until the laboratory visit at week 4. During the second 4-week period, participants were required to self-monitor their BP in the home using a HBPM device.

6.2.6. Resting measures

Laboratory-based measures

Both experimental and control participants were required to attend the laboratory for resting cardiovascular measures. Resting haemodynamic and cardiac autonomic measures were taken at baseline, mid-training (week 4) and post-training (week 8). Post-training resting measures were taken 72 hours after the final bout exercise at week 4 and week 8 (Wiles *et al.*, 2008) to avoid any transient effects which may persist post-exercise (Kenney and Seals 1993). Before attending the laboratory, participants were asked to avoid any food for 2 hours, caffeine for 4 hours, and alcohol for 12 hours pretesting (James, Leidy Sievert and Flanagan, 2004; Rezk *et al.*, 2006). Upon arrival at the laboratory, participants rested in a seated position for 15 minutes. Following the seated rest, sBP, dBP, MAP, $\dot{Q}$, SV, TPR, BRS, LF, HF, LFnu, HFnu, and PSD-RRI were measured continuously for 5 minutes in the seated position using the TFM. After this time, the mean values for each variable were calculated offline for the 5-minute period. A number of measures were indexed to BSA. Full details of the protocol to obtain resting measures can be seen in Chapter 2 (section 2.4).

Home-based blood pressure monitoring

Home-based blood pressure monitoring was used to explore the trend of BP alterations throughout second 4-week training period. Based on ESH guidelines (Mancia *et al.*, 2023) two BP readings were taken in the morning (within 2 hours of waking) and two in the evening (within 2 hours of sleeping) for each day that home-based BP monitoring was required. The mean BP values for each week was used for analysis. Full details of the HBPM protocol can be found in Chapter 2 (section 2.7).

6.2.7. Data analysis

All data were checked for normality and homogeneity of variances (Field, 2013). Where the parametric assumptions were met, a one-way analysis of covariance (ANCOVA) was carried out to explore the possible differences in each dependent variable, using baseline measures as the covariate. If the ANCOVA was statistically significant, a least significant difference (LSD) post-hoc test was used to explore any differences detected between the experimental and control groups at the 8-week mark. For analysis at the 4-week time point, an ANCOVA was used with all experimental data collated (n=80) compared against the control group (n=20) (as seen in Chapter 3). An ANCOVA was selected to maintain statistical power and reduce the probability of a type II error. Where data were not normally distributed, a Quade non-parametric ANCOVA was used which rank transforms the data to achieve a normal distribution pattern. For all tests, an alpha level of <0.05 was set as the

threshold for statistical significance. Data analysis was performed with IBM SPSS (BM SPSS Statistics for Windows, version 19.0, Armonk, NY: IBM Corporation).

6.3. Results

100 participants (M=55: F=45) completed the study (36 ± 11 years; 79 ± 14 kg; 173 ± 9 cm). During the first 4-week period, 77 out of 80 experimental participants completed all 12 training sessions. Of the remaining 3, each missed 1 session, and so completed 11 training sessions over the 4-week period. During the second 4-week period (weeks 4 to 8), all prescribed IWS sessions were adhered to for all groups. Resting haemodynamic and cardiac autonomic data were obtained from all experimental and control participants during the laboratory visits at baseline, week 4 and week 8.

Table 6:1 Participant demographics for all experimental and control groups

Variable	Control	0x per week	1x per week	2x per week	3x per week
Sex (M:F)	12:8	11:9	10:10	11:9	11:9
Age	34 ± 7	40 ± 9	40 ± 13	38 ± 10	35 ± 13
Body mass	74 ± 12	78 ± 9	82 ± 16	80 ± 11	83 ± 15
Height	174 ± 8	172 ± 10	173 ± 8	175 ± 10	175 ± 10

Mean values and SD for age (years), body mass (kg), and height (cm). The ratio of male and female (M:F) participants for each group are also presented.

6.3.1. Resting blood pressure

Following 4 weeks of IWS training there were significant reductions in sBP (-9.45 ± 6.69 mmHg) which was significantly different to the control group ($F(1,97) = 27.338$, $p<0.001$). Resting dBP was also reduced following IWS training (-5.62 ± 9.92 mmHg) and was significantly different to the control group ($F(1,98) = 7.719$, $p= 0.007$). Reductions in MAP (-6.90 ± 7.77 mmHg) were also significantly different from the control group following IWS training ($F(1,98) = 14.935$, $p <0.001$).

Following the 8-week training period there was a significant group effect for sBP ($F(4,95) = 12.478$, $p<0.001$), and MAP ($F(4,95) = 5.517$, $p<0.001$). Pairwise comparisons indicated that for sBP, the 3x ($p<0.001$), 2x ($p<0.001$), and 1x ($p=0.003$) per-week groups were significantly different from the control group at the 8-week time point. MAP also followed a similar pattern, with significant differences to the control in the 3x ($p<0.001$), 2x ($p=0.013$), and 1x ($p=0.027$) per-week group. There

was no main group effect for dBP (F(4,95) = 2.345, p=0.06). Mean values for sBP, dBP and MAP can be seen in Table 6:1.

Further between-group analysis was carried out for sBP and MAP at week 8. It was demonstrated that for sBP the 3x per-week group was significantly different compared to the 2x (p=0.003) and 1x (p<0.001) per-week group. However, there were no significant differences between the 2x and 1x per-week group for sBP (p=0.629). For MAP, there was a significant difference between the 3x and 1x (p=0.045) per-week group, but not the 3x and 2x (p=0.086) per-week group. There was also no significant difference between the 2x and 1x per-week group for MAP (p=0.766) (Figure 6:1).

6.3.2. Resting cardiac output, total peripheral resistance, heart rate and stroke volume

Following 4 weeks of IWS training there were reductions in TPR (-168.93 ± 372.8 dyne·s·cm^5) and TPRi (-87.73 ± 191.50 dyne·s·m^2·cm^5) which were significantly different to the control group (F(1,97) = 7.475, p=0.007, F(1,97) = 9.649, p=0.002, respectively). However, there were no significant differences in resting HR (-2.59 ± 10.59 beats·min^{-1}, F(1,98) = 0.22, p=0.64)) $\dot{Q}$ (0.29 ± 1.59 L·min^{-1}, F(1,98) = 2.65, p=0.11), $\dot{Q}i$ (-0.15 ± 0.83 L·min^{-1}·m^2, F(1,98) = 2.65, p=0.11), SV (-0.41 ± 21.89 mL, F(1,98) = 3.26, p=0.57) or Si (-0.24 ± 11.29 mL·m^2, F(1,97) = 1.01, p=0.32) compared to the control group.

Following 8 weeks of training there was a significant group effect for TPR (F(4,95) = 2.921, p=0.025), and TPRi (F(4,95) = 3.639, p=0.008). Pairwise comparisons indicated that for TPR at the 8-week time point only the 3x (p=0.013) per-week group was significantly different from the control group. For TPRi there were significant differences to the control in the 3x (p=0.003) and 2x (p=0.039) per-week group. There were no significant main group effects for HR (F(4,95) = 0.476, p=0.753), $\dot{Q}$ (F(4,95) = 1.012, p=0.405), $\dot{Q}i$ (F(4,95) = 0.575, p=0.681), SV (F(4,95) = 1.209, p=0.312) or Si (F(4,95) = 1.063, p=0.379). Mean values for TPR, HR, $\dot{Q}$, and SV can be seen in Table 6.2.

6.3.3. Resting heart rate variability and baroreceptor sensitivity

Following the 4-week time point there was an increase in PSD-RRI (917.19 ± 1645.28 ms^2), which was significantly different to the control group (F(1,98) = 5.19, p=0.025). There was an increase in HF components (576.13 ± 1115.38 ms^2) following IWS training which was significantly different to the control group (F(1,98) = 8.04, p=0.006). Although there was a slight increase in LF components (233.28 ± 1093.94 ms^2), it was not significantly different from the control group (F(1,98) = 0.53, p=0.47). As a consequence of these cardiac autonomic responses, there was a reduction in the LF:HF

ratio (-1.11 ± 2.21), which was significantly lower than the control group following training ($F(1,98) = 11.99$, $p<0.001$). There was also an increase in HFnu (10.65 ± 20.38%) accompanied by a reciprocal decrease in LFnu (-10.65 ± 20.38%) which were both significantly different to the control group following IWS training ($F(1,97) = 4.68$, $p=0.03$ and $F(1,97) = 4.68$, $p=0.03$, respectively). In addition, there was an increase in BRS (9.38 ± 12.19 ms·mmHg) which was significantly different from the control group following training ($F(1,98) = 4.96$, $p=0.028$).

Following the 8-week training period, LFnu ($F(4,95) = 2.688$, $p=0.036$), HFnu ($F(4,95) = 2.688$, $p=0.036$), LF ($F(4,95) = 3.977$, $p=0.005$), HF ($F(4,95) = 9.436$, $p<0.001$), LF:HF ($F(4,95) = 3.715$, $p=0.007$), PSD-RRI ($F(4,95) = 3.276$, $p=0.015$) and BRS ($F(4,95) = 5.282$, $p<0.001$) all had main group effects. Pairwise comparisons indicated that for LFnu ($p=0.004$), HFnu ($p=0.004$), LF ($p=0.046$), HF ($p<0.001$), LF:HF ($p<0.001$), PSD-RRI ($p=0.009$) and BRS ($p=0.023$) only the 3x per-week group was significantly different from the control group at week 8. Mean values for LFnu, HFnu, LF, HF, LF:HF, PSD-RRI and BRS can be seen in Table 6:3.

Table 6:2 Mean values for systolic, diastolic and mean blood pressure in each training group

Group		Baseline (mmHg)	Week 4 (mmHg)	Week 8 (mmHg)
3x p/week	sBP	131.20 ± 5.74	122.37 ± 7.77**	117.47 ± 6.39**
	dBP	84.39 ± 8.45	79.64 ± 6.71*	76.17 ± 10.04
	MAP	100.0 ± 6.61	93.88 ± 6.57**	89.94 ± 8.25**
2x p/week	sBP	129.44 ± 6.53	118.84 ± 7.36**	122.49 ± 7.48**
	dBP	84.02 ± 10.91	76.56 ± 10.42*	79.78 ± 8.96
	MAP	99.16 ± 8.62	90.65 ± 9.09**	94.02 ± 8.04*
1x p/week	sBP	129.89 ± 5.25	118.94 ± 5.25**	123.34 ± 7.19*
	dBP	84.96 ± 9.23	79.11 ± 8.47*	80.80 ± 8.24
	MAP	99.94 ± 6.94	92.39 ± 6.56**	94.98 ± 7.15*
0x p/week	sBP	131.53 ± 5.70	124.13 ± 7.36**	127.66 ± 4.40
	dBP	83.23 ± 8.75	79.42 ± 8.10*	82.75 ± 7.53
	MAP	99.33 ± 6.37	94.32 ± 6.62**	97.72 ± 4.44
Control	sBP	127.77 ± 5.99	126.98 ± 6.0	128.59 ± 6.27
	dBP	80.91 ± 10.08	83.10 ± 8.25	82.80 ± 9.91
	MAP	96.53 ± 7.56	97.73 ± 5.60	98.06 ± 6.89

Mean values and SD for resting systolic (sBP), diastolic (dBP) and mean arterial (MAP) blood pressure at baseline, week 4 and week 8 in the training and control conditions. The training frequencies outlined within this table are specific to the second 4-week training period. All training groups completed three sessions per week during the first 4-week period. * P<0.05 and *<0.001 for difference to control conditions.

Table 6:3 Mean values for total peripheral resistance, heart rate, cardiac output, and stroke volume

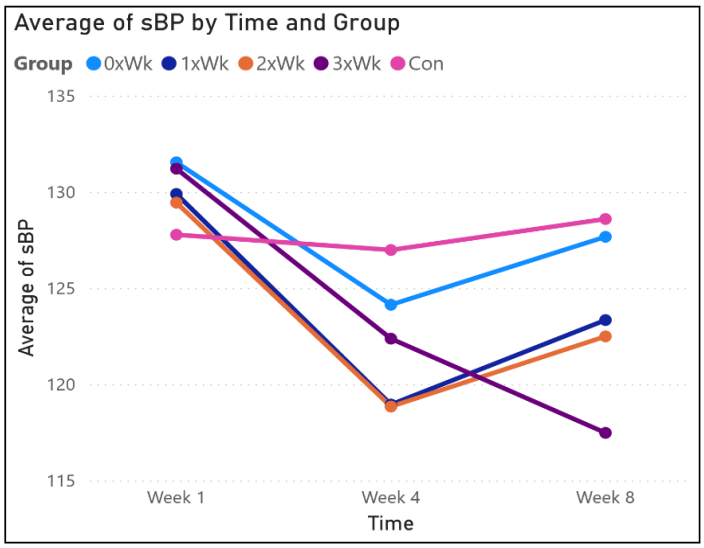
Group		Baseline	Week 4	Week 8
3x p/week	HR	72.47 ± 6.15	70.02 ± 9.73	69.65 ± 10.30
	TPR	1462.82 ± 428.99	1356.57 ± 386.75*	1264.78 ± 362.79*
	TPRi	741.63 ± 216.98	693.84 ± 210.83*	642.16 ± 196.10*
	SV	83.25 ± 22.46	83.52 ± 14.77	87.07 ± 13.76
	Si	42.86 ± 13.81	42.74 ± 10.02	44.56 ± 9.58
	Q̇	5.98 ± 1.48	5.79 ± 1.0	6.03 ± 1.12
	Q̇i	3.07 ± 0.92	2.95 ± 0.63	3.16 ± 1.01
2x p/week	HR	71.64 ± 10.41	68.67 ± 9.10	69.73 ± 11.68
	TPR	1406.26 ± 556.82	1287.89 ± 363.13*	1319.32 ± 470.66
	TPRi	732.25 ± 306.83	666.88 ± 196.98*	691.30 ± 278.73*
	SV	85.04 ± 19.82	83.58 ± 23.29	85.87 ± 33.88
	Si	43.78 ± 9.32	43.18 ± 11.54	43.99 ± 15.85
	Q̇	6.15 ± 1.90	5.67 ± 1.37	5.90 ± 2.34
	Q̇i	3.17 ± 0.95	2.95 ± 0.77	3.04 ± 1.17
1x p/week	HR	76.63 ± 11.15	74.03 ± 12.70	74.22 ± 11.58
	TPR	1383.51 ± 445.53	1229.65 ± 400.62*	1453.62 ± 445.01
	TPRi	710.49 ± 212.44	632.40 ± 206.78*	744.21 ± 214.62
	SV	76.0 ± 16.47	76.31 ± 20.25	72.19 ± 22.22
	Si	39.53 ± 9.81	39.56 ± 10.79	37.79 ± 13.24
	Q̇	5.84 ± 1.74	5.55 ± 1.44	5.39 ± 2.01
	Q̇i	3.03 ± 0.93	2.87 ± 0.76	2.83 ± 1.19
0x p/week	HR	71.78 ± 10.92	69.45 ± 9.86	70.19 ± 8.10
	TPR	1519.87 ± 370.37	1222.63 ± 393.70*	1709.36 ± 468.66
	TPRi	808.68 ± 276.49	649.02 ± 256.14*	905.14 ± 316.23
	SV	79.70 ± 25.74	78.96 ± 13.78	79.52 ± 22.23
	Si	42.20 ± 15.84	41.91 ± 11.95	42.11 ± 14.83
	Q̇	5.64 ± 1.62	5.46 ± 1.12	5.54 ± 1.53
	Q̇i	2.98 ± 0.96	2.89 ± 0.80	2.93 ± 0.97
Control	HR	68.28 ± 10.83	67.93 ± 6.76	69.50 ± 9.03
	TPR	1420.38 ± 533.74	1475.98 ± 439.61	1546.68 ± 428.31
	TPRi	771.69 ± 330.44	803.46 ± 283.72	827.80 ± 244.60
	SV	81.22 ± 18.91	84.15 ± 23.93	78.73 ± 22.48
	Si	43.30 ± 9.88	44.69 ± 11.81	42.32 ± 13.59
	Q̇	5.50 ± 1.36	5.69 ± 1.69	5.50 ± 1.87
	Q̇i	2.94 ± 0.77	3.03 ± 0.86	2.96 ± 1.12

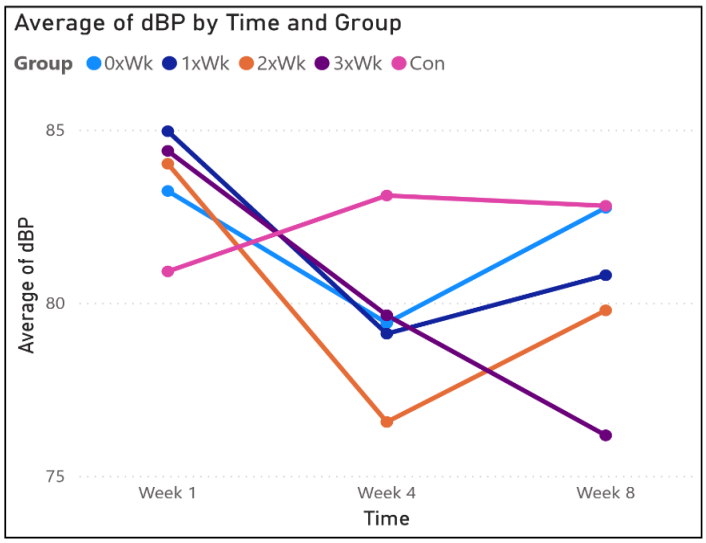
Mean values and SD for resting heart rate (HR bpm), total peripheral resistance (TPR dyne/s/cm^5), TPR index (TPRi dyne/s/m^2/cm^5), cardiac output (Q̇ l/min), cardiac output index (Q̇I l/min per m^2), stroke volume (SV ml) and SV index (SI ml/m^2) before, during and after the training and control conditions.* P<0.05 for difference between experimental and control conditions.

Table 6:4 Mean values for heart rate variability and baroreceptor sensitivity

Group		Baseline	Week 4	Week 8
3x p/week	Lfnu	71.70 ± 13.95	50.07 ± 17.32*	55.12 ± 15.97*
	Hfnu	28.30 ± 13.95	41.93 ± 17.32*	44.88 ± 15.97*
	LF	811.05 ± 462.45	1111.31 ± 749.41	1310.99 ± 760.66*
	HF	452.28 ± 450.49	820.92 ± 541.10*	1199.76 ± 711.93**
	LF:HF	3.11 ± 2.48	1.73 ± 1.52**	1.61 ± 1.62**
	PSD	1840.56 ± 820.60	2876.11 ± 816.75*	3085.37 ± 1895.59*
	BRS	11.84 ± 5.57	19.04 ± 14.17*	21.39 ± 11.42*
2x p/week	Lfnu	59.22 ± 16.70	50.22 ± 18.89*	62.14 ± 17.32
	Hfnu	40.78 ± 16.70	49.78 ± 18.89*	37.86 ± 17.32
	LF	1441.14 ± 1477.21	1644.95 ± 1818.83	1015.12 ± 735.85
	HF	707.13 ± 519.06	1378.63 ± 1549.82*	734.97 ± 1160.88
	LF:HF	2.24 ± 1.63	1.56 ± 1.0**	2.66 ± 2.08
	PSD	2732.86 ± 1704.76	3237.52 ± 1987.43*	2493.23 ± 1892.44
	BRS	14.27 ± 5.41	26.95 ± 9.71*	18.67 ± 9.57
1x p/week	Lfnu	67.17 ± 17.19	57.11 ± 16.71*	65.29 ± 14.14
	Hfnu	32.83 ± 17.19	42.89 ± 16.71*	34.71 ± 14.14
	LF	764.01 ± 589.80	857.70 ± 873.40	557.33 ± 393.12
	HF	388.34 ± 410.01	780.20 ± 795.26*	387.51 ± 451.17
	LF:HF	2.70 ± 1.36	2.0 ± 2.06**	2.41 ± 1.57
	PSD	1583.79 ± 965.43	2281.32 ± 1392.42*	1410.40 ± 971.69
	BRS	11.48 ± 5.99	20.70 ± 12.38*	12.69 ± 8.57
0x p/week	Lfnu	68.96 ± 15.78	59.08 ± 16.16*	66.37 ± 14.0
	Hfnu	31.04 ± 15.78	40.92 ± 16.16*	33.63 ± 14.0
	LF	1123.34 ± 771.58	1458.70 ± 961.24	893.61 ± 643.33
	HF	533.97 ± 526.40	1406.50 ± 1486.90*	396.76 ± 325.38
	LF:HF	3.35 ± 2.28	1.68 ± 0.99**	2.88 ± 1.89
	PSD	2122.70 ± 1392.0	3553.72 ± 2153.31*	1839.13 ± 1138.11
	BRS	13.07 ± 7.64	21.50 ± 13.07*	11.77 ± 7.49
Control	Lfnu	71.15 ± 14.11	66.84 ± 17.29	68.74 ± 16.75
	Hfnu	28.85 ± 14.11	33.16 ± 17.29	31.26 ± 16.75
	LF	944.40 ± 700.55	1040.12 ± 800.78	1196.18 ± 1190.88
	HF	597.77 ± 662.89	537.82 ± 605.90	571.42 ± 756.40
	LF:HF	2.84 ± 2.35	3.17 ± 2.37	3.23 ± 2.11
	PSD	2080.82 ± 1674.91	2049.28 ± 1296.02	1909.39 ± 1527.04
	BRS	13.48 ± 8.83	15.74 ± 5.71	13.12 ± 3.38

Mean values and SD for low frequency normalised units (LFnu %), high frequency normalised units (HFnu %), low frequency (LF ms^2), high frequency (HF ms^2), low/high frequency ratio (LF:HF), power spectral density (PSD–RRI ms^2) and baroreceptor reflex sensitivity (BRS ms/mmHg).* P<0.05 and **P<0.001 for difference between experimental and control conditions.





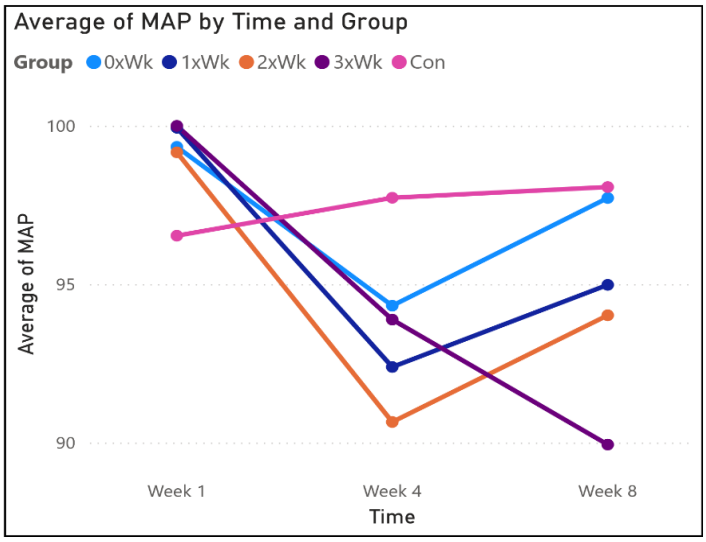


Figure 6:1 The sBP, dBP and MAP changes over the 8-week training period for each intervention group (3x per week, 2x per week, 1x per week, and 0x per week) and the control group.

6.4. Discussion

The aim of this final study was to investigate the minimum training frequency required to maintain BP reductions following IWS training. It was found that the sBP and MAP reductions observed after 4 weeks of standard IWS training were maintained for a further 4 weeks with only one IWS exercise session per week (4 x 2 minutes, 95% HR_{peak}). These findings support previous research from Cohen *et al.,* (2023) who also reported (despite the prescription inconsistencies and confounding factors previously identified) that sBP reductions were maintained following a 12-week IWS training period with one IWS session per week for 12 weeks. As previously outlined, one of the main benefits of a reduced training frequency during a follow-up period of training relates to mitigating against the most commonly cited barrier to exercise participation, a lack of time (Zunft *et al*., 1999; Alsobayel *et al.*, 2020). Many individuals report they do not have the time to exercise, which can lead to poor adherence and high attrition within exercise training programmes (Cunningham *et al.*, 2020). As such, the findings from the current study may help to further improve the time-efficiency of IWS training. Being able to reduce the IWS session frequency after the first month to just one session per week would likely increase the appeal of IWS training and make it an even more attractive and accessible intervention to reduce sBP.

The maintenance of the sBP reductions in the current study is likely related to the continuation of the original training intensity. As discussed in Chapter 1, evidence from the broad exercise training literature suggests that physiological adaptations can be maintained with a reduced training frequency and volume if there are no changes in the exercise intensity. However, it should be noted that participants in the Cohen *et al*., (2023) study performed IWS exercise at a 95° angle during the follow-up period which they were only exposed to for the last 2 weeks of the initial training period. Therefore, it could be argued the intensity during the detraining period was comparatively greater than the average intensity during the initial training period. The study did not report HR or RPE data during the IWS sessions in the follow-up period of training, but performing 4 x 2-minute bouts at a 95° angle would have likely caused a high HR response and high levels of fatigue (Goldring, Wiles and Coleman, 2014). Exercise adherence literature indicates that activities of higher intensities are less tolerable to the average individual than exercise at lower intensities (Dishman & Ickes, 1981). Although increased exercise intensity has been connected to larger improvements in health, fitness and increased longevity (Lee and Paffenbarger, 2000; Duncan *et al.*, 2005; Schnohr, Scharling and Jensen, 2007), research has shown that higher intensities are potentially related to poorer adherence (Dishman, 2020; Sallis & Owen, 1999). While participants in the Cohen *et al*., (2023) study were reported to have 100% adherence to the training programme, this was likely due to the

training being conducted in the workplace and under supervision. Comparatively, the current study continued the training prescription (95% HR_{peak}) that was used throughout the original training period, which was based upon relative exercise intensity (rather than an absolute knee angle of 95°) and thus avoided any exposure to excessive exercise intensities. During the follow-up period of training, HR and RPE were both monitored to ensure the intensity was maintained within the individual's calculated THRR and exertion levels were safe.

Another potential limitation to the findings by Cohen *et al.,* (2023) is that the study does not outline the physical activity level of the participants prior to testing (inclusion/exclusion criteria) or during the detraining period (continuation of pre-testing physical activity levels). The absence of physical activity monitoring throughout the detraining period means that participants may have engaged in further exercise which could have contributed to the sustained sBP reductions seen. This would then obscure whether the single weekly session alone was responsible for maintaining the BP reductions seen. It should also be highlighted that the study did not use a comparative detraining group, and so it is not known if the reductions could have also been maintained even with a complete cessation of exercise. As such, the maintenance of BP reductions in the current study are further validated using a comparative detraining group which demonstrated a reversal of BP reductions during the detraining period (as described in Chapter 5). This adds confidence to the findings and indicates that a minimum of one session per week is needed to maintain the reductions. Unlike Cohen *et al.,* (2023), the current study was also unsupervised and home-based, which is an important aspect of this research. In order to scale and implement IWS training to the wider population, home-based approaches need to be established in order to improve accessibility. As such, this is the first unsupervised study to demonstrate sBP reductions can be maintained during a follow-up period of training with a reduced training frequency.

The current study also used a shorter period of training and shorter maintenance period compared to Cohen *et al.,* (2023). Following a longer 12-week maintenance period, Cohen *et al.,* (2023) reported a slight further (not statistically significant) reduction in sBP (-1.8 mmHg). Conversely, the current study demonstrated a slight reversal (not statistically significant) in sBP over the shorter 4-week maintenance period (4.4 mmHg). Although there are potential concerns with the reporting of physical activity levels and the exercise intensity used in the follow-up period from Cohen *et al*., (2023), the greater maintenance of sBP reductions may be related to the longer initial period of training. As previously discussed in Chapter 5, longer periods of training lead to a slower reversal of BP reductions during a detraining period, potentially due to the occurrence of structural adaptation within the vasculature (Tinken *et al.*, 2008; 2010). As such, although only speculative, the greater maintenance of sBP reductions seen by Cohen *et al.,* (2023) may be related to the duration of

training and subsequent vascular adaptation. However, it may be related to the higher baseline BP values used in the Cohen *et al.,* (2023) study (141/87 mmHg), which has also been shown to affect the rate of BP reversal during a detraining period (Chapter 1, section 1.5).

Although sBP reductions were maintained with one session per week in the current study, there were no main effects between groups for dBP at the 8-week time point. This may indicate that one and two sessions per week did not produce statistically significant changes in dBP compared to the control group. However, as seen in Chapter 4, 8 weeks of IWS training with the continuation of three sessions per week was able to produce significant reductions in dBP compared to a control group. Although only speculative, this may suggest dBP reductions are more easily reversed and need a higher training frequency to maintain the level of reduction. Indeed, dBP reductions are not always seen following IET, or the reductions have a smaller magnitude than sBP reductions in dBP (Howden *et al.*, 2002; Taylor *et al.*, 2003; Peters *et al.*, 2006; McGowan, Levy, *et al.*, 2007; McGowan, Visocchi, *et al.*, 2007; Stiller-Moldovan, Kenno and McGowan, 2012; Baross, Wiles and Swaine, 2012; Badrov, Bartol, *et al.*, 2013, 2013; Millar *et al.*, 2013; Loaiza-Betancur and Chulvi-Medrano, 2020; Palmeira *et al.*, 2021; Kelley, Kelley and Stauffer, 2021; Cohen *et al.*, 2023) and so may need a greater stimulus to be maintained during a follow-up period of training. However, it is well-established that sBP is a more significant predictor of cardiovascular events (Whelton *et al.*, 2018), and so the lack of significant changes in dBP may be less clinically concerning.

Understanding the differences in the maintenance of sBP and dBP may be useful when planning and implementing training programmes. While anti-hypertensive interventions should ideally aim to reduce both sBP and dBP to within healthy ranges for improved cardiovascular health (Luo *et al.*, 2020), there may be specific cases where BP lowering targets are focused on either sBP or dBP in the context of a patient's age and overall cardiovascular risk profile. Research has shown that sBP is a more predictive of cardiovascular events and mortality, particularly in older adults who typically have increased arterial stiffness (Li *et al.*, 2014). Therefore, for some older individuals who may have a greater need to reduce sBP, reducing the frequency to 1x per week may be sufficient, particularly if the individual has a greater proclivity to drop out of an exercise training programme. However, elevated dBP can also be a significant predictor of cardiovascular events, particularly in younger individuals (<50 years) who have been shown to have a higher prevalence of isolated diastolic hypertension (McEvoy *et al.*, 2020). Therefore, special attention may need to be given to this population and the continuation of three sessions per week may be recommended. These findings potentially 'give options' to clinicians and practitioners and should help with the individualisation of training prescriptions. Although a greater reduction in cardiovascular risk factors is likely to be seen with the maintenance of both sBP and dBP reductions (Luo *et al.*, 2020), this should be taken into

context with patient-specific factors, such as age and cardiovascular risk profile, as well as personality types (i.e. those who may have a greater proclivity to drop out of training).

Another important aspect of the current data set is the analysis of between-group comparisons for BP measures at week 8. The data indicates that sBP reductions were statistically significantly greater in the 3x per-week group compared to the 2x and 1x per-week groups. However, no significant differences were found between the 2x and 1x per-week groups. When observing the change scores from baseline, the greatest reductions in sBP at week 8 were seen in the 3x per-week group, with a mean group reduction of -13.73 mmHg, compared to -6.95 mmHg in the 2x per-week group, -6.56 mmHg in the 1x per-week group, and -3.87 mmHg in the 0x per-week group. Moreover, when looking at the trend of sBP reductions, only the 3x per-week group showed a further reduction from week 4 to week 8 (-4.9 mmHg) compared to the small reversal in the 2x (3.65 mmHg) and 1x (4.37 mmHg) per-week groups. The 3x per-week group also had a higher occurrence of a CID 5 mmHg drop in sBP (95%), compared to the 2x (65%), 1x (65%) and 0x (45%) per-week groups, demonstrating greater cardioprotective effects (as discussed in Chapter 4). Overall, these findings highlight the greater benefits that can be seen with the continuation of a 3x per week training frequency but also demonstrate that for sBP, there are minimal differences in the benefits seen with either one or two sessions per week.

6.4.1. Physiological mechanisms

The current study also aimed to investigate the associative haemodynamic and cardiac autonomic variables during the follow-up period of training. The measurement of these variables was used to help in the understanding of the physiological responses underpinning the maintenance of BP reductions. It was found that at week 8 in the 3x per-week group there were significant differences to the control group in all HRV measures and BRS (Table 6:2), as well as TPRi (Table 6:3). Conversely, within the 2x per-week group only TPRi was maintained. All other resting measures at week 8 were not significantly different from the control group in the 2x or 1x per-week group, demonstrating a complete reversal of the associative cardiovascular adaptations underpinning the BP adaptations at week 4.

These findings highlight the temporary nature of the associated cardiovascular variables following a short 4-week training period. The complete reversal of all variables in the 1x per-week group demonstrates that this level of frequency is not sufficient to promote or maintain cardiovascular adaptation. As any reductions in BP are related to either TPR or $\dot{Q}$, the lack of cardiovascular adaptation may help to explain why despite significant differences to the control group at week 8,

there was a trend for BP reversal with the 1x per-week group. Although the sBP and MAP reductions were maintained in this group, due to the lack of wider cardiovascular adaptation it is likely that there is limited capacity for the BP reductions to be maintained for longer than 4 weeks. In the 2x per-week group there were significant reductions in TPRi compared to the control group during the follow-up period of training, potentially demonstrating that the higher level of training frequency is more optimal for vascular adaptation. Although only speculative, the maintenance of TPR may suggest sBP reductions could be maintained for a longer period of time in the 2x per week group.

The 3x per-week group was able to maintain adaptations in TPRi, BRS and all HRV parameters. The greater reduction in BP in this group is likely related to the maintenance and/or further changes in these cardiovascular parameters (as discussed in Chapter 4). Importantly, these findings show that a higher training frequency is needed to maintain most of the associated cardiovascular adaptations thought to underpin the BP reductions observed following 4 weeks of IWS training. Furthermore, an augmented HRV status, as seen in the 3x per-week group, provides further cardiovascular and health benefits independently of the reductions in resting BP (Taylor *et al*., 2019).

The reversal of cardiovascular adaptation in the 2x and 1x per-week groups alongside the trend of a reversal in BP suggests that continued intervention at 3x per week will likely be needed at some point to ensure BP reductions are maintained over extended periods (>8 weeks). However, an important caveat to this is that these responses are following a short 4-week training period. As previously outlined, following a longer 12-week training period, Cohen *et al.,* (2023) demonstrated a slight (although not statistically significant) further reduction in sBP following a 12-week maintenance period. This may suggest that the associated adaptations were also maintained, or potentially augmented, which may be related to the extended period of initial training and possible structural vascular adaptations (Tinken *et al.*, 2008; 2010). However, as previously outlined, there were some potential limitations with the study design from Cohen *et al.,* (2023), including a lack of reporting on the physical activity levels of participants throughout the study, which may have influenced these results.

6.4.2. Conclusion

Findings from this study have demonstrated that sBP and MAP reductions can be maintained with just one IWS session per week over a subsequent 4-week period. However, the same level of maintenance was not seen for dBP, suggesting that more frequent sessions are most likely required to sustain reductions in dBP. The analysis of TPRi in the current study also indicated that higher training frequencies (3x and 2x per week) were more effective in maintaining vascular adaptations.

Alterations in HRV parameters were only maintained in the 3x per-week group, potentially indicating that higher training frequencies are necessary for the maintenance of cardiac autonomic adaptation. These findings are crucial for the development of time-efficient, sustainable exercise interventions aimed at long-term BP management. For individuals unable to commit to higher training frequencies over the long term, even minimal engagement (1x per week) can provide significant benefits for sBP and MAP. However, for optimal BP reductions and the maintenance of a broader range of physiological adaptations, a frequency of 3x per week is recommended.

In summary, while a reduced frequency of IWS training can maintain key aspects of BP reduction, the optimal maintenance of cardiovascular adaptations likely requires a higher frequency of training. These insights offer may help with the individualisation of IET prescription to promote adherence and long-term cardiovascular benefits.

CHAPTER 7: GENERAL DISCUSSION

7.1. Executive summary of findings

The overarching aim of this thesis was to investigate the effects of IWS training and subsequent detraining on cardiovascular adaptation, with special reference to resting BP reductions. The specific aims of the four studies comprising this thesis were to 1) investigate the BP reductions and associated haemodynamic and cardiac autonomic adaptations following IWS training (Study 1, Chapter 3), 2) compare differences in the BP adaptations between male and female participants following IWS training (Study 1, Chapter 3), 3) determine the magnitude and trend of resting BP reductions, and changes in associated haemodynamic and cardiac autonomic variables, following 8 weeks of IWS training (Study 2, Chapter 4), 4) understand the effects of detraining on resting BP reductions and cardiovascular adaptation following the cessation of IWS training (Study 3, Chapter 5), 5) identify the minimum frequency of IWS sessions required to maintain resting BP reductions (Study 4, Chapter 6).

7.1.1. The main findings reported from these studies are:

1. Four weeks of IWS training is effective at reducing resting BP in male and female participants with normal and high normal BP (Study 1, Chapter 3).

2. The observed BP reductions were likely driven by decreases in TPR and adaptations to cardiac autonomic function rather than centrally mediated changes in $\dot{Q}$ (Study 1, Chapter 3).

3. Extending IWS training to 8 weeks resulted in greater sBP reductions, although the rate of reduction plateaued after 4 weeks (Study 2, Chapter 4).

4. A complete cessation of IWS training results in a reversal of resting BP reductions and all haemodynamic and cardiac autonomic adaptations (Study 3, Chapter 5).

5. Statistically significant reductions in resting sBP and MAP can be maintained with just one training session per week, although greater overall cardiovascular benefits are seen with three sessions per week (Study 4, Chapter 6).

7.2. The effectiveness of IWS training to reduce resting BP

This thesis provides robust evidence for the effectiveness of IWS training to produce significant reductions in BP following both 4 and 8 weeks of training. The first study in this thesis (Chapter 3) provided further evidence for the utility of IWS training in the reduction of resting BP. The magnitude of reduction was similar to previous IWS training studies that have used a similar intervention period and participant demographic (Taylor et al., 2019; Decaux et al., 2022; Lea, O'Driscoll and Wiles, 2023). The reductions seen also support the findings from a recent meta-analysis that highlighted the efficacy of IWS training compared to aerobic or dynamic resistance training for the reduction of resting BP (Edwards et al., 2023). It was also found that there were no significant differences in the BP reductions between males and females following 4-weeks of IET. This provides robust evidence for the utility of IET as an effective intervention for the reduction of BP in both sexes.

The findings from Chapter 3 also helped to elucidate the physiological mechanisms that underpin BP reductions following IWS training. Following the 4-week intervention period, there were significant reductions in TPR, and an improvement in autonomic modulation and BRS (represented by an increase in HF components and a decrease in the LF:HF ratio), compared to the control group. However, no changes in $\dot{Q}$ were found, suggesting that vascular adaptations were the primary mechanisms responsible for BP reductions post-IWS training. Due to the short period of training in the current study, it is likely that the reductions in TPR were primarily related to functional vascular adaptations (Tinken *et al.,* 2008; 2010), such as an increase in NO production and endothelial-dependant vasodilation (Olher *et al.*, 2020), or via a reduction in vagal activity and vascular tone (vasodilation) (Taylor *et al.*, 2019).

The results from the second study (Chapter 4) demonstrated that significantly greater sBP, but not dBP or MAP, reductions can be elicited following 8 weeks of IWS training. The study found that although significant reductions in sBP compared to the control group were found after 4 weeks of IWS training, the continuation of training for a further 4 weeks achieves approximately a 4% further reduction in sBP. The greater BP reductions seen following longer periods of training are likely related to a greater overall training volume and longer exposure to the exercise stimulus. However, despite the further reductions in sBP, overall there was limited cardiovascular adaptation detected in the second 4-week period. A plateau in the rate of BP reduction was also observed at the 4-week time point which may be related to the mode of IET (i.e. most of the adaptation occurred in the first

4 weeks due to the increased cardiovascular stimulus with IWS exercise), a lack of progressive overload (i.e. participants accommodated to the training stressor), and/or the participant demographic used (i.e. normal/high-normal participants have limited capacity for further adaptation). The identification of this trend was also noteworthy in relation to the aims of this thesis. As previously outlined, the aims of the thesis were to explore both the IWS training and detraining effects on resting BP. To explore the detraining effect and the maintenance of BP reductions, Chapter*s* 5 and 6 investigated BP changes following the total cessation of IWS training, or BP maintenance with a reduced training frequency. Although the study design was set up 'a prior' to the findings from Chapter 4, the demonstration of the increased rate of reduction over a 4-week period with IWS training validates the investigation of the detraining effect or maintenance period at this time point. Conversely, if no BP reductions were seen at the 4-week timepoint, and it took the full 8 weeks to observe any reductions, then utilising a detraining or maintenance period after 4 weeks would not be practical or logical. Therefore, the findings from Chapter 4 confirm the study design was set up appropriately to investigate the detraining effect and maintenance strategies following IWS training in Chapter 5 and 6.

7.3. Clinical and real-world impact of IWS training

The overall effectiveness of an intervention cannot be interpreted solely on statistical significance (Brignardello-Petersen *et al.*, 2013), as clinical insights cannot be indicated by just observing the size or direction of the outcome variable (Page, 2014). As such, it is also crucial to consider the data's clinical significance and practical utility (i.e. real-world impact) (Fethney, 2010; Brignardello-Petersen *et al.*, 2013). One method to establish clinical significance is to use an anchor-based method which compares the change score (e.g. drop in sBP) to another outcome variable of clinical interest (e.g. cardiovascular risk). To determine the clinical significance of an outcome variable it is important to establish a minimal clinically important difference (MCID) (Page, 2014) which is the smallest change that is considered worthwhile or important to an individual (Copay *et al.*, 2007). Previous estimates have suggested that sBP or dBP reductions of 2 mmHg could reduce the risk of coronary heart disease, stroke and mortality (Pescatello *et al.*, 2004).

When looking at the occurrence of a 2-mmHg MCID (Pescatello *et al.*, 2004) for resting BP following 4 weeks of IWS training in Chapter 3, it can be seen that 84% of the participants achieved a MCID in sBP. These findings are greater than previously reported by Wiles, Goldring and Coleman (2017), who found MCIDs were attainted by 68% of the participants for sBP. The greater % of responders

could be related to a higher mean BP at baseline compared to Wiles, Goldring and Coleman (2017), which is well established as a direct correlate to greater BP reductions following IET (Inder *et al.,* 2016; Ishikawa-Takata *et al*., 2003). However, following the 8-week training period in Chapter 4, it was also found that 100% of the participants experienced an MCID of 2 mmHg in sBP, highlighting the greater reductions in cardiovascular risk that can be seen over an 8-week training period.

Notwithstanding the above, recent work has demonstrated a 5-mmHg reduction of sBP may be more clinically practical. A 5-mmHg reduction can be referred to as a clinically important difference (CID) as it reduces the risk of major cardiovascular events by about 10%, even amongst individuals with normal or high–normal BP values (Rahimi *et al.*, 2021). The risk of stroke and heart failure is also reduced by 13%, coronary heart disease by 8% and overall death from cardiovascular diseases by 5% (Rahimi *et al*., 2021). Following 4-weeks of training in Chapter 3, 76% of participants experienced a reduction in sBP of 5 mmHg or more. However, impressively, after 8 weeks of training in Chapter 4, 95% of participants were above the threshold, demonstrating the homogeneity of IWS training in reducing cardiovascular risk over an 8-week period.

As outlined above, the data presented suggests greater reductions in cardiovascular risk when performing 8 weeks of IWS training compared to 4 weeks. However, when assessing the real-world impact of the results from the longer training period, the implications for cardiovascular disease and mortality should be taken into account based on the additional benefits seen relative to the further reductions in sBP. Following the 4-week period in Chapter 3, the mean sBP levels were reduced from 131 mmHg to 121 mmHg, moving from the high-normal to the normal category. This drop of nearly 10 mmHg has been shown to reduce the overall risk of mortality by around 13% (Ettehad *et al.*, 2016). However, the sBP values following the 8-week training period in Chapter 4 (131 to 117 mmHg) were within the optimal BP (<120 mmHg) range according to the 2023 ESH guidelines (Mancia *et al.*, 2023). It has been shown that reducing sBP below 120 mmHg into the optimal BP ranges compared to below 140 mmHg lowers the incidence of several important outcomes, including heart failure (38% lower relative risk), death from cardiovascular causes (43% lower relative risk), and death from any cause (27% lower relative risk) (Wright *et al.*, 2021). Observational studies have also shown a progressive increase in cardiovascular risk as sBP rises above 115 mmHg, which highlights the importance of lowering BP towards these targets (Lewington *et al.*, 2002).

Another important clinical aspect of the data which demonstrates its prophylactic importance is the reclassification of individual participants into new BP categories. In the 4-week study in Chapter 3, out of the 80 experimental participants who volunteered to take part in the study, 48% initially had high-normal BP (sBP 130/139 mmHg) and 52% normal BP (sBP 120/129 mmHg) based on the current

2023 ESH guidelines (Mancia *et al.*, 2023). Following the 4-week IWS training period, 46% now had normal BP, 44% had optimal BP, and 10% high-normal BP. At the start of the 8-week intervention in Chapter 4, 50% had normal BP and 50% had high-normal BP. Following the first 4-week period there were similar results to Chapter 3*,* with 55% now having normal BP, 30% having optimal BP and 15% having high-normal BP. However, following the full 8 weeks, only 5% of participants remained high-normal, with 35% now classified as having normal BP, and 60% with optimal BP. These individual differences emphasise and highlight the effect that the full 8 weeks of IWS training can have on BP reduction, and as previously outlined, the associated decreased risk of cardiovascular disease in the normal and optimal BP categories (Rahimi *et al.,* 2021).

Aside from the potential reductions in cardiovascular risk mentioned above, the real-world impact should also be taken into context alongside the current levels of hypertension and associated costs on healthcare systems worldwide. As outlined in Chapter 1, hypertension is one of the leading risks for mortality, morbidity and disability worldwide, affecting around 31.1% of the global adult population (Mills, Stefanescu and He, 2020). Over the past decade, the number of deaths related to high BP has increased by 56.1%, and despite marked improvements in modern medicine and pharmacological treatments, remains a major cause of premature death worldwide (Virani *et al.*, 2020). A global pooled analysis of 1201 population-based studies from 1990 to 2019 discovered that the number of people living with hypertension between the age of 30–79 years has doubled, from 331 million females and 317 million males in 1990 to 626 million females and 652 million males in 2019, with the majority of the rise in low and middle-income regions (Zhou *et al.*, 2021). In the U.K., the latest figures from the Office of National Statistics (2023) show that around 1/3 of adults living in private households have hypertension, with around 29%, or around 4.2 million adults, having undiagnosed hypertension. Although numerous pharmacological treatments have been shown to effectively reduce BP into lower BP ranges (for most this is <140/90 mmHg (Mancia *et al.*, 2023), although BP targets are dependent upon individual treatment objectives), they often come with unwanted side effects and mostly involve lifelong adherence (Heidenreich *et al.*, 2011). Recent data also shows that the total cost to the NHS for BP and cardiovascular-related issues is estimated at £7.4 billion per year (NHS, 2023), with the worldwide economic cost approximately £300 billion per year (Valenzuela *et al.*, 2021). Therefore, effective, affordable, and scalable solutions to improve the global incidence of hypertension and reduce healthcare costs globally are needed. Given the effectiveness of IWS training for the reduction of resting BP seen in the current study, alongside the accessibility and low economic costs, widespread adoption of IWS training could help to alleviate the strain on healthcare systems and lead to substantial public health benefits.

7.4. The detraining effect and maintenance of resting BP reductions following IWS training.

Whilst the findings from Chapter 3 and Chapter 4 have provided valuable data to support the advancement of IWS training as a therapeutic intervention for the reduction of resting BP, these results largely reinforce existing knowledge rather than introducing novel insights. However, the investigation into maintenance strategies following IWS training, including the exploration of a detraining period, remains underexplored. Understanding the detraining effect and minimum maintenance dose required after IWS training is crucial, given the well-documented challenges of poor adherence and high attrition rates in exercise programs (Dishman, 1988; Ettinger *et al.*, 1997; Resnick & Spellbring, 2000). Despite the time efficiency and accessibility advantages of IWS training, longer studies have still reported high dropout rates (Wiles et al., 2024). Therefore, understanding the detraining effect once training stops, alongside maintenance with a reduced training dose, is key to anticipating BP changes and ensuring long-term benefits.

It was found in Chapter 5 that resting BP reductions are reversed following the complete cessation of IWS training. This finding demonstrates that BP reductions following short periods of IWS training are easily reversed, which may be related to the functional nature of any associated physiological adaptations. In support of this notion, it was found that reductions in TPR and improvements in HRV that were seen at week 4 were also reversed within the 4-week detraining period, which provides further evidence that the reductions were facilitated through short-term functional changes (Murray, Delaney and Bell, 2006; Tinken *et al.*, 2008; 2010).

In Chapter 6 it was observed that sBP and MAP reductions can be maintained with one or two IWS exercise sessions per week. The ability to maintain resting sBP and MAP reductions with just one session per week will likely have huge practical implications for the adoption of IWS training due to the minimal weekly time commitment needed (14 minutes per week). However, no main statistical effects were found for dBP reductions at week 8 when performing IWS training once or twice per week. Furthermore, when looking at the mechanistic variables that were also measured in Chapter 6, it was identified that in the 1x per-week group there was a complete reversal of all the physiological adaptations measured. Although the sBP and MAP reductions were maintained in this group, due to the lack of associated cardiovascular adaptation, it is likely that there is limited capacity for the BP reductions to be maintained for further than 4 weeks (any reductions in BP must be facilitated by alterations in TPR or $\dot{Q}$). In the 2x per-week group there were significant reductions in TPRi compared to the control group during the follow-up period of training, potentially

demonstrating that the higher level of training frequency is more optimal for vascular adaptation. Although only speculative, the maintenance of TPRi may suggest sBP reductions could be maintained for longer in the 2x per week group.

Despite the maintenance of sBP reductions in the 2x and 1x per-week group, it should be noted there was a slight trend for reversal in these groups (3.65 and 4.37 mmHg, respectively), which is likely related to the diminution of the associated mechanistic adaptations outlined above. Conversely, in the 3x per-week group there was a significant further reduction in sBP (-4.9 mmHg) (as outlined in Chapter 4). The 3x per-week group was also able to maintain adaptations in TPRi, BRS and all HRV parameters. The further reduction in sBP in this group is likely related to the maintenance and/or further changes in these mechanistic parameters (as discussed in Chapter 4). Importantly, these findings show that a higher training frequency is needed to maintain measurable improvements in these adaptations following 4 weeks of IWS training. The reversal of physiological adaptation in the 2x and 1x per-week groups, alongside a trend of a reversal in BP, suggests that continued intervention at 3x per-week group will likely be required at some point to ensure BP reductions are maintained over extended periods (>8 weeks).

7.5. Practical applications of the findings from Chapter 5 and 6

There are several important practical findings from Chapter 5 and 6 that may help to guide and shape future IWS training prescription. Firstly, understanding that BP reductions can be maintained for at least 3 weeks following the cessation of IWS training has several important implications. From a practical perspective, these data demonstrate that if there are periods of time where individuals abstain from training (holidays, low motivation, busy work periods, injury), it is likely that BP reductions can be maintained for at least 3 weeks following the cessation of training. The data also indicates that for studies using a crossover study design where researchers may implement washout periods, ideally, a 4-week period is needed due to the possibility of sustained reductions after 3 weeks. Secondly, the findings also highlight the chronic nature of the BP reductions observed. Although the week-4 laboratory BP readings were taken 72 hours following the last IWS exercise session to avoid any acute interference (post-exercise hypotension) (Wiles, 2008), the duration of BP reductions throughout the detraining period improves the confidence in the BP reductions seen and confirms that the BP reductions observed were the result of a chronic ‘adaptation’, rather than an acute ‘response’. It should also be acknowledged that despite the complete reversal of mean BP reductions following the 4-week detraining period, 45% of the participants still had a 5-mmHg CID

(Rahimi *et al.*, 2021) which may indicate high inter-individual differences in the BP detraining effect (Moker *et al.*, 2014), and that for some, the cardioprotective effects can be sustained for longer periods. This may also have implications for crossover training studies using washout periods, as it is likely that some participants may still have an augmented BP status even when using a 4-week washout period.

The real-world implications of the findings in Chapter 5 are also important in the context of managing hypertension, a condition that affects millions of people worldwide and is a leading risk factor for cardiovascular disease (Zhou *et al.*, 2021). Despite the 3-week period of sustained BP reduction following the cessation of IWS training, the reversal of BP reductions upon cessation of IWS training observed suggests that individuals cannot rely on short periods of IWS training to provide long-lasting protection against raised BP and hypertension. Instead, there is a need for long-term adherence to IWS training to sustain BP control and reduce cardiovascular risk (as seen with anti-hypertensive pharmacological treatment (Paz *et al.*, 2016)), which ultimately has direct implications for the prescription of IWS in clinical and public health settings. These findings are particularly relevant given the high rates of attrition and poor adherence in exercise programmes previously discussed, and indicate that interventions need to be designed with long-term sustainability and user-friendliness in mind. Clinicians and practitioners should therefore continue to emphasise the need for regular exercise and also provide strategies to further enhance adherence, such as utilising the minimal training-dose required to maintain resting BP reductions as seen in Chapter 6.

Indeed, the insights from Chapter 6 have important real-world implications for supporting cardiovascular health through IWS training, particularly in addressing the adherence challenges previously discussed. The finding that just one weekly IWS session can sustain sBP and MAP reductions for up to 4 weeks offers a practical, low-effort strategy that can help individuals maintain these benefits over time. This minimal-dose approach directly tackles the high attrition rates and poor adherence often seen in exercise programs, providing a user-friendly option that aligns with the need for sustainable interventions. Clinicians and practitioners can leverage these findings to design flexible IWS training plans, encouraging individuals to adopt regular and manageable exercise routines that fit their lifestyles, while still delivering meaningful health benefits, ultimately enhancing the potential for long-term engagement and cardiovascular risk reduction.

One of the key and novel aspects from the findings from Chapter 6 is the ability to explore the between-group analysis of different training frequencies on the maintenance of BP (i.e. is 2x per week more effective at maintaining BP reductions than 1x per week). It was demonstrated that the

sBP and MAP reductions at week 8 in the 3x per-week group were significantly lower than the 2x or 1x per-week group. The 3x per-week group also had a higher occurrence of a CID 5 mmHg difference in sBP (95%), compared to the 2x (65%), 1x (65%) and 0x (45%) per-week groups, demonstrating greater cardioprotective effects. Moreover, as outlined in Chapter 4, the greater sBP reductions in the 8-week IWS training study (3x per-week group) moved sBP values into the optimal category which decreases the associated risk for cardiovascular diseases compared to being in the normal BP category (Wright *et al.*, 2021). However, sBP lowering to below 120 mmHg is not recommended or needed for all individuals. Current 2023 ESH guidelines (Mancia *et al.*, 2023) outline potential benefits for BP lowering below 120 mmHg in some high-risk populations, citing the SPRINT trial paper that found greater cardiovascular benefits below 120 mmHg, but also mention low BP targets should be approached with caution due to associated risks (e.g. hypotension and syncope), and to individualise treatment goals based on patient-specific factors (Wright *et al.*, 2021). The SPRINT trial also raised important practical issues in relation to population level BP control. Hypertension control to below 140 mmHg sBP is only accomplished in 50% of the population in the U.S. (Nwankwo et al., 2013), and achieving a sBP target of less than 120 mmHg in the overall population of patients with hypertension would be even more demanding and time-consuming for both providers and patients, potentially increasing adherence and attrition issues over the long term. However, the guidelines state that for most individuals, a BP-lowering target of between 120/129-mmHg is suitable (Mancia *et al.*, 2023). As the sBP values were 123 and 122-mmHg, respectively, in the 2x and 1x per-week group, which is at the lower end of the normal BP category, it may be that for some individuals (potentially those who have a proclivity to drop out of exercise training programmes) a reduced training dose to maintain BP reductions within the normal range may be more suited, with the option to reinstate the original training dose at a future period if deemed necessary (which will likely be necessary based on the trend of BP to reverse following the short 4-week training period utilised within Chapter 6).

Furthermore, although greater BP reductions can be seen with three sessions per week, the continuation of the high training frequency may increase the risk of attrition and adherence issues. This presents an important dichotomy: a more optimal BP profile can be maintained with three sessions per week, although sBP reductions can still be maintained with one session per week. This raises the obvious question as to which should be recommended? Although a greater reduction in cardiovascular risk factors is likely to be seen with the maintenance of both sBP and dBP reductions (Luo *et al.*, 2020), this question should be taken into context with patient-specific factors, such as age, BP status, cardiovascular risk profile and personality types (i.e. those who may have a greater proclivity to drop out of training). For example, some individuals may have a greater need for dBP

reductions and may not be as susceptible to dropping out of training in response to higher training frequencies (e.g. <50 years of age) (McEvoy *et al.*, 2020) and so may be recommended to implement IWS training 3x per week. On the other hand, those individuals who have a greater need for reductions in sBP (e.g. those with comorbidities or >50 years of age) and also have a proclivity to drop out of exercise training programmes (Li *et al.*, 2014), may be recommended to implement IWS training once per week to ensure they still maintain some BP-lowering benefits, but do not run the risk of discontinuing training.

Whilst writing this final chapter, a new study has been published by Baross *et al.,* (2024) that has also investigated the effects of a maintenance period of training following IET. The study found that following an 8-week supervised double leg-extension IET training programme, significant reductions compared to a control group in both 24-hour (−7 ± 5 mmHg, p=0.001) and daytime (−4 ± 5 mmHg, p=0.034) ambulatory BP, as well as 24-hour (−2.10 ± 1.71 mmHg, p=0.033) and daytime (−2.34 ± 2.49 mmHg, p=0.002) average real variability, were maintained with just one IET session per week over an 8-week follow-up period. The study also found that significant reductions in morning BP surge (−8 ± 9 mmHg, p=0.008) were maintained with one session per week. The study largely supports and aligns with the data presented within this thesis, in that reductions in sBP can be maintained with just one training session per week. However, demonstrating the maintenance of sBP with ambulatory BP is valuable, as ambulatory BP has been shown to be more closely associated with cardiovascular risk factors than resting BP (Mancia *et al.*, 2023). In addition, morning BP surge is closely associated with end-organ damage and atherosclerotic plaques (Kario, 2010). Nonetheless, while the benefits of ambulatory BP measurements are useful, it should be acknowledged that the close alignment of the results from this thesis with those of Baross *et al.,* (2024) suggests that ambulatory reductions can be potentially predicted by taking much simpler and user-friendly laboratory/office BP measurements. The results from Baross *et al.*, (2024) also support those of Cohen *et al.*, (2023), as no significant differences in dBP compared to the control group were found following the 8-week training period or following the maintenance period. This demonstrates that reductions in dBP are harder to obtain and/or are smaller in magnitude (as also demonstrated by the smaller effect sizes seen in Chapter 3 within this thesis), and also harder to maintain during a follow-up period of training (as demonstrated by the lack of dBP maintenance in Chapter 6).

Despite the release of this research, the findings from this thesis are still novel for several reasons. Firstly, Chapter 6 used a large sample size of participants and also utilised multiple comparative groups (0x per week, 1x per week, 2x per week and a continuation at 3x per week). Using these comparative groups allowed deeper investigation into the dose-response, providing a more detailed output in relation to the BP changes with differing training frequencies. Using a 0x per-week group

(detraining group) provides additional experimental control, as highlighting the differences between the 0x per-week group and the 1x per-week group indicates the BP reductions were likely maintained due to the continuation of IWS training, rather than due to any chronic adaptation that had not reversed, even with a cessation of IET. Secondly, Chapter 6 is the first to investigate associated cardiovascular mechanisms during a maintenance period. Investigating these associated variables helped to explain how sBP and MAP were maintained with changes in training frequency and overall provides a deeper understanding of the physiological processes underpinning the BP/dose-response relationship. However, overall, the results from Baross *et al*., (2024) confirm the main findings from Chapter 6 within this thesis and add to an increasing body of research demonstrating the potential for IET as a long-term sustainable therapeutic intervention for the reduction of resting BP. Moreover, the study also demonstrates that the research topic of a minimum training dose following IET is warranted and highlights the growing interest in this area to progress the clinical utility of IET.

7.6. Future research

While the findings from this thesis are important and will help to shape and inform future IWS training prescription, there are some important areas for future research that may help to further progress the clinical utility of IWS training. Firstly, future research comparing the maintenance dose following short and long-term IWS interventions could provide useful insights for the implementation of a maintenance dose. As outlined previously, the overall training duration in the study was short. Although short 4-week studies provide valuable information and are pragmatic given the time constraints of research interventions, exercise training programmes are typically prescribed for longer than 4 weeks (Edwards *et al.*, 2023). The short 4-week training period may also be why there was a trend for BP reductions to reverse during the follow-up period of training (4.4 mmHg), as compared to Cohen *et al*., (2023) who reported a slight further reduction in sBP (-1.8 mmHg) when using a longer 12-week training period. As previously discussed, longer periods of training are linked to structural adaptation within the vasculature which may help to maintain the BP reductions seen (Tinken *et al.*, 2008; 2010). As such, it is likely that a longer period of initial training is needed if BP reductions are to be maintained for extended periods of time without the reintroduction of the original training dose (3x per week). Exploring further mechanistic differences (e.g. vascular adaptations) between short-term and long-term training could also provide deeper insights into how exercise duration influences the detraining effect.

Secondly, although the general consensus is that intensity needs to be maintained during a follow-up period of training, there are currently no studies that have investigated the effects of a reduction in exercise intensity during a follow-up period of training in relation to IET and BP reductions. While Decaux *et al*., (2022) demonstrated a reduced intensity sham group was unable to achieve BP reductions following a 4-week IWS training period, it is currently unknown if BP reductions can be maintained with a reduced exercise intensity once BP has been reduced and there is a baseline level of cardiovascular adaptation. This research could be important as exercise adherence literature indicates that activities of higher intensities are less tolerable to the average individual (Dishman & Ickes, 1981) and are also related to poorer adherence (Dishman, 2020; Sallis & Owen, 1999). As such, reducing the intensity of the exercise will likely reduce the perceived exertion and may help with long-term adherence.

Thirdly, from a training prescription perspective, periods of rest or reduced training volume are common practise as they let individuals or athletes recover and allow time for adaptations to occur before moving on to a subsequent phase of training (Le Meur, Hausswirth and Mujika, 2012). In terms of IET and BP reductions, over the long term, using periods of reduced training frequency or volume will likely increase adherence to exercise (due to reduced time constraints), but may also enhance adaptations by reducing any residual fatigue and allowing supercompensation (Bompa and Haff, 2009). However, there are currently no studies that have investigated the impact of intermittent IWS training (i.e. periods of regular training interspersed with periods of reduced training frequency/volume) on BP reductions. This research could offer practical guidance for exercise prescription and may help with the sustainability and long-term benefits of IWS training.

Lastly, the investigation to try and identify training/BP responders and non-responders to IET is a worthy topic for future research. The current study was set up to allocate participants into experimental groups at baseline, rather than at the mid-point of training. This was to ensure there was no recruiter bias and that the group allocation was random. It was concluded (a prior) that there would be an overall homogenous majority drop in BP at week 4 due to the high occurrence of BP reductions and large effect sizes typically seen within IWS training studies (Wiles, Goldring and Coleman, 2017; Taylor *et al.*, 2019; Decaux *et al.*, 2022; Lea, O'Driscoll and Wiles, 2023). Indeed, when exploring the responders and non-responders in the current study - using a >0 mmHg as the threshold for responders (Moker *et al.*, 2014) - 95% of the 80 experimental participants were responders for sBP at week 4. However, only 78% were responders for dBP, which is aligned with previous estimates that have shown there can be considerable individual variability in the BP response to exercise training, with between 20–25% of individuals not lowering BP following exercise training (Pescatello and Kulikowich, 2001). Although beyond the scope of this thesis, future

research could examine the effects of training responders and non-responders on the maintenance of BP with a reduced training dose to assess whether there are any correlations (i.e. those who have a greater BP reduction following the initial period of training are able to maintain BP reductions for longer periods). Identifying potential non-responders at an early stage (ideally before the initiation of IET) could help with the individualisation of IET prescription. The differences could also be analysed in relation to individual factors such as age, gender, and potential existing health conditions (Moker *et al.*, 2014) which could help in identifying predictors of success or failure with IWS training and tailoring interventions to individual needs. However, recent work from Kelley, Kelley and Stauffer (2021) found that there were no differences between inter-individual differences and random variation with BP reductions following IET, and suggested that a search for potential moderators that influence BP reductions may not be warranted.

7.7. Strengths of this thesis

1. The thesis makes a meaningful contribution to the clinical utility of IWS training by providing evidence-based recommendations. The optimal training duration, the need for continued intervention to avoid detraining, and the minimal maintenance frequency provide actionable guidance for clinicians and health-care professionals. These recommendations are particularly relevant given the global burden of hypertension and the need for effective, non-pharmacological interventions that can complement or reduce reliance on pharmacological treatments.
2. The IWS experimental groups consistently showed BP reductions at least 2 mmHg greater than control groups across all studies. Given the clinical impact and reductions in cardiovascular risk associated with a MCID of 2 mmHg, the homogeneity of these results further underscores the reliability and effectiveness of IWS training as a non-pharmacological approach to BP management.
3. Both male and female participants were included in this thesis which significantly enhances the generalisability and applicability of the findings. By demonstrating that IWS training effectively reduces resting BP in both sexes, this work addresses a critical gap in IET research, where studies have typically been male dominated. The consistent BP reductions observed between sexes validates the robustness of IWS training as an equitable intervention for both males and females.
4. The large sample size in Chapter 3 is a key strength as it improves the applicability of the findings. By including an increased number of participants compared to previous work, the

reliability of the data is enhanced which minimises the chance that the observed BP reductions are due to random variation (Type 1 error). The large participant cohort also increases the statistical power, which allows more precise estimates and the detection of smaller differences that might be overlooked in previous studies with smaller samples (Type 2 error).

7.8. Limitations of this thesis

1. In terms of the real-world application of IWS training based upon the findings within this thesis, perhaps the worthiest limitation is the use of an incremental IWS test to prescribe exercise intensity. The incremental test involves a trip into the laboratory (or similar facility) and the use of specialist equipment (e.g. HR monitors) which potentially decreases the protocols accessibility for widespread adoption. It should also be noted that the maximal nature of the incremental test may need to be addressed, as ideally, participants are required to continue the test until maximum intensity/fatigue. The maximal nature of the IWS incremental test raises questions about its suitability for all populations (e.g. sedentary individuals who may have lower motivation/tolerance to strenuous exercise). However, newer protocols, such as the RPE based model from Lea, O'Driscoll and Wiles (2023) have also recently been used to self-prescribe IWS exercise intensity. To prescribe intensity, participants performed a 30-second IWS at a height that would elicit a score of 4 on the RPE scale after a 2-minute contraction. Participants then completed 4 x 2-minute IWS exercise bouts, adjusting the squat height based on RPE scores to match target zones, and used the final squat height for the first training session. The model used by Lea, O'Driscoll and Wiles (2023) does not require any laboratory-based equipment, improving the scalability and accessibility of the protocol to the wider population. The protocol also does not involve any maximal testing which may improve the user-friendliness and acceptability. There were also no significant differences in the BP reductions seen between the RPE-based model (sBP -9 ± 6 and dBP -6 ± 4 mmHg) and the HR-based model (as used in this thesis) (sBP -14 ± 6 and dBP -6 ± 4 mmHg) in the study from Lea, O'Driscoll and Wiles (2023), demonstrating the effectiveness of using RPE for IWS training prescription.
2. Reusing the same control group across multiple studies may have implications for research validity. Firstly, it increases the risk of inflated Type I error rates because each comparison to the shared control group lacks independence, elevating the chance of false positives. Conducting several tests without adjustment potential pushes the overall probability of at

least one Type I error beyond the typical 5% threshold. Secondly, the lack of independence violates assumptions underpinning many statistical tests, potentially rendering p-values and confidence intervals unreliable. Lastly, any bias or unrepresentativeness in the control group affects all comparisons, and therefore generalisability and external validity suffers if the control group fails to reflect the broader population. However, despite these potential limitations, the study was set up in the most appropriate and pragmatic way given the constraints of the PhD research process. Recruiting independent control groups for each study would have required more time and recruitment, which was not practically achievable. Moreover, it should be noted that the statistical power of the studies was very high (>90% for sBP in all studies) due to the large effect sizes seen following IWS training (>0.8 Cohen's *d*). P-values were also consistently <0.001, obtained from robust statistical tests (ANCOVA), which adjust for baseline covariates. These results indicate that the findings were highly unlikely to result from chance variation, reinforcing their reliability despite the reuse of a control group.

3. Participants in this thesis were university students and staff, who may have been more motivated to participate in the training programme compared to the general population. This increased motivation could stem from their close connection to the university and the research environment. As a result, their higher engagement might have led to better adherence to the training, potentially exaggerating the interventions observed effects. Additionally, university students and staff do not reflect real-world participants, as they are typically more educated and possibly more health-conscious than the broader population. This lack of diversity limits the study's external validity and applicability to people outside an academic setting, who might face greater challenges such as limited time, fewer resources, or lower motivation to train.

7.9. Conclusion

The work in this thesis contributes to the growing body of evidence supporting IWS training as an effective, non-pharmacological intervention for the reduction of resting BP and also offers valuable insights for the long-term implementation of IWS training in both clinical and public health settings. The large sample size used within this thesis improves confidence in the BP reductions seen following IWS training and also allows effective interpretation of associated mechanistic variables that may be responsible for the BP reductions. The thesis also highlights the importance of continued intervention as BP reductions are reversed upon cessation of short-term IWS training. It

was also found that the benefits of IWS training can be sustained with just one IWS session per week, making it a practical and scalable option for public health intervention. Some important areas for future research were also identified, including the use of longer-duration training studies, further mechanistic studies with larger sample sizes, intermittent IWS training and the investigation of training responders and non-responders. These future directions may help to maximise the potential of IWS training as a non-pharmacological intervention for the reduction of resting BP. Overall, this thesis provides a strong foundation for the widespread implementation of IWS training as an effective and sustainable approach to BP management, with the potential to enhance public health outcomes and reduce the growing burden on healthcare systems worldwide.

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Appendices

9.1. Appendix 1

Canterbury Christ Church University

19th December 2019 Ref: 19/SAS/12C

Harry Swift
c/o School of Human & Life Sciences (Sport & Exercise Science)
Faculty of Social & Applied Sciences

Dear Harry,

Confirmation of ethics compliance for your study – *'The influence of isometric exercise training frequency upon cardiovascular adaptation with special reference to resting blood pressure.'*

The Faculty Ethics Chair has reviewed your Ethics Review Checklist application and appropriate supporting documentation for the above project. The Chair has confirmed that your application complies fully with the requirements for proportionate ethical review, as set out in this University's Research Ethics and Governance Procedures.

In confirming compliance for your study, you are reminded that it is your responsibility to follow, as appropriate, the policies and procedures set out in the *Research Governance Framework* (http://www.canterbury.ac.uk/research-and-consultancy/governance-and-ethics/governance-and-ethics.aspx) and any relevant academic or professional guidelines. This includes providing, if appropriate, information sheets and consent forms, and ensuring confidentiality in the storage and use of data.

Any significant change in the question, design or conduct of the study over its course should be notified via email to red.resgov@canterbury.ac.uk and may require a new application for ethics approval.

It is a condition of compliance that you must inform red.resgov@canterbury.ac.uk once your research has completed.

Wishing you every success with your research.

Yours sincerely,

Penny

Penny Keogh
Research Integrity & Development Officer
Email: red.resgov@canterbury.ac.uk

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Professor Rama Thirunamachandran, Vice Chancellor and Principal

9.2. Appendix 2

PARTICIPANT INFORMATION SHEET

A research study is being conducted at Canterbury Christ Church University (CCCU) by Harry Swift under the supervision of Dr Jim Wiles and Dr Jamie O'Driscoll.

Background

Previous research has demonstrated that isometric exercise (IE) training is an effective method to reduce resting blood pressure (BP). Reductions in resting BP have been shown to reduce the risk of cardiovascular diseases. However, there is limited research in relation to the long-term effects on BP following this type of exercise. The purpose of this project is to determine the rate of reversibility with BP reductions following a 4-week home-based isometric wall squat (IWS) programme (how quickly the BP reductions are reversed), and also to investigate the minimum session stimulus needed to maintain any resting BP reductions following a 4-week IWS programme (what is the minimum amount of IE that is needed to maintain the reductions). This research will help support the efficacy of IE as a viable treatment route for individuals with hypertension (high BP).

What will you be required to do?

Participants will be expected to attend the lab on three different occasions: one pre-testing, one mid-testing, and one post-testing. Participants will need to bring sports kit (trainers, shorts/tracksuit bottoms, and a t-shirt) to each session. During the first session participants will complete an incremental isometric exercise test (to determine knee joint angle for the IWS) with the results being used to prescribe their home-based isometric exercise training intensity. Resting BP measurements will also be taken within this first session. The participant will also be familiarised with the isometric wall squat protocol in this session so that the researcher can guide and assist with the correct techniques. The participant will then complete 4-weeks of home-based IWS, consisting of 4 x 2-min bouts of IWS, carried out three times per week. Following the first 4-weeks, the participant will be required to attend the laboratory to have their resting BP taken again. They will then complete a second 4-week period of home-based IWS. During this second 4-week period, the frequency of exercise will either stay at three times per week or will be reduced to either twice or once a week, or the participant will be asked to abstain from IWS altogether – the selection of which will be randomly allocated. Following the second 4-week period, the participant will be required to visit the lab for their final resting measures.

To participate in this research you must:

- Not injured (able bodied)

- Normotensive (absent from clinically high BP)
- Not on any BP medication
- Not partake in any regular intense exercise

Laboratory based procedures

Resting cardiovascular measures will be taken during each laboratory visit. Resting measures consist of 15 mins of supine rest, in which the participant will be monitored via haemodynamic and autonomic assessment. During the first lab visit, an incremental IE wall squat test will also be conducted following the resting measures. This test is comprised of a continuous exercise assessment in which the participant will be required to perform continuous isometric wall squat exercise in stages of increasing intensity. The intensity will be adjusted by decreasing knee joint angle. The first stage will begin at 135˚ of knee flexion and participants will be instructed to hold this position for two minutes. Once each stage is complete the knee joint angle will be decreased by 10˚. The exercise intensity will be increased every two minutes until the participant reaches the end of 95˚ stage, or can no longer maintain the knee joint angle within 5˚of the target value (volitional fatigue). The participant will also be given all equipment needed to conduct home-based IWS exercise (bend and squat device, HR monitor, and training manual). The participant will be given a full demonstration and will then be observed carrying out the IWS protocol to ensure full competency with procedures.

Feedback

Participants will be provided with their personal results upon request.

Confidentiality

All data and personal information will be stored securely within CCCU premises in accordance with the Data Protection Act 1998 and the University's own data protection requirements. Data can only be accessed by Harry Swift, Dr Jim Wiles and Dr Jamie O'Driscoll. After completion of the study, all data will be made anonymous (i.e. all personal information associated with the data will be removed).

Deciding whether to participate

If you have any questions or concerns about the nature, procedures or requirements for participation do not hesitate to contact me. Should you decide to participate, you will be free to withdraw at any time without having to give a reason.

Any questions?

Please contact Harry Swift at harry.swift@canterbury.ac.uk**.**

9.3. Appendix 3

Faculty of Human and Life Science

Sport Science Informed Consent & Health and Fitness Questionnaire

Name: …….

Date of Birth: …… **Age: ……** **Sex: ……**

Please answer the following questions by ***circling*** the appropriate response and if necessary providing extra information in the spaces provided.

ANY INFORMATION CONTAINED HEREIN WILL BE TREATED AS CONFIDENTIAL

1. How would you describe your present level of fitness?
Untrained / Moderately trained / Trained / Highly trained

2. Average number of hours spent exercising **…….……per wk**

3. How would you describe your present bodyweight?
Underweight / Ideal / Slightly overweight / Very overweight

4. How would you describe your smoking habits?
Non smoker / Previous smoker / Currently smoking

5. How would you describe your alcohol intake?
Never Drink / An occasional drink / A drink every day / More than one drink a day

(Note 1 drink = 1 unit)

6. Have you had to consult your doctor within the last six months?
Yes / No
If you have answered **yes**, please give details:**…….**

7. Are you presently taking any form of medication?
Yes / No
If you have answered **yes**, please give details: **……**

8. Are you presently taking any substances which may affect your performance?
If you have answered **yes**, please give details:**.....**

9. Do you suffer or have you ever suffered from any of the following?

a. Diabetes **Yes / No** b. Asthma **Yes / No**

c. Epilepsy **Yes / No** d. Bronchitis **Yes / No**

e. Any form of heart complaint **Yes / No** f. Serious Back or Neck Injury **Yes / No**

g. High blood pressure **Yes / No** h. Aneurysm [1] or Embolism[2] **Yes / No**

i: Arterial wall weakness causing dilation. **Yes / No** j: Obstruction in the Artery. **Yes / No**

10. Is there a history of heart complaint in your family?
Yes / No
If you have answered **yes**, please give details: **……**

11. Do you have any allergies?
Yes / No
If you have answered **yes**, please give details: **……**

12. Do you currently have any form of muscle or joint injury?
Yes / No
If you have answered **yes**, please give details: **……**

13. Have you had to suspend your normal training/physical activity in the last two weeks? **Yes / No**
If you have answered **yes**, please give details: **……**

14. Do you have a regular menstrual cycle?
If you have answered **no**, please give details: **……**

15. Are you currently taking any form of contraception that may affect your menstrual cycle?
If you have answered **yes**, please give details: **……**

Signature of Subject: ……..

Signature of Sport Scientist: ……..

Date: …….

9.4. Appendix 4

CONSENT FORM

Title of Project: The Detraining Effects of Isometric Exercise

Name of Researcher: Harry Swift

Contact details:

Address: Canterbury Christ Church University, North Holmes Road
Canterbury
CT1 1QU

Tel: 01227 922292

Email: harry.swift@canterbury.ac.uk

Please initial box

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.	☐
3. I understand that any personal information that I provide to the researchers will be kept strictly confidential	☐
4. I agree to take part in the above study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

9.5. Appendix 5

Home-Based Blood Pressure Manual

Requirements

- You will be required to self-report your resting blood pressure twice per day.
- This will be done once in the morning and once in the evening.
- Try and keep the timing consistent – i.e. if you take your BP first thing when you wake up then stick to that for the duration.

Before taking your reading

- You should not smoke, have a drink containing caffeine (such as coffee) or exercise for 30 minutes before you take your blood pressure reading. You should also avoid measuring your blood pressure when you need to use the toilet.
- It is important that you always measure your blood pressure in the same arm. You should use the arm which your doctor or nurse uses when they take your blood pressure, or whichever arm they ask you to use.
- Do not wear any tight or restrictive clothing around the arm you are measuring your blood pressure in. For example, you should avoid rolling up tight shirt sleeves.
- You should rest for at least five minutes before measuring your blood pressure. During this time you should sit down in a quiet place, try to relax and avoid speaking to anyone.

Taking your reading

- Place the cuff on your arm and make sure the bottom of the cuff is approximately 2cm above the bend in your elbow.
- Make sure that you are sitting down when taking your blood pressure readings and that you have both of your feet flat on the floor. You should not cross your legs as this can raise your blood pressure. The arm that you are measuring your blood pressure in should be support on a firm surface (such as a table or desk) with your palm facing up and should be at the same level as your heart.
- Take at least two readings, leaving at least a minute between each. After each measurement, you should write the reading down in your diary. Remember to write down the exact numbers that appear on the screen - do not round the numbers up or down. If the first two readings you take are very different, take 2 or 3 further readings. You should write all of your readings down in your blood pressure diary.

***If you are unable to take your BP for any reason please do not hesitate to contact Harry Swift (via mobile: 07540077418 or email: harry.swift@canterbury.ac.uk).**

9.6. Appendix 6

Training Session Manual

Name: …… Participant I.D: ……

Training Session Information

- You will complete 12 training sessions in total over a 4-week period (3 sessions per week).
- Each training session requires you to perform a total of 4 wall squat exercises each lasting 2 minutes.
- Each wall squat will be performed at a specific angle (calculated from your incremental test) so that you reach your target heart rate.
- There will be 2 minutes seated rest between each wall squat.
- Each training session will last 14 minutes in total (see Exercise Protocol, *page* 3).
- You must leave 24 hours between each training session to ensure adequate recovery.
- You should try to ensure that all training sessions are at the same time of the day (see *Training Time*table*, page* 9).
- You must adhere to the pre-training session requirements (see *page* 4).

Equipment

You will be given the following equipment to use whilst exercising at home:

1*. Bend and Squat*

- The Bend & Squat is a piece of exercise equipment designed to ensure that you are squatting at the correct angle.
- You will need to adjust the Bend & Squat for your specific training angle (see *Bend & Squat Instructions, page* 5).
- Your Bend & Squat measurements are:

WALL: …… **FLOOR**: ……..

- You must ensure that the Bend & Squat is always set to these measurements before use.

- For instructions on how to use the Bend & Squat to perform the Isometric Wall Squat Exercise see *page* 6.

2*. Heart Rate Monitor*

- You will record heart rate throughout the wall squat using the heart rate monitor provided (see *Heart Rate Monitor Instructions, page* 7).
- At the end of every training week you will need to text or email Harry Swift your heart rate and RPE data (see *Sending Data, page* 8).

3*. Rate of Perceived Exertion (RPE) Scale*

- You will be provided with an RPE scale (see *page* 2). This scale is used to measure how much exertion you feel in your legs (quadriceps).
- At the end of every 2-minute wall squat you need to write down your RPE on the data sheet provided (see *page* 1). Text or email Harry Swift your RPE data (see *Sending Data, page* 8).

***If you are unable to continue with the training sessions for any reason please do not hesitate to contact Harry Swift (via mobile: xxxxxxxx or email xxxxxxxxx).**

Contents

Data Sheet

	Training Session	Resting	Bout 1		Bout 2		Bout 3		Bout 4	
		Heart Rate	Heart Rate	RPE	Heart Rate	RPE	Heart Rate	RPE	Heart Rate	RPE
WEEK 1	1									
	2									
	3									
WEEK 2	4									
	5									
	6									
WEEK 3	7									
	8									
	9									
WEEK 4	10									
	11									
	12									

RPE Scale

How hard do you feel your muscles are working?

Rating	Description	TTF
0	Rest	100%
0.5		
1	Extremely Easy	90%
1.5		
2	Very Easy	80%
2.5		
3	Easy	70%
3.5		
4	Somewhat Easy	60%
4.5		
5	Moderate	50%
5.5		
6	Somewhat Hard	40%
6.5		
7	Hard	30%
7.5		
8	Very Hard	20%
8.5		
9	Extremely Hard	10%
9.5		
10	Maximal	0%

*Please turn over for RPE instructions

Scale Instructions

This scale is used to rate how hard you think your active muscles are working.

This scale has 3 different columns: Rating, Description and TTF. The '**Rating**' numbers are from 0-10 and are used to rate the exertion or effort in the active muscle group(s). The '**Description**' words and '**TTF'** are used to help you choose a rating.

0 - "**Rest**" is absolutely no effort, as felt during complete rest.

5 - "**Moderate**" is right in the middle of 0 and 10. It's not especially hard and it is no problem to continue; but, it no longer feels comfortable.

10 - "**Maximal**" is maximum effort; your muscles are working as hard as they can, and you have seconds before you will have to stop.

TTF (Time to Failure) indicates the amount of time remaining, during an isometric contraction, before you will be unable to continue. In other words, this describes how much you have left in your 'fuel tank'.

100% your muscles are fresh; you haven't started the contraction yet (fuel tank is full).

50% means you can continue to hold the contraction for the same amount of time that you have already completed (fuel tank is half full)

0% your muscles are failing/have failed (fuel tank is empty).

When you give your rating; focus only on the muscle group(s) that is working. You can use the 'Description' words, the Time to Failure (TTF), and/or you can simply rate the exertion out of ten.

Setup the Bend & Squat against a flat wall (see instructions, see page 5).

Put on and start the heart rate monitor (see instructions, see page 7).

Stay seated for 5 min to caculate resting HR

Mark a lap on your watch after 5 mins of seated rest

0 mins

1. Perform the wall squat exercise for 2 minutes.

→ Mark a lap at the START and END of the 2 minute wall squat.

→Record HR and RPE at the END of the 2 minute wall squat.

REST for 2 minutes in a **SEATED** position.

2 mins

2. Perform the wall squat exercise for 2 minutes.

→ Mark a lap at the START and END of the 2 minute wall squat.

→ Record HR and RPE at the END of the 2 minute wall squat.

4 mins

REST for 2 minutes in a **SEATED** position.

6 mins

3. Perform the wall squat exercise for 2 minutes.

→ Mark a lap at the START and END of the 2 minute wall squat.

→ Record HR and RPE at the END of the 2 minute wall squat.

8 mins

REST for 2 minutes in a **SEATED** position.

10 mins

4. Perform the wall squat exercise for 2 minutes.

→ Mark a lap at the START and END of the 2 minute wall squat.

→ Record HR and RPE at the END of the 2 minute wall squat.

12 mins

STOP the heart rate monitor

14 mins

Record your HR data onto your data sheet and send me your results after **EVERY** training session

(see instructions, see page 8).

Please adhere to the following before **EVERY** lab visit:

- No caffeine (tea, coffee, fizzy drinks, chocolate) 4 hours before the lab visit

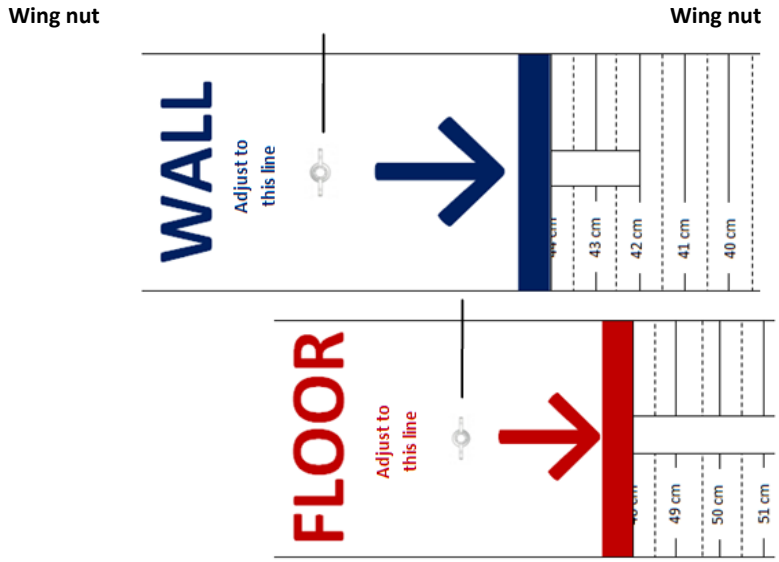
- No alcohol 24 hours before the lab visit

- No strenuous physical exercise 24 hours before the lab visit. If you feel fatigued prior to a lab visit please do not hesitate to contact Harry Swift for advice.

- No large amounts of food 4 hours before the lab visit, however you are allowed to drink water or have a small snack if your visit is early in the morning.

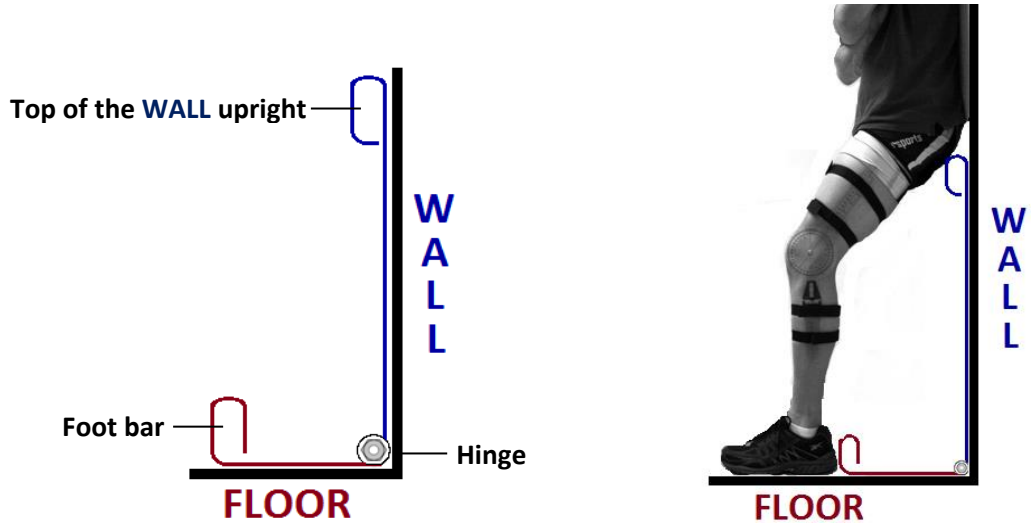
Bend and Squat Instruction

1. Adjust the **WALL** section to the required length by loosening wing nut (*turn anticlockwise*). Then slide the **blue** line to the required measurement and tighten the wing nut (*turn clockwise*). Make sure that the **WALL** section is secure and cannot move.



2. Adjust the **FLOOR** section to the required length by loosening wing nut (*turn anticlockwise*). Then slide the **red** line to the required measurement and tighten the wing nut (*turn clockwise*). Make sure that the **FLOOR** section is secure and cannot move.

3. Put the bend and squat at a 90-degree angle against a flat wall, making sure that the hinge is in the corner between the wall and the floor.



Isometric Wall Squat Exercise

- Stand with your head and back firmly against a flat, sturdy wall that supports the full weight of your body.
- Position your feet shoulder-width apart against the **Bend & Squat** bar with your toes facing forward. Make sure your feet are firmly on the floor, as you may find that they slide forward (try and wear the same foot ware, or no foot ware for all the training sessions).
- To perform a wall squat, slowly bend your knees and allow your back to slide down the wall until your bottom is touching the upright of the **Bend & Squat**. ***DO NOT** use the **Bend & Squat** as a seat. It should **NOT** support your body weight*
- Look straight forward and hold this position for 2 minutes.
- Keep your arms crossed loosely or down by your side throughout the exercise and breathe steadily. ***DO NOT** hold your breath. *
- When you have completed the 2-minute wall squat, use your hands to push yourself away from the wall.

Do:

- ✓ Make sure the **Bend & Squat** is set up correctly.
- ✓ Keep your feet shoulder width apart.
- ✓ Keep your arms crossed loosely.
- ✓ Hold the exercise position for 2 minutes.
- ✓ Breathe steadily throughout the exercise.

Do NOT:

- X Sit on the **Bend & Squat**.
- X Slide down/up the wall.
- X Move your feet.
- X Hold your breath.

Polar M200 Instructions

Starting a **training session**

1. Wear your M200, and tighten the wristband.
2. Press and hold the RIGHT button.
3. Browse through the sport profiles with the RIGHT button until you reach 'Indoor other'.

   M200 has found your heart rate when the heart rate icon stops blinking and your heart rate is shown.

5. Press and hold the RIGHT button to start recording your training session.

Pausing/**Stop**ping a **training** session

To pause recording a training session, press the LEFT button. **Recording paused** is shown. To continue the recording, press the RIGHT button.

To stop recording a training session, press and **hold** the LEFT button. **Recording ended** is shown.

You can then save the training session by pressing the RIGHT button. Following this, press the LEFT button to return to the main menu.

Sending Data

After **EVERY** training session you will need to text **OR** email your heart rate and RPE data to the principle researcher, Harry Swift.

This is to ensure that you are working at the correct intensity and that no data gets lost.

The simplest way to send the HR data after each session is via text or email:

- **Text :**xxx
- **Email:** xxx

Training Session Timetable

Week 1							
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
AM							
Mid-Day							
Evening							

Week 2							
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
AM							
Mid-Day							
Evening							

Week 3							
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
AM							
Mid-Day							
Evening							

Week 4							
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
AM							
Mid-Day							
Evening							

Disclaimer

In the unlikely event of an adverse reaction occurring during a home-based exercise session (e.g. severe muscle pain, unusual shortness of breath, dizziness, chest pain/discomfort), you should stop exercising immediately and seek advice from a qualified medical practitioner.

Do not continue with the training programme until you have contacted:

Harry Swift

Tel: xxxx

Email: xxxx