The effect of a cardiac rehabilitation programme on carotid stiffness and haemodynamic properties of patients diagnosed with a transient ischaemic attack: a pilot study

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"I certify that all material in this research report which is not my own work has been identified and that no material is included for which a degree has previously been conferred upon me

……."

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List of abbreviations

ANOVA – Analysis of variance

ACE – Angiotensin-converting-enzyme inhibitors

AII – Angiotensin II

ARB – Angiotensin receptor blockers

AT_1 – Angiotensin type-1

BF – Blood flow

BFV – Blood flow velocity

BFV_{mean} – Mean blood flow velocity

BFV_{max} – Maximum blood flow velocity

BL – Baseline

BMI – Body mass index

BP – Blood pressure

BRS – Baroreflex sensitivity

Ca^{2+} – Calcium

CAD – Coronary artery disease

CC – Compliance coefficient

CCA – Common carotid artery

CON – Control

CR – Cardiac rehabilitation

DBP – Diastolic blood pressure

DC – Distensibility coefficient

ECG - Electrocardiogram

eNOS – Endothelial nitric oxide synthase

EX – Exercise

FBG – Fasting blood glucose

HDL – High-density-lipoproteins

HIIE – High-intensity intermittent exercise

HR – Heart rate

HR_{max} – Maximum heart rate

IMT – Intima-media thickness

LDL – Low-density-lipoproteins

LTPA – Leisure-time physical activity

NO – Nitric oxide

PI – Post-intervention

PP – Pulse pressure

PW – Pulse wave

PWV – Pulse wave velocity

$\dot{Q}$ – Cardiac output

RAAS – Renin-angiotensin-aldosterone system

RPE – Ratings of perceived exertion

SAC – Systemic arterial compliance

SBP – Systolic blood pressure

StiffINX – Stiffness index β

SV – Stroke volume

TC – Total cholesterol

TIA – Transient ischaemic attack

$\dot{V}O_{2max}$ – Maximal oxygen uptake

$\dot{V}O_{2peak}$ – Peak oxygen uptake

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Abstract

Arterial stiffness is associated with cardiovascular risk factors (e.g., hypertension, abnormal blood lipids and lipoproteins, physical inactivity and obesity) and the existence of atherosclerosis, and is identified as an independent risk factor for coronary artery disease and ischaemic stroke. The common carotid artery is the major conduit supplying blood to the brain is of particular interest. Research has demonstrated that interventions, which target the aforementioned risk factors, reduce the risk of occurring vascular events. The aims of this study were to 1) identify whether an 8-week cardiac rehabilitation programme reduces the stiffness of the common carotid artery, as determined by changes in arterial compliance, distensibility and stiffness index β, in transient ischaemic attack (TIA), and; 2) investigate the relationship between changes to arterial stiffness and haemodynamic properties of the common carotid artery. Eighteen male and female participants (mean ± SD; 65 ± 11 y, 1.72 ± 0.07 m, 85.6 ± 11.5 kg) recruited within a 14 day period following a TIA, volunteered to take part in the present study. Initial risk stratification assessments (i.e., cholesterol, glucose, ECG, etc) were completed prior to assessing arterial stiffness and haemodynamic properties. An ultrasound device was used to obtain arterial measures while participants were rested and in a supine position. Participants were then randomised to either an exercise (EX; 8-week intervention), or to a usual-care control (CON) condition. Identical vascular measures were obtained post-intervention. Results revealed a significant Test by Condition interaction for arterial compliance, distensibility and stiffness index β, and for compliance and distensibility following the 8-week exercise intervention (all $P < 0.05$). Post-hoc analysis demonstrated a significantly greater change in compliance and distensibility for the EX condition. No significant changes were observed in arterial haemodynamic properties or CAD risk stratification measures. The present study has demonstrated that exercise leads to improved

vascular health, as determined by a decrease in arterial stiffness, thus potentially leading to a reduced risk of an ensuing or recurring cardio- or cerebrovascular event.

1. Introduction

Behind all cancers and ischaemic heart disease, stroke is the third leading cause of mortality in New Zealand (NZ) and the Western World, and causes long-term disability (Gommans et al., 2009; Ministry of Health, 2009). A transient ischaemic attack (TIA) or 'mini stroke' comprises of a loss of focal neurological function, which typically resolves within 24 hours (Gommans et al., 2009). Individuals presenting with a TIA frequently have an elevated risk of recurrent TIA or stroke and other cardiovascular events including myocardial infarction and sudden death (Gommans et al., 2009; Prior et al., 2011). This risk can be as high as 12 % within 7 days and 20 % within 90 days of an initial TIA. Approximately half of these recurrent strokes occur within the first 48 hours of diagnosis and up to 85 % of strokes that follow a TIA will be fatal or disabling (Gommans et al., 2009).

Coronary artery disease (CAD) and ischaemic stroke share many of the same predisposing and potentially modifiable risk factors including hypertension, abnormal blood lipids and lipoproteins, smoking, physical inactivity, obesity and diabetes mellitus (Lennon & Blake, 2009; MacKay-Lyons et al., 2010; Prior et al., 2011). Analogous to these risk factors, the elastic properties of large arteries (i.e., the aorta and its major branches) pose a strong and independent risk factor for stroke (Laurent & Boutouyrie, 2005). Indeed, associations between these risk factors and arterial stiffness have been observed in cross-sectional investigations (Blacher et al., 1998; Weber et al., 2004), although no causal relationships have been established (Vlachopoulos et al., 2006). However, longitudinal research has directly demonstrated that arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive (Blacher et al., 1999a; Laurent et al., 2001), CAD (Boutouyrie et al., 2002) and end-stage renal disease patients (Blacher et al., 1999b).

Arterial stiffening occurs as a result of a progressive reduction in elastin content, smooth muscle cell numbers, and an increase in collagen composition within the vascular wall (Zieman et al., 2005). Many disease states such as diabetes mellitus, hypertension and renal disease are believed to amplify the vascular changes associated with arterial stiffening (Zieman et al., 2005). As large elastic arteries progressively stiffen, the ability of these vessels to effectively dampen the arterial pressure wave during each cardiac cycle is impaired (Filipovsky et al., 2005). Accordingly, reflecting sites appear closer to the descending aorta resulting in an earlier pulse wave reflection, which affects the mechanical properties of the aortic wall (Safar et al., 2003). Pressure during late systole is augmented increasing systolic blood pressure (SBP) and therefore pulse pressure (PP; PP = SBP – diastolic BP) at the site of both central and peripheral arteries (Laurent & Boutouyrie, 2005; Tahvanainen et al., 2009b). As such, the development of plaques and likelihood of subsequent plaque rupture increases (Laurent et al., 2003) thus increasing the risk of cardio- and cerebrovascular events. The elastic properties of carotid and peripheral arteries can be assessed by determining the dynamic properties of the arterial walls through the measurement of arterial distension and local blood pressures (Stoner at al., 2011).

Presently, the mechanisms currently employed for reducing vascular stiffness and/or its cardiac effects focus on pharmacological therapy including diuretics, nitrates, statins and renin-angiotensin-aldosterone system inhibitors (Zieman et al., 2005), focusing little on the effects of physical activity. Exercise-based cardiac rehabilitation (CR), which comprises lifestyle modification and drug therapy components, is used as a strategy to aid in the management and prevention of CAD. Accordingly, such a multifactorial approach leads to a 20 % – 32 % reduction in all cause cardiovascular mortality (Taylor et al., 2004). The significance of exercise as a secondary preventative strategy in individuals who sustained a TIA has been demonstrated in recent research (Faulkner et al., In Press; Prior et al., 2011) in

which investigations observed a significant reduction in CAD risk factors and an increase in cardiorespiratory fitness. Moreover, in individuals following an initial stroke or TIA exercise-based CR is believed to lead to an 80 % reduction in recurrent vascular events (Lawrence et al., 2011).

The effects of exercise on arterial stiffness have yet to be fully established; however, recent research has demonstrated that exercise leads to a significant decrease in arterial stiffness as determined by an increase in arterial compliance in diabetic patients with manifest CAD (Mourot et al., 2009). Furthermore, research has demonstrated a relationship between blood flow and/or shear stress during acute (Green et al., 2005; Padilla et al., 2008; Tanaka et al., 2006), long-term (Ivey et al., 2011) and habitual exercise (Ainslie et al., 2008). It is therefore plausible to speculate that exercise will have positive effects on vascular health in patients with manifest cerebrovascular disease. The aims of the present investigation were to: i) identify whether an 8-week cardiac rehabilitation exercise programme results in a reduction in arterial stiffening as determined by changes to local arterial compliance, distensibility and stiffness index β, and; ii) identify whether a concomitant improvement in several haemodynamic properties of the carotid artery occurs as determined by changes in blood flow, blood flow velocity and shear rate in TIA patients. As research has demonstrated significant changes to local arterial stiffness following exercise, it was hypothesised that an 8 week exercise programme would result in an increase in local arterial compliance and distensibility, thus having a positive effect on haemodynamic properties.

2. Literature review

2.1. Stroke

2.1.1. Epidemiology

Stroke is the third leading cause of mortality in New Zealand (NZ) and the Western World (World Health Organisation, 2008), behind all cancers and ischaemic heart disease, and is a major cause of long-term adult disability (Gommans et al., 2009; MOH, 2009). Approximately 6,000 New Zealanders suffer strokes each year, constituting a substantial physical, psychological and financial burden for patients, their families/whānau, health professionals and the wider community (Lennon & Blake, 2009). Furthermore, approximately one-third of those with stroke die within the first 12 months, with 2674 (1000 male) recorded deaths from stroke in 2006 (Ministry of Health, 2009), According to the NZ Clinical Guidelines for Stroke Management (2010), approximately 32,000 individuals are currently living with stroke, of which 30% are capable of independently performing activities of daily living.

Individuals who experience a stroke or transient ischaemic attack (TIA; 'mini stroke') for the first time are at a heightened risk of a subsequent stroke. This risk can be as great as 8 % within the first 48 h, 12 % at 7 days and 20 % at 90 days (Gommans et al., 2009; Lawrence et al., 2011). Moreover, research estimates that within a 5 year period 30 – 40 % of individuals will have a recurrent stroke or TIA (Lawrence et al., 2011). Within a 10-year period, however, the recurrent risk is slightly less at ~19 %, although according to Llyod-Jones et al. (2010) the combined risk of stroke, myocardial infarction or vascular death is ~43 %. Although the prevalence and mortality rate of stroke is currently on the decline in NZ, with a significant decrease in stroke mortality rates evident between 1987 and 2006, Māori mortality rates remain higher than non-Māori. The male age-standardised mortality rate in

2006 was 47.8 % lower than in 1987 and the female rate was 44.4 % lower (Ministry of Health, 2009).

2.1.2. Pathophysiology of transient ischaemic attack

A TIA, according to Gommans et al. (2009), may be defined as stroke signs and symptoms that resolve within 24 hours; although in most cases, symptoms usually resolve within 30-60 minutes. Typical symptoms of a TIA involve loss of focal or global neurological functions including unilateral weakness of the face, arm and/or leg, unilateral altered sensation, dysphasia (speech impediment), monocular blindness (partial loss of vision in one eye) and hemianopia (loss of vision in the left or right eye, or both). This temporary episode of neurological dysfunction is caused by a reduced blood flow to the brain – although without permanent death of brain tissue – or to the spinal cord or retina (Lloyd-Jones et al., 2010). Atherosclerotic disease of the carotid artery is believed to be responsible for between 20 % and 30 % of all strokes (Wakhloo et al., 2004). According to Gommans et al. (2009), approximately 25 % of people who suffer from an ischaemic stroke would have had a preceding TIA.

In a recent investigation O'Donnell et al. (2010) identified ten established and emerging risk factors for stroke, including hypertension, tobacco smoking, high waist-to-hip ratio, unhealthy diet, physical inactivity, diabetes mellitus, excessive alcohol intake, psychosocial stress and depression, cardiac pathologies (e.g., atrial fibrillation) and high ratio of high-density lipoprotein to cholesterol. These risk factors were found to be associated with 90 % of the risk of all stroke (O'Donnell et al., 2010). Indeed, individuals who present with a TIA have elevated levels of the above mentioned risk factors. In a cohort of stroke survivors, 80 % were pre-hypertensive or hypertensive, 34 % had low high-density lipoprotein (HDL) levels, 67 % were found to be overweight or obese and 45 % had impaired fasting blood

glucose (Kopunek et al., 2007). According to MacKay-Lyons et al. (2010) systolic blood pressure is the most robust independent predictor of secondary vascular events such as myocardial infarction or recurrent stroke. Evidently, interventions that target these factors have the potential to reduce the risk of a recurrent stroke and disability, and may have major public health benefits by reducing the burden of stroke and TIA on the state (Faulkner et al., In Press).

Current treatment strategies employed as a preventative measure to reduce the risk of a recurrent stroke or TIA, or other cardiovascular event, predominantly include the prescribing of anti-platelet agents, anti-coagulation, BP-lowering and cholesterol-lowering treatments (Gommans et al., 2009). However, strategies to promote behaviour change and lifestyle modification must also be addressed. As such, those diagnosed with a TIA require assessments and information regarding risk factors for stroke, in addition to other cardiovascular events, and strategies currently employed to modify these (Gommans et al., 2009). Of most concern is the fact that out of the 21 District Health Boards (DHB) established within NZ, only six (29 %) provide a dedicated out-patient service for the management of TIA patients (Brownlee et al., 2009). Moreover, ~40 % of DHBs were identified as having no guidelines for TIA management (Brownlee et al., 2009). A failure to both rapidly assess and appropriately manage patients presenting with a TIA represents a missed opportunity for the prevention of a recurrent TIA or stroke (Brownlee et al., 2009). The modification of lifestyle risk factors including tobacco smoking, unhealthy diet, excessive alcohol consumption and physical inactivity (Gommans et al., 2009; Lawrence et al., 2011), should therefore be addressed. As physical inactivity has alone been identified as an independent risk factor for stroke (Lee et al., 2003), engaging in regular exercise evidently leads to a reduction in BP and/or TC (Shephard & Balady, 1999), and may also lead to a reduction in stroke risk.

2.1.3. Physical activity and risk factor reduction

According to Hackam and Spence (2007), at least 80 % of recurrent vascular events in patients with manifest cerebrovascular disease are preventable by the application of a comprehensive, multifactorial approach. Accordingly, the combination of several proven strategies, including medical treatment (aspirin, statins and antihypertensive medications), dietary modification and physical activity, could reduce the risk of recurrent events in survivors of an initial stroke or TIA, thus reducing stroke burden (Hackam & Spence, 2007; O'Donnell et al., 2010). Exercise-based cardiac rehabilitation (CR), a multifactorial paradigm comprising physical activity, educational, psychological and drug therapy components, has been identified as an influential method in the secondary prevention and management of coronary artery disease (CAD) in randomised trials (Prior et al., 2011; Taylor et al., 2004). Accordingly, meta-analyses of the effects of exercise-based interventions in CAD patients have observed a 20 % – 32 % reduction in total and cardiac mortality (Taylor et al., 2004).

Specific to the purpose of the present study, a 10-week comprehensive CR programme demonstrated significant improvements in risk factors in participants who sustained a stroke 1 to 12 years prior to participation (Lennon et al., 2008). Both CAD and ischaemic stroke share many of the above mentioned predisposing and potentially modifiable risk factors. Indeed, physical activity leads to a reduction in BP, improves blood lipid and lipoprotein profile, reduces weight and positively influences diabetes mellitus. Recent research has directly demonstrated the significance of CR as a secondary component in reducing the risk of a recurrent stroke or TIA (Faulkner et al., In Press; Prior et al., 2011). For example, in a prospective cohort design, Prior et al. (2011) observed significant changes in key predisposing risk factors including aerobic capacity, total cholesterol (LDL and HDL), TC:HDL ratio, waist circumference, body mass index (BMI) and BP following a comprehensive CR programme. Similarly, in a randomised, parallel-group clinical trial,

Faulkner et al. (In Press) observed favourable changes in CAD risk factors including a ~6 % decrease in systolic blood pressure (SBP), ~11 % decrease in TC and an increase in aerobic capacity subsequent to participants completing an 8-week CR programme. Encouragingly, these changes remained significant 3 months following the intervention (Faulkner et al., In Press).

2.2. Arterial stiffness

2.2.1. Arterial functions

The arterial system has two directly interrelated haemodynamic functions: (i) the network of conduits, which deliver an adequate blood supply from the heart to peripheral tissues (London & Pannier, 2010), and; (ii) the elasticity of large arteries, which act to cushion and absorb the pulsatile energy of ventricular ejection during systole by dampening the arterial pressure wave and subsequently transforming the pulsatile pressure into continuous pressure as it propagates through the arterial tree (Kinlay et al., 2001; Laurent & Boutouyrie, 2005; London & Pannier, 2010; O'Rourke & Safar, 2005). The efficiency of this function is dependent on the elastic properties of the arterial walls in addition to the geometry of the arteries, including their diameter and length (London & Pannier, 2010). Distensibility and compliance collectively describe the ability of the vasculature to accommodate the change in pressure with ventricular ejection, and thus describe the stiffness of the arterial system both locally (i.e., common carotid artery) and systemically (London & Pannier, 2010; Stoner et al., 2012).

Local arterial compliance is expressed as compliance coefficient (CC)[1] and is determined by the absolute change in cross-sectional area per unit of pressure (Van Bortel et

[1] $CC = (2d \bullet \Delta d + \Delta d^2) / 4\Delta P$

al., 2002). Similarly, local arterial distensibility, expressed as distensibility coefficient (DC)[2], is defined as the relative change in arterial cross-sectional area per unit of pressure (Van Bortel et al., 2002). According to Oliver and Webb (2003), the elasticity of a given arterial segment is not consistent but instead depends on its distending pressure. At low distending pressure, the tension is borne by elastin-distensible fibres, whereas at high distending pressure, the tension is predominantly transferred and borne by less extensible collagen fibres, and the arterial wall becomes stiffer. Thus, the stiffness can only be defined in terms of a given pressure since stiffness increases with increases in BP (London & Pannier, 2010).

2.2.2. Mechanisms of arterial stiffness

The stability and resilience of the vascular wall of large arteries (i.e., the aorta and its major branches), and their ability to comply or stretch with a given change in pressure, are dependent on the relative contribution of collagen and elastin proteins (Zieman et al., 2005). Both proteins provide the vascular wall with structural integrity and elasticity (Zieman et al., 2005). These properties are not homogeneous throughout the arterial tree as elastin content progressively declines towards the periphery. The relative content of these scaffolding proteins is normally held stable by the slow but dynamic process of protein production and degradation (Zieman et al., 2005). However, arterial elastin is susceptible to the degenerative effects of continual pulsatile stresses caused by oscillatory arterial pressure (Avolio et al., 1998), and as such, with age, this regulatory process becomes impaired leading to the progressive deterioration of normal elastin content (Zieman et al., 2005). Accordingly, structural changes to the vascular wall arise, resulting in elevated arterial stiffening (Mattace-Raso et al., 2006). Although age exerts the most marked influence on arterial stiffening (Tuttolomondo et al., 2010), changes in haemodynamic forces (i.e., shear stress and tensile

[2] $DC = (2\Delta d \bullet d + \Delta d^2) / (\Delta P \bullet d^2)$

stress), which increase luminal pressure, amplify this vascular change by stimulating excessive collagen production (Zieman et al., 2005). Alteration of arterial elasticity due to structural modifications of elastin matrix results in functional changes of arterial properties, affecting arterial pressure through altered vessel compliance, wave transmission properties and secondary effects of wave reflection (Avolio et al., 1998).

2.2.3. Endothelial function

Endothelial cells, which line the inner surface of blood vessels, function as a structural barrier between the vessel wall and blood, preventing platelet and leukocycte aggregation and adhesion, as well as controlling permeability for plasma components and modulating blood flow (Marti et al., 2012). Additionally, studies suggest that the endothelium is an important regulator of arterial stiffness (Oliver & Webb, 2003). Many studies have established the role of endothelial dysfunction in vascular stiffening, in which the endothelium regulates stiffness, but recent studies have also suggested that the opposite holds as well in that arterial stiffening could alter or have adverse effects on endothelial function and thereby worsen stiffening (Oliver & Webb, 2003; Zieman et al., 2005). Indeed, both endothelial dysfunction and increased arterial stiffness coexist in individuals with an increased risk of cardiovascular disease, such as diabetics and smokers (Oliver & Webb, 2003). This has led to the hypothesis that cardiovascular risk factors influence arterial stiffening through endothelial dysfunction (Oliver & Webb, 2003).

The healthy endothelium regulates vascular tone by controlling the production of vasodilators and vasoconstrictors in response to various stimuli (Marti et al., 2012). In healthy arteries, the continuous production of nitric oxide (NO), one such endothelial-derived vasodilator, regulates vascular smooth muscle tone and arterial dimension (Kinlay et al., 2001). Once released by the endothelium in response to stimuli including bradykinin,

acetylcholine and catecholamines, and temperature and shear stress, NO defuses into the vessel wall (Marti et al., 2012). According to Tuttolomondo and colleagues (2010), investigations have demonstrated that endothelium-derived NO is one mechanism, which regulates large artery stiffness. Indeed, disruption of the endothelium-derived NO synthase gene within mice was found to promote abnormal arterial remodelling and facilitate pathological changes in the vessel wall (Rudic et al., 1998). However, it is unclear whether an inability of the vessel walls to effectively comply in turn further impacts on endothelial function and leads to a decline in endothelium-derived NO activity. Safar et al. (2001) indicated that a significant relationship does exists between NO-dependent endothelial function and arterial stiffness in spontaneously hypertensive rats, and speculated that a negative feedback may be established between NO and also PP through concomitant changes to arterial structure and function. Evidently, further studies are needed to fundamentally establish the cause-and-effect relationship between arterial stiffness and endothelial function.

2.2.4. Arterial structure and function, and stroke risk

Fernhall and Agiovlasitis (2008) mentioned that CAD risk factors that are present in childhood can predict the outcome of cardiovascular disease in adulthood. Recent studies suggested that risk factors such as hypertension, elevated LDL-cholesterol and obesity can predict the development of increased arterial stiffness and therefore a decreased arterial compliance in adulthood (Fernhall & Agiovlasitis, 2008). Stiffening of the aorta and its major conduits, which accompany age and cardiovascular risk factors are caused by various phenomena, including breaks in elastin fibres, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications and diffusion of macromolecules within the arterial wall; all of these have also been described at the site of the cerebral vasculature (Laurent & Boutouyrie, 2005). As such, supplementary to classic

CAD risk factors, arterial stiffness represents a valuable marker for cardiovascular disease risk within the community (Mitchell et al., 2010).

In addition to the abovementioned classic CAD risk factors, the elastic properties of large arteries (i.e., the aorta and its major branches) pose a strong and independent risk factor for stroke. However, it is important to note that research has predominantly focused on the influence of central (i.e., the aorta and it's major branches) or regional arterial stiffness on stroke risk and have neglected the importance of local arterial stiffness, specifically that of the common carotid artery. Although not too dissimilar, the mechanisms by which central and local arterial stiffness lead to stroke are illustrated in Figure 2.1. Cross-sectional studies have illustrated the importance of central arterial stiffness as a cardiovascular risk factor, and predictor of cardiovascular morbidity and mortality due to associations between other markers of cardiovascular risk or the magnitude of atherosclerosis (Laurent & Boutouyrie, 2005); however, prospective longitudinal studies have directly demonstrated the significance of arterial elastic properties as an independent risk factor and predictor of all-cause and cardiovascular mortality (Blacher et al., 1999b; Laurent et al., 2003; London & Pannier, 2010). This has been demonstrated in both healthy individuals (Mattace-Raso et al., 2006) and individuals with underlying pathologies including renal disease and hypertension.

As mentioned above, arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive (Blacher et al., 1999a; Laurent et al., 2001), CAD (Boutouyrie et al., 2002) and end-stage renal disease patients (Blacher et al., 1999b). In recent investigations including Mattace-Raso et al. (2006) and Mitchell et al. (2010) a significant association between higher aortic stiffness, as determined by a greater pulse wave velocity (PWV), and an increased risk of a first cardiovascular event was observed. In hypertensive patients arterial stiffness, which is increased in response to the higher distending pressure, may expose these patients to a higher risk of stroke (Laurent et al., 2003). Within

this investigation, however, Laurent and colleagues (2003), observed a significant association between measures of aortic stiffness and the occurrence of fatal stroke in a large cohort of 1715 essential hypertensive patients with no overt cardiovascular disease. The effects of classic risk factors on PWV were analysed by univariate and multivariate regression analysis. Results demonstrated that PWV was significantly associated with a 72 % increase in stroke risk. Participants were subject to follow-up assessments (mean duration was 7.9 y) in which 25 fatal strokes occurred (Laurent et al., 2003). As such, PWV significantly predicted stroke occurrence, an association found to be independent of classic risk factors (Laurent et al., 2003).

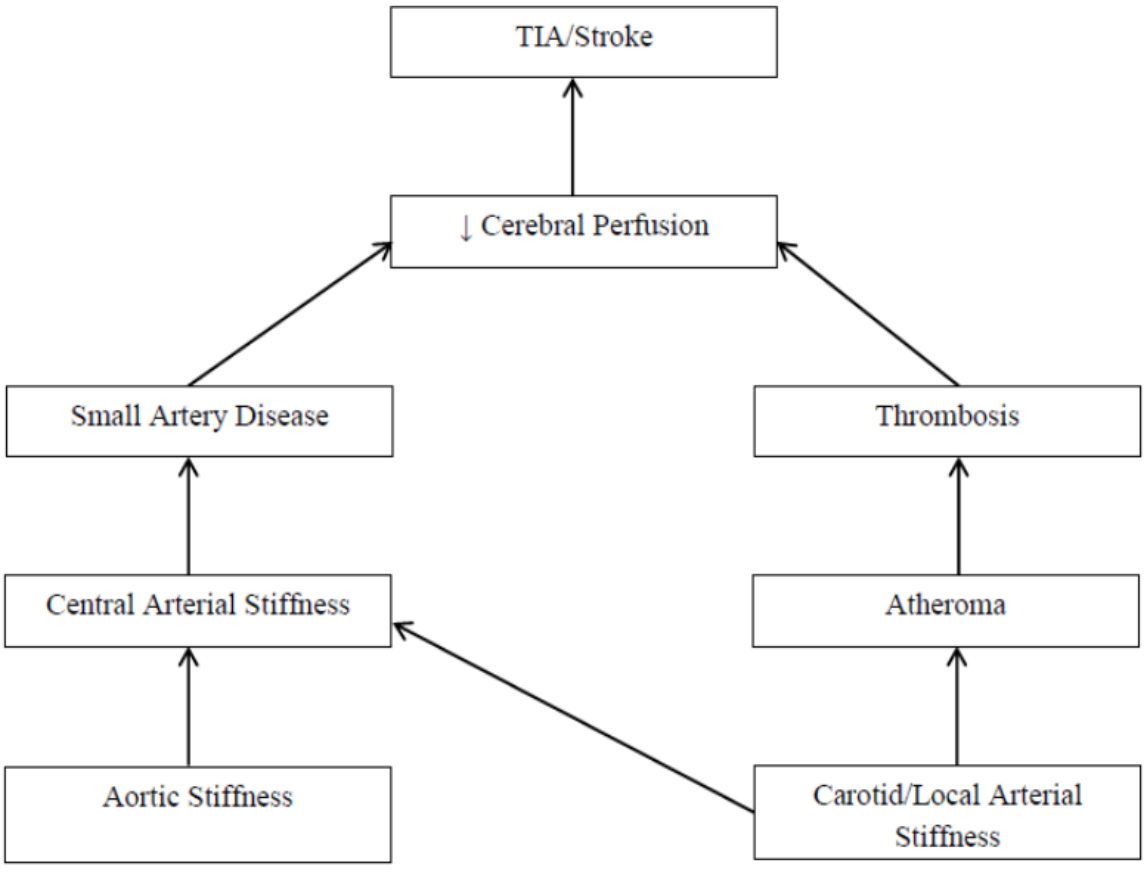


Figure 2.1: Illustration of the mechanisms by which central and local arterial stiffness lead to the occurrence of stroke.

It was recently demonstrated that patients presenting with acute ischaemic stroke exhibit higher arterial stiffness values when compared to non-stroke controls (Tuttolomondo et al., 2010). This was observed in 107 stroke patients in whom a greater PWV was exhibited (11.8 ± 3.3 m.s^{-1} as compared to 10.02 ± 2.29 m$\cdot$s^{-1}; Tuttolomondo et al., 2010). Interestingly, ~37 % of stroke patients recruited to take part in this study had suffered a preceding TIA. However, the association between arterial stiffening and the relative risk of a new vascular event in individuals with manifest cardiovascular or cerebrovascular disease remains unclear (Dijk et al., 2005). Research has shown that lower aortic stiffness is associated with favourable short- and long-term functional outcome in individuals following an ischaemic stroke (Gasecki et al., 2012a; Gasecki et al., 2012b). Accordingly, a lower carotid-femoral PWV, assessed within 7 days of suffering a stroke, leads to greater neurological improvements and hence shorter hospital admission (Gasecki et al., 2012a). Since indices of arterial stiffness have been recognised as an important factor indicating an individual's arterial age (Gasecki et al., 2012a), arterial stiffness could be related to future cardio- or cerebrovascular events. Early detection or identification of those at greater risk may therefore be warranted.

2.2.5. Effects of arterial stiffening

In a recent review Laurent and Boutouyrie (2005) identified several mechanisms through which increased arterial stiffness may in theory lead to increased risk of fatal stroke, including: (i) an increase in central pulse pressure (PP; ii) damage to cerebral vasculature, and; (iii) coronary heart disease and myocardial infarction concomitant with an augmented PP and arterial stiffening. Isolated systolic hypertension and elevated PP are two clinical manifestations of decreased vascular distensibility (Zieman et al., 2005). Although some of these mechanisms may explain the association between aortic stiffness and stroke, it is

believed that aortic stiffness reflects the existence of stiffness within other conduits (Mattace-Raso et al., 2006).

Research has suggested that increased arterial stiffness may be predictive of cerebrovascular disease through an increase in central PP (Tuttolomondo et al., 2010). With each cardiac cycle, the ejection of blood from the left ventricle during systole initiates an arterial pulse pressure wave, which travels toward the periphery (Laurent & Boutouyrie, 2005; Oliver & Webb, 2003; Safar et al., 2003; Zoungas & Asmar, 2007). As the pulse pressure wave reaches sites of impedance mismatch, predominantly at high-resistance or branching arterioles, it is reflected back towards the descending aorta. (Oliver & Webb, 2003; Safar et al., 2003; Zoungas & Asmar, 2007). According to Oliver and Webb (2003), the contour and amplitude of the arterial pulse pressure wave is influenced by large artery PWV ; the speed at which the pulse pressure wave travels along an arterial segment (Zoungas & Asmar, 2007). In young healthy individuals, PWV is slow and reflected waves return to the heart merged into the pulse that generated them (Oliver & Webb, 2003). At the site of central arteries diastolic blood pressure (DBP) is augmented (Oliver & Webb, 2003) Comparatively, in the peripheral circulation the reflected wave results in an increase in both SBP and PP (PP = SBP – DBP) producing a greater PP within the peripheral than central arteries (Oliver & Webb, 2003; Zoungas & Asmar, 2007). As large elastic arteries progressively stiffen, the ability of these arteries to effectively dampen the arterial pressure wave is impaired (Filipovsky et al., 2005) causing PWV to quicken (Safar et al., 2003). Accordingly, reflecting sites appear closer to the descending aorta, resulting in an earlier pulse wave reflection (Safar et al., 2003). Pressure augments during late systole, increasing SBP and PP at the site of both central and, to a lesser extent, peripheral arteries (Laurent & Boutouyrie, 2005; Tahvanainen et al., 2009b).

The consequential increase in arterial PP, as a result of arterial stiffening, has a marginal effect on systemic circulation to a majority of the bodily tissues (O'Rourke & Safar, 2005). However, due to the impaired ability of large elastic arteries to dampen the pressure waves generated by the heart, blood flow in the microcirculation becomes pulsatile, which has the potential to cause damage to circulation within the brain (Tahvanainen et al., 2009b) in addition to rousing carotid plaque rupture (Dijk et al., 2004; Mattace-Raso et al., 2006). Research suggests that the augmentation of PP may be considered a major determinant of small artery disease, as it influences arterial remodelling, increasing wall thickness at the site of both intra- and extra-cranial arteries and thereby increasing stroke risk (Laurent & Boutouyrie, 2005; Mattace-Raso et al., 2006). Research suggests that damage to the vessel wall in relation to arterial stiffness develops more frequently in the micro-vessels of end-organs (Kim et al., 2011). Indeed, the increased arterial stiffness measured locally within the common carotid artery may potentially reflect an increased arterial stiffness and thus PP within the intra-cerebral vasculature (Dijk et al., 2004). However, as a consequence, the increased pulsatile stresses imposed, may cause tearing to both endothelial and smooth muscle cells within the vessel wall (O'Rourke & Safar, 2005). This may lead to the development of small arterial dilations and aneurysms.

According to Dijk et al. (2004), the resulting increase in pulsatile stresses are believed to be a potent stimulus for carotid plaque rupture. Stiffer arteries are believed to contribute to plaque rupture especially when an inhomogeneity in stiffness in and around the plaque is present (Mattace-Raso et al., 2006). Indeed, previous investigations have identified substantial relationships between arterial stiffness and markers of cerebral atherosclerosis, which include carotid plaques, thickening of the carotid intima media and cerebral arterial calcification (Kim et al., 2011). A narrowing of the vessel lumen arises, which according to Filipovsky et al. (2005) impairs the conduit function of the vessel. It has been shown that PP

is independently associated with arterial plaque ulceration (Lovett et al., 2003; Mattace-Raso et al., 2006). This supports the hypothesis that the greater pulsatile haemodynamic forces are an important cause of plaque rupture as a result of an increased shear stress (Lovett et al., 2003; Mattace-Raso et al., 2006). Patients with a carotid artery stenosis, including those with an asymptomatic or moderate stenosis, have a considerable risk of ischaemic stroke (Dijk et al., 2004). In a recent investigation, Dijk et al. (2004) observed an association between increased carotid stiffness and the prevalence of TIA and ischaemic stroke in patients with ≥50 % stenosis. However, it is unclear whether a causal relationship exists between arterial stiffness and intra-cerebral small artery disease or with an embolism from stenosis of the carotid artery, or both.

As previously mentioned, vascular stiffening induces an earlier pulse wave reflection, which augments pressure during late systole increasing SBP and PP at the site of both central and peripheral arteries. As a consequence of this mechanism, the efficiency of ejection fraction reduces, increasing left ventricular workload which subsequently manifests as left ventricular hypertrophy (Laurent & Boutouyrie, 2005; Mattace-Raso et al., 2006; Zieman et al., 2005). As the heart ejects into a stiffer arterial system higher end-systolic pressures must be generated for the same net stroke volume (SV). Consequently, a greater energy requirement for a given level of ejected flow is needed to maintain cardiac output ($\dot{Q}$).. According to Kingwell (2002a), with important consequences for myocardial work capacity, aortic stiffness is a key factor modulating the relationship between myocardial blood supply and demand. As such, maximal $\dot{Q}$ may be compromised due to the potential influence of large artery stiffness whereby such effects would be expected to negatively impact on both exercise capacity and cardiovascular risk (Figure 2.2; Kingwell, 2002).

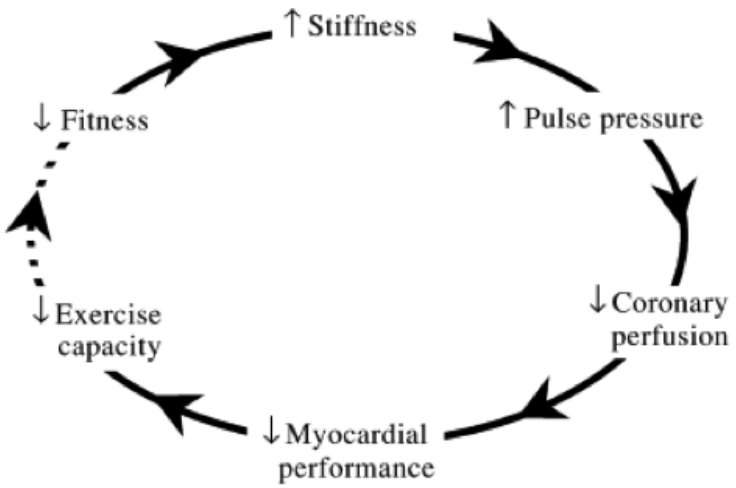


Figure 2.2: An illustration representing the circular nature of the relationship between stiffness of large elastic arteries, exercise capacity and cardiovascular risk (Kingwell, 2002**;** pg. 215). Accordingly, arterial stiffening augments pulse pressure, which leads to a decrease in diastolic blood pressure and a decrease in coronary perfusion. Myocardial performance is negatively affected, which results in a reduced exercise capacity and thus physical fitness. Ultimately, a lower physical fitness leads to progressive vascular stiffening. Kingwell, B. A. (2002). Large artery stiffness: implications for exercise capacity and cardiovascular risk. *Clinical and Experimental Pharmacology & Physiology*, *29*(3), 214-217.

Maximal exercise capacity in CAD patients is, according to Kingwell (2002a), largely related to myocardial ischaemia in which a reduced myocardial performance results in a diminished exercise capacity. However, this condition is not conducive to activity and may therefore lead to a diminished fitness level, a condition associated with further stiffening of the arteries and greater cardiovascular risk. Interestingly, Kingwell et al. (2002b) examined the relationship between large artery stiffness measured at rest, with time to onset of ischaemia during treadmill testing, as determined by a standardised level of ST-segment depression (1.5 mm). Accordingly, an individual's ischaemic threshold is primarily determined by both coronary perfusion and cardiac work. Kingwell and colleagues (2002b) hypothesised that for any given level of CAD, patients with a lower ischaemic threshold will have stiffer large elastic arteries. Results confirmed this hypothesis in which arterial stiffness was inversely related with time to ischaemia onset (Kingwell et al., 2002b); however,

research has yet to determine whether a similar relationship exists in TIA patients. While it is unclear whether individuals with stiffer arteries are predisposed with a low exercise capacity, it is clear that, once initiated, a vicious cycle promoting disease progression and diminished physical fitness ensues (Figure 2.2; Kingwell, 2002a). Therefore, as individuals with a low arterial stiffness experience fewer cerebrovascular events (Dijk et al., 2004), interventions that will lead to a reduction in arterial stiffening may break or reverse this vicious cycle decreasing the risk of a recurring vascular event.

2.2.6. Pharmacological interventions for reducing arterial stiffness

Among the pharmacological approaches for reducing vascular stiffness and/or its cardiac effects, diuretics, nitrates and renin-angiotensin-aldosterone system (RAAS) inhibitors are most commonly used (Zieman et al., 2005). Although effective when prescribed to reduce BP, the ability of such drug therapy to improve vascular function and structure is limited (Zieman et al., 2005). For instance, according to Mahmud (2006), the prescription of a diuretic (i.e., Hydrochlorthiazide or Indapamide), based on the concept that salt intake contributes to vascular stiffening, to reduce arterial stiffness have yielded contradicting results in several placebo-controlled studies. Despite reducing BP, no change in PWV was observed when participants ingested Indapamide (Laurent et al., 1990) or Hydrochlorthiazide (Benetos et al., 1996). In contrast, however, following treatment with a combination of Hydrochlorthiazide and Amiloride, Girerd and colleagues (1998) saw an improvement in arterial stiffness in hypertensive patients. Likewise, the use of nitrates do not substantially reduce arterial stiffness, although this drug therapy effectively reduces SBP and PP, the latter by inducing minimal changes in diastolic or mean pressure and by attenuating arterial wave reflections (Mahmud, 2007; Oliver & Webb, 2003; Zieman et al., 2005).

However, long-term treatment could lead to the development of nitrate tolerance (Oliver & Webb, 2003; Zieman et al., 2005).

According to Mahmud (2007), one mechanism by which RAAS may alter arterial stiffness is through angiotensin II (AII), a potent vasoconstrictor. Enhanced AII activity, mediated by the angiotensin type-1 (AT_1) receptor, is associated with collagen degradation, smooth muscle proliferation and the development of fibrosis, thus increasing vascular stiffness (Mahmud, 2007). However, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have been shown to have favourable effects on arterial stiffness. For example, in a cross-over study patients with essential hypertension received a 4-week course of the AT_1 receptor antagonist Losartan, which led to a decrease in PWV (Mahmud & Feely, 2002). Interestingly, the effects of Losartan were more favourable than the 4-week course of Hydrochlorthiazide. Cholesterol lowering therapy, including 3-hydroxyl-3-methylglutaryl coenzyme A inhibitors (statins), has also been investigated and found to increase arterial compliance. Consequently, the effects of statins are more pronounced in muscular arteries than in larger elastic arteries such as the descending aorta and carotid artery (Zieman et al., 2005). Lastly, the uses of ACE inhibitors and statins have also been found to improve endothelial function in a number of interventions (Oliver & Webb, 2003).

2.3. The effect of exercise on arterial stiffness

Epidemiological studies have fundamentally established that physically active men and women have a lower incidence of cardiovascular disease as compared to their sedentary peers (Tanaka et al., 2000). Engaging in regular physical activity leads to a reduced incidence of recurrent vascular events in manifest cardio- and cerebrovascular disease. Although the

mechanisms underlying this protective effect most certainly include favourable changes to, or favourable values of, CAD risk factors including BP, blood lipids and lipoproteins (Ronnback et al., 2007; Tanaka et al., 2000), it is possible that an enhanced central arterial compliance adds to this protective effect. Indeed, individuals who take part in regular physical activity regardless of the mode have more compliant arteries than less active individuals. For instance, Schmidt-Trucksass and colleagues (1999a) investigated the association between leisure-time physical activity (LTPA) with the structural and functional properties of the common carotid artery in male participants. This investigation used the Freiburger Questionnaire for Physical Activity, a self-administered questionnaire, which consisted of 12 questions including basic and recreational activities, and activities performed regularly to maintain and improve physical fitness. It was concluded that higher levels of LTPA were associated with reduced arterial stiffness of the common carotid artery, thus demonstrating the efficacy of regular physical activity (Schmidt-Trucksass et al., 1999a).

2.3.1. Aerobic (endurance) exercise

Although longitudinal research examining the effects of exercise on arterial stiffness is limited, according to Zieman et al. (2005), engaging in regular aerobic exercise diminishes the progressive stiffening of large elastic arteries. This has been demonstrated by means of cross-sectional investigations. A higher state of physical conditioning, as indicated by a greater maximal oxygen uptake ($\dot{V}O_{2max}$), is associated with reduced arterial stiffness (Vaitkevicius et al., 1993). Therefore, an improved aerobic capacity may mitigate the progressive stiffening of the arterial tree with age in addition to many diseased states (Vaitkevicius et al., 1993). However, it is unclear whether low-to-moderate aerobic exercise imparts a similar response upon the arterial tree (Zieman et al., 2005). Cameron and Dart (1994) observed a significant increase in systemic arterial compliance (SAC), where an

increase in arterial compliance corresponded to a decrease in arterial stiffness, following a 4-week exercise intervention in previously sedentary young adults (ages 18 – 32 y). In this investigation, subjects were required to cycle on a stationary ergometer for 30 min at 75 % $\dot{V}O_{2max}$ as determined by baseline assessments (Cameron & Dart, 1994). Notwithstanding, the increased SAC was concomitant with an increased mean $\dot{V}O_{2max}$ (5.1 ml•kg^{-1}•min^{-1}) and a decreased mean SBP (8.4 mmHg). Similarly, Tanaka et al. (2000) observed an increase in central arterial compliance following a 3-month exercise intervention in sedentary men. Where arterial compliance increased, however, BP, aerobic capacity and atherosclerotic risk factors (i.e., lipoproteins) remained unchanged.

Twelve weeks of high-intensity intermittent exercise (HIIE), in which young male participants performed 20 minutes of 8 s sprint bouts followed by 12 s recovery on a cycle ergometer 3 days per week, elicited a 37 % decrease in arterial stiffness (Heydari et al., 2012). More specific to the purpose of the present study, Monahan et al. (2001) observed a 29 % increase in carotid arterial compliance following a 3 month exercise intervention in which 13 men with no apparent cardiovascular disease (mean age of 56 ± 2 y) were required to walk or walk-jog on most days of the week for 40 – 45 min at 60 – 85 % of their HR_{max} (Monahan et al., 2001). Although, these studies demonstrate that, in addition to eliciting favourable effects on cardiac health, regular aerobic exercise positively influences arterial stiffness and as such vascular health, the subjects recruited to take part had no overt cardio- or cerebrovascular disease. Furthermore, each of these investigations used different methods and modalities.

In 32 individuals with type II diabetes mellitus, Mourot et al. (2009) demonstrated that arterial compliance significantly increased in both small and large arteries after participants completed a 6-week cardiac rehabilitation programme. Participants performed physical activity 5 times per week including 45 minutes of endurance-based exercise on a

stationary cycle ergometer at an intensity corresponding to the ventilatory threshold HR and 1 h of resistance-based exercise. Contrary to the findings of Mourot et al. (2009) and the aforementioned investigations, however, Ferrier et al. (2001) concluded that large-artery stiffening, associated with isolated systolic hypertension, is resistant to short-term aerobic exercise. In this investigation participants took part in an 8-week exercise intervention, which comprised of stationary cycling 3 times per week at an intensity of 65 % HR_{max} (Ferrier et al., 2001). It is possible that the exercise intensity chosen by Farrier and colleagues (2001) did not offer an ideal stimulus to promote vascular changes observed in previous investigations.

2.3.2. Resistance exercise

In contrast to aerobic exercise, resistance exercise does not promote the same effects on arterial stiffness (Vlachopoulos et al., 2006). According to Kingwell (2002a), the abrupt and large elevations in pressure associated with resistance training result in concentric left ventricular hypertrophy and as such may impact on the structural and functional proficiency of the aorta. As arterial pressure can reach levels in excess of 250 mmHg during weight training, such a marked increase may result in greater smooth muscle content, thereby increasing arterial stiffness (Maeda, 2010). In a cross-sectional analysis, Bertovic et al. (1999) determined that exclusively high-resistance strength-trained athletes had stiffer large arteries with an associated elevation in both brachial and carotid PP. It may be speculated that this adaptation acts as a protective mechanism limiting the expansion of the aorta upon acute lifting; although this is thought not to limit lifting capacity (Kingwell, 2002a). Contrary to the findings presented by Bertovic and colleagues (1999), however, Heffernan et al. (2007) found no significant evidence to suggest differences in indices of arterial stiffness between resistance trained (>7 y experience) and sedentary or recreationally active young men. Moreover, a bout of acute resistance exercise was found to have no significant effect on

arterial stiffness (Rakobowchuk et al., 2005). In an investigation compiled by Rakobowchuk et al. (2005), 28 young, healthy and physically active men took part in a 12-week resistance-based exercise intervention in which whole-body resistance exercises were completed five times per week. Accordingly, participants completed 3 sets of each exercise at ≥80 % of each participant's pre-determined 1 repetition maximum. Interestingly, the exercise intensities used in the investigations by Kingwell (2002a) and Rakobowchuk et al. (2005) were not too dissimilar, although providing contradicting evidence. As such further research is warranted.

Although the mechanisms to which aerobic exercise improves arterial stiffness are not clear, several hypotheses have been speculated. According to Monahan et al. (2001), structural changes to the arterial wall are thought to occur over years and as such short-term exercise is unlikely to improve arterial stiffness via this mechanism. It has been speculated, however, that an increased PP and mechanical descending pressure during a bout of exercise stretches the collagen fibres, modifying cross-linking and arterial compliance (Bruel et al., 1998). Arterial stiffness may also be altered by modulating the sympathetic-adrenergic tone of smooth muscle cells within the vessel wall (Barenbrock et al., 1996; Boutouyrie et al., 1994). This mechanism may be possible as a result of the enhanced sympathoinhibitory effects of NO influenced by regular exercise, which reduces the chronic suppressive influence exerted by sympathetic-adrenergic tone (Monahan et al., 2001; Tanaka et al., 2000).

2.4. Arterial haemodynamic properties

As blood flows through the arterial tree, the development of oscillating, or circumferential, and shear stresses near the walls of the vessel mediate the haemodynamic conditions within the blood vessels (Stoner & Sabatier, 2012). The latter, shear stress, is the frictional force that acts tangentially to the endothelial surface (Carallo et al., 1999) and may be considered the primary stimulus regulating endothelial cell function (Scissons et al.,

1999). Briefly, as blood flows parallel to the vessel wall, the average velocity of the red blood cells will increase from the lowest velocity at the periphery to the greatest velocity towards the centre of the lumen (Stoner & Sabatier, 2012). The resulting gradient of velocities produces a parabolic-like shape whereby the shear stress creates a frictional force at the surface of the endothelium (Figure 2.3; Stoner & Sabatier, 2012). The shear stress-induced deformation of endothelial cells is detected by mechano-receptors leading to a signalling cascade in which vasodilators diffuse across the interstitial space and enter the vascular smooth muscle cells. Calcium (Ca^{2+}) concentration subsequently lowers following which smooth muscle cells relax (Stoner & Sabatier, 2012). According to Stoner and Sabatier (2012), shear rate, derived from Poiseuille's Law, is a suitable substitute for shear stress and as such both conditions will be used interchangeably in accordance with the literature.

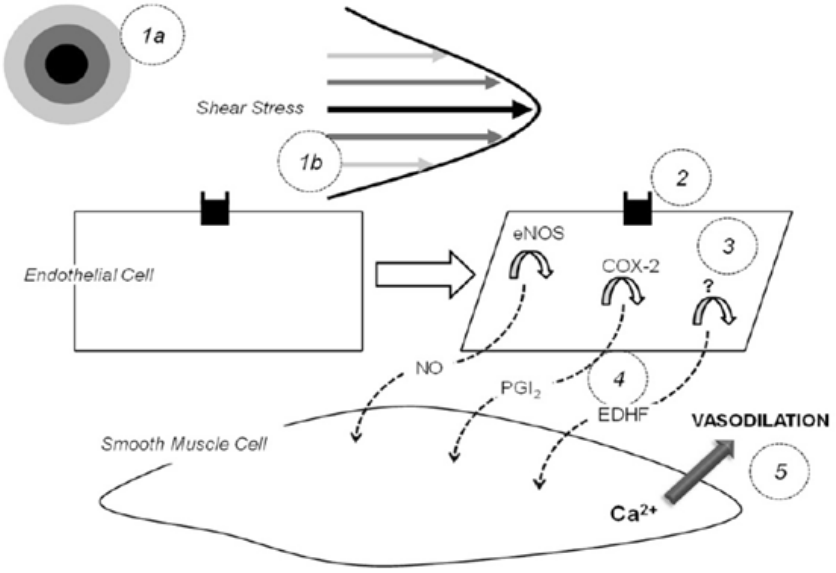


Figure 2.3: Endothelium-dependent dilation (Stoner & Sabatier, 2012; pg. 410). As blood flows parallel to the vessel wall, it creates a shearing stress at the surface of the endothelium. The average velocity of the red blood cells will increase from the lowest velocity at the periphery to the greatest velocity towards the centre of the lumen where the resulting gradient of velocities produces a parabolic-like shape (1a & b). Mechano-receptors detect the shear stress-induced deformation of the endothelial cells releasing a signalling cascade that leads to smooth muscle cell relaxation (2 – 5). Stoner, L., & Sabatier, M. J. (2012). Use of Ultrasound for Non-Invasive Assessment of Flow-Mediated Dilation. *Journal of Atherosclerosis and Thrombosis, 19*(5), 407-421.

Arterial wall shear stress may contribute to the acceleration of plaque ulceration through the haemodynamic property's interaction with endothelial cell function (Scissons et al., 1999; Wakhloo et al., 2004). Plaque ulceration is believed to occur at vascular sites with a combination of both low oscillating and shear stresses (Wakhloo et al., 2004). For example, lower shear stress values were observed in carotid arteries where plaques were present when compared to the plaque-free contralateral carotid artery (Gnasso et al., 1997). Vascular sites with a high shear stress have been shown to be relatively disease free; however, investigations have also speculated that as a consequence of endothelial damage, plaque ulceration may indeed occur at sites with high wall shear stress (Fry, 1968). Scissons et al. (1999), for example, found that high shear rates were observed within the same vascular site as the plaque formation, in contrast to previously reported findings. Indeed, shear rates are non-uniform throughout the arterial tree (Stroev et al., 2007). To accommodate this, the endothelium has mechanosensors, which detect changes to stress and adjust the lumen diameter accordingly, thereby modulating blood flow through the vessel (Stoner & Sabatier, 2012; Stroev et al., 2007). In order to maintain physiological levels of shear stress within the vessel, vascular tissues respond to the changes in shear stress with minor/acute adjustments to vascular tone (Figure 2.3; Stoner & Sabatier, 2012). However, research has identified a significant association between shear stress and carotid artery intima-media thickness (IMT), a manifestation of arterial stiffness (Zieman et al., 2005), demonstrating that shear stress is markedly lower in vessels with a thicker as compared to a thinner arterial wall (Carallo et al., 1999). Based on these results, Carallo and colleagues (1999) hypothesised that the alterations of the elastic properties within the tunica-media of large arteries makes the vessels unable to determine levels of stress forces, thus leading to a reduction in local wall shear stress. This may potentially predispose individuals to atherosclerosis (Carallo et al., 1999).

The diameter of the arterial lumen increases in size within the common carotid artery (CCA) with age and arterial stiffening (Bai et al., 2007), and plays an integral role with regards to maintaining haemodynamic properties within the blood vessels. The lumen constricts or dilates in response to certain stimuli. Some researchers have reported that the CCA diameter is associated with CAD risk factors, including BMI, smoking, BP and lipid profiles (Bai et al., 2007; Kawamoto et al., 2006). Indeed, research has demonstrated that individuals with less compliant arteries have larger lumen diameters (Sugawara et al., 2005). It has been postulated, for coronary arteries, that atherosclerotic plaques that occupy ≤40 % of the potential lumen area induce an increase in blood flow velocity and consequent vessel dilation, possibly to restore wall shear stress to physiological levels (Carallo et al., 1999). Although in some situations this may be an over-compensatory response for the enlarged diameters (Carallo et al., 1999), the same response could be speculated to occur within the carotid artery or other conduits. As a result of the degenerative changes which may occur to the common carotid wall, the increase in carotid artery diameter in relation to arterial wall shear stress might be related to the reduced distensibility of the examined vessels (Ferrara et al., 1995). This finding has been observed in patients with uncomplicated hypertension (Ferrara et al., 1995). The measurement of cerebral BF may be identified as an important factor in the diagnosis and follow-up assessments of cerebrovascular disease (Yazici et al., 2005; Albayrak et al., 2007). However, in a recent investigation Bai et al. (2007) concluded that acute and stable-chronic stroke survivors have lower blood flow velocities and volume, but larger CCA diameters, than non-stroke. Therefore, although BFV may increase to maintain shear stress within atherosclerotic coronary arteries, the same may not be true within the carotid arteries, which in turn may cause further plaque ulceration.

2.5. Effects of exercise on arterial haemodynamic properties

According to Padilla et al. (2008), habitual exercise provides repeated episodes of elevated vascular shear stress, which may be a mechanism responsible for the repair of endothelial dysfunction. However, different modes of exercise may evoke different haemodynamic responses within the endothelium, which could result in contrasting effects of shear stress on the vasculature (Green et al., 2005). To date, ample research has been conducted examining the relationship between blood flow and shear stress during exercise (Green et al., 2005; Padilla et al., 2008; Tanaka et al., 2006). For example, in a recent investigation, Padilla et al. (2008) observed a significant increase in brachial artery shear stress in 14 men (aged 46 – 68) immediately following high-intensity walking (45 min at 75 % $\dot{V}O_{2peak}$). Moreover, this increase was concomitant with an increase in BFV and arterial diameter (Padilla et al., 2008). Interestingly, Tanaka et al. (2006) reported an increase in BF in the non-exercising limb of 8 females completing single arm and leg cycle ergometry. Tanaka et al. (2006) concluded that conduit arteries are nonetheless exposed to greater BF and shear stress during exercise. It may, then, be speculated that the resulting increased shear stress may positively influence endothelial dysfunction within damaged/diseased conduit arteries or peripheral microcirculation, improving systemic haemodynamic properties. Indeed, global cerebral BF increases during moderate exercise in which Hellstrom and colleagues (1996) observed a 33 % increase in CCA BF with participants exercising at 60 – 67 % of maximal capacity. These investigations, however, have only reported the effects of acute exercise on BF and shear stress in healthy individuals.

To date, little research exists demonstrating the efficacy of habitual physical activity in improving haemodynamic properties in human subjects, although aerobic exercise training has been demonstrated to positively influence cerebral BF in animals (Ivey et al., 2011). Indeed, regular aerobic exercise is associated with a greater BFV in men aged 18 – 79 y when

compared to sedentary individuals (Ainslie et al., 2008). Individuals (of any age) with higher aerobic fitness (≥2 y experience), however, exhibit a greater BFV within the middle cerebral artery of 9.1 ± 3.3 $cm \cdot s^{-1}$ (~17 %) at rest as compared to age-matched controls. However, according to Ainslie et al. (2008), the decline in cerebral BF with age occurs independent of training status; although lower BFV may be the consequence of a lower cardiac output (Schmidt-Trucksass et al., 1999b). In contrast Murrell et al. (2011) observed no differences in resting BFV between trained and untrained participants of any age.

As it was demonstrated that habitual exercise positively maintains cerebral perfusion in a healthy aging population, it is plausible that exercise improves cerebral perfusion among stroke patients. However, the extent to which physical activity can be used as a strategy to improve cerebral blood flow and reduce potential brain injury following cerebral ischaemia is currently unknown (Ainslie et al., 2008). Animal studies have demonstrated that exercise improves long-term stroke outcome, improving cerebral BF (Ainslie et al., 2008). In a recent investigation, Ivey et al. (2011) observed a significant increase in middle cerebral artery blood flow velocity following a 6-month exercise intervention in stroke patients. Thirty-eight patients took part in this investigation in which nineteen patients were randomised to the exercise intervention and nineteen to a control group, which included non-aerobic stretching. The exercise group incorporated the use of aerobic exercise training on a treadmill. Notwithstanding, the increased blood flow velocity was concomitant with an increased aerobic capacity (Ivey et al., 2011).

2.6. Focus of the present study

As mentioned earlier in this literature review, arterial stiffness has been recognised as a CAD risk factor independent of the more classic CAD risk factors (i.e., hypertension,

cigarette smoking, obesity, physical inactivity). Moreover, endothelial cell function, regulated by the haemodynamic conditions within the blood vessels, is also associated with vascular stiffening (Carallo et al., 1999; Scissons et al., 1999; Stoner & Sabatier, 2012). Given the important pathophysiological and prognostic role of arterial stiffness, it is anticipated that a part of the reduction in cardiovascular risk is mediated through the improvement of arterial elastic properties (Vlachopoulos et al., 2006). As the use of drug therapy (i.e., diuretics) to improve vascular function and structure is limited (Zieman et al., 2005), more emphasis needs to be placed upon increasing levels of physical activity. Exercise-based cardiac rehabilitation positively influences CAD risk factors associated with vascular disease and recently has been identified as a secondary preventative treatment therapy to reduce the risk of recurring TIA or stroke (Faulkner et al., In Press). Therefore the primary aim of this investigation is to identify whether an 8-week cardiac rehabilitation exercise programme reduces indices of arterial stiffness including local arterial compliance, distensibility and stiffness index β in TIA patients. Secondary to this, the present study aims to identify whether a concomitant improvement in haemodynamic properties of the carotid artery occurs as determined by changes in blood flow, blood flow velocity, shear rate and vascular conductance. As recent research has demonstrated that exercise leads to a significant improvements in indices of arterial stiffness in both healthy (Monahan et al., 2001) and clinical populations (Mourot et al., 2009), it was hypothesised that exercise-based cardiac rehabilitation would improve vascular stiffness. Ultimately, these changes may be illustrated by an increase in arterial compliance and distensibility, and a reduction in stiffness index β. Furthermore, although research investigating the effects of exercise in arterial haemodynamic properties in stroke patients is limited, based on previous research (Ivey et al., 2011) it was hypothesised that exercise would positively influence arterial haemodynamic properties. To the knowledge of the research team, this is the first study to investigate the effects of an 8-

week exercise-based cardiac rehabilitation programme on arterial stiffness and haemodynamic properties of the common carotid artery in TIA patients.

3. Methods

3.1. Participants

Eighteen participants (mean ± SD; 65 ± 11 y, 1.72 ± 0.07 m, 85.6 ± 11.5 kg) diagnosed with a TIA volunteered for the present study. A TIA was diagnosed by a specialist stroke physician from the Wellington Regional Hospital according to the NZ TIA guidelines (2008). Participants were eligible if TIA diagnosis was within 7 days of symptom onset and if the patient resided within the Capital and Coast District Health Board. Exclusion criteria included: oxygen dependence, uncontrolled angina, unstable cardiac conditions, uncontrolled diabetes mellitus, major medical conditions, claudication, febrile illness, significant cognitive impairment and immobility.

A Clinical Nurse Specialist provided an information sheet (Appendix A) and invitation letter (Appendix B) to TIA patients who met study inclusion criteria. Verbal consent from the patient enabled the Clinical Nurse Specialist to provide the Massey University investigators with the patients name, date-of-birth, home address and telephone number, date of symptom onset and date of diagnosis. The principal investigator contacted each potential participant by telephone to determine whether they were willing to take part in the study. In accordance with recent research (Faulkner et al., In Press), those patients who were willing to take part in the study completed a baseline (BL) assessment within 14 days of symptom onset. All participants provided written informed consent prior to proceeding with BL testing procedures (Appendix C).

The present study was conducted in agreement with the policies and guidelines of the Northern X Regional Health and Disabilities Ethics Committee (Appendix D). Data reported in this study is registered with the Australian and New Zealand Clinical Trials Registry

(ACTRN12612000567820). The trial was undertaken in Wellington (NZ) between May 2012 and December 2012.

3.2. Procedures

All participants completed two laboratory based assessments; a baseline (BL) and post-intervention (PI) assessment. At the BL assessment, participants were firstly asked to complete a pre-exercise health screening questionnaire and to undergo a coronary artery disease (CAD) risk stratification assessments in accordance with the procedures outlined by the American College of Sports Medicine (ACSM, 2010). On completion of these CAD measures, each participant performed local arterial stiffness and haemodynamic measures followed by an exercise ECG treadmill stress test. Following the completion of BL assessments, participants were randomised to either an 8-week exercise intervention (EX) or to a control (CON) condition. Identical laboratory based assessments to BL were completed PI for all participants (EX & CON).

3.3. Measures undertaken at BL and PI assessments

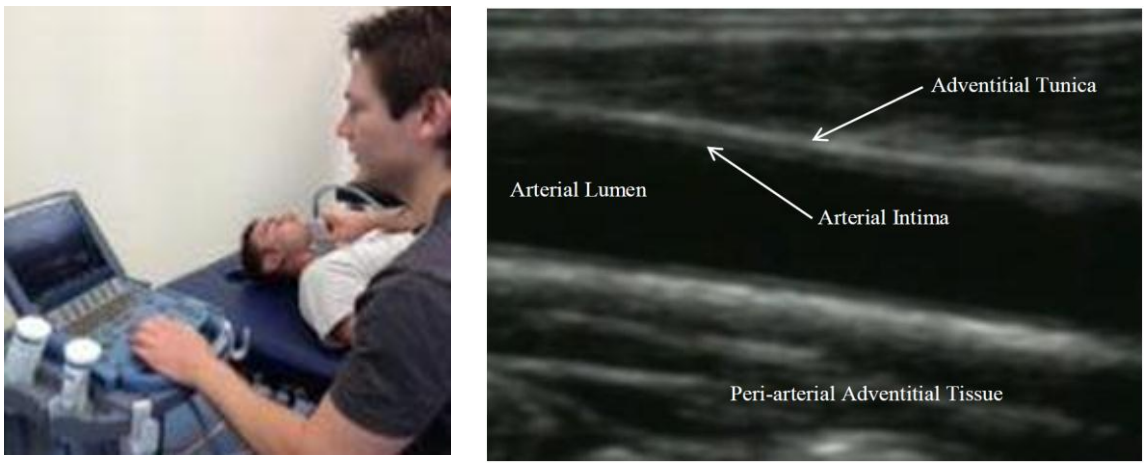
3.3.1. Coronary artery disease risk stratification

Fasting-blood glucose (FBG), total cholesterol (TC), high-density lipoproteins (HDL), TC:HDL ratio, blood pressure (systolic and diastolic blood pressure [SBP & DBP, respectively]), smoking history and family history of cardiovascular diseases were assessed (Appendix E). A health history questionnaire (Appendix F) was completed by each participant, which provided pertinent information regarding personal and family health history, current pharmacological therapy and physical activity status. Standard

anthropometrical measures, including height, weight and hip and waist circumference were also obtained.

3.3.2. Carotid artery stiffness

Local arterial stiffness was assessed using a portable Ultrasound system (Sonosite MicroMaxx, USA) equipped with a 13-6 MHz bandwidth transducer, which provided high-resolution Brightness mode (B-mode) measurements. Participants were examined on the right side, in a supine position, and with their head tilted at 45^{o} (angled to the left; Figure 3.1a). Measurements were obtained from the right common carotid artery 1 – 2 cm beneath the bifurcation (Paini et al., 2006). Care was taken to ensure that the vessel clearly extended across the entire imaging plane to minimize the likelihood of skewing the vessel walls. Magnification was then adjusted to optimise imaging of the proximal and distal vessel walls (Figure 3.1b). Accordingly, following a 15-minute rest period (Schmidt-Trucksass et al., 1999b), three video recordings, captured at 30 frames per second, were gathered during which participants were asked to hold their breath to reduce movement of the vessel as a result of respiration. Each recording lasted 10 s and typically comprised of at least five cardiac cycles.



(B) Participant position **(A) Ultrasound image**

Figure 3.1: Local arterial stiffness and haemodynamic assessments. (A) Participants lay supine with their head tilted 45^{o} away from the examined right side. (B) Magnified ultrasound image of the common carotid artery.

During the 15-minute rest period, BP was measured on three separate occasions with a 4-minute interim period between each measure. Upon data analysis, the closest two BP readings were averaged, in accordance with the ACSM (2010), and used to calculate PP applying the following equation:

$$PP = SBP - DBP$$

3.3.3. Blood flow velocity

Blood flow velocity was assessed with Pulsed Wave (PW) Doppler using the abovementioned portable Ultrasound device. Data was gathered subsequent to gathering arterial stiffness measures. Participants were in an identical position as to when obtaining measures of carotid arterial stiffness (Figure 3.1a & b). The insonation angle was set at 45 – 60^{o} (Yazici et al., 2005) and then aligned with the vessel wall by rocking the transducer (heel/toe adjustments). The steering angle was set at $+15^{o}$ to minimise potential error associated with the heel/toe adjustments (Figure 3.2). The gate size was adjusted depending on the vessel size to accommodate and to sample most of the vessel. A 60 s video recording of the Doppler Spectral Trace (Figure 3.3), captured at 30 frames per second, was obtained from the carotid artery.

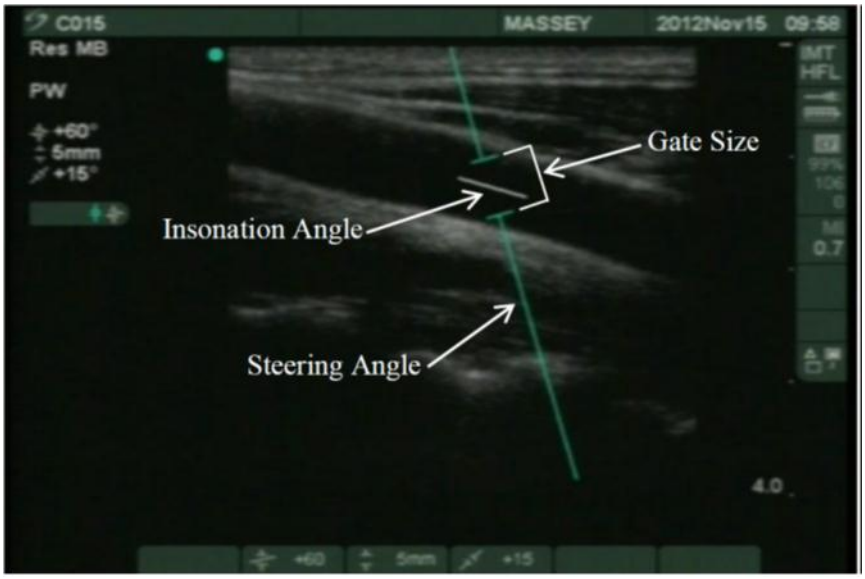


Figure 3.2: Visual representation of the common carotid artery with the Insonation Angle, Steering Angle and Gate size illustrated.

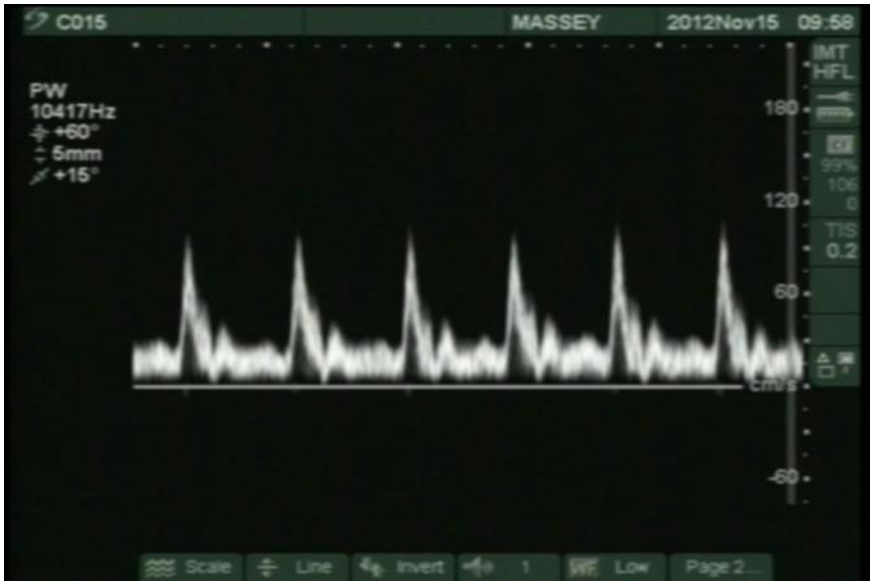


Figure 3.3: Doppler Spectral Trace over a 4.8 s period.

3.3.4. Treadmill exercise stress test

Each participant completed a resting and exercise 12-lead electrocardiogram (ECG). During rest, the participant's heart rate (HR) and BP were monitored. For the exercise ECG, participants performed a walking stress test using a standardised Modified Bruce Protocol (ACSM, 2010). This test consisted of several 3-minute stages whereby upon completion of

each stage the treadmill speed and gradient increased. During the initial two stages of the exercise test, for instance, participants walked at 2.7 $km.hr^{-1}$ with 0 % and then 10 % gradient. Thereafter, the treadmill speed and gradient simultaneously increased. Blood pressure readings were gathered towards the end of each 3-minute stage and participants were asked to provide subjective perception of exertion using the Borg 6-20 Ratings of Perceived Exertion (RPE) Scale (Borg, 1998) in the final 30 s of each stage. The test was terminated if a heart rate equivalent to 85 % of age-predicted maximum was achieved, if the investigators conducting the test terminate the test based on the physiological responses observed from the exercise ECG (i.e., ST depression of 2 mm, frequent premature ventricular contractions) or if the participant reported volitional exhaustion (can stop the test at any time point). Similar procedures to those outlined here have been adopted elsewhere (Faulkner et al., In Press).

3.4. Randomisation

Randomisation to the EX or CON condition occurred after BL assessments. Allocation to groups was by means of sealed envelopes drawn by the participants, designed for a 50:50 allocation between groups. Due to the nature of the intervention, it was not feasible to blind patients or researchers to group allocation.

3.5. Exercise intervention

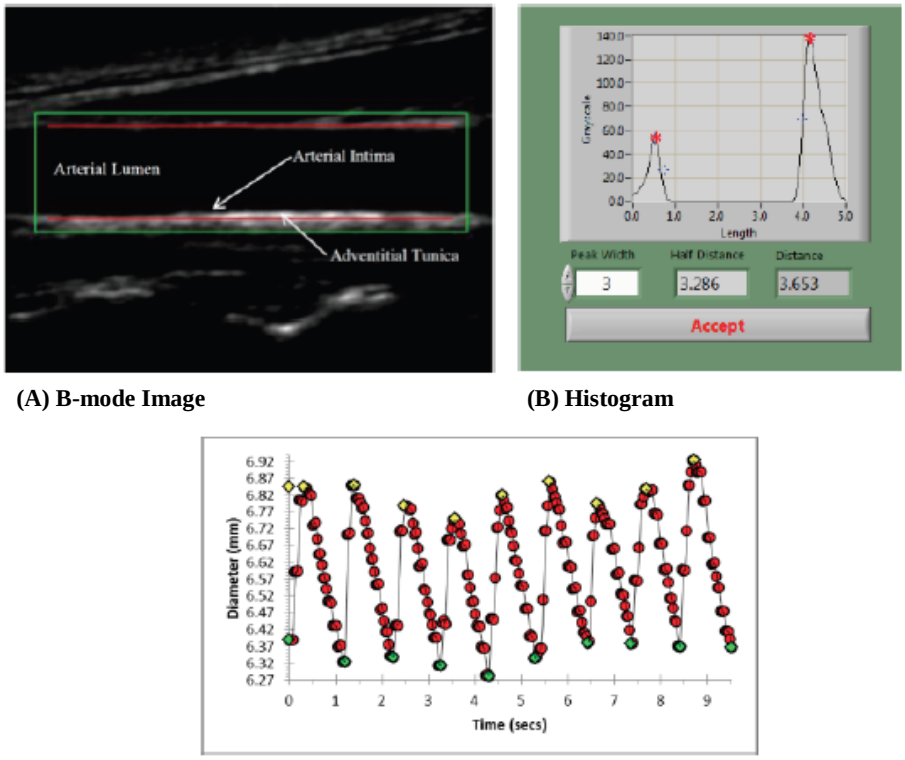
Participants randomised to the exercise condition were required to take part in an 8-week, twice-weekly exercise intervention, similar to that of an exercise-based cardiac rehabilitation programme (Faulkner et al., In Press). Recent research has demonstrated that an 8-week exercise intervention significantly improved TC, BP and aerobic capacity in 30 newly

diagnosed (within 2 weeks of symptom onset) TIA patients (Faulkner et al., In Press). Participants were supervised by and worked one-on-one with a clinical exercise practitioner. Exercise sessions lasted 90 minutes and consisted of a total of 30 minutes of aerobic exercise, 45 minutes of upper and lower body resistance (i.e., shoulder press, squats, biceps curls), balance and core-stability exercises and approximately 15 minutes of stretching. The 30-minute aerobic session included two 15-minute periods in which the participants walked on a treadmill and cycled on an ergometer. Exercise intensity was self-selected and used the 6 – 20 RPE scale (Borg, 1998); however, data obtained from the exercise ECG and HR thresholds were also used to guide the exercise intensity where necessary. Following a week of familiarisation (sessions 1 – 2), participants were asked to exercise at an RPE of 13 (somewhat hard; sessions 2 – 9) and then an RPE of 15 (hard; sessions 10 – 16), increasing or decreasing the resistance level accordingly during both the aerobic and resistance exercises.

3.6. Data analysis

3.6.1. Arterial diameter measurement

The video recordings obtained from each participant were decompiled into separate Joint Photographic Experts Group (JPEG) images, which provided 30 diameter measurements per second. The images were then subsequently analysed using semi-automated edge-detection image-analysis software custom written to interface with LabVIEW (version 6.1). Briefly, subsequent to calibrating the images, a line corresponding with the long axis of the artery was manually inputted. A region of interest (ROI) along the length of the artery was then selected. Custom written Excel Visual Basic code was used to fit peaks and troughs to the diameter waveforms to calculate diastolic, systolic and mean diameters (Figure 3.4). Similar procedures have been used elsewhere (Stoner et al. 2011).



(A) B-mode Image **(B) Histogram**

(C) Diameter waveforms

Figure 3.4: Semi-automated edge-detection image-analysis software. (A) B-mode image of the common carotid artery, which corresponds with the (B) histogram. The stars correspond to the vessel walls. The distance between the brightest horizontal segments was recorded. (C) Diameter waveform representing nine cardiac cycles. The yellow markers represent systole while the green markers represent diastole.

3.6.2. Arterial stiffness calculations

Local arterial stiffness was defined by three functional characteristics of the vascular wall including compliance, distensibility and stiffness index β. Local arterial compliance was expressed as compliance coefficient (CC) and defined as the compliance per unit of length, which is the absolute change in cross-sectional area (ΔA) per unit of pressure (ΔP; Van Bortel et al., 2002). This is represented by the following equation:

$$CC = (2d \bullet \Delta d + \Delta d^2) / 4\Delta P$$

where d is diameter and Δd is distension. Local arterial distensibility was expressed as distensibility coefficient (DC) and defined as the relative change in cross-sectional area

(ΔA/A) of the vessel per unit of pressure (Van Bortel et al., 2002). This is represented by the following equation:

$$DC = (2\Delta d \bullet d + \Delta d^2) / (\Delta P \bullet d^2)$$

Stiffness index β is defined as the ratio of the natural logarithm of SBP/DBP to the relative change in diameter, and represents the mechanical properties of the vascular walls of large elastic arteries (Oliver & Webb, 2003; Wada et al., 1994) as represented in the following equation:

$$\text{Stiffness Index } \beta = \text{In}(P_s/P_d) / [(D_s\text{-}D_d) / D_d)]$$

where P_s is systolic pressure, P_d is diastolic pressure, D_s is the inner diameter of the vessel at systole and D_d is the inner diameter at diastole. Pulse pressure, calculated from the BP recordings mentioned above, during the cardiac cycle is equal to ΔP (Van Bortel et al., 2002).

3.6.3. Blood flow velocity analysis

Each 60 s recording was decompiled into JPEG images. Custom software designed to interface with MatLab (Version) was used. Each image illustrated the complete 4.8 s velocity data sample, as shown in Figure 3.5, from which time average mean, maximum and minimum blood flow velocity for each cycle was determined.

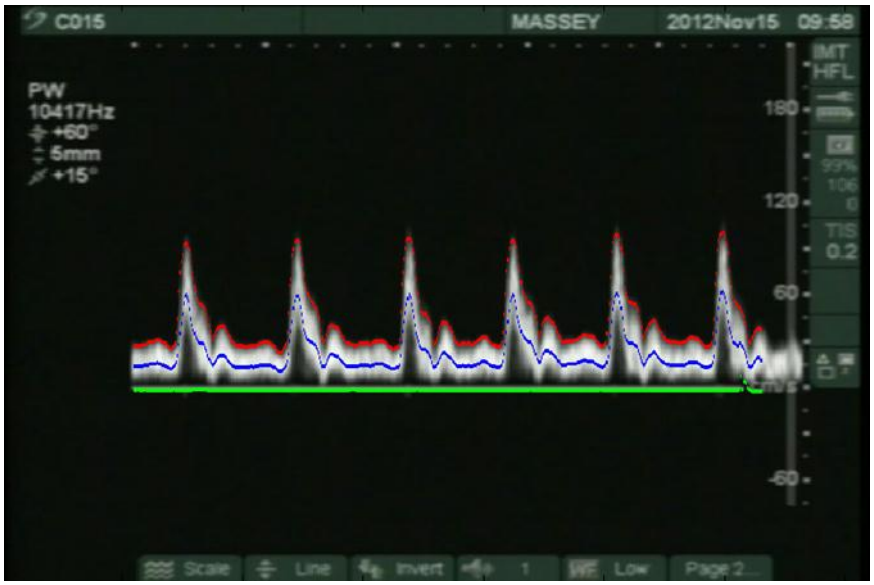


Figure 3.5: Analysis of the Doppler Spectral Trace. Representation of time average mean (blue line), maximum (red line) and minimum (green line) for each cardiac cycle over the 4.8 s period.

3.6.4. Blood flow

Blood flow was calculated from the area of the vessel and time average maximum blood flow velocity using the following equation:

$$BF = (a \bullet BFV) \bullet 60$$

where a is representative of the area of the vessel.

3.6.5. Shear rate

Shear rate was calculated from mean blood velocity and the internal lumen diameter using the following equation (Celermajer et al., 1992):

$$\text{Shear rate} = (8 \bullet \text{mean blood velocity}) / d$$

where the numerator of 8 represents an assumed parabolic profile.

3.6.6. Conductance

Conductance was calculated from blood flow and mean arterial pressure (MAP) by applying the following equation:

$$\text{Conductance} = \text{BF} / \text{MAP}$$

3.7. Statistical analysis

Independent samples t-test were used to compare BL data (i.e., age, height, weight, BMI, medication) between EX and CON conditions. Levene's Test was used to assess the equality of variance between conditions. A two-factor repeated-measures analysis of variance (ANOVA); Test (BL and PI) × Condition (EX vs.CON) was used to assess changes CAD risk factors, markers of arterial stiffness, lumen diameter and arterial haemodynamic properties. A three-factor repeated-measures ANOVA; Test × Condition × Time was used to determine the changes in cardiorespiratory fitness (first 2 stages of exercise stress test, BP, HR and RPE). Mauchly's Test of Sphericity was used to test assumptions of equality of variance. Greenhouse-Geisser Epsilon was used where violations of sphericity were evident. Where statistical differences were observed, a Bonferroni adjustment was used when undertaking multiple significant tests to reduce the risk of type I error. Significance level was set at $P < 0.05$. All data was analysed using SPSS version 18. Effect sizes were reported to describe the importance of the relevant findings in practical terms (Richardson, 2011). Partial eta squared (η_p^2) was used as a measure of effect size, with 0.0099, 0.0588 and 0.1379 representing a small, medium and large effect (Cohen, 1969).

4. Results

4.1. Recruitment

Thirty-five individuals met the inclusion criteria and were invited to participate in the present study. Eighteen TIA patients were recruited to take part in the present study out of the possible 35 referred from Wellington Regional Hospital. This demonstrated a 51 % recruitment rate over a 6 month period.

4.2. Participant characteristics at BL

As demonstrated in Table 4.1, there were no significant differences in participant descriptives or prescribed medication at the BL assessment between conditions (all $P > 0.05$).

Table 4.1: Baseline characteristics of both exercise (EX) and control (CON) conditions displayed as mean ± SD.

Variables	**EX patients *n* = 9**	**CON patients *n* = 9**	***P***
Age (y)	67 ± 10	64 ± 12	0.597
Height (m)	1.73 ± 0.08	1.71 ± 0.06	0.610
Weight (kg)	86.4 ± 10.5	84.8 ± 13.0	0.789
BMI (kg.m^2)	28.8 ± 2.8	29.0 ± 4.9	0.947
Statin therapy (*n* [%])	8 (89 %)	8 (89 %)	1.000
Antihypertensive therapy (*n* [%])	5 (56 %)	3 (33 %)	0.372
Aspirin therapy (*n* [%])	9 (100 %)	8 (89 %)	0.332

4.3. Arterial stiffness

4.3.1. Arterial compliance

A significant Test by Condition interaction was observed ($F_{(1, 16)} = 7.74$, $P < 0.05$, $\eta_p^2 = 0.326$). Post-hoc analysis demonstrated a significantly greater change in arterial compliance coefficient for EX than CON (Table 4.2). Similar findings were reported when the arterial compliance coefficient was expressed as a proportion of BL. A significantly greater percentage change in compliance for EX (30.4 %) compared to the CON group (4.9 %; Figure 4.1).

4.3.2. Arterial distensibility

ANOVA revealed a significant Test by Condition interaction ($F_{(1, 16)} = 8.70$, $P < 0.05$, $\eta_p^2 = 0.352$). Post-hoc analysis demonstrated a significantly greater change in distensibility for EX compared to CON (Table 4.2). A significantly greater percentage change in distensibility was observed for EX (39.7 %) compared to CON (7.4 %; $t_{(16)} = -2.75$, $P < 0.05$; Figure 4.1).

4.3.3. Stiffness index β

There was no Condition main effect or a Test by Condition interaction for stiffness index β (both $P > 0.05$). However, a significant Test main effect was observed for stiffness index β ($F_{(1, 16)} = 9.31$, $P < 0.05$). A lesser stiffness index β was revealed for PI as compared to BL (12.28 ± 3.14 cf. 14.34 ± 4.57, respectively). When expressed as a proportion of BL, a similar change in stiffness index β was revealed for EX and CON (Figure 4.1).

Table 4.2: Properties of arterial stiffness including compliance coefficient (CC), distensibility coefficient (DC) and stiffness index β (StiffINX) at baseline (BL) and post-intervention (PI) between Control (CON) and Exercise (EX) conditions. Values displayed as mean ± SD. Effect sizes (η_p^2) reported as small (0.0099), medium (0.0588) and large (0.1379).

	BL		PI		
Variables	**EX**	**CON**	**EX**	**CON**	η_p^2
CC ($mm^2 \cdot kPa^{-1}$)	0.69 ± 0.16	0.62 ± 0.15	0.88 ± 0.19*#	0.62 ± 0.11	0.326
DC ($10^{-3} \cdot kPa^{-1}$)	15.19 ± 5.68	15.40 ± 4.34	20.31 ± 5.69*#	15.77 ± 2.59	0.352
StiffINX β	14.19 ± 5.72	14.50 ± 3.40	11.17 ± 3.74#	13.40 ± 2.03	0.112

*Significant Test by Condition interaction; #Significant change from BL to PI assessments

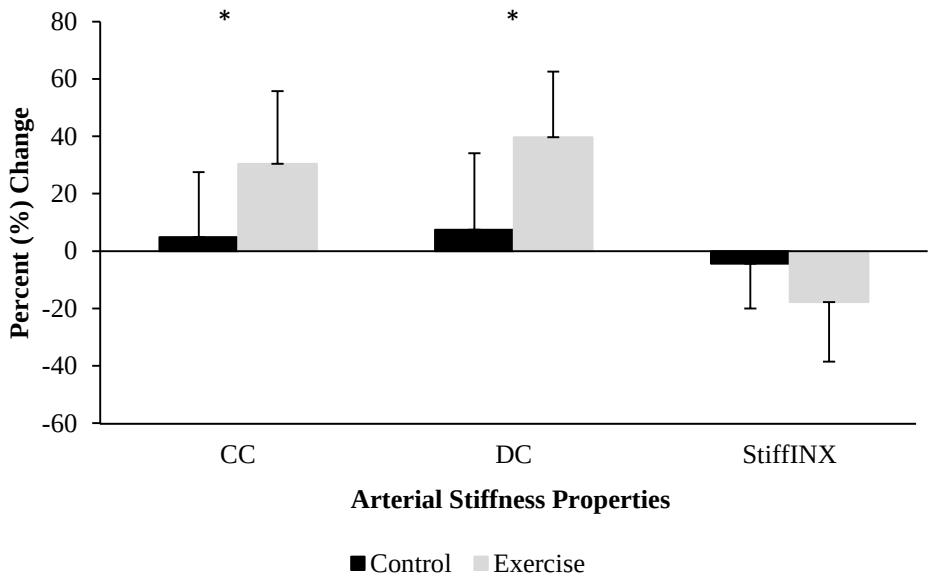


Figure 4.1: Mean percent (%) change in compliance coefficient (CC), distensibility coefficient (DC) and stiffness index β (StiffINX). Displayed as mean ± SD. *Significant difference between Control and Exercise conditions.

4.3.4. Lumen diameter

Although there was no main effect for Condition or a Test by Condition interaction (both $P > 0.05$), a significant Test main effect was revealed for lumen diameter during diastole ($F_{(1, 16)} = 5.81$, $P > 0.05$). A smaller lumen diameter was revealed PI compared to BL

(7.36 ± 0.76 cf. 7.51 ± 0.85 mm, respectively). When expressed as a proportion of BL, no differences in lumen diameter were reported between EX and CON (3.0 ± 3.0 cf. 0.8 ± 3.9 %, respectively; $P > 0.05$).

4.3.5. Systolic blood pressure

A significant Test by Condition interaction was observed ($F_{(1, 16)} = 8.19$, $P < 0.05$). Post-hoc analysis revealed a significant change in SBP between BL and PI for EX (144 ± 17 cf. 131 ± 10 mmHg, respectively) but not for CON (124 ± 12 cf. 126 ± 13 mmHg).

4.3.6. Diastolic blood pressure

ANOVA revealed a significant Test by Condition interaction for resting DBP ($F_{(1, 16)} = 9.54$, $P < 0.05$). Post-hoc analysis revealed a greater change in resting DBP in the EX condition between BL and PI assessments (83 ± 12 cf. 76 ± 9 mmHg) as compared to the CON condition (77 ± 8 cf. 78 ± 8 mmHg, respectively).

4.3.7. Pulse pressure

ANOVA revealed no Test or Condition main effects or a Test by Condition interaction for resting PP (all $P > 0.05$).

4.4. Arterial haemodynamic properties

There was no Test or Condition main effect, or a Test by Condition interaction for BFV_{mean}, BFV_{max}, BF, shear rate and conductance (all $P > 0.05$; Table 4.3). Similar findings were reported when each of the aforementioned markers were expressed as a proportion of BL.

Table 4.3: Arterial haemodynamic properties including mean blood flow velocity (BFV_{mean}), maximum blood flow velocity (BFV_{max}), blood flow (BF), shear rate and conductance at baseline (BL) and post-intervention (PI) between exercise (EX) and control (CON) conditions. Values displayed as mean ± SD. Effect sizes (η_p^2) reported as small (0.0099), medium (0.0588) and large (0.1379).

	BL		PI		
Variables	**EX**	**CON**	**EX**	**CON**	η_p^2
BFV_{mean} (cm)	15.56 ± 2.57	16.31 ± 6.18	14.75 ± 3.63	16.09 ± 5.06	0.006
BFV_{max} (cm)	29.33 ± 5.03	31.40 ± 11.02	28.80 ± 6.14	30.50 ±9.10	0.001
BF (ml/min)	447.67 ±107.22	393.13 ± 154.28	396 09 ± 102.96	375.41 ± 107.88	0.021
Shear Rate	161.98 ± 36.13	185.30 ± 79.73	158.59 ± 47.17	185.53 ± 68.30	0.002
Conductance	4.39 ± 1.17	4.29 ± 1.72	4.20 ± 1.14	4.06 ± 1.40	0.000

4.5. Coronary artery disease risk stratification

There were no significant changes in CAD risk factors (TC, HDL, TC:HDL, FBG and hip and waist circumference) for EX and CON conditions following PI assessments (all $P > 0.05$; Table 4.4).

Table 4.4: Coronary artery disease risk stratification measures including total cholesterol (TC), high-density lipoproteins (HDL), TC:HDL ratio, fasting blood glucose (FBG) and hip and waist circumference between baseline (BL and post-intervention (PI) assessments in exercise (EX) and control (CON) conditions. Values displayed as mean ± SD.

	BL		PI	
Variables	**EX**	**CON**	**EX**	**CON**
TC ($mmol/L^{-1}$)	3.46 ± 0.83	3.52 ± 0.52	3.54 ± 0.82	3.61 ± 0.90
HDL ($mmol/L^{-1}$)	1.13 ± 0.34	1.27 ± 0.38	1.11 ± 0.26	1.42 ± 0.47
TC:HDL ($mmol/L^{-1}$)	3.3 ± 1.1	3.1 ± 1.2	3.6 ± 1.3	2.6 ± 1.1
FBG ($mmol/L^{-1}$)	6.60 ± 2.51	7.06 ± 2.55	6.61 ± 4.57	6.64 ± 2.62
Waist (cm)	96.9 ± 8.3	97.0 ± 9.6	97.1 ± 8.4	95.2 ± 9.4
Hip (cm)	101.2 ± 8.7	100.5 ± 9.9	99.3 ± 7.8	99.4 ± 8.1

4.6. Cardiorespiratory fitness

A significant Test by Condition interaction ($F_{(1, 16)} = 15.12$, $P < 0.05$) was observed for the exercise duration of the exercise stress test. A greater exercise duration was completed PI compared to BL (10.98 ± 2.40 cf. 8.98 ± 2.60 min, respectively). Subjects randomised to EX exhibited a greater increase in walking duration between BL and PI (8.35 ± 3.04 cf. 11.84 ± 2.55 min) compared to CON (9.58 ± 2.05 cf. 10.13 ± 2.04 min, respectively).

A significant Test and Time main effect was revealed for SBP, DBP, HR and RPE (all $P < 0.05$). ANOVA revealed lower SBP, DBP, HR and RPE values for PI compared to BL, and stages 1 and 2 of the exercise stress test. A significant Time by Condition interaction was observed for SBP ($F_{(1, 15)} = 8.83$, $P < 0.05$), HR ($F_{(1, 16)} = 5.60$, $P < 0.05$) and RPE ($F_{(1, 16)} = 4.72$ $P < 0.05$). Post-hoc analysis revealed a greater change in the EX condition in SBP, HR and RPE between stages 1 and 2 compared to CON. No Test by Time interactions were observed for SBP, DBP, HR and RPE (all $P > 0.05$).

5. Discussion

This randomized controlled trial investigated the effects of an 8-week cardiac-based rehabilitation programme on arterial stiffness and haemodynamic properties of the common carotid artery in patients having experienced a TIA. In this study, a significant improvement in arterial stiffness was observed in participants randomised to the exercise condition. Moreover, a concomitant increase in cardiorespiratory fitness was also demonstrated as shown by lower BP, HR and RPE values for a given exercise intensity. However, no statistical changes to arterial haemodynamic properties and CAD risk factors were exhibited.

5.1. Arterial stiffness

Consistent with previous research (Cameron & Dart, 1994; Monahan et al., 2001; Mourot et al., 2009; Tanaka et al., 2000), local arterial compliance and distensibility significantly increased (30.4 % and 39.7 %, respectively; Figure 4.1), and stiffness index β significantly decreased (17.8 %; Figure 4.1), collectively illustrating a more compliant vessel, in response to an 8-week exercise intervention. Subsequent to participants completing a 3-month exercise intervention, Tanaka et al. (2000) observed a 25 % increase and a ~20 % decrease in arterial compliance and stiffness index β, respectively, in middle-aged (53 ± 2 y) men. Similarly, Monahan et al. (2001) reported a 29 % increase in arterial compliance after 13 middle-aged and previously sedentary men completed a 3-month exercise intervention. The changes observed in the present study were similar to those reported in the abovementioned investigations; although this occurred following an 8-week exercise intervention demonstrating the efficacy of the early engagement of exercise in TIA patients.

The improved capacity of carotid artery to comply with a given change in pressure occurred concomitantly with an improved cardiorespiratory fitness as determined by the walking stress test. For a given exercise intensity, participants randomised to the EX condition exhibited lower BP, HR and RPE, as compared to those within the CON condition. Indeed, previous investigations have reported that individuals with a greater physical conditioning status, as indicated by a greater $\dot{V}O_{2max}$ (Vaitkevicius et al., 1993), or who habitually take part in regular physical activity (Schmidt-Trucksass et al., 1999a; Seals et al., 2008), have more compliant arteries than their less active counterparts. In addition, as many studies have established that physically active individuals have lower incidences of cardiovascular disease, it may be postulated that regular physical activity participation leads to a reduced incidence of recurrent vascular events. The present study demonstrates that, a short-term bout of exercise can attenuate reductions in local arterial stiffness in previously sedentary TIA participants. Although this may serve as one mechanism by which the risk of recurrent TIA or stroke is reduced, further research is warranted to investigate the long-term effects of exercise on arterial stiffness.

To date, the mechanisms by which regular or short-term aerobic exercise improves arterial stiffness have not been fully established. According to Kingwell (2002), it is difficult to determine whether a causative relationship exists between arterial elasticity and physical fitness despite evidence demonstrating concomitant increases in human participants. Although the effect of regular exercise is mainly evident in central arterial stiffness, peripheral arterial stiffness may not be altered (Vlachopoulos et al., 2006). Monahan et al. (2001) states that as structural changes to the vessel wall occur over years and are unlikely to occur following short-term exercise, other processes must be at work. However, recent research has offered several hypotheses. Monahan et al. (2001) speculated that during exercise bouts an increase in PP and distending pressure stretches the collagen fibres and

modifies the covalent cross-links which stabilise collagen and elastin proteins within the vessel wall, thereby increasing arterial compliance. Although there is no current data available regarding how resting arterial properties influence central pressures during exercise, it is likely that individuals with stiffer vessels at rest experience higher PP at maximal exercise (Kingwell, 2002). However, as these collagen cross-links are integral components, providing mechanical stability to the vessel wall, modification of the cross-linking processes may result in the destabilisation of the vessel wall reducing strength and increasing diameter (Bruel et al., 1998).

Arterial compliance may be further altered by modulating the sympathetic-adrenergic tone of smooth muscle cells within the arterial wall; although this may only occur over a short period of time (Monahan et al., 2001). Regular exercise is believed to increase arterial compliance by reducing the chronic restraint exerted by the sympathetic-adrenergic tone of vascular smooth muscle, either directly or by enhancing the sympatho-inhibitory effect of NO (Monahan et al., 2001). However, studies that have investigated the associations between vascular smooth muscle tone and arterial stiffness have reported conflicting results. Where some investigations have reported that an increase in vascular smooth muscle tone decreases arterial stiffness in vitro, other investigations have reported the opposite (Boutouyrie et al., 1994). Nevertheless, as the aorta and its major branches contain a large proportion of elastic fibres and only a small proportion of smooth muscle cells, any increase in smooth muscle tone will most likely have only a minor influence on the compliance of large elastic arteries (Barenbrock et al., 1996). Zieman et al. (2005) mentioned that the vascular benefits of exercise are indirectly related to a decline in the release of neurohumoral vasoconstrictors and a reduced sympathetic smooth muscle tone. Zieman et al. (2005) also mentioned that an increased pulsatile flow and stretch associated with an altered endothelial mechanical-signalling and enhanced NO stimulation which appears to persist after exercise training,

improve arterial compliance. It is also worth noting that improvements in arterial stiffness may be influenced by an enhanced shear stress profile exhibited during exercise.

The participants randomised to the CON condition experienced non-significant increases in arterial compliance and distensibility of 4.8 % and 7.4 %, respectively, and a 4.3 % decrease in stiffness index β. The changes in arterial compliance may be attributed to the medication prescribed post-TIA. For instance, ~90 % of the participants in the CON condition were prescribed a statin, which according to Zieman et al. (2005) leads to an increase in arterial compliance; although the effects of statins are more pronounced in muscular arteries than large elastic arteries including the aorta or carotid artery (Zieman et al., 2005).

The present study observed a significant decrease in resting BP between BL and PI assessments in the EX condition (~9 % and ~7 % for SBP and DBP, respectively). No such change was observed in the CON condition (a 1.5 % and a 2.3 % increase in SBP and DBP, respectively). These results remain consistent with previous research (Faulkner et al., In Press; Prior et al., 2011). Moreover, Mourot and colleagues (2009) recently reported a significant increase in arterial compliance after participants completed a 6-week CR programme. Interestingly, this change occurred in patients whose anti-hypertensive medication and BP values remained unchanged, suggesting that the alterations to the elastic properties of the vessel occurred independent of BP reduction (Mourot et al., 2009). In the present study, the decrease in resting BP in the EX condition was concomitant with the reduction in carotid artery stiffness, which may suggest that BP had a greater influence in reducing arterial stiffness than potential modifications to the elastic properties of the vessel., Pulse pressure also decreased, although not significantly, exhibiting a ~10 % reduction in the EX condition. As the relationship between arterial stiffness and PP involves wave reflections (Laurent & Boutouyrie, 2005), more compliant arteries reduce the magnitude of the arterial

pressure wave by dampening the pulsatile energy as determined by a slower PWV. Reflected waves arrive in diastole, which inherently may have led to the decrease in PP, and thus SBP, observed in the present study at the site of central arteries. As a result, workload on the left ventricle attenuates, reducing cardiovascular risk. A reduction in PP may also decrease the likelihood of plaque rupture. Indeed, an increased arterial stiffness may be predictive of cerebrovascular events through an increased PP locally at the site of intra- and extra-cerebral arteries (Laurent & Boutouyrie, 2005). However, the difference in carotid and brachial PP can be as great as 8 mmHg in assumed healthy individuals and 2.6 mmHg in CAD patients (Mattace-Raso et al., 2006), which suggests that this may not be representative of changes to central PP. Moreover, this may not reflect the PP acting at the site of extra- and intra-cerebral arteries (Laurent & Boutouyrie, 2005). It is also worth noting that following BL assessments, resting SBP was found to be significantly lower in the CON as compared to the EX condition (124 ± 12 cf. 144 ± 17 mmHg, respectively). This bias may have influenced the statistical change in SBP following PI assessments in the EX condition thus potentially limiting the significance of this occurrence.

5.2. Coronary artery disease risk stratification

Apart from the significant decrease in both SBP and DBP in the EX condition, the present study observed no significant changes to other CAD risk factors. As such, TC, HDL, TC:HDL, waist and hip circumference, and FBG remained unchanged between BL and PI assessments (Table 4.4). These findings were not in accordance with previous research, with Prior et al. (2011) and Faulkner et al. (In Press) reporting positive changes. For example, Prior and colleagues (2011) reported favourable improvements in TC, LDL, HDL and TC:HDL following a 6-month comprehensive CR intervention in 80 participants having

sustained a TIA or non-disabling stroke. Previous research conducted within our laboratory with 60 TIA patients has shown improvements in TC, HDL and TC:HDL following a similar 8-week CR exercise intervention (Faulkner et al., In Press). Low participant numbers in the present study most likely influenced the statistical power which may have been gained from the analysis of these measures. However, it may also be speculated that the addition of an educational element in conjunction with the physical activity used in these investigations influenced the change in CAD risk factors to a greater extent than exercise alone; although it is unlikely that this would have influenced the primary outcome/finding of this investigation. The reduction in carotid artery stiffness observed in the present study occurred independent of these classic risk factors. Indeed, arterial stiffness is an independent risk factor, which has been identified as a predictor of all-cause and cardiovascular mortality (Blacher at al., 1999b; Laurent et al., 2003; London & Pannier, 2010). Whether this decrease in carotid artery stiffness leads to an improved prognosis in TIA patients can only be speculated at this present moment in time. Clearly, further randomized controlled trials are needed to identify whether these changes lead to a long-lasting positive outcome in TIA and ischaemic stroke patients.

5.3. Arterial haemodynamic properties

To this researcher's knowledge, this study is one of few human studies (Ivey et al., 2011) to investigate the effects of exercise on arterial haemodynamic properties in stroke patients. The results obtained from the present investigation exhibited no significant change to arterial haemodynamic properties of the common carotid artery including BFV_{mean}, BFV_{max}, BF, shear rate and vascular conductance (Table 4.3). Previous stroke research investigating the effects of exercise on arterial haemodynamic properties has predominantly come from animal studies (Endres et al., 2003; Gertz et al., 2006). Ivey et al. (2011) provided

the first evidence to suggest that exercise leads to cerebral BFV improvements in stroke survivors and implied that this may act as a protective mechanism against recurrent vascular events. Although these investigations reported favourable changes, with cerebral BF (Endres et al., 2003; Gertz et al., 2006) and BFV (Ivey et al., 2011) increasing in response to physical activity, the present study exhibited contrasting results. Indeed, stroke is strongly associated with lower BFV in both acute and chronic phase of ischaemic stroke (Bai et al., 2007). Notwithstanding, the investigation compiled by Gertz and colleagues (2006) demonstrated that physical activity not only promotes an improved long-term functional outcome 4 weeks after stroke, but also provides a prophylactic treatment strategy for increasing angiogenesis, cerebral BF and reducing brain injury following stroke. The large between-subject variances and low participant numbers exhibited in the present study would have certainly influenced the observed statistical power from the analysis of arterial haemodynamic properties. The significance of these measures is therefore limited.

Since arterial compliance differed in the two conditions following the 8-week exercise intervention, values of these indexes may not necessarily reflect comparable haemodynamic properties within the intra- and extra-cerebral vasculature. It is conceivable, according to Ferrara et al. (1995), that in an early stage of hypertensive disease, the impairment in distensibility of the CCA does not influence the auto-regulation of the small arteries of the intra-cerebral circulation, which remains normal (Ferrara et al., 1995). Indeed, it has been postulated that in response to plaque ulceration a compensatory enlargement of the artery occurs (Glagov et al., 1987; Steinke et al., 1994) as a result of an increased local wall shear stress (Steinke et al., 1994). According to Stroev et al. (2007), the lumen diameter adjusts depending on wall shear stress and, as such, a greater shear stress may stimulate endothelium-dependent arterial dilation, which represents a normal response to shear stress stimuli (Steinke et al., 1994). Carallo et al. (1999), however, stated that the consequent vessel

dilation occurs in order to restore wall shear stress as research has demonstrated that plaque ulceration is believed to occur at vascular sites with a low shear stress (Gnasso et al., 1997; Wakhloo et al., 2004). Although this is believed to occur within coronary arteries, a greater carotid artery lumen diameter is evident in stroke patients (Bai et al., 2007), suggesting that other vessels may be prone to the same effect. Moreover, the decrease in vascular conductance, although not significant, may have occurred in direct relation to the decrease in BF. For instance, during exercise, Secher et al. (2008) reported that an increase in BF is representative of an increase in cerebral vascular conductance.

Research can only speculate as to the mechanisms underlying the potential changes to cerebral BF and associated haemodynamic properties in response to physical activity; although a link has been established between endothelial function and cerebrovascular function (Ainslie et al., 2008). Indeed, Endres et al. (2003) and Gertz et al. (2006) state that an enhanced up-regulation of endothelial nitric oxide synthase (eNOS), in response to physical exercise, leads to an improved endothelial function, thereby augmenting cerebral BF. This was associated with higher numbers of circulating endothelial progenitor cells in the blood and an enhanced neovascularisation (Gertz et al., 2006). However, other factors, including insulin-like growth factor-1 and brain-derived neurotrophic factor have also been implicated as mediators of the neuro-protective actions of exercise. According to Ainslie et al. (2008) the up-regulation of eNOS has been implicated as a key mechanism to increase cerebral BF and reduce brain injury during ischaemic stroke. Notwithstanding, an improved endothelial function as a result of physical activity may positively influence levels of shear stress, maintaining physiological levels and thus decreasing risk of plaque ulceration.

5.4. Clinical implications

The findings of the present study have identified several potentially important clinical implications. As it was recently demonstrated that patients with acute ischaemic stroke exhibit greater arterial stiffness as compared to non-stroke controls (Tuttolomondo et al., 2010), indices of arterial stiffness may therefore be considered important factors indicating an individual's arterial age (Gasecki et al., 2012a). As the significance of arterial stiffening on the relative risk of a new vascular event is less certain (Dijk et al., 2005), greater arterial stiffness could be related to future vascular events in patients with manifest cardio- or cerebrovascular disease, and therefore the early detection or identification of those at greater risk would prove beneficial. Ultimately, the benefits of physical activity are well established and are associated with a decreased incidence of cardio- and cerebrovascular events, yielding positive effects on CAD risk factors (Shephard & Balady, 1999). Indeed, men and women who regularly partake in bouts of physical activity have a lower incidence of cardiovascular disease when compared to their sedentary peers (Tanaka et al., 2000). It has also been demonstrated that physically active individuals have greater arterial compliance and an enhanced cerebral BF (Tanaka et al., 2000; Ainslie et al., 2008). Therefore, regular physical activity may induce molecular, cellular and systemic effects that contribute to neuro-protection (Endres et al., 2003).

5.5. Study limitations

Although this investigation was considered a pilot study, the number of participants recruited to take part was lower than originally conceived. In 2011, over a 10-month period (February to December), our research laboratory received 97 TIA referrals from Wellington hospital (~10 per month; Faulkner et al., 2012). It was initially anticipated that a similar

referral rate would be achieved for this study. However, over the course of a 6-month period, only 35 referrals were received from the hospital (~5 per month), possibly due to the involvement of a less research-active lead stroke physician there. Accordingly, although the current study demonstrated a decrease in arterial stiffness following an 8-week exercise programme, there is most likely a lack of statistical power when considering some of the secondary outcome measures (CAD risk factors; haemodynamic markers). Further recruitment is, however, currently taking place with the intention to recruit at least 30 participants to this pilot study.

The fact that the primary researcher was heavily involved in every aspect of this investigation, and as such not blind to any outcome measures, may also be considered a significant study limitation. Blinding prevents bias by ensuring that the researchers are not influenced by knowledge, and transfer their inclinations and/or attitudes to the participants (Schulz & Grimes, 2002). The individuals randomised to the EX condition may have therefore been subject to researcher bias, for example, during the exercising ECG the primary researcher might have provided more encouragement or "pushed" the participant a little more during PI assessment. As such, it is possible that the researcher may have subconsciously skewed the results in favour of the hypothesis.

Although research has reported contradicting results surrounding the effects of resistance and aerobic exercise on arterial stiffness, potential positive or negative effects of resistance or aerobic exercise on arterial stiffness and haemodynamic properties as an individual component could not be established.

The present study focused on the changes to the common carotid artery, a vessel which supplies blood to both the brain, via the internal carotid artery, and to the face, via the external artery. It may be speculated that, had the present study investigated the internal carotid or vertebral arteries, changes in haemodynamic properties may have arisen. In

addition, as mentioned previously, the difference in carotid and brachial PP is believed to be as great as 8 mmHg in assumed healthy individuals and 2.6 mmHg in CAD patients (Mattace-Raso et al., 2006). This may limit the present study as values obtained from the brachial artery may not be representative of changes to central PP and thus not reflect the PP acting at the site of both extra- and intra-cerebral arteries (Laurent & Boutouyrie, 2005).

5.6. Future research

This investigation demonstrated that a short-term (8-week) bout of exercise led to a reduction in carotid arterial stiffness in TIA patients. However, after participants completed PI assessments no long-term effects of exercise were determined. Faulkner et al. (In press) reported that the favourable effects of exercise on CAD risk factors remained at least 3 months after those randomised to the exercise condition completed the intervention. To date, research has yet to establish the long-term effects of exercise on arterial stiffening in healthy or clinical populations. This may provide an interesting avenue for future research projects.

As previously mentioned, a comprehensive CR programme comprises several components including drug therapy, physical activity and education. This investigation predominantly assessed the effects of exercise on arterial stiffness and haemodynamic properties, which allowed the researchers to control variables. However, as lifestyle modifications, including smoking cessation, dietary intake and alcohol consumption, are as significant in reducing recurrent vascular events as increasing physical activity, the inclusion of an educational component in future investigations may add a more holistic approach.

As a consequence of infarcted brain tissue (Gottesman & Hillis, 2010) and inadequate cerebral perfusion (Hillis et al., 2006), cognitive impairments contribute to the long-term disability of adults following ischaemic stroke. Consequently, this will have a substantial impact on an individual's livelihood affecting their ability to complete activities of daily

living. Future research may wish to investigate the effects of exercise on the structural and functional properties of large elastic arteries (i.e., internal and external carotid artery) and how this may affect cerebral blood flow and perfusion. Whether this is of prominent concern for TIA patients, for example, needs further consideration.

The immediate effects of exercise on arterial haemodynamic properties have been previously reported (Green et al., 2005; Padilla et al., 2008; Tanaka et al., 2006) in healthy populations. However, although animal studies (Endres et al., 2003; Gertz et al., 2006) have reported an increase in cerebral BF in ischaemic stroke following exercise, little is known with regards to the immediate effects of exercise on haemodynamic properties in stroke. As such, research may wish to investigate the immediate effects of exercise on haemodynamic properties in stroke, and whether the neuro-protective effects of exercise are evident following a single bout of exercise.

Where contradicting results have been reported regarding the effects of resistance (Heffernan et al., 2007; Rakobowchuk et al., 2005) and/or aerobic (Ferrier et al., 2001; Monahan et al., 2001; Mourot et al., 2009) exercise on arterial stiffness, future research may include establishing the differences associated with performing an acute and chronic bout of aerobic- vs. resistance-based exercise in TIA and stroke.

Cardiovagal baroreflex sensitivity (BRS) is associated with increased long-term mortality after ischaemic stroke (Robinson et al., 2003). However, as research has reported a strong and positive relationship between arterial stiffness and cardiovagal BRS (Monahan et al., 2001), future research may wish to attempt to establish whether exercise leads to an improved cardiovagal BRS after TIA or stroke and whether impaired BRS holds any prognostic significance.

6. Conclusion

In conclusion, the present study has demonstrated that an 8-week exercise intervention, similar to that of a cardiac rehabilitation programme, leads to significant improvements in indices of arterial stiffness (compliance, distensibility and stiffness index β) of the common carotid artery in TIA patients. Importantly, the results suggest that exercise improves vascular health, thus potentially improving long-term functional outcome and reducing the risk of recurrent TIA or stroke. More compliant arteries may also contribute to augmented left ventricular function and a concomitant increase in aerobic capacity, and an improved cardiovagal BRS in TIA and stroke. However, as no significant changes were observed in arterial haemodynamic properties of the carotid artery, certainly due to a limited sample size, it is difficult to conclude that exercise indeed leads to an improved long-term functional outcome following a TIA. The mechanisms by which exercise attenuates arterial stiffening has yet to be fully established; however, it is believed that exercise alters the sympathetic-adrenergic tone of smooth muscle cells within the arterial wall by enhancing the sympatho-inhibitory effect of NO. As indices of arterial stiffness provide an indication of arterial age and may predict ensuing cardio- or cerebrovascular events, the early detection of individuals at greater risk would prove beneficial. Future research may wish to: i) identify the long-term effects of exercise on arterial stiffness; ii) identify whether improved arterial compliance improves cerebral BF and perfusion; iii) investigate the immediate effects of exercise on arterial haemodynamic properties in stroke; iv) investigate the acute and chronic effects of resistance vs. aerobic exercise on arterial stiffness and haemodynamic properties, and; v) identify whether exercise leads to an improved cardiovagal BRS in TIA and stroke.

7. References

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Appendices

Appendix A – Information sheet

Appendix B – Invitation letter

Appendix C – Informed consent

Appendix D – Letter of ethical approval

Appendix E – Coronary artery disease risk stratification

Appendix F – Health history questionnaire

Information Sheet

Title of Research: **Do transient ischaemic attacks impair balance?**

Investigators: **Dr. James Faulkner**, Lecturer and Exercise Physiologist, Massey University
Mr Brandon Woolley, Masters Student, Massey University
Lai-Kin Wong, Clinical Nurse Specialist for Strokes, Wellington Hospital
Dr Danielle Lambrick, Lecturer, Massey University, Wellington
Dr Sally Lark, Senior Lecturer, Massey University, Wellington

Kia Ora,

You are invited to take part in a research study to determine whether balance and balance confidence is impaired in TIA patients as compared to age-matched controls. Before agreeing to participate in this research study it is important that you read the following explanation of this study. There is no obligation for you to participate if you do not wish to take part.

Participation
Your participation is entirely voluntary (your choice). You do not have to take part. If you do agree to take part, you can withdraw from the study at any time without prejudice or having to give a reason.

About the Study
The aim of this study is to identify whether balance and balance confidence is impaired in acute and long-term (>3 months) TIA patients as compared to age-matched controls. In addition, this investigation will also aim to identify whether a 6 week balance-based exercise intervention positively affects balance and balance confidence in acute TIA patients. Up to 75 participants will be involved in the study. All participants will have experienced a TIA. Participants will be identified and invited to partake in the study at Wellington Hospital. All baseline assessments will take place at Massey University. The participant's GP will be informed of their involvement in the study.

The participants recruited for the purpose of this investigation will be characterised into one of four groups (or study arms):

1) **Acute TIA** - TIA diagnosis within 7 days of symptom onset. Individuals will have been diagnosed with a TIA by the stroke physician and referred to the study from the Clinical Nurse Specialist for Strokes. It is expected that individuals within this group will have been recruited within 7 to 14 days of the onset of their TIA symptoms.
2) **Long-term TIA control** – More than 3 months since original TIA diagnosis
3) **Long-term TIA exercise** – Although more than 3 months since original TIA diagnosis, individuals completed structured exercise within the first three months of diagnosis.
4) **Age-matched Controls.**

Participants will initially be invited to complete a baseline assessment at the physiology laboratories at Massey University. During the assessment researchers will assess the participant's health status, using a health questionnaire and a series of risk stratification

assessments (i.e., family history of cardiovascular disease, BMI, fasting blood glucose, total cholesterol, blood pressure, activity status). Participants will then undergo a non-invasive procedure to measure blood flow, before and after a change in postural position (i.e., from lying down to a more upright seated position), and arterial stiffness of the right common carotid artery. Thereafter, participants will complete an exercise ECG stress test on a treadmill. This test will start at a slow walking speed and will increase in intensity throughout the exercise test.

Participants will then be asked to complete a subjective balance confidence questionnaire followed by a series of functional balance assessments. These tests will be performed with the assistance of the primary investigator and an experienced clinical practitioner and will include:

- The Activities-specific Balance Confidence (ABC) Scale
- The Berg Balance Scale (BBS) – clinical balance ability
- A 10 m Timed Walk Test
- The Dynamic Balance Index (DGI) – balance during gait activities
- A Postural Sway Test & Electromyography (EMG) Activity – gathered during the postural sway test

These tests will enable us to measure balance ability while sitting, standing and walking, walking speed and trunk stability, and will take approximately 90 minutes to complete.

Following the completion of the abovementioned baseline assessments, participants within the Acute TIA group will be randomised into one of two conditions: an exercise group (balanced-based intervention) and a control group. Half of the Acute TIA sample, randomised to the exercise group, will take part in a balance-based exercise intervention twice a week for 8 weeks. Each exercise session will last approximately 60 minutes and involve one-on-one training with an experienced clinical exercise practitioner. The clinical practitioner will follow a universal balance-based exercise programme devised for the purpose of this investigation by the principal investigator. Progressions in exercise intensity (i.e., number of repetitions or sets) will be made accordingly. Acute TIA participants randomised to the control group will be asked to continue on with their everyday activities until they are contacted for follow-up assessments.

Each Acute TIA participant (the exercise and control groups) will then undergo the same series of baseline measures including risk stratification assessments, carotid blood flow and arterial stiffness, and exercise ECG followed by the same balance measures (ABC scale, BBS, 10 m timed walk test, DGI and postural sway and EMG activity) 8 weeks and 3 months after initial baseline assessments.

Benefits, risks and safety

Participants may become more aware of their physical activity level and the importance of balance to ensure activities of daily living can be performed safely and confidently. The risk stratification assessment will also provide participants with a comprehensive overview of their coronary artery disease profile. Individual feedback will be provided to participants both orally and in a written format.

The possible discomfort (if any) may be normal fatigue associated with any moderate intensity exercise. The risks involved in baseline assessment are low but the participant may experience shortness of breath, and increased heart rate as they would during every-day walking exercise during the baseline assessment. The participant can voluntarily stop at any time point if they feel they cannot do more, or if they experience considerable discomfort. Participants will get the opportunity to familiarise themselves with walking on a treadmill prior to the exercise ECG stress test. The Investigator will remain with the participant throughout all exercise tests and exercise sessions.

While performing the functional balance assessments, falling may be a potential risk for all participants. An additional exercise practitioner will be present during all functional assessments to ensure safety and provide support to the participant where necessary. Acute TIA participants randomised to the balance-based exercise intervention may also be at risk of potential falls while performing certain exercises. However, each participant will receive one-on-one training with an exercise practitioner to whom they can rely on for support where necessary to minimise this risk.

It is the participant's responsibility to inform the study investigators if you feel dizzy, ill or other symptoms before, during and/or after the assessment and intervention sessions.

When obtaining a finger-prick blood sample there is minimal risk due to using correct and aseptic techniques. Correct technique will minimise any discomfort. Alcohol swabs and gloves will be worn to minimise the risk of infection. A plaster will be used to protect the fingerprick site after the assessment.

You will not be paid to participate in this research project nor will you be charged for participating. However, the study will reimburse you for your travel expenses (bus ticket, petrol). Parking will be free at Massey University.

Confidentiality

All information gathered during the course of this study will remain confidential. No material that could personally identify you will be used in any reports on this study. All individual data will only be known to the participant and the investigators named at the head of this information sheet. All data will be stored in a locked cabinet in a secure office for a period of 5 years. It is hoped the results from this study will be published in a scientific forum (conference or journal) but only group means will be published. There will be a considerable delay between data collection and publication of results.

Statement of approval

This study has received ethical approval from the Northern X Regional Ethics Committee, ethics reference number.....

Please feel free to contact the researchers if you have any questions about this study.

Dr. James Faulkner (04) 801 5799 ext. 62104

Mr Brandon Woolley 021 850 259

Participant reply form

Your signature below indicates that you have received, read and understood this information sheet, and that you are willing to take part in the study.

_____ _____

Signature of Participant Date

_____

Participant name (printed)

_____ _____

Signature of Researcher Date

Please return the Participant reply slip to Dr James Faulkner, School of Sport & Exercise, Massey University, Private Bag 356, Wellington, 6140

School of Sport and Exercise
Private Box 756
Wellington, 6140
New Zealand
T: 64 4 801 2794 ext. 6937
F: 64 4 801 4994

E: SoSE@massey.ac.nz

MASSEY UNIVERSITY
COLLEGE OF SCIENCES
TE WĀHANGA PŪTAIAO

Do transient ischaemic attacks impair balance?

Kia Ora,

This is an invitation to participate in research being conducted by Dr James Faulkner, from Massey University, Wellington.

You are being invited to take part in this study because you have experienced a TIA or have expressed an interest in taking part as an age-matched control participant. The purpose of this investigation is to identify whether balance and balance confidence is impaired in TIA patients as compared to age-matched controls. In addition, this investigation will also aim to identify whether a 6 week balance-based exercise intervention positively affects balance and balance confidence in acute TIA patients.

The participants recruited for the purpose of this investigation will be characterised into one of four groups:

1) Acute TIA – TIA diagnosis within 7 days of symptom onset.
2) Long-term TIA control – More than 3 months since original TIA diagnosis.
3) Long-term TIA exercise – More than 3 months since original TIA diagnosis, but individuals completed structured exercise within the first 3 months of diagnosis.
4) Age-matched controls**.**

Participants will initially be invited to a baseline assessment session where you will be asked to undertake a series of risk stratification measures (blood glucose, blood pressure, lipid profile etc), an exercise ECG, measurements of carotid blood flow and arterial stiffness (both non-invasive procedures), a self-administered subjective balance confidence questionnaire and a series of functional balance assessments. Physiological (heart rate), physical (exercise intensity) and psychological (perceived exertion) markers will be monitored during the baseline assessments.

Following the completion of the baseline assessments, the Acute TIA participants will be randomised into one of two conditions: an exercise group (balance-based intervention) and a

control group. Those randomised (half of the Acute TIA participants) to the exercise group will undergo a 60 minute balance-based intervention, twice a week for 8 weeks with an experienced clinical exercise practitioner. The exercise and control groups will then undergo the same baseline assessments 8 weeks and 3 months after initial baseline assessments.

Participation in the study is entirely voluntary, and if you decide not to participate then that is absolutely fine. Any information that you provide will be treated with confidentiality and will not be disclosed to anyone else. Any published information will be fully anonymous.

Please read the enclosed study information sheet before you decide whether or not you are interested in taking part. If you would like more information, please contact Dr Faulkner on the following telephone number.

Dr. James Faulkner, Lecturer and Exercise Physiologist, Massey University

Telephone: (04) 801 5799 ext. 62104

If after reading the information sheet provided you think you would like to take part in the study please complete the Participant Reply Sheet (last page on the information sheet) and return it to Dr James Faulkner. You will be given the opportunity to have the study fully explained when you meet with the researcher, please feel free to ask any questions you may have and to keep the information sheet.

Thank you for your time and consideration in participating in this study.

Yours faithfully

Dr James Faulkner
Principal Investigator
Massey University
63 Wallace Street,
Wellington
6140

Participant Consent Form

Do transient ischaemic attacks impair balance?

I have read and I understand the information sheet dated 01/04/2012 for volunteers taking part in the study designed to identify whether balance and balance confidence is impaired in transient ischaemic attack.

Yes ☐ No ☐

I have had the opportunity to discuss this study, and I am satisfied with the answers I have been given.

Yes ☐ No ☐

I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.

Yes ☐ No ☐

I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my future health care.

Yes ☐ No ☐

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

Yes ☐ No ☐

I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.

Yes ☐ No ☐

I understand that my GP will be informed of my participation in the study and of any clinically significant abnormal results obtained from the study.

Yes ☐ No ☐

I have had time to consider whether to take part in the study.

Yes ☐ No ☐

I would like the researcher to discuss the outcomes of the study with me.

Yes ☐ No ☐

I ……hereby consent to take part in this study.

Participant's Signature:…….....
Date:……...

Full name of researcher: Dr James Faulkner

Contact phone number for researcher: (04) 801 5799 ext. 62104

Project explained by: Dr James Faulkner

Project role: Principal Investigator

Signature: ……...

Date: ……

Health and Disability Ethics Committees

Northern X Regional Ethics Committee
Private Bag 92522
Wellesley Street
Auckland 1141
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Email: northernx_ethicscommittee@moh.govt.nz

5 April 2012

Dr James Faulkner
School of Sport & Exercise
Massey University
63 Wallace Street
Mt Cook Wellington

Dear James

Re: Ethics ref:	**NTX/12/02/009**	(please quote in all correspondence)
Study title:	Do transient ischaemic attacks impair balance? Protocol v#1, 24/1/12; Prot/amend, 03/12; PIS/Cons v#3, 29/3/12	
Investigators:	Dr James Faulkner, Mr Brandon Woolley, Mr Lai-Kin Wong, Ms Danielle Lambrick, Dr Sally Lark	
Localities:	Capital and Coast DHB, Massey University	

Thank you for your email received 30 March 2012 with changes to the study.

The protocol amendment and documentation were reviewed by the Deputy Chairperson of the Northern X Regional Ethics Committee under delegated authority.

Ethical approval is granted to:

- Protocol amendment (undated, received 30/3/12)
- Information sheet/Consent Form version [3, dated 29/03/12]
- Invitation letter [version 2, dated 29/03/12]

Yours sincerely

Cheh Chua
Administrator
Northern X Regional Ethics Committee

ACSM Coronary Artery Disease Risk Stratification Assessment

(This document is to guide the researcher through the risk stratification procedures)

The main purpose of pre-participation screening is to identify individuals at increased risk of cardiovascular injury or death during exercise. To this end, the client should complete the physical activity readiness questionnaire (PAR-Q, attached)

Cardiovascular disease risk factor profile

Cardiovascular disease (CVD) is an umbrella term referring to the diseases of the heart and circulatory system. Around 50% of CVD deaths are due to coronary heart disease and around 25% are due to stroke. It is important to determine an individual's CVD risk factor profile because CVD is the main cause of exercise-induced death in middle-aged men. Table 1 lists the risk factors that are typically assessed in determining an individual's CVD risk factor profile.

- Family history is assessed because the presence of premature CVD in first-degree relatives is associated with a two- to six-fold increase in CVD risk. Enter 1 if the client's father or brother suffered a heart attack before 55 or if the client's mother or sister suffered a heart attack before 65 years-of-age.
- The CVD death rate of smokers is at least twice that of non-smokers. Enter 1 if the client has smoked at all in the last six months.

- There is a linear relationship between blood pressure and CVD risk. Measure blood pressure in accordance with the procedures described in Box 1 and enter 1 if systolic blood pressure is $\geq$140 mm Hg or if diastolic blood pressure is $\geq$90 mmHg.
- Compared to men with desirable cholesterol levels, the six-year CVD death rate is twice as high in men with concentrations $\geq$5.25 mmol·l^{-1} (Stamler, Wentworth, & Neaton, 1986). Measure total cholesterol in accordance with the procedures described in Box 2 and enter 1 if the fingerprick concentration is >5.2 mmol·l^{-1}.
- Fasting blood glucose is assessed because most diabetics are at increased risk of CVD. Measure blood glucose in accordance with the procedures described in Box 2 and enter 1 if the fingerprick concentration is >6.1 mmol·l^{-1} on at least two separate occasions. Non-fasting blood glucose concentration should be <11.1 mmol·l^{-1}.
- Body mass index (BMI) and waist girth are determined because obesity predisposes to diabetes and heart disease. Measure height, weight and waist girth as described in Box 3 and enter 1 if BMI is greater than 30 kg·m^2 or if waist girth is >102 cm in men or >88 cm in women.
- Enter 1 if the client does not undertake 30 minutes of moderate-intensity physical activity on three or more days of the week or if the client is not engaged in a exercise programme consisting of around 20 minutes of vigorous activity on three or more days of the week.
- CVD is not inevitable, but age is an indirect measure of an individual's exposure to other risk factors. Enter 1 if the client is a man older than 45 or a woman older than 55.
- HDL-cholesterol fights atherosclerosis and every 0.026 mmol·l^{-1} increase in HDL-C reduces CVD risk by 2–3% (Gordon et al., 1989). Accordingly, high HDL-C is regarded as a 'negative risk factor' and a concentration >1.6 mmol·l^{-1} removes 1 score from the total risk factor count. Enter 0 if HDL-C concentration is unknown.

Subtract the negative risk factor count from the sum of positive risk factors to determine the risk factor score. 'Low-risk' individuals are asymptomatic men ≤45 years and asymptomatic women ≤55 years whose risk factor score is no more than one. Low-risk individuals can undergo a maximal exercise test and participate in moderate or vigorous exercise training. 'Moderate-risk' individuals are asymptomatic men >45 years, asymptomatic women >55 years, and, regardless of age, individuals whose risk factor score is two or more. Moderate-risk individuals can undergo a sub-maximal exercise test and can begin a programme of moderate-intensity exercise. It is recommended that moderate-risk individuals undergo a medical examination before engaging in vigorous exercise. 'High-risk' individuals are those with signs or symptoms of heart disease, as indicated by any 'yes' answer on the PAR-Q. High-risk individuals should consult their GP before engaging in exercise testing or exercise training. Moderate-intensity exercise is that below the lactate threshold, which is equivalent to RPE 12–13 or a positive talk test. Vigorous-intensity exercise is that between the lactate threshold and the lactate turnpoint, which is equivalent to RPE 14–16 or an equivocal talk test (Persinger, Foster, Gibson, Fater, & Porcari, 2004).

Table 1. Risk factor counting and interpretation for exercise testing and exercise prescription

	enter 1 for yes or 0 for no		
Family history*	_____		
Current smoker or smoker in last six months	_____		
SBP ≥140 *or* DBP ≥90 mm Hg	_____		
Total cholesterol >5.2 mmol·l^{-1}	_____	TC	_____
Fasting blood glucose ≥6.1 mmol·l^{-1}†	_____	HDL	_____
BMI ≥30, or waist girth >102 cm in men or >88 cm in women‡	_____	TC:HDL	_____
Sedentary§	_____		
Age >45 if male or >55 if female	_____		
Sum of positive risk factors (A):	☐		
HDL-C >1.6 mmol·l^{-1}	_____		
Negative risk factor count (B):	☐		
Risk factor score (A–B):	☐		
Height	_____		
Weight	_____		
Waist	_____		
Hip	_____		
Seated BP	_____		
Standing BP	_____		

*Family history refers to heart attack in father or brother before age 55 or mother or sister before age 65. † Impaired fasting glucose should be confirmed by measurements on at least two separate occasions. ‡Waist girth should be measured with an inelastic tape in a horizontal plane at the narrowest part of the torso. §Sedentary refers to individuals not engaged in a regular exercise programme or those not undertaking 30 minutes of moderate-intensity physical activity on three or more days of the week.

Interpretation: 'Low-risk' individuals are asymptomatic men ≤45 years and asymptomatic women ≤55 years whose risk factor score is no more than one. Low-risk individuals can undergo a maximal exercise test and participate in vigorous exercise training. 'Moderate-risk' individuals are asymptomatic men >45 years, asymptomatic women >55 years, and, regardless of age, individuals whose risk factor score is two or more. 'Moderate-risk' individuals can undergo a sub-maximal exercise test and can begin a programme of moderate-intensity exercise. 'High-risk' individuals are those with signs or symptoms of heart disease, as indicated by any 'yes' answer on the PAR-Q. High-risk individuals should consult their GP before engaging in exercise testing or exercise training.

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ACSM Health History Questionnaire

GENDER: M / F

DESCENT: European, Maori, Pacific Islander, Asian, Indian, Other TODAY'S DATE _____

NAME _____ AGE _____ DATE OF BIRTH _____

ADDRESS _____
Street City State Zip

TELEPHONE: HOME/CELL _____/ _____ E-MAIL ADDRESS _____

OCCUPATION/EMPLOYER _____/ _____ BUSINESS PHONE _____

MARITAL STATUS: (check one) SINGLE ☐ MARRIED ☐ DIVORCED ☐ WIDOWED ☐

PERSONAL PHYSICIAN _____ PHONE # _____

ADDRESS _____

Reason for last doctor visit? _____ Date of last physical exam: _____

Have you ever had any other exercise stress test? YES ☐ NO ☐ DATE & LOCATION OF TEST: _____

Have you ever had any cardiovascular tests? YES ☐ NO ☐ DATE & LOCATION: _____

Person to contact in case of an emergency _____ Phone _____ (relationship) _____

Please provide responses (YES or NO) to the following concerning family history, your own history, and any symptoms you have had:

FAMILY HISTORY

Have any immediate family members had a:

	YES	NO
heart attack	o	o
heart surgery	o	o
coronary stent	o	o
cardiac catheterization	o	o
congenital heart defect	o	o
stroke	o	o

Other chronic disease: _____

PERSONAL HISTORY

Have you ever had:

	YES	NO
High blood pressure	o	o
High cholesterol	o	o
Diabetes	o	o
Any heart problems	o	o
Disease of arteries	o	o
Thyroid disease	o	o
Lung disease	o	o
Asthma	o	o
Cancer	o	o
Kidney disease	o	o
Hepatitis	o	o

Other: _____

SYMPTOMS

Have you ever had:

	YES	NO
Chest pain	o	o
Shortness of breath	o	o
Heart palpitations	o	o
Skipped heartbeats	o	o
Heart murmur	o	o
Intermittent leg pain	o	o
Dizziness or fainting	o	o
Fatigue -- usual activities	o	o
Snoring	o	o
Back pain	o	o
Orthopedic problems	o	o

Other: _____

STAFF COMMENTS: _____

Have you ever had your cholesterol measured? Yes ☐ No ☐ If yes, value _____ Where: _____

Are you taking any prescription (include birth control pills) or nonprescription medications? Yes ☐ No ☐

For each of your current medications, provide the following information:

MEDICATION Dosage—times/day Time taken Years on medication Reason for taking

HOSPITALIZATIONS: Please list recent hospitalizations (Women: do not list normal pregnancies)

Year Location Reason

_____

_____

_____

Any other medical problems/concerns not already identified? Yes ☐ No ☐ If so, please list: _____

_____

_____

LIFESTYLE HABITS

Do you ever have an uncomfortable shortness of breath during exercise or when doing activities?
Yes ☐ No ☐

Do you ever have chest discomfort during exercise? Yes ☐ No ☐
If so, does it go away with rest? Yes ☐ No ☐

_____

Do you currently smoke? Yes ☐ No ☐ If so, what? Cigarettes ☐ Cigars ☐ Pipe ☐
How long have you smoked? _____ years
How much per day: <½ pack ☐ ½ to 1 pack ☐ 1 to 1½ packs ☐ 1½ to 2 packs ☐ >2 packs ☐
Have you ever quit smoking? Yes ☐ No ☐ When? _____
How many years and how much did you smoke? _____
Do you drink any alcoholic beverages? Yes ☐ No ☐ If yes, how much in 1 week? (indicate below)
Beer _____ (cans) Wine _____ (glasses) Hard liquor _____ (drinks)
Do you drink any caffeinated beverages? Yes ☐ No ☐ If yes, how much in 1 week? (indicate below)
Coffee _____ (cups) Tea _____ (glasses) Soft drinks _____ (cans)
Are you currently following a weight reduction diet plan? Yes ☐ No ☐
If so, how long have you been dieting? _____ months
Is the plan prescribed by your doctor? Yes ☐ No ☐
Have you used weight reduction diets in the past? Yes ☐ No ☐ If yes, how often and what type? _____

_____

ACTIVITY LEVEL EVALUATION

What is your occupational activity level? Sedentary ☐ Light ☐ Moderate ☐ Heavy ☐
Do you currently engage in vigorous physical activity on a regular basis? Yes ☐ No ☐
If so, what type(s)? _____ How many days per week? _____
How much time per day? <15 min ☐ 15–30 min ☐ 31–60 min ☐ >60 min ☐
How long have you engaged in this type of activity? <3 months ☐ 3–12 months ☐ >1 year ☐

_____

Do you engage in any recreational or leisure-time physical activities on a regular basis? Yes ☐ No ☐
If so, what activities? _____
On average: How often?_____ times/week; for how long? _____ time/session
How long have you engaged in this type of activity? <3 months 3–12 months >1 year

_____

Your fitness goals and objectives are: _____

_____

STAFF COMMENTS: _____

_____

_____