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The reproducibility of oscillometric assessment of central haemodynamics and the efficacy of acute and chronic physical activity interventions in an older population and after stroke

Submitted by Andrew Mitchelmore to the University of Winchester as a thesis for the degree of Doctor of Philosophy in Applied Sport and Exercise Science (March, 2019)

I confirm that all material within which is not my own work is identified and referenced, and none of this work has been submitted and approved for the award of another degree by this or another University

Andy Mitchelmore

Acknowledgements

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List of abbreviations

AF – Atrial fibrillation

AIx – Augmentation index

AIx75 – Augmentation index corrected to a heart rate of 75b-min^{-1}

ANOVA – Analysis of variance

AP – Augmented pressure

BP – Blood pressure

cBP – Central blood pressure

cDBP – Central diastolic blood pressure

CON – Control condition

cSBP – Central systolic blood pressure

cPP – Central pulse pressure

CVD – Cardiovascular disease

DBP – Diastolic blood pressure

DP – Double product

HR – Heart rate

HRC – Heel raise group

ICC – Intra-class correlation coefficient

ICH – Intra-cerebral haemorrhage

MAP – Mean arterial pressure

mmHg – Millimeters of mercury

NIHSS – National Institute of Health stroke scale

OSA – Obstructive sleep apnoea

PTT – Pulse transit time

PWA – Pulse wave analysis

PWV – Pulse wave velocity

SBP – Systolic blood pressure

SD – Standard deviation

SDC – Smallest detectable change

SEM – Standard error of measurement

TIA – Transient ischaemic attack

η_p^2 **-** Partial eta squared

Thesis abstract

Non-invasive measures of central blood pressure through pulse wave analysis may be key to future management of cardiovascular disease risk in currently healthy and clinical populations. One device that can non-invasively estimate central blood pressure is the SphygmoCor XCEL. The validity of this device has been demonstrated compared to invasive measures, but the reliability has previously only been demonstrated in younger, non-clinical populations. In day-to-day life, blood pressure measures are taken in a variety of postures and fasting states depending on user preference, clinician preference, time of day and environment. The acute effects of posture and fasting state on these central measures have not been widely investigated.

Therefore the purpose of the first and second studies in this thesis was to focus on a) reporting the between-day reliability of the SphygmoCor XCEL in an older, non-clinical sample (age >50y) and a hyper-acute stroke sample, and b) report the individual and combined effects of posture and fasting state on a variety of peripheral and central blood pressure measures in these populations.

The SphygmoCor XCEL was demonstrated to have generally excellent between-day reliability (using an intra-class correlation coefficient > 0.75 as the criterion excellence value) in fasted and non-fasted, and seated and supine states in both populations. Posture had a significant effect on diastolic pressures in both populations ($p < .05$), whereas fasting state had a significant effect on the majority of peripheral and central systolic and diastolic pressures, as well as measures of arterial stiffness (Augmentation Index, Augmentation Index at a heart rate of 75 $b \cdot min^{-1}$; $p < .05$). These studies demonstrate that the SphygmoCor XCEL is a reliable tool for use in population demographics where its findings are particularly pertinent (those

over the age of 50 or those suffering from stroke), and that posture and fasting state should both be taken into consideration when interpreting peripheral and central blood pressure measures.

Increased levels of sedentary time and reduced physical activity are common after stroke, potentially due to the perception that sedentary time is a normal and an important way of relaxing after stroke. The third study in this thesis investigated the effects of sedentary time on peripheral and central blood pressure measures and measures of arterial stiffness, thereby investigating whether low level physical activity (intermittent heel raises) could prevent this damaging process. Three hours of sedentary time was sufficient to cause significant increases in peripheral and central blood pressure ($p < .05$). Intermittent heel raises significantly mitigated this damage but did not prevent it (increases of 10.7 mmHg peripheral systolic blood pressure and 9.6 mmHg central blood pressure in the three-hour sedentary condition compared with increases of 5.2 mmHg and 5.6 mmHg respectively in the three-hour heel raise condition). Due to the significant effects observed in study 3, a pilot 'heel raise intervention' trial was undertaken (the fourth study of this thesis). Participants completed a heel raise protocol on six days per week for ten weeks to determine whether the acute effects demonstrated in the third study could be replicated chronically. This study found no significant improvements in any body composition, central and peripheral haemodynamic, arterial stiffness or cognitive variables ($p > .05$).

This thesis has demonstrated the reliability of the SphygmoCor XCEL in new populations and demonstrated the effect of posture and fasting state on peripheral and central measures. It has also reported that three hours of sedentary time is sufficient to cause significant increases in BP but this can be mitigated through lower limb physical activity. Although this lower limb

physical activity causes acute improvements in blood pressure, this does not translate into chronic improvements over the course of a ten-week exercise programme, although these findings must be interpreted with caution due to the small sample size.

Research outputs

Outputs from this thesis:

Publications

Mitchelmore, A., Stoner, L., Lambrick, D., Jobson, S. & Faulkner, J. Reliability of oscillometric central blood pressure and central systolic loading in individuals over 50 years: Effect of posture and fasting. *Atherosclerosis*, 2018; 269, 79-85. (Appendix 1a)

Mitchelmore, A., Stoner, L., Lambrick, D., Sykes, L., Eglinton, C., Jobson, S., Faulkner J. Oscillometric central blood pressure and central systolic loading in stroke patients: Short-term reproducibility and effects of posture and fasting state. *PLoS ONE*, 2018; 13 (11): e0206329. (Appendix 2a)

Faulkner, J., Lambrick, D., Mitchelmore, A., Paine, E., Stoner, L. (2019) 'Letter to the Editor: English et al. Frequent, short bouts of light-intensity exercises while standing decreases systolic blood pressure: Breaking Up Sitting Time after Stroke (BUST-Stroke)', *International Journal of Stroke*, in press. (Appendix 3a)

Mitchelmore, A., Lambrick, D., Jobson, S., Stoner, L., Faulkner, J. Effects of a heel raise program on central hemodynamics and cognitive performance in chronic stroke: study protocol for a randomized, controlled, crossover trial. *Clinical Trials and Degenerative Diseases*, 2018; 3 (3):0-0. (Appendix 4a)

Poster presentations

Mitchelmore, A., Jobson, S., Stoner, L., Lambrick, D., Faulkner. J. The effect of posture and fasting state on blood pressure responses in individuals with normotension and stage 1 hypertension. *BASES Conference.* November 30 2016 in Nottingham, UK.

Mitchelmore, A., Jobson, S., Lambrick D., Faulkner, J. The effect of posture and fasting state on central and peripheral blood pressure in patients with stroke. *BASES Student Conference*. March 23 2016 in Bangor, UK.

Faulkner, J., Mitchelmore, A., Stoner, L., Jobson, S., Sykes, L., Eglington, C., Lambrick, D. The effect of posture and fasting state on central blood pressure and measures of central systolic loading in acute stroke patients: Between-day reliability of the SphygmoCor XCEL. *27th European Stroke Conference*. April 11 - 13, 2018 in Athens, Greece.

Mitchelmore A., Lambrick, D., Jobson, S., Stoner, L., Credeur, D., Faulkner, J. Lower limb physical activity to break up sedentary time after stroke: effect on central and peripheral blood pressure measures. *UK Stroke Forum*. December 4 – 6 2018 in Telford, UK.

Oral presentation

Mitchelmore, A., Stoner, L., Lambrick, D., Sykes, L., Eglinton, C., Jobson, S. & Faulkner, J. Non-invasive assessment of central haemodynamics in acute stroke patients – between day reliability and the effect of fasting state and posture. *23rd Annual Congress of the European College of Sport Science*. July 3 – 8 2018 in Dublin, Ireland.

Output external to PhD:

Faulkner, J., Stoner, L., Lanford, J., Jolliffe, E., Mitchelmore, A., Lambrick, D. Long-term effect of participation in an early exercise and education program on clinical outcomes and cost implications, in patients with TIA and minor, non-disabling stroke. *Translational Stroke Research*, 2017; 8 (3), 220-227.

Chapter 1: Introduction

1.1 *Introduction to stroke*

Cardiovascular disease (CVD) is related to significant morbidity and mortality (World Health Organisation, 2018) and is the cause of death for over 18 million people each year, one in three of all deaths worldwide (Roth *et al*., 2017). Generally, the umbrella term of CVD refers to chronic heart disease, congestive heart failure and stroke; this thesis focuses on the latter. Each year in England, there are 57,000 first strokes (Public Health England, 2018), and approximately 30,000 stroke-related deaths (Office for National Statistics, 2017). At time of writing, there are approximately 1.2 million stroke survivors in the United Kingdom (Stroke Association, 2018).

Mortality as a result of stroke has decreased worldwide over the last two decades (Feigin *et al*., 2014) due to improved medical care in the hyper-acute setting and, as a result, more people are surviving stroke to experience its long-term consequences (Crichton *et al*., 2016). Although CVD mortality is declining in the United Kingdom, the burden of the disease also involves those living with it (Bhatnagar *et al*., 2016). Therefore, the requirement for effective stroke rehabilitation is likely to remain a key aspect of stroke care for the foreseeable future (Winstein *et al.*, 2016).

Once an individual has suffered from stroke, they are immediately at an increased risk of further events. A key aspect of chronic stroke treatment is therefore the prescription of anti-hypertensive medication to minimise this risk. However, adherence to medication is low. Up to 25% of patients are reported to not even fill in initial prescriptions for anti-hypertensive medication (Whelton *et al*., 2018) and other research reports 14% of participants admitting to not adhering to their prescriptions (Bushnell *et al*., 2011).

One key method used to track recovery and recurrent stroke risk is through the management and modification of blood pressure (BP). In fact, treating increased BP may be the most important intervention when attempting to prevent recurrent strokes (Kernan *et al*., 2014).

Blood pressure is traditionally assessed using the brachial artery, which does not directly reflect BP at the central organs. Differences in the composition of the arterial wall of the brachial artery compared to central arteries leads to brachial BP overestimating BP at the heart itself, whereas central blood pressure (cBP) represents the pressure on the heart itself (Agabiti-Rosei *et al*., 2007; Yadav *et al*., 2018). This assessment of BP is measured in a range of different circumstances (e.g. time of day, room temperature, stress, posture, fasting state).

There is interest in identifying risk factors of CVD to allow high-risk individuals to be targeted by interventions (Wong *et al*., 2018) and to reduce the risk of recurrent CVD, including stroke. The non-invasive assessment of cBP is a potentially crucial tool in identifying risk factors of incident and recurrent stroke, above and beyond traditional BP. This is a technique which has not been widely investigated in clinical populations.

A further contemporary focus of research in stroke is the reduction of sedentary time. After stroke has occurred, increased levels of sedentary behaviour are common. This may be because sedentary time is perceived as normal and seen as an important way of relaxing after stroke (Ezeugwu *et al*., 2016). The latest American Heart Association guidelines for stroke survivors now recommend reductions in sedentary behaviour (Billinger *et al*., 2014) and reducing sedentary time after stroke is now seen as a promising intervention target (Morton *et al*., 2019).

1.2 *Summary*:

The studies in this thesis develop an understanding of non-invasive measurement of cBP through oscillometric pulse wave analysis. This thesis initially investigates the reliability of the SphygmoCor XCEL in providing these measures for an older, non-clinical population and determining the effects of posture and fasting state on peripheral and central haemodynamics (Chapter 3). The population over the age of 50 are a population demographic to which cBP may be particularly pertinent in terms of reducing risk of CVD.

Similar parameters are then investigated in a hyper-acute stroke population (Chapter 4). The monitoring of cBP in acute stroke patients is expected to become the norm in the future but this cannot take place until the reliability of devices like the SphygmoCor XCEL has been demonstrated. As pharmacological decisions are at least partly based on BP readings in hospital settings and BP is recorded in a range of postures and fasting states, this work also investigates the influence that these variables have on peripheral and central haemodynamics.

As reported in the introduction, sedentary time is linked to poorer outcomes after stroke. As a response to this, this investigation develops the theory that low-intensity intermittent lower limb movements reduce the damage caused by extended sedentary time. As such, the effect of sedentary time on peripheral and central haemodynamics as well as executive function is observed, before ascertaining whether heel-raises throughout a three-hour time course are able to acutely mitigate the potential damage taking place through sedentary time (Chapter 5).

Finally, the thesis investigates whether these heel raises are of a sufficient intensity to elicit physiological benefits over the course of a ten-week training plan. In a pilot study,

oscillometric peripheral and central haemodynamics are investigated alongside executive function in a randomised crossover trial (Chapter 7).

Chapter 2: Literature review

2.1 Stroke pathology

The brain depends on a continuous supply of blood to maintain neurological function and is passively perfused through the cardiac cycle (O'Rourke & Safar, 2005). When this vascular supply is interrupted due to ischaemia or haemorrhage, a stroke occurs, causing an abrupt impairment of brain function involving one or several cerebral blood vessels (Sjogren *et al*., 2013). Stroke is typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours, or these disturbances resulting in death (WHO, 1978).

Strokes are broadly divided into two primary categories. Ischaemic strokes are vascular events caused by a blockage of cerebral blood vessels (Alberts & Atkinson, 2004) with a consequent interruption in blood supply to the brain (American Heart Association, 2012). This disturbance in delivery causes cell necrosis (Zoerink & Carter, 2015) and, consequently, a sudden decrease in human function. Ischaemic strokes are the most common form of cerebral event, comprising ~88% of all strokes (Gordon *et al*., 2004; Go *et al*., 2014; Zoerink & Carter, 2015) and are divided into five categories: large artero-atherosclerosis (~19% of ischaemic strokes), cardio-embolism (up to ~26%), small vessel occlusion (~44%), strokes of other determined aetiology (~5%) and stroke of undetermined aetiology (~6% worldwide; Adams *et al*., 1993; O'Donnell *et al*., 2010). The most common underlying cause of ischaemic stroke is atherosclerosis (Gordon *et al*., 2004), causing a narrowing of the cerebral arteries (Figure 2.1). This figure displays the chronic stages of atherosclerotic plaque formation, potentially leading to complete occlusion (leading to a thrombotic stroke) or an unstable plaque fragmenting (potentially leading to an embolic stroke). The second broad category of stroke is haemorrhage. Cerebral haemorrhages occur due to arterial bleeds or ruptures increasing the

pressure on the brain (CDC, 2013) and can be classified as intracerebral or subarachnoid haemorrhages (Stroke Association, 2015). Intracerebral haemorrhages form 11% of all strokes and can cause a rapid deterioration in patient welfare (Royal College of Physicians, 2016). Subarachnoid haemorrhages occur due to aneurysm or vascular malformation in the subarachnoid space and, although haemorrhagic strokes tend to have poor short- and long-term prognoses (Krishnamurthi *et al*., 2014), levels of mortality due to haemorrhage have improved in recent years (Mukhtar *et al*., 2016).

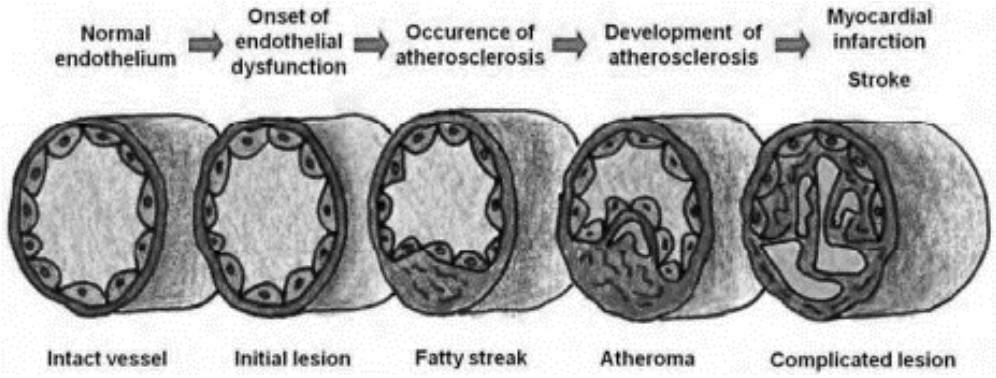


Figure 2.1: Steps involved in atherosclerosis progression, from Rodella & Rezzani, 2012

Transient ischaemic attack (TIA) is a transient period of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia but without acute infarction (Spurgeon, James & Sackley, 2013). These "mini strokes" share pathological mechanisms of stroke but prognoses differ widely depending on severity (Kernan *et al*., 2013). TIA are under 24 hours in duration but usually last under an hour (Horer *et al.,* 2011; Faulkner *et al*., 2015). All symptoms are resolved 24 hours post-TIA (Hillsdon, Kersten & Kirk, 2013) but the occurrence of a TIA is a warning sign of future stroke. Patients who have suffered a TIA are at a heightened risk of early stroke (Easton *et al*., 2009) with 5% of TIA patients suffering a stroke within seven days (Perry *et al.,* 2016) and 20% suffering a stroke within a month (Fisher, 2008). Around 15% of

ischaemic strokes are preceded by a TIA (Hankey, 1996) but prevention strategies for incident stroke and TIA are extremely similar (Easton *et al*., 2009).

2.2 Symptoms of stroke

Symptoms of stroke commonly include numbness, weakness or paralysis, slurred speech, blurred vision, confusion and severe headaches (NICE, 2008) and these symptoms first manifest outside of the hospital setting in 95% of patients (Royal College of Physicians, 2016). As a result, time is critical for improving overall outcomes, and quick identification and assessment is vital to reduce secondary damage during transport to hospital (Kobayashi *et al*., 2017). The most common screening tool of stroke is FAST (Face, Arms, Speech, Time to call [Harbison *et al*., 2003]) and, following admission to hospital, brain imaging should take place within one hour (Royal College of Physicians, 2016). The National Institute of Health Stroke Scale (NIHSS) is then used to determine the severity of stroke-induced neurologic deficit (Brott *et al*., 1989; Furlanis *et al*., 2018). Quantifying TIA severity takes place using the ABCD2 scale, with a score of four or above classifying an individual as having a high risk of stroke (NICE, 2008).

2.3 Incidence of stroke

For the purpose of this thesis, cardiovascular diseases (CVD) refer to chronic heart disease, congestive heart failure and stroke. CVD kills more than 18 million people worldwide per year, constituting one in three of all deaths (Roth *et al*., 2017) and is the leading individual cause of death worldwide (Benjamin *et al*., 2017). Stroke is the third leading cause of death in western societies (Aquilani *et al*., 2011); however, an increasing proportion of those presenting with

stroke symptoms actually have stroke mimics, with only 45% of a sample of 1881 admissions resulting in a stroke diagnosis and 38.2% resulting in a diagnosis of stroke mimics (other conditions presenting with stroke-like symptoms [Faiz *et al*., 2017]). There are between 129,000 and 150,000 reported strokes or TIA per year in the United Kingdom with ~46,000 people suffering a first TIA and 1.2 million people living with the consequences of stroke (National Audit Office, 2005; Scarborough *et al*., 2009; Kirk *et al*., 2014; Stroke Association, 2015). Around 85,000 stroke admissions are reported in England per year resulting in 32,000 stroke-related deaths (Office for National Statistics, 2017; Public Health England, 2018). Less adequate stroke management in low-income countries is linked to higher mortality rates (Feigin *et al*., 2014) and, by 2030, it is estimated that annual global deaths due to stroke will rise from a current 6.7 million to 7.8 million, with an estimated 77 million people living with the effects of stroke (Strong, Mathers & Bonita, 2007; WHO, 2014). Around the world, people are living longer but with an increased proportion of this time spent in ill health (Newton *et al*., 2015). The significance of stroke increases as populations age (Ingall, 2004). Due to this ageing population and changing demographic, the incidence of stroke worldwide is expected to rise (White *et al*., 2013). The number of younger people (aged 20-64y) who had a stroke also increased by 25% between 1990 and 2010 (Feigin *et al*., 2014). Stroke is projected to be one of the leading causes of morbidity and mortality for the foreseeable future (WHO, 2011), whether it be in high- or low-income countries, or in a young or old population.

Mortality rates after stroke vary depending on a variety of factors, particularly stroke subtype, concurrent morbidities, medication, body composition, lifestyle and the quality of healthcare provision. There is reported to be a 10-23% risk of 30-day mortality post-stroke which rises to 30% after six months and 25-50% after one year (Hankey *et al*., 1998; Jamrozik *et al*., 2000; Stroke Association, 2015). Recent decreases in stroke mortality have been observed across

both sexes and in all ethnic groups (Lackland *et al*., 2014). This may be due to positive advances in acute stroke care (Edwards *et al*., 2017), although apparent trends in stroke mortality may be due to a high error rate in issuing cause of death and the definition of "stroke mortality" differing between studies (Lackland *et al*., 2014). Regardless of this, the number of people surviving first stroke seems to be on the rise, resulting in greater pressure on rehabilitation services and increased numbers of total strokes due to a greater number of repeated strokes taking place.

The direct cost of stroke care annually in the United Kingdom is estimated to be £4 billion, which rises to £9 billion when taking into account health and social care costs (49%), informal care costs (27%), productivity losses (15%) and benefit payments (9% [Saka *et al*., 2009; Stroke Association, 2012a]). By 2020, the total cost of stroke care is predicted to represent 6.2% of the total illness burden in industrialised countries (Demaerschalk, Hwang & Leung, 2010), including losses in work productivity due to disability and death, currently estimated to be £1.5 billion per year in the UK (Saka *et al*., 2009).

2.4 Risk factors for stroke

Up to 80% of strokes are preventable (Chiuve *et al*., 2008; Gorelick, 2008) through the control of a variety of risk factors (discussed below). However, individuals are unaware of, and give little attention to, their stroke warning signs and risk factors (White *et al*., 2016). In around 25% of strokes, no cause is immediately evident, particularly in young patients (Royal College of Physicians, 2016), but risk factors can be categorised into three major groups (Figure 2.2). The first are non-modifiable risk factors, the second are medically-modifiable risk factors and the third are behaviourally-modifiable risk factors (Billinger *et al*., 2014). Over 90% of stroke

burden may be attributed to modifiable risk factors (Huangfu *et al*., 2017). Risk factors for CVD tend to occur in combinations, with more than three risk factors observed in 17% of stroke patients (Wilson *et al*., 1999). The presence of more than two CVD risk factors causes a lifetime risk of CVD death, non-fatal myocardial infarction and fatal or non-fatal stroke that is substantially higher than in those with only one risk factor (Wilson *et al*., 1999; Berry *et al*., 2012). This thesis will categorise risk factors based on Billinger and colleagues' work (2014). Some measures are controllable through both medical and lifestyle interventions (e.g. obesity, hypertension, hyperlipidaemia) but are listed in one category only below.

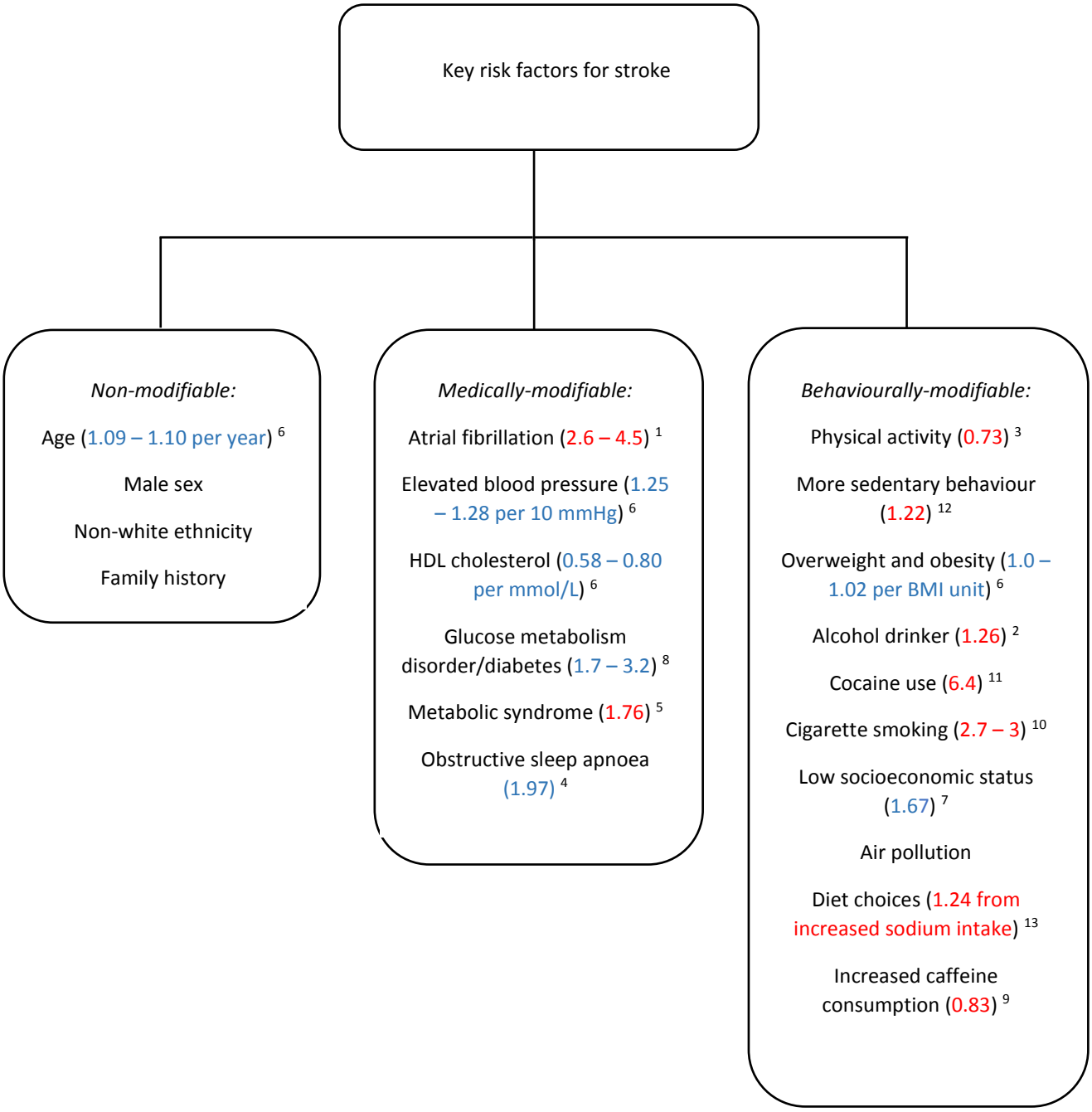


Figure 2.2: Key risk factors of stroke (relative risk ratios in red text, adjusted hazard ratios in blue text – ratios reported where available). [1] Wolf *et al.*, 1991, [2] Ben Shlomo *et al.*, 1992, [3] Lee, *et al.*, 2003, [4] Yaggi *et al.*, 2005, [5] Galassi *et al.*, 2006, [6] Asplund *et al.*, 2009, [7] Addo *et al.*, 2012, [8] Banerjee *et al.*, 2012, [9] Kim *et al.*, 2012, [10] Jha *et al.*, 2013, [11] Cheng *et al.*, 2016, [12] Yu *et al.*, 2018a, [13] Aburto *et al.*, 2013.

2.5 *Non-modifiable risk factors and stroke*

Premature birth and increasing age

Premature birth has been linked to elevated BP in later life. A 4 mmHg higher SBP and a 3 mmHg greater DBP has been observed in adulthood in previously premature individuals, with this exacerbated in females (Juhola *et al*., 2012; Parkinson *et al*., 2013). As life progresses, there is a clear relationship between age and stroke risk (Arzt *et al*., 2005) with ageing being the most important non-modifiable risk factor of stroke (Cocho *et al*., 2018). Stroke risk more than doubles in each successive decade over the age of 55 (Brown, *et al*., 1996; Wolf *et al*., 1992). Increased age at stroke onset is also associated with post-stroke disability (Kelly-Hayes *et al*., 2003), partly due to a reduced effectiveness of anti-platelet therapies at greater ages (van Walraven *et al*., 2009). Systolic and diastolic BP increases linearly until the fifth or sixth decade of life where DBP begins to decrease (Duprez, 2008). Because of these natural increases, 90% of adults who are normotensive aged 55-65 develop hypertension in their lifetimes (Vasan *et al*., 2002). The average age of first stroke has dropped from 71 years in men and 77 years in females (Lee, Shafe & Cowie, 2009) to 68 years in men and 73 years in females (Public Health England, 2018b). In the United Kingdom, the number of individuals aged 100 or over has risen by 65% in the past decade (Office for National Statistics, 2016), demonstrating an ageing population. Alongside stroke severity scores, old age is one of the crucial prognostic factors of stroke (Hung *et al*., 2018) although it has been recently reported that the oldest-old patients have recovery potential equal to their younger counterparts (Cocho *et al*., 2018). The number of older adults worldwide is rising (Cohen, 2003) and due to this ageing population in western society, the burden of stroke will continue to grow in the years to come.

Sex

Females suffer only 37% of global cases of stroke (O'Donnell *et al*., 2010). Males are also more likely to suffer stroke at a younger age due to a combination of lifestyle-based and physiological factors (Appelros, Stegmayr & Terent, 2009). Males are more likely to smoke and abuse alcohol than females (Hung *et al*., 2018) and oestrogen can counteract some unfavourable effects of the poor lifestyle choices that females do make. The benefits of oestrogen secretion include improving insulin sensitivity and decreased inflammation (Guo *et al*., 2018). This is a potential mechanism for hypertension being less common in females until around the fifth decade of life but becoming more common in old age (Benjamin *et al*., 2017). Carotid plaque specimens in males have also been reported to contain less smooth muscle, more macrophages and greater fat content than specimens found in females (Hellings *et al*., 2007). This may lead to atherosclerotic plaques being less stable in males than females (Stoberock *et al*., 2016). Although males may suffer strokes earlier than females, more dependency is caused after stroke in females (Appelros *et al*., 2009) and poorer stroke outcomes at 90 days are observed when compared with males (Hung *et al*., 2018); potentially due to the average increased age of stroke in females.

Ethnicity

Ethnicity is also a non-modifiable stroke risk factor. Racial differences in BP levels have long been documented (Gillum, 1979), with elevated BP observed in all decades of life in the black population compared to other races and ethnicities (Whelton *et al*., 2018). This is potentially due to greater BP increases after salt intake (Wright *et al*., 2003) and greater risk of refractory hypertension (uncontrolled BP despite the use of three or more antihypertensive agent

classes [Lackland, 2014; Calhoun *et al*., 2008]). Sickle cell anaemia is also a major risk factor for stroke, particularly in the black population (Adams *et al*., 1997). This erythrocyte abnormality causes a 333-fold increase of stroke risk in children (Verudzco & Nathan, 2009) but is a major cause of stroke in all ages for those who have the condition (Platt *et al*., 1994). As a result of these factors, the black population have a 1.3–2-fold increased risk of stroke compared to the white population (Wang, Rudd & Wolfe, 2013; Benjamin *et al*., 2017) and African-Americans are more impacted by stroke than any other racial group (Kleindorfer, 2009). In individuals diagnosed with hypertension, control of the condition is better in the white population than any other race (Yoon *et al*., 2015). The south Asian population have strokes significantly younger than white individuals (Rees, Williams & Gladwin, 2010), where Japanese individuals have a larger morning BP surge than Europeans (Hoshide *et al*., 2015). The average age of stroke has been reported to be around eight years younger in African populations than high-income countries (O'Donnell *et al*., 2010). The extent to which some of these figures are skewed by poorer quality of medical care rather than physiological variables is not always clear, but a trend is unmistakeable.

Family history

A family history of stroke is an independent risk factor for all stroke other than cardioembolic and undetermined stroke types (Polychronopoulos *et al*., 2002), particularly in ischaemic stroke before the age of 70 (Jood *et al*., 2005). Over 25 rare mutations and 120 single-nucleotide polymorphisms have been linked to elevated BP (Lifton *et al*., 2001; Dominiczak & Kuo, 2017), and several genes have been linked to stroke – particularly intracerebral haemorrhage (Woo *et al*., 2014). A meta-analysis from Yu and colleagues (2018b)

demonstrates pooled risk ratios of 1.4 (CI: 1.18-1.67) for paternal history and 1.36 (CI: 1.20-1.53) demonstrating increased susceptibility to stroke in children of stroke patients. Seshadri *et al*. (2010) also observed a parental history of stroke as being associated with elevated risk of incident stroke in offspring, speculating that this may be due to familial susceptibility to hypertension and stroke (Flossman & Rothwell, 2005) or shared physical environments (Liao *et al*., 1997).

2.6 Medically-modifiable risk factors and stroke

Dysrhythmias

Atrial dysrhythmias are associated with an increased risk of ischaemic stroke (Al-Kawaz *et al*., 2018). Atrial fibrillation (AF) is an atrial tachyarrhythmia that leads to blood pooling in the ventricles and an increased risk of potential clotting (Stroke Association, 2015) and affects over 30 million people worldwide (Mulukutla *et al*., 2018). The likelihood of AF varies due to age (Benjamin *et al*., 1994), ethnicity (Davis *et al*., 2012), diabetes (Benjamin *et al*., 1994), obesity (Watanabe *et al*., 2008), hypertension (Schoonderwoerd *et al*., 2008) and left atrial size (Mulukutla *et al*., 2018). Hypertension is frequently found alongside AF due to its association with left ventricular hypertrophy, impaired diastolic function with impaired left ventricular filling, increased left atrial pressures with left atrial hypertrophy, increased atrial fibrosis, and the slowing of intra-atrial and inter-atrial conduction velocities (Healey & Connolly, 2003; Whelton *et al*., 2018). These side effects of hypertension increase the prevalence of AF, which in turn increases the stroke risk of an individual by five times (Savelieva, Baipai & Camm, 2007). This condition is reported to be the most common cause

of thromboembolism and ischaemic stroke worldwide (O'Donnell *et al*., 2010; Anca, Mirela & Florina, 2015) and presents in 29% of hospital admissions in the United Kingdom where the patient is > 65 years of age (Rizos *et al*., 2012). Strokes related to AF in females have higher mortality than similar strokes in males (Friberg *et al*., 2004) but the presence of AF raises the risk of recurrent stroke indiscriminately between the sexes after an initial event (Sposato *et al*., 2015). Anti-coagulants are recommended for those with AF (January *et al*., 2014; Kirchof *et al*., 2016) but in one ten-year time analysis, only 25% of stroke patients with AF were given anti-coagulants before stroke (Lee, Shafe & Cowie, 2011). As much as 30% of the population suffering with AF may be yet undiagnosed (Public Health England, 2017), leading to uncontrolled risk factors for stroke and CVD.

Elevated blood pressure and hypertension

Uncontrolled elevated BP leading to hypertension is the single greatest risk factor of early mortality worldwide (Lim *et al*., 2012). Although hypertension cannot be classified solely by discrete BP thresholds (Giles, Kostis & Fernandez, 2018), elevated BP represents the onset of hypertension in the body. This increase in BP is caused by an increase in cardiac output and/or an increase in vascular resistance (Clark, Zahradka & Taylor, 2015). The presence of hypertension is one of the most prevalent chronic diseases (Werneck *et al*., 2018), is the most common condition seen in primary care (James *et al*., 2014), and is the cause of death of more than ten million people per year worldwide (Frieden & Jaffe, 2018). The estimated number of adults with raised BP increased from 594 million in 1975 to 1.13 billion in 2015 (Zhou *et al*, 2017) – predominantly due to population growth and ageing. Increased BP is the leading risk factor for death and disability worldwide (Lim *et al*., 2012) and a large review involving 1.25

million individuals has demonstrated that the existence of hypertension raises risk of CVD from 46.1% to 63.3% (Rapsomaniki *et al*., 2014). However, hypertension control is only around 14% worldwide (Mills *et al*., 2016). This highlights the importance of elevated BP as a global public health concern (Briet & Schiffrin, 2013). This is particularly the case as the greatest levels of hypertension worldwide are now found in low-income and middle-income countries (Zhou *et al*, 2017). Hypertension is a condition which frequently coincides with other CVD risk factors (Whelton *et al*., 2018) and usually develops with age. Shihab and colleagues (2012) reported hypertension rates of 0.3%, 6.5% and 37% at ages 24, 45 and 65 respectively in a longitudinal study design. Isolated systolic hypertension (leading to increased pulse pressure [PP]) is the most common form of hypertension seen in those over 50 years of age (Franklin, 1999; Franklin *et al*., 2001).

The cut off point for the onset of hypertension has traditionally been set at > 140/90 mmHg (Pickering *et al*., 2005; Table 2.1). Further decreases in the marker designating the beginning of hypertension were predicted due to the wide prevalence of elevated BP (Touyz & Dominiczak, 2016), before new guidelines were introduced (Whelton *et al*., 2018). These guidelines, outlined in Table 2.2, lower the onset of elevated BP and the onset of hypertension even further and change the status of millions of “healthy” people to “hypertensive patients” (O’Brien *et al*., 2018).

Table 2.1: Traditional blood pressure categories (pre- July 2018)

BP Category	SBP		DBP
Optimal	< 120 mmHg	and	< 80 mmHg
Normal	120-129 mmHg	and/or	80-84 mmHg
High-normal	130-139 mmHg	and/or	85-89 mmHg
Grade I HT	140-159 mmHg	and/or	90-99 mmHg
Grade II HT	160-179 mmHg	and/or	100-109 mmHg
Grade III HT	≥ 140 mmHg	and	≥ 110 mmHg

Abbrevs: BP – Blood pressure, DBP – Diastolic blood pressure, HT – Hypertension, SBP – Systolic blood pressure

Table 2.2: Advised blood pressure categories as of July 2018 from the American College of Cardiology/American Heart Association

BP Category	SBP		DBP
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120–129 mmHg	and	< 80 mmHg
Hypertension			
Stage 1	130–139 mmHg	or	80–89 mmHg
Stage 2	≥ 140 mmHg	or	≥ 90 mmHg

Abbrevs: DBP – Diastolic blood pressure, SBP – Systolic blood pressure

From *Whelton et al.,* 2018 (p4)

Both Guo and colleagues (2013) and Huang and colleagues (2013) have reported increased risk ratios for CVD (including stroke) in patients with a BP of 130–139/85–89 mmHg compared to 120–129/80–84 mmHg. Previous work has also noted that two thirds of individuals with what was previously defined as pre-hypertension (SBP > 130 mmHg) developed hypertension within four years (Julius *et al*., 2006). As a result, categorising individuals as hypertensive earlier may reduce this seemingly natural progression towards even more elevated BP if effective treatments are available. Decreasing BP significantly reduces vascular risk and lowering BP to < 130 mmHg should be the goal (Ettehad *et al*., 2015). Nevertheless, the categories outlined in Table 2.2 have received criticism. Bakris and Sorrentino (2018) suggest that these changes may be problematic due to over-burdening the primary physician work force and that for non-high-risk patients, it may be sensible to continue defining hypertension using the 140/90 mmHg guidelines. The SPRINT group (2015) also note that achieving BP goals of < 120 mmHg would be more demanding for consumers and providers than the previous < 140 mmHg targets and may cause increased costs of medications. It is also worth noting that an increase in prevalence of hypertensive medications may lead to a greater prevalence of side-effects and polypharmacy. These new guidelines were, however, created to assist rather than dictate decision making (Schwartzbard *et al*., 2018).

Hypertension exposes the brain to excessive haemodynamic stress (Pase *et al*., 2013). This excess stress is a risk factor for reductions in cognitive function in those free from stroke. This takes place because of metabolic imbalances, atherogenesis, altered distribution of cerebral blood flow and demyelination or microinfarction in cerebral white matter (Elias *et al*., 2003). Elevated BP also leads to atherosclerosis and causes blood vessels in the brain, heart and limbs to harden and weaken (Tang *et al*., 2017). Links between hypertension and a range of clinical conditions can be seen in Table 2.3. Hypertension is the most relevant and prevalent

risk factor of stroke (SPS3, 2013). This relationship was first identified in the 1920s (Society of Actuaries, 1959) and it is now accepted that hypertension is positively and continuously related to the risk of stroke (Chalmers & Chapman, 2001; Chatterjee, Roberts & Boden-Albala, 2015).

Table 2.3: Key conditions linked with elevated blood pressure and hypertension

Hypertension linked with:	**Reference**
Stroke	McManus & Liebeskind, 2016
Transient ischaemic attack	Khare, 2016
Coronary artery disease	Weber *et al*., 2016
Chronic kidney disease	Ravera *et al*., 2006
Retinopathy	Van Leiden *et al*., 2002
Osteoporosis	Varenna *et al*., 2013
Metabolic syndrome	Mendizabal, Llorens & Nava, 2013
Sleep apnoea	Bradley & Floras, 2009
Vascular dementia	Nagai, Hoshide & Kario, 2010a

Approximately 50% of ischaemic strokes are caused by hypertension and the condition is the main risk factor for intracerebral haemorrhage (Royal College of Physicians, 2016). Raised BP is associated with left atrial hypertrophy, impaired diastolic function, cardiac structure and subclinical markers of left ventricular systolic function (Whelton *et al*., 2018) and, as a result, a BP < 120/80 mmHg substantially lowers the lifetime risk of CVD (SPRINT, 2015). The risk of CVD increases in a linear fashion from SBP < 115 mmHg to > 180 mmHg (Lewington *et al*., 2002). Blood pressure is elevated by CVD risk factors through activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, inhibition of

the cardiac natriuretic peptide system and endothelial dysfunction (Grassi *et al*., 1995; Kim *et al*., 2006; Sarzani *et al*., 2008). There is a strong and positive correlation between BP and target organ damage risk (Carretero & Oparil, 2000) and, therefore, lowering BP is likely to prevent stroke and death in those with grade I hypertension (Sundstrom *et al*., 2015). Conversely, increases of 20 mmHg systolic or 10 mmHg diastolic BP double the risk of stroke and CVD (Lewington *et al*., 2002) and so accurate measurement is of vital importance.

Blood pressure variability is also an independent predictor of stroke, coronary heart disease, cognitive dysfunction and all-cause mortality (Epstein *et al*., 2013; Muntner *et al*., 2015). Elevated arterial stiffness due to hypertension and ageing may amplify random BP changes and increase BP variability (Yang *et al*., 2018).

When treating hypertension in a population without a history of heart disease or stroke, intense treatments have been reported to be preferable to avoid future major cardiovascular events including myocardial infarction, coronary syndromes, stroke and premature death (SPRINT Research Group, 2015; Xie *et al*., 2016), even compared to less intense therapy (Thomopolous *et al*., 2016). Intensive BP lowering (to < 120 mmHg) has been shown to reduce all-cause mortality by 27% and cardiovascular mortality by 43% (SPRINT, 2015) and large decreases in left ventricular hypertrophy (Soliman *et al*., 2015). This has led to the "lower is better" attitude being adopted with patients at high risk of CVD (Bundy *et al*., 2017). Adverse events are, however, more frequently reported after intense BP lowering therapy, including hypotension, syncope, electrolyte abnormalities and acute kidney injury (SPRINT, 2015). Nevertheless, intensive interventions are recommended to prevent strokes and improve the prevention of mortality due to CVD (Verdecchia *et al*., 2016).

Hyperlipidaemia

Hyperlipidaemia is caused by high-fat diets, smoking, lack of exercise, excessive alcohol intake, kidney disease, liver disease and genetic predisposition (Stroke Association, 2015) and is characterised by increased cholesterol; particularly low-density lipoproteins. Total cholesterol/high density lipoprotein-C ratio may best predict stroke risk in males whereas triglyceride levels may be the strongest predictor of stroke risk in females (Liu, Yan & Xue, 2019). This increase in cholesterol is directly associated with an increased risk of ischaemic stroke (Tirschwell *et al*., 2004; Cui *et al*., 2012; Zhang *et al*., 2012) and relatively small reductions in total cholesterol have an impact on vascular health. A decrease of 1 mmol/l in total cholesterol is linked to a 21% reduction in stroke risk. These decreases in cholesterol can be achieved through lipid lowering treatments (Royal College of Physicians, 2016). Modifications to lifestyle also have the potential to reduce hyperlipidaemia, and telephone-based education about the subject has been demonstrated to lead to non-significant reductions in cholesterol (Adie & James, 2010). Even reductions in cholesterol which do not meet statistical significance may have meaningful impact on the lives of individuals with hyperlipidaemia.

Glucose metabolism disorders

Glucose metabolism disorders include type one diabetes mellitus, pre-diabetes mellitus and type two diabetes mellitus (Kernan *et al*., 2014). Type one diabetes mellitus occurs in genetically predisposed individuals due to the destruction of insulin depleting cells (Type 1 Diabetes Study Group, 2002) and is generally diagnosed at a young age. Pre-diabetes mellitus encompasses impaired fasting blood glucose, impaired glucose tolerance and intermediate

elevations in haemoglobin A_{1C} (Kernan *et al*., 2014) but without the development of type two diabetes. Type two diabetes is a chronic disorder characterised by hyperglycemia and later development of vascular and neuropathic complications (Inzucchi *et al*., 2011). Around one in sixteen people in the UK is diabetic (3.9 million; Diabetes UK, 2015) with an estimated 850,000 currently undiagnosed individuals (Department of Health, 2013). Diabetes mellitus as a whole is one of the most common chronic diseases (Guo *et al*., 2018) and significantly increases cardiovascular morbidity and mortality risk (Beckman, Creager & Libby, 2002). Diabetic individuals have a greatly increased risk of incident ischaemic stroke (Goldstein *et al*., 2011), with double the risk of stroke even after correcting for other risk factors in comparison to those without diabetes mellitus (Luitse *et al*., 2012). This increase in risk is particularly prevalent in females (Peters, Huxley & Woodward, 2014). Seventy-one percent of adults who have been diagnosed with diabetes mellitus are hypertensive (CDC, 2014). It is not clear whether or not the elevated stroke risk associated with glucose metabolism disorders is due directly to the lack of blood glucose control or due to frequent co-existing conditions (such as elevated BP) in metabolic syndrome.

Metabolic syndrome

Metabolic syndrome is the presence of a variety of abnormalities including being overweight, hypertriglyceridaemia, low HDL-C, elevated BP and hyperglycaemia (Kernan *et al*., 2014). This presents as visceral fat accumulation, insulin resistance, hyperinsulinaemia and hyperlipidaemia (Whelton *et al*., (2018). A three-fold risk of stroke exists in those presenting with metabolic syndrome (Isomaa *et al*., 2001) but whether or not this is clinically useful as a medical term is uncertain as its pathogenesis is debatable (Kernan *et al*., 2014), due to the

wide range of physiological variables contributing to its contraction. Insulin resistance may be the core defect, leading to the development of other conditions associated with the syndrome (Kernan *et al*., 2014). Recent recommendations have outlined lifestyle modification as the cornerstone of treating metabolic syndrome (Whelton *et al*., 2018) – with the focus on lifestyle changes in these recommendations being unprecedented (Schwartzbard *et al*., 2018). Dietary modification and weight reduction are the two primary means of reducing the burden of metabolic syndrome and the consequent elevated risk of incident stroke.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a condition characterised by upper airway obstructions due to reductions in pharyngeal muscle tone during sleep (Turkington *et al*., 2002). Recurrent collapses of the upper airway cause intermittent apnoea, hypoxaemia and a resulting disruption in sleep (Parati *et al*., 2012). This condition is the most common form of sleep-disordered breathing (Dong *et al*., 2018) and is present in 2-7% of the general adult population (Lattanzi, Brigo & Silvestrini, 2018a). The presence of OSA is linked to a heightened risk of hypertension (Marin *et al*., 2012) and, once the condition begins to manifest nocturnally, derangements may begin to take place during the daytime too; causing alterations to circadian rhythms (Lattanzi *et al*., 2018a). Prominent risk factors of OSA include age, being of the male sex, snoring, increased body mass index and increased neck circumference (Turkington *et al*., 2002). The presence of OSA increases the risk of cerebrovascular disease and the end-point of stroke and death (Yaggi *et al*., 2005; Redline *et al*., 2010; Dong *et al*., 2018). Whilst OSA is only present in 2-7% of the general population (Lattanzi *et al*., 2018a), it

was reported in 72% of a sample of stroke patients (Johnson & Johnson, 2010), with 63% suffering > 10 reductions in air flow per hour and 38% suffering > 20 events per hour.

2.7 Behaviourally modifiable risk factors and stroke

Physical activity

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen, Powell & Christenson, 1985), whereas physical inactivity is "the presence of insufficient physical activity levels to meet present physical activity recommendations" (Morton *et al*., 2018). These physical activity guidelines are outlined in Table 2.4. Recommendations from the Department of Health and Social Care (2011) are similar between adults and older adults but a stronger rationale is offered for the need for activity in older adults.

Table 2.4: Physical activity guidelines for adults and the older adults

19-64	65+
Be active daily. 150 minutes of moderate intense activity in bouts of 10 minutes or more per week	Be active daily. 150 minutes of moderate intensity activity in bouts of 10 minutes or more per week
75 minutes of vigorous intense activity across the week	For those who can, 75 minutes of vigorous intense activity across the week
Physical activity to improve muscle strength ≥ 2 days per week	Physical activity to improve muscle strength on two days per week
Minimising sedentary time	Minimising sedentary time
	If at a risk of falls, incorporate balance and co-ordination skills on two days per week

Adapted from Department of Health and Social Care, 2011

Incorporating sufficient physical activity to meet guidelines is associated with a decrease in stroke, other CVD risk, and all-cause mortality, particularly in terms of ischaemic stroke (Thrift, Donnan & McNeil, 2002; Reimers *et al*., 2009; O'Donnell *et al*., 2010; Department of Health, 2011; Li & Siegrist, 2012; Autenrieth *et al*., 2013; Aidar *et al*., 2014). According to a meta-analysis of 23 studies, individuals who are very physically active have a 27% lower risk of incident stroke than those with low levels of low physical activity (Lee, Folsom & Blair, 2003) with physical activity interventions seen as a viable option for stroke prevention in the > 80 years old demographic (Willey *et al*., 2017). Introducing physical activity as a lifestyle choice is the cornerstone of risk reduction therapy for the prevention and treatment of stroke (Gordon *et al*., 2004) and provides a non-pharmacological option to slow age-related

cognitive decline and disease-related impairment in the older population (Kirk-Sanchez & McGough, 2014).

Physical activity is beneficial to vascular health due to the reduction of peripheral resistance (Kokkinos *et al*., 2009) and increases in nitric oxide release (Zanesco & Atunes, 2007) and a systematic review reports that undertaking physical activity has a positive influence on key variables relating to the progression of atherosclerosis (Palmefors *et al*., 2014). However, although physical activity may attenuate the stresses placed on the body by overweight and obesity through hypertension, it does not eliminate them entirely (Werneck *et al*., 2018). Undertaking physical activity may help incident stroke prevention through improving traditional vascular risk factors (such as BP) but may also improve the human response to stroke, potentially reducing infarct size and minimising severity (Middleton *et al*., 2013).

Physical inactivity and sedentary time

Physical inactivity is a major risk factor for chronic diseases (Jones *et al*., 2018), including increased risk of incident and recurrent stroke (McDonnell *et al*., 2013; Feigin *et al*., 2014) by around 50% (World Health Organisation, 2004). Most research studies use the term 'inactive' to describe those who are performing less moderate-vigorous intensity physical activity than guidelines recommend (van der Ploeg & Hillsdon, 2017). Distinguishing between physical inactivity and sedentary time is vital when addressing lifestyle changes (Morton *et al*., 2018). Sedentary time is "any waking behaviour characterised by an energy expenditure < 1.5 METs while in a sitting or reclining posture" (Barnes *et al*., 2012) and there is growing concern about the amount of time people spend sedentary (Martin *et al*., 2015). Sedentary individuals are 25-30% more likely to have a stroke than less sedentary peers (Goldstein *et al*., 2011) and less

likely to take part in exercise outside of their sedentary time. Even if individuals do take part in exercise, extended time spent in sedentary behaviours is associated with poor health, regardless of the level of outside physical activity (Martin *et al*., 2015). For example, for every five hours of extra television viewing per week, there is a significant increase in the biomarkers for diabetes risk (Hansen *et al*., 2012) and consequently stroke risk. This may be due to the association between prolonged television viewing time and increased BP (Beijer *et al*., 2018). Sedentary behaviours are associated with lower cognitive performance (Falck, Davis & Liu-Ambrose, 2017), decreased verbal memory (Kesse-Guyot *et al*., 2014), executive function (Steinberg *et al*., 2015) and all-cause dementia risk (Kivipelto *et al*., 2008). For every 25-30 minutes of sedentary behaviour per day, the risk of CVD increases by 1% (Fitzgerald *et al*., 2015) and prolonged bouts of sedentary time are particularly harmful to the body (Healy *et al*., 2008; Healy *et al*., 2011).

Exercise

The concept that taking part in exercise is beneficial to health is not a new one, with reductions in resting heart rate (Levy *et al*., 1998), BP (Whelton *et al*., 2002), and improvements in heart rate variability (Malfatto *et al*., 1996) noted after exercise programmes. Exercise is defined as a "subset of physical activity that is planned, structured and repetitive and has a final or an intermediate objective of the improvement or maintenance of physical fitness" (Caspersen *et al*., 1985, p. 126). Exercise is associated with a higher quality of life and better health compared to sedentary individuals (Naci & Ioannidis, 2013) with those who exercise enough to fall in the highest quartile of energy expenditure having a 15% lower risk of dementia than those in the lowest quartile of energy expenditure

(Podewils *et al*., 2005). Aerobic exercise and resistance exercise have both been shown to reduce BP (Cornelissen *et al*., 2011; Rossi *et al*., 2013; Cornelissen & Smart, 2013). Running has been shown to increase brain derived neurotrophic factor – a growth factor key in terms of contributing to cell survival and neurite growth (Thomas *et al*., 2012) and therefore particularly pertinent to stroke. Nevertheless, only 14% of adults in the United Kingdom exercise regularly (Townsend *et al*., 2012) but those who run more than 8km per day have a 60% reduced risk of stroke compared to individuals who run fewer than 2km per day. Whilst running over 8km per day may not be a feasible option for most people, even running more than 2km per day significantly reduces the risk of stroke (Williams, 2009). The picture is becoming clearer and clearer that lifestyle choices are the first line of defence against CVD (Croymans *et al*., 2014).

Overweight and obesity

The prevalence of overweight and obesity (body mass index > 25kg·m^2 and body mass index > 30kg·m^2 respectively) is on the rise. Although there are criticisms of the system, including the lack of classification of where fat is situation (Nuttall, 2015) , this is still a widely used classification tool in the general population. In the United Kingdom, 58% of females and 65% of males are either overweight or obese and the average body mass index (BMI) for the population is 27.2kg·m^2, an overweight BMI classification (Health and Social Care Information Centre, 2016). As the prevalence of overweight and obesity grows, there is potential for elevated BP to follow (Forouzanfar *et al.,* 2017). This condition is a major health and societal problem (Chrysant, 2018), accounting for one in five deaths worldwide (Masters *et al*., 2013) due to its links with elevated BP (Hall *et al*., 1999; Hall, 2003; Saydah *et al*., 2014; Werneck *et*

al., 2018), atherosclerosis (Roberts & Barnard, 2005) and OSA (Romero-Corral *et al*., 2010). Overweight and obesity are directly linked to stroke (Kurth *et al*., 2005; Strazzullo *et al*., 2010) with 18-44% of stroke patients reported to be obese by available estimates using BMI as a categoriser (Kernan *et al*., 2013). Being overweight or obese increases stroke risk by 22% and 50% respectively (Strazullo *et al*., 2010) whilst a possible linear relationship exists between BMI and stroke with every increase of 1kg·m^2 above 20kg·m^2 representing a 5% increase in stroke risk (Kernan *et al*., 2014). This is due to the activation of systemic inflammation and increased oxidative stress, potentiating endothelial dysfunction and vascular hypertrophy (Dorresteijn, Visseren & Spiering, 2012). When trying to reduce BP, weight loss is one of the most important interventions available, with decreases in BP observed after successful weight loss interventions (THOP Phase II, 1997; Neter *et al*., 2003) and a 1 mmHg reduction in brachial BP expected for each 1kg of body mass reduction (Whelton *et al*., 2018).

Alcohol intake

Low alcohol intake has been reported to reduce the risk of ischaemic stroke, moderate alcohol intake to have little effect on stroke risk and heavy alcohol intake to have an increased risk of stroke with an apparent dose/response relationship (Zhang *et al*., 2014). There is a school of thought, however, that light alcohol consumption may reduce the risk of ischaemic stroke (Reynolds *et al*., 2003). This may occur due to increased levels of HDL-C, decreased fibrinogen levels and lower platelet aggregation (Mukamal *et al*., 2005; Brien *et al*., 2011), with these factors leading to fewer atherosclerotic plaques (Sundell *et al*., 2008). Nevertheless, a number of research studies have reported that BP increases linearly with alcohol intake (Taylor *et al*., 2009) and that reducing alcohol intake is associated with significant reductions in BP (Xin *et*

al., 2001). There seems to be a predictable and direct relationship between alcohol intake and BP, particularly when alcohol intake goes above three drinks per day (Whelton *et al*., 2018). The two habits which seem particularly damaging to stroke risk are drinking over thirty alcoholic drinks per month and binge drinking (Reynolds *et al*., 2003; Sundell *et al*., 2008; O'Donnell *et al*., 2010). Binge drinking is defined as males consuming six or more drinks of the same beverage on one occasion or females consuming four or more drinks on one occasion (Sundell *et al*., 2008). The risk of ischaemic stroke is increased among infrequent drinkers and occasional binge drinkers compared to those who do not drink at all (Hansagi *et al*., 1995) and drinking large amounts of alcohol on one occasion may increase BP more than the same volume over a greater length of time (Wannamathee & Shaper, 1991). These sudden consumptions of a large amount of alcohol that amount to binge drinking may cause temporary BP spikes which may lead to potential ruptures of the small arteries or to an aneurysm (Sundell *et al*., 2008).

Illegal drug use

Illegal drug use is also linked directly to stroke and may be the most common behaviour leading to stroke in those under 35 years old (Esse, Fossati-Bellani & Traylor, 2011). Drug users aged 15-44 years are 6.5 times more likely to have a stroke at an early age than non-drug users (Kaku & Lowenstein, 1990) and around 12% of young adult stroke patients report illegal drug use (Sloan *et al*., 1998) – a number which may underestimate the true figure. Using cocaine, amphetamines, ecstasy, heroin, phencyclidine, lysergic acid diethylamide and marijuana may all start mechanisms that increase the likelihood of stroke (Sloan *et al*., 1998), with cocaine and amphetamines specifically reported to be strong risk factors for stroke

(Petitti *et al*., 1998), although Dutta and colleagues argue against the link between marijuana and stroke (Dutta *et al*., 2014).

Tobacco smoking

One in four strokes in England can be attributed to tobacco smoking, as smokers have up to three times the risk of stroke compared to non-smokers (Royal College of Physicians, 2016). Around half of participants (52%) under the age of 45 in research from de los Rios and colleagues (2012) were active smokers at the time of stroke. Cigarette smoking has long been recognised as an independent risk factor for stroke (Wolfe *et al*., 1988; O'Donnell *et al*., 2010) with a dose-response relationship observed between the number of cigarettes smoked and level of stroke risk (Shinton & Beevers, 1989). The primary mechanism relating smoking to stroke seems to be AF, as the risk of AF is increased five-fold in those who smoke (Savelieva *et al*., 2007; Albertsen *et al*., 2015). It is the co-existence of smoking and hypertension, however, which seems to create the greatest risk of ischaemic stroke (Huangfu *et al*., 2017). However, the popularity of cigarette smoking is on the decline. Only 19% of adults in Great Britain are smokers (down from a peak of 46% in 1974) and 19% of adults in the USA are smokers (down from a peak of 42% in 1965 [CDC, 2012; Office for National Statistics, 2014]). The short-term and long-term effects of vaping and passive vaping have not yet become clear and longitudinal data must be collected to relate this to stroke risk as this form of smoking becomes more common.

Socioeconomic status

Being exposed to particulate air pollution is linked to higher stroke risk. This is perhaps one of the reasons why people from more deprived socioeconomic backgrounds are at higher risk, with those who live in economically deprived parts of the UK two to three times more likely to have a stroke than those in the least deprived areas (Scarborough *et al*., 2009; Public Health England, 2013). Socio-economic status is directly linked to an increased likelihood of stroke (Kerr *et al*., 2011). On a global level, people in low and middle-income countries have strokes five years younger than in higher income countries (Feigin *et al*., 2014). Incidence and thirty-day fatality rates are also higher in India compared to more developed countries (Das *et al*., 2007; Dalal *et al*., 2007). Although socio-economic status is only modifiable to a certain extent, it plays a large part in deciding stroke risk for an individual.

Air pollution

One potentially related variable to socio-economic status is air pollution and stroke. Inhaling air pollution may lead to a pro-inflammatory response, increasing blood coagulation. This increase in air pollution and blood coagulation may lead to increased BP (Liang *et al*., 2014) and a rise in ischaemic stroke risk (Brook *et al*., 2010). Work from Sjogren and colleagues (2013) suggests that after adjusting for age, socioeconomic status and population density, participants exposed to small pollutant particles (e.g. machine drivers) or large particles (e.g. engineering workers, construction workers, welders) have an increased risk of ischaemic stroke compared to those unexposed (e.g. nurse assistants, show assistants). A combination of low socio-economic status and employment in physically degraded environments therefore seems likely to predispose cerebrovascular events. Physical activity in the

workplace may give even more protection from stroke than leisure time physical activities (Wendel-Vos *et al*., 2004) but when this physically active work is in an environment with high levels of air pollution, it is extremely detrimental to an individual's health and drastically increases stroke risk.

Diet

A healthy lifestyle involves consuming a nutritious diet and balance of macro and micronutrients. This combination of beneficial foods and nutrients may reduce inflammatory cytokines and reduce the risk of cardiovascular alterations (Hu, 2002).

The Mediterranean diet is optimal for improving BP control, decrease inflammation and maximise endothelial function (Nordmann *et al*., 2011; Kernan *et al*., 2014; Schwingshackl & Hoffman, 2014; Ruiz-Canela *et al*., 2015). This diet is characterised by high levels of oily fish, fruits, nuts and seeds (O'Donnell *et al*., 2010; Ndanuko *et al*., 2017). Table 2.5 displays key findings of a range of studies relating to diet and chronic disease.

Table 2.5: Studies presenting the influence of diet on chronic disease risk

Authors	Dietary aspect examined	Key findings
O'Donnell *et al*., 2010	Increased intake of red meat, eggs, fried foods, salty snacks, foods containing lard	Consumption related to increased overall stroke risk
Mangat *et al*., 2013	Excess dietary fat intake	Increased fat intake leads to greater risk of hypertension
Van Dam *et al*., 2003	Red meat, coffee, potatoes, beer and saturated fats	Consumption of these products related to elevated systolic blood pressure
Abete *et al*., 2018	Lifestyle incorporating semi-skimmed dairy products, fish, fruit and vegetables, wholemeal cereals and olive oil	These foodstuffs may favour the control of C-reactive protein and HDL-C
Campbell *et al*., 2012	Fish oil supplementation	Fish oil supplementation may cause significant decreases in systolic blood pressure
Jaaskelainin *et al*., 2012	Vegetable consumption as a child	Increased vegetable consumption at a young age decreases risk of elevated blood pressure in later life
Fung *et al*., 2004	Intake of fruit and vegetables, fish and whole grains	Consuming these foodstuffs may protect against stroke
He, Nowson & MacGregor, 2006	Fruit and vegetable consumption	Increased consumption of fruit and vegetables reduces the risk of stroke
Boeing *et al*., 2012	A critical review examining fruit and vegetable intake and chronic disease	Fruit and vegetable consumption throughout life is related to a reduced risk of chronic diseases including CVD, stroke, cancer, eye diseases and osteoporosis

Flavonoids found in fruit suppress rises in BP in those with hypertension and metabolic syndrome through restoring endothelial function (Clark *et al*., 2015). One class of flavonoid are anthocyanins – found in fruits such as blueberries and raspberries. Improvements in long-term health prognoses after fruit intake may take place due to anthocyanin induced decrease

in arterial stiffness. Fruits high in anthocyanins may improve vascular function through increasing the bioavailability of nitric acid – a vasodilator (Jennings *et al*., 2012).

Sugar sweetened beverages are strongly linked to obesity (Hu, 2013) and artificially sweetened soft drink consumption is also associated with an elevated risk of stroke (Pase *et al*., 2017). Coffee is one of the most commonly consumed drinks in the world (Crippa *et al*., 2014) and has been linked to decreased rates of cancer, cardiovascular disorders, cardiovascular mortality and all-cause mortality (Beaudoin & Graham, 2011; Crippa *et al*., 2014). The substance has also been linked with a decreased risk of ischaemic stroke, but not haemorrhagic stroke (Lopez-Garcia *et al*., 2009). The overall picture is not clear as smoking and caffeine consumption tend to take place concurrently (Bjorngaard *et al*., 2017) but heavier daily coffee consumption may be linked to lesser stroke prevalence, although causality is unclear (Liebeskind *et al*., 2016). As with alcohol intake, naïve coffee drinkers double their risk of stroke in the next hour compared to regular coffee drinkers (Mostofsky *et al*., 2010) due to this sudden spike in BP after consumption.

Prescription drugs

The use of prescription drugs has risen sharply in the United Kingdom (NHS, 2012) and the medical research landscape increasingly favours drug interventions over lifestyle modification (Naci & Ioannidis, 2013). Funding of pharmacological interventions is more likely to be provided by wealthy corporations than behavioural change studies which may be less financially profitable. Yusuf and collaegues (2005) listed nine key factors: hypertension, current smoking, abdominal obesity, physical activity, diet, diabetes mellitus, alcohol intake, psychosocial factors and apolipoproteins. These nine factors are narrowed down to five by

O'Donnell and colleagues (2010): hypertension, current smoking, abdominal obesity, diet and physical activity. O'Donnell and colleagues concluded that hypertension is the strongest risk factor for all stroke (Odds ratio (99% confidence interval: 2.64 [2.26 – 3.08]; 34.6% population-attributable risk {30.4-39.5}). They claim that the main target of interventions aiming to reduce the global burden of stroke should involve reducing hypertension, smoking cessation, physical activity instigation and a healthy diet. The factors listed in this thesis, whether they are non-modifiable (e.g. age, ethnicity), medically modifiable (e.g. OSA, metabolic syndrome) or behaviourally modifiable (e.g. sedentary time, physical activity, exercise, diet, alcohol) all relate back to vascular health, elevated BP and hypertension.

2.8 Stroke occurrence

After ischaemic stroke occurs, protein synthesis is completely suppressed in the tissue adjacent to the infarct (the ischaemic penumbra [Xie *et al*., 1989]). There is a lowering of adenosine triphosphate in the immediately surrounding area as the cellular pH decreases (Hossmann *et al*., 1985) and this decrease in protein synthesis leads to cell death if not quickly reversed (Aquilani *et al*., 2011).

Managing risk factors after stroke through pharmacological methods and lifestyle changes is the cornerstone of strategies intending to reduce the likelihood of recurrent stroke (Kono *et al*., 2013). Due to the fact that treatment of incident stroke is constantly improving, more patients are surviving their strokes than ever before. This leads to a larger number of patients being discharged with an elevated risk of future strokes, greater burden being placed on rehabilitation services and more pressure on those services trying to prevent recurrent strokes from taking place. Understanding and acting on the consequences of having and

surviving a stroke is vital. The consequences of stroke can be broken down broadly into physiological and psychological/psychosocial categories depending on the individual and the precise location of the stroke.

2.9 Treatment after stroke

Immediately following stroke, the use of thrombolysis (using alteplase, reteplase [r-tPA] or tenecteplase and tissue plasminogen activator [tPA]) is administered to ischaemic patients. A systematic review by Qin and colleagues (2018) reported reduced long-term mortality in ischamic stroke patients who were treated with intravenous r-tPA, although a greater risk of death in the first 7-10 days has been demonstrated due to increased occurrence of fatal ICH (Wardlaw *et al*., 2014). This treatment is permitted up to 4.5 hours post ischaemic stroke in the United Kingdom (SIGN, 2008; NICE, 2012) and should be prescribed with a dosage of $0.9mg \cdot kg^{-1}$ (Furlanis *et al*., 2018). Only a small proportion of stroke patients are treated with tPA (Lackland *et al*., 2014) due to the narrow window of safe and effective treatment. As only one in nine patients with acute stroke receive thrombolysis (Intercollegiate Stroke Working Party, 2016) and older patients with higher NIHSS scores have longer door to needle time (Birnbaum *et al*., 2016), there is now a focus on minimising pre-hospital and in-hospital delay (Faiz *et al*., 2017).

Anti-platelet therapy is one of the most important methods of reducing secondary stroke risk (Antithrombotic Trialists' Collaboration, 2002; Royal College of Physicians, 2016). The intake of aspirin within 48 hours of ischaemic stroke may reduce mortality risk between one and three-months post-stroke (Sandercock *et al*., 2008), but an increased risk of bleeding (Morgan, 2005) and of future haemorrhagic stroke (Morgan & Elwood, 2011) have been

observed. Although the largest beneficial effect of aspirin has been observed at 325mg per day, between 75mg and 100mg per day balances efficacy and safety (Singer *et al*., 2008; Kernan *et al*., 2014). Clopidogrel is a second anti-platelet drug which is effective for ischaemic stroke prevention (Ikeda-Sakai, Sasaki & Nakase, 2017).

Whilst using these drugs in isolation is beneficial, combination therapy trials have yielded mixed results. Although a combination of the two drugs has been suggested to reduce the risk of stroke compared to aspirin alone (Zhou *et al*., 2012), the effectiveness may be 'modest at best' (Connolly *et al*., 2011). There is an increased risk of haemorrhage widely reported after this combination therapy (Diener *et al*., 2004; Geraghty *et al*., 2010; Lackland *et al*., 2014). Guidelines therefore advise against the use of the two drugs in tandem (Furie *et al*., 2011). Other anti-platelet treatments include dipyridamole, which, when combined with aspirin, has been reported to reduce the risk of recurrent stroke compared with aspirin alone (Diener *et al*., 1996) and ticlopidine, which has been reported to reduce the risk of major events compared with aspirin but with greater safety concerns (Antithrombotic Trialists' Collaboration, 2002).

Anti-coagulant therapy is now usually restricted to long-term secondary prevention (Royal College of Physicians, 2016). The most common prescribed therapy is warfarin which may reduce fatal and non-fatal stroke by around 50% in those with AF (Aguilar, Hart & Pearce, 2007). Earlier research suggests that the use of warfarin may reduce annual risk of recurrent stroke from 12% to 4% (EAFT Study Group, 1993). However, there may be an increased risk of bleeding after the use of warfarin (Shah *et al*., 2014) – these authors suggesting that the drug may not even be useful in reducing stroke risk in those with AF undergoing dialysis.

Statins (most commonly atorvastatin) are frequently used for individuals suffering from ischaemic strokes. Discharge statin therapy is linked with a lower risk of major adverse cardiovascular events (O'Brien *et al*., 2015) and may risk the risk of dementia (Pan *et al*., 2018) but must not be used with patients where haemorrhage is a plausible cause for stroke. A five-fold increased risk of recurrent haemorrhage is the result of prescribing statins incorrectly after haemorrhagic stroke (Goldstein, Mascitelli & Pezzetta, 2009). High dose statin therapy is recommended to those with dyslipidaemia to prevent second strokes (Amarenco *et al*., 2009a).

Once anti-hypertensive medication is prescribed, it is usually continued for life but one in four patients could be successfully withdrawn for two years or more (van der Wardt *et al*., 2017) and 22-50% of patients could be withdrawn for one year or longer without elevated BP returning. Although achieved BP reductions have been found to be comparable between males and females (Turnbull *et al*., 2008), females are more likely to suffer adverse effects of the therapy (Lewis *et al*., 1996).

2.10 Physiological consequences of stroke

Stroke causes the largest range of disabilities of any clinical condition (Adamson *et al*., 2004) and is the leading cause of disability in the elderly (Hung *et al*., 2018). Immediately after stroke, patients are at great risk of dehydration, malnutrition, infection, hypoxia and hyperglycaemia (Royal College of Physicians, 2016). The vast majority of stroke survivors then suffer from subsequent disabilities including hemiparesis, spasticity, cognitive dysfunction and aphasia (Billinger *et al*., 2014) with neurological deficits observed in most patients (Kobayashi, 2015). Cognitive impairments, observed in over half of stroke survivors, may

impede rehabilitation and functional recovery (Swatridge *et al*., 2017) as well as being associated with increased risk of mortality (Oksala *et al*., 2009). The large levels of morbidity after stroke tend to be due to a combination of neurological impairment, the social consequences of the impairment and the high risk of stroke recurrence (Kernan *et al*., 2014). Table 2.6 demonstrates the frequency of a variety of physical disabilities post- stroke, highlighting the large prevalence of life-altering disability after stroke.

Table 2.6: Physical disability post- stroke

Consequence of Stroke	**% patients affected**	**Statistics from**
Upper limb/arm weakness	~70%	Royal College of Physicians SSNAP, 2016
Lower limb/leg weakness	72%	Lawrence *et al*., 2001
Visual problems	60%	Rowe *et al.,* 2013
Slurred speech	50%	Harwood, Huwez & Good, 2010
Problems with bladder control	50%	Harwood, Huwez & Good, 2010
Problems swallowing	45%	Lawrence *et al*., 2001
Aphasia	20-40%	Engelter *et al*. (2006); Berthier (2005); Dickey *et al*. (2010) Furlanis *et al*. (2018)
Sensory Loss	Up to 80%	Doyle *et al*., 2010
Problems with bowel control	33%	Harwood, Huwez & Good (2010)
Epilepsy	2-14%	Menon & Shorvon, 2009

Adapted from *Stroke Association, 2015*

Deconditioning is frequently observed after stroke (Stein *et al*., 2006) and the assessment of this is central to the rehabilitation process (Royal College of Physicians, 2016). Around 65% of stroke survivors report severe disability after stroke (Adamson *et al*., 2004) and 40% report difficulties with basic self-care (Mayo *et al*., 2002). Although rehabilitation services aim to recover as much original movement as possible, the condition of altered arm function persists in around 40% of patients (Royal College of Physicians, 2016). Up to 50% of older stroke patients suffer permanent loss of some physical function after stroke (Mizrahi *et al*., 2007) and half or more of stroke survivors report having one or more unmet needs between one- and five-years post-stroke (McKevitt *et al*., 2011). This is frequently due to the decreased cardio-respiratory and musculoskeletal fitness in the stroke population compared to age-matched healthy controls. Some motor improvements may occur after stroke due to the resolution of reversible damage to neurons and ganglia including changes in membrane potentials, axon conduction and neurotransmission (Dobkin, 2008). However, the loss of movement patterns is frequent due to lesions of the corticospinal pathways, leading to affected co-ordination of the joints (Dobkin, 2008).

The consequences of stroke compromise living and social activities (Aidar *et al*., 2014), but those recovering after stroke can make meaningful gains in functional movement, functional fitness and functional balance after interventions (Lindberg *et al*., 2004). Functional fitness is the "physical capacity of the individual to meet ordinary and unexpected demands of daily life safely and effectively" (Bravo *et al*., 1994, p. 67), whereas functional balance is "the capacity to maintain various positions, to make automatic postural responses to voluntary changes in the body and its segments to react to external disturbances" (Berg *et al*., 1989, p. 304). Loss of balance and falls are frequent after stroke (Persson, Hansson & Sunnerhagen, 2011) with as many as 48% of stroke patients falling during in-patient post- stroke care (Suzuki

et al., 2005). Even after discharge, between 13% and 25% of those doing exercise training suffer falls (Pang *et al*., 2005; Mead *et al*., 2007). These falls are due to decreases in proprioception and balance, decreased strength, difficulties processing information, lack of dual tasking and difficulties during the planning and excecution of tasks (Barros de Oliveira *et al*., 2008; Baetens *et al*., 2013). Disturbed alertness is also common after stroke (Royal College of Physicians, 2016) and may contribute to the high rate of falls.

As a result of deconditioning due to the consequences listed in Table 2.6, chronic stroke patients display very low cardiovascular fitness (Michael, Allen & Macko, 2005). Survivors commonly present with selective muscle atrophy, decreased agonist muscle activation and impaired trunk muscle performance (Duncan *et al*., 2003; Silva-Couto *et al*., 2014). Interestingly, left hemiparesis has been reported to result in lower step counts, slower walking skills and greater gait asymmetries than right hemiparesis (Cassvan *et al*., 1976; Chen *et al*., 2014; Ezeugwu & Manns, 2016) but, across the board, fitness suffers. Peak oxygen uptake in sub-acute stroke patients has been reported to be only 60% of that of age- and sex-matched normative values even in sedentary adults (Mackay-Lyons & Makrides, 2002).

Cognitive deficits after stroke frequently include memory impairment (Novitzke, 2008) and reductions in concentration (Rasquin *et al*., 2002), cognitive control (Li *et al*., 2013), language (Pedersen *et al*., 2004), mental speed (Winkens *et al*., 2006), and executive functioning (Poulin *et al*., 2012). Dysarthria is neurological motor speech impairment with slow, weak, imprecise and/or un-coordinated movements of the speech musculature and is common after stroke (Royal College of Physicians, 2016), as is aphasia, a language disorder affecting verbal production or verbal comprehension, although cognitive function remains unaffected (Watila

& Balarabe, 2015). These cognitive deficits frequently complicate programmes to enhance physical recovery.

2.11 Psychological and psychosocial consequences of stroke

After stroke, a range of psychological conditions are frequently found in patients which limit quality of life and damage long- term prognoses. These psychological symptoms can be described as reactions to clinical consequences including motor disability and physical limitations in daily life (Kneebone & Lincoln, 2012). These symptoms may be due to cerebral lesions or depletion of serotonin, noradrenaline and dopamine (Bhogal *et al*., 2004; Buono *et al*., 2018).

Vulnerable individuals are at risk of poor physical, psychological, and/or social health (Aday, 1994). Vulnerability is common after stroke and mortality risk is reported to be five times higher in vulnerable patients than non-vulnerable patients (Gaynor *et al*., 2018). There is an argument that a stroke- specific definition of vulnerable is required, as there is a fair rationale that all stroke patients are vulnerable based on Aday's more generic definition. Around 30% of stroke survivors experience post- stroke depression (Villain *et al*., 2017) which has characteristics including decreased interest, pessimism, lack of initiative and general fatigue (Li *et al*., 2017). The presence of this condition after stroke has been linked to continued smoking (Gravely-Witte *et al*., 2009), decreased motivation to eat healthily or be physically active (Lawrence *et al*., 2010), lowered performance in daily living activities (Kotila *et al*., 1984), increased dependency (Langhorne *et al*., 2000), decreased quality of life (Sturm *et al*., 2004) and reduced social interactions (Murrel *et al*., 2011). Depressive symptoms are also linked to increased risk of further CVD through hyperactivity of the hypothalamic-pituitary-

adrenocortical axis, decreased heart rate variability, myocardial infarction, ventricular instability and changes in platelet receptors and reactivity (Musselman, Evans & Nemeroff, 1998). Patients with depression are also at a heightened risk of death due to stroke (Razmara *et al*., 2017), particularly those under the age of 65 (Ayerbe *et al*., 2014). Whilst depressive symptoms may be alleviated by physical activity and exercise (Graven *et al*., 2011), physical limitations and fatigue may prevent this from taking place in many stroke survivors.

Anxiety (the existence of at least one current clinically significant anxiety disorder [Sagen *et al*., 2010]) and emotionalism (the habit of weakly yielding to emotion, usually involving crying but sometimes laughing [Hackett *et al*., 2010]) have emerged as common reactions to stroke (Broomfield *et al*., 2014) and TIA (Verbraak *et al*., 2012). Around 18-25% of patients suffer from anxiety and approximately 20% suffer from emotionalism (Astrom, 1996; Hackett *et al*., 2010) during recovery. This presence of post- stroke emotionalism has been linked to low testosterone levels (Choi *et al*., 2018). Anxiety and depression are both associated with elevated mortality after stroke (Bartoli *et al*., 2013) although the mechanisms behind this remain unclear (Razmara *et al*., 2017). Research into anxiety is less extensive than post-stroke depression but a combination of anxiety, depression, emotionalism and a lack of physical ability can lead to losses of confidence. Confidence, a positive mood state (Doyle, 2002), is lacking in 73% of stroke patients (Stroke Association, 2013). This lack of confidence relates to carrying out every-day functions, social interactions, physical activity, and a lack of trust in the patient's own body (Hare *et al*., 2006; Spurgeon *et al*., 2013). Stroke survivors have reported that there may be little reason in treating physical problems during recovery if a patient does not have the confidence to leave the house even when they are physically able to (Pollock *et al*., 2012). A combination of these conditions may lead to overall low mood, with impulsive behaviours, verbal aggression and hostility seen after stroke (Choi *et al*., 2018).

Low mood may be the cause and consequence of low physical activity which may have a consequential damaging effect on self-efficacy, motivation and self-determination (Morris *et al*., 2012). The Stroke Association (2013) report that 63% of stroke survivors live in fear of another stroke, 44% find it hard to talk about stroke and 44% either break up or consider breaking up with their significant other. When considering how late in life strokes tend to occur, this proportion of patients considering breaking up with, or actually breaking up with, a significant other demonstrates the psychological difficulties encountered after stroke. One in four survivors live alone (Stroke Association, 2012a) and 69% of 25-59 year-old survivors are unable to return to work (Stroke Association, 2012b). This isolation in the chronic stage of recovery follows in-patient stays where patients spend most of their time alone (West & Bernhardt, 2012). A combination of these situations, combined with 18% of stroke survivors having access to care services reduced or withdrawn (Stroke Association, 2012a), can lead to a lack of social interaction. Decreased social interactions can, in turn, combine with losing self-identity to produce low levels of independence and negative health outcomes (Horne *et al*., 2014).

2.12 Predisposition to second stroke

Survivors of stroke and TIA naturally have a high risk of recurrent stroke (Gordon *et al*., 2004; Phillips *et al*., 2015) whether the incident stroke was ischaemic, haemorrhagic or a TIA (Wu, McLaughlin & Lorenzetti, 2007 Rutten-Jacobs *et al*., 2013). Three in ten stroke survivors suffer a recurrent stroke or TIA (Stroke Association, 2015), although Dawes (2012) and Hardie *et al*. (2004) report a 43% likelihood of recurrent event after an initial stroke and van Wijk and colleagues suggest a 10-year risk of 44.1% after a minor stroke or TIA. After initial minor

stroke, cerebrovascular accidents and coronary heart disease are the most frequent causes of death (Clark, Murphy & Rothwell, 2003) but the prescription of anti-platelet and anti-coagulant agents and lipid lowering treatments lower the risk of secondary events (Amarenco *et al*., 2009b; Lennon *et al*., 2013). When recurrent stroke does occur, the likelihood of fatality within 30 days of the event is almost double that of a first stroke (Hankey, 2003), with a reported 41% case mortality after recurrent stroke, compared with 22% after an initial stroke (Hardie *et al*., 2004). Improvements in secondary prevention have the potential to reduce recurrent events by as much as 80% (Hackham & Spence, 2007) but risk factor control for chronic disease in conditions such as stroke remains poor (Ellis & Breland, 2014). As discussed previously, risk factors for incident stroke include medically modifiable and behaviourally modifiable risk factors. The same risk factors can be applied to recurrent stroke in a vulnerable population.

2.13 Medically modifiable risk factors and recurrent stroke

Atrial fibrillation

Observing AF in stroke care is common, with 29% of stroke patients presenting with this symptom and around 10% of stroke patients developing AF during their time as in-patients (Rizos *et al*., 2012), although this number is reported to be lower (6%) in ICH patients (Prats-Sanchez *et al*., 2018). The existence of AF in a stroke patient is an independent early risk factor for recurrent stroke (Moroney *et al*., 1998), with the risk of ischaemic stroke recurrence within 14 days of the initial event as high as 8% (Berge *et al*., 2000). As a result, treating AF in those with a history of stroke is now a strong focus of neurology care (Kernan *et al*., 2014).

Blood pressure after stroke

Sudden increases in BP are common during stroke and occur in 75-80% of patients before a decrease and plateau within 90 minutes of symptom onset (Leoo *et al*., 2008; Whelton *et al*., 2018). The relationship between high BP variables (including PP) and stroke recurrence and poor outcomes is strong (Aslanyan, Weir & Lees, 2004; Sacco *et al*., 2006; Tang *et al*., 2017; Whelton *et al*., 2018) and treating elevated BP may be the most important intervention when preventing second strokes (Kernan *et al*., 2014). Appropriate BP lowering therapies may cause a 30% decrease in the risk of recurrent stroke (Lakhan & Sapko, 2009; Whelton *et al*., 2018) but this requires engagement with patients, families, providers and healthcare systems (Go *et al*., 2014). The prescription of appropriate BP lowering therapies must consider both the timing and aggression of the dose; both of which have received attention in the literature.

Reducing BP immediately after stroke through anti-hypertensive therapy has been linked to reductions in haematoma growth after ICH and may be well tolerated (Anderson *et al*., 2008), leading to better BP control two weeks post-stroke but may be ineffective in preventing death or major disability (Robinson *et al*., 2010; He *et al*., 2014; Wang *et al*., 2014). This may be due to the fact that early interventions may lead to brain hypoperfusion (He *et al*., 2018) and that BP in the low-normal range may be linked to poorer mortality outcomes compared to elevated BP (Kim *et al*., 2014; Lin *et al*., 2015). General consensus is now that anti-hypertensive treatment is only required in the first 24 hours after stroke in extreme situations (e.g. BP > 220/120 mmHg [Kernan *et al*., 2014]). Research including a Cochrane review by Zonneveld and colleagues (2018) reported pooled risk ratios for recurrent stroke of 0.81 after BP lowering medications (95% confidence interval = 0.70 – 0.93) in a sample of 38,742 patients from eight research studies.

The intensity of BP reduction after stroke, however, remains controversial. Both high and low BPs have been associated with poor outcomes after ischaemic stroke (Ntaios *et al*., 2010) and the optimal range of BP after stroke in hypertensive individuals is controversial (He *et al*., 2018). Elevated BP after stroke may cause cerebral vasospasm, leading to decreased cerebral flow and negative outcomes (Ishitsuka *et al*., 2014) and some research reports that the use of a BP target of less than 130mm Hg is likely to be beneficial after stroke (SPS3 Study Group, 2013). After intracerebral haemorrhage, Tsivgoulis and colleagues (2014) and Anderson and colleagues (2013) suggest that intensive lowering of BP may lead to better functional outcomes. However, Qureshi *et al*. (2016) argue that there is no benefit of lowering SBP to less than 140 mmHg in this population and that doing so may be harmful, with twice the likelihood of renal adverse events in the intensely treated group. The overwhelming consensus for stroke is that aggressive reductions in BP after stroke are advised against (NICE, 2008; Ovbiagele *et al*., 2011a; Williamson *et al*., 2016; Whelton *et al*., 2018). There may be no benefit of achieving a brachial SBP < 120 mmHg versus < 140 mmHg (ACCORD Study Group, 2010) in stroke as a whole and doing so may expose patients to elevated risk of harm (Ovbiagele *et al*., 2011a). Optimal neurofunctional recovery has been observed with SBP of 161-177 mmHg and DBP of 103-114 mmHg in a recent sample of 732 hypertensive stroke patients (He *et al*., 2018). The debate as to optimal and appropriate BP lowering immediately after stroke continues.

Hyperlipidaemia

Modifying blood serum lipid biomarkers is important when reducing recurrent stroke risk (Kernan *et al*., 2014) as 56% of those suffering from recurrent stroke have been reported to

present with hyperlipidaemia (Leoo *et al*., 2008). Even in children, a significant relative risk of second stroke is present in those with elevated lipoprotein levels (Strater *et al*., 2002), potentially due to the fact that low HDL-C levels are suggested to contribute to neurological deterioration after ischaemic stroke (Ryu *et al*., 2016). Reducing LDL-C by > 50% is associated with a 35% decrease in the risk of recurrent fatal or non-fatal stroke (Amarenco *et al*., 2007) and this may be achieved through exercise after stroke (Rimmer *et al*., 2009) – something which should be advised to stroke patients presenting with or without hyperlipidaemia.

Glucose metabolism disorders

Diabetes mellitus, reported in 24% of stroke patients recruited by Leoo and colleagues (2008), is related to poor prognosis after stroke (Tanaka *et al*., 2013) – in particular new-onset diabetes mellitus (Mapoure *et al*., 2018). Even hyperglycaemia on admission is a predictor of poor clinical outcomes (Mapoure *et al*., 2018) and glucose metabolism disorders as a whole are linked to an elevated risk of recurrent stroke (Hankey *et al*., 1998; Callahan *et al*., 2011). Aggressive management of blood glucose is vital in reducing death and improving functional outcomes (Mapoure *et al*., 2018). Metabolic syndrome, a condition involving low blood glucose control, may also be linked to the risk of recurrent stroke (Ovbiagele *et al*., 2006), although other published literature has not discovered a link between metabolic syndrome and recurrent stroke (Callahan *et al*., 2011).

Obstructive sleep apnoea

The presence of OSA is frequent after stroke and may lead to drowsiness during the day (Dobkin, 2008), complicating attempts to be physically active and complete physiotherapy sessions. Stroke patients who lie in a supine position will suffer significantly more respiratory disturbances than in any other body position (Turkington *et al*., 2002), with these disturbances leading to increased rates of recurrent AF (Kanagala *et al*., 2003). Patients with OSA tend to have worse outcomes after stroke, spend longer in hospital and have a greater risk of secondary stroke (Kaneko *et al*., 2003; Rola *et al*., 2008). The best predictors of upper airway obstruction after stroke are body mass index and neck circumference (Turkington *et al*., 2002). Prevention of OSA through weight loss is therefore a useful strategy in lowering the risk of recurrent events.

2.14 Behaviourally modifiable risk factors and second stroke

Changing unhealthy behaviours is of huge importance when trying to reduce the consequences of stroke and minimise the risk of future events (McCarthy *et al*., 2013). Non-pharmacological therapy is the preferred therapy for adults with hypertension (Whelton *et al*., 2018), making lifestyle changes even more important.

Medication adherence

Even when incorporating lifestyle modification strategies, pharmacological interventions are important when reducing recurrent stroke risk and the first behaviourally modifiable factor is prescription adherence. Unsurprisingly, high adherence to anti-hypertensive therapy is

associated with a 38% decrease in the risk of cardiovascular events (Mazzaglia *et al*., 2009). Somewhat more surprisingly, low adherence to anti-hypertensive therapy is one of the major contributors to low rates of BP control (Peck, 2018). Up to 25% of patients do not fill in an initial prescription for anti-hypertensive treatment (Whelton *et al*., 2018) and 14% of participants, in work by Bushnell and colleagues (2011), admitted to not adhering to their prescribed medications. Up to 50% of patients with chronic disease as a whole do not take their medications as prescribed (Brown & Bussell, 2011), and the average hypertensive patient only takes their anti-hypertensive therapy 50% of the time, with only one in five patients adhering to their regimen strictly enough to achieve benefits seen in clinical trials (Petrilla *et al*., 2005; Gwadry-Sridhar *et al*., 2013). Research into non-adherence has been sparse (Phillips *et al*., 2015) but reasons may include negative perceptions about the medications, forgetting or being unable to take prescriptions and real or perceived side effects (Tong *et al*., 2010). Adherence has been reported to be greatest with once-daily dosing and decreases as daily dosing frequency increases (Claxton, Cramer & Pierce, 2001; Iskedjian *et al*., 2002; Schroeder *et al*., 2004). Involving third parties in terms of accountability also has positive effects on adherence, with pharmacists and nurses being involved in interventions likely to increase BP control (Carter *et al*., 2009). Telephone-based case management has been demonstrated to improve BP control for one year before control decreased (Bosworth *et al*., 2011) and the use of the internet to increase accountability reduced BPs significantly compared to usual care (Liu *et al*., 2013). These low levels of pharmacological adherence inevitably lead to increased stroke recurrence and place even more importance on lifestyle interventions.

Physical activity and inactivity levels

After stroke, low levels of physical activity are common (Field *et al*., 2013; Saunders *et al*., 2016) with individuals who have suffered from stroke likely to accrue half the daily step counts of their healthy counterparts (English *et al*., 2014). Stroke patients are more likely to report inabilities to meet physical activity recommendations (Butler & Evenson, 2014), suffer cardiovascular deconditioning (Leoo *et al*., 2008; Prout *et al*., 2017) and subsequently have lower fitness levels (Ivey, Hafer-Macko & Macko, 2008), leading to fitting the profile of high sitting time and very low physical activity (English *et al*., 2018).

Increased physical activity soon after stroke can promote better long-term outcomes (Askim *et al*., 2014). For example, stronger walking ability is associated with higher physical activity levels after stroke (Field *et al*., 2013). Early mobilisation is a key element of acute stroke care due to benefiical effects on oxygenation and reductions in complications (NICE, 2008). Mobilisation within 24 hours of stroke may result in earlier walking and functional recovery (Cumming *et al*., 2011) whilst reducing the risk of vascular dementia (Verdelho *et al*., 2012) and, when used alongside exercise, may lower BP (Millen *et al*., 2013) even more than dietary interventions (Nordstrand *et al*., 2013). However, this early mobilisation has been reported to lead to greater disability at three months after stroke in the AVERT Trial (Bernhardt *et* al., 2015). This may mean that too much, too soon is detrimental to long-term health. Frequent short episodes of physical treatment should be the predominant pattern in the first fortnight after stroke (Royal College of Physicians, 2016). Physical activity is low after stroke but increases between three- and six- months post-stroke but not from six months onwards (Persson *et al*., 2016). As such, there is an obvious need to encourage stroke survivors to increase physical activity, but the best way of going about this is not yet clear (Nicholson *et*

al., 2013). One barrier to increasing activity after discharge is that access to community rehabilitation services is poor, with up to 57% of stroke survivors not receiving recommended therapy after hospital discharge (Hall *et al*., 2016).

Physical activity may be the most important modifiable risk factor preventing recurrent events and improving quality of life after stroke (Wolf & Koster, 2013), reducing neural injury and stroke severity after the incident (Middleton *et al*., 2013). However, many stroke survivors are physically able to undertake some physical activity but still choose not to do so (Rand *et al*., 2009). This decision to be physically inactive post- stroke leads individuals into a destructive cycle of physical inactivity leading to medical complications which result in further inactivity (Billinger *et al*., 2014).

A frequently cited rationale for physical inactivity is fatigue. Fatigue is described as a chronic, debilitating, persistent and profound sense of tiredness resulting from physical and mental exertion (Lerdal *et al*., 2009). It is a disproportionate lack of energy triggered by simple activities (Lagogianni, Thomas & Lincoln, 2018) and can be related to both acute (Christensen *et al*., 2008) and chronic (Schepers *et al*., 2006) time frames. Although fatigue only affects 11% of the general population (Mahon *et al*., 2018), it may be experienced by up to 85% of ischaemic stroke patients (Chestnut, 2011) and was listed by 40% of stroke patients as their worst or one of their most debilitating symptoms in work by Ingles, Eskes and Phillips (1999). Stroke-related fatigue influences the life of an individual for years after the event (Hackett *et al*., 2005) and many stroke survivors remain inactive, whether it is due to fatigue, physical inabilities or a lack of confidence in their body. The presence of fatigue is linked to an increased risk of mortality (Glader *et al*., 2002) and is one of the top priorities for research on life after stroke (Pollock *et al*., 2014).

The three main rehabilitation goals for a stroke patient are preventing complications of prolonged inactivity, decreasing recurrent stroke and cardiovascular events, and increasing aerobic fitness (Gordon *et al*., 2004). Physical activity interventions have the potential to target all three of these goals and are therefore key to stroke recovery. The key elements of a physical activity intervention are the number of sessions, the mode of delivery, the type of follow up and monitoring (Billinger *et al*., 2014). These should all be taken into consideration for any individual patient before suggestions are made as to their rehabilitation schedule. As well as improving functional skills, functional capacity, daily activities and quality of life after stroke (Mobily, 2009; Billinger *et al*., 2014), physical activities provide the opportunity for chronic stroke patients to interact with therapists and caregivers (Karthikabu *et al*., 2017) and are psychosocially beneficial.

Sedentary time

After stroke, survivors spend almost 11 hours per day (75% of waking hours) sitting (English *et al*., 2016), with estimates ranging up to 80% of the day being spent sedentary, compared to 50-60% for healthy adults (Rand *et al*., 2009; Matthews *et al*., 2012; Paul *et al*., 2016). Sedentary periods after stroke are often longer compared to age-matched healthy controls (English *et al*., 2016) – a particular concern when bearing in mind that prolonged sitting may be particularly bad for health (Dunstan *et al*., 2012). However, less is known about sedentary behaviour and stroke, particularly extended sitting, although it is believed to slow recovery (Butler & Evenson, 2014). There is limited awareness of the risks of sedentary behaviour amongst stroke survivors (Ezeugwu, Garga & Manns, 2016) but current American Heart Association guidelines for stroke survivors now include reducing sedentary behaviours

(Billinger *et al*., 2014). Focusing on reducing sedentary time after stroke is a promising intervention target (Morton *et al*., 2018) because if sedentary behaviour interventions are not put in place, advances made during inpatient rehabilitation may be lost (Ezeugwu *et al*., 2016). Further research is necessary to determine whether light intensity activities to break up prolonged sitting have benefits for those with stroke (English *et al*., 2016).

Increased sedentary behaviour after stroke may be perceived as normal and even an important way of relaxing after stroke (Ezeugwu *et al*., 2016). However, whilst adequate sleep maintains body function, prevents adverse cardiovascular outcomes and is fundamental to health (Lattanzi, Brigo & Silvestrini, 2018b; Lo *et al*., 2018), too much time in bed and too much sleep is related to poor outcome, recovery and increased stroke risk (Langhorne, de Villiers & Pandian, 2012; Fang, Wheaton & Ayala, 2014). Sleeping too much is associated with increased C-reactive protein – a biomarker of inflammation (Patel *et al*., 2009) and white matter sensitivity (Ramos *et al*., 2014), both markers of elevated stroke risk. Chronic sleep deprivation has been linked with an elevated risk of stroke, heart disease, reduced cognitive function and all-cause mortality (Cappuccio *et al*., 2011; Ferrie *et al*., 2011) and is one of the most common sleep-related conditions in the west with individuals sleeping an average of 90 minutes fewer per night than 100 years ago (Nagai, Hoshide & Kario, 2010b). Sleep quality is also related to cardiovascular health. Low sleep quality and duration are contributors to increased fasting plasma glucose levels (Lee, Ng & Chin, 2017) which, in turn, are related to increased cardiovascular mortality in those with hypertension (Henry *et al*., 2002). Sleep structure disruption also causes episodic hypoxemia and general stress, leading to catecholamine surge and baroceptor sensitivity impairment (Lattanzi, Brigo & Silvestrini, 2018c; Lesske *et al*., 1997).

Exercise and physical fitness

The fitness levels of stroke patients are well below age-matched average non-stroke individuals (Ivey *et al*., 2008) and, due to this, few people exercise after stroke with even fewer commencing long-term exercise programmes (Simpson *et al*., 2017). Lower levels of exercise due to disability can increase other risk factors for recurrent stroke (Dobkin, 2008) but a lack of information describing how to exercise safely has been reported after stroke (Nicholson *et al*., 2014). A lack of exercise after stroke may be due to barriers including environmental factors (e.g. transport, cost) or personal factors (impairments, embarrassment, fear [Nicholson *et al*., 2013]). These impairments result in deconditioning and a more sedentary lifestyle (Gordon *et al*., 2004). Exercise may have similar effectiveness to drug interventions in cardiovascular conditions other than in heart failure (Naci & Ioannidis, 2013); therefore, incorporating exercise programmes into stroke rehabilitation is of the utmost importance. Increasing aerobic fitness naturally aids the body of an individual recovering from stroke to carry out daily living exercises but there is a lack of research addressing how soon after a stroke it is safe to run a graded exercise test to determine fitness (Billinger *et al*., 2014). An analysis by Stoller and colleagues (2012) suggests that aerobic exercise post-stroke is feasible between seven days and six months after event with a low relative risk of adverse effects but < 7 days is more of an unknown quantity. This is an extremely broad range of suggested feasibility. The concept of exercise after stroke is that the health benefits must outweigh the risks involved (Billinger *et al*., 2014) and each case must be treated on an individual basis when deciding an appropriate level of intensity and regularity.

After stroke, exercise is linked with improved glucose tolerance (Ivey *et al*., 2007), improvements in peak VO_2 (Lennon *et al*., 2008), improved mobility, balance and endurance (Duncan *et al*., 2003), muscle strength and gait (Weiss *et al*., 2000), improved attention (Swatridge *et al*., 2017) and community integration (Karthikbabu *et al*., 2017). In healthy subjects, exercise training has also been demonstrated to improve arterial stiffness (Tanaka *et al*., 2000; Currie, Thomas & Goodwin, 2009) – a measure of key importance in stroke prevention. Training is also known to reduce resting heart rate, particularly in the morning. This is something that may be of particular relevance to those with cardiovascular risk as strokes are most likely to occur in the morning (Shiotani *et al*., 2009). When prescribing exercise after stroke, it is important for patients to continue long-term. The beneficial effects of a 12-week training programme appear to diminish six months post-treatment after a stroke trial conducted by Duncan and colleagues (2003).

Underweight, overweight and obesity

Around 2% of adults in England are underweight (Baker, 2018) and this condition is associated with an increased risk of mortality after stroke (Dehlendorff *et al*., 2014). The prevalence of overweight and obesity is far greater. As previously discussed, overweight and obesity are directly linked to stroke (Kurth *et al*., 2005; Strazzullo *et al*., 2010), with these conditions increasing stroke risk by 22% and 50% respectively (Strazzulo *et al*., 2010). After stroke occurs, there is a school of thought that increased adiposity may have a protective effect. Overweight and obese patients are suggested to have a lower mortality rate after stroke (Scherbakov, Dirnagl & Doehner, 2011; Doehner *et al*., 2013), with obese patients presenting a 27% lower mortality rate than stroke patients with a “normal” body mass (Olsen *et al*., 2008); a concept

referred to as the obesity paradox (Gruberg *et al*., 2002; Ovbiagele *et al*., 2011b). Obesity may also be linked with a reduction in the likelihood of readmission for recurrent stroke (Andersen & Olsen, 2015). This pattern has also been observed in overweight patients who demonstrate lower mortality after sudden cardiac arrest in the presence of a shockable rhythm (Jain *et al*., 2010), although the reasons for this are speculative (Matinrazm *et al*., 2017). One plausible explanation is that in the cases of cancer and kidney disease, overweight patients may live longer due to increased body weight and caloric reserves to sustain an individual through treatment (Park *et al*., 2014; Schlesinger *et al*., 2014). Higher body mass index may also allow use of higher doses of cardio-protective medications thus leading to better outcomes (Sharma *et al*., 2014).

This "obesity paradox" may have been observed due to study bias (Hennekens & Andreotti, 2013) but it has led to uncertainty about secondary prevention (Dehlendorff, Andersen & Olsen, 2014), with some authors suggesting the term should be abandoned due to its lack of definition, oversimplification and cause of misunderstanding in the field (Flegal & Ioannidis, 2017). Criticism of the concept of the paradox has been frequent, with the suggestion that if this is to be believed, the wrong message is being given to obese individuals, damaging efforts to reduce obesity rates (Chrysant, 2018), and resulting in inappropriate weight guidelines for diseased patients (Flegal & Ioannidis, 2017). The concept is in direct opposition to reports that weight loss in 12 months following stroke is associated with lower cardiovascular mortality (Caterson *et al*., 2012) and argues against decades of literature suggesting that a "normal" body mass index is optimal for health in all states. Suggestions have even been made that journals should not accept articles relating to the obesity paradox (Peeters, 2018) due to the damage it could do to stroke recovery services, although the ethics behind suppressing literature is clearly questionable.

Alcohol consumption and cigarette smoking

Poor lifestyle habits such as alcohol and smoking are common after stroke. Increased alcohol consumption is frequent, with patients potentially drinking due to the stress relieving effects (Lawrence *et al*., 2010). Modest alcohol intake after stroke or TIA may have a protective effect against further ischaemic stroke (Mostofsky *et al*., 2010), possibly due to the blood thinning properties of alcohol. However, consumption of the substance as a whole increases the risk of stroke recurrence (Lawrence *et al*., 2010). Research into drug use after stroke is sparse, but cannabis use has been associated with recurrent stroke on a case study basis (Mateo *et al*., 2005). Smoking cigarettes after stroke is a substantial risk factor for recurrent stroke and poor overall health outcomes (Kaplan *et al*., 2005; Kammersgaard, 2006; Lawrence *et al*., 2010) and smoking cessation after stroke has been linked to lower all-cause mortality (Towfighi, Markovic & Ovbiagele, 2012). Although serious health events can be a wake-up call and inspire individuals to adopt healthier lifestyles (McCarthy *et al*., 2013), over three quarters of those who smoke before a stroke continue to smoke up to two years after the event (Newsom *et al*., 2011). This may be due to the use of cigarettes as stress relievers after stroke (Lawrence *et al*., 2010). Demographic factors have been identified which predispose an individual to continue smoking after stroke has taken place. These include youth, being male, Caucasian ethnicity, lower economic standing and better physical fitness (Bak *et al*., 2002; Ives *et al*., 2008; Redfern *et al*., 2000; Sienkiewicz-Jarosz *et al*., 2009). Factors which have been suggested to increase smoking cessation after stroke include a longer time spent in hospital (McCarthy *et al*., 2013) and the assistance of family members (Lawrence *et al*., 2010). A written intention to quit smoking may be twice as successful as verbal intentions after myocardial infarction (Hajek, Taylor & Mills, 2002) but it is not clear whether this applies to stroke recovery.

Diet

An unhealthy diet increases the risk of recurrent stroke (Lawrence *et al*., 2010) but almost 50% of stroke sufferers report receiving no dietary advice (Stroke Association, 2005). Although there is no gold standard method for diagnosing under-nutrition (Kernan *et al*., 2014), the condition is associated with poor prognoses after stroke (FOOD Trial Collaboration, 2003), causing increased incidences of cardiovascular events, infectious diseases and all-cause mortality after stroke (Maruyama *et al*., 2017). Malnutrition is more common after stroke in the rehabilitation stage (after discharge) than the acute stage (Foley *et al*., 2009): patients may not consume the diet which optimises their recovery plan. This can result in rises in BP, sustained hyperlipidaemia, hyperglycaemia, poor functional recovery and a consequent elevation in recurrent stroke risk.

Despite the risk of recurrent stroke and the increased mortality rates after recurrent stroke compared to incident, survivors tend to continue unhealthy lifestyle behaviours (Cheng *et al*., 2005). A combination of exercise, diet modification and use of cholesterol-lowering, hypertension-lowering and aspirin medications has the potential to lower the risk of recurrent stroke by as much as 80% (Hackam & Spence, 2007). Much like the range of risk factors of incident stroke, the vast proportion of factors predicting recurrent stroke are directly related to rises in BP and sustained hypertension. Assessments of BP therefore hold the key to measuring and reducing the likelihood of incident and recurrent strokes. These blood pressures can be reduced using medical interventions, lifestyle modifications or a combination of the two to minimise stroke risk in patients with and without a history of cardiovascular events.

2.15 Brachial blood pressure

The brachial cuff sphygmomanometer was introduced over a century ago (McEniery *et al*., 2004) and allows clinicians to identify patients with hypertension (a brachial SBP of > 130 mmHg or a brachial DBP of > 80 mmHg [Whelton *et al*., 2018]). These recent recommendations are lower than previous boundaries (140/90 mmHg [Pickering *et al*., 2005]) and have been introduced to attempt to lower the long-term global burden of elevated BPs. Brachial SBP is determined primarily by arterial compliance and total peripheral resistance (Smulyan & Safer, 1997; Stergiopulos & Westerhof, 1998) and is a more useful predictor of heart disease in those aged over 50 than DBP (Franklin *et al*., 2001). Hypertension is the most common condition seen in primary care (James *et al*., 2014) and a major risk factor for CVD and organ damage (Hansson *et al*., 1998; Rudic & Fulton, 2009) with brachial hypertension indicating a raised risk of CVD from 46.1% to 63.3% in a longitudinal observation of 1.25 million patients (Rapsomaniki *et al*., 2014). Elevated BP is the leading cause of death and disability worldwide (Lim *et al*., 2010) and affects a billion people globally, with nine million deaths occurring annually due to hypertension (Yarmolinsky *et al*., 2015). Lowering BP reduces the likelihood of cardiovascular events (Lewington *et al*., 2002; Blood Pressure Lowering Treatment Trialists' Collaboration, 2003) due to ongoing hypertension exposing the brain to haemodynamic stress (Pase *et al*., 2013), but hypertension control is only estimated to be 14% worldwide (Mills *et al*., 2016).

Increased BP is a major risk factor for stroke (Chatterjee *et al*., 2015), with hypertension positively and continuously related to stroke risk (Chalmers & Chapman, 2001). As life progresses, alterations to large arterial walls lead to increased arterial stiffness. These changes include overproduction of collagen, underproduction of elastin, medial smooth muscle hypertrophy, increased intimal permeability, migration of monocytes and

macrophages, and fibrosis of the adventitia (Zieman *et* al., 2005). Approximately 45% of all strokes may be because of uncontrolled BP (Li *et al*., 2005) as an increase of 20 mmHg in brachial SBP may increase the risk of death due to stroke two-fold (Lewington *et al*., 2002). Decreasing brachial SBP by just 4.7 mmHg may reduce the risk of stroke mortality by 17.5% (Lackland *et al*., 2008), whilst reductions of 10 mmHg could reduce incident stroke risk by 41% (Law, Morris & Wald, 2009). Reductions in SBP of 12-13 mmHg have also been reported to cause reductions of 37% in stroke mortality (He & Whelton, 1999). As such, a combination of improving hypertension control to 50%, reducing sodium intake by 30% and eradicating artificial trans-fats could save around 100 million lives worldwide in the next thirty years (Frieden & Jaffe, 2018).

A wide range of variables cause variations in brachial BP measures. Long-term fasting has a significant influence on brachial BP, with significant drops in BP reported after a 48-hour fast (Andersson *et al*., 1988). Longer term fasting may also lead to decreases in BP due to weight reduction (Neter *et al*., 2003). Cardiovascular responses to altered posture rely on interactions between the autonomic nervous system and cerebral autoregulation (Olufsen *et al*., 2005). Blood pressures increase in a seated compared to supine position (Cavelaars *et al*., 2004) and are higher still in standing positions (Beevers, Lip & O'Brien, 2001). Brachial measures are also altered due to acute and chronic stress. An exaggerated acute response to stress may be an indicator of a heightened risk of hypertension (Steptoe *et al*., 2016), whilst chronic stress is associated with increased BP and cardiovascular problems (Hawkley *et al*., 2006; Birditt *et al*., 2016).

Alongside SBP and DBP measures, brachial PP may be indicative of cardiovascular health. Pulse pressure is calculated as the difference between SBP and DBP and is determined by

arterial compliance and stroke volume (Dart & Kingwell, 2001; Tang *et al*., 2017). These pressures are particularly relevant as a diagnostic marker in older populations (Balietti *et al*., 2018) and males (Tadic *et al*., 2018). This measure is associated with increased afterload and myocardial oxygen demands (Takahashi *et al*., 2018) and an increased PP reflects large arterial stiffness (Lima, 2018), causing pressure overload on the heart, leading to cardiac dysfunction (Boutouyrie *et al*., 1995). Elevated PP reflect increases in arterial stiffness due to atherosclerosis and arteriosclerosis (Verdecchia *et al*., 1998) and, as a result, may be related to the risk of poor cardiovascular outcomes independent of other risk factors (Palmieri *et al*., 2006; Selvaraj *et al*., 2016). It is important to differentiate between arteriosclerosis and atherosclerosis. The former represents the degenerative stiffness of arterial beds (Cavalcante *et al*., 2011), whereas the latter is due to hardening fatty deposits on the inner walls of the arteries, making the vessels vulnerable to blockage (Royal College of Physicians, 2016). The assessment of PP may even be superior to traditional SBP and DBP at predicting ventricular wall stress (Takahashi *et al*., 2018) and cardiovascular death (Lee, Rosner & Weiss, 1999). A PP cut-off point of 60 mmHg is suggested to be a marker of elevated arterial stiffness and asymptomatic organ damage in older hypertensive individuals (Mancia *et al*., 2013) and the measure has been significantly related to brain atrophy and cognitive decline (Nation *et al*., 2016).

It has long been accepted that BP exhibits a circadian rhythm in humans (Millarcraig, Bishop & Raftery, 1978) with pressures rising during the day and falling during the night (Rudic & Fulton, 2009). The increase in BP immediately after waking is known as a BP surge and both myocardial infarction and stroke are more likely to occur in the morning due to this daily spike in pressures (Marler *et al*., 1989; Kario *et al*. 2003; Manfredini. *et al*., 2005; Figure 2.3).

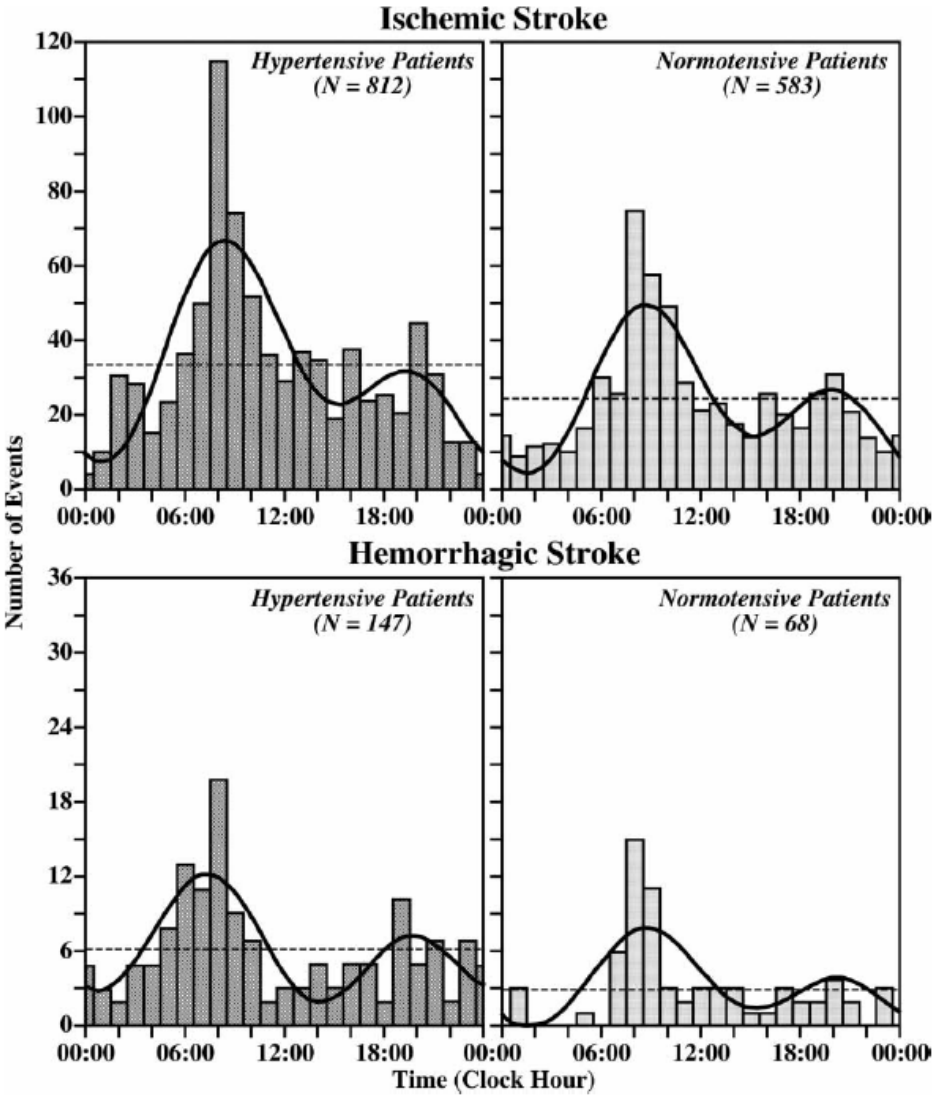


Figure 2.3: Occurrence of stroke throughout the day, *from Casetta et al., 2002a; 2002b in Manfredini et al., 2005*

Morning surges in BP and nocturnal dips occur after activation of the sympathetic nervous system due to varying levels of catecholamine, vasoactive intestinal peptide and melatonin (Ignarro *et al*., 1987; Albers *et al*., 1991; Scheer *et al*., 2004; Rudic & Fulton, 2009; Juhanoja *et al*., 2016). Blood pressure dips nocturnally by 10-20% in a healthy individual (Rodrigues *et al*., 2018) but those with abnormal circadian BP patterns can be classified as non-dippers

(O'Brien, Sheridan & O'Malley, 1988), extreme dippers (Kario *et al*., 1996) and reverse dippers (Kario *et al*., 2001). Non-dippers present with a < 10% nocturnal reduction in SBP and extreme dippers with a > 20% nocturnal reduction in SBP (Rodrigues *et al*., 2018). Whilst regular dippers have significantly better blood pressure than non-dippers (Lo *et al*., 2018), extreme dipping status results in the highest left ventricular mass and the greatest likelihood of early morning blood pressure surges. This nocturnal hypotension may reduce myocardial perfusion pressure, causing hypoxemia and myocardial inflammation and leading to myocardial hypertrophy (Rogrigues *et al*., 2018). Non-dipping individuals may have the worst prognosis of all abnormal classifications (Verdecchia *et al*., 1994; Ben-Dov *et al*., 2007). Non-dipping status presents with increased sympathetic nervous system activity and decreased para-sympathetic nervous system activity (Nakano *et al*., 2001) and may be associated with low quality of sleep and sleep disruption (Lo *et al*., 2018). This demonstrates a potential causative link between OSA (resulting in disrupted and low-quality sleep) and elevated nocturnal blood pressure. Even aside from dipping status, lower sleep efficiency (asleep for < 85% of time spent in bed) has been linked to hypertension (Javaheri *et al*., 2008). Nocturnal blood pressure and blood pressure variability may be even more closely associated with target-organ damage risk than awake blood pressure and blood pressure variability (Boggia *et al.*, 2007; Palatini *et al*., 2014). It is perhaps for this reason – the control of nocturnal BP rather than diurnal BP – that ramipril, an angiotensin-converting enzyme inhibitor, has been reported to significantly reduce rates of death, myocardial infarction and stroke (Yusuf *et al*., 2000). Rather than controlling blood pressure during the day, ramipril has been suggested to reduce clinical events through lowering nocturnal blood pressure rather than daytime blood pressure (Svensson *et al*., 2001). Consequently, it may be equally as important to control and monitor

nocturnal blood pressure as it is to manage daytime blood pressure, although the latter is the usual focus of research.

Although assessment of brachial (peripheral) blood pressures have been the clinical standard for assessing CV risk and have a dose-response relationship with mortality (Burns *et al*., 2018), they are a compromised measure due to technical limitations (Cheng *et al*., 2013) and do not directly measure blood pressure at the heart.

2.16 Central blood pressure

Although brachial blood pressures are directly related to vascular mortality (Lewington *et al*., 2002), blood pressure is augmented in the periphery compared to the aorta (Nichols & O'Rourke, 2005). This augmentation is due to distal arteries becoming progressively stiffer due to increased predominance of collagen fibres rather than elastin in the periphery compared to the aorta (Cavalcante *et al*., 2011).

In contrast, cBP represent the pressure exerted on the heart and brain and are not the same as blood pressure in limbs such as the arms (Yadav *et al*., 2018). Due to differing composition of the arterial wall, such as peripheral measures tend to overestimate blood pressure at the heart itself (Agabiti-Rosei *et al*., 2007), with blood pressure up to 40 mmHg higher in the brachial artery than the aorta (McEniery *et al*., 2014). The dissociation between peripheral and central measures is higher in those with greater baseline blood pressures (Williams, 2012) and central pressures may be more influenced by accelerated aging and hypertension than traditional brachial measures (Avolio *et al*., 1983; McEniery *et al*., 2005). The systemic large arteries more than double in stiffness with age (Butlin & Avolio, 2014) and these central pressures have been reported to be more relevant to the work load of the ventricles and

coronary arteries (Croymans *et al*., 2014; Burns *et al*., 2018), cardiovascular risk and mortality (Roman *et al*., 2007; Ott *et al*., 2017) and organ damage (Booysen *et al*., 2013; Zeigler *et al*., 2018),

The relevance of recording cBP is highlighted by McEniery and colleagues (2014) who note that 30% of peripherally normotensive men and 10% of normotensive women may have central pressures in common with those in stage I peripheral hypertension. These figures are based on more traditional hypertension guidelines (> 140/90 mmHg) so these percentages may be even greater using new recommendations. If this is the case, individuals presenting with normotensive brachial blood pressure may be more at risk of cardiovascular events than their peripheral blood pressures may suggest. An example of this can be seen in Figure 2.4. This is of particular relevance when considering that increased cBP is associated with an elevated risk of cardiovascular events (Agabiti-Rosei *et al*., 2007).

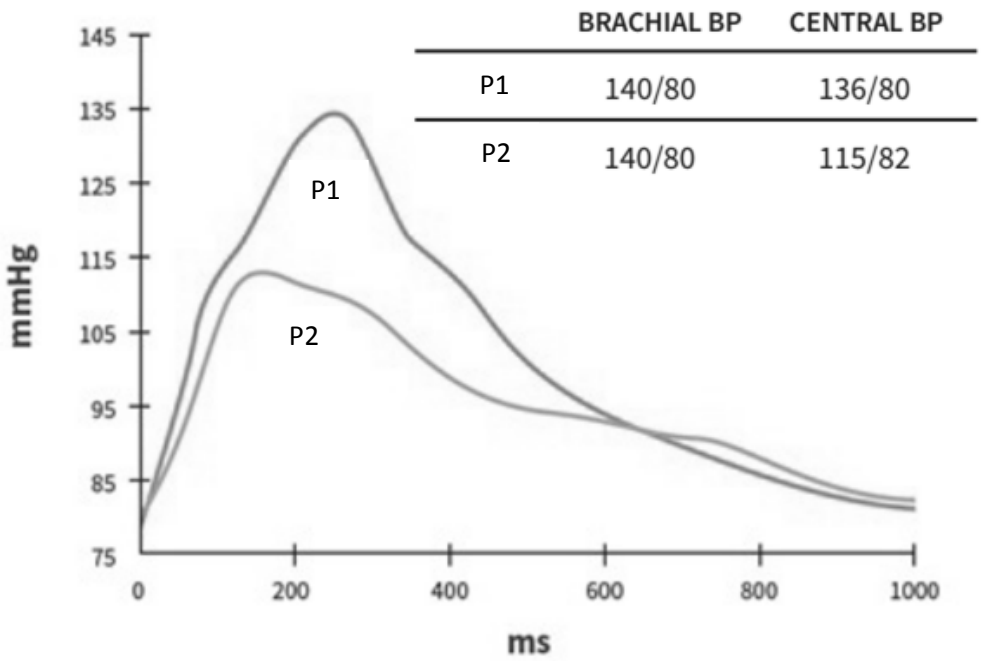


Figure 2.4: An example of two central blood pressure waveforms from individuals with identical brachial blood pressure, from *AtCor, 2017*

Different blood pressure lowering drugs may have substantially different effects on cBP, despite similar influences on brachial blood pressure (Williams *et al*., 2006), with reductions in brachial blood pressure not always mirrored in cBP (McGauhey *et al*., 2015). As such, peripheral blood pressure assessments are not necessarily an appropriate surrogate for measuring the effects of anti-hypertensive medication on central haemodynamics (Williams *et al*., 2006). Only measuring blood pressure at the brachial artery neglects valuable information (Williams *et al*., 2006) and, consequently, cBP assessment is expected to become standard clinical practice in the future (Shoji *et al*., 2016).

Traditionally, cBP measurement has been an invasive procedure involving catheterisation of the aorta. This process is usually contraindicated in healthy populations (Dawson *et al*., 2009) but central measures can now be measured using non-invasive methods (Agabiti-Rosei *et al*., 2007), such as pulse wave analysis (PWA). cBP is determined by the stiffness of conduit arteries and the timing and magnitude of wave reflections (Williams *et al*., 2006). When the wall of an aorta is stiff, increased systolic and pulse pressures occur after faster backward travelling pressure waves. This causes increased wall tensions and alterations to the elastic components in the artery (Vlachopoulos *et al*., 2000). These factors play a key role in the pathogenesis and progression of hypertension.

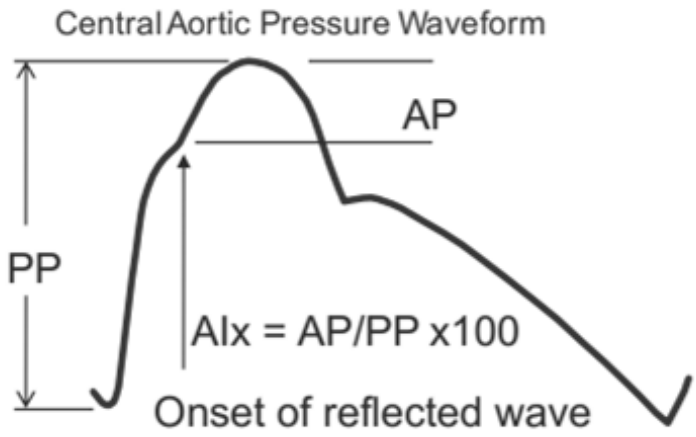
Whilst elevated peripheral blood pressure is now recognised as > 130/90 mmHg (Whelton *et al*., 2018), no such cut-off point has been determined for cBP assessments (McEniery *et al*., 2014). Cheng and colleagues (2013) have proposed an optimal cBP reading of 110/80 mmHg with significantly higher cardiovascular risk in those with central pressures of 130/89 mmHg. Small changes in cBP can have large effects on cardiovascular risk, with a cSBP of 125 mmHg associated with a 10-30 mmHg increase in risk when compared to 121 mmHg (Williams *et al*.,

2006). This demonstrates the importance of the recognition of normative values and cut-off points for central hypertension. These must be determined before the non-invasive methods of cBP can be integrated into clinical settings.

Other than cSBP and cDBP, non-invasive measurement of other central variables may offer further insight into cardiovascular health than previously possible before technological advances. A central pulse pressure (cPP) of > 50 mmHg in those without CVD may indicate an increased likelihood of poor cardiovascular outcomes (Roman *et al*., 2009). Central pulse pressures tend to increase more than peripheral PP due to aging (McEniery *et al*., 2005), and may be superior to peripheral SBP in predicting cardiovascular events (Shoji *et al*., 2016). Central pulse pressures have also been associated with poor cognition, including low memory scores (Hanon *et al*., 2005; Scuteri *et al*., 2005; Mitchell *et al*., 2011) - measures particularly relevant to the acute and chronic stroke population.

The aorta naturally stiffens with age, a process which takes place at a greater speed when arterial hypertension exists (Cavalante *et al*., 2011). Gradual damage occurs through changes in the cross-linking of extra-cellular matrix components, medial elastocalcinosis and the degeneration of elastin fibres (Dao *et al*., 2005; Payne *et al*., 2009). Increased arterial stiffness reduces the ability of an artery to contract and relax (Sherlock *et al*., 2014) and PWA can also provide measures of AIx. This is an indirect measure of arterial stiffness relating to how much of the central pressure is accounted for by the reflected pulse wave (Zeigler *et al*., 2018). The assessment of AIx is calculated as a ratio of amplitude of the pressure wave above its systolic shoulder to the total PP expressed as a percentage (P_2-P_1/PP*100 [Sherlock *et al*., 2014]), as visualised in Figure 2.5. Assessment of arterial stiffness is of importance due to its link with insulin resistance (Lee *et al*., 2007), diabetes (Wadwa *et al*., 2010), blood pressure (Kaess *et*

al., 2012; Diaz *et al*., 2017), cognitive impairment (Muela *et al*., 2017) and cardiovascular risk (Weber *et al*., 2004; McEniery *et al*., 2010; Ben Shlomo *et al*., 2014; Doumas *et al*., 2018). As a tool to represent arterial stiffness, a ten percent increase in AIx has been linked to a 1.5-fold increased risk of cardiovascular events or death (London *et al*., 2001). The stiffening of arteries and subsequent increase in AIx may lead to increased pulse wave velocity, leading to enlarged PP and age-related hypertension (Dao *et al*., 2005).



Abbrevs: AP – Augmentation pressure, AIx – Augmentation index, PP – Pulse pressure

Figure 2.5: AIx calculation using a central pressure pulse wave, from *AtCor, 2017*

2.17 Pulse wave velocity

The assessment of pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness due to its simplicity, accuracy, reproducibility and predictive value (Laurent *et al*., 2006; Diaz *et al*., 2017). Measures of PWV depend on vessel size and the elastic properties of the aortic wall (Muela *et al*., 2017). Pulse waves travel faster in sclerotic vessels (Vlachopoulos *et al*., 2015). As a result, PWV has an important role in identifying increased left ventricular load (Cavalcante *et al*., 2011), vascular target organ injury (Persu & De Plaen, 2004), risk of

later hypertension development (Naijar *et al*., 2008), cognitive impairment (Muela *et al*., 2017), endothelial dysfunction (Wallace *et al*., 2007), atherosclerosis (Persu & De Plaen, 2004), coronary heart disease, stroke and overall mortality (Mattace-Raso *et al*., 2006). The use of PWV is therefore crucial to the identification of high-risk populations for CVD risk factor management (Ben-Shlomo *et al*., 2014; Brinkmann, Jordan & Tank, 2015). A cut-off value of 10 $m \cdot s^{-1}$ has been suggested as the cut-off for the diagnosis of altered arterial stiffness (Mancia *et al*., 2013) but a single "normal" limit of PWV may not be useful due to PWV changing with age and the rate of change varying in the older population (Diaz *et al*., 2017).

2.18 SphygmoCor XCEL

One novel device allowing for the non-invasive estimate of cBP is the SphygmoCor XCEL (AtCor Medical, Sydney, Australia). SphygmoCor products are widely used in clinical studies and the XCEL uses a novel algorithm to assess aortic measurements using a brachial cuff. After being cleared by the USA Food and Drug Administration as substantially equivalent to previously validated systems (FDA, 2012) the SphygmoCor XCEL entered the market and is a fast, accurate and a trouble-free way to measure PWA and PWV (Yadav *et al*., 2018).

After an initial brachial blood pressure measure, the XCEL completes a second sub-systolic recording. As a pulse wave travels forward in circulation, a combination of changes in vessel calibre, plaque and areas of arterial stiffness in the wall generate wave reflection (Townsend *et al*., 2015; Burns *et al*., 2018). As the outward waves and reflected waves sum together, an aortic pressure wave is created. The XCEL then reports the inflection point between the forward and reflected waveforms, producing validated measures of cBP without the need for a traditionally invasive procedure. The forward and reflected wave interaction is influenced

by the speed of the waves. The faster the waves travel, the less separation between the two as they interact. Data outputs for PWA can be seen in Figure 2.6.

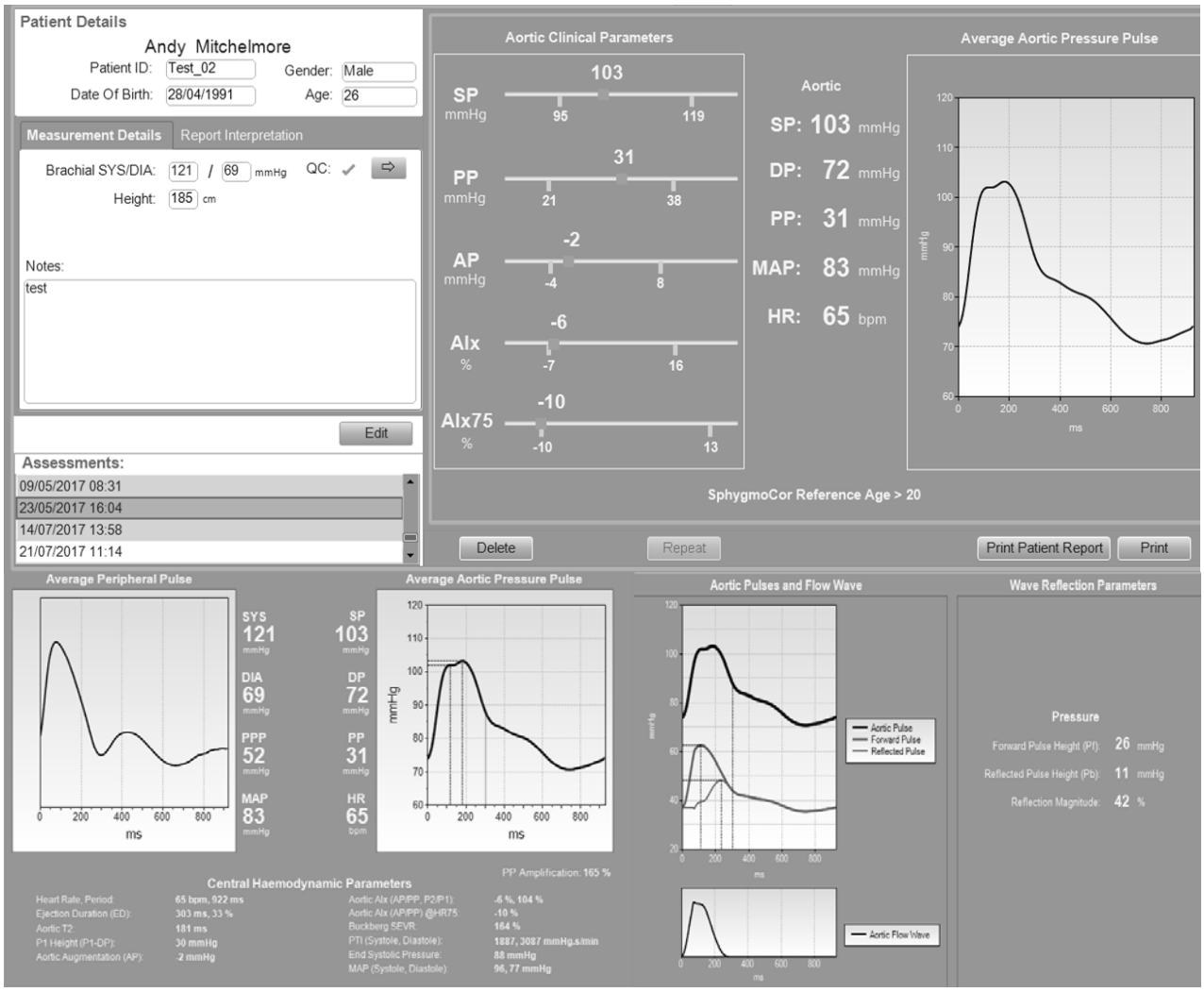
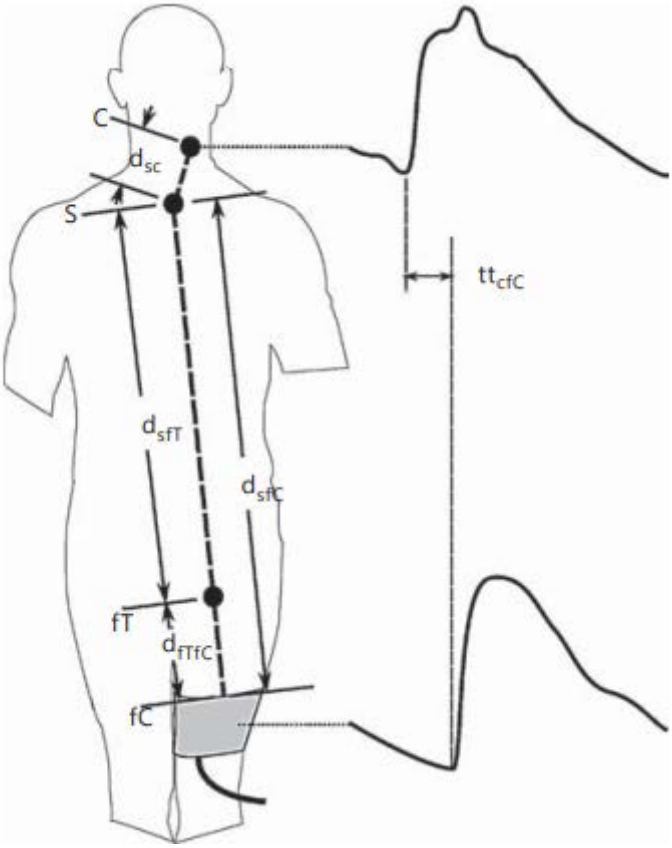


Figure 2.6: Full pulse wave analysis output from the SphygmoCor XCEL

The SphygmoCor XCEL is also able to assess PWV. This involves a cuff being placed around the femoral artery, a tonometer pressure sensor being placed to collect a carotid waveform and pulse transit time denotes the pulse time required to travel from the carotid to femoral artery between the initial upstroke of the recorded waveforms at each site (Cavalcante *et al*., 2011;

Rezk-Hanna *et al*., 2018; Yadav *et al*., 2018). Figure 2.7 demonstrates the key measures when measuring PWV using the XCEL.



Abbrevs: c – Carotid; C – Cuff; d – Distances; f – Femoral; fC – Femoral cuff; s – Suprasternal notch; tt – Transit time

Figure 2.7: SphygmoCor XCEL PWV setup, from *Butlin & Qasem, 2016*

The XCEL provides comparable estimations of central pressures with radial applanation (Peng *et al*., 2016), and has been shown to be a valid method of assessing central haemodynamics in healthy populations (Butlin *et al*., 2012; Hwang *et al*., 2014). Previous work has reported that the SphygmoCor XCEL exceeds the criterion for acceptable reliability in a young, healthy population in a range of fasting and postural states (Young *et al*., 2015). As such, the

SphygmoCor XCEL device is a useful device in both research and clinical arenas (Hwang *et al*., 2014) and can reliably assess central haemodynamic variables (Young *et al*., 2015). While calculating PWV, the SphygmoCor has also been shown to be valid when compared against the widely validated SphygmoCor MM3 in a clinically healthy population (Hwang *et al*., 2014).

Most reliability studies thus far have been conducted in non-clinical populations, although Peng *et al*. recruited a hypertensive population to their research. The reliability of the SphygmoCor XCEL and other tools non-invasively estimating central pressures outside of the healthy groups previously mentioned must be determined before they can be fully adopted into clinical environments.

The majority of research into blood pressure and stroke has focused on peripheral blood pressure. Elevated peripheral blood pressure accounts for 62% of stroke (He, Pombo-Rodrigues & MacGregor, 2014) so it is unsurprising that there has been a large scope for research in the area. However, central pressures are of great importance with regards to stroke as it is the large central arteries which supply blood to the brain, not the brachial arteries (Pase *et al*., 2013). As peripheral pressures may not completely reflect the heath of central organs (Protogerou *et al*., 2007), central measures may offer a more accurate reflection of the condition of the heart (Croymans *et al*., 2014). The use of central measures in stroke may be of particular importance as anti-hypertensive drugs, frequently prescribed after stroke, may cause differing effects on peripheral pressures than central pressures (McEniery *et al*., 2014). It may therefore be the case that central pressures respond differently to external factors (e.g. posture and fasting state) than peripheral measures. Further understanding of these variables and the consequences of reliable non-invasive measurements in clinical groups may lead to dramatic improvements in both the acute and

chronic care of stroke patients and prevention of recurrent events days, months and years after incident stroke.

2.19 Synthesis of review

The vast majority of the risk factors for stroke discussed in this literature review are related to one overriding theme: elevated BP and hypertension. Although age and ethnicity are non-modifiable risk factors (Duprez, 2008; Whelton *et al*., 2018), the medically modifiable and lifestyle modifiable risk factors for disease are all prevalent alongside hypertension, including AF (Schoonderwoerd *et al*., 2008), hyperlipidaemia (Ames, 1991), impaired glucose metabolism (Mahfoud *et al*., 2011), OSA (Marin *et al*., 2012), excess alcohol intake (Taylor *et al*., 2009), Illicit drug use (Ferdinand, 2000), cigarette smoking (Virdis *et al*., 2010) and air pollution (Liang *et al*., 2014). This recurrent theme is also due to physical inactivity (Aljadhey, 2012), sedentary behaviours (Beunza *et al*., 2007) and overweight and obesity (Forouzanfar *et al*., 2016). As such, it is unsurprisingly that hypertension is regarded as the strongest risk factor for all stroke (O'Donnell *et al*. 2010).

For this reason, it is of the utmost importance to monitor BP reliably and accurately. Traditionally, the assessment of BP has been recorded using the brachial artery, but pressures are augmented in the periphery due to an increased predominance of collagen fibres rather than elastin in the periphery (Cavalcante *et al*., 2011). Brachial pressures therefore may not truly reflect the health of the central organs and, specifically the aorta. This is particularly pertinent in stroke patients as it is the aorta that supplies the brain with oxygenated blood, not the brachial artery. It is only recently that measures of central BP have become possible without invasive aortic catheterisation taking place. One technique to do this is through oscillometric PWA using the SphygmoCor XCEL, as previously described.

Focusing on sedentary time after stroke is now an extremely important target for interventions (Morton *et al*., 2018). Stroke survivors complete half the daily steps of non-stroke survivors (English *et al*., 2014), with bouts of sedentary time taking place in longer bouts after stroke than in a healthy population (English *et al*., 2016). As a result, acute and chronic interventions to alleviate the potential damage caused by sedentary time to both peripheral and central BP must be addressed. The mechanisms behind sedentary time and poor health are not completely understood, but they may be linked to increases in BP, which have also been linked to poor executive function. It is therefore of importance to examine blood pressure over a course of sedentary time and whether activities improving blood pressure through this time-course translate into improved executive function which could be applied to a rehabilitation setting.

The non-invasive assessment of central blood pressures may hold the key to future cardiovascular risk management. It is vital to determine whether or not the measurement of these variables can be done reliably in populations where they are of particular importance (i.e. the older population and clinical groups). Addressing sedentary time after stroke is also a strong focus in contemporary research. Most interventions relating to sedentary time are of an intensity that may not be viable for a stroke population who struggle with sit-stand transitions, so the acute and chronic benefits of physical activities such as intermittent heel raises to interrupt sedentary time are of importance. This thesis will therefore aim to demonstrate the between-day reliability of the SphygmoCor XCEL in an older, healthy population and an acute stroke population, before examining the efficacy of a heel-raise protocol to interrupt sedentary time both acutely, and over a ten-week programme.

Chapter 3: Study one – Reliability of oscillometric central blood pressure and arterial stiffness measures in individuals over 50 years of age: The effect of posture and fasting state

3.1 Abstract

Background: The between-day reliability of oscillometric pulse wave analysis has been demonstrated in a young, healthy population but not in an older sample. This study examined the between-day reliability of the SphygmoCor XCEL in individuals over 50 years. As blood pressure is measured in a range of postures and fasting states (supine/seated, fasted/non-fasted), this study also investigated the effect of these variables on central blood pressure and arterial stiffness. **Methods:** Fifty-one adults (m=21; age 57y ± 6.4y) were tested on three mornings in supine and seated conditions and in fasted and non-fasted states. Data was analysed as a whole and for normotensive (n=25) and hypertensive participants (n=26). **Results:** SphygmoCor XCEL demonstrated strong reliability in the whole sample for cSBP and cDBP, AIx and AIx75 (ICC=0.77–0.95). Significant interaction effects were observed in cDBP, cPP, AIx and AIx75 ($p < 0.05$; $\eta_p^2 = 0.10 – 0.23$). Fasting state had a greater influence on central pressures in a seated than supine posture, but a greater effect on arterial stiffness measures in a supine posture. **Conclusions:** The SphygmoCor XCEL is a reliable tool to assess central haemodynamic variables in an older population. It would be pertinent for clinicians and researchers to record central measures in a supine posture to minimise the effects of food consumption. Conversely, the assessment of arterial stiffness should occur in a seated condition to minimise the influence of varying fasting states.

3.2 Introduction

Hypertension is the most common condition seen in primary care worldwide (James *et al*., 2014) and the major cause of death across the globe (He *et al*., 2007). Due to non-modifiable, behaviourally modifiable and medically modifiable risk factors, over 29% of adults in the United Kingdom and United States present as hypertensive (British Hypertension Society, 2014; Merai *et al*., 2016) based on traditional cut-offs of 140/90 mmHg. Recently implemented guidelines suggest reducing the cut-off of stage 1 hypertension to 130/80 mmHg (Whelton *et al*., 2018), therefore increasing the prevalence of hypertension even further.

Although brachial BP measurement is traditionally used to monitor vascular health, cBP may be more closely related to the pathophysiology of end-organ damage (Protogerou *et al*., 2007). Systolic blood pressure may be increased in the periphery by as much as 40 mmHg due to increased arterial stiffness away from the aorta (McEniery *et al*., 2014) due to elevated levels of collagen fibres compared to elastin in the periphery compared to the central arteries (Cavalcante *et al*., 2011). Therefore, cBP more directly represents the pressure exerted on the heart and brain and is not the same as blood pressure in the limbs (Yadav *et al*., 2018). Around 30% of peripherally normotensive males and 10% of peripherally normotensive females may share central pressures in common with those with stage I peripheral hypertension (McEniery *et al*., 2014). Central haemodynamic parameters may therefore be a superior measure for clinicians than traditional peripheral BP readings (Young *et al*., 2015). Before these readings are incorporated into clinical practice, the between-day reliability of these measures in normal operating conditions must be assessed.

Traditionally, cBP assessment has been an invasive procedure involving catheterisation of the aorta; a procedure which is usually contraindicated in healthy populations (Dawson *et al*., 2009). However, technological advances mean these measures can now be estimated non-invasively using oscillometric-based pulse wave analysis.

The SphygmoCor XCEL non-invasively estimates measures of central haemodynamics through the interaction of forward and reflected pulse waves during a sub-systolic brachial cuff compression. Additional variables are recorded by the SphygmoCor XCEL, including MAP (1/3 [SBP-DBP] + DBP), AP (contribution of reflected waveform), AIx (AP/PP * 100) and AIx75 (AIx corrected to a HR of 75b-min^{-1}). This device is re-calibrated at one-year intervals to ensure the accuracy of readings (for further information, see page 91). The SphygmoCor XCEL also provides measures of PWV. This measure involves a more skill-dependent technique, with user experience required to a greater degree than during PWA assessments. The successful identification of a clean carotid pulse-wave using a tonometer can be confounded by confounding variables including excess subcutaneous fat stores, or partial/complete occlusion of the carotid artery.

Before any instruments or tools can be used in clinical settings, their reliability must be determined to ensure pharmacological decisions are not based on unreliable data. This reliability can be demonstrated as intra-class correlation coefficient (ICC); a score that reflects the degree of correlation and agreement between measurements (Koo & Li, 2016). Although devices non-invasively estimating cBP through oscillometric readings have been shown to be valid (Lowe *et al*., 2009; Butlin *et al*., 2012; Lin *et al*., 2012; Hwang *et al*., 2014), more research is required to demonstrate the reliability and optimal operating conditions for the function of these devices. Research by Young and colleagues (2015) demonstrated central

haemodynamic parameters and arterial stiffness readings to be reliable using the SphygmoCor XCEL in a young, healthy population (ICCs of 0.73–0.89), particularly in a supine and fasted state. However, the between-day reliability of these measures has not been demonstrated in a more aging demographic where peripheral and central pressures are more pertinent. Hypertension is more commonly found in later life and, as BP measures frequently inform medication prescription, devices recording these measures must be reliable enough to provide the basis for appropriate clinical decisions.

It is also of great importance to consider the effect of posture and fasting state in older individuals as BP is routinely measured in a range of postures and prandial states (i.e. within primary and secondary care), depending on personal preference and available facilities. Both posture (Cavelaars *et al*., 2004; Eser *et al*., 2007) and fasting state (Andersson *et al*., 1988) have been reported to influence brachial blood pressures but the information about the influence that posture and fasting state have on central measures is limited. Young and colleagues (2015) suggested no significant difference in cBP after food consumption but, conversely, Ahuja, Robertson & Ball (2009) reported a significant post-prandial drop in cBP in a participant sample aged between 21 and 80 years; a wide-ranging age demographic.

This study aimed to quantify measurement error of the SphygmoCor XCEL in adults over the age of 50 years. It was also hypothesised that posture and fasting state would cause significant differences in non-invasive measures of central and peripheral blood pressure and arterial stiffness.

3.3 Methods

3.3.1 Participants

Fifty-one participants (m=21; f=30; age 57y ± 6.4y) were recruited to the study. Participants were recruited through the provision of free health check-ups at the University of Winchester, with the collected data provided to individuals along with appropriate lifestyle advice. Participant demographics can be observed in Table 3.1. Ethical approval was received from the University of Winchester Ethics Committee (BLS/16/19). The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Participants provided written informed consent and maintained the right to withdraw at any time. Participants were recruited if they were over the age of 50 and excluded if they were mentally unable to give consent. The information sheet and consent form for this study can be seen in Appendix 1b and Appendix 1c.

Table 3.1: Participant demographic data

		Whole sample		Normotensive		Hypertensive	
		n	%	*n*	%	*n*	%
Participants		51		25		26	
Age (y)		57.1y ±6.4y		57.3y ±7.1y		56.9y ±5.8y	
Sex	Male	21	*42*	9	*36*	12	*46*
	Female	30	*58*	16	*64*	14	*54*
Descent	European	51	*100*	25	*100*	26	*100*
Family history of CVD	Myocardial infarction	14	*28*	8	*32*	6	*23*
	Heart surgery	5	*10*	3	*12*	2	*8*
	Stent	3	*6*	2	*8*	1	*4*
	Catheter	1	*2*	1	*4*	0	*0*
	Heart defect	8	*16*	1	*4*	7	*27*
	Stroke	19	*37*	9	*36*	10	*38*
Personal history of CVD	Hypertension	14	*27*	2	*8*	12	*46*
	High cholesterol	14	*27*	5	*20*	9	*35*
	Diabetes	1	*2*	0	*0*	1	*4*
	Heart problems	4	*8*	4	*16*	0	*0*
	Artery diseases	1	*2*	0	*0*	1	*4*
	Thyroid disease	3	*6*	1	*4*	2	*8*
	Lung disease	1	*2*	0	*0*	1	*4*
	Asthma	11	*22*	4	*16*	7	*27*
	Cancer	4	*8*	1	*4*	3	*12*
	Kidney disease	0	*0*	0	*0*	0	*0*
	Hepatitis	3	*6*	1	*4*	2	*8*
Signs and symptoms of CVD	Chest pain	8	*16*	4	*16*	4	*15*
	Dyspnoea	10	*20*	6	*24*	4	*15*
	Heart palpitations	8	*16*	5	*20*	3	*12*
	Skipped heartbeats	4	*8*	4	*16*	0	*0*
	Heart murmur	5	*10*	5	*20*	0	*0*
	Intermittent leg pain	9	*18*	3	*12*	6	*23*
	Syncope	12	*24*	7	*28*	5	*19*
	Fatigue	12	*24*	4	*16*	8	*31*
	Snoring	29	*57*	13	*52*	16	*62*
	Back pain	22	*43*	13	*52*	9	*34*
Lifestyle factors	Current smoker	4	*8*	2	*8*	2	*8*
	Previous smoker	18	*35*	7	*28*	11	*42*
	Current alcohol drinkers	40	*78*	19	*76*	21	*81*
	Current weight loss plan	4	*8*	1	*4*	3	*12*
Everyday activity	Sedentary	22	*43*	11	*44*	11	*42*
	Lightly active	15	*29*	9	*36*	6	*23*
	Moderately active	14	*27*	5	*20*	9	*34*
	Vigorously active	0	*0*	0	*0*	0	*0*
Medication	Statins	3	*6*	2	*8*	1	*4*
	Anti-thrombotic	0	*0*	0	*0*	0	*0*
	Diuretics	0	*0*	0	*0*	0	*0*
	Calcium blockers	2	*4*	0	*0*	2	*8*
	Alpha blockers	2	*4*	1	*4*	1	*4*
	Beta blockers	2	*4*	1	*4*	1	*4*
	Anticoagulants	0	*0*	0	*0*	0	*0*
	Other anti-hypertensive medication	7	*14*	2	*8*	5	*19*

Abbrev: CVD – Cardiovascular Disease

3.3.2 Experimental Design

Participants were tested on three mornings (all three visits within three weeks and between the hours of 07:00 and 10:00) and had consumed only water for the 12 hours before and refrained from intense physical activity for 24 hours preceding testing. Participants were allocated to either the supine first or seated first condition using a computerised random number generator. They then adopted the allocated posture for twenty minutes before a minimum of two pulse wave analysis measurements were taken using the SphygmoCor XCEL (AtCor Medical, Sydney, Australia) with a three-minute interval. If a difference of > 5 mmHg and a difference of > 4% AIx was noted under manufacturer guidelines, a third measure was taken and data from the two closest points were averaged, as per manufacturer guidelines. After twenty minutes in the other posture, these measures were repeated. A breakfast of two slices of white toast with butter, marmalade and orange juice was then provided (330 kcal, 60g carbohydrate, 7g total fat, 5g protein) – a provision that was repeated during each visit. This meal was chosen as it closely replicated the macronutrients provided in a normal hospital meal in the morning (282-291kcal, 56-60g carbohydrate, 3-4g total fat, 8-9g protein [chapter four - see page 124]) – a setting where the SphygmoCor XCEL may be most commonly used in the future. The protocol was then repeated in both supine and seated non-fasted conditions in the same order as the fasted state, leading to final measures being approximately 45 minutes post-food consumption.

3.3.3 Sample Size

A minimum sample of 25 participants per group was identified using G*Power (Faul *et* al., 2007) with *p* set at 0.05, a power of 0.80 and a moderate effect size (0.50) whilst accounting for a 10% drop-out.

3.3.4 Statistics

Statistical Package for Social Sciences v.22 (SPSS, Inc., Chicago, Illinois, USA) was used to analyse data. Statistical significance was set at $p < 0.05$. Analysis of variance for repeated measures with two within-participant factors (posture and fasting state) was used to assess differences in peripheral and central haemodynamic parameters (SBP, DBP, PP, cSBP, cDBP, cPP, heart rate (HR), AIx and AIx75. Effect sizes were reported using partial eta squared (η_p^2) with 0.01, 0.06 and 0.14 representing small, medium and large effects (Cohen *et al*., 1969). Intra-class correlation coefficient (ICC), standard error of measurement (SEM) and the Smallest Detectable Change (SDC) were used to assess the between-day reliability of the XCEL (for calculations, see Young *et al*., 2015). Identical analysis was performed with the sample split into two groups: normotensive (peripheral blood pressure < 130/80 mmHg) and hypertensive (peripheral blood pressure ≥ 130/80 mmHg [Whelton *et al*., 2018).

3.4 Results

3.4.1 Central and peripheral blood pressures

Whole Sample

Tables 3.2 and 3.3 summarise the mean values for central and peripheral haemodynamic measures for the whole sample. Significant interaction effects were reported for cDBP and cPP ($p < 0.05$; $\eta_p^2 = 0.10 - 0.23$), with greater differences observed between fasted and non-fasted whilst seated than when supine. Fasting state was found to have a significant main effect on cSBP and HR. For all cBP variables, ICC values were above the 0.75 criterion in each condition, demonstrating excellent between-day reliability (Table 3.4).

Table 3.2: Mean (SD) central and peripheral blood pressures and arterial stiffness values for the whole sample - supine and seated, fasted and non-fasted

		Supine		**Seated**		**Interaction**		**Posture**		**Fasted**	
		Fast	Non	Fast	Non	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
MAP (mmHg)	X	97	96	99	98	0.85	0.00	**<.01**	0.19	**<.01**	0.23
	SD	*13*	*13*	*13*	*14*						
SBP (mm Hg)	X	133	133	133	135	0.19	0.03	0.08	0.06	0.20	0.03
	SD	*18*	*18*	*18*	*18*						
DBP (mm Hg)	X	81	79	84	81	**0.02**	0.10	**<.01**	0.30	**<.01**	0.45
	SD	*11*	*11*	*12*	*12*						
cSBP (mm Hg)	*X*	123	121	124	122	0.20	0.03	0.14	0.04	**<.01**	0.19
	SD	*17*	*16*	*16*	*17*						
cDBP (mm Hg)	X	82	80	85	82	**0.03**	0.10	**<.01**	0.29	**<.01**	0.37
	SD	*11*	*11*	*12*	*12*						
cPP (mm Hg)	X	41	41	39	40	**<.01**	0.23	**<.01**	0.16	0.40	0.01
	SD	*9*	*10*	*9*	*10*						
AP (mm Hg)	X	14	11	12	10	**<.01**	0.23	**<.01**	0.19	**<.01**	0.53
	SD	*6*	*5*	*6*	*6*						
AIx (%)	X	33	25	29	24	**0.02**	0.10	**<.01**	0.20	**<.01**	0.66
	SD	*10*	*9*	*12*	*10*						
AIx@75 (%)	X	26	20	24	28	**<.01**	0.18	**<.01**	0.29	0.67	0.04
	SD	*11*	*10*	*11*	*12*						
HR ($b \cdot min^{-1}$)	X	62	65	64	67	0.25	0.03	**<.01**	0.33	**<.01**	0.57
	SD	*8*	*8*	*8*	*9*						

Abbrevs: AIx – Augmentation index, AIx75 – Augmentation index @ 75 $b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, Fast – Fasted, Non – Non-fasted, HR – Heart rate, MAP – Mean arterial pressure, SBP – Systolic blood pressure

Table 3.3: Mean (SD) central and peripheral blood pressures and arterial stiffness values for normotensive and hypertensive groups - supine and seated, fasted and non-fasted

		Supine		**Seated**		**Interaction**		**Posture**		**Fasted**	
		Fast	Non	Fast	Non	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
Normotensive											
MAP (mmHg)	X	88	87	90	88	0.50	0.02	0.13	0.10	0.03	0.19
	SD	*7*	*8*	*7*	*8*						
SBP (mm Hg)	X	119	120	119	120	0.62	0.01	0.76	0.00	0.47	0.02
	SD	*7*	*8*	*6*	*7*						
DBP (mm Hg	X	74	73	77	74	0.06	0.14	**0.01**	0.23	**<.01**	0.36
	SD	*6*	*7*	*7*	*8*						
cSBP (mmHg)	*X*	111	109	111	109	0.65	0.01	0.94	0.00	**0.04**	0.17
	SD	*8*	*8*	*7*	*7*						
cDBP (mmHg)	X	75	74	78	75	**0.03**	0.18	**0.02**	0.20	**<.01**	0.28
	SD	*6*	*7*	*7*	*8*						
cPP (mmHg)	X	37	35	34	36	**0.02**	0.22	**<.01**	0.33	0.81	0.00
	SD	*9*	*6*	*7*	*7*						
AP (mmHg)	X	13	9	11	9	**0.03**	0.18	**0.01**	0.23	**<.01**	0.54
	SD	*7*	*4*	*7*	*5*						
AIx (%)	X	32	24	29	23	0.29	0.05	**0.03**	0.19	**<.01**	0.70
	SD	*12*	*10*	*14*	*11*						
AIx@75 (%)	X	26	19	23	26	**<.01**	0.74	**<.01**	0.53	**<.01**	0.99
	SD	*12*	*11*	*12*	*12*						
HR ($b \cdot min^{-1}$)	X	*62*	*65*	*64*	*68*	0.33	0.04	**0.01**	0.25	**<.01**	0.66
	SD	*10*	*9*	*8*	*10*						
Hypertensive											
MAP (mmHg)	X	106	104	108	107	0.74	0.01	**<.01**	0.29	**<.01**	0.28
	SD	*11*	*11*	*12*	*12*						
SBP (mm Hg)	X	146	146	147	148	0.22	0.06	0.06	0.13	0.28	0.05
	SD	*16*	*15*	*15*	*15*						
DBP (mm Hg	X	87	85	91	88	0.17	0.07	**<.01**	0.38	**<.01**	0.54
	SD	*10*	*11*	*11*	*12*						
cSBP (mmHg)	*X*	134	132	136	135	0.22	0.06	0.09	0.12	**0.02**	0.20
	SD	*15*	*14*	*14*	*14*						
cDBP (mmHg)	X	88	86	92	89	0.31	0.04	**<.01**	0.38	**<.01**	0.48
	SD	*10*	*12*	*11*	*12*						
cPP (mmHg)	X	46	46	44	46	**<.01**	0.25	0.17	0.08	0.36	0.03
	SD	*8*	*10*	*9*	*9*						
AP (mmHg)	X	16	12	13	12	**<.01**	0.28	**0.03**	0.17	**<.01**	0.52
	SD	*5*	*5*	*5*	*6*						
AIx (%)	X	33	27	30	25	**0.02**	0.20	**0.02**	0.21	**<.01**	0.64
	SD	*9*	*9*	*9*	*10*						
AIx@75 (%)	X	27	22	25	30	0.05	0.29	0.07	0.20	**0.01**	0.19
	SD	*9*	*9*	*10*	*11*						
HR ($b \cdot min^{-1}$)	X	*62*	*64*	*64*	*66*	0.55	0.02	**<.01**	0.43	**<.01**	0.49
	SD	*7*	*8*	*8*	*8*						

Abbrevs: AIx – Augmentation index, AIx75 – Augmentation index @ 75 $b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, Fast – Fasted, Non – Non-fasted, HR – Heart rate, MAP – Mean arterial pressure, SBP – Systolic blood pressure

Table 3.4: Reliability of the SphygmoCor XCEL in each sample group

	Supine-F			Supine-NF			Seated-F			Seated-NF		
	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC
Whole Population												
MAP (mmHg)	0.90	4.0	11.0	0.93	3.4	9.3	0.91	4.1	11.2	0.94	3.3	9.1
SBP (mm Hg)	0.90	5.8	16.1	0.90	5.7	15.8	0.92	5.0	13.9	0.91	5.4	15.1
DBP (mm Hg	0.90	3.4	9.4	0.92	3.0	8.4	0.90	3.6	10.0	0.94	3.1	8.6
cSBP (mmHg)	0.89	5.4	15.0	0.92	4.5	12.5	0.90	5.2	14.3	0.92	4.7	13.1
cDBP (mmHg)	0.89	3.5	9.6	0.89	3.7	10.3	0.90	3.6	10.1	0.94	3.1	8.7
cPP (mmHg)	0.83	3.7	10.3	0.86	3.6	10.1	0.84	3.7	10.2	0.85	3.7	10.2
AP (mmHg)	0.75	3.0	8.3	0.84	1.9	5.3	0.82	2.6	7.3	0.86	2.2	6.0
AIx (%)	0.77	4.9	13.4	0.85	3.5	9.8	0.83	4.7	13.1	0.80	4.5	12.5
AIx75 (%)	0.75	5.3	14.6	0.87	3.7	10.3	0.82	4.7	13.0	0.84	4.6	12.8
HR ($b \cdot min^{-1}$)	0.86	3.1	8.6	0.84	3.3	9.2	0.86	3.0	8.4	0.80	4.0	11.0
Normotensive												
MAP (mmHg)	0.71	3.5	9.8	0.85	2.9	8.1	0.68	4.0	11.0	0.86	2.9	8.0
SBP (mm Hg)	0.59	4.7	13.0	0.76	3.9	10.7	0.51	4.4	12.3	0.74	3.8	10.5
DBP (mm Hg	0.75	2.9	8.0	0.83	2.8	7.8	0.73	3.7	10.3	0.88	2.8	7.8
cSBP (mmHg)	0.68	4.7	13.1	0.77	3.7	10.2	0.58	4.4	12.1	0.75	3.4	9.5
cDBP (mmHg)	0.74	3.0	8.4	0.87	2.6	7.2	0.73	3.8	10.4	0.87	2.9	8.1
cPP (mmHg)	0.78	4.3	12.0	0.79	2.6	7.3	0.76	3.5	9.7	0.77	3.2	8.9
AP (mmHg)	0.80	2.9	8.1	0.81	1.9	5.3	0.84	2.8	7.7	0.86	2.0	5.5
AIx (%)	0.80	5.2	14.5	0.84	4.0	11.0	0.86	5.2	14.4	0.77	5.1	14.1
AIx75 (%)	0.76	5.9	16.3	0.86	4.1	11.5	0.83	5.1	14.0	0.83	5.0	13.9
HR ($b \cdot min^{-1}$)	0.88	3.3	9.3	0.80	3.8	10.6	0.85	3.1	8.7	0.84	3.9	10.7
Hypertensive												
MAP (mmHg)	0.88	3.9	10.9	0.89	3.6	10.0	0.91	3.6	9.9	0.92	3.4	9.5
SBP (mm Hg)	0.87	5.7	15.8	0.86	5.6	15.4	0.87	5.4	14.9	0.82	6.3	17.4
DBP (mm Hg	0.88	3.6	9.9	0.91	3.1	8.6	0.92	3.2	8.8	0.93	3.3	9.1
cSBP (mmHg)	0.86	5.3	14.8	0.88	4.9	13.5	0.88	4.8	13.4	0.85	5.4	14.9
cDBP (mmHg)	0.87	3.6	9.9	0.84	4.6	12.9	0.92	3.1	8.7	0.93	3.2	8.8
cPP (mmHg)	0.79	3.7	10.2	0.79	4.5	12.4	0.80	3.8	10.7	0.84	3.8	10.4
AP (mmHg)	0.67	3.0	8.2	0.85	1.9	5.2	0.78	2.5	6.9	0.84	2.3	6.4
AIx (%)	0.73	4.5	12.4	0.87	3.1	8.6	0.79	4.3	11.8	0.83	4.0	11.0
AIx75 (%)	0.74	4.7	12.9	0.88	3.3	9.1	0.79	4.3	12.0	0.85	4.2	11.7
HR ($b \cdot min^{-1}$)	0.85	2.9	7.9	0.89	2.8	7.8	0.87	2.9	8.1	0.75	4.1	11.3

Abbrevs: AIx – Augmentation Index, AIx75 – Augmentation index @ 75 $b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, ICC – Intra-class correlation coefficient, F – Fasted, HR – Heart rate, MAP – Mean arterial pressure, NF – Non-fasted, SBP – Systolic blood pressure, SDC – Smallest detectable change, SEM – Standard error of measurement

Normotensive group

Significant interaction effects were observed for cDBP ($p < 0.05$, $\eta_p^2 = 0.18$) and cPP ($p < 0.05$; $\eta_p^2 = 0.22$). For cDBP, greater differences were seen between prandial states (fasted vs. non-fasted) whilst seated than supine. For cPP, a post-prandial increase was observed when supine, but a decrease was shown in the seated condition. Fasted state, but not posture, had a significantly large effect on cSBP whereas both fasting state and posture had a significant main effect on HR. For cBP variables, ICC values generally exceeded the criterion value of 0.75 for the four conditions (Table 3.4), except for SBP in the supine-fasted condition between visits 1-2, SBP in the seated-fasted condition in visits 1-2 and 2-3 and PP in seated-fasted condition in visits 1-2 and 2-3 (Supp. Table; Appendix 1d).

Hypertensive group

Significant interaction effects were observed for cPP ($p < 0.01$; $\eta_p^2 = 0.25$; Table 3.2) with greater differences seen between prandial states whilst seated than supine. Posture was shown to have a significant main effect on DBP, cDBP and HR, whereas fasted state had a significant effect on DBP, PP, cSBP, cDBP and HR (all $p < 0.05$). The between-day reliability of the XCEL was demonstrated by ICC values > 0.75 for all central haemodynamic variables in all conditions between visits 1-2 and 2-3 (Supp. Table, Appendix 1d).

3.4.2 Arterial stiffness

Whole sample

Mean values for arterial stiffness variables in the whole participant sample are shown in Table 3.2. Significant interaction effects were observed for AIx and AIx75 ($p < 0.05$; $\eta_p^2 = 0.10\text{-}0.18$) with greater differences observed between prandial states whilst supine than seated. The between-day ICC of 0.75 was exceeded in all conditions for AIx and AIx75 (Table 3.4).

Normotensive group

The normotensive group presented significant interaction effects for AIx75 ($p < .01$; $\eta_p^2 = 0.74$) with larger differences reported between prandial states whilst supine compared to seated. Posture caused a significant main effect on AIx ($p < .05$; $\eta_p^2 = 0.19$) as did fasting state (AIx $p < .05$; $\eta_p^2 = 0.70$ [Table 3.3]). ICC values exceeded 0.75 for all arterial stiffness variables in all conditions (Table 3.4).

Hypertensive group

Significant interaction effects were observed for AIx ($p < 0.05$; $\eta_p^2 = 0.20$) and AIx75 ($p < 0.05$; $\eta_p^2 = 0.29$). In the hypertensive group, and following food consumption, greater changes in AIx were demonstrated when supine compared to seated. For AIx75, food consumption elicited a 5.2% decrease in the supine condition whereas a 5.2% increase was observed in the seated condition. ICC values of ≥ 0.75 were observed in both variables in all conditions other

than supine-fasted (ICC = 0.73 and 0.74 [Table 3.4]), but after breaking data down, ICC values exceeded 0.75 in visits 1 – 2 and 2 – 3 (AIx = 0.76 - 0.92; AIx75 = 0.77 – 0.92; [Supp. Table, Appendix 1d]).

3.5 Discussion

This study demonstrated that the SphygmoCor XCEL is a reliable tool for measuring central haemodynamic variables in a non-clinical participant sample > 50 years old in a range of normotensive and hypertensive individuals. Importantly, fasting state was shown to have a greater influence on central measures in a seated than a supine posture. Smaller differences between postures after food consumption were observed in arterial stiffness variables.

3.5.1 Central and peripheral blood pressures

The results of this study demonstrate that the SphygmoCor XCEL can reliably record central markers of blood pressure. The ICC values we observed for cSBP for the whole group (0.89 – 0.92) and after splitting of data (normotensive = 0.58 – 0.77; hypertensive = 0.85 – 0.88) are similar to previous research in a younger sample (ICC = 0.89; [Young *et al*., 2015]) and suggest that the SphygmoCor XCEL is a reliable tool for assessing cBP in non-clinical participant sample over the age of 50. However, despite excellent reliability between visits one and two and visits two and three (Supp. Table, Appendix 1d) for the whole study sample and the hypertensive group, moderate correlations were only reported for the normotensive sample. This may be due to the presence of white coat syndrome and should be considered in terms of recommendations for blood pressure assessment protocols. This point may be particularly

relevant in GP practices where blood pressure measures tend to only be completed once per visit, potentially giving a false indication of a patient's blood pressure at that time.

Significant interaction effects were observed for cDBP and cPP in the whole group, with similar findings generally reported for both the normotensive and hypertensive groups. The present study has shown smaller differences in blood pressures (cDBP, cPP) between fasted and non-fasted conditions when a participant is supine (mean difference of 1.4 mmHg and 0.8 mmHg, respectively) than seated (mean difference of 2.7 mmHg and 1.5 mmHg, respectively). This may be due to increased speed of early-stage digestion taking place in a seated position because of gravity; leading to subsequent greater vasodilation and a drop in BP not seen in a supine position. This finding may be important in clinical environments such as GP practices where blood pressure is measured in a variety of fasting states but frequently in a seated rather than supine posture. These findings were mirrored in the normotensive and the hypertensive group.

Greater variability in the cDBP and cPP response to food was seen in a seated posture than a supine posture, and thus the seated posture traditionally adopted in a clinical setting may be sub-optimal, particularly as cPP is potentially a more direct indicator of vascular aging than other blood pressure variables (Xiao *et al*., 2015). In accordance with Young and colleagues (2015), the SphygmoCor XCEL has optimal reliability in a supine posture with an older population, due to the smaller changes caused by prandial state.

The posture of a patient is important to consider when measuring blood pressure (Cavelaars *et al*., 2004) and the role posture plays in aortic haemodynamics is less well known (Vrachatis *et al*., 2014). Our results would suggest the greater differences observed for changes in some central variables in fasting state in a seated posture may also be insufficiently recognised in

the literature. We observed a significant increase in cDBP in the seated compared to supine posture in the whole sample as well as the normotensive and hypertensive sub-groups. This agrees with previous studies investigating DBP (Cicolini *et al*., 2011; Shoji *et al*., 2017), although research incorporating only 1 - 5-minute postural conditions before assessments has shown a greater peripheral blood pressure in a supine than seated posture [Netea *et al*., 2003; Cavelaars *et al*., 2004); highlighting the differing acute and chronic responses to postural change.

A forty-eight hour fast has been demonstrated to significantly lower peripheral blood pressures (Eser *et al*., 2007), but the acute effects of food on vascular haemodynamics have received less attention. Our observations of a significant drop in cBP and non-significant responses of peripheral SBP in a post-prandial state are in support of previous work (Andersson *et al*., 1988). These significant decreases in cSBP and cDBP in the post-prandial state were reported in the sample as a whole and in both sub-groups.

3.5.2 Arterial stiffness

The strong between-day reliability when measuring AIx and AIx75 (ICC > 0.75) in our older participant sample supports previous research undertaken with a young, healthy sample (ICC = 0.71 – 0.82; [Young *et al*., 2015]). Smaller differences were observed between visits 1 - 2 and 2 - 3 for AIx and AIx75 than cBP measures (Supp. Table Appendix 1d), meaning that the physiological mechanisms resulting in potential white coat syndrome in peripheral and central pressures may not extend to AIx and AIx75 measures.

The significant interaction effects observed for AIx and AIx75 for the whole sample suggested greater post-prandial variability in a supine posture (mean differences of 7.2% and 2.9%

respectively) than seated (mean differences of 5.3% and 1.8% respectively). These results are converse to the findings in this study with regards to cBP measures and suggest that, when assessing arterial stiffness, a seated posture is optimal to reduce the variability caused by food consumption. These interaction effects were not observed in previous research using a younger sample (Young *et al*., 2015) and suggest that arterial stiffness becomes more variable as a person grows older.

Significant differences were observed in AIx and AIx75 in the whole sample due to postural alterations. These differences were not seen in previous work (Young *et al*., 2015), although after the calculation of AIx75, augmentation index was reported to be lower in a supine posture than seated in young females (Jaccoud *et al*., 2012). Fasting state was reported to cause a significant drop in AIx. This may be due to alterations of the tone of small vessel beds, large artery function and large artery geometry (Young *et al*., 2015). Vasodilation after food consumption may lead to a lessening of wave reflection intensity, leading to this decrease in arterial stiffness.

3.5.3 Clinical Inference

The present study suggests that the SphygmoCor XCEL is a reliable measure when assessing cBP and arterial stiffness variables. Clinicians and researchers may find it useful to measure cBP in a supine posture due to the reduced effect of food intake, but that arterial stiffness variables are recorded in a seated position.

3.5.4 Limitations and Strengths

Limitations and strengths should be noted to allow better contextualisation of the results. One limitation was that we recruited a mixed sex sample of healthy adults over the age of 50. Previous work has suggested that the effect which posture has on peripheral BP may be sex specific (Gerber *et al*., 2015) and future work should recruit unisex cohorts to similar protocols to determine whether this is the case for cBP measures. It is worth noting that AIx75 may be physiologically and statistically inappropriate as a standalone measure, due to the assumption being made that the relationship between HR and AIx is linear (Stoner *et al*., 2013). Consequently, our statistical analysis reports both AIx and AIx75. The structure of the present study did, however, involve post-prandial measures up to 45 minutes after food intake which is in accordance with Ahuja and colleagues' (2009) recommendations for assessing changes to haemodynamic variables after food intake. Furthermore, the overnight fast undertaken by participants and randomised order of conditions result in a robust protocol and data collection was consistently undertaken at the same time of day, reducing the likelihood of circadian blood pressure cycles influencing results. It should be noted that two of the thirty female participants were pre-menopausal at the time of assessment due to the age demographic of our population. An international study of ~19,000 women reported the median age of natural menopause to be 50 (median range of 49 – 52y (Morabia & Constanza, 1998). Although this is a condition which causes increased prevalence of hypertension (Johnson *et al*., 2015), further analysis demonstrated that study outcomes were not influenced by menopausal state.

3.6 Conclusion

Blood pressure assessments occur in a range of postures and fasting states depending on an almost endless number of variables both at home and in the clinical environment. This study highlights the significant effect that fasting state can have on central haemodynamic variables and measures of arterial stiffness. This study also notes that the influence food consumption has on central haemodynamics is minimised with the use of a supine posture – a position which has also previously been shown to cause the greatest between-day reliability of the SphygmoCor XCEL. Although previous work has highlighted the possibility of white coat syndrome and the necessity for second blood pressure measures to be recorded, this study suggests that more than one visit may be necessary, particularly for a normotensive population. The SphygmoCor XCEL is a reliable tool in assessing cBP and measures of arterial stiffness in a non-clinical sample over the age of 50 and trials should now begin to determine the reliability of this equipment in clinical populations.

Chapter 4: Study two – Oscillometric central blood pressure and arterial stiffness measurement in acute stroke patients: reliability and the effects of posture and fasting state

4.1 Abstract

Background: Reliable measures of blood pressure are key in the treatment of acute stroke. This study investigated the between-day reliability of non-invasive estimates of central and peripheral blood pressure and markers of arterial stiffness (AIx and AIx75) and the effect of posture and fasting state on these variables in acute stroke patients. **Methods:** Twenty-two acute stroke patients (72y ± 10y) had blood pressure measured using the SphygmoCor XCEL in supine and seated postures and whilst fasted and non-fasted. **Results:** Excellent between-day reliability (ICC > 0.75) was reported for all peripheral and central variables in all conditions (ICC = 0.77 – 0.90) and for AIx and AIx75 in both fasted postures (ICC = 0.78 – 0.81). All peripheral and central blood pressures were significantly lowered by food consumption (p < 0.05; η_p^2 = 0.20 – 0.55). Participants had significantly higher AIx in the seated posture than supine (p < 0.05; η_p^2 = 0.22). Fasting state had significant main effects on AIx and AIx75 (p < 0.05; η_p^2 = 0.14 – 0.22). **Conclusions:** Oscillometric measures of central blood pressure can be recorded with excellent between-day reliability in different postures and fasting states in acute stroke patients. Fasting state has a large effect on central and peripheral blood pressures and on measures of arterial stiffness. It is important for clinicians to be aware of optimal assessment conditions and the importance of consistency in these conditions without impact on patient wellbeing.

Clinical trial registry name: NCT02537652, https://clinicaltrials.gov/ct2/show/NCT02537652

4.2 Introduction

Hypertension is positively and continuously related to first-time stroke [Chalmers & Chapman, 2001; Chatterjee Roberts & Boden-Albala, 2014) due to added haemodynamic stresses on the brain (Pase *et al*., 2013). Controlling hypertension is a cornerstone of recurrent stroke risk reduction (Biffi *et al*., 2015) and can be approached from pharmacological and lifestyle perspectives. Increased stresses on the brain (such as those caused by hypertension) cause poor neurological recovery after stroke (Ishitsuka *et al*., 2014) and lead to elevated risk of stroke recurrence (Sacco *et al*., 2006). However, how intensive treatment should be in lowering blood pressure after stroke is frequently debated. The consensus now warns against intense lowering of blood pressure after stroke (Ovbiagele *et al*., 2011a; Williamson *et al*., 2016; Whelton *et al*., 2018). Treating hypertension efficiently may be the most important tool in preventing recurrent strokes (Kernan *et al*., 2014) and maximising quality of life post-stroke.

Blood pressure is normally assessed by occluding the brachial artery (peripheral blood pressure), but cBP measures (either measured directly or derived from brachial pulse waves) may be more closely related to cardiovascular risk (Shimizu *et al*., 2015). The invasive measurement of cBP is usually contraindicated (Dawson *et al*., 2009), but novel techniques are now able to non-invasively estimate central pressures using oscillometric pulse wave analysis (PWA). There is good agreement with PWA and tonometer-based methods of measuring cBP in patients with atrial fibrillation (Sabahi *et al*., 2013), a frequent indicator of elevated stroke risk. Although oscillometric devices have been demonstrated to be valid (Lowe *et al*., 2009; Butlin *et al*., 2012; Lin *et al*., 2012; Hwang *et al*., 2014), research is required to report the reliability of these devices when assessing central haemodynamic variables before they can be used diagnostically and prognostically in clinical research and treatment

settings where they may have a large impact in terms of monitoring treatment plans after clinical events such as stroke. Further details relating to the use of the SphygmoCor XCEL can be found in the literature review of this thesis (page 91) and in chapter three (pages 99).

Identifying the optimal operating conditions of devices able to non-invasively calculate central haemodynamic variables in terms of both posture and fasting state is an important step in their introduction to research and clinical use. Posture [Cavelaars *et al*., 2004; Eser *et al*., 2007) and fasting state (Andersson *et al*., 1988) have been found to alter peripheral blood pressure measures in non-clinical populations (aged 18-62y). Whilst the acute effects of postural change and fasting state on cBP and arterial stiffness (AIx) have been investigated in both young and older non-clinical populations (Ahuja *et al*., 2009; Young *et al*., 2015; Mitchelmore *et al*., 2018 [chapter three of this thesis]), the between-day reliability of these variables has not been investigated in a stroke population where they are of particular prognostic importance. Testing these variables in different conditions is important as blood pressures are measured in a variety of postures and fasting states within clinical settings according to several environmental and situational factors.

This study examined the effect of posture and fasting state on the between-day reliability of peripheral and central pressures and arterial stiffness in an acute stroke population using a non-invasive, oscillometric device (SphygmoCor XCEL). This will also involve investigating the effects that posture and fasted state have on these variables. This study hypothesised that posture and fasting state would have a significant effect on peripheral and cBP and markers of arterial stiffness. It was also hypothesised that oscillometric PWA would report high between-day reliability in an acute stroke population. These findings will be of importance to

those considering the use of the non-invasive oscillometric devices to estimate cBPs in research and clinical settings.

As with chapter three, we hypothesised that the SphygmoCor XCEL would reliably measure peripheral and central BP and measures of arterial stiffness. We also hypothesised that posture and fasting state would have a significant effect on measures of peripheral and central BP and measures of arterial stiffness. Our null hypothesis, therefore, was that the SphygmoCor XCEL would not reliably report peripheral and central BP and measures of arterial stiffness, and that posture and fasting state would have no significant effect on these variables.

4.3 Methods

The methods of this study are reported in accordance with the Helsinki Declaration of 1975 and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm *et al*., 2007).

4.3.1 Participants

Twenty-two stroke patients (M=16; age: 72.3 ± 10.4 y; National Institutes of Health Stroke Scale [NIHSS]: 8.1 ± 5.1; time after stroke: 13.2 ± 12.2 days) were initially contacted by a research nurse before formal consent was provided after a full description of the study and provision of information sheets. All patients gave written consent whilst they were in-patients in a hyper-acute stroke ward in a hospital in Hampshire, United Kingdom. The information sheet and consent form for this study can be seen as appendices 2b and 2c. Patients were

excluded if they were end-of-life stroke patients, had an unstable cardiac condition, were oxygen-dependent, had significant dementia, were unable to swallow normally, lacked capacity to consent, were diagnosed more than eight weeks prior to assessment, had either type I or II diabetes mellitus or were hypoglycaemic at hospital admission. All participants completed a health history questionnaire (ACSM, 2013; [Table 4.1]). Ethical approval was granted by the Health Research Authority (REC reference: 15/SC/0559) South Central – Hampshire A Research Ethics Committee. The study was registered as a clinical trial:

NCT02537652; https://clinicaltrials.gov/ct2/show/NCT02537652.

Table 4.1: Participant demographic data

		n	%
Participants		22	
Age (y)		72.3 ±10.4	
Sex	Male	16	73
	Female	6	27
Descent	European	22	100
Stroke subtype	Small vessel lacunar	2	9
	Partial anterior circulation stroke	8	36
	Total anterior circulation stroke	3	14
	Posterior circulation stroke	1	5
	Intracerebral haemorrhage	6	27
	Undetermined	2	9
Family history of CVD	Myocardial infarction	9	41
	Heart surgery	1	5
	Stent	0	0
	Catheter	1	5
	Heart defect	1	5
	Stroke	7	32
Personal history of CVD	Hypertension	10	45
	High cholesterol	6	27
	Diabetes	0	0
	Coronary artery disease/heart failure	5	23
	Atrial Fibrillation	8	36
Comorbidities	Thyroid disease	2	9
	Lung disease	0	0
	Asthma	0	0
	Cancer	2	9
	Kidney disease	1	5
	Hepatitis	2	9
Lifestyle factors	Current smoker	2	9
	Previous smoker	6	27
	Current alcohol drinkers	17	77
	Current weight loss plan	1	5
Everyday activity	Sedentary	3	14
	Lightly active	3	14
	Moderately active	15	68
	Vigorously active	1	5
Medication	Statins	2	9
	Anti-thrombotic	14	64
	Diuretics	1	5
	Calcium blockers	5	23
	Alpha blockers	1	5
	Beta blockers	5	23
	Anticoagulants	1	5
	Other anti-hypertensive medication	5	23
	ACE-I	4	18
	ARB	2	9

Abbrevs: ACE-I – Angiotensin-converting-enzyme inhibitor, ARB – Angiotensin II receptor blockers, CVD – Cardiovascular disease

4.3.2 Experimental design

Participants followed the same experimental design as those in Chapter three, with the only difference being the setting of a hyper-acute stroke ward in a hospital in Hampshire, United Kingdom. Participants were tested on three consecutive mornings, having consumed only water in the 12 hours prior to data collection. After random allocation to a supine-first or seated-first condition using a computerised random number generator, participants assumed this posture in a fasted state for twenty minutes. A minimum of two PWA measurements were completed using the SphygmoCor XCEL (AtCor Medical, Sydney, Australia) with a three-minute interval. As described in chapter three, if SBP differed by > 5 mmHg and AIx differed by > 4% between the first and second measures, a third assessment was conducted. Measures of PWA consisted of a peripheral blood pressure measure followed by a 10-second sub-systolic recording. The merging points of the forward and reflected waves were identified on the aortic pressure waveform (Young *et al*., 2015). Measurements were taken at heart level in both postures to ensure no changes in AIx were found due to alterations in arm angle. Participants rested for twenty further minutes in the alternative posture before these measures were repeated to complete the fasted condition on each morning. A standard hospital breakfast was consumed which constituted of cereal, milk and juice (282kcal, 60g carbohydrate, 3g total fat, 8g protein) or a bread roll with butter and juice (291kcal, 56g carbohydrate, 4g total fat, 9g protein), allowing results to be compared directly with chapter three of this thesis (320kcal, 60g carbohydrate, 7g fat, 5g protein). Participants consumed the same breakfast on all three days of participation in the study. The testing protocol was then repeated in the same order but in a non-fasted state. Order of fasted state was not randomised due to measurements occurring in a narrow timing window to avoid blood pressure differences caused by circadian rhythms and timing constraints in terms of days of

data collection per participant before discharge. This protocol led to the final measures being approximately 45 minutes after food intake.

4.3.3 Sample size

A priori sample size calculations were based on cSBP measures as the primary outcome and assumed a typical error of 6.4 mmHg adopted from a previous reliability study with healthy participants (Filipovsky *et al*., 2000). The maximum chances of a type 1 or 2 error were set at 5% (very unlikely) and an approximate total of eight participants were required to detect a 6-mmHg change (based on the smallest change reported in previous blood pressure studies [Ahuja *et al*., 2009]).

4.3.4 Statistics

Analyses were run using Statistical Package for Social Sciences v.22 (SPSS, Inc., Chicago, Illinois, USA). All presented data are means (standard deviation, SD). Statistical significance was set at $p < 0.05$ (two tailed). Analysis of variance for repeated measures with two within-participant factors (posture and fasting state) examined differences in central and peripheral pressures and arterial stiffness. An independent samples t-test was run to ensure that gender had no significant effect on measures of blood pressure, AIx or AIx75 ($p > 0.05$). Effect sizes were reported using partial eta squared (η_p^2) with 0.01, 0.06 and 0.14 representing small, medium and large effects (Cohen, 1969).

The between-day reliability of the device was measured by calculating the intra-class correlation coefficient (ICC), standard error of measurement (SEM) and smallest detectable

change (SDC; the critical difference in a variable which must be exceeded between two sequential results for a statistically significant change to occur ([Fraser, 2001]). Excellent reliability was reported as an ICC > 0.75 (Fleiss, 1986).

4.4 Results

4.4.1 Central and peripheral blood pressures

When measuring SBP and cSBP, the SphygmoCor XCEL reported excellent between-day reliability in all variables with ICCs exceeding the 0.75 criterion for excellent reliability (ICC = 0.77 – 0.90; Table 4.2). No interaction effects were observed. Posture was reported to have a significant main effect on DBP and cDBP (p < 0.01; η_p^2 = 0.43), with DBP and cDBP both significantly increasing in a seated posture relative to supine. Fasted state had a significant main effect on central and peripheral haemodynamics, with significant decreases in SBP, DBP, pPP, cSBP, cDBP and cPP reported (p < 0.05; η_p^2 = 0.20 – 0.55; Table 4.3 & Supp. Table, Appendix 2d).

Table 4.2: Reliability of SphygmoCor XCEL in measuring peripheral and central blood pressures

	Supine-F			Supine-NF			Seated-F			Seated-NF		
	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC	ICC	SEM	SDC
MAP (mmHg)	0.88	4.6	12.7	0.81	5.6	15.4	0.83	5.1	14.3	0.84	5.8	16.0
SBP (mmHg)	0.84	7.3	20.4	0.84	7.8	21.7	0.83	7.3	20.3	0.85	7.6	21.1
DBP (mmHg)	0.89	3.6	9.9	0.80	4.5	12.5	0.82	4.5	12.5	0.81	5.3	14.6
PP (mmHg)	0.80	5.4	15.1	0.89	4.9	13.5	0.77	5.8	16.2	0.82	5.7	15.9
cSBP (mmHg)	0.85	6.3	17.4	0.83	7.0	19.4	0.81	6.3	17.5	0.83	7.0	19.4
cDBP (mmHg)	0.90	3.5	9.7	0.82	4.4	12.2	0.83	4.4	12.2	0.83	5.1	14.2
cPP (mmHg)	0.84	4.1	11.4	0.88	3.8	10.4	0.79	4.5	12.6	0.83	4.3	11.9
Heart rate ($b \cdot min^{-1}$)	0.89	3.3	9.2	0.83	4.4	12.3	0.88	3.8	10.6	0.85	4.0	11.0
AP (mmHg)	0.76	2.8	7.8	0.66	3.0	8.4	0.72	3.5	9.7	0.71	2.9	8.1
AIx (%)	0.81	3.7	10.3	0.66	5.1	14.0	0.78	5.1	14.2	0.73	5.1	14.1
AIx75 (%)	0.81	4.7	12.9	0.70	5.6	15.4	0.78	6.2	17.1	0.74	5.8	16.1

Abbrevs: AIx – Augmentation index, AIx75 – Augmentation index @ $75b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, F – Fasted, ICC – Intraclass correlation coefficient, MAP – Mean arterial pressure, NF – Non-fasted, SDC – Smallest detectable change, SEM – Standard error of measurement, SBP – Systolic blood pressure

Table 4.3: Mean and SD for peripheral and central haemodynamic variables

		Total	Supine		Seated		Interaction		Posture		Fasted	
			Fast	Non	Fast	Non	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
MAP (mmHg)	$\bar{X}$	99	102	93	105	96	.86	.00	**<.01**	.34	**<.01**	.52
	SD	*14*	*14*	*13*	*13*	*15*						
SBP (mmHg)	$\bar{X}$	142	146	136	149	138	.82	.00	.09	.14	**<.01**	.48
	SD	*19*	*19*	*20*	*17*	*19*						
DBP (mmHg)	$\bar{X}$	78	81	73	84	76	.90	.00	**<.01**	.43	**<.01**	.53
	SD	*12*	*11*	*10*	*11*	*12*						
PP (mmHg)	$\bar{X}$	66	67	65	67	64	.57	.02	.33	.05	**.04**	.20
	SD	*16*	*16*	*17*	*16*	*17*						
cSBP (mmHg)	$\bar{X}$	129	134	122	136	124	.82	.03	.06	.16	**<.01**	.59
	SD	*17*	*16*	*17*	*14*	*17*						
cDBP (mmHg)	$\bar{X}$	80	82	74	85	77	.95	.00	**<.01**	.43	**<.01**	.50
	SD	*12*	*11*	*11*	*11*	*12*						
cPP (mmHg)	$\bar{X}$	50	52	48	51	47	.71	.01	.06	.16	**<.01**	.55
	SD	*10*	*10*	*11*	*10*	*10*						
Heart rate ($b \cdot min^{-1}$)	$\bar{X}$	67	65	68	66	70	.30	.05	**.04**	.19	**<.01**	.60
	SD	*11*	*10*	*11*	*11*	*10*						
AP (mmHg)	$\bar{X}$	16.6	20	15	18	14	.65	.01	**.02**	.22	**<.01**	.61
	SD	*6.4*	*7*	*6*	*7*	*6*						
AIx (%)	$\bar{X}$	32.3	36	31	34	29	.97	.00	**.02**	.22	**<.01**	.43
	SD	*10*	*9*	*10*	*11*	*10*						
AIx75 (%)	$\bar{X}$	28.6	31	28	29	27	.54	.02	.08	.14	**.03**	.20
	SD	*11.3*	*11*	*11*	*13*	*11*						

Abbrevs: AIx – Augmentation index, AIx75 – Augmentation index @ $75b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, F – Fasted, N – Non-fasted, MAP – Mean arterial pressure, PP – Pulse pressure, SBP – Systolic blood pressure

4.4.2 Arterial stiffness

When assessing AIx and AIx75, the SphygmoCor XCEL device reported excellent between-day reliability in both fasted postures (ICC = 0.78 – 0.81) and moderate reliability in both non-fasted postures (ICC = 0.66 – 0.74 [Table 4.2]). Posture had a significant main effect on AIx, with a significant decrease observed in the seated posture (p = 0.02; η_p^2 = 0.22) but not in AIx75; suggesting that these differences were mainly due to the significant changes in heart rate observed in this study. Fasting state had a significant main effect on both AIx and AIx75 with significant decreases reported after food consumption ($p < 0.05$; η_p^2 = 0.14 – 0.22 [Table 4.3 & Supp. Table, Appendix 2d).

4.5 Discussion

The SphygmoCor XCEL exhibits high between-day reliability in different fasting states and postures when assessing peripheral and central BP measures, but arterial stiffness variables were more reproducible in a fasted than non-fasted state. Fasting state was demonstrated to have a large influence on both peripheral and cBP and arterial stiffness measures, whereas posture significantly influenced DBP, CDBP and AIx, but no other variables recorded. The lack of statistical differences in AIx75 between postures suggests that differences in AIx are caused by fluctuations in heart rate caused by postural change. This is in line with previous research showing that AIx is confounded by the timing of the reflected wave (Stoner *et al*., 2017). When measuring peripheral and central BP in a stroke population, patients should be in a fasted state to optimise the accuracy and reliability of collected data. If patients are non-fasted, it is important that researchers and clinicians are aware of the immediate effects of food intake on these measures and analyse these blood pressure measures accordingly. Due to the high

reliability and the demonstrated effect of posture and fasting state on central haemodynamic variables, the experimental hypotheses of this study were accepted.

4.5.1 Central and peripheral blood pressures

High between-day reliability was reported when assessing central and peripheral blood pressure measures, with ICCs exceeding the 0.75 criterion of excellence in all conditions. These ICCs (0.77 – 0.90) are consistent with, but slightly better than, previous work examining the reliability of the SphygmoCor XCEL in a younger, healthy population which reported ICCs of 0.68 – 0.90 for peripheral and central measures (Young *et al*., 2015). No work found during an extensive literature review has investigated the reliability of this device in an acute stroke population. Based upon the ICC analysis, this study suggests that non-invasive measures may be suitable for the assessment of central haemodynamics. However, it is interesting to note that the SDCs were wider than those reported using the same device in a young, healthy population (Young *et al*., 2015).

No significant interaction effects were reported. Significant main effects were observed for both posture and fasting state on peripheral and central BP. Due to technological advances, the measurement of these variables non-invasively may become widespread. As a result, research into factors influencing central measures is of great importance. It is possible that medications may induce different responses between peripheral and central BP measures (McEniery *et al*., 2014). The significant increase in DBP and cDBP in a seated position compared to supine mirrors the findings of previous work (Cavelaars *et al*., 2004; Cicolini *et al*., 2011). This, alongside a non-significant change in systolic measures, caused a non-significant decrease in cPP. Due to the fact that cPP is recognised as being extremely relevant

to vascular ageing (Xiao *et al*., 2015), the significant influence of posture on cDBP is particularly relevant.

Fasting state was demonstrated to cause significant decreases in SBP, DBP, pPP, cSBP, cDBP and cPP. A post-prandial decrease of ~10 mmHg was reported in SBP and ~12 mmHg in cSBP. A smaller decrease in DBP (8 – 9 mmHg) and cDBP (8 mmHg) caused a large change in pPP and cPP to occur. Significant decreases in cBP after food consumption have been observed in a non-clinical population over the age of 50 (Mitchelmore *et al*., 2018 [Chapter three of this thesis]) but not in a young, healthy sample (Young *et al*., 2015). This suggests that healthy populations may be able to make necessary autonomic adjustments to redirect blood flow without a drop in cBP, but older and clinical populations may be less able to do so effectively. A post-prandial drop in central variables was observed by Ahuja *et al* (2009) who reported a decrease of 6.1 mmHg after food and water consumption compared to water alone but recruited a wide-ranging sample aged 21 – 80 years old. After food consumption, this decrease in blood pressure may be due to a post-prandial reduction in arterial stiffness in the splanchnic bed, allowing cardiac output to be maintained alongside a decrease in blood pressure. Ahuja and colleagues (2009) suggest a peak timeframe of 45 minutes for a blood pressure drop after food intake; indicating that the data reported in this study may reflect the greatest changes in a post-prandial state. It is worth noting that as well as physiological adaptations, these changes in blood pressure may be contributed to by the presence of regression to the mean effect due to the repeated measures taken; a potential bias which is inevitably present for as long as there is less-than-perfect repeatability in the measurement of blood pressure (Atkinson, 2015). It should be at the discretion of consultants as to how these optimal operating conditions are balanced against practical patient care, with

nutritional strategies adopted to avoid poor outcomes and prolonged stays in hospital (Aquilani *et al*., 2011).

4.5.2 Arterial stiffness

This study reports that the SphygmoCor XCEL has high between-day reliability when reporting AIx and AIx75, particularly in fasted participants. ICCs of 0.78 – 0.81 were observed when recording AIx and AIx75 in a fasted state, whereas this lowered to 0.66 – 0.73 and 0.70 – 0.74 for AIx and AIx75, respectively, when participants were non-fasted. The digestive process causes alterations in vasodilation which may vary on a day-to-day or meal-to-meal basis depending on extraneous factors (e.g., meal composition, temperature, hydration status). This may cause the assessment of AIx and AIx75 to become less stable when the body is not at rest as it would be more likely to be in a fasted state. The significant main effect observed for posture in AIx but not in AIx75 may add credence to the concept that AIx and HR may not be entirely linearly related; a suggestion which reduces the propriety of AIx75 being reported without AIx alongside (Stoner *et al*., 2013). Significant changes to AIx and AIx75 in different postures have not been observed in previous work in a healthy, young population (Young *et al*., 2015). However, a significant change in AIx but not AIx75 has also been reported in hypertensive participants over the age of 50 (Mitchelmore *et al*., 2018 [see chapter three of this thesis]) but not in the normotensive sample in the same study, who demonstrated significant differences in both AIx and AIx75 in supine and seated postures. A reduction in AIx75 has been reported in a supine state compared to a seated position in a female-only population (Jaccoud *et al*., 2012). Such a finding was not mirrored in this study, with measurements of AIx and AIx75 being 1-2% lower in the seated posture compared to supine.

This finding was not statistically significant (p = 0.08), whilst wide ranges in the reported 95% confidence intervals were reported (see Supp Table, Appendix 2d). This may be due to a potential lack of statistical power to detect an association of this magnitude in this sample of 22 stroke patients. The finding that fasting state had a significant main effect on AIx and AIx75 with post-prandial reductions observed in both measures aligns with previous research and may be a result of increased arterial compliance due to tone alterations in the small vessel beds, large artery function and large artery geometry (Young *et al*., 2015).

4.5.3 Clinical significance

This study suggests that non-invasive cBP assessments provide reproducible measurements of peripheral and central haemodynamics. Significant decreases in peripheral and central BP were observed after food consumption. During hospitalisation after stroke, assessments of central and peripheral BP should therefore be assessed in a fasted state to reduce the variability caused by food intake. This is particularly true when medication prescription is at least partially based on these routine blood pressure measures. The combined effect of post-stroke medication and fasting state should also be considered when monitoring patient health, as both variables cause a decrease in peripheral and central BP measures.

With regards to arterial stiffness, increased arterial stiffness is reported to be significantly associated with reduced cognitive function in stroke patients (Lee *et al*., 2014). Reporting this decrease in arterial stiffness in terms of prandial state may have some importance with regards to perfusion pressures and the timing and assessment of cognitive state examinations in a clinical setting around mealtimes. Further work should investigate any potential links

between arterial stiffness, perfusion pressures and cognitive performance both before and after food intake in clinical populations.

4.5.4 Strengths and limitations

The recognition of areas of strength and limitation is vital during the interpretation of results. Firstly, we did not recruit a unisex sample, a fact which may influence results due to potential differences in responses to postural changes in peripheral blood pressure between sexes (Gerber *et al*., 2015). Secondly, due to stringent exclusion criteria and subsequent slow levels of recruitment, we recruited a sample with a range of stroke subtypes and severity according to NIHSS (range: 1 – 18). Although the global burden of stroke is predicted to continue to increase as a greater proportion of patients survive their first stroke, fewer than half of all stroke trials recruit their target number of patients (Berge *et al*., 2016). Participant recruitment is arguably the most difficult part of research (Blanton *et al*., 2006), and if successful recruitment does not occur, there are implications for statistical power and internal and external validity (Berge *et al*., 2016).

To optimise patient recruitment, Gorelick and colleagues (1998) proposed a recruitment triangle involving the patients themselves, their key family members and friends, and the primary doctors and other medical personnel. Each of these corners of the triangle were addressed throughout the research process, with consent taken from patients during visiting hours to allow family members to be a part of the decision-making process to minimise participant dropout.

Further work should examine whether there are differences in the reliability of the SphygmoCor XCEL in more severe strokes, and between stroke subtypes. The study was also

not able to take into account the effect of body mass or body composition variables on changes of peripheral and central haemodynamics as patients were not routinely weighed on admission. Finally, the sample contained participants with and without atrial fibrillation; a condition which may lead to some inconsistencies in measured data due to inconsistent stroke volumes. Focusing on cBP assessments in those specifically with atrial fibrillation has the potential to be an interesting area of future study. However, the timeframes involved in the data collection process ensured that post-prandial measures after food consumption were in accordance with recommendations set out by Ahuja and colleagues (2009) in terms of capturing the peak effects of food intake on haemodynamic variables. Additionally, the in-patient nature of the study ensured a controlled environment for data collection to occur. Furthermore, the randomisation of condition order and standardised overnight fast also contributed to a strong protocol. Finally, assessments occurred at the same time each day, reducing the likelihood of circadian rhythms altering the blood pressures recorded in the morning.

4.6 Conclusion

In conclusion, this study demonstrates that the SphygmoCor XCEL, a non-invasive oscillometric PWA device, possesses high between-day reliability in assessing both central and peripheral BP measures in both fasted and non-fasted states, and good reliability when assessing markers of arterial stiffness, particularly in a fasted state. The current study demonstrates that posture has a significant effect on DBP, cDBP and AIx, whereas, fasting state significantly influences all peripheral and central variables, as well as both AIx and AIx75, in acute stroke patients. The findings of this study are pertinent to researchers and clinicians,

although consideration around the practicalities of implementing these measures within practice (e.g. optimising conditions for BP assessment whilst minimising adverse events associated with fasting state) is necessary.

Chapter 5: Study three - The acute effect of heel raises on central haemodynamics, arterial stiffness and cognitive function in chronic stroke to interrupt extended periods of sedentary time

5.1 Abstract

Extended sedentary time is common after stroke and leads to increases in blood pressure (BP) and poor health outcomes. This study investigated whether intermittent heel raises could reduce these rises in BP over a three-hour time period and consequently improve cognitive function. Fifteen stroke survivors (69.3y ± 10.8y) took part in a randomised crossover trial. Participants attended a familiarisation session involving pulse wave analysis and pulse wave velocity measures using the SphygmoCor XCEL and five Stroop tasks. Participants then attended two sessions of three hours of stationary, seated time. In one of these visits, ten heel raises were completed at ten-minute intervals throughout. Measures of central haemodynamics and cognitive function at the ten-minute time-point and three-hour time-point were compared. Intermittent heel raises had a large significant condition by time interaction effect on peripheral and cBP (p = 0.02 – 0.04; η_p^2 = 0.28 – 0.32). Increases of 10.7 mmHg and 9.6 mmHg were observed in peripheral and cBP over the sedentary three hours as opposed to increases of 5.2 mmHg and 5.6 mmHg respectively in the heel raise protocol. No significant changes in cognitive function were observed (p > 0.05). Intermittent heel raises significantly mitigated the rise in peripheral and cBP due to seated time, but an increase was observed in both conditions.

Clinical trial registry name: NCT03423433, https://clinicaltrials.gov/ct2/show/NCT03423433

5.2 Introduction

Risk factor control in chronic diseases including stroke is poor (Ellis & Breland, 2014) and, although life expectancy continues to increase, a greater proportion of this lifespan is now spent in ill health (Newton *et al*., 2015). Treating elevated blood pressure (BP) may be the most important intervention when preventing second stroke (Kernan *et al*., 2014), but low adherence to anti-hypertensive therapy is one of the major contributors to low rates of blood pressure control (Peck, 2018). As such, implementing lifestyle interventions takes on a key role in improving vascular health after stroke and reducing secondary stroke risk. Hypertension is a potential risk factor for post-stroke cognitive impairment (Sun, Tan & Yu, 2014), with arterial stiffness also linked to cognitive impairment in hypertensive individuals (Muela *et al*., 2017). The link between hypertension and cognitive impairment can be explained by a combination of impaired enthothelial function, reduced beta-amyloid clearance, excessive blood pressure dipping or non-dipping during sleep, white matter disease, abnormal insulin signalling in the brain and pharmacological factors (Gorelick *et al*., 2012). However, improved cognition has been reported in centenarians with elevated blood pressure, (Richmond *et al*., 2011; Duarte *et al*., 2017), possibly due to increased maintenance of cerebral perfusion (Lima, 2018). Increased PP is a risk factor of white matter lesions and transient self-limited haemorrhage, both of which are related to cognitive decline (Mitchell, 2008; Wei *et al*., 2018).

Sedentary behaviour is characterised by an energy expenditure of ≤ 1.5 METs while in a seated or reclining posture (Barnes *et al*., 2012) and is frequently linked to low levels of physical activity, defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” (Caspersen, Powell & Christenson, 1985 p.126). Increased incidence of sedentary time (involving prolonged sitting) and decreased levels of physical activity both

adversely affect BP (Larsen *et al*., 2014). Long periods of seated time are detrimental to health, even if adults meet the government recommended physical activity guidelines (Biswas *et al*., 2015). Little is known about the independent detrimental health effects of sitting (Stamatakis *et al*., 2019) and even less is known about sedentary behaviour and stroke, particularly sitting, although it is reported to slow recovery (Butler & Evenson, 2014). Nonetheless, low levels of physical activity are common after stroke (Field *et al*., 2013; Saunders *et al*., 2016) with individuals suffering from stroke likely to accrue half the daily step counts of their healthy counterparts (English *et al*., 2014) with significantly more seated time each day (English *et al*., 2015). This may be due to sedentary behaviours being perceived as normal or an important way of relaxing after a stroke (Ezeugwu *et al*., 2016). The prevalence of this issue has reached the extent that association guidelines for stroke survivors now include reducing sedentary behaviours (Billinger *et al*., 2014). After a stroke has taken place, focusing on the reduction of sedentary time is now a promising intervention target (Morton *et al*., 2018) as in-patient gains may be lost if sedentary behaviours are not addressed after hospital discharge (Ezeugwu *et al*., 2016). English and colleagues (2018) have reported SBP decreases of 3.5 mmHg while doing light intensity exercises whilst standing versus sitting for eight hours uninterrupted in stroke survivors – suggesting that relatively small movements may lead to noticeable changes in BP over an extended time period of seated time. However, stroke frequently causes impairments in sit-to-stand movements (Janssen *et al*., 2010). As such, investigating movements which may lead to similar improvements in BP for those unable to frequently transition from sit-to-stand is of importance.

Sedentary individuals tend to present with elevated BP (Weisser, Hacke & Wegner, 2014). However, cBP may be more relevant to organ damage (Booysen *et al*., 2013; Zeigler *et al*., 2018), cardiovascular risk and mortality (Roman *et al*., 2007; Ott *et al*., 2017). Although

previously an invasive procedure, the assessment of central pressures can now be completed using non-invasive methods (Agabiti-Rosei *et al*., 2007) through pulse wave analysis (PWA) which also allows for measures of AIx. Pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness due to its simplicity, accuracy and predictive value (Laurent *et al*., 2006; Diaz *et al*., 2017). Both of these measures can be ascertained using the SphygmoCor XCEL which has been demonstrated to be reliable in healthy young and older adults and acute stroke populations (Young *et al*., 2015; Mitchelmore *et al*., 2018 [see chapter three of this thesis]; Mitchelmore *et al*., 2018 {see chapter four of this thesis}).

One possible intervention to reduce damaging increases to PWA and PWV caused by extended and uninterrupted sedentary time is the incorporation of low intensity movements such as intermittent heel raises. This movement is viable for all stroke survivors with the ability to plantarflex; a greater proportion than may be able to complete more intensive physical activity or exercise programmes. It has been previously reported that sedentary behaviours are linked to lower executive function (Steinberg *et al*., 2015) and lower cognitive performance (Falck, Davis & Liu-Ambrose, 2017). However, the acute impact of heel raises on vascular measures (PWA, PWV) and whether this translates into improved executive function has not been investigated. Lower limb physical activity may stimulate increased blood delivery to the periphery to provide oxygenated blood for ATP production at the muscle. Hypothetically, a consequential increase in the circulation of oxygenated blood to the brain may translate into improved executive function.

This study will investigate the consequences of uninterrupted sitting time on measures of PWA, PWV and cognitive performance compared to a heel raise protocol to break up an identical period of sedentary time in chronic stroke patients. This study hypothesised that

completing a set of heel raises every ten minutes over a three-hour period would have a significant effect on peripheral and central BP, measures of arterial stiffness, and improve executive function at the end of the sedentary time. Conversely, our null hypothesis predicted that heel raises would have no significant effect on peripheral and central BP, arterial stiffness, or executive function.

5.3 Methods

5.3.1 Participants

Fifteen chronic stroke patients (m=10, age: 69.3y ± 10.8y, 170.6cm ± 8.6cm, 75.5kg ± 9.7kg) were recruited to the study through stroke support groups. Participant demographics can be seen in Table 5.1. The University of Winchester Ethics Committee provided ethical approval (BLS/17/11). An information sheet (Appendix 3b) summarising the purpose of this study was provided to participants who provided informed consent (Appendix 3c) prior to the study commencing. Participants were eligible for this study if they were > 3 months and < 10 years after their stroke and able to walk independently (including use of a walking aid) with the ability to plantarflex. This trial was registered to the National Clinical Trials Database (NCT03423433).

Table 5.1: Participant demographics

		n	%
Participants		15	
Age (y)		69.3	
Sex	Male	10	67
	Female	5	33
Descent	European	15	100
Stroke type	Ischaemia	11	73
	Haemorrhage	4	27
Side affected	Left	6	40
	Right	9	60
Family history of CVD	Myocardial infarction	6	40
	Heart surgery	5	33
	Stent	3	20
	Catheter	1	7
	Heart defect	2	13
	Stroke	3	20
Personal history of CVD	Hypertension	8	53
	High cholesterol	5	33
	Diabetes	1	7
	Coronary artery disease/heart failure	7	47
Comorbidities	Thyroid disease	0	0
	Lung disease	0	0
	Asthma	2	13
	Cancer	1	7
	Kidney disease	0	0
	Hepatitis	1	7
Lifestyle factors	Current smoker	0	0
	Previous smoker	6	40
	Current alcohol drinkers	14	93
	Current weight loss plan	0	0
Everyday activity	Sedentary	0	0
	Lightly active	10	67
	Moderately active	5	33
	Vigorously active	0	0
Medication	Statins	8	53
	Anti-thrombotic	7	47
	Calcium blockers	3	20
	Alpha blockers	0	0
	Beta blockers	2	13
	ACE-I	3	20
	ARB	2	13

5.3.2 Experimental design

This was a randomised crossover trial involving three visits to the physiology laboratory at the University of Winchester. As in studies one and two, participants were fasted for 12 hours before each session and had abstained from caffeine and physical activity for 24 hours before each session. Participants first completed a familiarisation session involving baseline PWA and PWV measures to reduce any risk of a white coat response to having these measures assessed. These measures were taken on the symptomatic side of the body. At each time point, two measures of PWA were taken. If SBP was greater than 5 mmHg different and AIx was more than 4% different between the two readings, a third measure was recorded, and an average calculated of the closest two measures.

Participants also completed five Stroop tasks to remove the risks of a learning effect from the second and third (sedentary and heel raise) visits. Previous literature has demonstrated a learning effect in Stroop tasks (Figure 5.1) in both mean response time and response error. As such, five blocks of tests were considered sufficient for scores to have plateaued.

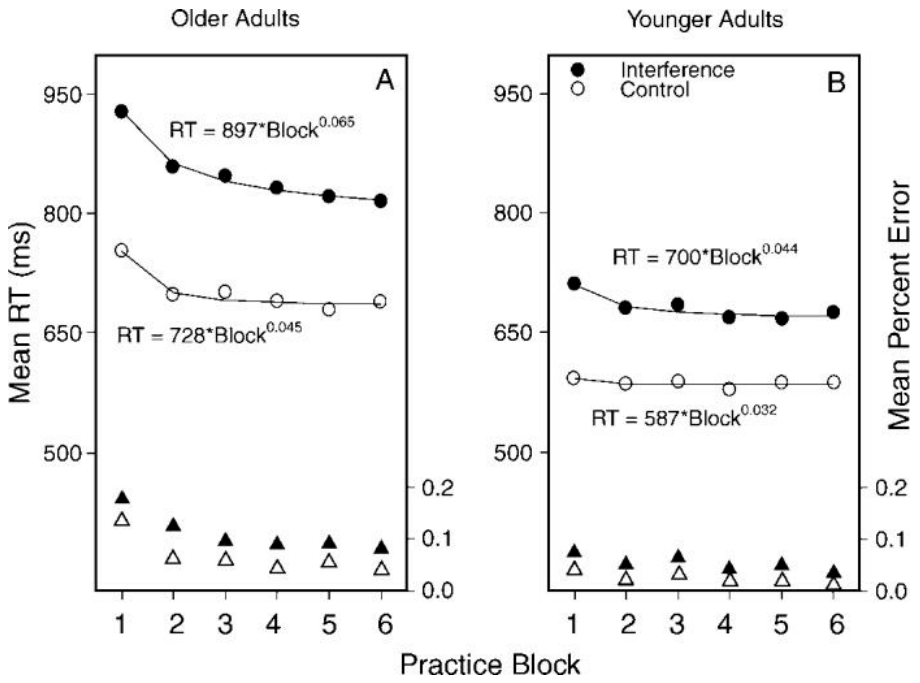
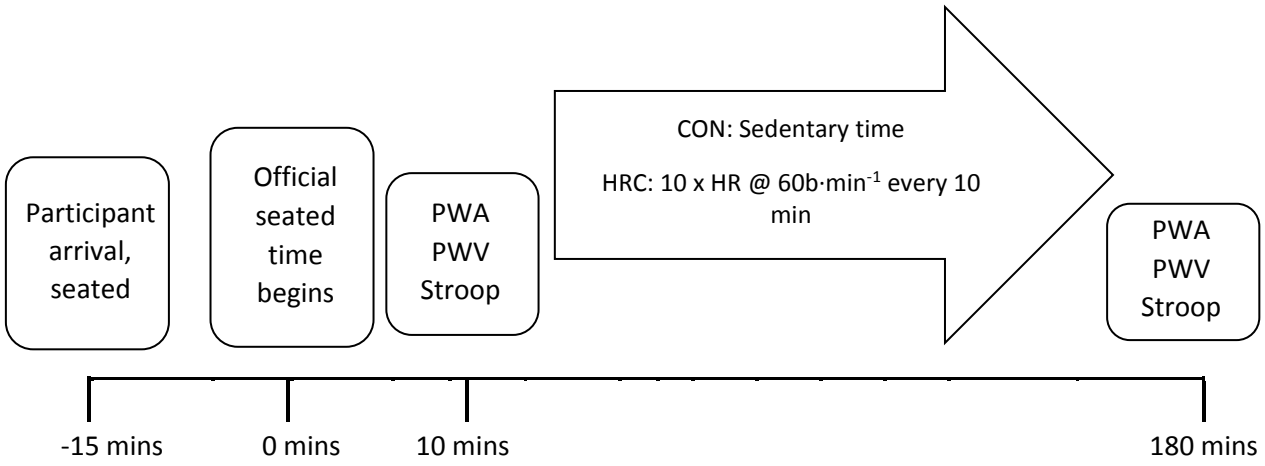


Figure 5.1: Improvements in mean response time in older and younger adults across six practice blocks, each comprising of 128 questions. Interference represents colour-word interference (described as incongruent trials in this thesis), From *Davidson, Zacks and Williams, 2003*

A computer-based randomiser then allocated participants to a sedentary (CON) or heel raise condition (HRC) first. After arrival, 15 minutes of seated time allowed BP to plateau before a three-hour timeframe began. The protocol is outlined as a schematic in Figure 5.2. Heel raises were undertaken at 60b·min^{-1}. This was controlled using a metronome. Stroop tasks consisted of 48 questions on a laptop using a pre-created programme. One half of these questions were congruent (e.g. 'Blue' written in blue text [Figure 5.3]) and the other half were incongruent (e.g. 'Blue' written in yellow text). The order of these questions was randomised to ensure no learnable patterns in answer order. Correct score (out of 48), mean congruent response time, mean incongruent response time, mean response time and total time to complete test were all recorded.



Abbrevs: CON – Control condition, HR – Heel raise, HRC – Heel raise condition, PWA – Pulse wave analysis, PWV – Pulse wave velocity

Figure 5.2: Schematic of study visits two and three

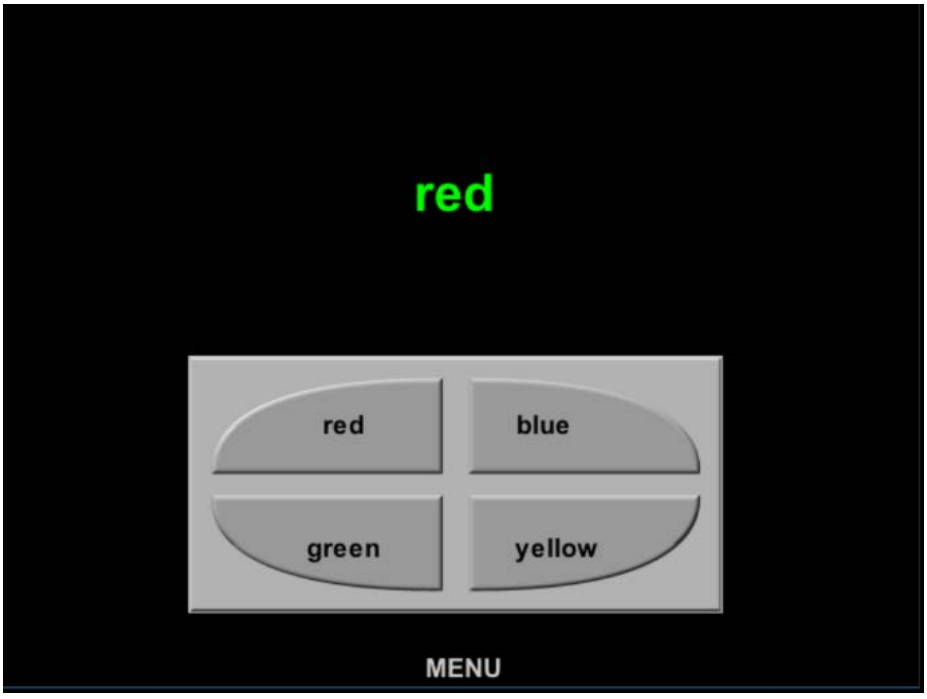


Figure 5.3: Example of Stroop protocol question

5.3.3 Statistics

Analysis of variance for repeated measures with two within-participant factors (condition and time-point) was used to assess differences in peripheral and central haemodynamic parameters, PWV and cognitive performance between the first seated time-point (ten minutes) and final seated time-point (three hours). Effect sizes were calculated using partial eta squared (η_p^2) with 0.01, 0.06 and 0.14 representing small, medium and large effects (Cohen, 1969). Statistical Package for Social Sciences v.22 (SPSS, Inc. Chicago, Illinois, USA) was used to analyse data with statistical significance set at $p < 0.05$.

5.4 Results

5.4.1 Central and peripheral blood pressures, arterial stiffness

The effect of intermittent heel raises on PWA and PWV over a three-hour time-course can be seen in Table 5.2. Significant condition by time interaction effects were reported for SBP ($F_{(1, 14)} = 6.5$, $p = .02$, $\eta_p^2 = 0.32$). This involved an increase of 10.7 mmHg between 10 minutes and three hours in CON, versus increases of 5.2mm Hg over the time-course in the HRC. Similar findings were observed for cSBP ($F_{(1, 14)} = 5.4$, $p = 0.04$, $\eta_p^2 = 0.28$) with an increase of 9.6 mmHg reported in CON vs. increases of 5.6 mmHg in HRC over the three hours of seated time. Whether or not participants completed heel raises, time had a significant main effect on peripheral and cSBP were observed ($p < 0.01$), but the interaction effects reported demonstrate that heel raises significantly mitigated this increase.

No significant interaction effects were observed for AIx or AIx75 (p = 0.18 – 0.79, η_p^2 = 0.18 – 0.35) but large effect sizes were noted with decreases in AIx of 1.2% reported in CON vs. decreases of 3.4% in HRC. Heel raises had no significant effect on PWV, although a large significant interaction effect was observed in heart rate ($F_{(1, 11)}$ = 7.5, p = 0.02, η_p^2 = 0.41). Decreases of 0.8 b·min^{-1} were observed in the CON over three hours versus decreases of 5.3 b·min^{-1} after HRC. Significant interaction effects were observed for double product (DP) – the product of SBP and HR ($F_{(1, 11)}$ = 13.7, p < 0.01, η_p^2 = 0.55), with an increase of 554.9 mmHg x b·min^{-1} between ten- and 180- minute time points in CON compared to a decrease of 162 mmHg x b·min^{-1} in HRC. Supp. Table 3d illustrates data outputs for additional PWA variables.

Table 5.2: Mean (SD) central and peripheral blood pressures and arterial stiffness values pre- and post- control and heel raise conditions

		Sedentary Vis		Heel Raise Vis		Interaction		Condition		Time	
		10 Min	180 min	10 min	180 min	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
MAP (mmHg)	*X*	92	99	89	95	0.43	0.06	0.99	<.01	**0.01**	0.49
	SD	*15*	*14*	*12*	*11*						
SBP (mmHg)	*X*	130	141	131	136	**0.02**	0.32	0.48	0.04	**0.02**	0.31
	SD	*20*	*23*	*23*	*21*						
DBP (mmHg)	*X*	75	79	76	79	0.39	0.05	0.93	<.01	0.05	0.26
	SD	*13*	*12*	*13*	*9*						
cSBP (mmHg)	*X*	121	131	122	127	**0.04**	0.28	0.57	0.02	**0.02**	0.32
	SD	*18*	*21*	*21*	*20*						
cDBP (mmHg)	*X*	76	81	77	80	0.29	0.08	0.88	0.02	0.06	0.23
	SD	*13*	*12*	*13*	*9*						
cPP (mmHg)	*X*	45	50	45	48	0.21	0.11	0.47	0.04	0.14	0.15
	SD	*14*	*19*	*13*	*16*						
AP (mmHg)	*X*	17	19	17	18	0.33	0.07	0.47	0.04	0.55	0.03
	SD	*9*	*11*	*8*	*10*						
AIx (%)	*X*	37	35	38	35	0.35	0.06	0.79	0.01	0.24	0.1
	SD	*15*	*14*	*15*	*13*						
AIx@75 (%)	*X*	28	27	31	25	0.18	0.13	0.64	0.02	0.04	0.27
	SD	*16*	*15*	*17*	*15*						
HR ($b \cdot min^{-1}$)	*X*	58	57	59	54	**0.02**	0.41	0.74	0.1	0.11	0.22
	SD	*7*	*10*	*7*	*8*						
PTT (ms) *	*X*	*44*	*37*	*41*	*40*	0.33	0.19	0.65	0.05	0.21	0.29
	SD	*15*	*9*	*6*	*5*						
PWV ($m \cdot s^{-1}$) *	*X*	*11*	*13*	*12*	*12*	0.34	0.18	0.94	<0.01	0.19	0.32
	SD	*3*	*3*	*2*	*2*						
DP	*X*	7096	7651	7398	*7236*	**<.01**	0.55	0.79	.01	0.38	.07
	SD	*1185*	*1544*	*1146*	*1663*						

***Measures of PWV/PTT reported for seven full data sets due to lack of clean pulse waves on affected side of stroke patients

Abbrevs: AIx – Augmentation index, AIx75 – Augmentation index @ 75 $b \cdot min^{-1}$, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, DP – Double product (HR*SBP), HR – Heart rate, MAP – Mean arterial pressure, PTT – Pulse transit time, PWV – Pulse wave velocity, SBP – Systolic blood pressure, Vis – Visit

5.4.2 Cognitive performance

Table 5.3 displays data representing cognitive performance in the 48-question Stroop tests. No significant interaction effects were observed (p > 0.05) with improvements in all parameters observed between ten minutes and three hours in both conditions.

Table 5.3: Mean (SD) Stroop measures, pre- and post- the control and heel raise conditions

		Total	Sedentary Vis		Heel Raise Vis		Interaction		Condition		Time	
		X	10 Min	180 min	10 min	180 min	*P*	η2 p	*P*	η2 p	*P*	η2 p
Mean Correct	*X*	47	46.9	47.2	46.8	47.2	.58	.03	.7	.01	.21	.13
	SD	*1.9*	*2*	*1.5*	*2.4*	*1.7*						
Mean Congruent (ms)	*X*	1623	1840	1641	1512	1499	.46	.05	.03	.34	.21	.13
	SD	*682*	*931*	*611*	*542*	*600*						
Mean Incongruent (ms)	*X*	1975	2296	1949	1911	1743	.38	.06	.03	.34	.12	.19
	SD	*1060*	*1523*	*935*	*962*	*691*						
Mean Response (ms)	*X*	1880	2173	1871	1801	1676	.40	.06	.02	.36	.12	.19
	SD	*936*	*1349*	*826*	*800*	*659*						
Total Time (s)	*X*	100.5	114.6	99.8	96.1	91.3	.36	.07	.04	.31	.15	.17
	SD	*46*	*67.8*	*40*	*37.7*	*32.1*						

5.5 Discussion

Heel raises at ten-minute intervals throughout a three-hour period of sedentary time significantly mitigated the increases in blood pressure that were observed in both conditions and are therefore of sufficient intensity to act as a form of physical activity and reduce the damage caused by extended sedentary time. These improvements in peripheral and central haemodynamics did not translate to improved executive function at the end of the three-hour time course.

5.5.1 Central and peripheral blood pressures, arterial stiffness

This study suggests that intermittent heel raises may significantly mitigate the damaging effects of sedentary time on BP through a three-hour time course. The focus on reducing sedentary time after stroke is now a promising intervention target (Morton *et al*., 2018) with reducing sedentary behaviours a goal in association guidelines post-stroke (Billinger *et al*., 2014). This study supports these suggestions, as even with the incorporation of heel raises, SBP increased by an average of 5.2 mmHg (4%) over three hours and central by an average of 5.6 mmHg (4.6%); both demonstrating significant main effects of time (p = 0.02). Without the incorporation of heel raises, peripheral and central BP increased by 10.7 mmHg (8.2%) and 9.6 mmHg respectively (7.9%). Nevertheless, large significant condition by time interaction effects were reported for the use of heel raises, suggesting that these simple movements significantly alleviate the increase in BP seen during extended sedentary time. Brooks and colleagues (2004) note that substantial fidgeting may contribute to physical activity level but may not produce the health benefits of sustained and vigorous exercise, but this study demonstrates that heel raises may be of a vigorous enough intensity to cause acute benefits in central haemodynamics. Double product is the product of SBP and HR and is a well-established measure expressing the load on the heart (Domka-Jopek *et al*., 2018).

It has been previously reported that healthy individuals are significantly less sedentary than stroke survivors (English *et al*., 2015). Supplementary Figure 3e depicts a common pattern of sedentary behaviour across a twelve-hour period including a gym or rehabilitation visit for a stroke survivor based on estimates that stroke patients are sedentary for around 20.4h per day versus 17.4h in a healthy population (Paul *et al*., 2016). Sedentary behaviours are associated with poor health, regardless of the level of outside physical activity (Martin *et al*.,

2015), with prolonged sitting particularly bad for health (Dunstan *et al*., 2012). As such, even individuals attending rehabilitation sessions but being sedentary for the rest of the day (for example, the pattern created in Supplementary Figure 3e) may still be demonstrating increases in peripheral and cBP whilst sedentary before and after rehabilitation sessions. Movements such as heel raises may therefore be relevant to all stroke survivors, whether or not they are actively pursuing rehabilitation programmes throughout the chronic recovery process. Previous work has reported that double product (DP) may be more associated with mortality than SBP or HR alone (Inoue *et al*., 2012) but other studies have suggested SBP as a stronger predictor of CV events and stroke (Schutte *et al*., 2013). This study reports that intermittent heel raises over the course of a three-hour bout of sedentary time may significantly improve DP in chronic stroke patients.

When considering arterial wave reflection, no significant interaction effects were observed. Despite this, there were encouraging trends in the data in favour of HRC, as supported by the moderate-large effect sizes observed in this study (η^2_p = 0.06 – 0.13). This is supported by descriptive statistics which demonstrate that AIx decreased by an average of 1.2% in the CON vs. 3.4% in the HRC, and AIx75 decreased by 1.8% in CON compared to 5.8% in HRC. A previous meta-analysis (Pierce, Doma & Leicht, 2018) has reported overall AIx decreases of 4.54% after aerobic exercise (18 studies, *n* = 396) and increases of 1.63% after resistance exercise (five studies, *n* = 83). As such, these results suggest that similar benefits in AIx can be accrued through heel raises than through aerobic exercise in a population who are largely unable to undertake more intense exercise. The similarities in our results with the findings of the aerobic studies examined by Pierce and colleagues may be due to lower intensities of exercise relying on lipid metabolism and, therefore, aerobic pathways of energy production. As such, intermittent heel raises may influence arterial stiffness, with the stimulation of the lower

limbs leading to increases in arterial compliance, potentially due to the significant decreases in HR observed in HRC. Future work should address whether upper body movements may accrue similar benefits in BP control.

5.5.2 Cognitive performance

No significant interaction effects were observed in this study, suggesting that intermittent heel raises had no significant effect on cognitive performance involving a 48 question Stroop protocol. Longer term exercise may improve executive functions (Predovan *et al*., 2012) but a single bout of aerobic exercise has been reported to have no effect on executive function in Stroop performance (Vincent & Hall, 2017); work our findings would corroborate.

Condition had a significant main effect on mean congruent response time, mean incongruent response time and mean overall response time (p = 0.02 – 0.03), with these variables significantly improved in the HRC. Due to the fact that the ten-minute Stroop task was completed before the first set of heel-raises, this condition main effect demonstrates that results were improved as a whole in the heel-raise visit, not because of the heel-raises themselves. The order of conditions in this study was randomised, so the reasons for this are unclear. As a whole, results are inconclusive from this study and further research is needed to investigate whether improvements in cognitive function result from the benefits in arterial health observed due to interrupting sedentary time with heel raises.

5.5.3 Strengths and limitations

It is important for strengths and limitations to be identified to allow contextualisation of any conclusions drawn from a research study. One limitation of this work was the duration of

sedentary time undertaken by participants. Previous work in the area has observed eight hours of sedentary time (English *et al*., 2018), whereas this study only incorporated a three-hour protocol. Whilst this allowed us to observe how quickly increases in SBP and cSBP can take place, this restricted us in terms of observing the longer effects of seated time.

A second limitation was the wide range of cognitive abilities recruited as demonstrated by the wide range of standard deviations in the reported Stroop data. This study did not control for cognitive ability, which is a consideration with a sample size of 15. There may also have been a learning effect in place even during the Stroop protocols even with the incorporation of the initial familiarisation session and the randomisation of the condition order. Nevertheless, the chronological improvements in performance across both conditions suggest a learning effect may have been present. The mean age for first stroke has dropped to 68.2y in males and 73y in females (Public Health England, 2018b) and the mean age recruited to this study was 69.3y; demonstrating a close match with the 'average' sufferer of a first stroke. This study was also highly controlled. Timings were exact, all sessions took place in the same laboratory at the same time of day. The speed at which heel raises were undertaken was also standardised due to the use of a metronome and all data was collected by one researcher, removing the risk of inter-researcher bias.

5.6 Conclusion

There is an epidemic of sedentary time after stroke leading to increases in BP, particularly during extended seated time. This study demonstrates that three hours of seated time is enough to cause large increases in peripheral and cBP and that intermittent heel raises have the potential to alleviate some of this damage by significantly reducing this rise in arterial

stiffness. Even stroke patients attending daily rehabilitation sessions should incorporate low intensity activities such as heel raises to improve vascular health during spells of sedentary time throughout the day.

Chapter 6: Study four - The effects of a ten-week heel raise programme on central haemodynamics and cognitive function in individuals with chronic stroke: pilot study

6.1 Abstract

Background: Excessive sedentary time after stroke is extremely common and a risk factor for poor health outcomes in the long run. As such, identifying simple movements to interrupt bouts of extended sedentary time may be beneficial to vascular health and cognitive function. **Methods:** This pilot study recruited eight chronic stroke patients (age 72y ±11.6y; 167.1cm ±6.8cm; 75.2kg ±9.4kg) into a randomised, crossover trial involving a ten-week control period and a ten-week heel raise intervention involving 180 heel raises over the course of three hours of sedentary time, six days per week. **Results:** No significant improvements were observed in measures of body composition (body mass, waist and hip circumferences, calf circumferences [$p > 0.05$]). The heel raise protocol also had no significant effect on peripheral or central haemodyamics (assessed using the SphygmoCor XCEL). Significantly greater improvements in cognitive performance (repeated Stroop tasks) were observed in the control condition, but this may have been due to worse initial performances in the pre- control condition vs. the pre- intervention condition. **Conclusion:** Previous work has suggested that intermittent heel raises may lead to acute improvements in the parameters investigated in this study. However, this work suggests that these acute improvements may not translate into persisting gains in the longer-term.

Clinical trial registry name: NCT03423433, https://clinicaltrials.gov/ct2/show/NCT03423433

6.2 Introduction

With the burden of disease caused by stroke expected to double by 2030, there is good evidence to support interventions in stroke rehabilitation (NICE, 2018) to counter risk factors of primary and recurrent stroke. Controlling peripheral and central BP after stroke has the potential to be the mainstay of secondary prevention. The SphygmoCor XCEL has been shown to be reliable in both healthy (Young *et al*., 2015; Mitchelmore *et al*., 2018a [see chapter three]) and acute stroke (Mitchelmore *et al*, 2018b [see chapter four]) populations when measuring peripheral and central haemodynamics with excellent reliability being defined as an ICC > 0.75. As well as SBP and cSBP, the SphygmoCor XCEL provides cPP. This variable has also been associated with poor cognition and low memory scores (Hanon *et al*., 2005; Scuteri *et al*., 2005; Mitchell *et al*., 2011). Poor cognition has been linked to depressive symptoms and decreased quality of life after stroke (Nys *et al*., 2006), which in turn have been associated with increased mortality 12- and 24- months post- stroke (House *et al*., 2001)

Behaviourally modifiable risk factors such as physical inactivity, overweight and obesity, cigarette smoking, alcohol consumption and diet can be targeted through lifestyle changes. One aspect of lifestyle which is relatively easy to target post-stroke is the application of interventions that may decrease sedentary time. Around 70% of stroke survivors suffer from lower limb weakness (Lawrence *et al*., 2001) and, due to poor balance, more than 50% of survivors have falls within a year of their stroke (Weerdesteyn *et al*., 2008). Functional balance is the capacity to maintain various positions, to make automatic postural responses to voluntary changes in the body and its segments to react to external disturbances (Berg *et al*., 1989, p. 304). As this functional balance is impaired by stroke, low levels of physical activity and high levels of sedentary time are common after stroke (Saunders *et al*., 2016). Stroke

survivors typically spend 11 hours per day in a seated position (75% of waking hours), many during prolonged bouts of sitting (English *et al*., 2016). Sedentary time after stroke is seen as 'normal' and may be perceived by stroke survivors as a relaxing part of the recovery process (Ezeugwu, Garga & Manns, 2017). This may manifest as prolonged time watching the television, which has been linked with increased blood pressure (Beijer *et al*., 2018) with a significant increase in biomarkers of diabetes risk observed for every five hours of extra television viewing each week (Hansen *et al*., 2012). However, prolonged bouts of sedentary time are particularly harmful (Healy *et al*., 2008; Healy *et al*., 2011) and may lead to increase hospitalisations, increased dependence on medications and a subsequent greater reliance on the health service.

Cognitive deficits after stroke are common, with concentration (Rasquin *et al*., 2002), mental speed (Winkens *et al*., 2006), executive functioning (Poulin *et al*., 2012) and memory impairment (Novitzke, 2008). Sedentary behaviour has itself been linked with mild cognitive impairment (Falck, Davis & Liu-Ambrose, 2017); thus, interventions to counter sedentary behaviours should be put in place. If not, the physiological and cognitive improvements that may be observed during in-patient stays may be lost in the months and years that follow hospital discharge (Ezeugwu *et al*, 2017). Physical activity is now the cornerstone of risk reduction therapy for the prevention and treatment of stroke (Gordon *et al*., 2004). Movement patterns such as heel raises may reduce the physical damage caused by extended sedentary time.

Chapter five of this thesis demonstrated that intermittent heel raises (every ten minutes over a three-hour time course) significantly mitigated the rises in peripheral and central BP that were observed during extended sedentary time. These benefits may have been due to

improved circulation (arterial delivery and venous return) and reducing pooling in the lower extremities.

Heel raises have been demonstrated to elicit physiological changes over the course of a prescribed programme in elderly populations. Daily bouts of 100 heel raises over 40 days (Fujiwara *et al*., 2010), six weeks (Lee *et al*., 2017), and two months (Fujiwara *et al*., 2011) have been reported to show significant improvement in plantarflexor strength, balance, gait speed, improvements in ankle movement and decreases in postural fluctuation. The effect of resistance-free heel raises on physiological measures such as peripheral and central BP and arterial stiffness has not, to our knowledge, been investigated, despite each of these measures being indicative of cerebrovascular risk both before and after stroke.

This pilot study will investigate whether a daily, ten-week, heel raise intervention affects peripheral and central haemodynamics and cognitive performance. Based on the findings of chapter five of this thesis, we hypothesised that a daily, ten-week heel raise protocol would have a significant effect on peripheral and central BP, arterial stiffness, and executive functioning in individuals living with stroke. As such, our null hypothesis was that a ten-week heel raise programme would have no significant effect on peripheral and central BP, arterial stiffness or executive function.

6.3 Methods

6.3.1 Participants

Eight participants (age 72y ±11.6y; 167.1cm ±6.8cm; 75.2kg ±9.4kg) were recruited from community-based stroke support groups. The information sheet and consent form for this study can be found as appendices 4b and 4c. Participant demographics can be observed in Table 6.1.

Table 6.1: Participant demographics

		n	%
Participants		8	
Age (y)		72	
Sex	Male	5	62.5
	Female	3	37.5
Descent	European	8	100
Stroke type	Ischaemia	4	50
	Haemorrhage	4	50
Side affected	Left	2	25
	Right	6	75
Family history of CVD	Myocardial infarction	5	62.5
	Heart surgery	2	25
	Stent	2	25
	Catheter	0	0
	Heart defect	0	0
	Stroke	4	50
Personal history of CVD	Hypertension	5	62.5
	High cholesterol	3	37.5
	Diabetes	0	0
	Coronary artery disease/heart failure	3	37.5
	Atrial fibrillation	5	62.5
Comorbidities	Thyroid disease	0	0
	Lung disease	0	0
	Asthma	1	12.5
	Cancer	1	12.5
	Kidney disease	0	0
	Hepatitis	1	12.5
Lifestyle factors	Current smoker	0	0
	Previous smoker	2	25
	Current alcohol drinkers	7	87.5
	Current weight loss plan	1	12.5
Everyday activity	Sedentary	0	0
	Lightly active	3	37.5
	Moderately active	5	62.5
	Vigorously active	0	0
Medication	Statins	4	50
	Anti-thrombotic	4	50
	Calcium blockers	2	25
	Alpha blockers	0	0
	Beta blockers	2	25
	ACE-I	1	12.5
	ARB	2	25

The inclusion and exclusion criteria were as follow:

Inclusion criteria

- Over the age of 50 years
- Diagnosed with stroke by a stroke consultant from a UK National Health Service Foundation Trust three months to five years before study start date
- Patients who were cognitively aware and able to provide informed consent
- Patients who were currently medically stable
- Patients who were able to complete the full range of motion in plantarflexion when seated (heel raise)

Exclusion criteria

- Unresolved deep vein thrombosis
- Dementia or an inability to provide informed consent
- Type I or II diabetes or unstable glycaemic control

6.3.2 Experimental design

Participants were fasted for twelve hours before each visit and had not undertaken strenuous exercise for 24 hours before their visits. All visits occurred between 07:30 and 09:30 in the physiology lab at the University of Winchester. Participants completed an initial familiarisation visit to the physiology laboratory where they undertook Stroop tasks and PWA/PWV measures to reduce the likelihood of a white-coat response to blood pressure measures and to reduce the learning effect of Stroop protocols (outlined in chapter five). After this familiarisation session, they were randomised into a control-first or intervention-first

condition. During each subsequent visit, two supine measures of PWA and PWV were taken using the SphygmoCor XCEL (AtCor, Sydney). If cSBP was > 5 mmHg different and AIx was > 4% different between the two measures, a third was taken (as per manufacturer guidelines outlined in previous chapters). Five Stroop tests were administered during each visit. Stroop protocols are a test of selective attention and interference susceptibility (Rasquin *et al*., 2004) and have been used widely to assess executive function and overall cognitive function after stroke (Pohjasvaara *et al*., 2002; Rand *et al*., 2010; Park *et al*., 2011). This Stroop protocol was as used in chapter five of this thesis (48 questions on a pre-programmed computer programme; 24 congruent and 24 incongruent questions). Measures of body mass, affected calf circumference and unaffected calf circumference were also noted.

In the control condition, participants continued their usual care for ten weeks before a follow-up session was conducted. In the heel raise intervention, participants completed a total of 180 heel raises each day. This volume had been demonstrated in chapter five of this thesis to have a significant acute effect on measures of peripheral and central BP. These heel raises were completed on six days per week (one day of rest to avoid dropout due to fatigue) for ten weeks. Participants completed these in sets of ten at ten-minute intervals over the course of three hours of seated time. Tick sheets were provided to allow participants to self-monitor, and participants were contacted at the half way point to ensure adherence. After one condition was completed, a two-week wash-out period took place before the second condition commenced. Washout periods are used in crossover studies to avoid carryover effects from one condition to the other (Spieth *et al*., 2016). One-week washout periods have been used in previous exercise-based crossover trials (Page *et al*., 2008; Lamina, 2010; Zeigler *et al*., 2018b) so two weeks was deemed sufficient for this study.

Ethical approval was provided by the University of Winchester Ethics Committee (BLS/17/11) and the study was registered with the clinicaltrials.gov system (NCT03423433). Informed consent was provided by all participants and the right to withdraw was always maintained.

6.3.3 Statistics

Descriptive statistics (Mean, SD) were calculated before a repeated measures analysis of variance with between- (Condition; heel raise intervention, control) and within- (Time; baseline, follow-up) subjects factors was used to identify whether a heel raise programme had a significant effect on all outcome measures. Statistical significance was be set at $P < 0.05$ using Statistical Package for Social Sciences v.22 (SPSS, Inc., Chicago, Illinois, USA). Effect sizes were calculated using partial eta squared (η_p^2) with 0.01, 0.06 and 0.14 representing small, medium and large effects (Cohen *et al*., 1969).

6.4 Results

6.4.1 Peripheral and central blood pressure, arterial stiffness

Statistical analysis for PWA and PWV is displayed in Table 6.2. No significant interaction effects were observed for any peripheral or central BP variables. Significant main effects by condition were observed for DBP, cDBP, AIx and AIx75. Baseline peripheral and central SBP in the control condition (mean 138.8 mmHg [±12.2] and 129.8 [±11.6] mmHg respectively) were noticeably different to the heel raise condition (mean 131.8 mmHg [±12.1] and 122.1 [±12.7] mmHg respectively), a demonstrable difference between the two conditions despite the

randomised crossover design. Despite the randomising of condition order, this may imply that the two-week washout was insufficient to nullify any effects of the heel raise programme which did occur. No significant main effects for any variable were observed for time. Additional pulse wave measures can be seen in the Supplementary Table (Appendix 4d).

Table 6.2: Mean (SD) central and peripheral blood pressures and arterial stiffness values pre- and post- control and heel raise intervention conditions

		Total	**Control**		**Intervention**		**Interaction**		**Condition**		**Time**	
		X	Pre-	Post-	Pre-	Post-	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
MAP (mmHg)	*X*	94.2	95.9	98.3	91.1	91.3	.12	.41	.12	.42	.46	.12
	SD	*9.4*	*7.1*	*7.2*	*10.1*	*12.1*						
SBP (mmHg)	*X*	135.8	138.8	139.9	131.8	132.9	.99	<.01	.13	.30	.51	.07
	SD	*11.8*	*12.2*	*10.2*	*12.1*	*12.8*						
DBP (mmHg)	*X*	75.4	77.1	78.9	73.4	72.3	.23	.20	**.03**	.50	.84	.01
	SD	*9.1*	*8.7*	*8*	*8.4*	*11.2*						
cSBP (mmHg)	*X*	126.3	129.8	130.4	122.1	122.9	.93	<.01	.08	.39	.65	.03
	SD	*11.9*	*11.6*	*10.9*	*12.7*	*12.1*						
cDBP (mmHg)	*X*	76.5	78.3	80.2	74.3	73.2	.27	.17	**.04**	.49	.76	.01
	SD	*9.1*	*8.6*	*7.1*	*8.9*	*11.3*						
cPP (mmHg)	*X*	49.8	51.6	50.2	47.8	49.7	.37	.12	.41	.01	.84	.01
	SD	*11.1*	*14.7*	*11.2*	*10.1*	*9.9*						
AP (mmHg)	*X*	18.7	21.5	20.5	15.3	17.3	.12	.31	**<.01**	.74	.65	.03
	SD	*7.4*	*8.1*	*7.8*	*7.4*	*5.6*						
AIx (%)	*X*	37	41.3	39.9	31.6	35.3	.26	.18	**<.01**	.76	.50	.07
	SD	*9.7*	*8.2*	*9.6*	*9.5*	*10.1*						
AIx@75 (%)	*X*	29.6	33.5	32.9	25.1	26.7	.69	.03	**.01**	.66	.76	.14
	SD	*10.8*	*9.4*	*10.5*	*10.1*	*12.4*						
HR (b·min^{-1})	*X*	59.7	57.9	60.4	61.6	58.4	.30	.21	.98	<.01	.30	.21
	SD	*6.1*	*4.8*	*5.9*	*7.9*	*5.7*						
PTT (ms)*	*X*	*46.1*	*47.5*	*41.1*	*44.8*	*52.5*	**.03**	.94	**.01**	.98	.81	.04
	SD	*7.7*	*5.8*	*7.2*	*6.5*	*8.4*						
PWV (m/s)*	*X*	*10.1*	*9.5*	*11.7*	*9.9*	*9.2*	.33	.44	.41	.36	.07	.87
	SD	*2*	*1.4*	*2.9*	*1.4*	*1.7*						

***Measures of PWV/PTT reported for three full data sets due to lack of clean pulse waves on affected side of stroke patients

Abbrevs: AIx - Augmentation index, AIx75 - Augmentation index @ 75 b·min^{-1}, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, HR – Heart rate, MAP – Mean arterial pressure, PTT – Pulse transit time, PWV – Pulse wave velocity, SBP – Systolic blood pressure

6.4.2 Body mass and circumferences

There were no significant interactions or main effects were observed for the heel raise programme vs control condition ($p > 0.05$; Table 6.3). Large non-significant interaction effects were reported for body mass (-0.7kg in heel raise programme vs +0.4kg in control) and affected calf circumference (-0.3cm in heel raise programme vs +0.1cm in control [Table 6.3]).

Table 6.3: Mean (SD) body composition variables pre- and post- control and heel raise intervention conditions

		Total	**Control**		**Intervention**		**Interaction**		**Condition**		**Time**	
		X	Pre-	Post-	Pre-	Post-	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
Body Mass (kg)	*X*	75.2	75.6	76.0	75.0	74.3	.15	.27	.17	.25	.49	.07
	SD	*9.4*	*9.8*	*10.3*	*9.9*	*9.2*						
Affected Calf Circum (cm)	*X*	34.6	34.4	34.5	34.9	34.6	.24	.19	.74	.02	.38	.11
	SD	*3.1*	*3.9*	*3.8*	*2.6*	*2.2*						
Unaffected Calf Circum (cm)	*X*	35.8	35.7	35.5	36.1	35.8	.72	.02	.61	.04	.51	.06
	SD	*3*	*4*	*3.2*	*2.6*	*2.3*						
Waist Circum (cm)	*X*	93	94.8	88.8	96	92.3	.76	.01	.52	.06	.26	.18
	SD	*17.1*	*13.6*	*24.9*	*15.9*	*14*						
Hip Circum (cm)	*X*	102.2	103.2	104.2	101.3	100.2	.43	.09	.16	.26	.97	0
	SD	*11.8*	*13.1*	*13*	*12.8*	*9.8*						

6.4.3 Cognitive performance

Table 6.4 presents Stroop data for this study. Significant interaction effects were observed for mean congruent response time ($p = 0.01$), overall mean response ($p = 0.03$) and total time ($p = 0.02$). Participants improved significantly more in the control condition than the heel raise condition, although improvements were made between first and second sessions for all variables in both conditions.

Table 6.4: Mean (SD) Stroop responses pre- and post- control and heel raise intervention conditions

		Total	Control		Intervention		Interaction		Condition		Time	
		X	Pre-	Post-	Pre-	Post-	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
Total Correct	*X*	236.6	236	236.8	236.4	237.1	1	0	.7	.02	.2	.22
	SD	*5.5*	*5.6*	*4.3*	*5.7*	*7.3*						
Mean Correct	*X*	47.3	47.2	47.4	47.3	47.4	.99	0	.71	.02	.19	.23
	SD	*1.1*	*1.1*	*.9*	*1.2*	*1.5*						
Mean Congruent (ms)	*X*	1486.7	1795.3	1337.8	1502	1311.9	**.01**	.63	.08	.37	.15	.27
	SD	*717.9*	*1058.8*	*469.8*	*787.5*	*388.4*						
Mean Incongruent (ms)	*X*	1730.7	1995.6	1710.1	1641.6	1575.6	.05	.44	**.02**	.54	.15	.27
	SD	*835.9*	*1336.3*	*763.2*	*832.3*	*641.1*						
Mean Response (ms)	*X*	1661.1	1942.3	1615.4	1606.3	1480.5	**.03**	.53	**.04**	.49	.16	.26
	SD	*790.2*	1101.8	*684.7*	*820.5*	*505.4*						
Total Time (s)	*X*	89.7	102.7	87.5	86	82.5	**.02**	.55	**.02**	.57	.14	.29
	SD	*37.6*	*51*	*33.3*	*38.9*	*27.8*						

6.5 Discussion

6.5.1 Peripheral and central blood pressures, arterial stiffness

Despite a heel raise intervention significantly mitigating increases in peripheral and central BP acutely (See chapter five), long term exposure to these exercises in a ten-week heel raise protocol yielded no significant benefits. Peripheral SBP increased by 1.1 mmHg between pre- and post- visits in both conditions (interaction $\eta^2_{p:} < 0.01$), whilst cSBP increased by 0.6 mmHg in the control condition vs 0.8 mmHg in the heel raise condition over the time-course. Increases in cPP were observed after the heel raise condition of 1.9 mmHg as opposed to a decrease of 1.4 mmHg in the control condition. Thus, in this group of chronic stroke patients, a ten-week heel raise programme to interrupt sedentary time caused no benefits in peripheral or central haemodynamics. Exercise programmes of a higher intensity in chronic stroke patients have been shown to lead to significant decreases in peripheral BP (Rimmer *et al*., 2009; Wang *et al*., 2018) but high-intensity activities are physically not an option for all stroke

survivors. It appears that heel raises are not of sufficient intensity to accrue these benefits. Although the incorporation of heel raises for stroke patients may be acutely worthwhile due to the findings in chapter five, exercises of a greater intensity must be incorporated to cause more chronic benefits. It should be noted, however, that large within-subject differences can be observed between conditions. Mean differences of 7 mmHg in SBP, 7.8 mmHg in cSBP and 10% in AIx between the pre- control and pre- intervention measures can be seen with condition main effects approaching significance for SBP and cSBP (p = 0.08 – 0.13; η_p^2 = 0.30 – 0.39). The reasons for this are unclear and, due to the small sample size of this pilot study, make strong conclusions difficult to draw.

6.5.2 Body mass and circumferences

This pilot study found no significant condition by time interaction effects for any body mass or body circumference measures. However, an increase of 0.4kg was observed in body mass after the control condition versus a decrease of 0.7kg after the experimental condition. Although this does not reach significance, a large effect size was reported of (η_p^2 = 0.27). This may have been due to differing levels of physical activity outside of the intervention. In future work investigating these parameters and lower intensity movements, an objective measure of physical activity would be advised.

As there were no significant interaction effects were observed for affected and unaffected calf circumferences, this study suggests that improvements in key body composition measures are not accrued from a ten-week heel raise regimen.

6.5.3 Cognitive performance

This study demonstrated significant interaction effects for mean congruent response times, mean response time and total time, with greater improvements made in the control condition than the intervention condition. It is worth noting, however, that mean incongruent, mean response and total time scores were significantly better in the intervention condition (across both visits) than the control condition ($p < 0.05$). This may imply that the pre- control figures were anomalously poor in the pre- control session compared to all other timepoints. Follow-up studies with larger sample sizes to build on the findings of this pilot study will allow confirmation of whether reducing extended bouts of sedentary time over a longer time-period leads to improvements in cognitive functioning.

6.5.4 Strengths and limitations

It is important for studies to acknowledge strengths and weaknesses to allow appropriate interpretation of results. This study was designed to be a pilot study leading into future work and, as such, offers a low sample size. The purpose of this pilot study was to demonstrate potential trends, but results should be taken with caution. Participants were, however, well age-matched to the average age of first stroke (average age of 72y in this study vs. average first stroke at 73y in females and 68y in males [Public Health England, 2018b]) As with any prescribed programme, confirming adherence can be problematic. Brown and Bussell (2011) report that up to half of all patients with chronic disease do not take their medication as prescribed. If patients are unable to adhere to prescribed medications, the likelihood of their keeping to programmes requiring more physical effort could be questioned. To counter this, self-monitoring sheets were provided to participants in this study to aid with tracking

progress. Participants were also contacted at the half-way stage (five weeks) to verbally confirm they were continuing the heel raises.

The data collection sessions in this study had high control. Participants attended in a narrow time-window (07:30 – 09:30) and were explicitly asked to attend in a fasted state after drinking only water and having prescribed medications before attending. Participants had also abstained from any exercise for 24 hours before their sessions.

6.5.5 Study processes

A pilot study focuses on the processes of a potential main study, including ensuring recruitment, randomisation, and follow-up assessments run smoothly (National Institute for Health Research [online]). This study was classed as an internal pilot study as key outcomes of interest (i.e. SBP, cSBP, AIx, AIx75, executive function) were assessed, with the intention of continuing data collection to a greater degree to establish a well-powered study. Randomisation and follow-up assessments ran smoothly, but recruitment was slow for this study. Although this was executed as a pilot study, some aspects of a feasibility study have also been addressed. Recruitment was slow to this study, which is unsurprising bearing in mind that fewer than half of all stroke research studies recruit their target sample size (Berge *et al*., 2016). Once recruited, however, only one participant out of the nine originally recruited failed to complete the study (due to reported time demands). Adherence to any prescribed intervention is difficult to confirm through self-report measures, but participants were provided with tick-sheets to aid adherence and were contacted halfway through the ten--week intervention period to discuss any difficulties (none were noted except for one dropout). Some participants reported negative preconceptions as to whether they would be able to complete a high number of heel-raises each day due to fatigue, but after beginning the interventions, the acceptability of the intervention was high, with fatigue less of an issue than expected.

6.5.6 Future sample size calculations

It is of great importance for research studies to be adequately powered. Statistical power is defined as the probability of detecting as statistically significant a clinically or practically important difference of a pre-specified size, if such a difference truly exists (Batterham & Atkinson, 2005). The effect sizes recorded in this pilot study, combined with error calculations from this thesis, can be used to determine the adequate sample size for future work using the SphygmoCor XCEL for interventional studies of this nature.

Based on an SEM of 5.8 mmHg (chapter three of this thesis, a subsequent SD of changes (SDchange = SEM * √2) of 8.2 mmHg, and a minimal clinically important change in BP of 4 mmHg (Stuckey, Gill & Petrella, 2015), a sample size of 28 participants would be required to achieve statistical power of 0.8 in future studies of this nature with an effect size of 0.49. A 10% dropout rate was recorded in this pilot study, demonstrating that the heel-raises were of an appropriate intensity to allow stroke participants to complete the prescribed course of physical activity. This 10% dropout rate suggests that investigators running a full study based on this protocol should aim to recruit around 31 participants.

6.6 Conclusion

This pilot study demonstrated that interrupting sedentary time with heel raises daily over a time period of ten weeks may not elicit significant benefits in peripheral and central haemodynamics, or cognitive function. It is important for future work to determine what the minimum intensity of movement is to elicit such benefits and ensure that the burden of recurrent stroke due to increased sedentary time after stroke is minimised.

Chapter 7: Discussion

The purpose of this thesis was to investigate the use of non-invasive oscillometric measures of cBP in non-clinical and stroke populations. It was initially important to evaluate the reliability of the SphygmoCor XCEL in recording measures of central haemodynamics in populations where these variables are of the utmost importance. Once this had taken place, the thesis focused on sedentary time – one of the primary areas of current research in chronic stroke. The acute and chronic effects of interrupting extended seated time with intermittent heel raises was investigated, with acute benefits noted, but chronic benefits not observed.

7.1. The reliability of the SphygmoCor XCEL

When assessing central haemodynamics and variables representing arterial stiffness, it is imperative that measures are both valid and reliable for results to be credible. Validity refers to how well a tool measures an underlying outcome (Sullivan, 2011) and essentially refers to the accuracy of a device. Reliability refers to the reproducibility of values of a test in repeated trials on the same individuals (Hopkins, 2000) and this reliability of measurements is key knowledge to allow practitioners to decide whether measurements are of value (Koo & Li, 2016).

Intraclass correlation coefficients have been used to classify between-day reliability with ICCs of > 0.75 representing excellent reliability. Young and colleagues (2015) investigated the reliability of the SphygmoCor XCEL in a young, healthy population (28y, 24kg·m^2) and reported excellent between-day reliability with ICCs of 0.76 – 0.90 for pSBP, 0.73 – 0.89 for cSBP, 0.71 – 0.82 for AIx and 0.75 – 0.84 for AIx75 in different postures and fasting states. Similar findings were reported in work by Stoner *et al* (2015) who also recruited a young, healthy population

(26y, 24.7kg·m^2) and examined the reliability of this device at rest and in response to an orthostatic challenge. Excellent ICCs were reported for pSBP (0.75 – 0.84), cSBP (0.80 – 0.87), AIx (0.79 – 0.82) and AIx75 (0.81 – 0.88) in supine and tilted positions. As such, the SphygmoCor XCEL clearly possesses strong between-day reliability in younger, non-clinical populations. However, measures of central haemodynamics and arterial stiffness are particularly relevant to the population over the age of 50 years, as stroke risk more than doubles in each successive decade over the age of 55 (Wolf *et al*., 1992; Brown *et al*., 1996). Accordingly, Chapter three and chapter four assessed the reliability of the SphygmoCor XCEL, firstly with an older, healthy population, and then with individuals who had recently been diagnosed with stroke and were inpatients in a hype-acute stroke unit.

In this thesis, strong ICCs (> 0.75) were presented for healthy older individuals (normotensive and hypertensive) and individuals diagnosed with stroke. This was evident for peripheral and central BP, and for measures of arterial stiffness (AIx, AIx75). A comparison of ICCs across populations from chapters three and four can be seen in Table 7.1 with previous data from a young, healthy population as points of comparison (Young *et al*., 2015).

Table 7.1: ICCs of key variables in different postures and fasting states (seated/supine, fasted/non-fasted [Young *et al*. 2015; chapters three and four {Excellent reliability = ICC ≥ 0.75}])

	Healthy younger population (Young *et al*., 2015)	Healthy older population (whole)	Healthy older population (normotensive)	Healthy older population (hypertensive)	Acute stroke population
SBP	0.76 – 0.90	0.90 – 0.92	0.51 – 0.76	0.82 – 0.87	0.83 – 0.85
cSBP	0.73 – 0.89	0.89 – 0.92	0.58 – 0.77	0.85 – 0.88	0.81 – 0.85
cPP	0.61 – 0.84	0.83 – 0.86	0.76 – 0.78	0.79 – 0.84	0.79 – 0.88
AIx	0.71 – 0.82	0.77 – 0.85	0.77 – 0.86	0.73 – 0.87	0.66 – 0.81
AIx75	0.75 – 0.84	0.75 – 0.87	0.76 – 0.86	0.74 – 0.88	0.70 – 0.81

Abbrevs: AIx – Augmentation index, AIx75, Augmentation index @75b·min^{-1}, cSBP – Central systolic blood pressure, cPP – Central pulse pressure, SBP – Systolic blood pressure

Chapters three and four of this thesis demonstrate that non-invasive measures of cBP can be assessed as reliably as peripheral BP. Central blood pressures have been reported to be more relevant to the workload of the ventricles and coronary arteries (Croymans *et al*., 2014; Burns *et al*., 2018) and make an additional contribution to the prediction of cardiovascular outcomes, above and beyond peripheral blood pressure (Cheng *et al*., 2013). This work builds on previous literature in younger populations (Stoner *et al*., 2015; Young *et al*., 2015) to suggest that the SphygmoCor XCEL is reliable in a range of populations. When combined with strong validity results from previous work (Butlin *et al*., 2012; Hwang *et al*., 2014), the evidence from this thesis is the first to suggest that the SphygmoCor XCEL is a suitable tool for assessing central haemodynamics and measures of arterial stiffness in both research and clinical practices, including stroke. If, as these chapters suggest, central measures can be assessed as reliably as peripheral measures in older and clinical groups, the process of incorporating these central measures into clinical practice becomes of even greater

importance. The cost of these devices currently limits the availability of non-invasive measures of central haemodynamics in non-private clinical environments. As a result, collaborations between researchers and clinicans are particular great importance to introduce this technology as a diagnostic tool in the hospital setting.

7.2 The effect of posture and fasting state on peripheral and central haemodynamics and arterial stiffness

Blood pressure in humans is influenced by a wide range of factors, one of which is posture (Sala *et al*., 2006) and, as such, it is important to consider what posture is adopted when trying to accurately measure blood pressure (Cavelaars *et al*., 2004). For example, measures in a GP surgery may tend to take place in a seated posture, whereas inpatient settings are more likely to involve a supine posture, particularly early in the morning. The influence that posture has on blood pressure is dependent on the amount of time after a postural change has taken place. Research from Eser and colleagues (2006) reported significantly higher brachial blood pressure in a supine position compared to stood, seated and seated with legs crossed postures after one minute of time in each posture. Similar results were found by Cicolini *et al*. (2011), who incorporated a five-minute timeframe in sitting and supine postures and found significantly lower brachial blood pressure in a seated position compared to supine. After rest periods of 15 minutes in seated and supine postures, however, Young and colleagues (2015) found significantly increased SBP and cSBP in the seated posture. This highlights the importance of allowing blood pressure to normalise before measures are taken.

In the studies conducted during this thesis, posture had no significant effect on SBP or cSBP in the overall non-clinical cohort over the age of 50. Once this sample had been split into

normotensive and hypertensive groups, some differences did become apparent. Whilst changes in posture caused no difference in SBP or cSBP in the normotensive group, hypertensives showed an increased response compared to normotensivse (1.5 mmHg increase in SBP when seated, 2.5 mmHg increase in cSBP when seated). Although statistical significance was not demonstrated (p = .06 – .09), moderate to large effect sizes (η_p^2 = 0.12 – 0.13) were observed, suggesting a possible link between posture and SBP in the hypertensive population.

Measures of DBP were, on average, ~2.5 mmHg higher in a seated posture compared to supine (a significant interaction effect of posture and fasting state), in agreement with work by Netea *et al*. (1998) and Young *et al*. (2015). These results mirror Cicolini's findings (2011) who found increases of 2 mmHg in the seated posture compared to supine. In the acute stroke population, posture had asimilar effect on peripheral and central BP. Significant increases with a large effect size in DBP and cDBP were observed in the seated posture versus supine with an average difference of ~3 mmHg between the two postures. Increases in DBP from supine to standing postures have been previously observed due to excessive orthostatic pooling causing decreases in cardiac output and subsequent arteriolar constriction (Sparrow *et al*., 1984). When looking at the first two research studies in this thesis, posture clearly has a moderate impact on both peripheral and central BP readings. Blood pressures are assessed in a range of postures in GP surgeries and hospital environments depending on patient preference, clinician preference, and individual circumstance. An awareness of the changes caused by postural change is important to ensure accurate interpretation of these results, which medical decisions are frequently at least partially based upon.

Posture and fasting state had a large, significant interaction effect on AIx for the population of over 50s as a whole and the hypertensive group, with this measure of arterial stiffness lower in a seated posture than supine. This finding was mirrored in the population of acute stroke patients, suggesting an increase in elasticity of small arteries and arterioles. This finding is in opposition to previous work using a young, healthy population (Young *et al*., 2015) who reported no significant effect of posture on AIx. This suggests that the vascular reactions to postural changes in older age groups are more sensitive than in younger individuals; potentially reflecting less stability in vascular control. Age leads to the loss of arterial elasticity and a subsequent reduction in arterial compliance (Jani & Rajkumar, 2006). Age-related losses in vascular function and blood vessel tone (including vasodilation capacity) due to a lack of nitric oxide bioavailability may lead to less consistent and efficient responses to food consumption, resulting in these increased responses.

The first two studies of this thesis also report posture to have a moderate-to-large effect on cPP. Both peripheral (Takahashi *et al*., 2018) and central (Shoji *et al*., 2016) PP may be superior to SBP in predicting cardiovascular risk as PP are associated with increased arterial stiffness, causing pressure overload on the heart (Boutouyrie *et al*., 1995). Significant increases in cPP in a supine posture compared to a seated posture were observed in the overall non-clinical sample in the first study of this thesis and for both blood pressure classification groups. In the acute stroke population, figures approaching significance were reached (p = 0.06) with an increase in cPP was observed in the supine condition with a large effect size (η_p^2 = 0.16); suggesting that a relationship may exist between posture and cPP that could be significant with a larger sample size (and subsequently more statistical power). These findings agree with previous work from Vrachatis and colleagues (2014) who found significant increases in

cPP in a supine posture in a sample group with an average age of 50 years. Young *et al*. (2015), however, reported no significant differences in cPP between postures in a sample with an average age of 28 years. Again, when pulse pressures used as a diagnostic tool after blood pressure is assessed in multiple postures based on the previously mentioned criteria, an awareness of the impact of posture on these measures should be ensured in clinicians. The strength of the link between cPP post- stroke and long-term outcomes compared to traditional BP measures is an area of research which should be addressed in the future.

There is limited literature investigating vascular responses to changes in fasting state, meaning comparative data is in short supply. In the short-term, 48-hour fasting has been linked to significant decreases in blood pressure (Eser *et al*., 2007). Longer-term fasting (specifically intermittent fasting) has been shown to significantly decreased body mass over twelve weeks (Varady *et al*, 2013) and, in turn, systematic reviews have linked these decreases in body mass with lower blood pressure (Aucott *et al*., 2009). However, the acute effects of food intake on peripheral and central measures have not been widely investigated. Literature from Young and colleagues (2015) found food intake to have no significant effect on SBP or cSBP, but to cause significant decreases in AIx and AIx75 (drops of ~4.5% after consumption). In contrast, research from Ahuja *et al*. (2009) reported significant drops in non-invasively measured cSBP of 7% after food and water intake; concluding that central measures were more sensitive to food consumption than peripheral measures. This may have been due to sudden reductions in arterial stiffness in the splanchnic bed in response to nutrient delivery leading to smooth muscle relaxation.

Fasting state was found to influence measures of blood pressure and arterial stiffness in the research studies conducted in this thesis. No significant difference was found for SBP in the

overall sample of the healthy population study. However, a large, significant main effect was found for cSBP with food intake leading to an average 2 mmHg decrease in the healthy sample as a whole. The acute stroke sample reported drastic effects of food intake on peripheral and central measures. Significant decreases in SBP (~9.5 mmHg) and cSBP (~12 mmHg) were observed after food consumption, representing a ~9% drop in cSBP – similar to the 7% reported by Ahuja and colleagues (2009). Consuming a meal may influence the tone of small vessels and large artery function (Young *et al*., 2015) due to nutrient delivery leading to smooth muscle relaxation, culminating in changes to peripheral and central BP. Smaller changes due to prandial state in central pressures were noted in a supine position. This may be due to gravity causing a slightly greater speed of early-stage digestion when seated. Posture has been found to have an effect on digestion speed, with studies as dated as early as 1918 reporting accelerated barium emptying when supine on the right side compared to other postures (Queckenberg & Fuhr, 2008). Gastric emptying (in the later stages of digestion) is delayed in the supine posture (Moore *et al*., 1988; Asado *et al*., 1989; Spiegel *et al*. 2000). This may translate to the earlier stages of digestion, which would explain the more stable results found in the supine posture immediately post- food consumption. It may therefore be optimal to measure blood pressure in a supine state to minimise the influence that fasting state has on these variables.

The findings that post-prandial decreases in cSBP were greater in the stroke population than the healthy population over 50 years in age, which were greater than the changes observed in a young healthy population (Young *et* al., 2015), may indicate impaired vascular responses to food consumption. In a healthy individual, post-prandial vasoconstriction would be expected to occur to maintain a stable BP. In an older population, these responses may be

blunted, and in a stroke population, baroreceptor sensitivity may be severely impaired. This impairment would lead to sub-optimal maintenance of BP.

The elevated response of cSBP compared to SBP after food consumption is also an example of how peripheral and central measures should not be assumed to react in the same way to changeable variables. McEniery and colleagues (2014) report that cBP may respond differently to medications than peripheral blood pressures, so peripheral measures are not necessarily an appropriate surrogate for measuring the effects of medication on the central arteries (Williams *et al*., 2006). This also seems to be the case for alterations such as change of fasting state, with minimal changes observed in SBP but large decreases reported in cSBP.

This thesis has demonstrated that fasting state has a large effect on the peripheral and central vasculature through non-invasive oscillometric measures of central haemodynamics. Uncontrolled blood pressure leading to hypertension is the largest risk factor for premature mortality worldwide (Lim *et al*., 2012) and control of blood pressure begins with accurate measurements leading to appropriate diagnoses and treatment decisions (Jones *et al*., 2003). The results of these studies demonstrate the necessity for the general public, researchers and clinicians to understand the importance of standardising blood pressure measuring protocols at home and in clinical environments.

7.3 Breaking up sedentary time with intermittent heel raises

Despite encouraging findings regarding the acute effect of intermittent heel raises on peripheral and central haemodynamics in breaking up sedentary time after stroke, there was no chronic benefit to these parameters after a prolonged, ten-week intervention.

In the acute heel raise study (chapter five), intermittent heel raises significantly mitigated the rises in SBP and cSBP observed between ten-minute and three-hour time points. During the control (sedentary) visit, increases were observed of 10.7 mmHg (+ 8.2%) in SBP, 9.6 mmHg (+ 7.9%) cSBP and 555 in double product (DP [HR x SBP], + 7.8%). Heel raises significantly mitigated this damage to vascular health, with increases of 5.2 mmHg (+ 4%) in SBP and 5.6 mmHg (+ 4.6%) in cSBP over the three-hour time course. The observed increase in DP during the control period was completely negated by the heel raise protocol, with a decrease of 162 (HR x SBP, - 2.2%). As DP has been significantly associated with mortality over a 12-year follow up in a sample of over 2,500 participants (Inoue *et al*., 2012), this is a finding of particular interest.

This study reported that SBP increased by 5.5 mmHg less during the heel raise condition than the seated condition. These findings can be directly contrasted with work by English and colleagues (2018) who incorporated an eight-hour seated period with light-intensity bouts of stood exercise every 30 minutes (marching on spot, small amplitude squats, calf raises). English *et al*. reported decreases of 3.5 mmHg in the standing-exercise condition compared to a seated condition. The greater decreases in SBP in this study may highlight the importance of continually interrupting seated time. Although the exercises in the study by English *et al*. were of a higher intensity, the lower-intensity exercise implemented more frequently in this thesis led to greater reductions in blood pressure. The heel raises integrated into this thesis also offer benefit to those stroke survivors who are unable to engage in activities while standing due to difficulties completing sit-stand transitions.

Even though heel raises significantly mitigated raises in SBP and cSBP, there was a significant main effect of time on these variables, suggesting that even with intermittent activity,

vascular damage takes place in just three hours of sedentary time. Heel raises only mitigate this damage; they do not prevent it completely. No other research found during the literature review of this thesis has found work investigating the effects of sedentary time on central haemodynamics.

The precise mechanisms leading sedentary time to have a negative effect on health are not fully understood (English *et al*., 2018) but this thesis demonstrates that acute increases in blood pressure at the central organs may be a large contributor to this damage. Chapter five of this study demonstrates that the damage caused by sedentary time extends to the central arteries, not purely the periphery as has been demonstrated previously.

However, the mitigation in blood pressure increases throughout the sedentary time did not translate into improved executive function. Previous work has found conflicting results, with some work reporting improvements in executive function (specifically processing speed and incongruent trials of the Stroop protocol) after 30 minutes of stair-climbing exercise (Tam, 2013). Other research suggests that single bouts of aerobic exercise (of greater intensity than was studied here) have no effect on executive function in Stroop performance (Vincent & Hall, 2017). It may be the case that the heel raises implemented here simply were not of a great enough intensity to elicit benefits leading to improved executive functioning. Hypoxia has been directly linked to reduced executive functioning (specifically, Stroop performance [Genta *et al*., 2018]), so stimulating skeletal muscle and consequently increased levels of O_2 circulating to the periphery (and brain) may have the potential to improve executive function. Longer term exercise interventions may improve executive function (Predovan *et al*., 2012), but these gains were not observed in this acute environment.

The natural progression of this research was to see if the acute improvements in SBP and cSBP translated into more chronic benefits. As a result, chapter six involved a pilot study to investigate potential benefits of a ten-week period of breaking up sedentary time each day through an identical number of heel-raises as were shown to acutely benefit central haemodynamics in chapter five. This pilot study concluded that the improvements demonstrated in chapter five did not translate into more chronic benefits with no improvements observed in any peripheral or central haemodynamic variable, or in any measures of arterial stiffness.

Sedentary behaviour refers to activities not increasing energy expenditure substantially above resting levels and includes activities like sleeping, sitting, lying down and watching television (Pate et al., 2008). The link between this sedentary time and stroke is well established, with sedentary individuals 25 – 30% more likely to have a stroke than their less sedentary peers (Goldstein *et al*., 2011). After stroke has occurred, excessive time is spent sedentary as in-patients (Mattlage *et al*., 2015; Barrett *et al*., 2018), with one study of 104 hospital-based stroke rehabilitation patients finding 74% of the observed day to be spent sedentary (Sjoholm *et al*., 2014). After discharge, these sedentary behaviours tend to continue, with survivors extremely sedentary during a year of follow-up after leaving hospital (Tieges *et al*., 2015). This sedentary time tends to take place in longer bouts after stroke than sedentary time does in the general population (English *et al*., 2018), with this prolonged sitting particularly bad for an individual's health (Dunstan *et al*., 2012). Traditionally, research has traditionally focused on the higher end of the activity intensity spectrum, but an equal amount of research should be focused on the lower end of this spectrum (Pate, O'Neill & Lobelo, 2008). English and colleagues (2016) note that research is necessary to investigate

whether light intensity activities are beneficial when breaking up sedentary time after stroke and this is the research gap which the latter part of this thesis aimed to investigate.

7.4 Real-world thesis relevance

Measures of cBP and arterial stiffness are likely to become commonplace in clinical settings in the future as the cost of the devices capable of measuring these begins to decrease. Central blood pressure may be more relevant to the workload of the ventricles and coronary arteries (Croymans *et al*., 2014; Burns *et al*., 2018) and purely measuring peripheral blood pressure neglects valuable information (Williams *et al*., 2006). It is therefore a huge step forward in medical care for cuffs able to non-invasively estimate cBP in clinical settings.

This thesis contains work which demonstrates for the first time that the SphygmoCor XCEL can reliably assess central haemodynamics and measures of arterial stiffness in populations who are more likely to have vascular impairments (i.e. those over 50 years of age, acute stroke patients). This is a major step towards incorporating the SphgmoCor XCEL into clinical use for diagnostic and prognostic purposes.

The first two studies of this thesis also demonstrate the importance of standardising posture and, in particular, fasting state when assessing peripheral BP and cBP. After comparison with previous work, these results suggest that this standardisation of procedure is particularly important in an older and clinical population. The assessment of cBP is particularly relevant in these higher-risk populations, so an awareness of how unstable BP responses to food are is key. Nurses and clinicians should, as a minimum, be noting the posture of stroke patients and time since last meal when adding to hospital notes. If standardising posture is a realistic option, this should take place in a supine position as this minimises the changes caused by

prandial state and has previously been suggested to maximise the reliability of the SphygmoCor XCEL (Young *et al*., 2015).

It is widely accepted that stroke causes individuals to be less physically active and to live more sedentary lifestyles, with these periods of sedentary time being longer in duration than in healthy individuals. This thesis contains work which may be the first to demonstrate that just three hours of sedentary time causes significant increases in peripheral BP and cBP. Increases in cBP have been strongly suggested to increase the risk of a wide range of clinical conditions including stroke. As a result, these increases in BP may provide a causal explanation for the link between sedentary time and stroke incidence. This thesis demonstrates that breaking up sedentary time using low-intensity activities (such as heel raises) has the potential to mitigate the damaged caused by this lack of physical movement. After stroke, patients are extremely sedentary as in-patients and as these behaviours translate into lifestyle habits after hospital discharge. Chapter five of this thesis provides evidence that this is specifically damaging to BP, a major risk factor of morbidity and mortality in the months and years following stroke. Evidence is provided here that instructions to in-patients to keep moving, even in a hospital bed, may be beneficial to recovery. Although acute benefits have been observed as a result of intermittent heel raises, chronic improvements were not reported over a ten-week period. This suggests that to attain longer-term benefits, exercise programmes may need to be of a greater intensity than prescribed in chapter six of this thesis.

7.5 Strengths and limitations of this thesis

The studies compiled in this thesis provide novel information about the use of the SphygmoCor XCEL, the variables assessed by this device, and the effect of sedentary time on

these measures of central haemodynamics in participant demographics where these variables are particularly relevant.

Throughout this thesis, all possible measures were taken to ensure accurate and reliable results. There was extremely high control throughout the data collection sessions of these studies. All studies were conducted in the same physiology laboratory (chapters three, five and six) or in a hyper-acute stroke ward (chapter four) at the same time of day (beginning 07:30 – 08:30), in fasted conditions with the same practitioner recording data. This minimised the effect of extraneous variables on the independent variables being examined and strengthened these studies greatly.

Chapters three and four of this thesis investigated the effect of posture on a variety of peripheral and central haemodynamic variables using mixed-sex samples. Previous work has reported that responses of peripheral blood pressure to postural changes between sexes may differ (Gerber *et al*., 2015), with DBP reported to rise significantly in a standing position versus supine in males, but not in females. Future work involving a similar protocol should recruit a unisex sample to check for sex-related differences in central haemodynamic responses to postural change.

Difficulties recruiting from stroke populations were encountered during this doctoral research. Fewer than half of all stroke trials recruit their target sample size (Berge *et al*., 2016). The recruitment triangle outlined by Gorelick *et al*. (1998) consists of involving the patients themselves, key family members and friends, and the primary doctors and other medical personnel. Throughout this thesis, each of these corners of the triangle were addressed during recruitment. Acute stroke patients were visited in person during visiting hours, when family and friends were frequently present. A rapport was built with these individuals to

maximise the likelihood of recruitment. Positive relationships were also fostered with the clinicians and nursing staff on the ward to allow for a seamless process where possible. The seven key issues causing poor recruitment in stroke research reported by Alexandrov (2006) are as competing trials, slow start (insufficient site recruitment, unforeseen obstacles, etc.), complex protocols, trial fatigue by investigators, patients not willing to participate, excessive (though necessary or often unavoidable) and lengthy regulatory work, and regulatory issues with drugs and devices, their combinations, and evolving technologies

These were all considered throughout the research process, with competing trials and unforeseen obstacles (a lack of patients meeting the inclusion criteria) the primary limiting factors to recruitment. Due to the study taking place around breakfast times, the presence of diabetes mellitus was added as an exclusion criterion. This proved to be a common condition which restricted participants from qualifying for the study, even though breakfast times were not manipulated at any time in this work.

Chapter six of this thesis involved a ten-week heel raise programme. Whilst participants were contacted at the half-way mark to check for adherence to this programme, they were not physically monitored on a day-to-day basis for practical reasons. Low adherence to anti-hypertensive therapy is a major contributor to low blood pressure control (Peck, 2018). If patients are reportedly struggling to adhere to something as physically easy as taking medications, it is plausible that they are not adhering to interventions that require more effort, such as heel raises over a course of ten weeks. The studies also required patients to attend sessions in a fasted state, without having consumed caffeine or having completed any exercise. This was purely based on self-report and a reliance on the participants. In future work, resting blood glucose measures will be taken to ensure participants are in a fasted state.

All participants who completed these studies reported that they had adhered to all that was requested.

Overall, the studies in this thesis provide novel findings in relation to the non-invasive assessment of central haemodynamics in healthy individuals and stroke patients. These studies were conducted in highly controlled environments and contribute useful data as cBP assessment moves towards becoming common practice in research and clinical environments.

7.6 Future research

Longitudinal studies have demonstrated that central haemodynamic indexes are independent predictors of future cardiovascular events and all-cause mortality (Vlachopoulos *et al*., 2010). As a result, the assessment of cBP is likely to become more common in daily practice (Bulas *et al*., 2017). In the past decades, stroke incidence has remained fairly stable, but a remarkable increase in the number of stroke survivors has been observed (Wijkman, 2018). The hyper-acute treatment of stroke has clearly improved greatly, but as a result, the overall burden of stoke has increased. Therefore, a key focus in future research must be determining the optimal methods of managing risk factors of recurrent stroke. Treating elevated BP may be the most important intervention when preventing second strokes (Kernan *et al*., 2014) and if cBP are as superior as the data would suggest, a focus on cBP after stroke is imperative in the immediate and future literature.

The current cost of non-invasive estimation of central haemodynamics through oscillometric methods vastly exceeds brachial measures, with the SphygmoCor XCEL costing approximately £19,400 and the Vicorder (another device offering measures of similar parameters) retailing

at approximately £15,000. Conversely, Omron brachial cuffs vary from around £39.39 ($49.99) to around £86 ($109.99 [Omron Online, 2019]). The potential use of non-invasive cBP monitoring opens up a variety of avenues of investigation. However, this disparity in price means that a large number of questions must be answered in the research setting before these devices can be utilised in a clinical environment.

Firstly, data is needed to determine whether central haemodynamic measures are significantly better than traditional BP measures in predicting short- and long-term outcomes after stroke has occurred. If they are, it becomes imperative to identify optimal cBP targets in the hours, days and weeks after stroke has occurred. The focus on BP targets for stroke has been identified as a critical global need (Feigin *et al*., 2017), and the identification of cBP targets may be even more critical as it is the central arteries that supply the brain, not the brachial artery. This focus links in with optimising lowering BP strategies after stroke to determine whether aggressive or cautious approaches are optimal. A collection of longitudinal data is required which collects cBP, AIx and PWV at regular time-points post-stroke whilst collecting data for a variety of endpoints (e.g. mortality, recurrent stroke).

Secondly, the relevance of central BP variability after stroke must be examined. Brachial BP variability in the 24 hours after stroke has been associated with a higher risk of death within 90 days (de Havenon *et al*., 2019). This is due to the fact that increased arterial stiffness due to hypertension and ageing amplifying random BP changes and consequently increasing BP variability (Yang *et al*., 2018). Whether similar or magnified results are observed when monitoring central pressures is an interesting area of future investigation.

A third area of research to be undertaken relates to circadian rhythms. Circadian rhythms relating to peripheral BP are well established, with a 10-20% decrease in SBP observed

nocturnally (Rodrigues *et al*., 2018). Those who categorise as non-dippers (nocturnal SBP decrease < 10%) or as extreme dippers (nocturnal SBP decrease >20%) are well recognised to be at elevated risk of cardiovascular disease and premature mortality. Nocturnal BP and BP variability may even be more closely associated with target-organ damage than awake BP and awake BP variability (Boggia *et al.*, 2007; Palatini *et al*., 2014). Ambulatory monitoring of cBP would allow researchers to determine whether the nocturnal response of cBP is comparatively muted or exaggerated, with further longitudinal data demonstrating the use of circadian rhythm assessments involving cBP.

Fourthly, investigations into sedentary time after stroke (for example the sixth chapter of this thesis) could be improved through the collection of a wider range of variables. For example, this thesis focused on central haemodynamics and executive function over a period of sedentary time. The use of near infra-red spectroscopy would allow the monitoring of cerebral perfusion throughout a sedentary time-course. Reduced cerebral perfusion in the frontal gyrus has been linked to impaired attention and cognition (Craggs *et al*., 2014) and the assessment of this variable alongside executive functioning tasks and BP measures may provide a causative link between BP measures and cognitive performance.

Chapter 8: Summary and conclusions

This thesis initially aimed to ascertain the reliability of the SphygmoCor XCEL and examine the effect of posture and fasting state on peripheral and central haemodynamics, and measures of arterial stiffness. Previous literature had investigated young, healthy populations but there was a lack of research involving older and clinical populations, where blood pressure is particularly important. The SphygmoCor XCEL was demonstrated to have generally excellent reliability in a population over the age of 50 and in an acute stroke population (mean age = 57y). Fasting state in particular was demonstrated to have a large effect on cBP and measures of arterial stiffness, with significant decreases seen after food consumption in healthy and stroke populations. Central blood pressure was more sensitive to fasting state than peripheral blood pressure and stroke patients reported greater changes in haemodynamics than their non-clinical counterparts. As blood pressure is assessed in a range of postures and fasting states at home and in clinical settings and cBP may be the future of cardiovascular risk management, these findings have importance to patients and clinicians alike.

This thesis also investigated the effect of sedentary time on central haemodynamics – an avenue of research which was not found to have been addressed in the literature review conducted for this doctoral paper. The effect of breaking up sedentary time with intermittent light activities is a necessary avenue of research, particularly in stroke rehabilitation. Stroke survivors are sedentary as inpatients and continue these sedentary behaviours long into their recovery. These behaviours may be perceived as a restful recovery but are damaging to long term prognoses. Whilst many stroke survivors are not physically able to undertake high-intensity exercise programmes to benefit their health, identifying lower-intensity activities which are able to break up extended sedentary time has the potential to improve health in

the long term. Peripheral and central BP increased significantly due to three hours of sedentary time, with intermittent heel raises significantly mitigating this damage (but not eliminating it), and significantly reducing double product (HR * SBP). The general population and clinicians should be aware of how quickly peripheral and central pressures begin to rise during sedentary time. Stroke patients should be staying active with simple movements from their bed or seat throughout the day to prevent the rises in blood pressure which may increase the risk of recurrent events.

Although the acute benefits of heel raises were demonstrated, there was no effect of long-term exposure. Although this pilot study only offers tentative conclusions due to the low sample size, it seems likely that heel raises are not of the intensity required to elicit improvements after a prescribed programme. Future work should endeavour to find lower intensity movements that the majority of stroke survivors are able to complete that may break up sedentary time and lead to some of the physiological improvements caused by higher-intensity exercise.

This thesis has furthered our knowledge and understanding surrounding the assessment of cBP in individuals with stroke, and the consequences of sedentary time on these measures. Non-invasive measures of central haemodynamics have the potential to be an integral part of recurrent stroke risk reduction and research into their prognostic value in stroke must be taken through its infancy. As the acute clinical treatment of stroke continues to improve, control of risk factors through lifestyle changes also grows in importance. Identifying methods to reduce these lifestyle factors, including reducing sedentary time, may be the cornerstone of reducing the overall burden of stroke in years to come.

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Appendices

Appendix 1a: Reliability of oscillometric central blood pressure and central systolic loading in individuals over 50 years: Effect of posture and fasting – Atherosclerosis publication

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Reliability of oscillometric central blood pressure and central systolic loading in individuals over 50 years: Effects of posture and fasting

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ABSTRACT

Background and aims: The between-day reliability of oscillometric pulse wave analysis has been demonstrated in a young, healthy population but not in an older sample. This study examined the between-day reliability of the SphygmoCor XCEL in individuals over 50 years. As blood pressure is measured in a range of postures and fasting states (supine/seated, fasted/non-fasted), this study also investigated the effect of these variables on central blood pressure and central systolic loading.
Methods: Fifty-one adults (m = 21; age 57 ± 6.4 y) were tested on three mornings in supine and seated conditions and in fasted and non-fasted states. Data was analysed as a whole and for normotensive (n = 25) and hypertensive participants (n = 26).
Results: SphygmoCor XCEL demonstrated strong reliability in the whole sample for central systolic and diastolic blood pressures, augmentation index (AIx) and AIx75 (ICC = 0.77–0.95). Significant interaction effects were observed in central diastolic blood pressure, central pulse pressure, augmentation index (AIx) and AIx75 ($p < 0.05$; $\eta_p^2 = 0.10–0.23$). Fasting state had a greater influence on central pressures in a seated than supine posture, but a greater effect on central systolic loading measures in a supine posture.
Conclusions: The SphygmoCor XCEL is a reliable tool to assess central haemodynamic variables in an older population. It would be pertinent for clinicians and researchers to record central measures in a supine posture to minimise the effects of food consumption. Conversely, the assessment of central systolic loading should occur in a seated condition to minimise the influence of varying fasting states.

1. Introduction

Globally, hypertension is the most common condition seen in primary care [1] and the major cause of death worldwide [2], with ≥29% of adults in the United Kingdom and United States presenting as hypertensive [3,4]. Although peripheral blood pressure (BP) measurement is traditionally used to monitor BP, central blood pressures may be more closely related to the pathophysiology of end-organ damage [5]. Systolic blood pressure (SBP) may be increased in the periphery by as much as 40 mmHg due to increased arterial stiffness away from the aorta [6]. Around 30% of peripherally normotensive males and 10% of peripherally normotensive females may share central pressures in common with those with stage I peripheral hypertension [6]. Central haemodynamic parameters may therefore be a superior measure for clinicians than traditional peripheral BP readings [7]. Before these readings are incorporated into clinical practice, the between-day reliability of these measures in normal operating conditions must be assessed.

Central pressures have previously been recorded invasively; a procedure usually contraindicated in healthy populations [8]. Recent technological advances mean these measures can now be estimated non-invasively using oscillometric-based pulse wave analysis. Although these devices have been shown to be valid [9–12], including with an older population sample [13], further work is needed to demonstrate the reliability and optimal

Abbreviations: AIx, augmentation index; AIx75, augmentation index corrected to a heart rate of 75b·min^{-1}; AP, augmented pressure; BP, blood pressure; cBP, central blood pressure; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; cPP, central pulse pressure; DBP, diastolic blood pressure; ICC, intra-class correlation coefficient; SBP, systolic blood pressure.

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Appendix 1b: Information sheet for healthy population study (chapter three)

THE UNIVERSITY OF WINCHESTER

DSE DEPARTMENT OF SPORT AND EXERCISE

v2.0 10th NOVEMBER 2015

EFFECT OF POSTURE AND FASTING STATE ON CENTRAL AND PERIPHERAL BLOOD PRESSURE

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study on the effect of posture and fasting state on blood pressure. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason. If you do want to take part now, but change your mind later, you can leave the study at any time.

Why are we doing the study?

Blood pressure measurements are very important indicators of health. Measuring central blood pressure (the blood pressure at the heart) may give even more useful information than peripheral blood pressure (blood pressure in the upper arm). We would like to investigate how central and peripheral blood pressures are influenced by seated position and before and after you have eaten food.

What is involved?

If you are able to take part in the study, then we ask that you read this information sheet fully and carefully, and once any questions you can think of have been answered, we ask that you sign the consent form. If you decide to take part you will be asked to be part of three 90 minute assessments, with a minimum of 24 hours recovery in between. These assessments will take place in the Physiology Laboratory at the University of Winchester.

Procedures:

During each assessment, you will be tested before (fasted) and after (non-fasted) breakfast. You will be asked not to consume food from 10 pm the night before any session but water can be drunk during this time. All measures will take place between 7 and 10am. A fingertip blood sample will be taken using a small needle to measure glucose levels in your blood. You will remain rested in a lying position for 15 minutes. We will then place a blood pressure cuff around your upper, left arm. This cuff will look and feel like any normal blood pressure cuff but will give us information about your central blood pressures (at the heart) and the blood pressure in your arm. We will take two measures over a three-minute interval. If there is too much of a difference between the first and second measures, a third measure will be taken. After this you will be moved to a seated position. You will remain rested in this position for 15 minutes. We will then measure your blood pressure using the same measures as before. Following this, you will be able to eat your breakfast. Caffeine will not be allowed to be taken during this time. Thirty minutes after eating, we will repeat the methods in a lying and seated position. We will use the same protocol for your second and third measures.

NB. Please be aware that the measuring of your blood pressure is not invasive and should not cause any major discomfort or harm.

What are the benefits for taking part in the study?

If you wish, you will have the opportunity to receive information about all measures (central and peripheral blood pressure) in verbal and written forms.

Are there any risks to being part of this study?

The risks involved in the study are low but you may feel mild discomfort in the left upper arm during blood pressure assessments. This level of discomfort will be the same as any usual blood pressure assessment. To minimise the burden, you will have a 90 second recovery between assessments.

What are the rights of participants in the study?
Taking part in this study is voluntary. You are free to say no to participating, or to leave the research study at any time, without any disadvantage. You have the right to access any information that we obtain on you from the study. Any of your personal information will be anonymised to make sure the study is confidential and will be stored in a locked cabinet in a secure office (Dr Faulkner's office at the University of Winchester).

You will not be paid or charged to take part in this research project Parking will be free at the University of Winchester if you are due to be assessed at the University.

What will happen after the study ends, or if you pull out?
All data will be stored in a locked cabinet in a secure office for 7 years.

Who is in the study team?

Mr Andrew Mitchelmore, PhD student, Department of Sport and Exercise (DSE), University of Winchester, Tel: 01962 827046

Dr James Faulkner, Senior Lecturer, DSE, University of Winchester, Tel: 01962 624932

Dr John Duffy, Stroke consultant, Hampshire Hospitals NHS Foundation Trust, Tel: 01962 825567

Approval for this study will been given by the University of Winchester RKE Ethics Committee.

THIS PROJECT IS FUNDED BY:

Department of Sport and Exercise, University of Winchester

Appendix 1c: Consent form for healthy population study (chapter three)

EFFECT OF POSTURE AND FASTING STATE ON CENTRAL AND PERIPHERAL BLOOD PRESSURE

CONSENT FORM

Name of Researchers: Mr Andrew Mitchelmore, Dr James Faulkner

Please initial boxes below

1. I confirm that I have read and understood the Patient Information Sheet (V1.0, dated 3rd November 2015) for the above study and have had the opportunity to ask questions. I understand that the data in this study will be included in future related clinical research projects. ☐
2. I confirm that I have had sufficient time to consider whether or not to take part in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
4. I agree to take part in the above study. ☐

Name of participant (please PRINT)	Date (DD/MM/YY)	Signature of participant

Name of person taking consent (please PRINT)	Date (DD/MM/YY)	Signature of person taking consent

Appendix 1d: Supplementary table: Reliability of the SphygmoCor XCEL in each population group for visits 1 – 2 and 2 – 3

	Supine-F Vis 1-2			Supine-F Vis 2-3			Supine-NF Vis 1-2			Supine-NF Vis 2-3			Seated-F Vis 1-2			Seated-F Vis 2-3			Seated-NF Vis 1-2			Seated-NF Vis 2-3		
	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC	ICC	SEM	RC
Whole Population																								
MAP (mmHg)	0.91	3.8	10.4	0.95	2.8	7.7	0.94	2.9	8	0.95	2.8	7.7	0.91	3.8	10.6	0.95	3	8.3	0.95	3.1	8.5	0.96	2.9	8
SBP (mmHg)	0.9	5.7	15.8	0.95	4	11.1	0.91	5.3	14.7	0.93	5	13.8	0.92	4.8	13.4	0.95	3.9	10.9	0.91	5.3	14.7	0.94	4.6	12.7
DBP (mmHg)	0.91	3.2	8.8	0.94	2.6	7.3	0.94	2.7	7.4	0.95	2.5	6.8	0.9	3.5	9.7	0.95	2.8	7.7	0.93	3.2	8.9	0.95	2.6	7.1
PP (mmHg)	0.85	4.2	11.7	0.93	2.9	7.9	0.89	3.8	10.5	0.91	3.3	9.2	0.85	4.3	11.9	0.87	4	11.1	0.82	5.1	14.1	0.92	3.2	8.9
cSBP (mmHg)	0.89	5.4	15	0.95	3.6	10.1	0.92	4.3	12	0.95	3.6	9.9	0.9	5.1	14	0.94	4.2	11.7	0.93	4.4	12.2	0.94	4.1	11.3
cDBP (mmHg)	0.91	3.2	8.9	0.93	2.8	7.8	9.4	2.6	7.1	0.95	2.5	7	0.91	3.4	9.5	0.94	2.8	7.9	0.94	3	8.4	0.95	2.6	7.3
cPP (mmHg)	0.83	3.8	10.6	0.9	2.9	7.9	0.89	2.9	8.2	0.88	3.6	9.8	0.84	3.7	10.2	0.89	3.2	8.8	0.88	3.5	9.8	0.93	2.4	6.8
Heart rate (bpm)	0.84	3.3	9.1	0.91	2.4	6.7	0.89	3.1	8.6	0.87	3.1	8.6	0.9	2.7	7.5	0.91	2.4	6.6	0.82	3.8	10.4	0.88	3.7	10.3
AP (mmHg)	0.76	3	8.3	0.83	2.4	6.7	0.88	1.7	4.7	0.89	1.6	4.4	0.82	2.5	6.8	0.89	2.2	6.1	0.92	1.6	4.4	0.89	1.9	5.4
AIx (%)	0.77	4.8	13.3	0.85	4.1	11.3	0.89	3.2	8.8	0.9	3	8.3	0.85	4.2	11.6	0.9	4	11.1	0.89	3.5	9.7	0.84	4.1	11.4
AIx75 (%)	0.78	5.1	14.1	0.83	4.4	12.3	0.9	3.4	9.3	0.89	3.5	9.6	0.83	4.5	12.4	0.9	3.7	10.3	0.91	3.6	10	0.87	4.3	11.9
Normotensive Population																								
MAP (mmHg)	0.75	3.5	9.7	0.84	2.5	6.9	0.87	2.7	7.4	0.93	2.1	5.8	0.69	3.9	10.9	0.85	2.7	7.6	0.9	2.5	6.9	0.85	2.8	7.9
SBP (mmHg)	0.66	4.8	13.2	0.77	3.3	9	0.75	4	11	0.9	2.7	7.5	0.57	4.4	12.3	0.64	3.9	10.9	0.76	3.5	9.6	0.76	3.8	10.4
DBP (mmHg)	0.81	2.7	7.5	0.86	2.1	5.8	0.83	2.7	7.6	0.94	1.8	5	0.73	3.6	10	0.84	2.8	7.7	0.89	2.7	7.6	0.88	2.6	7.3
PP (mmHg)	0.75	3.7	10.4	0.79	2.7	7.4	0.73	3.4	9.5	0.85	2.3	6.3	0.61	3.7	10.3	0.6	3.1	8.5	0.73	3.3	9.2	0.76	2.9	8.1
cSBP (mmHg)	0.75	4.7	13	0.84	3	8.2	0.76	3.7	10.3	0.9	2.5	7.1	0.63	4.5	12.5	0.72	3.5	9.6	0.8	3	8.4	0.76	3.5	9.6
cDBP (mmHg)	0.79	2.8	7.9	0.83	2.4	6.5	0.88	2.4	6.8	0.94	1.9	5.2	0.74	3.6	10.1	0.85	2.8	7.8	0.9	2.7	7.5	0.87	2.7	7.5
cPP (mmHg)	0.8	4.7	13	0.86	2.7	7.4	0.8	2.7	7.3	0.86	2.1	5.8	0.79	3.4	9.5	0.77	3	8.3	0.81	2.9	8	0.78	3	8.4
Heart rate (bpm)	0.87	3.4	9.3	0.89	2.8	7.9	0.88	3.6	10.1	0.8	3.9	10.8	0.9	2.7	7.5	0.89	2.6	7.1	0.86	3.2	8.9	0.93	3.1	8.7
AP (mmHg)	0.81	3	8.2	0.92	1.7	4.6	0.81	1.9	5.2	0.85	1.7	4.7	0.85	2.5	6.9	0.89	2.2	6	0.95	1.2	3.3	0.85	2	5.5
AIx (%)	0.78	5.3	14.7	0.91	3.5	9.8	0.86	3.7	10.3	0.88	3.5	9.8	0.88	4.3	12	0.91	4.4	12.2	0.88	3.7	10.2	0.8	4.7	13
AIx75 (%)	0.75	6.1	16.9	0.87	4.2	11.5	0.9	3.7	10.2	0.87	4.1	11.4	0.84	4.9	13.7	0.91	3.8	10.5	0.9	3.7	10.3	0.86	4.8	13.2
Hypertensive Population																								
MAP (mmHg)	0.92	2.9	7.9	0.9	3.6	10.1	0.93	3	8.2	0.92	3.3	9.2	0.92	3.2	8.8	0.93	3.1	8.5	0.92	3.5	9.6	0.95	2.7	7.6
SBP (mmHg)	0.87	5.8	16	0.91	4.3	11.8	0.89	5.2	14.3	0.9	4.9	13.5	0.89	4.9	13.7	0.89	5.1	14.1	0.81	6.3	17.5	0.89	4.8	13.4
DBP (mmHg)	0.89	3.5	9.6	0.9	3	8.4	0.94	2.4	6.7	0.92	3	8.4	0.92	3	8.3	0.94	2.6	7.2	0.91	3.5	9.8	0.96	2.4	6.7
PP (mmHg)	0.82	4.4	12.1	0.91	2.8	7.8	0.89	3.8	10.5	0.86	4.1	11.5	0.85	4.3	11.8	0.85	4.2	11.7	0.77	5.2	14.5	0.92	3.2	9
cSBP (mmHg)	0.85	5.6	15.5	0.91	4	11	0.9	4.5	12.4	0.9	4.4	12.1	0.88	4.7	12.9	0.91	4.4	12.1	0.85	5.3	14.6	0.91	4.2	11.7
cDBP (mmHg)	0.9	3.3	9.2	0.9	3	8.4	0.93	2.6	7.1	0.91	3.1	8.6	0.93	2.9	7.9	0.94	2.7	7.5	0.93	3.2	9	0.95	2.4	6.8
cPP (mmHg)	0.77	3.8	10.6	0.84	3.2	8.9	0.88	3.2	8.8	0.86	3.2	8.9	0.82	3.7	10.2	0.85	3.5	9.8	0.85	3.5	9.8	0.94	2.4	6.5
Heart rate (bpm)	0.81	3.2	8.9	0.93	2	5.6	0.91	2.6	7.1	0.93	2.3	6.4	0.89	2.7	7.6	0.93	2.2	6.1	0.79	4.3	11.9	0.8	4.2	11.6
AP (mmHg)	0.68	2.9	8.1	0.72	3	8.2	0.92	1.5	4.1	0.91	1.5	4.1	0.79	2.4	6.7	0.88	2.2	6.1	0.89	1.9	5.3	0.9	1.8	5.1
AIx (%)	0.77	4.3	11.9	0.76	4.5	12.4	0.91	2.7	7.4	0.92	2.5	6.9	0.81	4.1	11.2	0.88	3.6	9.9	0.89	3.3	9.2	0.87	3.5	9.7
AIx75 (%)	0.82	4.1	11.3	0.77	4.7	12.9	0.9	3.1	8.5	0.9	2.9	8	0.83	4.1	11.2	0.88	3.7	10.2	0.92	3.5	9.6	0.87	3.8	10.5

Abbrevs: AIx - Augmentation index, AIx75 - Augmentation index @ 75 b·min^{-1}, AP – Augmented pressure, cDBP – Central diastolic blood pressure, cPP – Central pulse pressure, cSBP – Central systolic blood pressure, DBP – Diastolic blood pressure, ICC – Intra-class correlation coefficient, F – Fasted, NF – Non-fasted, MAP – Mean arterial pressure, SBP – Systolic blood pressure, SDC – Smallest detectable change, SEM – Standard error of Measurement

Appendix 2a: Oscillometric central blood pressure and central systolic loading in stroke patients: Short-term reproducibility and effects of posture and fasting state – PLOS ONE publication

PLOS ONE

RESEARCH ARTICLE

Oscillometric central blood pressure and central systolic loading in stroke patients: Short-term reproducibility and effects of posture and fasting state

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OPEN ACCESS

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

This study examined the short-term reproducibility of non-invasive estimates of central and peripheral blood pressure and markers of central systolic loading (augmentation index [AIx; a measure of central systolic loading] and AIx75 [AIx standardised to 75 b·min^{-1} heart rate]) and the effect of posture and fasting state on these variables in patients with acute stroke.

Methods

Twenty-two acute stroke patients (72 ± 10y) had blood pressure measured using the SphygmoCor XCEL in supine and seated postures and whilst fasted and non-fasted.

Results

Acceptable short-term reproducibility (ICC >0.75) was reported for all peripheral and central variables in all conditions (ICC = 0.77–0.90) and for AIx and AIx75 in both fasted postures (ICC = 0.78–0.81). Food consumption significantly lowered all blood pressures (p <0.05; η^2_p = 0.20–0.55). The seated posture resulted in a significantly greater AIx than supine (p <0.05; η^2_p = 0.22). Fasting state had significant main effects on AIx and AIx75 (p <0.05; η^2_p = 0.14–0.22).

Conclusions

Oscillometric estimates of central blood pressure have high short-term reproducibility in different postures and fasting states but markers of systolic load should be assessed whilst fasted. Fasting state has a large effect on central and peripheral blood pressures and on measures of systolic loading. It is important for clinicians to be aware of optimal assessment conditions without this impacting on patient wellbeing.

Appendix 2b: Information sheet for acute stroke population study (chapter four)

Hampshire Hospitals NHS
NHS Foundation Trust

THE UNIVERSITY OF WINCHESTER

EFFECT OF POSTURE AND FASTING STATE ON CENTRAL AND PERIPHERAL BLOOD PRESSURE IN PATIENTS WITH STROKE

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study on the effect of posture and fasting state on blood pressure in patients who have had stroke or transient ischaemic attack (TIA). Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason, and it will not affect the care you receive. If you do want to take part now, but change your mind later, you can leave the study at any time. If you have any questions after reading this information sheet, please ask them.

Why are we doing the study?

Stroke is a leading cause of long-term physical and mental disability. Blood pressure control is important for good health in stroke patients. Measuring central blood pressure (the blood pressure which is found at the heart) and measuring how stiff your arteries are may give stroke consultants and GPs important information over and above what is usually obtained from peripheral blood pressure in the arm. Central blood pressure measurements may improve the management of patients with high blood pressure and be a better way to predict heart disease. As measuring peripheral blood pressure is routine practice, we would like to see how central and peripheral blood pressures are affected by sitting or standing, and before and after you have eaten food. We would also like to see if the type of stroke you have had and whether you have eaten or not have an influence on how stiff the walls of your arteries are.

If you choose to take part in this study you will receive the usual care which is given after a stroke or TIA. However, as the measurement of central blood pressures is not a part of usual care, we would like to take some extra measures.

What is involved?

Once you have been told that you have had a stroke or TIA by the stroke consultant, you will be invited to take part in this study.

If you are able to take part in the study, then we ask that you read this information sheet fully and carefully, and once any questions you can think of have been answered, we ask that you sign the consent form. If you decide to take part you will be asked to be part of three 90 minute assessments, with a minimum of 24 hours recovery in between. If you have been told that you have a major or minor stroke and are staying in the acute stroke ward at the hospital, each assessment will take place in the hospital. If you have been told that you have had a minor stroke or TIA, and have left the hospital, each assessment will take place in the Physiology Laboratory at the University of Winchester.

Procedures:

During each assessment, you will be tested before (fasted) and after (non-fasted) breakfast. You will be asked not to consume food from 10 pm the night before any session but water can be drunk

during this time. All measures will take place between 7 and 10am. Assessments can begin once you have taken your medication on the morning of the assessment. Following this, you will remain rested in a lying position for 15 minutes. We will then place a blood pressure cuff around your upper, left arm. This cuff will look and feel like any normal blood pressure cuff but will give us information about your central blood pressures (at the heart) and the blood pressure in your arm. We will take two measures over a three-minute interval. If there is too much of a difference between the first and second measures, a third measure will be taken. We will then measure how stiff your arteries are. This will involve a blood pressure cuff around the top of your leg and a tonometer which measures the pulse on the side of your neck.

After this you will be moved to a seated position. You will remain rested in this position for 15 minutes. We will then measure your blood pressure using the same measures as before. Following this, you will be able to eat your breakfast. Caffeine will not be allowed to be taken during this time. Thirty minutes after eating, we will repeat the methods in a lying and seated position. We will use the same protocol for your second and third measures. You will be continuously monitored during each assessment to ensure your good health and that you still have the capacity to give consent.

NB. Please be aware that the measuring of your blood pressure and arterial stiffness are not invasive and should not cause any major discomfort or harm.

What are the benefits for taking part in the study?

You will receive information about all measures (central and peripheral blood pressure) in verbal and written forms. This information will be given to stroke consultants/GPs, which in turn could influence the management of your condition.

Are there any risks to being part of this study?

The risks involved in the study are low but you may feel mild discomfort in the left upper arm during blood pressure assessments. This level of discomfort will be the same as any usual blood pressure assessment. To minimise the burden, you will have a 90 second recovery between assessments.

What are the rights of participants in the study?

Taking part in this study is voluntary. The measuring of your central blood pressures will be offered on top of the usual care that you will be given. You are free to say no to participating, or to leave the research study at any time, without any disadvantage. You have the right to access any information that we obtain on you from the study. Some parts of your medical notes will be viewed by the named researchers who will have been given NHS honorary contracts. You will be told of any news about any beneficial effects related to the study which may impact on the management of your health. Any of your personal information will be anonymised to make sure the study is confidential and will be stored in a locked cabinet in a secure office (Dr Faulkner's office at the University of Winchester).

You will not be paid or charged to take part in this research project Parking will be free at the University of Winchester if you are due to be assessed at the University.

What will happen after the study ends, or if you pull out?
Within two weeks of your participation in the study, you will be given written information about your data. All data will be stored in a locked cabinet in a secure office for 7 years.

Who is in the study team?

Mr Andrew Mitchelmore, PhD student, Department of Sport and Exercise (DSE), University of Winchester, Tel: 01962 827046, E-mail: Andrew.mitchelmore@winchester.ac.uk

Prof. Simon Jobson, Director of Research and Knowledge Exchange, University of Winchester, Tel: 01962 827516

Dr James Faulkner, Senior Lecturer, DSE, University of Winchester, Tel: 01962 624932

Dr Danielle Lambrick, Lecturer in Health Sciences, University of Southampton, Tel: 02380 595916

Dr John Duffy, Stroke consultant, Hampshire Hospitals NHS Foundation Trust, Tel: 01962 825567

Approval for this study has been given by the Hampshire Hospitals NHS Foundation Trust Research Department (ref:) and the South Central Research Ethics Committee (ref: 15/SC/0559)

Can I speak to anyone outside the research team about this study if I have any concerns?

Yes, you can speak with the Hampshire Hospitals NHS Foundation Trust Patient Advisory and Liaison Service (PALS) on (01256 486766).

THIS PROJECT IS FUNDED BY:

Department of Sport and Exercise, University of Winchester

Appendix 2c: Consent form for acute stroke population study (chapter four)

THE UNIVERSITY OF WINCHESTER

Hampshire Hospitals NHS
NHS Foundation Trust
Stroke, Medicine & Elderly Care,
Royal Hampshire County Hospital,
Winchester SO22 5DG
Switchboard: 01962 863535

V2.0 27th OCTOBER 2015

Patient Study Number: ☐☐☐☐☐

EFFECT OF POSTURE AND FASTING STATE ON CENTRAL AND PERIPHERAL BLOOD PRESSURE IN PATIENTS WITH STROKE

CONSENT FORM

Name of Researchers: Mr Andrew Mitchelmore, Professor Simon Jobson, Dr James Faulkner

Please initial boxes below

1. I confirm that I have read and understood the Patient Information Sheet (V4.0, dated 10th May 2016) for the above study and have had the opportunity to ask questions. I understand that the data in this study will be included in future related clinical research projects. ☐
2. I confirm that I have had sufficient time to consider whether or not to take part in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. Medical records may also be viewed by the named researchers in possession of honorary NHS contracts. I give permission for these individuals to have access to my patient records. ☐
5. I agree to my GP being informed of my participation in the study and that my GP will be sent a copy of this consent form and the information leaflet. ☐
6. I agree to take part in the above study. ☐

Name of participant (please PRINT)	Date (DD/MM/YY)	Signature of participant
Name of person taking consent (please PRINT)	Date (DD/MM/YY)	Signature of person taking consent

Appendix 2d: Supplementary table from acute stroke study: Mean values and 95% confidence intervals for outcome variables

	Posture					Fasting state				
Variable	Supine $\bar{X}$	Seated $\bar{X}$	$\bar{X}$ difference	*P* value for posture	Posture 95% C.I	Fasted $\bar{X}$	Non-fasted $\bar{X}$	$\bar{X}$ difference	*P* value for fasting state	Fasting state 95% C.I
SBP (mmHg)	141.4	143.2	1.8	.09	-4.0 - .29	147.5	137.1	10.4	**< .001**	5.5 – 15.3
DBP (mmHg)	77.0	79.8	2.8	**.001**	-4.2 - -1.3	82.4	74.4	8.0	**< .001**	4.6 – 11.6
PP (mmHg)	66.3	65.4	0.9	.33	- 1.0 – 2.8	67.0	64.6	2.4	**.04**	.2 – 4.7
cSBP (mmHg)	128.2	130.0	1.8	.06	-3.7 - .09	135.0	123.1	11.9	**< .001**	7.4 – 16.3
cDBP (mmHg)	78.0	81.0	3.0	**.001**	-4.5 - -1.4	83.5	75.6	7.9	**< .001**	4.3 – 11.5
cPP (mmHg)	50.2	49.1	1.1	.06	-.1 – 2.4	51.8	47.6	4.2	**< .001**	2.5 – 5.9
AIx (%)	33.4	31.3	2.1	**.02**	.3 – 4.0	34.8	29.9	4.9	**.001**	2.4 – 7.5
AIx75 (%)	29.4	27.8	1.6	.08	-.2 – 3.4	30.0	27.2	2.8	**.03**	.30 – 5.2

a. Abbrevations: Abbreviations: AIx - Augmentation Index, AIx75 - Augmentation Index @ 75bpm, cDBP - Central Diastolic Blood Pressure, C.I – Confidence Interval cPP - Central Pulse Pressure, cSBP - Central Systolic Blood Pressure, DBP - Diastolic Blood Pressure, PP – Pulse Pressure, SBP - Systolic Blood Pressure

b. **Bolded** *P*<.0

Appendix 3a: Letter to the Editor based on sedentary time and stroke – International Journal of Stroke publication

International Journal of Stroke
0(0) 1–2

DOI: 10.1177/1747493019833020
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SAGE

Letter to the Editor: English et al. Frequent, short bouts of light-intensity exercises while standing decreases systolic blood pressure: Breaking Up Sitting Time after Stroke (BUST-Stroke)

Dear Editor,

We read with great interest the English et al. articles on 'Breaking Up Sitting Time After Stroke' (BUST-Stroke) study,[1,2] in particular, the finding that frequent, short-bouts of light-intensity exercise while standing may significantly decrease peripheral systolic blood pressure (BP) in stroke survivors.[2] Despite this encouraging finding, further discussion is needed regarding: (i) the effect sizes reported for the peripheral systolic BP during the STAND-EX and WALK conditions, and (ii) the consideration of central hemodynamic parameters to aid the interpretation of this novel experimental design.

English et al.[2] do not contextualize their findings with respect to effect sizes. Effect sizes are important as they describe the importance of the relevant findings in practical terms.[3] This is an area which clearly warrants further attention as we calculated a small to moderate effect size (based on an n = 18) when comparing STAND-EX condition with SIT (Cohen's $d = 0.39$), and a small effect size when comparing the WALK condition with SIT ($d = 0.15$). Although small to moderate effect sizes across days may be meaningful, the importance of repeated (daily) exposure to frequent, short-bouts of light intensity exercise during prolonged sitting requires further attention.

The authors demonstrated a promising decrease in peripheral systolic BP of 3–4 mmHg between the STAND-EX and SIT conditions. However, the measurement of central hemodynamic parameters, including central systolic BP and arterial wave reflection (augmentation index), can provide clinicians with important diagnostic and prognostic information beyond that provided by peripheral BP readings. Considering the marked differences in pulse pressure between the central aorta and peripheral limbs, peripheral BP may not accurately reflect the effects of peak arterial BP on centrally located organs.[4] With central BP potentially a stronger determinant of cardiovascular events than peripheral BP,[5] the addition of central hemodynamic measures could have aided the interpretation of the BP data presented in this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix 3b: Chronic stroke, acute heel raise and sedentary time information sheet

UNIVERSITY OF WINCHESTER

UNIVERSITY OF WINCHESTER DEPARTMENT OF SPORT EXERCISE AND HEALTH

THE ACUTE EFFECT OF HEEL RAISES ON CENTRAL PRESSURES, CEREBRAL AND PERIPHERAL OXYGEN PERFUSION, AND MUSCLE ACTIVATION IN CHRONIC STROKE

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study on the acute effect of calf raises on blood pressure, oxygen delivery in your body, and your performance at a simple cognitive task. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason. If you do want to take part now, but change your mind later, you can leave the study at any time.

Why are we doing the study?

After a stroke, many people are very physically inactive. The best way to stay healthy after a stroke is to find ways to remain active. Although stroke sometimes makes it difficult for patients to do exercise, some simple physical activities may improve different aspects of your health. In this study, we will be researching how heel raises may improve measures of blood pressure, arterial stiffness and oxygen delivery to your brain and legs.

What is involved?

If you are able to take part in the study, then we ask that you read this information sheet fully and carefully, and once any questions you can think of have been answered, we ask that you sign the consent form. If you decide to take part you will be asked to be part of four assessments with a minimum of 24 hours recovery in between. The first assessment will take approximately 90 minutes whilst the second and third sessions will take approximately four hours. The final session will last around 90 minutes and take place ten weeks later. These assessments will take place in the Physiology Laboratory at the University of Winchester.

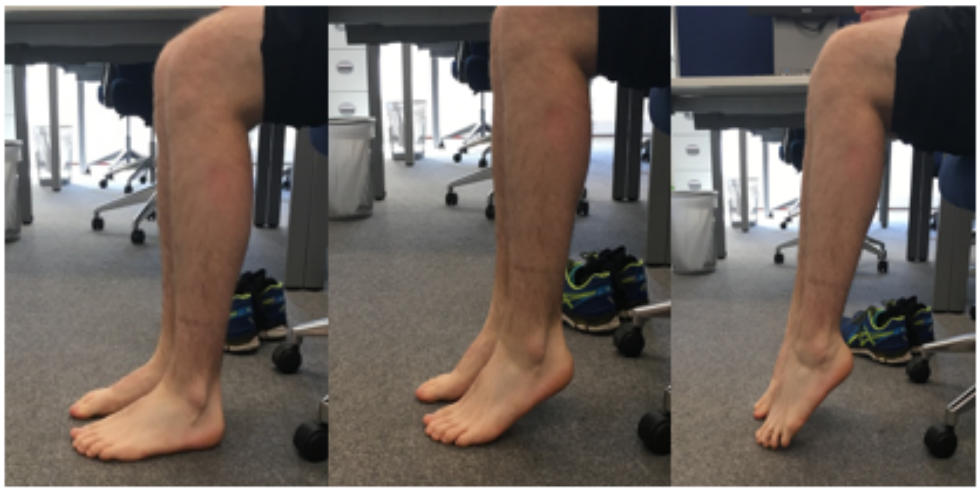
Procedures:

You will be asked to arrive at the University of Winchester before eating any breakfast for each session but we will provide you with food and drink in the laboratory. During the first assessment, you will complete five Stroop tests. These are short, simple tests which stimulate the brain. How quickly you answer the simple questions will give us information about your cognitive performance. You will have a short time spent in a lying down position before we measure your blood pressures using a cuff. This cuff will feel exactly the same as a normal blood pressure cuff but will give us information about your central pressures (at the heart). We will also measure your pulse wave velocity using a cuff on your upper leg and a small pen-like tonometer which will be placed on your neck. You will also be asked to perform three maximal heel raises so we can measure the electrical signal when your calf muscles are fully activated. We will also take some measurements of your head so we know where to place the surface electrodes which will measure oxygen delivery (one on your forehead, one on your leg) and muscle activation (one on each leg).

Your second visit will involve three hours in a seated position watching David Attenborough documentaries on television. The calming nature of the show ensures your blood pressure is not influenced by the documentaries. We will take measures of blood pressure, pulse wave velocity and oxygen delivery to the brain and leg after ten minutes, an hour and a half, and three hours

into the session. You will be asked to perform Stroop tests at each of these time points. This will give us baseline information which we can compare against after the third session.

Your third session will involve another three hours in a seated position watching television, but this time you will be asked to perform either ten or twenty heel raises every ten minutes. You will be asked to complete Stroop tests at the same times as the second session, and identical measures will be recorded. After the three hours have elapsed, we will collect a final set of measures after 15 minutes in a supine position.



Ten weeks after your third session, you will be asked to come back for a final follow-up appointment. This will involve the same tests as the first visit, including blood pressure measurements, measuring the electrical activation in your legs, and how much oxygen is in the blood flow to the brain and lower legs.

NB. Please be aware that all of these measures are non- invasive and should not cause any major discomfort or harm.

What are the benefits for taking part in the study?

If you wish, you will have the opportunity to receive information about all measures (central and peripheral blood pressure, oxygen delivery in the blood, muscle activation) in verbal and written forms.

Are there any risks to being part of this study?

The risks involved in the study are low but you may feel mild discomfort in the left upper arm during blood pressure assessments. This level of discomfort will be the same as any usual blood pressure assessment. To minimise the burden, you will have a 90 second recovery between assessments.

What are the rights of participants in the study?

Taking part in this study is voluntary. You are free to say no to participating, or to leave the research study at any time, without any disadvantage. You have the right to access any information that we obtain on you from the study. Any of your personal information will be anonymised to make sure the study is confidential and will be stored in a locked cabinet in a secure office (Dr Faulkner's office at the University of Winchester).

You will not be paid or charged to take part in this research project Parking will be free at the University of Winchester if you are due to be assessed at the University.

What will happen after the study ends, or if you pull out?
All data will be stored in a locked cabinet in a secure office for 7 years.

Who is in the study team?

Mr Andrew Mitchelmore, PhD student, Department of Sport and Exercise (DSE), University of Winchester, Tel: 01962 827046, E-mail: Andrew.mitchelmore@winchester.ac.uk

Dr James Faulkner, Senior Lecturer, DSE, University of Winchester, Tel: 01962 624932

Professor Simon Jobson, Professor of Sport and Exercise Physiology, DSE, University of Winchester, Tel: 01962 827516

Dr Danielle Lambrick, Lecturer in Life Sciences, University of Southampton, Tel: 02380 595916

Approval for this study will been given by the University of Winchester RKE Ethics Committee.

THIS PROJECT IS FUNDED BY:

Department of Sport and Exercise, University of Winchester

Appendix 3c: Chronic stroke, acute heel raise and sedentary time consent form

THE UNIVERSITY OF WINCHESTER

THE ACUTE EFFECT OF HEEL RAISES ON CENTRAL PRESSURES, CEREBRAL AND PERIPHERAL OXYGEN PERFUSION, AND MUSCLE ACTIVATION IN CHRONIC STROKE

CONSENT FORM

Name of Researchers: Mr Andrew Mitchelmore, Dr James Faulkner

Please initial boxes below

1. I confirm that I have read and understood the Patient Information Sheet (V4.0, dated 2nd May 2017) for the above study and have had the opportunity to ask questions. I understand that the data in this study will be included in future related clinical research projects. ☐
2. I confirm that I have had sufficient time to consider whether or not to take part in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
4. I agree to take part in the above study. ☐

Name of participant (please PRINT)	Date (DD/MM/YY)	Signature of participant

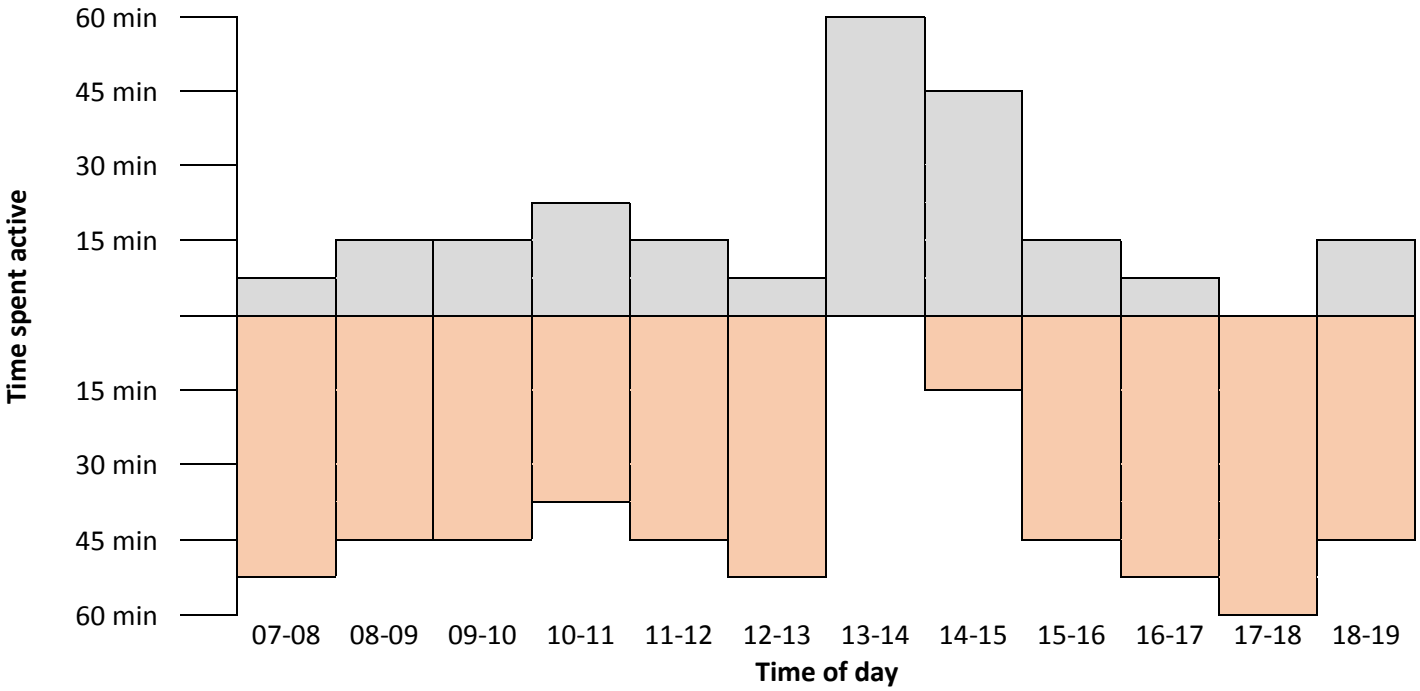
Name of person taking consent (please PRINT)	Date (DD/MM/YY)	Signature of person taking consent

Appendix 3d: Supplementary variables from pre- and post- sedentary and heel raise visits

		Total	Sedentary Vis		Heel Raise Vis		Interaction		Condition		Time	
		X	10 Min	180 min	10 min	180 min	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
ED (ms)	*X*	*340.4*	*333.6*	*342.3*	*333.3*	*352.8*	**0.02**	0.39	0.76	0.01	**0.03**	0.36
	SD	*30.3*	*25.6*	*36.2*	*32.1*	*25.1*						
AT2 (ms)	*X*	*235*	*233.3*	*233.4*	*234.3*	*239.8*	0.16	0.17	0.9	0.01	0.28	0.11
	SD	*16.1*	*16.1*	*15*	*18.9*	*15.1*						
P1 (mmHg)	*X*	*34.8*	*33.9*	*38.3*	*31.1*	*35.7*	0.87	0.01	0.3	0.1	**0.04**	0.32
	SD	*11.9*	*10.4*	*14.2*	*9.2*	*13*						
SEVR (%)	*X*	*164*	*163.5*	*163.1*	*161.5*	*167.4*	0.51	0.04	0.53	0.04	0.92	0.01
	SD	*27.2*	*18.2*	*25*	*27.7*	*38*						
ESP (mmHg)	*X*	*112*	*110.8*	*118.2*	*106*	*112.2*	0.32	0.09	0.58	0.03	**0.01**	0.45
	SD	*16.7*	*17.8*	*17.9*	*14.8*	*15.4*						
Pf (mmHg)	*X*	*28.5*	*28.1*	*31.3*	*26.2*	*28.4*	0.23	0.13	0.18	0.16	0.07	0.28
	SD	*7.7*	*7*	*9.3*	*5.2*	*8.6*						
Pb (mmHg)	*X*	*20.1*	*19.4*	*21.1*	*19.3*	*20.7*	0.58	0.03	0.91	0.01	0.15	0.18
	SD	*6.3*	*6.2*	*7*	*5.4*	*7.2*						
RM (%)	*X*	*70.6*	*68.6*	*67.9*	*73.8*	*72.5*	0.86	0.01	0.06	0.28	0.8	0.01
	SD	*10.8*	*10.8*	*10.6*	*13.1*	*8.2*						

Abbrevs: AT2 – Aortic T2, ED – Ejection duration, ESP – End systolic pressure, P1 – Peak 1 height, Pb – Reflected pulse height, Pf – Forward pulse height, RM – Reflection magnitude, SEVR – Subendocardial viability ratio

Appendix 3e: An example pattern of sedentary time across a 12-hour period for a stroke patient attending daily rehabilitation sessions (Adapted from Hamilton, Hamilton & Zderic, 2007)



Appendix 4a: Effects of a heel raise program on central on central hemodynamics and cognitive performance in chronic stroke: study protocol for a randomized, controlled, crossover trial. Clinical Trials and Degenerative Diseases publication

STUDY PROTOCOL

Effects of a heel raise program on central hemodynamics and cognitive performance in chronic stroke: study protocol for a randomized, controlled, crossover trial

Andrew Mitchelmore[1,*], Danielle Lambrick[2], Simon Jobson[1], Lee Stoner[3], James Faulkner[1]
1 Department of Sport, Exercise and Health, University of Winchester, Winchester, UK
2 Faculty of Health Sciences, University of Southampton, Southampton, UK
3 Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

*Correspondence to: Andrew Mitchelmore, MSc, Andrew.mitchelmore@winchester.ac.uk.
orcid: 0000-0002-1493-9735 (Andrew Mitchelmore)

Abstract

Background and objectives: As survival rates after incident stroke increase, the burden caused by secondary stroke and pressure placed on rehabilitation centers also rises. Lifestyle interventions have the potential to drive secondary-prevention treatments. Low-intensity interventions, such as heel raises, may offer a simple method of improving cardiovascular health and cognitive ability in chronic stroke. Here we present a protocol which attempts to determine whether a heel raise training program can improve markers of vascular health and cognitive function.
Design: A randomized, controlled, crossover trial.
Methods: Fifteen participants (> 3 months post-stroke diagnosis) will be randomly assigned to an intervention-first group ($n = 8$) or a control-first group ($n = 7$). In the intervention period, participants will complete 170 heel raises per day for 10 weeks. Heel raises will be completed in sets of ten, within a period of 170 minutes, from a seated position. In the control period, participants will go about their normal lives for 10 weeks. On completion of each program, participants will have a 4-week washout before commencing the alterative arm.
Outcome measures: The primary outcomes (pre- and post-measures of peripheral and central blood pressure and pulse wave velocity) will be recorded, as these variables are strongly linked to vascular health after stroke. Secondary outcomes (cognitive function and maximal voluntary contractions) will be assessed using the Stroop task and electromyography respectively. A mixed-model analysis of variance will identify whether a heel raise intervention has a significant effect on the proposed primary and secondary outcome variables.
Discussion: The potential improvements in vascular health may demonstrate that lower-limb heel raise exercise is a beneficial exercise stimulus for this population group.
Ethics and dissemination: The protocol received ethical approval from the University of Winchester Ethics Committee (approval No. BLS/17/11) on November 30, 2017 and will be conducted in accordance with the *Declaration of Helsinki*, formulated by the World Medical Association. Written informed consent will be obtained from all participants. Recruitment began in June 2018. Analysis of the primary and secondary outcome measures will be completed in January 2019, and the study will finish in February 2019.
Trial registration: The study was registered with ClinicalTrials.gov (NCT03423433) on February 6, 2018.

Key words: central blood pressure; stroke; sedentary time; training program; pulse wave velocity; randomized controlled trial

doi: 10.4103/2542-3975.248012
How to cite this article: Mitchelmore A, Lambrick D, Jobson S, Stoner L, Faulkner J. Effects of a heel raise program on central hemodynamics and cognitive performance in chronic stroke: study protocol for a randomized, controlled, crossover trial. Clin Trials Degener Dis. 2018;3(4):130-134.

Introduction

Stroke has enormous physical and psychosocial impacts on individuals' health-related quality of life. The risk of recurrent stroke is 26% within 5 years and 39% within 10 years of initial incidence of stroke.[1] With the burden of disease caused by stroke expected to double by 2030, there is now good evidence to support interventions in stroke rehabilitation.[2]

Blood pressure post-stroke

Peripheral blood pressures are positively and continuously related to stroke incident, however central blood pressures may be more indicative of the pathophysiology associated with central organ damage.[3,4] These measures are particularly pertinent as around 30% of peripherally normotensive males and 10% of peripherally normotensive females may have central pressures in common with those in stage I peripheral hypertension.[5] Although traditionally contraindicated due to the invasive nature of the procedure, recent technological advances in oscillometric devices allow central blood pressure to be estimated using brachial arm cuffs through pulse wave analysis (PWA).[6] Peripheral and central blood pressures are both risk factors of cardiovascular disease, including stroke.[5,7] Behaviourably modifiable risk factors can be targeted through lifestyle changes. One aspect of lifestyle which is relatively easy to target post-stroke is the application of interventions that may decrease sedentary time.

Sedentary behaviour post-stroke

Physical disability and the loss of physical function following a stroke frequently leads to increased levels of sedentary time.[8] Stroke survivors typically spend 11 hours per day in a seated position (75% of waking hours), of which many of these hours

Appendix 4b: Chronic stroke, heel raise training programme time information sheet

THE UNIVERSITY OF WINCHESTER

DSE DEPARTMENT OF SPORT AND EXERCISE

V1.0_ 30th NOVEMBER 2017

EFFECTS OF A HEEL-RAISE PROGRAMME ON CENTRAL AND PERIPHERAL BLOOD PRESSURE AND COGNITIVE PERFORMANCE IN CHRONIC STROKE

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study on the long-term effect of calf raises on different types of blood pressure, the electrical activity of your leg muscles, and your performance at a simple cognitive task. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason. If you do want to take part now, but change your mind later, you can leave the study at any time.

Why are we doing the study?

After a stroke, many people are very physically inactive. The best way to stay healthy after a stroke is to find ways to remain active. Although stroke sometimes makes it difficult for patients to do exercise, some simple physical activities may improve different aspects of your health. In this study, we will be researching how heel raises may improve measures of blood pressure, arterial stiffness and oxygen delivery to your brain and legs.

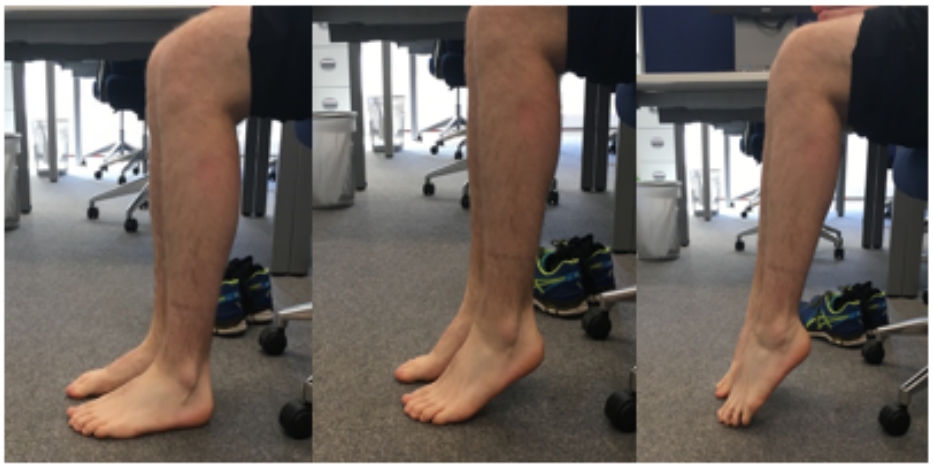
What is involved?

If you are able to take part in the study, then we ask that you read this information sheet fully and carefully, and once any questions you can think of have been answered, we ask that you sign the consent form. If you decide to take part you will be asked to be part of four assessments spaced twenty weeks apart. The first and second assessments will both take approximately 90 minutes. These assessments will take place in the Physiology Laboratory at the University of Winchester.

Procedures:

You will be asked to arrive at the University of Winchester before eating any breakfast for all sessions but we can provide you with food and drink in the laboratory after testing if requested. During the first assessment, you will complete five Stroop tests. These are short, simple tests which stimulate the brain. How quickly you answer the simple questions will give us information about your cognitive performance. We will then take ultrasound readings of one of your calf muscles. You will have a short time spent in a lying down position before we measure your blood pressures using a cuff. This cuff will feel exactly the same as a normal blood pressure cuff but will give us information about your central pressures (at the heart). We will also measure your pulse wave velocity using a cuff on your upper leg and a small pen-like tonometer which will be placed on your neck. You will also be asked to perform three maximal heel raises so we can measure the electrical signal when your calf muscles are fully activated. We will also ask you to complete some questionnaires about your health and levels of physical activity.

You will be randomly put into a heel-raise first group or a control first group. If you are put into the heel-raise first group, we will explain and demonstrate how to complete a heel raise (pictured below). You will be asked to do a total of 170 of these per day, six days per week, for ten weeks.



If you are placed in the control first group, you will not be asked to do heel raises and will be asked to just continue your life as usual until your second appointment.

Ten weeks after your first session, you will be asked to come back for a follow-up appointment. These will involve the same tests as the first visit, including blood pressure measurements, ultrasound of your lower leg, measuring the electrical activation in your legs, five more Stroop tests and some more questionnaires about your health and physical activity levels. These visits will also last around 90 minutes. After you have completed one of these conditions, you will begin the second condition (the one you have not previously taken part in) and the process will repeat.

NB. Please be aware that all of these measures are non- invasive and should not cause any major discomfort or harm.

What are the benefits for taking part in the study?

If you wish, you will have the opportunity to receive information about all measures (central and peripheral blood pressure, arterial stiffness, cognitive performance, muscle activation) in verbal and written forms.

Are there any risks to being part of this study?

The risks involved in the study are low but you may feel mild discomfort in the left upper arm during blood pressure assessments. This level of discomfort will be the same as any usual blood pressure assessment. To minimise the burden, you will have a 90 second recovery between assessments.

What are the rights of participants in the study?

Taking part in this study is voluntary. You are free to say no to participating, or to leave the research study at any time, without any disadvantage. You have the right to access any information that we obtain on you from the study. Any of your personal information will be anonymised to make sure the

study is confidential and will be stored in a locked cabinet in a secure office (Dr Faulkner's office at the University of Winchester).

You will not be paid or charged to take part in this research project Parking will be free at the University of Winchester if you are due to be assessed at the University.

What will happen after the study ends, or if you pull out?
All data will be stored in a locked cabinet in a secure office for 7 years.

Who is in the study team?

Mr Andrew Mitchelmore, PhD student, Department of Sport and Exercise (DSE), University of Winchester, Tel: 01962 827046, E-mail: Andrew.mitchelmore@winchester.ac.uk

Dr James Faulkner, Senior Lecturer, DSE, University of Winchester, Tel: 01962 624932

Professor Simon Jobson, Professor of Sport and Exercise Physiology, DSE, University of Winchester, Tel: 01962 827516

Dr Danielle Lambrick, Lecturer in Life Sciences, University of Southampton, Tel: 02380 595916

Dr Lee Stoner, Assistant Professor in Exercise Physiology, Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, North Carolina, 27599-8700, Tel: +9199620534

Approval for this study will been given by the University of Winchester RKE Ethics Committee.

THIS PROJECT IS FUNDED BY:

Department of Sport and Exercise, University of Winchester

Appendix 4c: Chronic stroke, heel raise training programme time consent form

THE UNIVERSITY OF WINCHESTER

EFFECTS OF A HEEL-RAISE PROGRAMME ON CENTRAL AND PERIPHERAL BLOOD PRESSURE AND COGNITIVE PERFORMANCE IN CHRONIC STROKE

CONSENT FORM

Name of Researchers: Mr Andrew Mitchelmore, Dr Danielle Lambrick, Dr Simon Jobson, Dr Lee Stoner, Dr James Faulkner

Please initial boxes below

1. I confirm that I have read and understood the Patient Information Sheet (V1.0, dated 30th November 2017) for the above study and have had the opportunity to ask questions. I understand that the data in this study will be included in future related clinical research projects. ☐
2. I confirm that I have had sufficient time to consider whether or not to take part in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
4. I agree to take part in the above study. ☐

Name of participant (please PRINT)	Date (DD/MM/YY)	Signature of participant

Name of person taking consent (please PRINT)	Date (DD/MM/YY)	Signature of person taking consent

Appendix 4d: Mean (SD) supplementary pulse wave analysis values pre- and post- control and heel raise intervention conditions

		Total	**Control**		**Intervention**		**Interaction**		**Condition**		**Time**	
		X	Pre-	Post-	Pre-	Post-	*P*	η^2_p	*P*	η^2_p	*P*	η^2_p
ED (ms)	*X*	*352*	*357*	*356*	*347*	*346*	.66	.04	.24	.26	.82	.01
	SD	*26*	*20*	*35*	*29*	*15*						
AT2 (ms)	*X*	*237*	*239*	*238*	*234*	*237*	.94	<.01	.21	.29	.62	.05
	SD	*13*	*10*	*13*	*17*	*12*						
P1 (mmHg)	*X*	*37*	*38*	*36*	*37*	*35*	.99	<.01	.52	.09	.07	.51
	SD	*9*	*11*	*8*	*7*	*11*						
SEVR (%)	*X*	*141*	*142*	*137*	*141*	*143*	.88	.01	.50	.10	.97	<.01
	SD	*14*	*20*	*15*	*10*	*10*						
ESP (mmHg)	*X*	*111*	*114*	*115*	*108*	*108*	.18	.33	.09	.46	.85	.01
	SD	*11*	*10*	*10*	*11*	*14*						
Pf (mmHg)	*X*	*31*	*32*	*31*	*29*	*30*	.65	.04	.08	.49	.85	.01
	SD	*7*	*8*	*6*	*5*	*8*						
Pb (mmHg)	*X*	*21*	*23*	*22*	*20*	*20*	.65	.05	.11	.43	.13	.39
	SD	*5*	*6*	*5*	*5*	*5*						
RM (%)	*X*	*70*	*71*	*69*	*70*	*69*	.31	.20	.51	.09	.32	.20
	SD	*8*	*6*	*6*	*11*	*10*						

Abbrevs: AT2 – Aortic T2, ED – Ejection duration, ESP – End systolic pressure, P1 – Peak 1 height, Pb – Reflected pulse height, Pf – Forward pulse height, RM – Reflection magnitude, SEVR – Subendocardial viability ratio