

Aerobic Exercise and Early Mobilisation in the Acute Phase of Stroke

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Aerobic Exercise and Early Mobilisation in the Acute Phase of Stroke

Nik Kudiersky

A thesis submitted in partial fulfilment of the requirements of
Sheffield Hallam University for the degree of Doctor of Philosophy

In collaboration with Sheffield Teaching Hospitals NHS Foundation Trust

September 2025

Candidate Declaration

I hereby declare that:

1. I have not been enrolled for another award of the University, or other academic or professional organisation, whilst undertaking my research degree.
2. None of the material contained in the thesis has been used in any other submission for an academic award.
3. I certify that this thesis is my own work. The use of all published or other sources of material consulted have been properly and fully acknowledged.
4. The work undertaken towards the thesis has been conducted in accordance with the SHU Principles of Integrity in Research and the SHU Research Ethics Policy, and ethics approval has been granted for all research studies in the thesis.

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Abstract

Stroke is a leading cause of long-term disability. Clinical guidelines recommend early mobilisation and early initiation of aerobic exercise to optimise recovery. However, the safety and efficacy of these interventions remain uncertain. Early mobilisation aims to prevent bed rest-related complications and enhance neuroplasticity, but evidence suggests this method could be detrimental due to cerebral hypoperfusion. Aerobic exercise is advocated to counteract deconditioning, enhance function and improve cardiovascular health, but is rarely implemented in the acute phase of stroke. Moreover, evidence supporting its use in the acute phase of stroke is lacking. This thesis investigated these interventions, aiming to address key gaps in the evidence base.

Study 1 assessed cerebral blood velocity (CBv) responses to early mobilisation using transcranial Doppler ultrasound. Standing induced a sustained decline in ipsilesional CBv by ~10%. An exploratory analysis indicated that CBv responses were not associated with clinical outcomes, but this was underpowered.

Study 2 was a randomised feasibility trial of an aerobic exercise intervention initiated 1–7 days post-stroke. The 5-session, light- to moderate-intensity recumbent cycling intervention was safe, attenuated quadriceps muscle atrophy and potentially improved disability outcomes.

Study 3 examined acute CBv and neurotrophic responses to a single bout of recumbent aerobic exercise (~10 days post-stroke), using transcranial Doppler ultrasound and enzyme-linked immunosorbent assays. CBv increased bilaterally during exercise by ~10–11% without causing adverse events, whereas peripheral BDNF measured after exercise did not change.

Study 4 explored patient and therapist perspectives about aerobic exercise. Patients generally found the intervention acceptable and beneficial, whereas therapists expressed mixed views, highlighting uncertainties about efficacy, concerns regarding fatigue and maladaptation, and resource constraints.

Collectively, these findings demonstrate that early mobilisation may compromise cerebral perfusion, whereas recumbent aerobic exercise safely increases CBv. In addition, aerobic exercise training is feasible, safe, and shows promise as an early stroke rehabilitation strategy.

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List of Abbreviations

Abbreviation	Description
ACSM	American College of Sports Medicine
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASU	Acute stroke unit
AVERT	A Very Early Rehabilitation Trial
BDNF	Brain-derived neurotrophic factor
CBF	Cerebral blood flow
CBv	Cerebral blood velocity
CPP	Cerebral perfusion pressure
CSA	Cross-sectional area
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-3L	EuroQol Quality of Life Index 3-Level
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
HASU	Hyperacute stroke unit
HR	Heart rate
HRmax	Maximum heart rate
HRR	Heart rate reserve
ICA	Internal carotid artery
ICH	Intracranial haemorrhage
ICU	Intensive care unit
IQR	Interquartile range
IRAS	Integrated Research Application System
LOS	Length of stay
LOT-R	Life Orientation Test - Revised
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCAv	Middle cerebral artery blood velocity
MET	Metabolic equivalent of task
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
PET	Positron emission tomography

PPI	Patient and public involvement
RCP	Respiratory compensation point
RCT	Randomised controlled trial
REC	Research Ethics Committee
RHH	Royal Hallamshire Hospital
RPP	Rate-pressure product
SBP	Systolic blood pressure
SD	Standard deviation
SPARC	Stroke Pathway Assessment and Rehabilitation Centre
SPPB	Short Physical Performance Battery
TCD	Transcranial Doppler ultrasound
TFA	Theoretical Framework of Acceptability
UK	United Kingdom
UTI	Urinary tract infection
VEM	Very early mobilisation
$\dot{V}O_2$	Volume of oxygen consumption
$\dot{V}O_{2max}$	Maximal oxygen consumption
$\dot{V}O_{2R}$	$\dot{V}O_2$ reserve
VT1	First ventilatory threshold
VT2	Second ventilatory threshold

Chapter 1 – Background and Rationale

A stroke is a medical emergency where the brain's blood supply is interrupted due to either a blockage (ischaemic stroke) or rupture (haemorrhagic stroke) of a blood vessel resulting in brain damage (1). Stroke is the leading cause of complex neurological disability throughout the world, and there are few effective treatments available beyond acute reperfusion and secondary prevention (2). In the United Kingdom (UK), there are approximately 1.3 million stroke survivors and the incidence of stroke is currently around 110,000 per year (3). Moreover, it is estimated that between 39-65% of stroke survivors are left with a long-term severe disability (4,5), and approximately 10–20% will suffer a recurrent stroke within 5–10 years (6,7). The estimated societal cost of stroke in the UK is currently £43 billion, equivalent to nearly 1.5% of gross domestic product. Furthermore, by 2035, the prevalence of stroke is predicted to rise to 2.1 million due to an ageing population and improved stroke survival rates. This will bring about a societal cost of approximately £75 billion (3). The escalating costs of stroke must be urgently addressed by identifying effective prevention, treatment and rehabilitation strategies.

Clinical guidelines recommend early mobilisation (out-of-bed activity) to promote neurological recovery and prevent bed rest-related complications (8). They also advocate the introduction of aerobic exercise (i.e., cardiorespiratory) training as soon as patients are medically stable, with the aims of improving physical function, mitigating deconditioning and enhancing cardiovascular health. However, the evidence base underpinning both of these recommendations is limited (9).

The physiological responses to early mobilisation and aerobic exercise in acute stroke remain poorly understood. Both interventions may support recovery by engaging neuromuscular pathways (10,11), but they also pose haemodynamic risks to perilesional brain tissue (9). In addition, although early mobilisation is embedded in routine care, the feasibility of initiating aerobic exercise training in the acute phase of stroke is unclear (12). This PhD thesis aims to bridge these knowledge gaps through a series of mechanistic investigations and an evaluation of the safety, acceptability, and preliminary efficacy of aerobic exercise training initiated in the acute phase of stroke (1-7 days post-stroke). This early window was selected based on pre-clinical evidence that

endogenous repair mechanisms are upregulated early after ischaemia and may respond positively to aerobic exercise. The hyperacute phase (0-24h) was avoided based on evidence from experimental models and clinical rehabilitation trials which indicate that intervening too early may worsen neurological outcomes (13,14).

Stroke pathology

Ischaemic stroke

An ischaemic stroke is defined as an episode of neurological dysfunction lasting longer than 24 hours, caused by a vascular occlusion (15). The blockage deprives downstream brain cells of oxygen and nutrients, leading to cellular energy depletion which triggers a pathological cascade including blood–brain barrier dysfunction, ionic imbalance, excitotoxicity, oxidative stress, inflammation, oedema, and ultimately, brain tissue death (16). This irreversibly damaged region of brain cells is known as the infarct core.

Surrounding the infarct core is an area of potentially salvageable tissue called the ischaemic penumbra, estimated to be viable for 24-48 hours post-stroke (17). The fate of the ischaemic penumbra is dependent on its residual blood supply, which is influenced by the collateral blood vessel architecture throughout perilesional territory. A ‘poor collateral score’, measured using contrast-enhanced imaging, predicts a poor outcome, reflecting limited capacity to bypass the occluded vessel. Conversely, a more extensive branching of the collateral blood vessel network (i.e., good collateral score) is more likely to sustain perilesional perfusion and limit infarct expansion (18,19). Without timely reperfusion, and with insufficient residual blood flow, the hypoperfused perilesional tissue may succumb to infarction (18,20). Beyond reperfusion therapies (thrombolysis and thrombectomy), there are currently no medical treatments that mitigate infarct expansion (18,21,22).

Haemorrhagic stroke

A haemorrhagic stroke occurs when a cerebral blood vessel ruptures and blood leaks into the surrounding brain parenchyma or ventricles (intracranial haemorrhage [ICH]), or subarachnoid space (subarachnoid haemorrhage) (23). The haemorrhage increases intracranial pressure which can compress, displace and damage brain tissue (23). In

addition, the haemorrhage disrupts the blood–brain barrier which allows serum proteins to leak into surrounding brain tissue, causing vasogenic oedema which compounds intracranial pressure (23). Further, in 73% of ICH cases, haematoma expansion occurs in the first 24 hours (24), which is associated with poorer outcomes (24,25). Following the primary injury phase which spans a few days (23), a secondary pathological cascade can occur lasting ~7-14 days including inflammation, neurotoxicity caused by exposure to blood components, oxidative stress, and ultimately cell death (23). There are currently no established treatments which attenuate these pathological cascades (23).

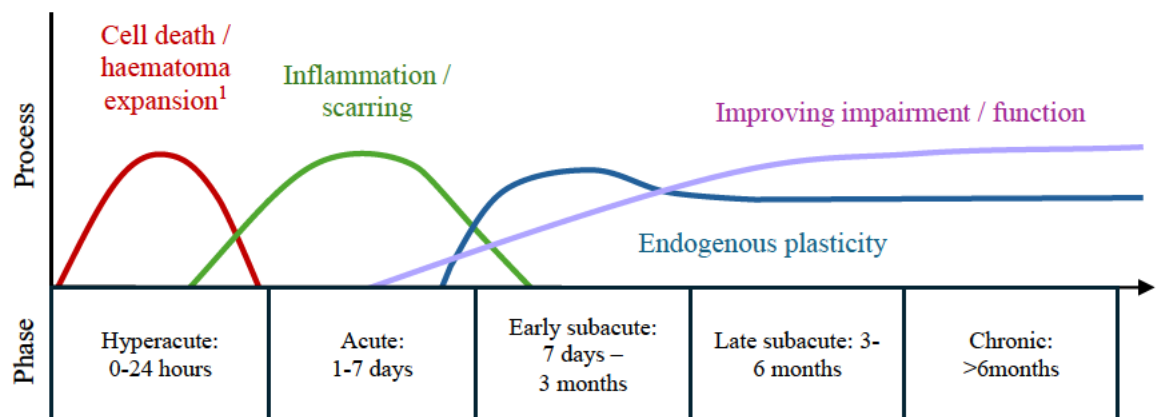


Figure 1.1 Schema of stroke phases and key biological and functional processes.

¹Haemorrhagic stroke specific. Adapted from Bernhardt et al., (26).

Cerebral blood flow regulation

The brain is 2% of total body mass yet accounts for 20% of resting energy expenditure (27,28). Despite its high metabolic demand, the brain has a limited capacity to store energy (27). Brain function is therefore highly reliant on rapid and precise delivery of blood-borne energy substrates and oxygen to match metabolic demands, and must be able to efficiently remove waste products (29).

Cerebral blood flow (CBF) is determined by the balance between cerebral perfusion pressure and cerebrovascular resistance. Cerebral perfusion pressure (CPP) is the pressure gradient which drives blood flow throughout the brain and is defined as the difference between mean arterial pressure (MAP) and intracranial pressure. Normal CPP ranges from 70-100mmHg (30). Below this range, CBF becomes insufficient to meet metabolic demand, increasing the risk of ischaemia (30). Conversely, when CPP

risers above this range, blood–brain barrier disruption can occur, increasing the risk of cerebral oedema, seizures and stroke (30).

Precise regulation of CBF is essential to protect the brain and optimise brain function. Cerebral autoregulation is a crucial homeostatic mechanism which buffers fluctuations in mean arterial pressure (MAP) through altering vascular tone (31). Under steady-state experimental conditions, cerebral autoregulation maintains relatively stable CBF across a broad range of MAP when pressure changes gradually. In healthy adults, this autoregulatory capacity typically spans MAP values of approximately 60–150 mmHg. The relationship between MAP and CBF measured under steady-state conditions over hours to days is known as static cerebral autoregulation (31).

During rapid changes in blood pressure (i.e., non-steady state), the cerebrovascular system quickly adjusts vessel diameter to stabilise CBF, but these responses have an inherent delay. As a result, the cerebral circulation cannot fully counter abrupt shifts in MAP, therefore CBF exhibits brief fluctuations before returning toward baseline. Dynamic cerebral autoregulation reflects the efficiency of these rapid adjustments and reflects how well the cerebral vessels can dampen sudden increases or decreases in mean arterial pressure. When dynamic autoregulation is intact, fast blood pressure changes are partially buffered, limiting their impact on CBF. When it is impaired, a greater proportion of these rapid blood pressure oscillations is transmitted to the brain, increasing the likelihood of pressure-dependent variability in CBF (31).

In addition to local cerebrovascular mechanisms, the arterial baroreflex plays a crucial role in regulating systemic blood pressure and in turn, CPP (32). The arterial baroreflex is the body's primary short-term blood pressure control system. Stretch-sensitive receptors located in the carotid sinus and aortic arch continuously sense arterial pressure and relay this information to autonomic centres in the brainstem. When blood pressure falls, the baroreflex rapidly withdraws vagal activity and increases sympathetic drive, causing peripheral vasoconstriction and increased cardiac output. Conversely, when baroreceptors detect a sudden rise in blood pressure, vagal activity is increased and sympathetic outflow is inhibited, which reduces cardiac output, and leads to peripheral vasodilation (32). These rapid autonomic adjustments help stabilise systemic blood pressure and thereby cerebral perfusion during sudden haemodynamic challenges such as standing, coughing, straining and intermittent physical exercise (33–36).

Additional mechanisms act in concert with cerebral autoregulation and the baroreflex to regulate CBF. Cerebrovascular reactivity is the mechanism whereby local changes in CO₂ concentration are detected by chemoreceptors triggering a rapid, global adjustment in cerebrovascular tone. In parallel, neurovascular coupling (i.e., functional hyperaemia) matches regional CBF to local neuronal activity, ensuring adequate nutrient and oxygen delivery to specific brain regions. Endothelium-dependent mechanisms further regulate CBF by altering vascular tone in response to changes in blood flow and shear stress (37). These neurovascular mechanisms are discussed in more detail below.

The neurovascular unit

The neurovascular unit — an ensemble of neurons, astrocytes, endothelial cells, vascular smooth muscle cells, and pericytes — operates as an integrated sensor of mechanical and chemical stimuli, which collectively regulates CBF, cerebral metabolism, and waste clearance (38).

Endothelial cells respond to increased shear stress by releasing nitric oxide, which relaxes adjacent vascular smooth muscle and promotes vasodilation (39). Conversely, when shear stress is reduced, nitric oxide availability declines, favouring vasoconstriction (39). Vascular smooth muscle cells also regulate tone through the myogenic response, which is activated by changes in intraluminal pressure rather than flow; constricting when intraluminal pressure rises and dilating when pressure falls, thereby buffering changes in pressure and helping stabilise downstream perfusion (40).

The neurovascular unit is also sensitive to gas composition and pH. CO₂ reactivity is primarily driven by vascular smooth muscle cells and perivascular astrocytes. These cells sense CO₂-induced changes in extracellular pH, which stimulate the release of vasoactive mediators that act on adjacent smooth muscle cells and pericytes to regulate vessel diameter and adjust downstream perfusion. This mechanism enables tight coupling between metabolic activity and cerebral perfusion, and also contributes to the maintenance of pH by facilitating clearance of excess CO₂ (41,42).

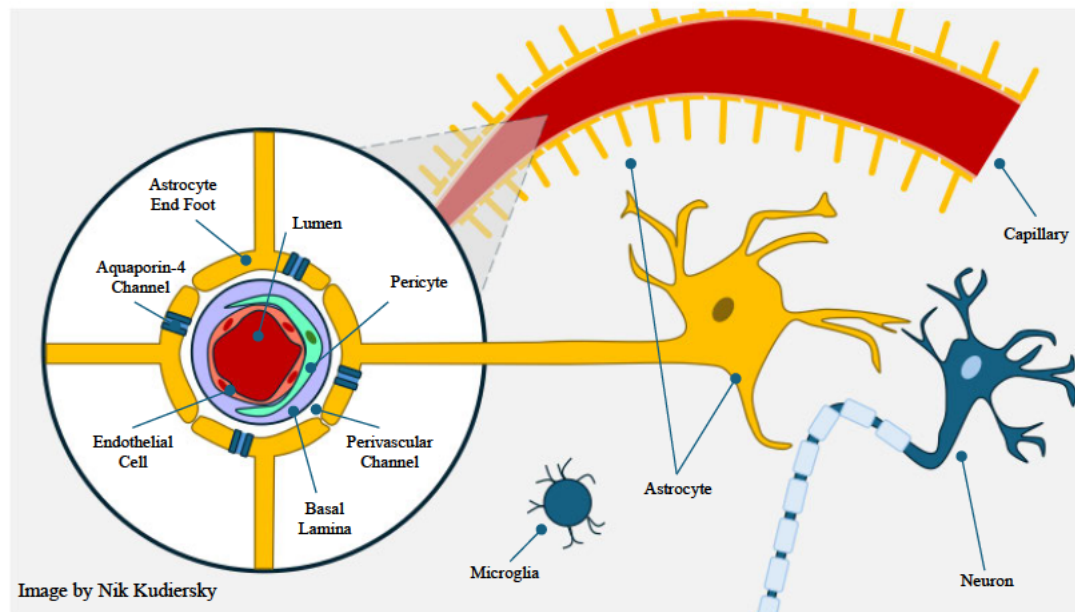


Figure 1.2 Neurovascular unit architecture of a capillary segment.

Astrocytes are a critical interface between neurons and the microvasculature. When neurons are active, glutamate is released into the synaptic cleft, which is absorbed and recycled by astrocytes, preventing excitotoxicity (43). Glutamate also activates signalling cascades within astrocytes, triggering the release of vasoactive mediators that act on adjacent smooth muscle cells and pericytes to modulate vessel tone and match local perfusion to neural activity — a mechanism known as neurovascular coupling (44).

Astrocytes also support cerebral metabolism by storing glycogen, which can be converted to glucose and lactate to support local energy demands (45). Additionally, astrocyte endfeet ensheath the vasculature to form perivascular channels, through which arterial pulsations drive cerebrospinal fluid into the interstitial compartment via aquaporin-4 channels, facilitating metabolic waste clearance from the brain (46). These astrocyte endfeet also form the outermost layer of the blood–brain barrier, beneath which pericytes reinforce the tight junctions between endothelial cells (the innermost layer), all anchored within a basal lamina scaffold (Figure 1.2). Collectively, the blood–brain barrier restricts the entry of pathogens, toxins and large molecules into the brain whilst facilitating the transport of nutrients and oxygen into the brain parenchyma (47).

Adapting to physiological challenges

A healthy neurovascular unit regulates CBF through integration of systemic and local regulatory mechanisms, whilst also adapting to physiological challenges such as fluctuations in MAP and arterial gas composition. Cerebral perfusion pressure provides the driving force for CBF, and cerebral autoregulatory mechanisms rapidly adjust cerebrovascular resistance to maintain relatively stable flow despite fluctuations in CPP (31).

For instance, moving from a sitting to a standing position causes blood to pool in the legs, which reduces venous return, MAP and cardiac output (48). The fall in MAP is sensed by stretch-sensitive baroreceptors located in the aortic and carotid arteries, which trigger a rapid sympathetic-mediated increase in heart rate, heart contractility, and peripheral vasoconstriction to restore MAP. Concurrently, cerebral autoregulation rapidly responds to the reduction in CPP by dilating cerebral arterioles via pressure-sensitive myogenic mechanisms (31).

During aerobic exercise, cardiac output and MAP increase in an intensity-dependent manner (49) which is buffered by the cerebral autoregulatory system through vasoconstriction of arterioles. Unlike the rapid baroreflex response that acts to counter orthostatic stress, during aerobic exercise the arterial baroreflex undergoes a 'functional reset' allowing blood pressure and heart rate to rise to meet increasing metabolic demand (50). There are, however, differential metabolic responses to exercise intensities to consider. During low-to-moderate intensity aerobic exercise, arterial CO₂ remains stable as ventilation increases proportionally to eliminate rising CO₂ produced as a metabolic byproduct of active skeletal muscle. At a vigorous intensity, however, arterial CO₂ rises faster than it can be cleared, and is detected by peripheral and central chemoreceptors, triggering hyperventilation, resulting in a fall in arterial CO₂, which stimulates cerebral vasoconstriction via CO₂ reactivity (34). This reduction in arterial CO₂ can override the influence of rising CPP, resulting in a decline in CBF at higher exercise intensities (34).

Following a stroke, the regulation of CBF can be disrupted due to disturbances in several key mechanisms including blunted CO₂ vasoreactivity, impaired neurovascular coupling, reduced endothelial-mediated vasodilatory reserve, and altered baroreflex control of systemic blood pressure. Together, these abnormalities heighten susceptibility

to both hypo- and hyperperfusion (30,51). Although ischaemic and haemorrhagic stroke have distinct aetiologies and pathological cascades, both typically result in impaired cerebrovascular (52–58) and baroreflex function (59). These impairments are most apparent in the first few weeks after onset, and may persist for several months (60–62). The haemodynamic effects of acute stroke interventions, whether pharmacological or rehabilitation focused, must therefore be carefully considered.

Acute stroke intervention aims

Acute stroke interventions have three overarching aims: 1) neuroprotection—the preservation of brain structure and function; 2) prevention of immobility-related complications including deconditioning; and 3) promotion of neuroplasticity—the reorganisation of neural networks to restore or compensate for lost neuronal function. An overview of acute stroke interventions, including medical treatment and rehabilitation methods is described below, including a critique of the evidence base underpinning early mobilisation and aerobic exercise training.

Neuroprotection

In ischaemic stroke, the most effective neuroprotective strategy is to restore cerebral blood flow as quickly as possible to minimise ischaemia and subsequent brain cell death (21). The first-line treatment for ischaemic stroke is to remove the vessel blockage via a catheter guided infusion of a thrombolytic drug (thrombolysis) or mechanical removal of the clot (thrombectomy), collectively referred to as reperfusion therapy (63). Approximately 90% of UK stroke patients do not receive reperfusion therapy (64) due to arriving at hospital too late, contraindications (e.g., high risk of bleeding), unknown stroke onset time (e.g., wake-up stroke), inefficient triage processes, or lack of neurointervention provision (65). In addition, reperfusion therapy is not always successful and can exacerbate inflammation and oedema, inducing secondary cell death and possibly haemorrhagic transformation (66). Beyond reperfusion therapy, there are currently no medical interventions that mitigate lesion expansion (67).

In haemorrhagic stroke, the primary neuroprotective strategy is to prevent a build-up of intracranial pressure and secondary damage to brain tissue caused by excess blood leakage (haematoma). In more severe haemorrhagic strokes, neurosurgery may be

performed to stem the bleed, repair injured or malformed blood vessels, and/or remove the haematoma (23).

For both stroke subtypes, a range of pharmacological strategies may be implemented to help restore and stabilise vital signs (body temperature, blood glucose, blood gases and blood pressure) within acceptable ranges to reduce the risk of deterioration and medical complications (68).

Blood pressure management is a particularly important consideration in acute stroke care, given its direct influence on CPP. Acute ischaemic stroke patients often present with hypertension, driven in part by preexisting hypertension as well as disturbed autoregulation and baroreflex function (59,60,69,70). This hypertensive response may represent a compensatory haemodynamic mechanism to maintain perfusion to the ischaemic penumbra. In the context of impaired cerebral autoregulation, elevated blood pressure could help sustain collateral perfusion to the penumbra, whereas aggressive blood pressure reduction risks lowering CPP below the threshold required to maintain penumbral perfusion, potentially causing infarct expansion. Clinical guidelines recommend a strategy of permissive hypertension in the hyperacute phase of ischaemic stroke, with the aim of preserving cerebral perfusion to the ischaemic penumbra via collateral vessels (70,71). Pharmacologically lowering blood pressure is avoided unless blood pressure is markedly raised (e.g., hypertensive crisis) or if reperfusion therapies such as thrombolysis or thrombectomy are planned, in which case tighter control is required (70).

In haemorrhagic stroke, cerebral autoregulation can also be impaired; however, the clinical dilemma differs from ischaemic stroke. The primary concern is haematoma expansion and rebleeding, which may justify early blood pressure reduction, but this must be balanced against the risk of hypoperfusion to vulnerable perihæmatomal tissue. Clinical guidelines support early blood pressure lowering in suitable patients with intracerebral haemorrhage, aiming for a sustained reduction over the first days of admission, and avoiding excessive, rapid declines that could compromise cerebral perfusion (70).

Despite the physiological rationale underpinning current blood pressure management strategies, the clinical trial evidence remains equivocal across both stroke subtypes, and optimal blood pressure targets are unclear (72,73). Aside from reperfusion therapy in ischaemic stroke and neurosurgery in severe haemorrhagic stroke cases, treatment options remain limited (67,74). Given that ~40% of stroke survivors live with a long-term disability (5), there is an urgent need to develop innovative acute stroke interventions that mitigate brain damage and enhance neurological recovery.

Preventing Deconditioning and Promoting Neuroplasticity

Once medically stable, two interrelated clinical objectives are introduced: 1) prevention of bed rest-related complications including deconditioning; and 2) promotion of experience-dependent neuroplasticity aiming to restore neurological function. Clinical guidelines recommend a range of rehabilitation strategies to address these objectives, including task-specific motor training (e.g., mobilisation) and constraint-induced movement therapy, resistance and aerobic exercise, plus adjunctive techniques such as electrical stimulation, mirror therapy, and mental practice (63).

Among these approaches, early mobilisation and aerobic exercise training are of particular interest because of their potential to perturb cerebral haemodynamics, with possible implications for perilesional perfusion. Early mobilisation is routinely implemented within stroke units, yet concerns persist regarding orthostatic hypotension and the potential for cerebral hypoperfusion. In contrast, moderate-intensity aerobic exercise transiently increases CBF in healthy and neurological populations, and enhances neuroplasticity in preclinical models of stroke. Despite these potential benefits, aerobic exercise is not routinely prescribed during the acute phase of stroke, and both mechanistic and feasibility investigations in this period remain limited. Research is needed to elucidate the optimal timing and dose, as well as the safety and effectiveness of these interventions when implemented early after stroke. The evidence base for early mobilisation and aerobic exercise is reviewed in the next chapter.

Chapter 2 – Literature Review of Early Mobilisation and Aerobic Exercise Training

This chapter begins by defining and differentiating early mobilisation and aerobic exercise—terms that are often conflated in the literature. Next, the rationale for these interventions is introduced. The subsequent section examines early mobilisation, exploring its origins within organised stroke units, historical concerns about upright positioning, and experimental evidence of how posture influences cerebral perfusion. Next, there is a critique of the preclinical neuroscience supporting early-initiated stroke rehabilitation and the challenges of translating those findings into clinical practice. The narrative then shifts to aerobic exercise training, starting with an overview of its neuroprotective and plasticity-promoting effects evidenced in preclinical studies. Human studies are then evaluated, focusing on the safety and efficacy of aerobic exercise in the early post-stroke period. Finally, the chapter concludes with an evaluation of evidence on how both early mobilisation and aerobic exercise may influence hospital-associated deconditioning.

Defining early mobilisation and aerobic exercise training

Before critiquing the science underpinning early mobilisation and aerobic exercise training, it is important to describe how these two interventions differ. This is necessary because the terms ‘mobilisation’ and ‘exercise’ are often used interchangeably, and many interventions that are categorised as mobilisation include both out-of-bed activity (mobilisation) and various types of exercise training (75–77). For clarity, within this thesis, mobilisation refers to any form of out-of-bed activity including sitting, standing and walking within 72 hours of stroke onset (78), but excludes activities that aim to improve cardiorespiratory fitness such as treadmill training. In addition, aerobic exercise is defined as structured physical activity involving continuous, rhythmic activation of large muscle groups which elicits a sustained increase in heart rate and breathing rate (79).

Scientific rationale for early mobilisation and aerobic exercise training

Stroke rehabilitation guidelines promote the implementation of physical activity interventions (including aerobic exercise and early mobilisation) to mitigate immobility-induced deconditioning and to ‘harness’ a window of neuroplasticity—defined as a time-limited period where the nervous system is more sensitive to rehabilitation (11). In addition, aerobic exercise training is recommended due to its beneficial effects on cardiorespiratory fitness and cardiovascular risk factors (63,80–84).

There is also substantial pre-clinical evidence indicating that early-initiated aerobic exercise training has neuroprotective effects (i.e., reduces brain damage after stroke), and promotes neuroplasticity (e.g., increased neurotrophic growth factors and neural growth) (13,85). However, there is currently a lack of evidence in clinical stroke populations, therefore aerobic exercise is not currently recommended for these purposes within clinical guidelines (see Table A2 in Appendix 2).

Early mobilisation: origins and evidence

In the pre-World War II era, stroke patients were admitted to general medical wards where prolonged bed rest was commonplace, prognosis was poor, and treatment was considered futile (86,87). A pioneering shift in stroke medicine and rehabilitation occurred in the 1950s with the advent of the organised stroke unit. Stroke patients admitted to an organised stroke unit received treatment, care and rehabilitation from a multidisciplinary team of specialists. In addition, rehabilitation emphasised earlier initiation and higher doses of therapy, including out-of-bed sitting, standing and walking (i.e., early mobilisation) (86,87). As organised stroke units propagated throughout the world, an increasing number of randomised controlled trials (RCTs) were performed to determine their effectiveness compared to general medical wards. By the beginning of the 21st century, several RCTs had demonstrated that being admitted to an organised stroke unit results in more favourable outcomes compared to admission to a general medical ward (88). The organised stroke unit model and the practice of early mobilisation subsequently became standard care throughout the world (89–92). However, because early mobilisation was introduced as part of the broader package of stroke unit interventions (e.g., acute assessments and investigations, patient monitoring

and management, and other therapies, delivered by a specialist team), it has not been possible to disentangle how early mobilisation contributes to the ‘stroke unit effect’. The first study attempting to identify the ‘active ingredients’ of organised stroke unit care was published in 1999. Based on an earlier RCT (93), which showed that patients treated on general medical wards had a higher risk of six-week mortality and one-year risk of institutionalisation than those allocated to an organised stroke unit, Indredavik and colleagues (94) conducted a retrospective multivariable analysis, reporting that earlier mobilisation was the strongest predictor of a favourable outcome (mean time to first mobilisation: 8 hours in the stroke unit vs 2.7 days on general wards). However, stroke unit patients also had more favourable blood pressure, blood glucose, and body temperature, which likely influenced recovery and confounded the results (94). This work inspired a sequence of studies by the A Very Early Rehabilitation Trial (AVERT) group, which have since had a significant impact on clinical practice globally.

The phase II AVERT study (95) investigated the safety, feasibility and preliminary efficacy of very early mobilisation (VEM) in acute stroke—defined as getting out of bed (sitting or standing as able) within 24 hours of stroke onset. The median time to first mobilisation was 18.1 hours in the VEM group (n=38) and 30.8 hours in the usual care (n=33) group. Importantly, the VEM group received approximately three additional sessions per day, amounting to a two-fold greater duration of daily therapy and total therapy (96). Whilst the authors concluded that VEM was safe and feasible to deliver, the mortality rate was doubled in the VEM group (21% vs. 9%), providing an early warning signal that VEM could be unsafe. The AVERT group was subsequently approved to progress to a phase III RCT (14).

In the phase III AVERT study, the VEM group’s first mobilisation was at a median of 18.5 hours post-stroke compared to 22.4 hours in the usual care group. The headline result was that VEM was associated with an increased risk of a poor neurological outcome three months after stroke. Moreover, there was no difference in immobility-related complications between groups. Akin to its preceding phase II trial, the phase III AVERT study did not standardise therapy dose; the VEM group engaged in an additional three bouts of mobilisation per day. Thus, the detrimental outcome could be attributed to earlier mobilisation, more frequent mobilisations, more time spent mobilising, or an interaction of these factors.

In addition to the AVERT II and III trials, numerous RCTs have assessed the safety and effectiveness of VEM compared to usual care. The most recent Cochrane systematic review of nine RCTs (n=2958) concluded that VEM (median time to first mobilisation = 18.5 hours) likely led to similar or slightly more deaths, and poorer neurological outcomes compared to delayed mobilisation (median = 33.3 hours) (97). These Cochrane results were, however, dominated by the phase III AVERT study which recruited 2104 participants (71% of total participants included in the Cochrane review) (14). While the underlying mechanisms in these RCTs were not investigated, a plausible explanation is that orthostatic stress may have compromised perfusion within perilesional brain tissue, leading to poorer outcomes.

Cerebral haemodynamic concerns about early mobilisation

There is a longstanding argument that early mobilisation may disrupt cerebral perfusion, which could injure the brain or delay recovery. For example, in an article published in 1958, Dr Fisher wrote:

Clinical observations indicate that strokes and ischemic attacks in many cases develop when the patient gets up from his bed, particularly in the morning or postoperatively. In the upright position the cerebral circulation falls, and for this reason it is recommended that patients with a stroke as the result of ischemic infarction should remain horizontal in bed for 7 to 10 days initially and that when ambulation starts special attention should be given to maintenance of the systemic circulation (the patient must avoid standing quietly for prolonged periods, must sit with feet up, etc.)(98).

In 1976, Caplan & Sergay (99), described the ‘positional cerebral ischaemia’ phenomenon. In their article, four detailed case studies were presented about stroke patients who experienced worsening of neurological deficits after transitioning from supine to an upright position, followed by an alleviation of symptoms after returning to a supine position. Based on this clinical experience, Dr Caplan and Dr Sergay recommended that patients who experience orthostatic worsening of symptoms should be encouraged to remain in a supine or Trendelenburg position.

In 1984, Dr Thomas (Consultant Neurologist) acknowledged that bed rest can be detrimental, and skilled nursing is required to prevent bedsores, contractures, and exposure keratitis. However, he also stated:

Premature attempts to mobilise a patient are not likely to be helpful and may actually be harmful (100).

Despite this series of opinion pieces questioning the safety of early mobilisation, there was also a growing body of evidence favouring the organised stroke unit model, which included early mobilisation as a core rehabilitation technique (93,101,102). As evidence mounted supporting the organised stroke unit model, clinical guidelines followed suit, promoting the rollout of organised stroke units throughout the world (89,103).

In response to this shift in clinical practice, Diserens and colleagues critiqued the evidence base underpinning early mobilisation, highlighting the lack of well-designed RCTs (104). Further, this group suggested that vulnerable penumbral tissue is more likely to be salvaged if patients remain in a horizontal position, avoiding episodes of orthostatic stress (gravity-induced downward shift in blood volume away from the head). This theory was based on their:

...frequent clinical experience that patients with worsening of their clinical deficit in the acute phase improve clinically by lying flat or even (transiently) in a Trendelenburg position (104).

In addition, in 2008, a survey of 202 stroke professionals (physicians, nurses, physiotherapists, occupational therapists, and speech and language therapists) revealed that 60% of respondents were concerned that mobilisation within 24 hours of stroke onset could be harmful, and therefore favoured bed rest (105).

Despite the abovementioned safety concerns about the impact of early mobilisation on cerebral perfusion (9,14,104,105), there is limited evidence of how standing up affects cerebral haemodynamics in acute stroke (106,107). The only study conducted to date on this topic recently highlighted that standing up within two days of stroke onset causes a pronounced decline in cerebral perfusion in the ipsilesional hemisphere (107), which corroborates the historical concerns about early mobilisation (see Chapter 4 for

literature review regarding effect of posture on cerebral haemodynamics).

In summary, clinical guidelines throughout the world promote early mobilisation (63,80–84). However, there is a lack of evidence to support current recommendations. To the contrary, the totality of evidence suggests that early mobilisation could impair recovery, and there is a plausible haemodynamic mechanism which may explain this—orthostatic stress (108). The cerebral haemodynamic effects of posture in acute stroke patients are evaluated in Chapter 4.

Harnessing neuroplasticity: translating environmental enrichment to clinical practice

This section examines the neuroscience underpinning early mobilisation, focusing on preclinical studies of environmental enrichment and highlighting how these differ from clinical stroke interventions.

A central rationale for initiating rehabilitation early after stroke onset is the prospect of harnessing the so-called ‘window of neuroplasticity’—a time-limited period after stroke whereby the neuromotor system is more amenable to environmental stimuli such as motor rehabilitation (11,14). This sensitive period, lasting around 14-30 days (11,109,110), is characterised by a transient upregulation of growth-promoting genes and neurotrophins, heightened cortical excitability, and structural remodelling in peri-infarct tissue including axonal sprouting, dendritic branching, synaptogenesis, and angiogenesis (111–113).

Experimental evidence for this window of neuroplasticity was provided by a landmark study conducted by Biernaskie and colleagues (2004) (114). Rodents were exposed to environmental enrichment (cages filled with a variety of objects intended to stimulate bimanual limb use) at days 5, 14 and 30 days after stroke onset, and their outcomes were compared to a social housing group (two to three caged rodents with no additional stimuli). The greatest improvements in functional recovery were exhibited in the day-5 group, with moderate improvements observed in the day-14 group, whereas the 30-day group did not differ from the social housing control group.

Importantly, the preclinical evidence which underpins early mobilisation involves environmental enrichment (described below) which does not reflect clinical practice. Acute stroke wards have been described as lonely, sedentary environments, where stroke survivors typically receive low doses of rehabilitation (115). For example, an observational study using accelerometers reported that during the acute phase of stroke, most patients spend over 98% (>23 hours) of their day physically inactive (lying or sitting), 1% (18 minutes) per day standing, and less than one minute per day walking (116). In addition, those with moderate stroke spent less than 30 minutes walking and less than 30 minutes standing. Whereas those with severe stroke spent over 95% of their day in bed, with the remaining time spent sitting in a bedside chair (115). In contrast, many environmental enrichment protocols facilitate high levels of physical activity.

Anatomical differences between rodents and humans

When translating preclinical findings to the human acute stroke setting, anatomical and haemodynamic differences between rodents and humans must be considered. Rodents are quadrupeds with horizontally orientated cardiovascular systems (117). Rodents are therefore less likely to experience large gravity-induced shifts in blood volume when engaging in habitual behaviours such as walking and running. By contrast, in humans the transition to an upright posture shifts a large proportion (~70%) of blood below heart level, promoting venous pooling in the legs (108). Whilst a healthy human brain can tolerate orthostatic stress, cerebrovascular function can be impaired after stroke meaning that upright activities such as walking and standing may provoke cerebral hypoperfusion (31,52–54,118). This hypoperfusion could, in turn, counteract neuroplastic processes that depend on adequate blood flow.

Aerobic exercise is a key ingredient of environmental enrichment

Preclinical environmental enrichment protocols are designed to improve rodents' physical and mental wellbeing by minimising stress and facilitating natural behaviours through exposure to stimuli beyond basic survival needs (119). In enriched environments, rodents are typically afforded opportunities to socialise and/or engage in stimulating activities such as climbing, tunnelling, burrowing, and use of a running wheel (i.e., aerobic exercise) (120). Although these studies aim to maximise external

validity by encouraging natural behaviour, the multiple components of environmental stimuli make it difficult to determine the ‘active ingredients’.

Some researchers have attempted to disentangle the most important components of environmental enrichment on neurological outcomes, and have demonstrated that aerobic exercise is a key driver of neuroplasticity. For example, Kobil et al., (2011) (121) set up four experimental conditions for healthy rodents: 1) toys and tunnels (environmental enrichment); 2) running wheels only (exercise); 3) toys, tunnels and running wheels (environmental enrichment plus exercise); and 4) empty cages (control). After 43 days of exposure, only rodents with access to running wheels exhibited increased neurogenesis and brain-derived neurotrophic factor concentration (a protein which promotes neuroplasticity) within the hippocampus (121). In contrast, having access to toys and tunnels alone did not induce neurogenesis. One limitation of this study was that the time spent engaging in each activity (i.e., dose) was not recorded.

Acknowledging these limitations, Mustroph et al., (2012) (122) conducted a similar experiment using healthy rodents but monitored daily time spent engaging in each activity, as well as total daily running distance. This study found that environmental enrichment without running did not elicit neurogenesis, whereas both running groups (running alone, and running combined with environmental enrichment) exhibited a twofold increase in new neurons compared to non-running groups. In addition, running distance was positively correlated with the number of new neurons generated, indicating a dose-response effect.

Evidence for aerobic exercise as an early stroke rehabilitation intervention

Building on the discussed environmental enrichment evidence, this section provides a narrative review of studies involving aerobic exercise delivered as a stand-alone intervention. The reviewed studies are organised by stroke phase (hyperacute: 0-24 hours; acute: 1-7 days; and early subacute stroke: 7-90 days) as defined by the Stroke Recovery Rehabilitation Roundtable (26). In addition, as this thesis focuses on *early-initiated* aerobic exercise training, the following narrative review is confined to studies where the average intervention initiation timepoint is less than or equal to 30 days post-stroke. This 30-day timepoint was selected because neuroplasticity is suggested to be

heightened in the first 2-4 weeks post-stroke (11,109,110,114), and blood–brain barrier function has been reported to be impaired in the first month after stroke (56,62,123). Where there is sufficient evidence, summaries are categorised by exercise mode (seated vs. walking) to help elucidate the potential influence of posture on outcomes. Lastly, the evidence regarding the effects of aerobic exercise training on hospital-acquired deconditioning is discussed.

Hyperacute and acute phase (0-7 days post-stroke): pre-clinical evidence

The timing of aerobic exercise training initiation relative to stroke onset is a critical factor. Most cell death and neurological deficit occurs within the first 24 hours after stroke, known as the hyperacute phase (26). Pre-clinical evidence suggests that undertaking aerobic exercise training in the hyperacute phase of stroke amplifies cellular stress and inflammation which exacerbates the cerebral injury and neurological deficit (124–127).

However, numerous pre-clinical studies have demonstrated that initiating aerobic exercise training in the acute phase of ischaemic stroke (1-7 days post-stroke) augments neuroplasticity, evidenced by enhanced structural reorganisation of neuronal networks (e.g., dendritic branching and synaptogenesis) and an increased presence of neural and vascular growth factors (85,128). The mechanisms underlying these effects are explored in detail in Chapter 6, including exercise-induced changes in cerebral blood flow, neurotrophic growth factors, and downstream cellular adaptations within the neurovascular unit. In rodent models of ischaemic stroke, the optimal exercise dose parameters which promote neuroplasticity are 30 minutes of moderate-intensity aerobic exercise per day, initiated 3 to 7 days post-stroke lasting at least two weeks (85).

Several pre-clinical studies have also demonstrated that aerobic exercise training initiated in the acute phase of stroke induces neuroprotection. Aerobic exercise training interventions starting 24 to 48 hours after stroke have been shown to reduce lesion volume and biomarkers of inflammation, oxidative stress and cell death (13). Neuroprotective effects are most commonly found with interventions that start in the early acute phase (24-48 hours vs. 3 to 7 days) and are carried out at light-to moderate-intensity for 20-30 minutes on 5-7 days per week, for a duration of at least two weeks (13).

With regards to haemorrhagic stroke, few studies have investigated the effects of early-initiated aerobic exercise training, but initial results are promising. One pre-clinical study found that two weeks of treadmill running (5 days/week, 20m/min, high-intensity (85)) initiated one day after haemorrhagic stroke led to improved performance in one of three motor outcome measures compared to delaying exercise until one week after stroke, and neither exercise condition caused haematoma expansion or oedema (129). Lee et al., (2005) (130) demonstrated that 30 minutes of treadmill running (8m/min, light-intensity (85)) for 10 days, beginning 24 hours after haemorrhagic stroke reduced lesion volume compared to delayed exercise starting 72 hours post-stroke. Further, Yoon et al., (2013) (131) compared treadmill training beginning 24 hours after haemorrhagic stroke to a non-exercise control group and demonstrated that aerobic exercise training reduced lesion volume. In contrast, Takamatsu et al., (2010) (132) compared early-initiated treadmill training intervention (starting 4 days post-stroke) for 11 consecutive days, and demonstrated that exercise did not reduce lesion volume. However, treadmill training improved motor function and dendritic branching compared to the control group (no treadmill exercise). The authors speculated that starting the intervention four days after stroke may have been too late to influence lesion formation.

Acute phase (1-7 days post-stroke): clinical evidence

Despite the promising pre-clinical evidence supporting the use of aerobic exercise to elicit neuroprotection and neuroplasticity, only three clinical studies have initiated aerobic exercise interventions in the acute phase of ischaemic stroke (1-7 days post-stroke). These studies provide preliminary insight into the feasibility, safety and potential effectiveness of aerobic exercise.

Firstly, Sandberg et al., (2020) (133) investigated the effects of early-initiated in-bed recumbent aerobic exercise training on physical function after ischaemic stroke. The intervention group participants (n=23) were mostly non-ambulatory at baseline (median modified Rankin Scale of 4), and the mean time to randomisation was 1.9 ± 1 days for the intervention group. Participants were encouraged to exercise using a recumbent in-bed cycle ergometer for up to 20 minutes per day, at a subjective exercise intensity of light- to somewhat hard (11 to 13 RPE) on five days per week for a total of three weeks (15 sessions in total). Control group participants (n=29) received usual care therapy.

Whilst the intervention was found to be safe, there were no between-group differences in physical function measured three months after stroke. A key limitation of this study is that the cycling intervention permitted passive cycling where the bike's motor moves the participant's legs (no exertion), yet there was a lack of detail to determine what proportion of exercise sessions involved active and passive cycling. In addition, the attained exercise intensity (e.g., actual heart rate or RPE values) and intervention fidelity were not reported.

Secondly, one small RCT including 20 ischaemic stroke participants with hemiparesis demonstrated that five consecutive daily 20-minute sessions of upright cycling exercise, with a target intensity of 50-70% predicted maximum heart rate (light- to-moderate intensity), beginning approximately 1-2 days after stroke (exact timeframe not specified) is safe and leads to increased leg muscle strength, improved mobility (ICU mobility scale) and walking ability compared to a control group. Whilst this study provides promising results, the reported exercise dose was unclear. This intervention also permitted both passive cycling (no exertion) and active cycling, but the proportion of sessions completed in passive and active exercise modes was not reported. In addition, the length of the conditioning component (exercise duration excluding the warm-up and cooldown), heart rate, RPE scores, and intervention fidelity were not reported (134).

Finally, one study assessed the feasibility of early-initiated treadmill training (mean 41.5 ± 14 hours after ischaemic stroke) involving five days of twice-daily 30-minute sessions (10 sessions in total) of moderate-intensity treadmill walking ($>50\%$ heart rate reserve [HRR]) with a harness support if needed (135). The target HRR was achieved in only 31% of sessions, which the authors attributed to poor motor function. The authors reported that this intervention was safe and feasible. However, adverse events occurred in almost 15% of sessions, and the most common issue was dizziness (8.5% of sessions).

The contrasting safety profile between these studies (namely, the occurrence of dizziness) may be explained by a combination of exercise dose and posture. Participants in the treadmill training study completed a higher weekly volume of exercise training (two sessions per day vs once per day) and therefore had greater exposure to orthostatic stress. Given that cerebral autoregulation can be impaired after stroke (31,52–54,118), it

is plausible that twice-daily treadmill training could have compromised cerebral perfusion, leading to dizziness.

Early subacute stroke (7-30 days post-stroke): clinical evidence

As discussed above, posture (i.e., exercise mode) is an important factor to consider when evaluating the safety and effectiveness of aerobic exercise interventions, particularly in brain injured populations (9). The following literature review of aerobic exercise interventions initiated within 7-30 days of stroke onset is therefore categorised by studies including and excluding walking. To maintain scope, interventions categorised as gait training were excluded from this review, as their primary aim is task-specific motor training rather than structured aerobic exercise training. The rationale for using 30 days as a cut-off is that the first month is considered as a critical period for neuroplasticity (11,109,110,114), however cerebral autoregulation and the baroreflex may still be impaired in this period (56,61,62,123). Thus, while there is potential to augment recovery through aerobic exercise, this must be balanced with the risk of perturbing cerebral perfusion during this early window.

Walking-based interventions (7-30 days post-stroke): clinical evidence

Toledano-Zarhi et al., (2011) (136) recruited 28 ischaemic stroke patients with minor disabilities. Participants were randomly allocated to either supervised exercise training (n=14) or usual care (home exercise booklet, n=14). The mean intervention initiation timepoint was 11 days post-stroke in both groups (usual care: ± 4 days; aerobic exercise: ± 5 days). The exercise intervention consisted of two exercise sessions per week for six weeks. One weekly session incorporated progressive aerobic exercise, whereas the other focused on strength, flexibility and motor coordination. The aerobic exercise intervention involved 35-55 minutes of light-to moderate-intensity exercise (50-70% predicted maximum heart rate), including treadmill training, arm cycling and leg cycling (six aerobic exercise sessions in total). The time spent engaging in each mode of aerobic exercise was not reported, therefore it is assumed that duration was equally distributed (33% of total exercise duration per mode: treadmill, arm cycling and leg cycling). Both groups significantly improved their six-minute walk distance, but the supervised exercise group improved to a greater extent (per protocol analysis). No adverse events occurred during the intervention.

Outermans et al., (2010) (137) recruited 44 ambulatory, mildly impaired subacute stroke patients (stroke type not specified) between 2-8 weeks post-stroke (intervention group, mean 23.5 ± 7.8 days post-stroke) and compared a walking training programme (n=22) to conventional physiotherapy (n=21). The walking intervention included circuit training exercises focused on improving gait, followed by 10 minutes of brisk walking progressing from moderate (40-50% HRR) to vigorous intensity (70-80% HRR) over four weeks. The intervention resulted in significantly greater improvements in six-minute walk distance and ten-metre walking speed compared to usual care. Further, no adverse events occurred during the intervention period.

Mackay-Lyons et al., (2013) (138) enrolled 50 ischaemic stroke patients (23 ± 5 days post-stroke) who were able to walk at least five metres with or without use of ambulatory aids at baseline. Participants were randomly allocated to supervised aerobic exercise training (n=24) or usual care (n=26). The aerobic exercise training intervention involved bodyweight supported treadmill walking gradually progressing from 5- to 10-minute bouts of light- to moderate-intensity exercise (heart rate corresponding to 40-50% of peak oxygen consumption) to 20 minutes at moderate- to vigorous-intensity (heart rate corresponding to 60-75% of peak oxygen consumption) over a 12-week period. Treadmill speed and incline was gradually progressed throughout the intervention. Exercise sessions were implemented five days per week for the initial six weeks, then three days per week for the final six weeks (48 sessions in total). The aerobic exercise training intervention was safe and led to a significantly greater increase in cardiorespiratory fitness and walking endurance compared to conventional physiotherapy.

Brauer et al., (2022) (139) randomly allocated 119 ischaemic and haemorrhagic stroke survivors with minor disability to usual care (n=59, 86% ischaemic) or treadmill training (n=60, 78% ischaemic). Patients needed to be able to walk 10 metres independently at baseline to participate. The treadmill intervention consisted of three moderate-intensity (40-60% HRR; or RPE 11-14, equivalent to light-to-moderate intensity), 30-minute treadmill training sessions per week for eight weeks (24 sessions in total). The mean intervention initiation timepoint was 28 ± 15 days after stroke. Although the treadmill training group had a significantly higher daily step count throughout the intervention period and at a six-month follow-up, there was no difference between groups in cardiorespiratory fitness, 10-metre walking ability, six-

minute walking distance, mood or quality of life. A key limitation of this study was that all participants had a relatively normal walking speed at baseline, possibly creating a ceiling effect. In addition, cardiorespiratory fitness (peak oxygen consumption) was measured using a portable gas analyser during a six-minute walk test which is not a valid method to assess peak oxygen consumption as it is self-paced, not incremental. The rate of adverse events was not reported in this study.

The PHYS-STROKE trial (140) recruited stroke patients (n=200; 91% ischaemic) who were deemed able to perform aerobic exercise by a physician. This trial compared early-initiated treadmill training (n=105) to relaxation sessions (n=95). The median treadmill training initiation timepoint was 30 days after stroke onset (IQR 17-39 days). The exercise intervention consisted of 25-minute, moderate-intensity treadmill training sessions (50-60% HRR), five times per week for four weeks (20 sessions in total). Exercise progression included increasing treadmill incline and reducing bodyweight support over the 20-day period. Treadmill training was associated with a higher rate of serious adverse events including falls, recurrent stroke and hospital admissions. In addition, 5% of participants self-reported dizziness on at least one occasion (5/105). The study demonstrated no between-group differences in disability or walking performance measures. These results highlight that treadmill training is not superior to relaxation and may increase the risk of harm. It is unclear why treadmill training was associated with a higher rate of serious adverse events. One potential explanation is that orthostatic stress caused excessive cerebral hypoperfusion in some participants, particularly if their cerebral autoregulatory or baroreflex function was impaired. It is also noteworthy that there were 8% more haemorrhagic stroke patients in the intervention group. Haemorrhagic stroke is associated with poorer outcomes post-stroke compared to ischaemic stroke (141,142). This difference in stroke sub-types may have skewed the results.

In summary of the aerobic exercise interventions incorporating treadmill training initiated within 7-30 days of stroke onset, there appears to be a mixed safety and efficacy profile. Three studies reported no adverse events (136–138), one study lacked safety information (139), and one study highlighted an increased risk of falls, recurrent stroke and hospital readmissions (140). The negative findings from the PHYS-STROKE trial, combined with evidence that treadmill training caused dizziness in 8.5% of sessions in an acute stroke cohort (135), may indicate that some acute stroke patients are

unable to tolerate orthostatic stress. The two studies which were associated with an increased risk of dizziness or serious adverse events involved 2.5 to 5 hours of moderate-intensity (50-60% HRR) walking completed over five consecutive days (135,140). In contrast, other studies (136–138) implemented safe and effective interventions which involved a gradual increase from light- to moderate-intensity exercise beginning with relatively short walking durations per session (5-10 minutes). A progressive, walking-based aerobic exercise intervention, beginning with a short duration at a lower intensity exercise may therefore be a safer and more effective approach during the early post-stroke period.

Seated ergometry interventions (7-30 days post-stroke): clinical evidence

The following literature review pertains to aerobic exercise training using seated ergometers (cycling or recumbent stepping), excluding overground or treadmill walking interventions.

Tang et al., (2009) (143) recruited 57 subacute stroke patients (74% ischaemic) with minor to moderate disability (NIHSS: ~ 5 ; able to walk at least five metres) at a mean of 19 ± 4 days post-stroke. Participants were allocated to aerobic exercise ($n=23$) training or usual care ($n=25$). The intervention consisted of three aerobic exercise sessions per week using a semi-recumbent cycle ergometer, and the mean exercise duration progressed from 17 minutes to 27 minutes throughout the intervention period (for 4-5 weeks or until discharge if earlier). The target exercise intensity was 50% to 75% of peak work rate (light- to vigorous-intensity) achieved in a graded maximal exercise test conducted at baseline. Progression methods were to increase to a 30-minute exercise duration, then increase work rate to tolerance. 90.5% of scheduled sessions were completed. No adverse events occurred during the intervention period. Additionally, there were no statistically significant differences in physical performance or disability outcomes between the control group and intervention group. Heart rate responses were not reported because several patients were taking chronotropic medications, and the dose of exercise attained by each participant was not described.

Sandberg et al., (2016) (144) performed a RCT to investigate the effects of an aerobic exercise programme, initiated three weeks (mean, 22 ± 10 days) after mild stroke (98% ischaemic; able to walk at least 5 metres independently) on physical function. The

intervention consisted of twice-weekly exercise sessions using an in-bed cycle ergometer. Each exercise session incorporated 16 minutes of aerobic exercise, gradually progressing from light- to moderate-intensity (11-13 RPE; 60% predicted maximum heart rate) through to vigorous-intensity (14-15 RPE; 80% predicted maximum heart rate) over a 12-week period. The control group received generic physical activity advice plus usual care therapy. A median of 19 exercise sessions per patient were completed by the intervention group. All intervention participants achieved the target exercise intensity measured using RPE, but heart rate responses were not reported. No adverse events occurred in relation to the intervention. Aerobic exercise training resulted in significantly greater improvements in multiple outcome measures compared to the control group, including aerobic capacity (peak cycling work rate), walking distance and speed, balance, sit-to-stand ability, quality of life and perceived recovery after stroke.

Biasin et al., (2014) (145) conducted a feasibility study to determine the safety of aerobic exercise training and adherence to exercise guidelines in an inpatient stroke rehabilitation setting. Thirty-three subacute stroke (78% ischaemic) patients (mean 25.9 ± 12.6 days post-stroke) participated in an aerobic exercise programme comprising up to eight sessions delivered over three weeks (up to three sessions per week) using a recumbent stepper. Prior to the exercise programme, a sub-maximal graded exercise test with ECG monitoring was conducted to determine patients' exercise tolerance and to detect cardiac abnormalities. Four patients were excluded based on ECG findings, demonstrating the importance of cardiac screening. The target exercise intensity was 50-80% of age-predicted maximum heart rate (light-to-vigorous intensity), and the target exercise duration was 30 minutes. The exercise dose was progressed by gradually increasing session duration (first session, 12.5 ± 4.3 mins; final session, 21.3 ± 21.3 mins) and workload (individualised). Despite participants completing a sub-maximal exercise test which terminated at 70% age-predicted maximum heart rate, the authors described that the supervising physiotherapist opted for a cautious progression of heart rate throughout the intervention. As a result, a low proportion of exercise sessions were spent above 50% age-predicted maximum heart rate (first session, 8.4 ± 6.1 mins; final session, 11.3 ± 10.2 mins). This study's conclusion was that aerobic exercise training in subacute stroke is safe (no adverse events occurred), but there was low attainment of the target exercise intensity. Changes in post-stroke fitness or function were not assessed.

Katz-Leurer et al., (2003) (146) randomly allocated 92 acute stroke patients (approximately 15 days post-stroke; 87% ischaemic) to either usual care or an 8-week leg cycling aerobic exercise intervention. The intervention was split into two phases. The initial two weeks consisted of five exercise sessions per week, and each exercise session comprised two-minute intervals interspersed with one-minute rest periods, gradually increasing from 10 to 20 minutes (one minute added per day) over the two-week period. The following phase (weeks 3-8) included 30-minutes sessions across three days per week. All exercise sessions were conducted at an intensity of <60% HRR (low to moderate intensity). The aerobic exercise intervention did not result in improvements in maximal walking distance, walking speed, and functional independence. However, leg cycling work rate and stair climbing performance were improved. The heart rate values attained by participants were not reported, therefore the exercise dose is unclear. In addition, the 220-age formula was used to estimate maximal heart rate. This formula underestimates maximal heart rate in older adults which may have resulted in a suboptimal exercise dose being prescribed to patients (147). Further, the rate of exercise progression was minimal (one minute per day) which may have been insufficient to elicit a significant training effect. Lastly, the rate of adverse events was not reported.

In summary, evidence regarding the effectiveness of cycling-based aerobic exercise training initiated 7-30 days post-stroke is mixed, with one study demonstrating no improvements in function (143), one study reporting an improvement in stair climbing ability (146), and another study reporting improvements in multiple physical function outcomes (144). In addition, the discussed studies reported no adverse events, yet none reported heart rate values attained by patients which obscures the safety profile of each intervention.

Aerobic Exercise Training Summary

In summary, animal studies demonstrate that aerobic exercise training initiated in the acute phase stroke elicits neuroprotection and neuroplasticity. However, starting aerobic exercise in the hyperacute phase (<24h post-stroke) may exacerbate the brain injury. It is important to note that rodent exercise interventions are conducted in their natural head down position, meaning that orthostatic stress is minimal. The underlying mechanisms linking aerobic exercise to post-stroke brain recovery are discussed in Chapter 6.

The benefits of aerobic exercise have not yet been translated to clinical acute stroke populations. Uncertainty remains about the optimal aerobic exercise intervention components including initiation timepoint, mode, frequency, intensity, and duration, volume and rate of progression. Clinical studies involving aerobic exercise training initiated in the acute phase of stroke have revealed conflicting results. Two recumbent cycling interventions have been conducted, with one study reporting null effects, and the other demonstrating improvements in muscle strength and functional capacity. In addition, one treadmill training intervention reported frequent dizziness, which is indicative of cerebral hypoperfusion.

Studies involving treadmill aerobic exercise interventions initiated 7-30 days post-stroke demonstrate mixed results. Earlier initiated and higher doses of treadmill exercise may increase the risk of falls, recurrent stroke and hospital readmissions. However, walking-based aerobic exercise interventions, gradually progressing from shorter-durations and lower-intensities appear to be safer and more effective during the early subacute period. With regards to seated ergometry aerobic exercise interventions initiated 7-30 days post-stroke, the evidence demonstrates a good safety profile, but mixed efficacy results. However, the exercise doses attained by participants are unclear.

In conclusion, there is uncertainty regarding the safety and effectiveness of aerobic exercise training initiated in the acute phase of stroke. Table 2.1 provides a summary of the reviewed exercise interventions and outcomes. Further research is needed to determine the feasibility and safety, and optimal timing, mode and dosage of aerobic exercise after stroke.

Table 2.1. Characteristics of aerobic exercise interventions initiated 1–30 days post-stroke

Stroke phase	Study	Mode	Intervention group sample (n, % ischaemic)	Stroke severity	Post-stroke initiation timepoint	Session frequency, intervention duration	Total sessions planned	Target session intensity and duration	% Completion / Adherence	Outcomes	Safety/issues	Attained exercise intensity
Acute phase (1–7 days)	Strømmen et al., (2016) (135)	Treadmill	n=20, 100%	Mild: mRS ≤ 2	41.5 $\pm$ 14 hrs	2x/day, 5 days	10	>50% HRR; 30 mins	88% completed, 97% initiated	Feasible, but low HR target attainment (31%)	Dizziness (8.5%), exhaustion (11%)	31% achieved over 50% HRR in all sessions; no RPE data
	Sandberg et al., (2020) (133)	In-bed, semi-recumbent cycling	n=23, 100%	Moderate-severe: mRS: 4 $\pm$ 1; NIHSS 13.0 $\pm$ 4.8	3–5 days	5x/week, 3 weeks	15	RPE 11–13; 20 mins	NR	No difference vs control	Safe	Passive vs active not reported; no HR response or RPE data
	da Rosa Pinheiro et al., (2021) (134)	Upright cycling	n=10, 100%	Hemiparesis (severity NR)	3–7 days	Daily, 5 days	5	50–70% HRmax; 20 mins	NR	$\uparrow$ Leg strength, $\uparrow$ ICU mobility	Safe	Passive vs active not reported; no HR response or RPE data
Early subacute phase (7–30 days)	Toledano-Zarhi et al., (2011) (136)	Mixed (treadmill, upright arm + leg cycling)	n=14, 100%	Mild: 50% mRS ≤ 1 ; 50% mRS 2	11 $\pm$ 5 days	2x/week, 6 weeks	12	50–70% HRmax; 35–55 mins across modes	84% $\pm$ 20%	$\uparrow$ 6MWD	Safe	No HR response or RPE data
	Outermans et al., (2010) (137)	Circuit training + treadmill	n=22, 100%	Mild: walk 10m unaided	22.5 $\pm$ 8 days	3x/week, 4 weeks	12	40–80% HRR; 45-minute circuit training, 10 min walking	NR	$\uparrow$ 6MWD, $\uparrow$ 10m walk speed	Safe	No HR response or RPE data
Walking	Mackay-Lyons et al., (2013) (138)	Bodyweight-supported treadmill	n=24, 100%	Mild: able to walk ≥ 5 m	23 $\pm$ 5 days	4x/week, 12 weeks	48	40–75% VO ₂ peak; 5–10 min bouts, progress to target of ≥ 20 mins	90%	$\uparrow$ CRF, $\uparrow$ 6MWD	Safe	No HR response or RPE data
	Brauer et al., (2022) (139)	Treadmill	n=60, 78%	Mild-moderate: mRS 2.8 $\pm$ 0.6	28 $\pm$ 15 days	3x/week, 8 weeks	24	40–60% HRR, RPE 11–14; up to 30 mins	80% $\pm$ 20%	No difference vs control	NR	No HR response or RPE data
Seated	Nave et al., (2019) (140)	Bodyweight-supported treadmill	n=105, 91%	Moderate: NIHSS 8 (median)	Median 30 days (IQR 17–39)	5x/week, 4 weeks	20	50–60% HRR; 25 minutes	80%	No difference vs control, $\uparrow$ AEs	$\uparrow$ Falls, $\uparrow$ stroke recurrence, $\uparrow$ hospital admissions	Target HR achieved in ~40–80% of sessions/week; mean delta HR 15 $\pm$ 9 bpm
	Tang et al., (2009) (143)	Semi-recumbent cycling	n=23, 74%	Mild-moderate: NIHSS 4.9 $\pm$ 0.5	17.8 $\pm$ 3.1 days (6–62 range)	3x/week, 4–5 weeks	12–15	50–75% peak work rate; up to 30 mins	90.5 $\pm$ 1.5%	No difference vs control	One withdrawal (uncontrolled BP), no related AEs reported	No HR response or RPE data
	Sandberg et al., (2016) (144)	In-bed, semi-recumbent cycling	n=29, 100%	Mild	22 $\pm$ 10 days	2x/week, 12 weeks	24	60–80% HRmax; RPE 11–15; 16 mins (2 x 8 min)	79%	$\uparrow$ CRF, $\uparrow$ 6MWD, $\uparrow$ 10m walk speed, $\uparrow$ balance, $\uparrow$ QOL	Safe	Broad RPE range (11–15; light to hard); all achieved RPE target; no HR response data
	Biasin et al., (2014) (145)	Recumbent stepper	n=31, 78.3%	Mild-moderate: NIHSS 3.9 $\pm$ 2.2	25.9 $\pm$ 12.6 days	3x/week (duration NR)	?	50–80% HRmax; up to 30 mins (typical session)	76.7%	Feasible	No AEs during sessions; AEs in pre-intervention exercise test	RPE 3/10 (moderate) in 85% of sessions; unclear decision rules re: HR zones
	Katz-Leurer et al., (2003) (146)	Upright leg cycling	n=44, 86.9%	Moderate; Neurologic score: 31.0 $\pm$ 8.5	15.4 days	5x/week (phase 1; 2 weeks), 3x/week (phase 2; 6 weeks)	28	$\leq$ 60% HRR; day1: up to 10 min, build up to 30 mins	NR	$\uparrow$ CRF, $\uparrow$ Stair climbing ability	NR	No HR response or RPE data

Note. Attained exercise intensity = actual exercise intensity achieved; % Completion/Adherence = proportion of planned sessions completed or attended. Abbreviations: 6MWD = six-minute walk distance; CRF = cardiorespiratory fitness; HR = heart rate; HRmax = maximum heart rate; HRR = heart rate reserve; RPE = rating of perceived exertion; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; QOL = quality of life; $\dot{V}O_2$ = oxygen uptake.

Prevention of hospital-acquired deconditioning

The evolution from bed rest therapy to mobilisation and exercise

In the early 20th century, bed rest was a widely recommended medical treatment. Exertion was known to provoke physiological stress such as dyspnoea in the respiratory patient, and angina in the cardiac patient, therefore it was thought that bed rest would prevent harm. However, the collateral damage of bed rest became increasingly recognised in the 1940s and 50s. As early as 1941, physicians Dripps and Waters (148) warned of the depressive effects of anaesthetics on respiratory function and pioneered the ‘stir-up’ protocol where patients were turned on their side, encouraged to cough and inflate their lungs deeply. This perspective was shared by Dock et al., (1944) in the thought-provoking article entitled ‘The Evil Sequelae of Complete Bed Rest’, in which he proposed:

The physician must always consider complete bed rest as a highly unphysiologic and definitely hazardous form of therapy, to be ordered only for specific indications and discontinued as early as possible. (149)

In the early 1950s, cardiac physicians Levine and Lown pioneered the simple, yet controversial method of positioning patients in a bedside armchair. The objective of ‘armchair treatment’ was to avoid bed rest-related complications such as pulmonary oedema, pulmonary embolisms, and hypovolemia-induced orthostatic intolerance (150). ‘Armchair treatment’ evolved into a more progressive mobilisation approach where cardiac patients were encouraged to undertake supervised daily activities progressing in difficulty throughout their hospital stay, such as getting dressed, walking, showering and stair climbing (150,151).

Throughout the mid- to late-twentieth century, several RCTs investigated the effects of ‘bed rest therapy’ on health outcomes in both healthy and clinical populations. The seminal Dallas Bed Rest and Training Study provided convincing evidence of the detrimental effects of prolonged bed rest, and the restorative effects of aerobic exercise training (10). This study demonstrated that three weeks of bed rest in healthy 20-year-olds caused large reductions in cardiorespiratory fitness and cardiac function. Participants were then followed up 30 and 40 years later (152). In each follow-up study,

participants completed a baseline fitness assessment, a six-month aerobic training intervention, and a repeat fitness assessment, but bed rest was not included. These follow-up studies revealed that cardiorespiratory fitness and cardiac function naturally decline with age, but aerobic exercise training is an effective way to improve physical function throughout the lifespan. Importantly, this series of studies highlighted that the rapid decline in cardiorespiratory fitness and cardiac function exhibited after just three weeks of bed rest is equivalent to 40 years of aging. In addition, completing an aerobic exercise training intervention at 60 years of age enabled participants to reverse the equivalent effects of 40 years of aging on cardiorespiratory fitness and cardiac function.

By the late 1990s, bed rest therapy had become firmly established as an inferior approach. In 1999, a systematic review of 39 trials concluded that prolonged bed rest is either ineffective or increases the risk of adverse symptoms, morbidity, and mortality (153). Around the same era, the term ‘hospital-associated deconditioning’ had emerged to describe the multi-system decline caused by immobilisation. This syndrome encompasses deterioration in muscle strength and structure, aerobic capacity, blood volume, autonomic and respiratory function, bone mineral density, skin integrity, and urinary continence (153–156).

Hospital-associated deconditioning after stroke

Stroke survivors are highly susceptible to hospital-associated deconditioning (157,158). Stroke can induce structural damage to motor neurons leading to denervation of skeletal muscle, and either partial or full loss of motor function (159). The subsequent decline in neural activity triggers a cascade of secondary complications including increased intramuscular fat, increased inflammation, insulin resistance and a decline in muscle mass, muscle function and perfusion (159). These complications are compounded by sedentary behaviour typically observed in acute stroke wards (116), and malnourishment which is prevalent in stroke patients with cognitive impairments and/or dysphagia (impaired swallowing) (160). Collectively, stroke-induced skeletal muscle denervation, sedentary behaviour, and in some cases, malnourishment, drive a vicious cycle of immobility, and structural and functional decline of skeletal muscle, which increase the risk of sarcopenia, frailty, and disability (159).

Several imaging studies have assessed changes in skeletal muscle structure within the first few weeks of stroke onset. Using muscle ultrasound, Nozoe et al., (2016) (161) reported that in the paretic limb, rectus femoris muscle thickness declined by 12.8% after one week of hospital admission (-1.83% per day), and a further 10.1% reduction after a second week, totalling -22.9% (-1.63% per day). In the non-paretic limb, rectus femoris muscle thickness declined by 9.3% (-1.33% per day) and a further 5.3% after the first and second weeks of admission, respectively, totalling a loss of -14.6% (-1.04% per day).

In addition, Nozoe (2020) (162) demonstrated that three weeks of stroke-related hospitalisation led to a 16.9% (-0.81% per day) and 11.3% (-0.54% per day) decline in rectus femoris muscle thickness in the paretic and non-paretic limbs, respectively (measured via ultrasound). It was also found that patients with a greater degree of muscle atrophy in the non-paretic limb, measured at two weeks post-stroke, were less likely to be independent three months after stroke onset.

Moukas et al., (2002) (163) assessed upper arm muscle thickness changes in patients admitted to an intensive care unit (ICU) using muscle ultrasound, comparing hemiplegic to non-hemiplegic patients. The authors reported that in hemiplegic patients, muscle thickness of the impaired upper limb declined by 20% within 10 days (-2% per day) of ICU admission. In contrast, a comparator group who were admitted to the ICU with lung conditions who had a similar nutritional status only lost 10% (-1% per day) of upper arm muscle mass within the same time period (163), suggesting denervation is an independent risk factor for muscle atrophy.

Lastly, Gungor et al., (2023) (164) recently assessed skeletal muscle mass via computed tomography on days 1 and 14 of hospital admission after stroke. The authors reported that arm muscle cross-sectional area (CSA) declined by 18% (-1.23% per day) and 10% (-0.71% per day) in the paretic and non-paretic arms, respectively. Further, leg muscle CSA declined by 13% (-0.93% per day) and 12% (-0.86 per day) in the paretic and non-paretic legs, respectively.

To conclude, skeletal muscle structure declines rapidly in the first three weeks after stroke onset (~1-2% per day), with a faster rate of muscle atrophy in the stroke affected limb (e.g., -1.63% per day vs 1.04% per day, within two weeks of stroke onset), and

quicker atrophy in the acute phase of stroke compared to delayed timepoints (e.g., first versus third week). This highlights the importance of acute stroke rehabilitation interventions designed to mitigate muscle atrophy and the subsequent risk of sarcopenia, frailty and associated non-communicable diseases.

Does early-initiated stroke rehabilitation mitigate hospital-associated deconditioning in acute stroke?

Although there is convincing evidence that skeletal muscle deteriorates quickly after stroke, there is a scarcity of research investigating if rehabilitation interventions can mitigate muscle atrophy in clinical stroke populations. To the author's knowledge, only one clinical study has investigated this phenomenon. Tamura et al., (2011) (165) assessed the effects of in-bed hip and lower limb strengthening exercises performed for 10 minutes per day for one week, initiated 3-5 days after stroke onset. Compared to a usual care control group, the resistance exercise intervention attenuated the loss of thigh muscle mass (intervention: $-2.1\% \pm 0.3\%$ per day vs. control: $-6.9\% \pm 1.0\%$ per day) measured by dual X-ray absorptiometry. A key limitation of this study is that it was not an RCT—the intervention was conducted after the control group observations (quasi-experimental design) over a period of five months. This study design is therefore susceptible to selection bias and potential confounding effects of changes in clinical practice (e.g., new staff, or changes in workforce capacity).

The remaining evidence pertaining to early-initiated post-stroke exercise interventions is limited to animal studies. Collectively, the pre-clinical evidence base demonstrates that exercise interventions initiated prior to or immediately after stroke have beneficial effects on muscle structure. For example, one study demonstrated that an exercise intervention prior to stroke (treadmill training for five weeks, 30 min/day, 5 days/week, at a speed of 14 m/min [moderate-intensity]) resulted in greater type-I fibre cross-sectional area and preserved vascular integrity compared to control animals (166).

In addition, Melo et al., (2020) (167) investigated the effects of a six-week, light-intensity exercise intervention (8 m/min; 30 mins/day; 5 days/week; initiated five days after stroke) on skeletal muscle structure. Compared to control animals, aerobic exercise training resulted in decreased muscle atrophy and increased retention of vascular cells.

Furthermore, McDonald et al., (2021) (168) reported that a combined aerobic exercise (45 mins at 70-80% $\dot{V}O_2\text{max}$ [moderate to vigorous intensity) and resistance training (weighted ladder climbing: 8-12 climbs until exhaustion) intervention (5 days/week for 5 weeks) mitigated early post-stroke skeletal muscle atrophy compared to a sedentary control group.

Finally, Choe et al., (2006) (169) investigated the effects of six light-intensity (10m/min) treadmill exercise sessions lasting 10-20 minutes per session, initiated 48 hours post-stroke, on measures of hind-limb muscle structure. Compared to a sedentary stroke control group, the exercise intervention increased muscle weight, type I and II fibre cross-sectional area, and myofibrillar protein content.

In conclusion, current clinical guidelines propose that early mobilisation and aerobic exercise may help mitigate post-stroke deconditioning. Although preclinical evidence is encouraging, clinical data to support these recommendations remain limited. Only one clinical study involving acute stroke patients has demonstrated exercise-induced improvements in muscle function (described in aerobic exercise section) (134), however, no studies have assessed direct markers of deconditioning. To strengthen the evidence base, studies assessing early mobilisation or aerobic exercise interventions should incorporate muscle architecture measures to clarify how early rehabilitation influences the deconditioning trajectory in acute stroke.

Chapter summary

Clinical guidelines recommend that stroke survivors should engage in early mobilisation and aerobic exercise training as soon as they are medically stable (63,80–84). However, there is limited evidence to support these recommendations, and current guidelines overlook how these interventions affect cerebral perfusion.

Accumulating evidence suggests that upright physical activities, including early mobilisation and intensive treadmill training (initiated 0-30 days after stroke) are associated with poorer neurological outcomes and increased rates of adverse events, respectively (14,97,135,140). Given that the brain's ability to regulate blood flow is impaired in the early weeks after stroke, it is plausible that frequent and prolonged episodes of orthostatic stress may expose vulnerable brain tissue to hypoperfusion

(53,53,54,123). This theory is corroborated by several studies which have demonstrated that upright positioning causes a sustained decline in cerebral blood velocity—a proxy for cerebral blood flow (reviewed in Chapter 4) (106,107).

The evidence base for aerobic exercise in the acute phase of stroke is particularly sparse. It has been reported that treadmill training provokes exhaustion and dizziness (135), whereas recumbent cycling interventions demonstrated either no effect (133), or improvements in functional capacity (134). Notably, the reporting of exercise dose in some of these studies is unclear, limiting the interpretation of safety and efficacy. Lastly, there is currently a lack of evidence to support the hypothesis that early mobilisation or aerobic exercise training prevents hospital-associated deconditioning during the early post-stroke hospital admission period.

Overview of research aims

This programme of research aims to address key gaps in the stroke rehabilitation evidence base by investigating:

1. The physiological responses to early mobilisation and aerobic exercise initiated early after stroke, with a key focus on cerebral haemodynamics and blood-borne brain-derived neurotrophic factor.
2. The safety and preliminary efficacy of a 5-day recumbent cycling aerobic exercise training intervention initiated in the acute phase of stroke, with a detailed description of exercise dose characteristics.
3. The acceptability of the aerobic exercise intervention, explored through qualitative interviews with patients and staff; and
4. The feasibility of conducting the intervention and study procedures to inform a future definitive trial.

Chapter 3 – Methodology

Overview

This chapter provides an overview and justification of the methodologies employed in this thesis. This programme of PhD research assesses the physiological effects of two distinct rehabilitation methods (early mobilisation and aerobic exercise) and provides insight into the development and evaluation of a novel aerobic exercise intervention. A logical starting point for this methodology chapter is to describe the research paradigms that frame this work. Secondly, a brief overview of studies provides context for the subsequent methodological discussion. Thirdly, the approaches taken to develop and evaluate the aerobic exercise intervention are detailed. Fourthly, a comprehensive explanation of exercise nomenclature is provided to help clarify the exercise intervention's components, safety profile and physiological effects. Lastly, this chapter concludes with an overview of data collection and measurement methods, along with key reference data.

Research paradigms

A research paradigm has been defined as “the set of common beliefs and agreements shared between scientists about how problems should be understood and addressed” (170). Ontology concerns the nature of reality—whether it exists independently of human perception or is socially constructed (171). Epistemology, on the other hand, explores how knowledge is created and validated, questioning whether truth is discovered through objective measurement or constructed through human experience (171).

A wide range of research paradigms may be utilised to create knowledge, and a detailed discussion of each paradigm is not within the scope of this thesis. Broadly speaking, there are two distinct research paradigms which sit at opposite ends of a spectrum: positivism and interpretivism. Positivism is the theory that there is a single truth or reality, and that knowledge can be created through quantitative, objective measurements and observations, testing hypotheses and exploring associations using valid and reliable tools (172). Conversely, interpretivism asserts that there is no single truth or reality, and that these are social constructs. An interpretivist develops knowledge through qualitative inquiry exploring the perceptions, experiences, and attitudes of people to

help explain the meaning of and motivations behind a phenomenon. Interpretivism is more suited to inductive data analysis, where the researcher starts the process without a hypothesis or predefined expectations (172).

There are numerous other research paradigms which sit along this spectrum, each differing in their ontological and epistemological perspectives. One of which is pragmatism, which is a flexible approach suited to mixed-methods research.

Pragmatism is a research paradigm that focuses on ‘what works’ to answer a research question. It emphasises practicality and flexibility, combining diverse methodologies as needed. Pragmatism allows for both deductive reasoning (e.g., using pre-defined framework used to understand data) and inductive analysis (a bottom-up, data-driven approach). When assessing the acceptability of an intervention, pragmatism is useful because it accommodates inductive reasoning to discover patterns or themes that may sit outside pre-defined frameworks. Pragmatism is not bound to a singular ontological or epistemological stance, it embraces a practical approach that adapts to the research needs (172).

This PhD thesis is a mixed-methods programme of research with a predominantly quantitative focus, complemented by qualitative inquiry. An overview of studies is presented in the next section. Two studies within this thesis are purely quantitative, which assess the acute physiological effects of stroke rehabilitation interventions (mobilisation and aerobic exercise). The other two studies centre around a complex intervention and use a range of data collection methods including physiological assessments, participant questionnaires, and one-to-one interviews with patients and therapists. Within this thesis, quantitative data collection methods align with a positivist paradigm as the aim was to measure physiological variables using valid and reliable tools, minimising the influence of human bias. The qualitative data component is grounded in the Theoretical Framework of Acceptability (173), adopting a predominantly deductive approach, complemented by an inductive, exploratory analysis to uncover additional insights (174). Although this thesis primarily follows a quantitative, positivist approach, the overarching mixed-methods design is situated within the pragmatist paradigm.

Overview of studies

The previous chapters provide a critical overview of two widely recommended acute stroke rehabilitation techniques: early mobilisation and aerobic exercise training. Currently, the cumulative evidence does not clearly justify the implementation of these rehabilitation interventions in the acute phase of stroke. Early mobilisation is predominantly supported by observational evidence and pre-clinical science, yet safety concerns have been raised in clinical trials. In addition, despite strong preclinical evidence, there is a lack of research supporting the use of aerobic exercise in the acute phase of stroke in humans, and questions remain regarding its safety and efficacy.

Evidence stemming from healthy and clinical populations highlights that active standing causes an acute decline in cerebral blood velocity (a proxy for blood flow) (reviewed in Chapter 4), whereas light- to moderate-intensity aerobic exercise may have the opposite effect (reviewed in Chapter 6). Given that cerebral autoregulation can be impaired early after stroke, it is critical to explore how early mobilisation and aerobic exercise affect cerebral perfusion. Studies 1 (Chapter 4) and 3 (Chapter 6) within this thesis investigate the cerebral haemodynamic response to active standing and aerobic exercise, respectively. Additionally, Study 3 (Chapter 6) assesses the acute effects of aerobic exercise on brain-derived neurotrophic factor (BDNF)—a blood biomarker associated with neuroprotection and neuroplasticity (mechanistic sub-study of Study 2). The rationale for assessing BDNF is based on evidence from animal models of stroke which demonstrates that aerobic exercise training upregulates BDNF production in the brain, as well as evidence from human populations indicating that an acute bout of aerobic exercise increases circulating BDNF.

Although it is widely recommended that aerobic exercise should be initiated as soon as patients are medically stable, the safety and efficacy of this approach are unclear. Study 2 (Chapter 5) assesses the feasibility, safety and preliminary efficacy of aerobic exercise training initiated in the acute phase of stroke. Furthermore, Study 2 also assesses the feasibility of conducting a RCT of aerobic exercise training in the acute stroke setting. Lastly, Study 4 explores the acceptability of the intervention from the perspective of patients who participated in the intervention and their stroke therapy team. The combined findings from Studies 2 and 4 will inform the decision whether to proceed to a definitive trial and if refinements are necessary.

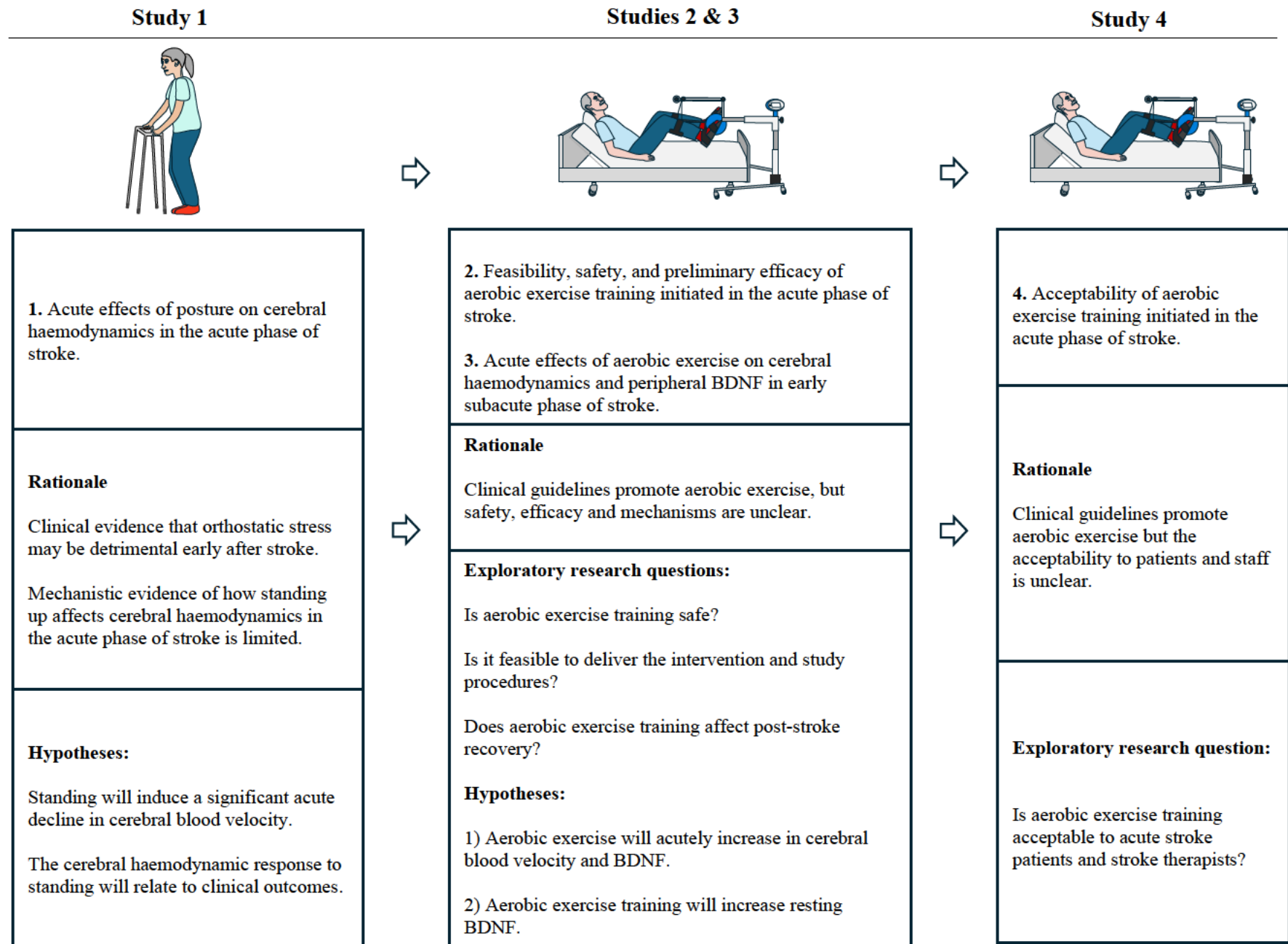


Figure 3.1 Overview of studies.

Medical Research Council framework for developing and evaluating complex interventions

In contrast to efficacy trials performed under ideal experimental conditions, research performed in real world settings (e.g., effectiveness trials) can be highly complex. Determining intervention efficacy does not guarantee that the intervention will produce beneficial outcomes in a healthcare setting (i.e., effectiveness). The Medical Research Council (MRC) considers an intervention to be ‘complex’ if it has multiple components, is dependent on expertise or skills of individuals delivering or receiving the intervention, if it permits flexibility in its delivery, or is delivered across different settings (175). Complex interventions are ‘events in systems’, and contextual nuances are important to consider, especially if interventions are to be delivered across multiple sites. Conducting a full-scale RCT without considering the complexity of healthcare settings can waste funding and resources, and lead to undue burden on patients. The MRC provides a framework to streamline the transition from developing new interventions through to their implementation (Figure 3.2).

A key step between the development and evaluation of an intervention is to assess its feasibility. Feasibility studies aim to understand ‘whether the future trial can be done, should be done, and, if so, how?’ (176). Feasibility studies provide valuable insight into how an intervention can be evaluated in a specific setting, and what changes may be needed to optimise the delivery of a future, definitive trial. The MRC advises that a feasibility study should include a pre-defined progression criteria which is related to the study procedures *and* delivery of the intervention (175).

The MRC recommends that each phase of the research pathway should consider six ‘core elements’—one of which is key stakeholder engagement (175). In the first year of this programme of research, multiple patient and public involvement events were conducted, and consultations with healthcare professionals were carried out. Early stakeholder engagement was a crucial process which improved my understanding of the healthcare context and gave patients and therapists a voice, which collectively shaped the design of this research. A brief description of this patient and public involvement is presented below, and a more detailed overview is provided in Appendix 4. Each of the core elements recommended by the MRC presented in Figure 3.2 below.

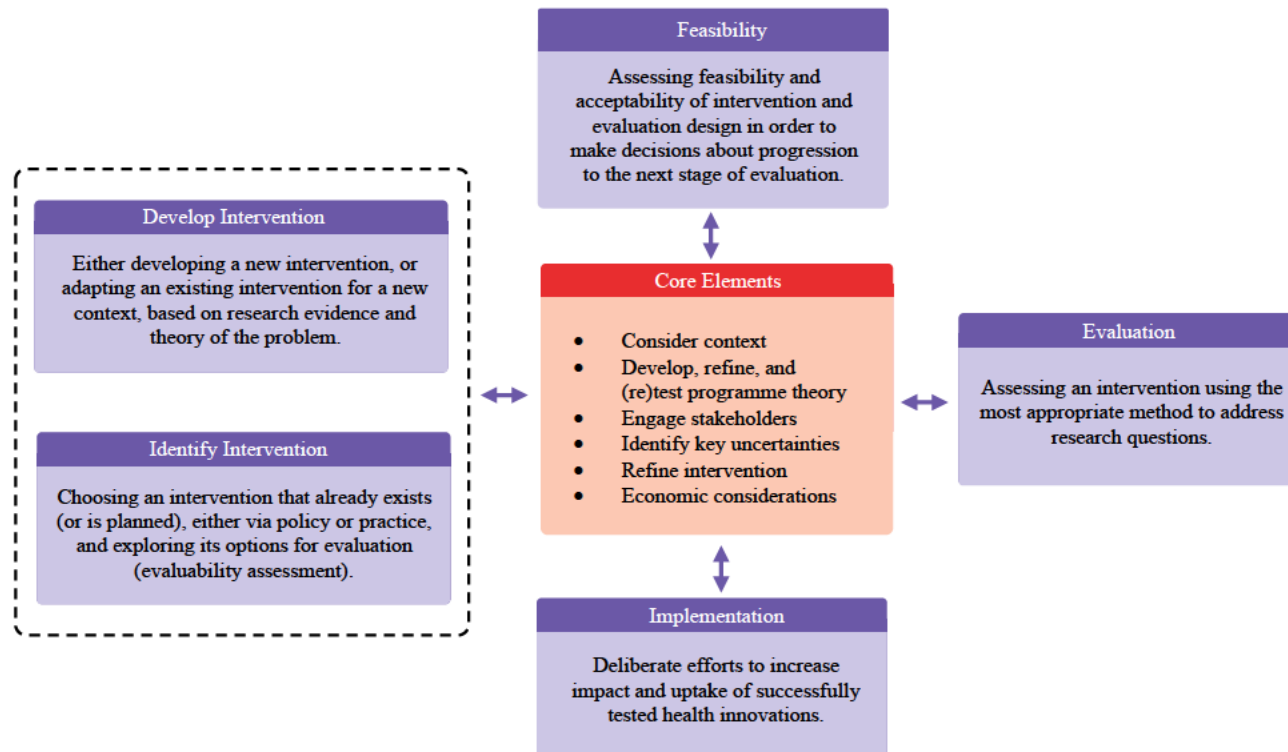


Figure 3.2 Medical Research Council Framework for Developing and Evaluating Complex Interventions, reproduced from Skivington et al., (2021).

Stakeholder engagement

In-person patient and public involvement event

In January 2020, a patient and public involvement (PPI) event was conducted at Graves Health and Sports Centre (Sheffield, UK). The event was advertised via Twitter, printed posters, and by directly contacting healthcare professionals, including the organiser of the Sheffield Stroke & Aphasia Patient & Public Involvement Group. Attendees included five stroke survivors, two physiotherapists, one stroke physician, one speech and language therapist, one community fitness instructor, two senior research fellows and two PhD students.

Stroke survivors and healthcare professionals stated that aerobic exercise training is uncommon in acute stroke rehabilitation. Stroke survivors and practitioners recognised the potential physical, psychological and emotional benefits of aerobic exercise training but there were various perceived barriers to implementation. Stroke survivors lacked confidence to exercise due to physical disability, fear of falling and concerns of health exacerbation. Practitioners shared these concerns but also highlighted the lack of evidence regarding aerobic exercise and unclear clinical guidance. The use of an in-bed cycle ergometer was well-received amongst the attendees. This mode of exercise removes the risk of falling and was perceived to serve as a preparatory exercise for more demanding activities such as walking. Key feedback regarding the proposed exercise protocol was that the exercise duration and intensity would need to be flexible depending on the patient's level of fatigue. In addition, the initial intervention duration was 'until discharge' but healthcare professionals and researchers advised that this should be shortened to accommodate patients who have a short length of stay, and avoid excessively long intervention for those that have prolonged hospital admission periods.

Based on this PPI feedback, the exercise protocol was adapted. Instead of a single 30-minute bout of moderate-intensity aerobic exercise, the protocol was revised to a progressive interval training design, beginning with two 5-minute bouts of moderate-intensity aerobic exercise in session 1, progressing to six 5-minute intervals in the final session (session 5). The exercise programme was already designed to be tailored to each participant's level of fatigue and ability (e.g., by adjusting resistance and cadence).

Lastly, based on PPI feedback, aphasia-friendly documents were designed to maximise inclusion. A full summary is available in Appendix 4.

Sheffield Stroke & Aphasia Patient & Public Involvement Group

In October 2020, an overview of the aerobic exercise feasibility study protocol was presented online to the Sheffield Stroke & Aphasia Patient & Public Involvement Group. This focused on the study procedures and accessibility of participant information. The presentation exhibited the first draft of an aphasia-friendly participant information sheet. Numerous suggestions were given by the PPI group, including:

- Clarify how cycling exercise might help recovery.
- Give reassurance that an increase in heart rate and blood pressure will be within safe limits.
- Provide participants with reminders about research requirements as they may not remember the initial recruitment conversation; and
- Engage with participants' family to support decision making.

These suggestions were incorporated into a revised participant information sheet, and informed discussions with study participants and their family members. The PPI group also suggested to create a video to help convey study information to patients. However, this was not feasible due to time and budget constraints but will be considered for future research trials. A full summary of PPI feedback is provided in Appendix 4.

Advanced Wellbeing Research Centre Public Involvement in Research Group

In February 2021, the Advanced Wellbeing Research Centre Public Involvement in Research Group (PIRG) reviewed the consent form and participant information sheet relating to early mobilisation (Study 1). The PIRG were not stroke survivors but provided feedback from a layperson perspective. Overall, the PIRG members thought that study information was easy to understand but suggested minor improvements. Based on the PIRG feedback, the following actions were taken:

- Simplified wording and removed duplication within the participant information sheet.
- Amended formatting in participant information sheet.
- Amended illustrations to make participants look more ‘human’.

A full summary is available in Appendix 4.

Nomenclature

The stroke rehabilitation nomenclature is ambiguous (177,178), making it challenging to define and interpret interventions. Notably, ‘dose’ and ‘intensity’ are used interchangeably to describe the session duration or number of exercise repetitions within a *single session* and the content of a *whole intervention period*, which may span days to months (179,180). In addition, ‘intensive’, ‘high-intensity’ and ‘high-dose’ interventions are commonly reported in the literature (177,179,180), yet there is no clear threshold to differentiate lower and higher intensities or doses. Typically, usual care therapy is used as the reference point for lower intensity/dose interventions, and an intervention which provides additional therapy is classed as higher intensity/dose.

Within the exercise science literature, intervention descriptions are also ambiguous, lacking key information such as intervention adherence or how progression is implemented (181,182). This problem inspired the development of the Consensus on Exercise Reporting Template (CERT) to help standardise the description of exercise interventions (182). The CERT framework recommends that the words ‘dose’ or ‘dosage’ should be used as the overarching term to encapsulate the core features of an intervention including the frequency (how often), intensity (exertion), time (how long per session/day and the intervention duration), type (exercise mode), and volume (how much per week/month). The CERT framework also recommends capturing details on how interventions are tailored (e.g., rationale for starting level and progression) (182).

Herein, where the word ‘dose’ is used, key contextual information will be provided, such as the time frame (session or intervention) and/or number of repetitions performed within that timeframe. In addition, the word ‘intensity’ will be used to refer to the estimated level of physical exertion (e.g., %HRR or RPE) of a bout of exercise or physical activity.

When designing an aerobic exercise intervention for acute stroke populations, it is essential to clearly define the exercise dose characteristics to determine its feasibility, safety, acceptability, and potential efficacy. Within the exercise science literature, ‘exercise intensity’ is a somewhat ambiguous concept. It can be quantified using various methods, including heart rate, oxygen consumption ($\dot{V}O_2$), metabolic equivalents (METs), power output, or perceived exertion scales (e.g., Borg RPE scale). However, the lack of standardised definitions across studies makes it difficult to compare findings and establish universal guidelines for exercise prescription in stroke rehabilitation. A detailed discussion of exercise intensity definitions is provided below.

Exercise intensity

The ambiguity in exercise intensity definitions likely stems from the wide range of measurement methods (181,183). A common approach is to define exercise intensity relative to a measure of maximal effort such as percentage of maximal heart rate, oxygen consumption ($\dot{V}O_{2max}$), or work rate (e.g., peak power output). However, this approach has been criticised (181,183) as it does not account for inter-individual differences in the metabolic responses to exercise. The gold-stand approach is to assess the metabolic response to exercise, using respiratory gas or blood lactate sampling outlined below.

Metabolic threshold method

During incremental exercise to volitional exhaustion, two metabolic landmarks can be detected which demarcate three exercise intensity domains: light, moderate and vigorous. It is noteworthy that in the exercise science literature, these three intensity domains are referred to as moderate, heavy and severe, respectively. Herein, the terms light, moderate and vigorous will be used in accordance with the American College of Sports Medicine (ACSM) (79). See Table 3.1 for an overview of intensity domain terminology.

Light- to moderate-intensity exercise

In the light-intensity exercise domain, exercise is mainly fuelled through oxidative phosphorylation of fat and carbohydrate, and can be sustained for prolonged periods before the onset of fatigue (184). As the energy expenditure of exercise increases, there becomes an increasing reliance on anaerobic glycolysis where glycogen is converted to adenosine triphosphate. This biochemical reaction also produces lactate, which is an anaerobic fuel source that can be shuttled into the muscle mitochondria and to other skeletal muscle fibres, or organs such as the liver, heart and brain (184,185). The conversion of glycogen to lactate releases hydrogen ions (H^+) which are implicated in the development of acute muscle fatigue. To prevent a decline in pH, bicarbonate binds with and neutralises H^+ . The bicarbonate buffering of H^+ creates carbon dioxide (CO_2) as byproduct which is expired through the lungs. The point at which CO_2 begins to rise at a greater rate than oxygen consumption indicates the boundary between the light and moderate intensity exercise domains (183,186). This is commonly known as the first ventilatory threshold. In addition, this demarcation can be detected through blood lactate sampling, where blood lactate increases slightly above resting levels—widely known as the first lactate threshold (183,186). There are several other terms used to describe the threshold demarcating light and moderate exercise intensities including: the ventilatory anaerobic threshold, the aerobic threshold and gas exchange threshold. Notably, the term anaerobic threshold is used interchangeably to describe both the light-moderate and moderate-vigorous intensity thresholds, adding further confusion (187,188). For clarity, it should be noted that the terms *light* and *moderate intensity* as defined by the ACSM differ from terminology used in the exercise science literature which categorises these intensity domains as *moderate* and *heavy*, respectively (see Table 3.1).

Moderate- to vigorous-intensity exercise

Steady state exercise in the moderate-intensity domain relies on the capacity of the bicarbonate buffering system to neutralise H^+ and thereby maintain a stable muscle pH. The amount of work performed in the moderate-intensity domain exercise intensity domain will vary depending on the exercise demands and an individual's fitness level. When the rate of anaerobic glycolysis exceeds the bicarbonate buffering capacity, lactate and H^+ begin to rise exponentially. The bicarbonate buffering of excessive H^+

leads to a rise in arterial CO₂ which stimulates hyperventilation to offload excess CO₂. The exponential rise in blood lactate and onset of hyperventilation marks the transition from the moderate-intensity to the vigorous-intensity domain (i.e., heavy to severe [exercise science terminology]) (79,189,190). Exercise performed in vigorous-intensity domain can only be sustained for relatively short periods depending on fitness level (183,189,190). The terms used to describe this threshold include: the respiratory compensation point, the second ventilatory threshold, the second lactate threshold, the maximal lactate steady state, the onset of blood lactate accumulation, and the anaerobic threshold (79,183,187,189,190). Moreover, the terms *moderate* and *vigorous intensity* defined by the ACSM, correspond with *heavy* and *severe*, respectively.

Demarcating light- and moderate-intensity exercise

Retrospective analyses of cardiopulmonary exercise test data demonstrate that the first ventilatory threshold (VT1; the boundary between the light- and moderate-intensity domains) occurs at relatively low fraction of HRR. For example, VT1 occurred at 35% HRR in people with metabolic syndrome (191), and 39% HRR in patients with cardiovascular disease (n=972) (192). Additionally, Milani et al., (2023) (192) reported that the interquartile range of %HRR at VT1 in CVD patients' (n=972) was 33-46% HRR (192). This variability is likely explained by differences in cardiorespiratory fitness level. For instance, Pymer et al., (2020) (193) reported that in cardiac patients with low fitness, the interquartile range for %HRR at VT1 on a treadmill was 26-49% HRR. By contrast, in cardiac patients with high fitness, the interquartile range was 52-78% HRR (193). Furthermore, it has been reported that endurance trained individuals reach VT1 at 70% ($\pm 10\%$) HRR (194), highlighting that the %HRR at VT1 increases in response to exercise training. Additionally, VT1 occurs approximately 10% lower HRR during cycling compared to treadmill exercise, and this discrepancy broadens as fitness level increases (193).

Demarcating moderate- and vigorous-intensity exercise

According to ACSM guidance, the vigorous intensity domain corresponds with 60-89% HRR. Whilst this intensity band is based on data from healthy populations, it is broadly consistent with clinical data. Research suggests that the second ventilatory threshold (VT2), also known as the respiratory compensation point (RCP)—which is the lower

boundary of the vigorous intensity domain—occurs at 78% HRR (IQR: 72–85%) in CVD patients ($\dot{V}O_{2peak}$: 22.1 mL/kg/min; IQR: 17.1–27.4) (192). This finding indicates that the upper portion of the ACSM vigorous-intensity range aligns well with VT2 in CVD patients, whereas the lower end (60–70% HRR) may underestimate the intensity associated with this threshold. Furthermore, VT2 has been reported to occur at 93 ($\pm 7\%$) HRR in healthy people with high cardiorespiratory fitness ($\dot{V}O_{2max}$ range: 49–57 mL/kg/min) (194), highlighting a rightward shift in metabolic response to exercise resulting from endurance training.

Collectively, these studies show that in comparison to ACSM guidance, VT1 occurs at a lower %HRR in people with reduced fitness or health conditions, and during cycling compared with treadmill exercise. In addition, studies suggest that %HRR at VT2 in both unfit and trained populations occurs in the upper portion of the ACSM vigorous intensity range. Both VT1 and VT2 occur at a lower %HRR in individuals with reduced fitness or chronic clinical conditions compared with trained individuals. These findings have important implications for estimating exercise-intensity domains in stroke survivors with motor impairments performing cycle ergometry. Specifically, the application of standard ACSM %HRR thresholds may misclassify exercise intensity, as heart rate responses conventionally described as “low intensity” may fall within the moderate-intensity domain in this population due to VT1 occurring at a lower %HRR. Conversely, maintaining exercise below ~60% HRR provides a conservative approach to reduce the likelihood of exceeding VT2, thereby increasing confidence that exercise remains within the moderate-intensity domain.

Heart rate-derived exercise intensity

Heart rate monitoring is a practical method used to estimate exercise intensity. The physiological basis for heart rate monitoring is that heart rate (HR) is linearly related to energy expenditure (i.e., oxygen consumption), and maximum HR (HR_{max}) occurs in close temporal proximity to maximal oxygen consumption ($\dot{V}O_{2max}$) (195). Prescribing or monitoring exercise intensity based on a percentage of $\dot{V}O_{2max}$ or HR_{max} is commonplace within the exercise science literature. However, this approach has been criticised due to variability in the inter-individual metabolic responses that occur at the same fixed percentage of maximal effort (192,196). Another limitation of the fixed percentage method is that it does not account for differences in resting metabolic rate

(i.e., oxygen consumption) or HR. Karvonen et al., (1957) (197) addressed this issue in 1957, introducing the concept of heart rate reserve (HRR)—the difference between resting and maximal heart rate. This inspired the development of $\dot{V}O_2$ reserve ($\dot{V}O_{2R}$) which the difference between resting and maximal oxygen consumption. Percentage of HRR and $\dot{V}O_{2R}$ are considered to be more accurate and reliable measures of exercise intensity, compared to using fixed percentages of maximal values (195,198–200).

The ACSM provides guidance on estimating exercise intensity using %HRR and %HRmax, and their equivalents % $\dot{V}O_{2R}$ and % $\dot{V}O_{2max}$ (79). An overview of the exercise intensity domains and common terminology is provided in Table 3.1. The ACSM exercise domains are based on the relationship between HR or $\dot{V}O_2$ and metabolic thresholds (195). The ACSM propose that the moderate-intensity exercise domain is equivalent to 40-59% HRR. It is important to recognise that these intensity bands were derived from studies in healthy populations, and the corresponding thresholds may differ in clinical populations where cardiovascular and metabolic responses to exercise are altered.

Limitations of heart rate monitoring

Multiple factors including ambient temperature, hydration status, and emotional state can affect heart rate independent of exercise intensity (201,202). Additionally, heart failure (203) and beta-blockers (204) attenuate the heart rate response. Around 10-55% of acute stroke patients receive beta-blocker drugs in the acute phase of stroke (204,205), and 10-24% have heart failure (206). It is therefore important to apply population-specific formulas if estimating maximal heart rate. Furthermore, exercise posture can significantly influence heart rate dynamics during exercise. The ACSM heart rate-derived exercise intensity domains are based on studies using either treadmill or upright cycle ergometry protocols. However, recumbent and supine cycling elicit a lower heart rate response coupled with an increased stroke volume compared to work-matched upright cycling (207,208). Therefore, the ACSM heart rate ranges may need to be adjusted for recumbent cycling exercise.

Metabolic equivalent method

In the field of public health, the metabolic equivalent (MET) method is often used to estimate exercise intensity. One MET represents resting energy expenditure (3.5 mL oxygen per kilogram of body mass per minute [mL/kg/min] for an adult; 2.7 mL/kg/min for older adults ≥ 60 years old). Physical activities are given a MET score based on their estimated energy expenditure relative to rest. For example, a slow walk has a score of 2.8 METs because it has 2.8 times the energy expenditure of rest (9.8 mL/kg/min vs. 3.5 mL/kg/min). The Compendium of Physical Activities provides a library of physical activities and corresponding MET values, categorised as sedentary (<1.5 METs), low (1.5-2.9 METs), moderate (3-5.9 METs) and vigorous (≥ 6 METs) (209). Public health organisations throughout the world utilise these MET intensity categories, advocating for a reduction in sedentary behaviour and regular participation in moderate- to vigorous-intensity physical activities (210–213). Whilst this public health messaging is simple and pragmatic, it encounters the same issue as using fixed percentages of maximal effort; arbitrary MET categories do not account for individual metabolic responses to exercise. In addition, this approach does not account for differences in resting energy expenditure. Lastly, the Compendium of Physical Activities does not currently include the estimated energy expenditure of recumbent cycling.

Rating of Perceived Exertion

The Rating of Perceived Exertion scales are subjective tools used to measure “the feeling of how heavy, strenuous and laborious exercise is”. An individual is asked to rate their perceived exertion using either a number or a corresponding descriptor (214) (see Figure 3.3). To aid the interpretation of the RPE scale descriptors, memory-anchoring should be used, where users are asked to think about the highest level of exertion they have experienced, and use this as the highest point on the scale (215). Borg’s first version of the RPE scale, developed in the 1960s, ranges from 6 (no exertion at all) to 20 (maximal exertion) was intended for use during steady state aerobic exercise. Borg subsequently developed a second version (Category Ratio-10 scale) which ranges from 0 (nothing at all) to >10 (maximal; scores above 10 can be given to avoid a ceiling effect), and a third scale ranging from 0-100 (Category Ratio-100 scale) (Borg, 2007) enabling a more granular assessment of exertion. The physiological basis for each RPE scale is that the perception of effort is linearly related with oxygen consumption (i.e., energy expenditure) and heart rate (RPE 6-20 scale represents heart rate range of 60-200 bpm) (215).

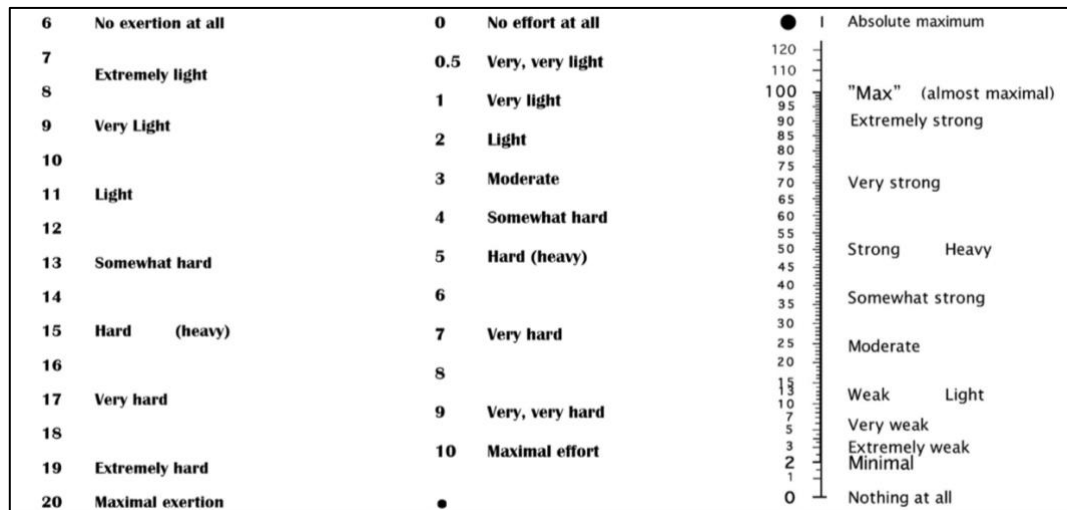


Figure 3.3 Different versions of the Rating of Perceived Exertion Scales sourced from Pageaux (215).

Several studies have assessed the relationship between RPE and the first ventilatory threshold ([VT1] i.e., the first lactate threshold) (216–223). For instance, Gaskill et al., (2023) (218) reviewed six datasets accumulating 863 participants with a wide range of fitness levels from sedentary adults to well-trained endurance athletes. This study revealed that mean RPE at VT1 ranged between 12 and 13 ('somewhat hard'). In contrast, Nichols et al., (2021) (221) reported more varied RPE scores at VT1 in patients with coronary artery disease, and demonstrated that cardiorespiratory fitness influenced RPE responses. Participants with low, moderate and higher cardiorespiratory fitness patients reported RPE scores of 10, 12 and 14, respectively at VT1 (n=70; age 63 ± 10 years). These findings suggest the need for a more nuanced approach when using RPE scales in populations with diverse fitness levels.

Research focused on the utility of RPE scales in stroke populations is limited, and overall, the findings highlight a disconnect between subjective and expected physiological responses. In a retrospective analysis of graded maximal exercise tests using a semi-recumbent cycle ergometer, Sage et al., (2013) (224) found that two-thirds of subacute stroke patients reported RPE scores within an expected range at moderate exercise intensities. However, in the vigorous intensity domain, 60% of participants reported RPE values outside the expected range, suggesting reduced accuracy with higher effort. In a different study, Lefeber et al., (2021) (225) conducted 20-minute bodyweight-supported treadmill exercise sessions, during which heart rate and oxygen consumption remained stable, yet RPE progressively rose from "very light" (7–8/20) to near "somewhat hard" (12/20), indicating a divergence between perceived effort and

physiological responses. Finally, Wu et al., (2015) (226) assessed daily activities (e.g., sit-to-stands, stair climbing, and walking) in a cohort of subacute stroke patients, and reported moderate correlations between oxygen consumption and heart rate but a weak correlation between RPE and oxygen consumption.

The disconnect between HR and RPE responses may be partly explained by neurological impairments. Perceived exertion reflects the brain's conscious awareness of the magnitude of the motor command signals (which control movement) which are relayed to cerebral sensory areas (227); a disruption of either of these pathways may influence the RPE. Secondly, unfamiliarity with the RPE scale is known to reduce its reliability (228). Thirdly, cognitive and visual impairments are likely to play a role; approximately 22–59% of acute stroke patients experience aphasia (229–231)—an acquired communication disorder that impairs the ability to understand written or spoken language (receptive aphasia) or to express thoughts verbally (expressive aphasia). Additionally, 12% of acute stroke patients experience visual loss or visual field defects (232). Accessible information should therefore be used to accommodate aphasia and visual impairment where possible.

The Talk Test

Contemporary physical activity guidelines provide guidance on how activities should affect breathing patterns. For example, US guidelines state that “a person doing moderate-intensity aerobic activity can talk, but not sing, during the activity”. Whereas during vigorous-intensity activity a person “cannot say more than a few words without pausing for a breath.” (211). This pragmatic approach is borrowed from the Talk Test (233) which is a subjective method to determine the ventilatory response to exercise. The point at which an individual transitions from being able to speak comfortably, to being ‘unsure’ if they can speak comfortably (i.e., the equivocal stage) typically corresponds with VT1. In addition, the point at which an individual can definitely not speak comfortably usually aligns with VT2 (234). The Talk Test can complement the RPE scale. However, in stroke populations with speech and language difficulties, its accuracy may be limited.

Exercise intensity summary

The scientific basis for commonly used exercise intensity terms has been critiqued. The metabolic threshold method is considered the gold standard, but it requires a cardiopulmonary exercise test in which participants must incrementally increase workload until the vigorous-intensity domain is reached. As the safety profile of aerobic exercise in the acute phase of stroke is unknown, a cardiopulmonary exercise test may not be appropriate. The metabolic equivalent method, derived from the Compendium of Physical Activities (209), is also unsuitable because it does not provide energy expenditure estimates for recumbent cycling, and is not suited to stroke populations. Although heart rate and subjective measures each have limitations, using them in combination is complementary. Accordingly, this doctoral research employed a combined strategy incorporating heart rate, perceived exertion, and the Talk Test to guide and monitor exercise (described below). Table 3.1 consolidates commonly used terminology, intensity domains, and corresponding measurement units, providing a framework for interpreting physiological responses, and evaluating the safety of aerobic exercise.

Combining multiple methods to guide and monitor exercise intensity

Preclinical evidence suggests that light- to -moderate intensity aerobic exercise training may be optimal for promoting neuroprotection and neuroplasticity in the acute phase of stroke. An RPE score of 13/20 ('somewhat hard') was therefore selected as the target intensity which typically corresponds with VT1 (the boundary between light- and moderate-intensity exercise), where breathing rate and depth is elevated but speech is manageable. An RPE of 15/20 ('Hard') was selected as a subjective upper exercise intensity limit, which approximately corresponds to VT2 (the boundary between moderate- and vigorous-intensity exercise), where speech becomes difficult due to heavy breathing.

An objective upper limit of 60% HRR was applied to avoid vigorous intensity, in line with ACSM guidelines (79). Notably, in a CPET study of CVD patients (n=972) using an upright bike, the lower quartile reached VT2 at 72% HRR (192). However, heart rate responses during recumbent cycling are typically 10–15 bpm lower than during upright

cycling at equivalent workloads (207,208). In adults aged 60–70 years with a resting heart rate of ~70 bpm, this difference translates to a 12–18% reduction in HRR—equivalent to ~54–61% HRR—which is consistent with the ACSM-defined boundary between moderate and vigorous intensity.

Lastly, the researcher continuously observed participants' breathing patterns. If heavy or laboured breathing was identified, workload was adjusted to maintain exercise within the target intensity domain. For participants with expressive aphasia who were unable to reliably self-report exertion using the Talk Test or RPE, exercise workload was instead guided by observed breathing effort in combination with heart rate responses.

Table 3.1. Exercise intensity domains according to ACSM (2021) classification and exercise science terminology

Intensity Domain						
ACSM Classification	Exercise Science Terminology	% HRR	% HRmax	% $\dot{V}O_2$ max	Rating of Perceived Exertion (6–20 scale)	Talk Test
Very light	Moderate	<30	<57	<37	Very light (RPE <9)	Able to talk comfortably; positive stage
Light		30–39	57–63	37–45	Very light to light (RPE 9–11)	
↓ First ventilatory threshold; gas exchange threshold; first lactate threshold ↓						
Moderate	Heavy	40–59	64–76	46–63	Light to somewhat hard (RPE 12–14)	Not sure if able to speak comfortably; can talk but not sing; equivocal stage
↓ Second ventilatory threshold; respiratory compensation point; maximal lactate steady state; second lactate threshold ↓						
Vigorous	Severe	60–89	77–95	64–90	Hard to very hard (RPE 15–17)	Definitely not able to talk comfortably; negative stage
Near-maximal to maximal	Extreme	≥90	≥96	≥91	Very hard (RPE 18), extremely hard (RPE 19), and maximal exertion (RPE 20)	

Note. ACSM = American College of Sports Medicine; HR_{max} = maximal heart rate; HRR = heart rate reserve; MET = metabolic equivalent; RPE = rating of perceived exertion; $\dot{V}O_{2max}$ = maximal oxygen consumption. Adapted from ACSM (2021), Page 148, Table 5.2. Threshold positioning is based on CPET data from Milani et al., (2023).

Assessments

A broad range of physiological, functional, psychometric, and qualitative assessments were used across the four studies in this PhD. The focus of each study, and the corresponding assessments, are outlined below:

- **Study 1:** Acute effects of posture on cerebral haemodynamics in acute stroke.
- **Study 2:** Feasibility, safety and preliminary efficacy of aerobic exercise training initiated in acute stroke.
- **Study 3:** Acute cerebral haemodynamic and neurotrophic effects of aerobic exercise.
- **Study 4:** Acceptability of aerobic exercise training initiated in acute stroke.

Table 3.2. Matrix of assessments used across the four studies

Assessments	Study			
	1	2	3	4
<i>Physiological</i>				
Transcranial Doppler ultrasound	✓		✓	
Heart rate	✓	✓	✓	
Blood pressure	✓	✓	✓	
BDNF enzyme-linked immunosorbent assay			✓	
Muscle ultrasound		✓		
Indirect calorimetry			✓	
<i>Physical activity / rehabilitation dose</i>				
Accelerometry		✓	✓	
Global Physical Activity Questionnaire		✓		
Rating of Perceived Exertion		✓	✓	
<i>Physical function</i>				
Short Physical Performance Battery		✓		
10-metre walk		✓		
Handgrip strength		✓		
<i>Disability / independence</i>				
Modified Rankin Scale	✓	✓		
Barthel Index	✓	✓		
<i>Psychometric</i>				
Chronic fatigue (Fatigue Severity Scale)		✓		
Mood (Hospital Anxiety and Depression Scale)		✓		
Optimism (Life Orientation Test-Revised)		✓		
Health related quality of life (EQ-5D-3L)		✓		
Exercise self-efficacy (Self-Efficacy for Exercise Scale)		✓		
<i>Qualitative</i>				
One-to-one, semi-structured interviews				✓

Data collection and measurement techniques

Transcranial Doppler ultrasound (TCD) (Studies 1 & 3)

Principles of transcranial Doppler ultrasound

Numerous imaging methods are available to assess cerebral haemodynamics. These can be broadly categorised into nuclear medicine imaging (e.g., positron emission tomography and single photon emission computed tomography), computed tomography (e.g., xenon-enhanced computed tomography and perfusion computed tomography), magnetic resonance imaging ([MRI] e.g., arterial spin labelling), and transcranial Doppler ultrasound (TCD) (219). Each technique differs in spatial and temporal resolution, invasiveness, portability, and cost. TCD is well-suited to assessing cerebral haemodynamic responses to postural changes and aerobic exercise within a hospital ward, as it is non-invasive, portable, relatively inexpensive, provides high temporal resolution, and is minimally influenced by head movement when the probes are securely fixed (220).

Transcranial Doppler ultrasound involves the transmission of ultrasound waves into an intracranial blood vessel via a thinned part of the skull, known as an acoustic window. Importantly, an adequate temporal acoustic window is not obtainable in approximately 20% of individuals, with higher failure rates reported in those of African and Asian descent, as well as in older adults and females (236). As such, the potential for sampling bias due to inadequate insonation should be recognised as a limitation of TCD. When an adequate acoustic window is present, the transmitted ultrasound waves are reflected by circulating blood cells and return to the receiver. The difference in frequencies between the transmitted and received signals, known as the Doppler shift, is proportional to cerebral blood flow (CBF) (237), assuming that the diameter of the insonated blood vessel remains constant. This assumption has been debated (238–241); MRI studies have demonstrated that middle cerebral artery (MCA) diameter is dynamic under certain experimental conditions (238–242). However, significant changes are only typically observed in response to stimuli that are not representative of real-world physiological perturbations such as severe hypercapnia (end-tidal CO₂, $\Delta \geq 10$ mmHg). Using more ecologically valid stimuli, such as dynamic handgrip exercise (240), visual stimulation

(243), simulated orthostatic hypotension (-20 to -40 mmHg) (244) or modest hypo- and hypercapnia (end-tidal CO₂, $\Delta\pm 7.5$ mmHg) (245), changes in MCA diameter are negligible. However, no MRI studies have measured MCA diameter in response to dynamic exercise involving large muscle groups (e.g., leg cycling) which warrants further investigation.

Factors influencing cerebral blood velocity

Cerebral blood velocity (CBv) is affected by multiple factors, including cerebral neuron activation, arterial CO₂ tension, systemic blood pressure and heart rate. Changes in posture and aerobic exercise can alter several of these variables simultaneously (246). The experimental protocols within this thesis were designed to control as many confounding factors as possible while retaining ecological validity. This was challenging due to patient fatigue or drowsiness, staff interruptions, and background noise. Where feasible, assessments were scheduled during quieter periods, environmental distractions were minimised, and patients were encouraged to keep their eyes open at rest, and to avoid the Valsalva manoeuvre during physical activities. At light-to-moderate exercise intensities, changes in end-tidal CO₂ levels are expected to be between 3-8 mmHg, peaking at VT2 (247,248). This magnitude of change is not expected to significantly alter middle cerebral artery (MCA) diameter (245).

Middle cerebral artery insonation

The MCA was selected as the region of interest (Figure 3.5) as this is a commonly studied blood vessel in stroke and exercise research (106,249–251), which perfuses multiple brain territories including the frontal, parietal and temporal lobes, and deeper structures of the brain such as the thalamus (252). Middle cerebral artery blood velocity was assessed using 2-MHz pulsed wave Doppler probes (6-10mm sample volume) positioned bilaterally over the transtemporal acoustic windows (Viasys Sonara, Viasys Healthcare Inc., USA), in accordance with guidelines (Figure 3.6) (253). Beginning with a depth of 50mm (approximate mid-point of M1-segment), the region superior to the zygomatic arch and anterior to the tragus were explored to obtain the largest positive waveform (blood flowing toward the probes). To confirm that the correct blood vessel was insonated, the blood vessel was followed until the inverse Doppler signal was

detected, corresponding to the bifurcation of the internal carotid artery, and origin of the anterior cerebral artery. Thereafter, the insonation depth was reduced until the largest and clearest waveform was located. The ultrasound probes were then fixed into place using a comfortable, lightweight headset containing a screw locking mechanism (Figure 3.7).

Signal acquisition and processing

Transcranial Doppler ultrasound data were recorded continuously and exported in CSV format for offline analysis. Mean MCA velocity (MCAv) was calculated using the following equation (254):

$$\text{MCAv (cm/s)} = \left(\frac{\text{peak systolic velocity} + (2 \times \text{end-diastolic velocity})}{3} \right)$$

In accordance with Billinger et al., (2017) (249), a change in mean MCAv of >10 cm/s between cardiac cycles was considered as signal artefact and such datapoints were removed. Normative data for acute cerebral haemodynamic responses to mobilisation and aerobic exercise are described in Chapters 4 and 6, respectively.

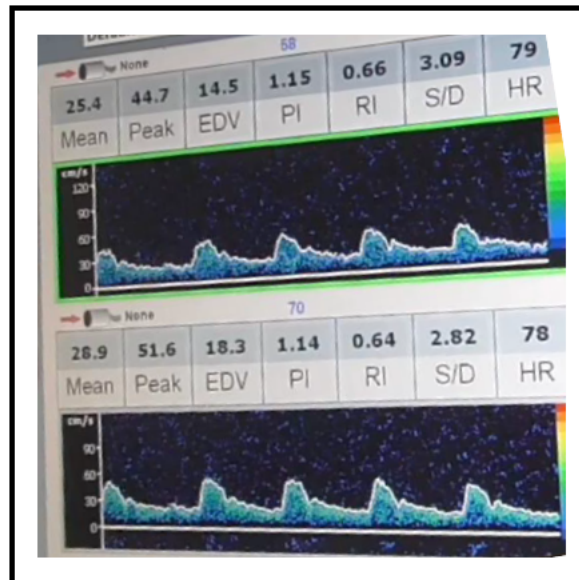


Figure 3.4 Image of TCD computer interface.

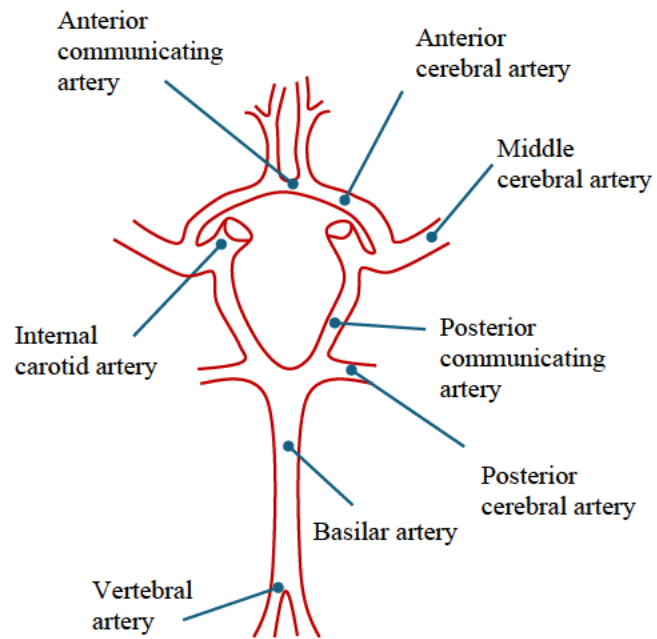


Figure 3.5 Circle of Willis.

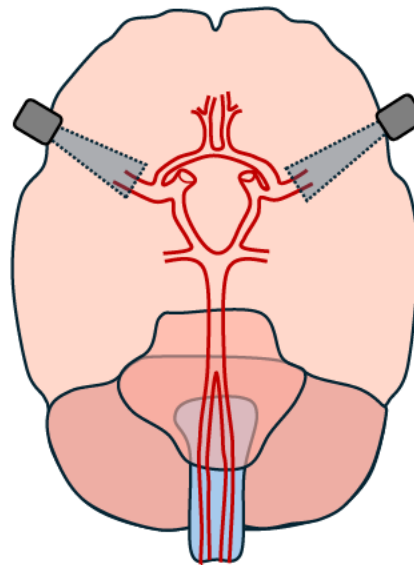


Figure 3.6 Ventral view of the brain with ultrasound probes positioned to insonate the middle cerebral arteries.

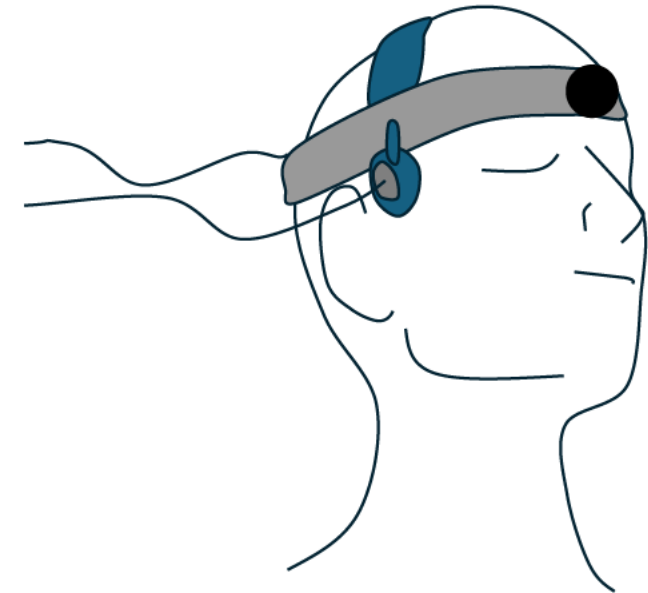


Figure 3.7 Transcranial Doppler ultrasound headset.

Heart rate (Studies 1, 2 & 3)

Heart rate was measured via an elasticated fabric chest band containing ECG electrodes (H10, Polar Electro, Kempele, Finland), positioned directly inferior to the xyphoid process. This device has been validated against an ECG Holter monitor (255). Heart rate was continuously measured in beats per minute at a sampling rate of 1Hz. The heart rate monitor was synced with the Polar Flow mobile application (Polar Flow, Polar Electro, Kempele, Finland). Heart rate data were uploaded to a cloud platform (Polar Flow, Polar Electro, Kempele, Finland), and downloaded in Microsoft Excel (Microsoft, Washington, USA) CSV format to be analysed offline.

Blood pressure (Studies 1, 2 & 3)

Blood pressure was measured at the brachial artery using a clinically validated oscillometric blood pressure monitor (DINAMAP, Carescape V100, GE Healthcare, Buckinghamshire, UK) (256).

Muscle ultrasound (Study 2)

The gold standard method to assess muscle structure is MRI due to its high resolution and ability to differentiate between muscle, fat and connective tissue. In addition, MRI is minimally influenced by the operator's skill level, which is a key consideration for a repeated measures design (257). However, MRI is expensive and its use for research is difficult in the hospital setting due to its high demand in routine clinical practice.

Muscle ultrasound is a practical alternative to assess skeletal muscle structure. Muscle ultrasound is a non-invasive, portable, low-cost, imaging method which is well-suited to hospital ward settings (258,259). However, it is important to consider the potential for human error when repeating measurements of the same muscle on different days. This error can be minimised by standardising measures relative to anatomical landmarks, and through provision of thorough operator training.

Quadricep muscle structure was measured using a portable B-Mode ultrasound with a linear transducer and 4cm field of view (Sonon 300L, Healcerion Co., Seoul, Korea). The ultrasound frequency was set at 10MHz for all assessments. All participants were resting in a semi-recumbent position in their hospital bed with a 30-degree back rest. A water-soluble ultrasound gel was applied to the transducer to optimise image clarity. Minimal pressure was applied to the skin to avoid muscle distortion. The regions of interest were the rectus femoris and the vastus lateralis.

Rationale for measuring rectus femoris and vastus lateralis

The rectus femoris and vastus lateralis are both knee extensors. In addition, the rectus femoris is involved in hip flexion (260). Both muscles play an important role in walking (260). The cross-sectional area (CSA), thickness and pennation angle of muscles are a key determinants of force production (261,262). In this thesis, rectus femoris, and vastus lateralis muscle thickness and pennation angle were measured. A detailed overview of muscle ultrasound measurement methods is provided in Chapter 5.

Reference data

A detailed review of the deconditioning literature is provided in Chapter 2. Briefly, skeletal muscle declines rapidly in the first two weeks after stroke (~1–2% per day), with faster atrophy in the paretic compared to the non-paretic limb (e.g., –1.63% vs –1.04% per day). By the third week, the rate of decline slows to ~0.8% per day in the paretic limb and ~0.5% per day in the non-paretic limb (161–164,263).

To the authors knowledge, data are not available for changes in vastus lateralis pennation angle in acute stroke populations. However, in elderly participants, two weeks of unilateral lower-limb casting resulted in a vastus lateralis pennation angle decline of 0.04 degrees per day (264). Additionally, Turton et al., (2016) reported that in critically ill patients, vastus lateralis pennation angle declined by 0.3 degrees per day over the first 10 days of hospitalisation (265).

Brain-derived neurotrophic factor (Study 3)

Brain-derived neurotrophic factor (BDNF) regulates the survival and remodelling of neurons (266), and is considered a critical protein underpinning post-stroke recovery. Blood-borne BDNF has been identified as a potential biomarker for a range of neurological and psychiatric conditions including stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and major depressive disorder (267). This has led to considerable research interest in the therapeutic potential of BDNF (268); however, pharmacological delivery of exogenous BDNF has proven largely unsuccessful, as it is rapidly cleared from systemic circulation (mainly via the liver), and although it binds to the brain's blood vessels, it is not transported across the blood–brain barrier (269).

There is strong pre-clinical evidence that aerobic exercise training, initiated early after stroke, increases BDNF content within the brain, which in turn, mitigates brain damage and enhances neurological recovery (13,85). Understanding whether this same phenomenon occurs in humans is, however, fundamentally constrained by the fact that direct measurement requires brain tissue sampling. Clinical studies therefore rely on blood-borne BDNF as a proxy for central changes, yet this relationship is equivocal, with some studies demonstrating a positive correlation (270), whereas others have found no correlation (271).

Although passage of exogenous BDNF through the blood–brain barrier is limited, research suggests that endogenous BDNF is detectable in the systemic circulation. This is evidenced by increased BDNF concentration in jugular venous blood relative to arterial blood at rest (272). Moreover, jugular vein BDNF levels increase following exercise, highlighting that acute exercise stimulates the release of BDNF from the brain (272). Many studies, including healthy populations and stroke participants have reported either a transient rise in peripheral BDNF after a single bout of exercise or a chronic increase in resting levels following an exercise intervention. Acute rises in BDNF appear to require either prolonged moderate-intensity or shorter vigorous-intensity exercise bouts. In addition, for chronic BDNF increases in resting levels, relatively large exercise intervention doses are needed (e.g., >20 hours) (273–275).

It is important to note that clinical studies typically draw blood samples from the arm, which is distal to the jugular vein, limiting insights into BDNF released from the brain. As Walsh and Tschakovsky (2018) have described in detail elsewhere (276), peripheral BDNF may be sequestered by platelets, meaning that BDNF released by the brain may not be detectable in blood samples. Additionally, there are several other peripheral sources of BDNF which contribute to the circulating pool, including liver, lungs, skeletal muscle and, critically, the spleen (276). Vigorous intensity exercise induces the splenic release of platelets into circulation (277), and platelets contain over 90% of circulating BDNF (278). Thus, changes in platelet count could substantially affect peripheral BDNF concentrations. Moreover, during exercise, water can shift between plasma and both the interstitial and intracellular fluid compartments of contracting skeletal muscle. Without correcting for plasma volume shift, this could lead to an erroneous increase in plasma solute concentration (e.g., BDNF). Of the many studies which have demonstrated aerobic exercise-induced changes in peripheral BDNF, only a few have corrected for platelet count or plasma volume (272,279,280).

Blood sampling and analysis (Study 3)

Serum BDNF reflects the total circulating pool, comprising both platelet-bound and freely circulating (unbound) BDNF, whereas plasma BDNF represents only the unbound fraction and therefore accounts for a much smaller proportion of the total circulating concentration. Serum BDNF concentrations are therefore approximately 100-200-fold higher than plasma levels (278,281). However, one study reported that plasma BDNF values can be as high as one-third of serum concentrations (282). Normative data are provided in the Dilutions section below.

Venepuncture

After cleaning the site with an alcohol wipe and allowing it to air dry, a single-use tourniquet was fastened proximally to the antecubital fossa. The site was visually inspected and palpated to identify a suitable vein, re-cleaned, the vein was anchored by applying light pressure to the skin, and a butterfly needle was inserted into the target vein at shallow angle (10-30°). Blood was then drawn into a 5mL serum separator vacutainer, followed by two 4mL vacutainers coated with an anticoagulant

(ethylenediaminetetraacetic acid [EDTA]). All vacutainers were gently inverted to 180° and back eight times to ensure sufficient mixing of blood with vacutainer contents. Resting samples were taken ≥30 minutes before usual care therapy or intervention exercise sessions, and post-exercise samples were collected during the 5-minute cooldown.

Blood sample preparation

According to Fujimura et al., (2002), approximately 90% of blood-borne BDNF is platelet-bound (278). To minimise platelet contamination in plasma, platelet-poor plasma was prepared using a two-step centrifugation process (283). Plasma samples were centrifuged for 10 minutes at 3800 rpm, after which the supernatant was carefully pipetted into a fresh EDTA tube and centrifuged again under identical conditions. The resulting supernatant was aliquoted into microvials and stored at –20 °C (recommended range: -20°C to -80°C) (284). When transferring plasma between EDTA tubes, care was taken to avoid disturbing the buffy coat—the intermediate layer between plasma and erythrocytes that contains leukocytes and platelets. The serum separator tube was left in a rack for 30 minutes at room temperature to coagulate. Serum separator tubes were then centrifuged at 3800 RPM for 10 minutes, aliquoted and stored at -20°C. One EDTA vacutainer of whole blood was sent to the haematology laboratory within 30 minutes for a full blood count analysis.

Platelet count and plasma volume

Platelet count, haematocrit, and haemoglobin concentration were calculated using an automated haematology analyser, performed by a hospital laboratory technician. The Dill and Costill method was used to estimate plasma volume shifts based on percentage changes in haemoglobin concentration and haematocrit values obtained from two samples (285):

$$\left(\frac{\text{Haemoglobin}_{\text{pre-exercise}} \times (1 - \text{Haematocrit}_{\text{post-exercise}})}{\text{Haemoglobin}_{\text{post-exercise}} \times (1 - \text{Haematocrit}_{\text{pre-exercise}})} - 1 \right)$$

Enzyme-linked immunosorbent assay

Serum and plasma samples were analysed using a mature BDNF enzyme-linked immunosorbent assay (BDNF Rapid™ ELISA Kit; Cat #: BEK-2211-2P, Biosensis Pty Ltd., SA, Australia) in accordance with the manufacturer's protocol (284).

Briefly, an enzyme-linked immunosorbent assay (ELISA) consists of a 96-well plate coated with antibodies. Using a known concentration of BDNF (1000 pg/mL), a 1:2 serial dilution was performed to generate a standard curve, enabling detection of concentrations in the range of 7.8 to 500 pg/mL. Subsequently, plasma and serum samples were diluted so that the expected BDNF concentration fell within the standard curve range. The diluted samples were then added to the wells, where mature BDNF antigens (molecules on the protein's outer surface) bound with the antibodies causing a change in colour that is proportional to the concentration of mature BDNF. All samples, including the standard curve, were assayed in duplicate and the mean value was subsequently reported.

Reference data and assay dilution factors

Serum BDNF

In a recent systematic review of 26 acute stroke cohorts (n=3298), serum BDNF values measured within one week of stroke onset ranged from 0.6 to 33 ng/mL, with a weighted mean of 12.9 ng/mL (286). Substantial variability has also been reported in healthy populations, with average concentrations of 18–26 ng/mL and a wide range from 3 to 80 ng/mL (287).

Plasma BDNF

In acute stroke, Mourão et al., (2019) (288) reported resting plasma BDNF concentrations of ~10 ng/mL measured within 72 hours of onset and again at discharge (4–30 days), with values remaining stable across time points. Øverberg et al., (2022) (289) observed admission plasma BDNF concentrations ranging from ~1.5 to 30 ng/mL, with a mean of ~7 ng/mL—approximately 2.5-fold lower than in age-matched controls. Similarly, Di Lazzaro et al., (2007) (290) measured plasma BDNF across the first four

days post-stroke and reported stable concentrations of ~5 ng/mL. Collectively, these findings suggest that plasma BDNF in acute stroke typically ranges from 5–10 ng/mL, although values between 1.5 and 30 ng/mL have been reported. However, it should be noted that these stroke studies reporting plasma BDNF concentrations obtained samples using a single centrifugation step, which would not be expected to generate platelet-poor plasma. Their reported values may therefore be influenced by residual platelet contamination, limiting comparisons with platelet-poor plasma.

BDNF response to aerobic exercise

Evidence for acute BDNF responses to aerobic exercise in the acute phase of stroke is lacking. In chronic stroke, increases in serum BDNF have only been observed at exercise intensities above 60% HRR (vigorous intensity) (273). By contrast, in healthy populations, moderate-intensity exercise of 20–60 minutes typically elicits serum BDNF increases of ~15–30% (291–294).

To the author's knowledge, no studies have assessed plasma BDNF responses to aerobic exercise in stroke populations. In elderly sedentary cohorts and other clinical groups, plasma BDNF responses to moderate-intensity exercise are highly variable, ranging from no change in older adults after 40 minutes of cycling (282), to increases of 35% in people with multiple sclerosis (exercise duration: 30 minutes) (295) and 66% in patients with major depressive disorder (exercise duration = 6 minutes) (296).

Dilution factors

Dilutions were selected based on two lines of rationale: (1) reported resting BDNF concentrations in acute stroke; and (2) possible exercise-induced changes. Although it has been reported that moderate-intensity exercise does not increase circulating serum BDNF in stroke populations, healthy populations have been shown to respond by +15 to +30%. In addition, although there is no evidence for exercise-induced plasma BDNF changes in stroke populations, other clinical cohorts have exhibited changes of +35 to +66%. The chosen dilutions (1:75 for serum, 1:30 for plasma) allow for these changes while ensuring values remain within the assay's standard curve range.

Physical activity (Study 2)

The dose of physical activity (i.e. rehabilitation) influences motor recovery after stroke (180,297). Whilst usual care rehabilitation dose can be estimated using therapy notes, patients only spend a minor proportion of their day engaging in supervised therapy. In Study 2, physical activity levels were quantified using a lightweight, triaxial accelerometer (activPAL, PAL Technologies Ltd., Glasgow, UK) secured to the anterior thigh of the unaffected limb using a hypoallergenic adhesive dressing (298). The activPAL accelerometer calculates time spent in sitting, standing and walking postures (299), and quantifies step count during walking and cycling. ActivPAL is accurate at walking speeds as slow as 0.9m/s, and outperforms waist-worn pedometers (300). However, a key limitation of this device is that its accuracy is diminished at walking speeds of less than 0.5 m/s or less than 45 steps/min, with only 0-30% of steps being detected (301). Notably, a meta-analysis of timed gait assessments in the acute and subacute phases of stroke reported that the average 10-m walking speed was 0.36 m/s (95% CI; 0.23-0.49) (302). Further, the activPAL validation studies were conducted with healthy participants with normal gait patterns. In people with abnormal gait, such as individuals with a unipedal lower limb prosthetic, activPAL underestimates total step count by 32% (303). Collectively, the evidence suggests that using activPAL to measure walking step count should be interpreted cautiously in acute stroke patients who have slow walking speeds and gait deficits. Besides walking step count, activPAL can be used to assess cycling cadence (304), which can be used to calculate the dose of cycling activity (number of repetitions). However, it is currently unknown how a recumbent cycling posture affects the accuracy of activPAL, therefore this data should be interpreted with caution.

Reference data

Few studies have assessed physical activity levels in the acute phase of stroke, but the available evidence shows that patients are highly sedentary. Sheedy et al., (2020) (116) reported that during the first week of admission, stroke patients spent over 98% of their time inactive (lying or sitting; >23 hours/day), with a median of 18 minutes standing and less than one minute walking. The corresponding median daily step count was only 169 (IQR 12–522). This cohort included a wide range of severities (NIHSS 0–25), with

only 29% being able to walk independently on admission. Another study which stratified results by stroke severity reported that in the acute phase of stroke, patients with mild stroke averaged ~1 hour/day walking and ~1 hour standing, those with moderate stroke spent <30 minutes walking and <30 minutes standing, and those with severe stroke spent >95% of the day in bed; however, step counts were not reported (115).

Global physical activity questionnaire (Study 2)

A higher level of physical activity pre-stroke is associated with more favourable recovery after stroke (305,306) therefore it is important to consider this confounding variable. In Study 2, pre-stroke physical activity levels were recorded at baseline using the Global Physical Activity Questionnaire (GPAQ). An additional GPAQ was conducted at the 3-month follow-up appointment to determine engagement in physical activity in the post-hospital recovery period. The GPAQ is a validated questionnaire (307) which assesses physical activity levels within three domains: work, transportation, and recreation. This questionnaire quantifies time spent engaging in sedentary behaviours, as well as moderate- and vigorous-intensity activities. Results are converted into MET-minutes per week, and respondents are categorised as having a low, moderate, or high physical activity level.

While the GPAQ provides a useful overview of physical activity levels, several limitations should be considered when interpreting the results, particularly in the acute stroke population. As a self-reported tool, its accuracy may be affected by cognitive impairments, recall issues and social desirability bias, leading to potential over- or underestimation of activity levels (308,309). Additionally, it lacks sensitivity to stroke-specific gait patterns which often have an increased energy cost compared to healthy populations (310). Lastly, the questionnaire's categorisation of work-related and transport-related activity may also be less relevant for stroke survivors who are no longer in employment due to retirement or disability.

Indirect calorimetry (Study 3)

Indirect calorimetry is a method used to estimate energy expenditure based on oxygen consumption (311). During exercise, increased energy turnover in working muscle leads to a rise in oxygen uptake ($\dot{V}O_2$), which can be expressed as metabolic equivalents (METs)—a commonly used measure of exercise intensity in public health research (209). Whilst indirect calorimetry is the gold-standard method for assessing energy expenditure, it also has limitations. The use of a face mask to collect expired air may be uncomfortable for patients, such as those with respiratory complications or facial weakness, which may affect exercise tolerance and data accuracy. Additionally, participants are required to minimise talking during the assessment to avoid disruptions in airflow measurement, which may be unfavourable for participants who want to discuss their feelings of exertion, or potential discomfort or during exercise.

Indirect calorimetry was initially included in Study 2 using a reliable metabolic gas analyser system (Metalyser 3B, Cortex Biophysik GmbH, Leipzig, Germany) (312). The device was calibrated according to the manufacturer's instructions. Briefly, the O_2 and CO_2 sensors were calibrated using ambient air, then a gas mixture of O_2 (15%) and CO_2 (5%); the pressure sensor was calibrated using a digital barometer; and the flow sensor was calibrated using a three-litre syringe. Expired air was collected using a Hans Rudolph face mask which was securely fitted around the nasal bone and below the mandible, creating a flush seal around the nose and mouth. The mask was checked for air leaks prior to data collection. Participants were reassured that their breathing would not be affected by the mask, and that they should breathe as normal but limit talking where possible. However, patients were encouraged to discuss any concerns such as feelings of pain or discomfort.

During first two attempts to use this equipment, participants reported discomfort wearing the face mask. To avoid interfering with delivery of the intervention, indirect calorimetry was subsequently omitted from the assessment protocol and logged as a protocol deviation.

Stroke severity and disability measures (Studies 1, 2 & 3)

National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) is a validated clinical tool used to assess the overall extent of stroke severity, evaluating 11 domains of neurological function to guide treatment and therapeutic interventions (313). The NIHSS is a comprehensive neurological assessment which routinely recorded as part of usual care on admission to hospital, and shortly after reperfusion therapy. The NIHSS is a useful baseline variable which served as a stratification factor for group allocation for the feasibility trial, and as a prognostic covariate for analysing recovery trajectories. A key limitation of the NIHSS is that it is weighted toward anterior circulation-related impairments (e.g., language and motor strength), and lacks sensitivity to deficits such as gait or truncal ataxia, and vestibular symptoms (314).

Modified Rankin Scale

The modified Rankin Scale (mRS) is a validated scale used to assess the degree of stroke severity (315). The scale items include: 0 (no symptoms); 1 (no significant disability, but some symptoms); 2 (slight disability, able to look after oneself but not do all previous activities); 3 (moderate disability, requires some help but can walk unassisted); 4 (moderately severe disability, unable to walk unassisted or attend to own bodily needs); 5 (severe disability, bedridden, incontinent, and requires constant nursing care); and 6 (dead).

The modified Rankin Scale has some limitations to consider. Firstly, subjectivity in scoring can lead to variability between raters. In this programme of research, mRS data was assessed in collaboration with therapists, and retrospectively using medical notes. All raters had received training in mRS scoring, which should have minimised inter-rater variability. Additionally, the scale's broad categories make it less sensitive to detecting small but clinically significant changes in function.

Barthel Index

The Barthel Index is a validated scale which evaluates a patient's ability to perform ten basic activities of daily living, including feeding, bathing, grooming, dressing, bowel function, bladder function, toilet use, transfers (bed to chair and back), mobility on level surface, and use of stairs. Scores range from 0 to 100, with higher scores indicating greater independence (208).

The Barthel Index has a few limitations to discuss. It primarily assesses physical function and does not account for cognitive, emotional, or social factors, which can significantly impact a patient's ability to perform daily activities. The scale is also affected by ceiling and floor effects, limiting its sensitivity in patients with either very mild or severe disability. Additionally, reporting bias can occur when input is provided by caregivers or patients, potentially leading to over- or underestimation of abilities (316).

Physical function measures (Study 2)

Handgrip strength

Handgrip strength, assessed via dynamometry, measures the force exerted by the hand, serving as proxy for upper limb muscle strength, physical function, frailty and stroke severity (317–319). Whilst the cycling-based aerobic exercise intervention does not target the upper limb musculature, upper limb motor function may be influenced by aerobic exercise indirectly via neuroprotection and/or increased neuroplasticity.

A key limitation of handgrip dynamometry is that it lacks specificity, as it only measures isolated grip force rather than broader upper limb function, coordination, or dexterity. In addition, variations in fatigue and mood may reduce measurement reliability across visits (320,321). Standardised instructions were given to participants to maximise the accuracy and reliability of handgrip strength assessments.

Reference data

Handgrip strength typically declines with age, and is higher in males and taller people; detailed height- and sex-specific normative data are available elsewhere (322). The European Working Group on Sarcopenia in Older Persons (EWGSOP) recommends a cut-off point of 2.5 standard deviations (SD) below a healthy reference population, equating to <27 kg for men and <16 kg for women. In addition, cutoff values of >15.1 kg for men and >9.5 kg for women have been proposed to indicate if stroke patients are ready to be discharged to home (323).

A study of elderly acute stroke patients (n=76, aged 60-67) with minor stroke (NIHSS ~3), reported that the average handgrip strength (including both hands) is 22kg (95% CI, 20-24kg) (324). In a study which included a broader range of acute stroke severities (n=358, 42% female, 69 ± 13 years, 56% with severe dependency), 49% were identified as having low handgrip strength (handgrip strength scores not specified), below the EWGSOP cut-offs (325).

At two weeks post-stroke, people with a mild stroke severity (NIHSS, 3 ± 2) have a between-limb deficit of ~60% (326). This deficit reduces to around 35% seven weeks post-stroke and is restored to 21% one year after stroke (326). In contrast, another study of chronic stroke survivors with mild-to-moderate hemiparesis reported a 29% between-hand strength deficit, measured an average of 4 ± 2 years post-stroke (range 1–10 years) (327). Notably, handgrip strength is strongly influenced by stroke type and severity which limits the value of normative benchmarks.

Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) evaluates lower extremity function through a series of tests, including balance, 4-metre walk speed, and sit-stand tasks. Scoring ranges from 0 to 12, with higher scores indicating higher function (328). A score of zero is given if participants are unable to complete the SPPB assessment.

Whilst the SPPB is a low-cost, pragmatic test battery, it has some limitations to mention. Stroke-related fatigue and cognitive impairments can negatively affect

performance on balance and walking tasks, which may skew the results (329). Additionally, the SPPB is prone to ceiling effects (330), but this may be not an issue for stroke patients admitted to an acute stroke ward, who are likely to have some degree of motor and/or balance impairment. In contrast, individuals with severe impairments may not be able to complete any of the SPPB tests, limiting its ability to track improvement in this group. This limitation is particularly relevant for the present PhD research, as one study aimed to recruit patients who were likely to be admitted to hospital for at least one week. Consequently, patients with minor deficits who have a short length of stay were less likely to be recruited, meaning that the sample was biased toward a higher stroke severity.

Reference data

An SPPB score of <10 has been defined as impaired mobility (331,332), and having a low score of between 4-6 is associated with a five-fold increased risk of long-term disability compared to high score of 10-12 (333). To the author's knowledge, normative SPPB data are not available for acute stroke populations. Data are available for subacute stroke patients, but 'normative' values are determined by the study inclusion criteria. In hemiplegic subacute stroke patients ($n=86$; 66.2 ± 13.4 years old; 80.6 ± 131.0 days post-stroke), of whom 42% were independently mobile, a median SPPB score of 5 (IQR: 1-10) has been reported (334). Another study involving 29 independently mobile subacute stroke patients (69 ± 11 years old; 66 ± 29 days post-stroke) reported a higher mean SPPB score of $9.3 (\pm 3.0)$; range, 2-12) (335). In a study involving 43 community dwelling chronic stroke patients (61.5 ± 9.8 years old) with mild to moderate hemiparetic gait, a mean SPPB score of 6.3 ± 2 (range, 3-12) (336) has been reported. The discrepancies between studies are likely explained by heterogeneity of participant characteristics.

10-metre walk speed

The 10-metre walk test is a simple measure of ambulatory function (337), walked at either a comfortable or a fast pace. Instead of measuring 10-metre walk speed separately to the SPPB 4-metre walk speed, the SPPB walk test was extended by six metres and walking ability was assessed across both distances at a comfortable pace. The 10-metre walk speed test shares similar limitations to the SPPB, including the potential for

fatigue and cognitive impairments to affect performance, as well as floor and ceiling effects that may limit its sensitivity to changes in individuals with severe or mild impairments. According to a systematic review of studies which assessed 10-metre walk speed in acute and subacute stroke patients, walking speed ranges between 0.04 to 0.71 m/s in the first two weeks after stroke, and 0.17 to 0.38 m/s in subacute stroke populations (mean 14 to 72 days post-stroke) (302). However, interpreting ‘normative’ data in the early post-stroke recovery period is difficult due to between-participant variability in post-stroke deficits.

For reference, in a study of community-dwelling stroke survivors, Perry et al., (1995) (338) defined functional walking categories based on 10-metre walk measured at least three months after stroke onset (see Table 3.3 below)

Table 3.3. Classification of walking handicap in stroke populations. Reproduced from (338)

Walk speed (m/s)	Category	Description
0.10	Physiological walker	Walks only at home or in therapy using parallel bars
0.23	Limited household walker	Requires assistance for some walking activities
0.27	Unlimited household walker	Walks independently within the home; has difficulties with stairs and uneven terrain; may use wheelchair outdoors
0.40	Most-limited community walker	Can manage limited short trips outside independently
0.58	Least limited community walker	Walks independently in moderately challenging conditions (e.g., uncrowded spaces)
0.80	Community walker	Walks independently in the community in challenging conditions (e.g., crowded spaces)

Psychometric assessments (Study 2)

Before describing each psychometric assessment, it is useful to highlight their shared limitations. Post-stroke cognitive deficits increase the risk of recall bias, and may lead to inaccurate responses (309). Communication deficits such as expressive aphasia, may also hinder participants' interpretation and response accuracy (339). Moreover, cognitive deficits, stroke-related fatigue, and mood symptoms can overlap, potentially affecting the results (329,340). Questionnaires are also susceptible to social desirability bias (308). Finally, some psychometric assessments are susceptible to floor or ceiling effects, limiting their sensitivity to detect meaningful changes over time.

Several strategies were implemented to address these limitations. Questionnaires were adapted in line with the Stroke Association's Accessible Information Guidelines (341). Key design features included a clear, legible typeface, large fonts, bolding key information, minimising text per page, and incorporating ample white space around content. As well as enhancing legibility, this accessible format is likely to reduce reading-induced fatigue, potentially improving response accuracy (342). To further mitigate fatigue, participants were offered breaks as needed. Additionally, to reduce the risk of social desirability bias, participants were informed that providing accurate responses was essential for advancing knowledge about stroke rehabilitation, and that there was no right or wrong answer. Lastly the research team were trained in aphasia-friendly communication techniques, and patient-facing support was provided by a speech and language therapist when needed.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a popular tool used to assess cognitive function in stroke patients (343). The MoCA evaluates multiple cognitive domains: memory, attention, concentration, executive function, language, visuospatial skills, and orientation. The MoCA score ranges from 0-30, with higher scores indicating increased cognitive function. The MoCA-Blind (344) is a modified version of the MoCA, developed to assess cognitive function in individuals who cannot complete visuospatial tasks. The MoCA-Blind is scored out of 22 points. Both versions of the MoCA can be converted to a percentage; above 85% (26/30 or 19/22) is considered as normal

cognitive function. A key limitation of the MoCA is its sensitivity to educational attainment (345); lower scores may reflect limited education rather than cognitive impairment. Education status was not recorded in this PhD research, therefore this confounding factor could not be accounted for.

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a widely used, self-report psychometric tool designed to measure the impact and severity of fatigue on daily functioning (346). The scale consists of nine statements that assess how fatigue interferes with physical, social, and professional activities. Respondents rate each statement on a 7-point Likert scale, ranging from one (strongly disagree) to seven (strongly agree). The total score, calculated as the average of the nine items, ranges from one to seven, with higher scores indicating greater fatigue severity. A key limitation is that the FSS lacks sensitivity to detect transient changes in fatigue during the early post-stroke period (e.g., first week), as it is designed to assess stable, chronic fatigue states. Additionally, fatigue levels can fluctuate daily due to factors like pain, sleep quality, or depression (347), which the FSS may not capture.

Self-Efficacy for Exercise Scale

The Self-Efficacy for Exercise Scale exercise (348) was initially included in Study 2 to assess participants' confidence in exercising regularly. The tool requires participants to rate their confidence (0 = no confidence, 10 = very confident) across nine scenarios, producing a total score of up to 90. Self-efficacy is an important determinant of exercise behaviours, with higher levels associated with better adoption and maintenance of physical activity (349).

Key limitations of this scale are that it is less applicable for patients with severe motor impairments who may be physically unable to exercise without specialised equipment, and it does not distinguish between types of exercise, potentially leading to ambiguity in responses. During the initial attempts using this scale, participants experienced difficulty differentiating aerobic exercise from routine rehabilitation, and many expressed uncertainty about the requirement for supervision, and equipment access.

Given this confusion, the scale was removed from the assessment battery and recorded as a protocol deviation.

The Revised Life Orientation Test

The Revised Life Orientation Test (LOT-R) is used to assess how optimistic a person is (350). Higher levels of optimism have been linked to healthier lifestyle behaviours (351) and more favourable cardiovascular risk factors (352). Assessing optimism may therefore provide insights into engagement with rehabilitation and adoption of health behaviours, and associated health outcomes. A key limitation of the LOT-R is that it is designed to measure dispositional optimism (a stable trait), yet responses may be influenced by transient changes in psychological state, reflecting state optimism (a temporary, fluctuating construct). This limitation is particularly relevant in the acute phase of stroke, when patients have experienced a profound, life-threatening event that may temporarily distort their outlook. As such, the LOT-R may be more appropriate for use in longer-term follow-up, when patients have had time to adapt to life outside of hospital.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is widely used to detect symptoms of anxiety and depression in medical settings (353). The HADS comprises 14 statements relating to feelings of depression or anxiety. Users are required to rate the extent to which they agree with statements or recall symptom frequency. Aerobic exercise is known to improve mood in a wide range of populations (354,355). In addition, depression and anxiety are prevalent in acute stroke (356). It was therefore of interest to explore how aerobic exercise influences mood in the acute stroke population. Initially, depression and anxiety were to be measured using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) scales. However, during study setup these were replaced by the Hospital Anxiety and Depression Scale (HADS). The rationale was that the HADS assesses symptoms over the preceding week, which better aligned with the acute stroke context, whereas the PHQ-9 and GAD-7 specify a two-week timeframe, making them less appropriate for

patients assessed within days of stroke onset.

EuroQol Quality of Life Index

The EuroQol Quality of Life Index 3-Level (EQ-5D-3L) (357) assesses participants' ability to walk, wash and dress, do daily activities (e.g., housework or socialise), and indicates their mood state, and level of pain or discomfort. Answers are calculated using a weighted scoring system and are summed to create an index score. In addition, participants rate their health on a scale of 0 (worst health) to 100 (best health). This provides an additional visual analogue scale score which can be analysed separately to the EQ-5D-3L index score. A limitation of the EQ5D is that its domains are very broad and do not specifically address stroke-related issues like fatigue, motor function loss, or cognitive deficits. This may fail to capture the more nuanced effects of stroke. Nevertheless, this scale is widely utilised, and is relevant for health economic analyses (358). Piloting this tool provides useful insight for future work.

Acceptability (Study 4)

Qualitative data

The Medical Research Council Framework for Developing and Evaluating Complex Interventions emphasises the importance of assessing intervention acceptability (175). To guide this process in Study 4, the Theoretical Framework of Acceptability (TFA) was applied. The rationale for using this framework is that it provides a theory-driven and clear definition of acceptability, alongside a set of clearly specified component constructs. Sekhon et al., (2017) (173) developed the TFA in response to the inconsistent and ambiguous use of the term 'acceptability' in healthcare research. Through a systematic review of 43 studies and subsequent expert consensus, they defined acceptability as:

A multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention (173).

Sekhon et al., (2017) (173) then developed seven core domains of acceptability which are outlined in Table 3.4 below. These domains provide a structured approach to assessing participants' experiences of a healthcare intervention.

Table 3.4. Theoretical Framework of Acceptability domains and descriptions.

Domain	Description
Affective Attitude	Feelings about the intervention (e.g., enjoyment or dissatisfaction).
Burden	Effort required to participate in the intervention.
Ethicality	Alignment of the intervention with personal values and beliefs.
Intervention Coherence	Understanding of the intervention's purpose and function.
Opportunity Costs	Perceived trade-offs or sacrifices compared to alternative uses of time/resources.
Perceived Effectiveness	Belief in the intervention's ability to achieve its intended outcomes.
Self-Efficacy	Confidence in one's ability to engage with and complete the intervention tasks.

Comfort Likert scale

In addition to the one-to-one interviews, participants were asked to rate how comfortable they thought the exercise bike was. This was a five-point scale including: 1 (very uncomfortable), 2 (uncomfortable), 3 (neutral), 4 (comfortable), and 5 (very comfortable). While not a validated instrument, this simple and pragmatic measure of perceived comfort contributed to the broader evaluation of intervention acceptability.

Study-specific methods and data analysis

This thesis involves a mixed-methods approach to address a variety of research questions. Data analysis techniques involve descriptive statistics to reveal patterns and

characteristics, inferential statistics to test hypotheses and explore relationships between variables, and qualitative analyses to understand people's experiences and opinions. Most methodological procedures are described in detail within the current methodology chapter. However, study-specific protocols and analyses are described within the subsequent experimental chapters. This approach avoids unnecessary repetition while ensuring that each chapter contains sufficient methodological information to allow the study to be understood and replicated.

Research setting and recruitment

This research was conducted in Sheffield, UK at the Royal Hallamshire Hospital (RHH), and the Stroke Pathway Assessment and Rehabilitation Centre (SPARC)—an inpatient rehabilitation unit. All recruitment activities and most study activities were completed on the hyperacute stroke unit (HASU), the acute stroke unit (ASU) or the neurology day care unit at the RHH. Follow-up assessments were conducted at either the RHH or SPARC. Figure 3.8 displays a diagram of the stroke pathway. Eligibility criteria are outlined in Chapters 4 and 5, along with specific recruitment methods.

Research team members involved in research activities

Except for the modified Rankin Scale and Barthel Index assessments conducted at outpatient follow-up appointments for Study 2 by the Study Doctor (AA), all other assessments were performed by the same researcher (NK). Data analysis was primarily undertaken by NK. Muscle ultrasound images were analysed by TMW, who was blinded to group allocation. A sample of interview transcripts was independently coded by HH and RY.

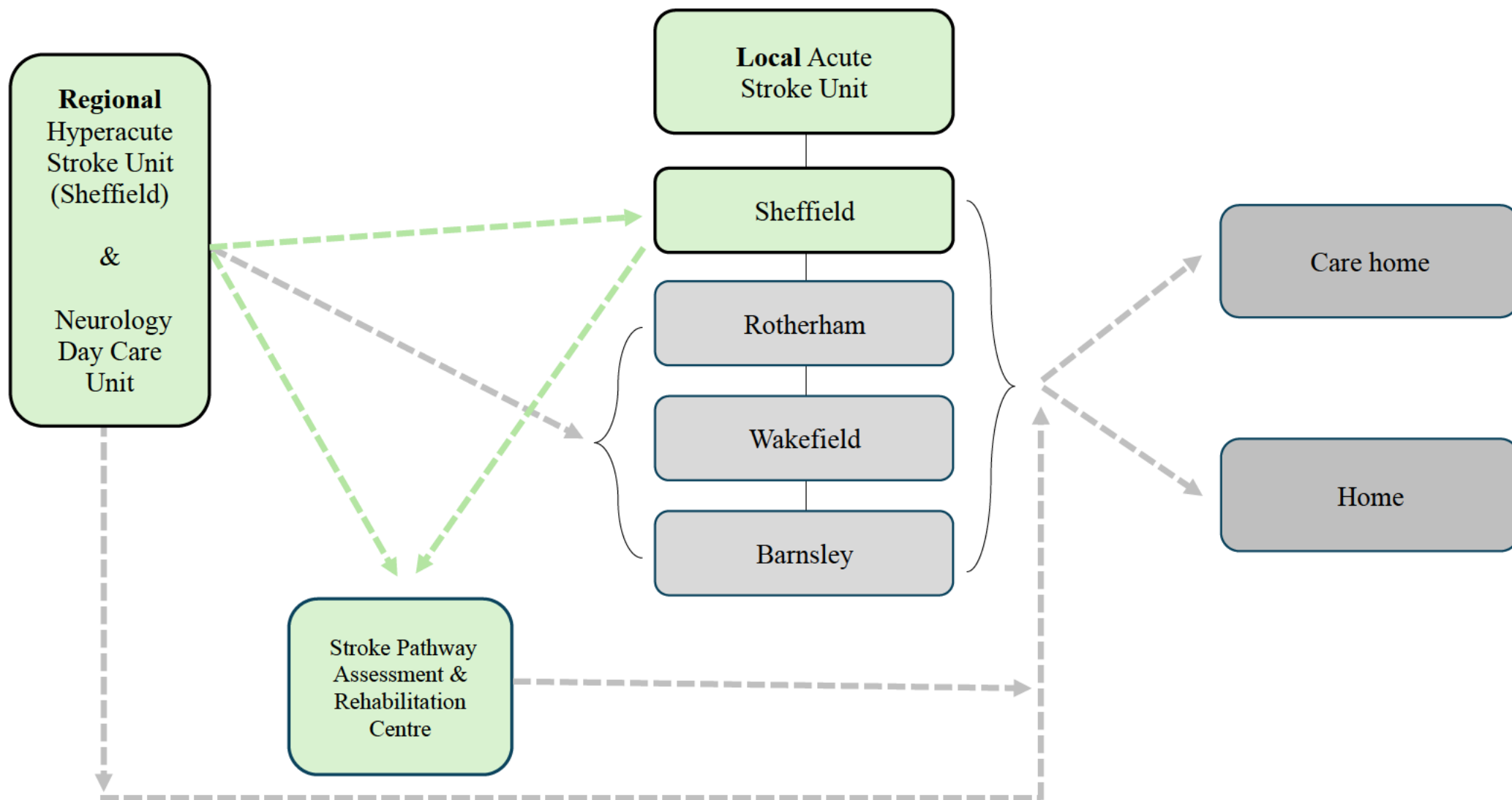


Figure 3.8 Diagram of South Yorkshire NHS stroke pathway. Green boxes and arrows indicate Sheffield inpatient rehabilitation/research sites and potential pathways, respectively. Grey arrows indicate pathways excluding patients from participating in this research. Grey boxes indicate non-research sites.

Ethical approval and clinical trials registration

The mechanistic study investigating the cerebral haemodynamic response to early mobilisation (Study 1) was approved by the North West - Greater Manchester West Research Ethics Committee (IRAS: 295752; REC Reference: 21/NW/0146) and Sheffield Hallam University Research Ethics Committee (Converis: ER31600091). This study was registered on ClinicalTrials.gov before recruitment started (NCT04972812).

The aerobic exercise feasibility study (Study 2) and mechanistic sub-study (Study 3) were approved by the Bradford Leeds NHS Research Ethics Committee (IRAS: 280320; REC Reference: 20/YH/0285), and Sheffield Hallam University Research Ethics Committee (Converis: ER25055563). These studies were registered under a single trial on ClinicalTrials.gov before recruitment started (NCT04742686).

Chapter 4 – The Acute Effect of Early Mobilisation on Cerebral Haemodynamics in Acute Stroke

Background

Stroke is a leading cause of mortality and long-term disability worldwide (2). Stroke diagnoses are broadly categorised into two subtypes: ischaemic (~85% of cases) and haemorrhagic (~15% of cases) (2). Ischaemic stroke results from an obstruction of blood flow, typically caused by a thrombus or embolus, resulting in hypoxia and infarction of brain cells (15). Haemorrhagic stroke involves the rupture of a blood vessel, leading to intracerebral bleeding, raised intracranial pressure and secondary injury due to a mass effect, neurotoxicity and brain cell death (23). Key treatment strategies for ischaemic stroke include thrombolysis and thrombectomy (359), while haemorrhagic stroke is managed with surgical evacuation and blood pressure medication (23,73). Despite their different aetiologies and treatments, both stroke subtypes can disrupt cerebral autoregulation, which is the ability to maintain stable cerebral blood flow despite fluctuations in arterial blood pressure (52,56,360). This mechanism ensures a constant supply of oxygen and nutrients, and protects the brain against hypo- and hyperperfusion. Impaired cerebral autoregulation presents a major challenge to the multidisciplinary stroke team. A key medical aim is to protect vulnerable brain tissue by avoiding significant perturbations in cerebral perfusion pressure (73,361). In parallel, stroke therapists aim to promote neuroplasticity and prevent deconditioning through practice of motor activities, which may compromise perilesional perfusion.

Early mobilisation—defined as out-of-bed sitting, standing and walking within 48-72 hours of stroke onset (78,97)—is a core acute stroke rehabilitation method recommended by clinical guidelines worldwide. The rationale for early mobilisation is threefold: (1) to avoid bed rest-related complications such as deep vein thrombosis (104,362); (2) to mitigate hospital-associated deconditioning (10,97,363); and (3) to harness a window of neuroplasticity (11,97). However, this rationale is based on observational clinical evidence, studies involving physical exercise interventions (not

mobilisation), and preclinical experiments, rather than definitive RCT evidence (11,97,104).

The role of early mobilisation in stroke rehabilitation has been debated for decades (14,94,95,97,98,104,105,364). Moving from a sitting to a standing position elicits orthostatic stress—a gravity-induced displacement of blood from the head and torso toward the lower limbs where it can pool, resulting in a drop in blood pressure and slowed venous return to the heart and brain (108). In healthy individuals, these rapid blood pressure changes are buffered by dynamic cerebral autoregulation, which quickly (within ~11 seconds) adjusts cerebrovascular resistance to compensate for fluctuations in perfusion pressure (31). Additionally, the arterial baroreflex responds to the fall in arterial pressure, whereby stretch-sensitive carotid and aortic baroreceptors relay signals to the brainstem which triggers rapid autonomic adjustments (within ~3 seconds); withdrawal of vagal tone and increased sympathetic activity, cause peripheral vasoconstriction and a pronounced increase in heart rate (typically peaking within 15 seconds), which both help restore systemic blood pressure (35,365). After stroke, both cerebral autoregulatory and baroreflex responses may be blunted or delayed due to either structural damage or compensatory changes in autonomic control, meaning that perilesional tissue may be at an increased risk of hypoperfusion during orthostatic stress (52–54,56,58,61,360,366).

Clinicians have long expressed concerns that upright postures can induce or exacerbate stroke symptoms. For example, in 1958, Fisher et al., (1958) wrote:

“Clinical observations indicate that strokes and ischaemic attacks in many cases develop when the patient gets up from his bed”, and that “the patient must avoid standing quietly for prolonged periods, must sit with feet up, etc” (98).

The exacerbation of stroke symptoms caused by upright positioning was coined ‘positional cerebral ischaemia’ by Caplan and Sergay in 1976 (99). More recently in 2006, Diserens et al., (2006) (104) described their:

“frequent clinical experience that patients with worsening of their clinical deficit in the acute phase improve clinically by lying flat or even (transiently) in a Trendelenburg position”.

These concerns, however, appear to have had little impact on clinical practice.

Early mobilisation became established in clinical practice at the turn of the 21st century—not as an isolated intervention, but as a core element of the multifaceted organised stroke unit model. This shift represented a move away from the prevailing belief that “bed rest is best” toward earlier and more intensive rehabilitation (89–92,153). During the 1990s and early 2000s, several RCTs demonstrated that specialist stroke units significantly reduced the risk of death, dependency, and the risk of progression or recurrence compared with care on general medical wards (362). However, because early mobilisation was introduced in parallel with other advances to stroke management and rehabilitation, its specific contribution to improved outcomes cannot be disentangled from the broader ‘stroke unit effect’.

In the first attempt to elucidate the ‘active ingredients’ of the stroke unit effect, Indredavik et al., (1999) (94) conducted a retrospective analysis of an RCT comparing general medical ward care to the organised stroke unit model. The authors found that being admitted to an organised stroke unit reduced the risk of mortality, and that the strongest predictor of a good recovery was earlier mobilisation (mean, 8 hours vs. 2.7 days). However, this result was confounded by the fact that patients allocated to the organised stroke unit also had favourable blood pressure, blood glucose and body temperature—all of which are likely to influence recovery.

This work inspired a series of influential studies by the A Very Early Rehabilitation Trial (AVERT) group, which assessed the safety, feasibility and effectiveness of very early (<24 hours post-stroke) versus delayed (24 hours post-stroke) mobilisation. Despite a two-fold higher mortality rate in the VEM group (21% vs. 9%), the phase II AVERT study reported that very early mobilisation (VEM) is safe and feasible to deliver (95). Notably, the intervention group received an additional three mobilisation sessions per day and therefore had more prolonged exposure to orthostatic stress which confound this study’s results. Despite the unfavourable mortality rate, the AVERT group proceeded to a large-scale phase III trial.

Numerous RCTs have subsequently been conducted to assess the safety and effectiveness of VEM compared to usual care (delayed mobilisation). The most up-to-date Cochrane systematic review of nine RCTs (n=2958) reported that VEM (median [IQR] time to first mobilisation 18.5 [13.1-43] hours) likely led to ‘similar or slightly more deaths’, and poorer neurological outcomes compared to delayed mobilisation (median 33.3 [IQR 22.5-71.5] hours) (14). The Cochrane review findings are dominated by the phase III AVERT results, a study which recruited 2104 participants (71% of total participants included in the Cochrane review). The headline result from the phase III AVERT study was that VEM was associated with an increased risk of a poor neurological outcome three months after stroke. Akin to its initial feasibility trial, the phase III AVERT study did not standardise therapy dose—The VEM group engaged in at least three additional bouts of mobilisation per day.

To explore associations between mobilisation dose components and neurological outcomes, the AVERT group also conducted a regression analysis (367). Their findings were contradictory, with greater time spent mobilising (>13.5 mins/day) associated with a poorer outcome, but a very high frequency of out-of-bed activities (>10 per day) associated with improved outcomes (modified Rankin Scale < 3). However, without detailed information about session content in each subgroup and the haemodynamic effects of mobilisation activities, it remains unclear whether the associations represent true effects or variability between subgroups. Moreover, these findings are based on small numbers, with only 11 patients (~0.5% of the 2,083 enrolled) mobilised more than 10 times per day (367).

Although the mechanisms behind the negative AVERT trial results remain unclear, they could reflect vulnerability of the perilesional tissue to orthostatic stress. Indeed, there is clear evidence that upright head positioning (30 degrees) causes a decline in cerebral blood velocity (a proxy for cerebral perfusion) in the acute phase of stroke. Carvalho et al., (2020) (106) performed a meta-analysis of studies comparing cerebral haemodynamics in supine and 30-degree positions within seven days of stroke, assessed using transcranial Doppler ultrasound. The pooled results of six trials revealed that in comparison to a supine position, a 30-degree head position elicited a significant 6.6 cm/s reduction (95% CI, -2.5, -10.7 cm/s) in ipsilesional CBv, but there was no significant difference in contralesional CBv (-2.3 cm/s, 95% CI, -1.04, 5.55). For

context, the 6.6 cm/s decline in ipsilesional CBv is equivalent to a 13% reduction in a person with a baseline CBv of 50 cm/s.

To date, only Carvalho et al., (2024) (107) have assessed CBv responses to sitting and standing during the acute phase of stroke. CBv was measured via transcranial Doppler ultrasound across a range of postures (0° to 30°, 70°, sitting, and standing) in acute stroke patients with occlusive disease (n = 13, median age 75 years [IQR: 70–83], median NIHSS 2 [IQR: 2,6]) and without occlusive disease (n = 29, median age 61 years [IQR: 59, 76], median NIHSS 5 [IQR: 2, 13]), at two time points: <48 hours and 3–7 days post-stroke. As baseline values were not reported, percentage changes discussed below are estimated using an assumed resting CBv of 50 cm/s, consistent with a systematic review conducted by Carvalho et al., (2020) (106).

At <48 hours post-stroke, participants with occlusive disease exhibited progressive CBv reductions in the ipsilesional hemisphere in more upright positions, with more pronounced declines observed in sitting (~-19.8%; -9.9 cm/s, 95% CI: -16.4 to -3.4) and standing (~-14.2%; -7.1 cm/s, 95% CI -14.3, 0.01). The contralesional hemisphere displayed smaller changes during sitting (~-7.6%; -3.8 cm/s, 95% CI -6.5, -1.1) and standing (~-6.4%; -3.2 cm/s, 95% CI -6.2, -0.3). In contrast, patients without occlusive disease exhibited more modest and more symmetrical reductions across hemispheres. In the ipsilesional hemisphere, CBv declined by -3.3 cm/s (-6.6%; 95% CI -5.6 to -1.1 cm/s) during sitting and -3.6 cm/s (-7.2%; 95% CI -5.9 to -1.3 cm/s) during standing. In the contralesional hemisphere, CBv declined by -4.5 cm/s (-9.0%; 95% CI -7.0 to -2.1 cm/s) during sitting and -3.9 cm/s (-7.8%; 95% CI -6.3 to -1.4 cm/s) during standing (107).

At 3–7 days post-stroke, patients with occlusive disease exhibited CBv reductions in both hemispheres. Ipsilesional CBv declined by -5.8 cm/s (-11.6%; 95% CI -8.5 to -1.8) during sitting and -7.4 cm/s (-14.8%; 95% CI -9.9 to -4.8) during standing, while contralesional CBv fell by -5.1 cm/s (-10.2%; 95% CI -8.5 to -1.8) in response to sitting and -3.3 cm/s (-6.6%; 95% CI -6.6 to -0.3) while standing. In patients without occlusive disease, ipsilesional reductions were of a similar magnitude (-5.2 cm/s [-10.4%] sitting; -6.7 cm/s [-13.4%] standing), but contralesional changes were minimal (-1.3 cm/s [-2.6%] sitting; -0.9 cm/s [-1.8%] standing) (107).

The only other study to examine CBv responses to sitting and standing, albeit in a chronic stroke cohort, was conducted by Novak et al., (2010) (368). Forty-three participants (mean 6.1 ± 4.9 years post-stroke; NIHSS 2.71 ± 2.72 ; mRS 1.2 ± 1.14) were assessed, comparing normotensive and hypertensive subgroups. In normotensive participants, ipsilesional CBv declined by ~ 4 cm/s ($\sim 11\%$) when sitting and ~ 5 cm/s ($\sim 14\%$) when standing, while contralesional reductions were smaller at ~ 1 cm/s ($\sim 3\%$) when sitting and ~ 3 cm/s ($\sim 9\%$) when standing. In hypertensive participants, the reductions were larger, with ipsilesional CBv falling by about ~ 5 cm/s ($\sim 12\%$) when sitting and ~ 7 cm/s ($\sim 17\%$) when standing. In the contralesional hemisphere, CBv declined by ~ 3 cm/s ($\sim 7\%$) when sitting and ~ 4 cm/s ($\sim 10\%$) when standing. For context, Novak et al., (2010) (368) also included non-stroke controls; both normotensive and hypertensive controls had a higher baseline CBv (~ 51 – 55 cm/s) compared with stroke participants (~ 37 – 42 cm/s) and exhibited smaller reductions in upright postures, ~ 3 to ~ 4 cm/s (~ 5 – 8%) (368). This comparison suggests that while upright posture reduces CBv in a range of populations, the effect is amplified after stroke, indicating increased vulnerability to orthostatic stress.

Collectively, the discussed evidence indicates that upright positioning consistently reduces CBv, with more pronounced declines in the ipsilesional hemisphere and in patients with occlusive disease or hypertension. However, a key limitation of the study of acute stroke patients by Carvalho et al., (2024) (107) is the inconsistent timing of CBv measurements between postures. For all postures except standing, measurements were taken after a 2-minute stabilisation period. In contrast, only the immediate CBv response was assessed during standing, recorded within the first minute. Measuring CBv after a 2-minute stabilisation period for other postures overlooks the immediate CBv response, which may be clinically relevant. Additionally, restricting the standing measurement to the first minute precludes the assessment of how CBv evolves over time.

Summary

Understanding cerebral haemodynamic responses to upright posture in the acute phase of stroke is critical for guiding safe rehabilitation and reducing the risk of secondary

brain injury. It may also offer mechanistic insight into why very early mobilisation is associated with poor outcomes. Current evidence indicates that sitting and standing reduce CBv, with more pronounced declines in the ipsilesional hemisphere and in patients with occlusive disease or hypertension. To date, only one study has assessed the CBv response to standing but this only included a 60-second measurement period. Research is required to assess CBv responses to standing with a more detailed temporal analysis, capturing both the initial and delayed phases.

Methods

Study design

An observational, repeated-measures study with an exploratory prospective analysis.

Study setting

The study was conducted at the Royal Hallamshire Hospital (RHH), Sheffield Teaching Hospitals NHS Foundation Trust, on the hyperacute stroke unit (HASU), the acute stroke unit (ASU) and the neurology day care unit.

Study aims

The primary aim of this study was to assess the cerebral haemodynamic response to mobilisation in acute stroke, involving a gradual transition from supine bed rest to standing, measured by transcranial Doppler ultrasound. A secondary exploratory aim was to investigate the association between the cerebral haemodynamic response to mobilisation and clinical outcomes.

Hypotheses

1. Standing up during the acute phase of stroke (1-7 days post-stroke), will cause a significant reduction in cerebral blood velocity compared to supine and seated rest.
2. The magnitude of decline in cerebral blood velocity will be associated with clinical outcomes measured three months after stroke onset.

Screening and recruitment

Patients were screened by a healthcare professional during daily ward rounds. A researcher provided eligible patients with a participant information sheet and answered patients' questions about the study. Where appropriate, aphasia-friendly documents were used, and a speech and language therapists assisted with communication. All participants provided informed consent. If participants were unable to provide a written signature due to a motor impairment, a healthcare professional independent to the study signed on their behalf.

Eligibility criteria

- Adult (age >18 years) patients diagnosed with any subtype of stroke (first or recurrent).
- Medically stable assessed by a stroke physician.
- Able to be enrolled within 7 days of stroke symptom onset.
- Able to sit independently.
- Able to stand with or without assistance, without experiencing orthostatic hypotension or adverse symptoms.
- English language comprehension and cognitive ability to understand the study protocol, give informed consent and follow instructions.

Sample size

The primary outcome measure was mean middle cerebral artery blood velocity (cm/s), assessed using TCD ultrasound. At the time of planning this study, before the publication of Carvalho et al., (2020) (106) a literature search indicated that upright head positioning (30°) reduced cerebral blood velocity by at least 14% (369,370). This equated to a small-to-medium effect size (Cohen's $f = 0.20$). To detect a difference of this magnitude with 90% power, with a p value of 0.05, in a repeated-measures design with four levels, a sample size of 32 participants was required (371).

Equipment

Two 2-MHz pulsed wave transcranial Doppler ultrasound (TCD) probes (Viasys Sonara, Viasys Healthcare Inc., USA) were attached to a lightweight headset and positioned bilaterally over participants' transtemporal acoustic windows. Depths of 45-65 mm were explored until an optimal middle cerebral artery (MCA) waveform was identified. The probes were then fixed into place. A telemetric heart rate monitor (H10, Polar Electro, Kempele, Finland) was fitted below the sternum using an elasticated strap. An oscillometric blood pressure cuff (DINAMAP, Carescape V100, GE Healthcare, Buckinghamshire, UK) was fitted over the brachial artery. All equipment was fitted while participants rested in their hospital bed with a head rest angle of 30°. All measurements were performed by one operator (NK) who had received training on TCD by a consultant neurologist, including >20 hours of practice with medical students at the Royal Hallamshire Hospital.

Mobilisation protocol

After fitting the equipment, participants were lowered to a supine position (0°) for five minutes of quiet rest before beginning the data collection protocol. Baseline measures (0°) were then collected over a three-minute period. Participants subsequently spent three minutes in each of the following positions: 30° with their head resting on a pillow, sitting at the edge of the bed with their feet touching the floor, and standing (with or without assistance). A remote control was used to raise the bed angle from 0° to 30° over a period of approximately 10 seconds. The transition from 30° to sitting, and from

sitting to standing varied depending on participants' physical function and level of assistance required by a therapist (e.g., to support balance and transfers). In accordance with routine clinical practice patients were mobilised with assistance of therapists or the use of standing aids if necessary. The 3-minute duration for each postural phase was a pragmatic methodological decision to reflect routine clinical mobilisation practice in acute stroke care, where patients are commonly mobilised for short, tolerable periods rather than prolonged steady-state standing. This approach prioritised feasibility and participant safety while capturing haemodynamic responses within a clinically relevant timeframe.

Cerebral blood velocity and heart rate were recorded continuously throughout the protocol. Blood pressure was recorded during the first and third minute of each position to assess both the transient and delayed haemodynamic responses, respectively (372). A stroke therapist assisted with sitting and standing where necessary. The mobilisation protocol formed part of each participant's usual care therapy session. Talking was permitted, but participants were asked to minimise speech to prevent ultrasound signal distortion. Sleeping was permitted in the supine and 30° positions. If the ultrasound signal weakened during the protocol, adjustments were made to the headset and probe angle.

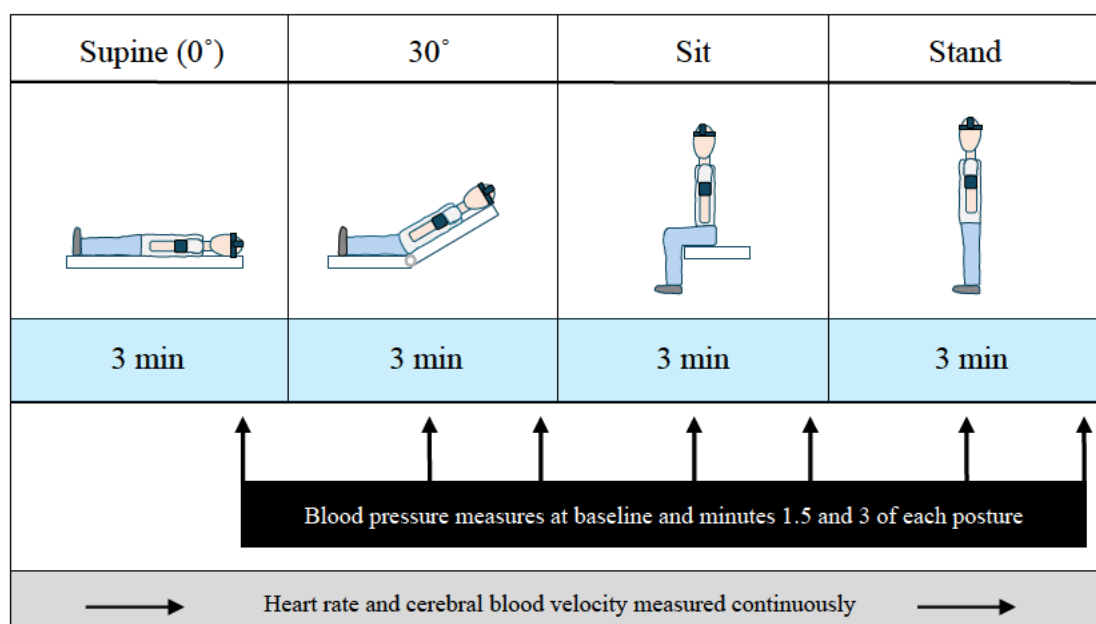


Figure 4.1 Schematic of the mobilisation data collection protocol. Participants were assessed in supine (0°), 30° incline, sitting, and standing postures, each maintained for 3 minutes. Blood pressure was measured at baseline and at 1.5 and 3 minutes of each posture. Heart rate and cerebral blood velocity were continuously monitored.

Clinical outcomes

One researcher (NK) conducted three-month follow-up telephone calls with participants. Participants were asked about their level of stroke impairment (modified Rankin Scale), physical independence (Barthel Index), and stroke-related hospital admissions. Using a binary approach, a poor clinical outcome was defined as: modified Rankin Scale $>2/6$, Barthel Index $<60/100$, secondary stroke, and death. If telephone contact could not be made, medical notes were reviewed to determine clinical outcomes. Where possible, patients' self-reported clinical outcomes were verified using medical notes.

Data analysis

Data were summarised using descriptive statistics, including frequencies, measures of central tendency and variability. Normally distributed data were reported as means and standard deviations, while non-normally distributed data were reported as medians and interquartile ranges. Mean differences were reported in absolute units (e.g., cm/s, mmHg) or percentages, both with 95% confidence intervals. Changes in CBv were assessed using two averaging methods: the whole 3-minute phase, and split into an initial (0 to 1.5 min) and delayed phase (1.5 min to 3 min). The initial 1.5-minute period was intended to capture the early haemodynamic response to each postural transition; however, this time-averaged approach and lack of beat-to-beat blood pressure monitoring precludes assessment of dynamic cerebral autoregulation. Consequently, this phase should be interpreted as an early haemodynamic adjustment, rather than dynamic or static cerebral autoregulation. In contrast, the second 1.5-minute (i.e., delayed) period was considered more representative of a steady-state haemodynamic condition following a stabilisation period. These pragmatic, short timeframes reflect clinical mobilisation protocols, where patients may stand for short periods, and aligns with methodologies common employed in the clinical research literature (106).

For each posture and phase, CBv and heart rate were averaged, whereas mean arterial pressure (MAP) was measured once in the first minute and once in the third minute. For the 3-minute phase analysis, only the second (delayed) MAP measure was included. The effect of posture (independent variable) on CBv, MAP, and heart rate was assessed

using a one-way repeated-measures analysis of variance (ANOVA) with four levels (supine, 30°, sitting, standing) and seven levels (three mobilisation postures split into first [initial] and second [delayed] phases, with the supine baseline as a single level). To account for the effects of occlusive disease, a sensitivity analysis was performed by removing four patients from the four level ANOVA. Normality and sphericity assumptions were tested using the Shapiro-Wilk test and Mauchly's test of sphericity, respectively. Greenhouse-Geisser corrections were used to correct for sphericity violations. Bonferroni-adjusted post-hoc comparisons identified pairwise differences while controlling for Type I error. Effect sizes were derived from partial eta squared and converted to Cohen's f for main ANOVA effects and Cohen's d for standardised mean differences, facilitating comparisons with prior research. Additionally, a binary logistic regression analysis explored relationships between haemodynamic variables (CBv, HR, MAP) and clinical outcomes (binary: poor vs. good). This method was selected to explore how predictor variables influence the probability of a poor clinical outcome, expressed as changes in likelihood per unit increase, while controlling for age and baseline stroke severity (NIHSS). All statistical analyses were conducted using SPSS (Version 26), with an alpha level of 0.05 (Bonferroni-adjusted where applicable).

Results

Thirty-two participants were recruited to this study and data were acquired for 26 individuals. Participant characteristics are displayed in Table 4.1. Only 24 full datasets were available for the repeated measures analysis of ipsilesional CBv and 22 full datasets for contralesional CBv. TCD ultrasound data were missing due to inadequate ultrasound signal acquisition, including poor temporal windows and intermittent signal dropout.

Because the final datasets were smaller than planned, retrospective power analyses were performed to clarify whether the study had sufficient power to detect the hypothesised changes in CBv. Retrospective power calculations are described in the results sections alongside each analysis.

Adverse events and orthostatic symptoms

No adverse events occurred during or on the same day as the mobilisation protocol. Minor, transient orthostatic symptoms were experienced by four participants during the data collection protocol (dizziness, 3/26 [11.5%]; limb tingling sensations, 2/26, [7.7%]).

Effect of mobilisation on haemodynamic variables

A series of one-way repeated-measures ANOVAs (four levels) was conducted to assess the effect of posture on bilateral CBv, HR and MAP. There was a significant main effect of posture on all dependent variables with large effects sizes. Most ANOVAs were Greenhouse-Geisser corrected due to a violation of sphericity. Descriptive statistics and one-way repeated measures ANOVA results are displayed in Table 4.2. Bonferroni-adjusted post-hoc pairwise comparisons are displayed in Tables 4.3-4.6.

Table 4.1. Participant characteristics

Characteristic	Total, n=26
Age (years), median (IQR)	76 (65-83)
Sex, n (%)	
Female	6 (23)
Male	20 (77)
Ethnicity, n (%)	
White	23 (88)
Asian	1 (4)
Mixed ethnic groups	1 (4)
Other ethnic group	1 (4)
Body mass index (kg/m ²), mean $\pm$ SD	26.6 $\pm$ 13.2
Days post-stroke, mean $\pm$ SD	3.5 $\pm$ 1
NIH stroke severity (0-42 scale), median (IQR)	6 (2.75-8.00)
Stroke type, n (%)	
Ischaemic	24 (92)
Haemorrhagic	2 (8)
Mobility at baseline, n (%)	
Independent	11 (42)
Assistance of one or requires walking aid	11 (42)
Assistance of two	4 (15)
Independent before stroke, n (%)	26 (100)
On blood pressure medication, n (%)	10 (38)
Cardiovascular comorbidity, n (%)	11 (42)
Type two diabetes, n (%)	7 (27)

Note. Cardiovascular comorbidity includes myocardial infarction, pacemaker, valve dysfunction, arrhythmia, percutaneous coronary intervention, coronary artery bypass, aortic aneurism, peripheral arterial disease. NIH = National Institutes of Health.

Table 4.2. Descriptive statistics and one-way repeated measures ANOVA results

Dependent Variable	n	Mean (Standard Deviation)				F (df1,df2)	p	Partial eta squared	Cohen's f	Effect Size Interpretation
		Supine	30°	Sit	Stand					
Ipsilesional CBv [cm/s]	24	38.88 (9.95)	37.71 (9.24)	36.61 (10.00)	35.04 (9.62)	5.65 (3, 69)	0.002*	0.212	0.52	Large
Contralesional CBv [cm/s]	22	40.26 (11.21)	39.73 (10.15)	38.83 (9.76)	37.24 (9.66)	4.56 (1.51, 31.78)	0.027*	0.178	0.47	Large
Heart rate [beats/min]	26	70 (13)	71 (11)	76 (12)	84 (14)	70.81 (1.46, 35.07)	<0.001*	0.739	1.68	Large
Mean arterial pressure [mmHg]	26	93 (12)	93 (12)	97 (12)	99 (14)	10.43 (2.02, 50.38)	<0.001*	0.294	0.65	Large

Note. *df* = degrees of freedom; *cm/s* = centimetres per second; *beats/min* = beats per minute; *mmHg* = millimetres of mercury; * denotes statistical significance at $p < 0.05$.

Ipsilesional cerebral blood velocity

Standing significantly reduced ipsilesional CBv compared to supine (-3.84 cm/s, -9.88%, $p < 0.001$, large effect), 30° (-2.67 cm/s, -7.08%, $p = 0.042$, medium effect), and sitting (-1.57 cm/s, -4.29%, $p = 0.010$, medium effect) postures (all $p < 0.05$).

Additionally, while sitting, ipsilesional CBv was significantly lower than supine (-2.27 cm/s, -5.84%, $p = 0.004$, large effect). No significant differences were identified between other postures (sitting vs. 30° or 30° vs. supine), with only small effect sizes observed (ipsilesional data are displayed in Table 4.3).

Contralesional cerebral blood velocity

Standing elicited a significant decrease in contralesional CBv compared to sitting (-1.58 cm/s, -4.07%, $p = 0.005$, large effect). All other comparisons were not significantly different ($p > 0.05$). However, medium effect sizes suggest that contralesional CBv during standing was lower than supine (-3.02 cm/s [95% CI -6.50, 0.47], -7.5%) and 30° (-2.49 cm/s [95% CI -5.18, 0.19], -6.2%) (contralesional data are displayed in Table 4.4).

Heart rate

Standing resulted in a significant increase in HR compared to supine (14 bpm, $p < 0.001$, large effect), 30° (14 bpm, $p < 0.001$, large effect) and sitting (8 bpm, $p < 0.001$, large effect). Additionally, sitting induced a significantly higher HR than supine (6 bpm, $p < 0.001$, large effect), and 30° (6 bpm, $p < 0.001$, large effect). No significant difference was observed between 30° and supine HR (negligible effect) (heart rate data are displayed in Table 4.5)

Mean arterial pressure

As MAP was not continuously measured, the value recorded in the second phase (minute three) was used for this 4-level repeated measures ANOVA. Standing induced a significant increase in MAP compared to supine (6 mmHg, $p = 0.006$, medium effect) and 30° (6 mmHg, $p = 0.006$, medium effect). However, there was no difference between standing and sitting (2 mmHg, $p = 1.00$, small effect). Sitting resulted in a significantly higher MAP than supine (4 mmHg, $p = 0.008$, medium effect) and 30° (4 mmHg, $p = 0.001$, large effect). No significant difference was observed between 30°

and supine MAP ($p = 1.00$, negligible effect) (blood pressure data are displayed in Table 4.6).

Table 4.3. Post-hoc Bonferroni-adjusted pairwise comparisons of **ipsilesional cerebral blood velocity** assessed in each posture (three-minute averages)

Comparison (n=24)	Ipsilesional Cerebral Blood Velocity (cm/s)				P	Standard Error	Cohen's d	Effect Size Interpretation
	Mean Difference		95% Confidence Intervals					
	cm/s	%Δ	cm/s	%Δ				
Stand vs Supine	-3.84	-9.88%	-5.76, -1.92	-14.82, -4.94	<0.001*	0.67	1.18	Large
Stand vs 30°	-2.67	-7.08%	-5.27, 0.07	-13.98, 0.19	0.042*	0.90	0.60	Medium
Stand vs. Sit	-1.57	-4.29%	-2.84, -0.29	-7.76, -0.79	0.010*	0.44	0.73	Medium
Sit vs. Supine	-2.27	-5.84%	-3.94, -0.60	-10.13, -1.54	0.004*	0.58	0.80	Large
Sit vs 30°	-1.10	-2.92%	-3.35, 1.15	-8.88, 3.05	1.00	0.78	0.29	Small
30° vs. Supine	-1.17	-3.01%	-3.23, 0.88	-8.31, 2.26	1.00	0.71	0.34	Small

Note. SD = standard deviation; cm/s = centimetres per second; %Δ = percentage change from supine (baseline); * = statistically significant after Bonferroni adjustment.

Table 4.4. Post-hoc Bonferroni-adjusted pairwise comparisons of **contralesional cerebral blood velocity** assessed in each posture (three-minute averages)

Comparison (n=22)	Contralesional Cerebral Blood Velocity (cm/s)				Standard Error	p	Cohen's d	Effect Size Interpretation
	Mean Difference		95% Confidence Intervals					
	cm/s	%Δ	cm/s	%Δ				
Stand vs Supine	-3.02	-7.50%	-6.5, 0.47	-16.17, 1.17	1.20	0.12	-0.54	Medium
Stand vs 30°	-2.49	-6.27%	-5.18, 0.19	-13.04, 0.48	0.92	0.08	-0.58	Medium
Stand vs. Sit	-1.58	-4.07%	-2.76, -0.41	-7.11, -1.06	0.40	0.005*	-0.84	Large
Sit vs. Supine	-1.44	-3.58%	-4.62, 1.74	-11.47, 4.32	1.10	1.00	-0.28	Small
Sit vs 30°	-0.91	-2.29%	-2.94, 1.12	-7.40, 2.82	0.70	1.00	-0.28	Small
30° vs. Supine	-0.53	-1.32%	-1.52, 2.57	-3.78, 6.38	0.70	1.00	-0.16	Negligible

Note. *SD* = standard deviation; *cm/s* = centimetres per second; %Δ = percentage change from supine (baseline); * = statistically significant after Bonferroni adjustment.

Table 4.5. Post-hoc Bonferroni-adjusted pairwise comparisons of **heart rate** assessed in each posture (three-minute averages)

Comparison (n=26)	Heart Rate (bpm)		Standard Error	p	Cohen's d	Effect Size Interpretation
	Mean Difference	95% Confidence Intervals				
Stand vs Supine	14.00	9.31, 18.70	1.64	<0.001*	1.67	Large
Stand vs 30°	13.69	9.66, 17.72	1.41	<0.001*	1.90	Large
Stand vs. Sit	7.89	4.50, 11.27	1.18	<0.001*	1.31	Large
Sit vs. Supine	6.12	4.16, 8.07	0.68	<0.001*	1.77	Large
Sit vs 30°	5.81	4.23, 7.38	0.55	<0.001*	2.07	Large
30° vs. Supine	0.31	-1.65, 2.27	0.68	1.00	0.09	Negligible

Note. bpm = beats per minute; * = statistically significant after Bonferroni adjustment.

Table 4.6. Post-hoc Bonferroni-adjusted pairwise comparisons of **mean arterial pressure** assessed in each posture (measured in third minute of each posture)

Comparison (n=26)	Mean Arterial Pressure (mmHg)		Standard Error	p	Cohen's d	Effect Size Interpretation
	Mean Difference	95% Confidence Intervals				
Stand vs Supine	6.08	1.46, 10.70	1.61	0.005*	0.74	Medium
Stand vs 30°	5.96	1.40, 10.53	1.59	0.006*	0.73	Medium
Stand vs. Sit	1.92	-2.54, 6.39	1.59	1.00	0.24	Small
Sit vs. Supine	4.15	0.86, 7.45	1.15	0.008*	0.71	Medium
Sit vs 30°	4.04	1.34, 6.74	0.94	0.001*	0.84	Large
30° vs. Supine	0.12	-2.16, 1.93	0.71	1.00	0.03	Negligible

Note. mmHg = millimetres of mercury; * = statistically significant after Bonferroni adjustment.

Sensitivity analysis: removal of patients with stenotic or occluded cerebral arteries

Stenosis (arterial narrowing) and occlusion (complete arterial blockage) can impede downstream perfusion. To account for the potential effect of stenosis and occlusion on group-level ipsilesional CBv data, a sensitivity analysis was performed, removing four patient datasets. Two patients had moderate stenosis ($n=1$, 50% narrowing of the ipsilesional vertebral artery; $n=1$, 60-69% narrowing of the ipsilesional internal carotid artery [ICA]), one patient had severe stenosis ($>70\%$ narrowing of the ipsilesional ICA), and one patient had a complete occlusion of the ipsilesional ICA. After removing these participants' data, the main effect (4-level repeated measures ANOVA) of posture on ipsilesional CBv remained statistically significant ($p<0.001$, Cohen's $f=0.68$, large effect). Bonferroni-adjusted post-hoc pairwise comparisons revealed that ipsilesional CBv was significantly lower during standing compared to sitting (-1.68 cm/s [IQR $-3.21, -0.15$], $p=0.026$), and supine (-3.94 cm/s [IQR $-6.19, -1.69$], $p<0.001$), but was not significantly different to 30 degrees (-2.97 cm/s [IQR $-6.10, 0.15$], $p=0.07$). These ipsilesional CBv changes are similar to the full analysis, indicating that occlusive patient cohort did not skew the main results.

In the overall analysis, the effect of posture on contralesional CBv was not significant despite a large effect size. However, after removing the four occlusive participants' data, a significant main effect of posture on contralesional CBv was identified (Cohen's $f=0.68$, large effect). This indicates the occlusive patients' contralesional CBv responses were highly varied which obscured the group-level effect of posture within the full analysis. In the sensitivity analysis, Bonferroni-adjusted post-hoc pairwise comparisons revealed that contralesional CBv was significantly lower during standing compared to sitting (-2.13 cm/s [IQR $-4.22, -0.04$], $p=0.04$, medium effect). All other comparisons were not statistically different, with either small or medium effect sizes.

Collectively, this sensitivity analysis confirms that the effect of posture on ipsilesional CBv is consistent, even after accounting for arterial stenosis and occlusion.

Additionally, it reveals a previously obscured effect, that in patients without stenosis or occlusive disease, contralesional CBv is significantly lower during standing compared to sitting.

Secondary analysis exploring temporal dynamics of cerebral blood velocity

The original data analysis plan was to compare CBv across the four postures, using a 3-minute average for each phase. However, an additional analysis was conducted to assess temporal changes within each posture by splitting each of the three mobilisation postures into initial and delayed 1.5-minute phases, resulting in 7 ANOVA levels (1 baseline + [3 postures $\times$ 2 time periods]). Conducting this secondary analysis with 7 levels, instead of the originally planned 4, impacts statistical power in several ways. Increasing the levels from 4 to 7 raises the degrees of freedom (from 3 to 6), and also increases the number of pairwise comparisons (from 6 to 21), which reduces post-hoc power after Bonferroni correction. Additionally, a sphericity violation (Mauchly's test, $p < 0.001$) required a Greenhouse-Geisser correction, lowering the degrees of freedom from 6 to 2.81 for ipsilesional CBv and to 2.03 for contralesional CBv. To assess the statistical power of this secondary analysis, a post-hoc power analysis was conducted using GPower (373).

The observed effect size of posture on ipsilesional CBv using a 7-level ANOVA was $\eta_p^2 = 0.301$. With a sample size of 23, 7 levels, a Greenhouse-Geisser correction, and an average correlation between repeated measures of 0.94 (calculated using bivariate correlation), the achieved power was 1.00 (GPower: critical $F = 2.811$, $df = 2.81$, 61.84). In addition, the observed effect size of posture on contralesional CBv using a 7-level ANOVA was $\eta_p^2 = 0.231$. With a sample size of 24, 7 levels, a Greenhouse-Geisser correction, and an average correlation between repeated measures of 0.94, the achieved power was approximately 0.99 (GPower: critical $F = 2.8$, $df = 2.03$, 46.80).

These post-hoc power analyses indicate that the secondary analysis was sufficiently powered for both dependent variables. The main effects of posture on both ipsilesional and contralesional CBv were statistically significant ($F[2.03, 46.80] = 6.602$, $p = 0.003$ for contralesional CBv; $F[2.81, 61.84] = 9.48$, $p < 0.001$ for ipsilesional CBv). Group-level and individual participant CBv data are presented as percentage change in Figures 4.2 and 4.3. Absolute changes in HR and MAP are displayed in Figures 4.4 and 4.5, respectively.

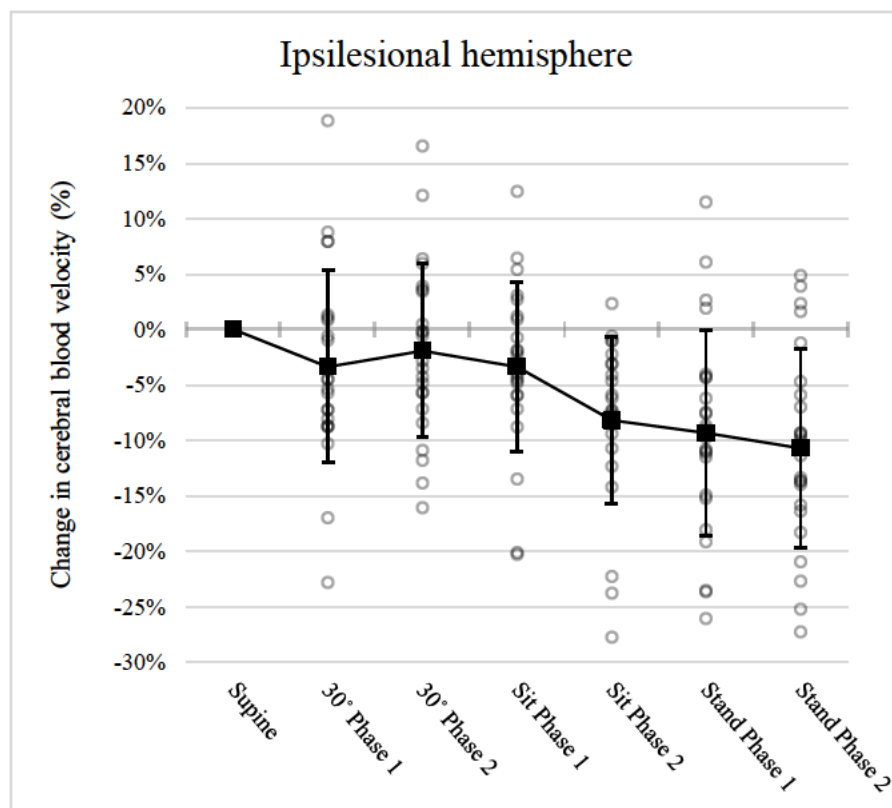


Figure 4.2 Percentage change in middle cerebral artery blood velocity of the *ipsilesional* (stroke-affected) hemisphere measured during supine, 30°, sitting and standing postures (n=24). Phase 1 = first 1.5-minute period; Phase two = second 1.5-minute period. Black squares and error bars represent mean and standard deviation. Grey circles represent individual data points.

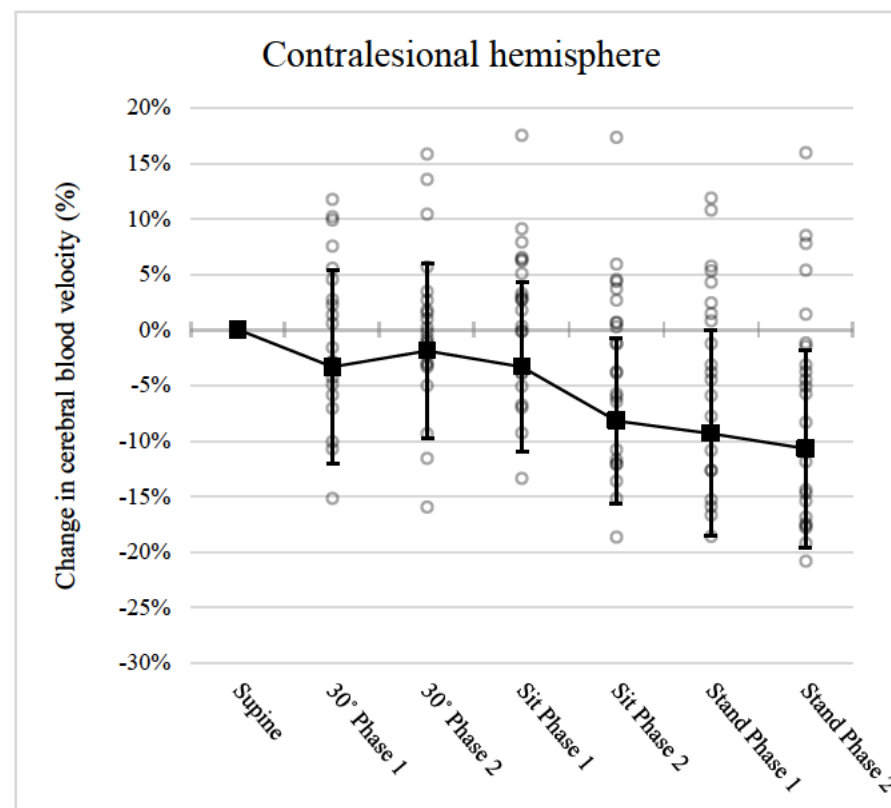


Figure 4.3 Percentage change in middle cerebral artery blood velocity of the *contralesional* (non-stroke) hemisphere measured during supine, 30°, sitting and standing postures (n=23). Phase 1 = first 1.5-minute period; Phase two = second 1.5-minute period. Black squares and error bars represent mean and standard deviation. Grey circles represent individual data points.

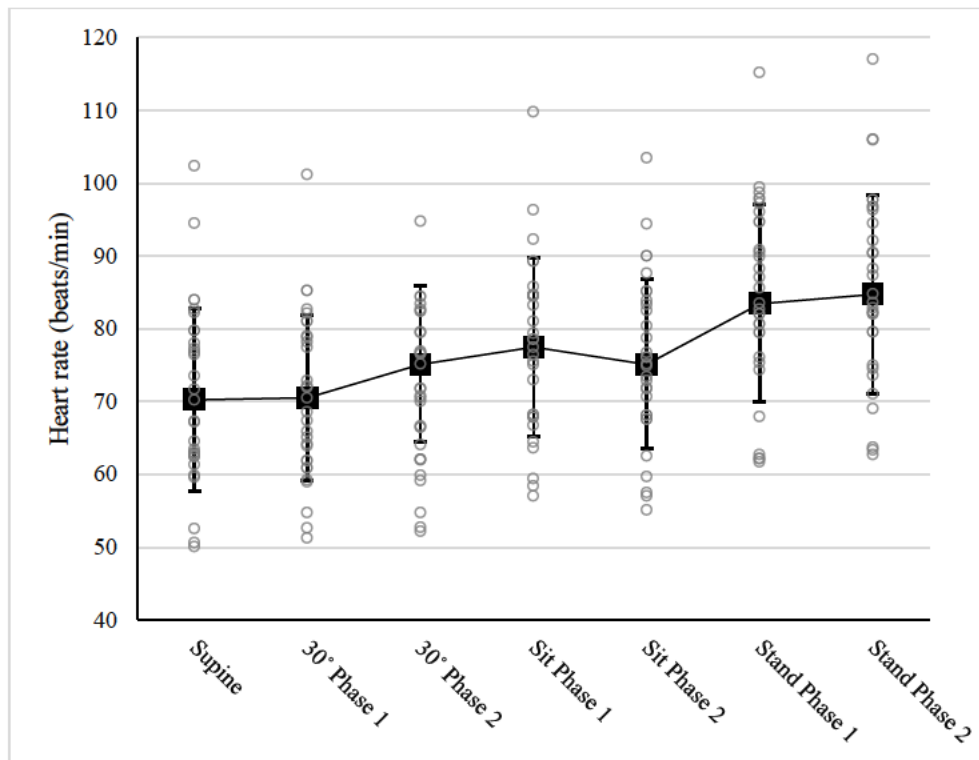


Figure 4.4 Heart rate (beats/min) measured during supine, 30°, sitting and standing postures (n=26). Phase 1 = first 1.5-minute period; Phase two = second 1.5-minute period. Black squares and error bars represent mean and standard deviation. Grey circles represent individual datapoints.

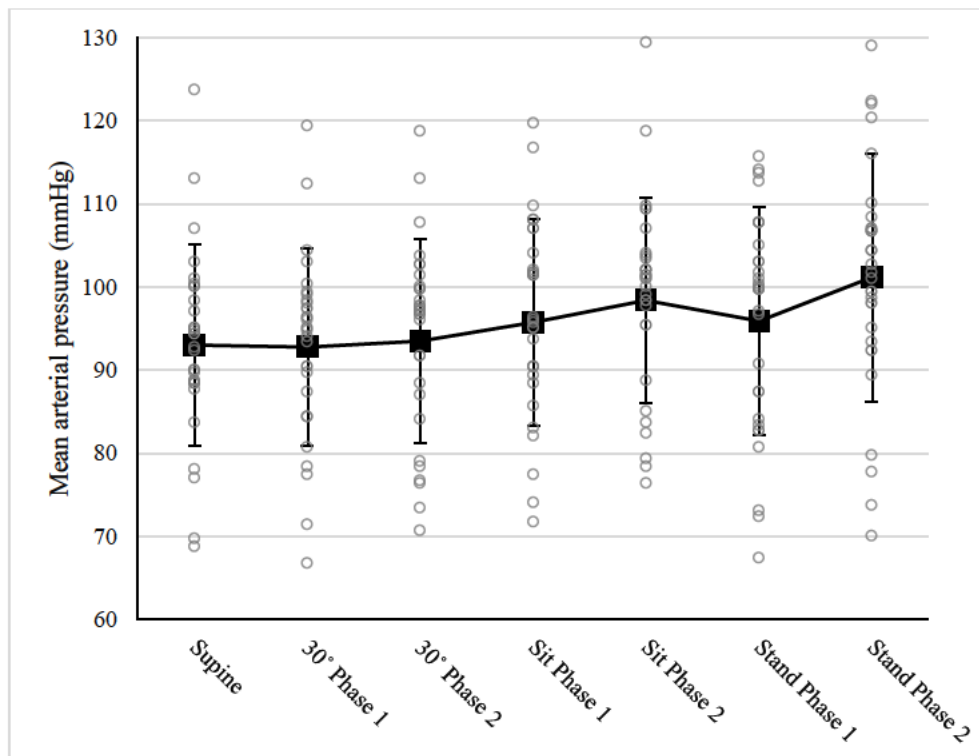


Figure 4.5 Mean arterial pressure (mmHg) measured during supine, 30°, sitting and standing postures (n=26). Phase 1 = first 1.5-minute period; Phase two = second 1.5-minute period. Black squares and error bars represent mean and standard deviation. Grey circles represent individual datapoints.

Secondary analysis: pairwise comparisons of initial and delayed phases

Ipsilesional cerebral blood velocity

Compared to supine, CBv significantly decreased in the first phase of standing (-3.49 cm/s, -8.92%, $p = 0.007$) and declined further in the second phase (-4.04 cm/s, -10.35%, $p < 0.001$). Compared to the first sitting phase, CBv significantly declined in the first phase of standing (-1.92 cm/s, -5.10%, $p = 0.04$) and declined further in the second phase of standing (-2.81 cm/s, -7.45%, $p = 0.004$). CBv did not significantly differ between standing and the 30-degree position. Although this may seem counterintuitive, this is likely attributed to the highly variable change in CBv after transitioning to 30 degrees from supine, ranging from -23% to +19% in the first phase, and -16% to +17% in second phase. A possible explanation for this variability is that some patients fell asleep in the supine position but awoke after the bed was raised to 30 degrees, potentially altering cognitive arousal and, thereby, neurovascular coupling (374). With regards to sitting, only the second phase elicited a significant reduction in CBv compared to supine (-2.85 cm/s, -7.30%, $p = 0.002$), indicating a delayed decline in CBv following the transition to an upright seated position. Sitting CBv was not different to 30 degrees.

Contralesional cerebral blood velocity

In the contralesional hemisphere, mobilisation induced less pronounced CBv changes compared to the ipsilesional hemisphere. Both standing phases resulted in significantly lower CBv than the first sitting phase (stand phase 1: -2.36 cm/s, -5.6%, $p = 0.028$; stand phase 2: -3.35 cm/s, -8.0%, $p = 0.008$). However, standing CBv was not different to the second sitting phase, possibly due to high variability in CBv responses to both sitting (-28% to +2%) and standing (-26% to +11%). In the second phase of standing, CBv was significantly lower compared to the second phase of the 30-degree position (-3.60 cm/s, -8.70%, $p = 0.036$). There were no statistically significant differences in contralesional CBv between any upright postures and the supine position. This lack of significance may be attributed to the substantial variability in contralesional CBv

responses to upright postures. For example, the transition from supine to 30 degrees (Phase 1) elicited CBv responses ranging from a 15% decline to 10% increase, while in the second phase of standing, responses ranged from a 21% decrease to a 16% increase relative to supine.

Orthostatic symptoms

Despite screening out patients with a history of orthostatic symptoms, 11.5% (n=3) of the study cohort experienced dizziness or minor neurological sensations (e.g., arm or leg tingling) while standing during the study protocol. Although these symptoms were mild and transient, their occurrence indicates orthostatic intolerance, which may be a sign of impaired cerebral autoregulation. Subgroup analyses of this symptomatic cohort was not performed due the small sample size.

The relationship between standing cerebral blood velocity and clinical outcomes

A binary logistic regression was conducted to examine the relationship between standing CBv and clinical outcomes. The two predictor variables were change in ipsilesional CBv and contralesional CBv during standing versus supine (cm/s, averaged over 3 minutes). The overall model was not significant (omnibus test: $\chi^2(2) = 5.807$, $p = 0.055$) and explained 36.9% of the variance in clinical outcomes (Nagelkerke $R^2 = 0.369$). The model had a good fit to the data (Hosmer-Lemeshow test: $\chi^2(7) = 7.265$, $p = 0.402$) which correctly classified 83.3% of cases (88.9% for good outcomes and 78.6% for poor outcomes). The change in contralesional CBv from supine to standing was not a significant predictor of a poor outcome (odds ratio [OR] = 1.44, 95% CI [0.99 – 2.08], $p = 0.058$). In addition, the change in ipsilesional CBv was also not a significant predictor of clinical outcomes (OR = 0.747, 95% CI [0.480, 1.162], $p = 0.195$).

Discussion

This study investigated the cerebral haemodynamic responses to a graded mobilisation protocol (supine, 30°, sitting, and standing) in acute stroke patients (n=26, mean 3.5 ± 1 days post-stroke, median NIHSS 6 [IQR 2.75-8]), using transcranial Doppler ultrasound. The primary hypothesis was that standing would significantly reduce CBv

compared to supine and seated postures, which the results supported. The largest changes in CBv were induced by standing, and the effect was more pronounced in the ipsilesional hemisphere, which aligns with prior research (106,107).

The sensitivity analysis, which excluded patients with arterial stenosis and occlusion, confirmed that the ipsilesional CBv reduction during standing remained statistically significant. This sensitivity analysis also revealed that standing significantly reduced contralesional CBv, which was not apparent in the full analysis. This discrepancy is attributed to higher variability in contralesional CBv responses to postural changes in people with occlusive disease.

The current study expands on previous research by reporting initial (first 1.5 mins) and delayed (1.5 to 3 mins) CBv responses to postural changes in the acute phase of stroke. The temporal analysis demonstrated that ipsilesional and contralesional CBv progressively decline over time during standing compared to most other postures. In the present study, the CBv response to the initial 1.5 minutes (-3.5 cm/s) in the ipsilesional hemispheres aligns with Carvalho et al, (2024) (107) who reported that one minute of standing elicited an ipsilesional CBv decline of 4.6cm/s. Whilst no studies have assessed the CBv response to standing for longer than one minute in the acute phase of stroke, Novak et al., (2010) (368) utilised a 3-minute period in the chronic phase of stroke, revealing a 13% reduction in the ipsilesional hemisphere, which is similar to this study's findings (~10%).

The reductions in CBv elicited by upright positioning are likely to be explained by orthostatic stress, whereby gravitational displacement of blood to the lower limbs challenges cerebral autoregulation—a compensatory mechanism that can be impaired early after stroke (375). The concurrent increases in HR (14 bpm during standing vs. supine) and MAP (6 mmHg during standing vs. supine) reflect systemic compensatory responses to a decline in CBv induced by orthostatic stress. The HR responses observed in the current study are somewhat consistent with findings from other acute stroke studies using similar protocols. For instance, Aries et al., (2012) (376) reported an increase of 17 bpm (supine vs. 3 minutes of standing), whereas Panayiotou et al., (1998) (377) observed increases of 5 bpm and 6 bpm (supine vs. 3 minutes of standing) on day 1 and day 7 after stroke, respectively.

The current study's MAP data also aligns with other acute stroke studies. For example, Aries et al., (2012) (376) reported an increase of 7.4mmHg and 3.8 mmHg (3 minutes of standing vs. supine) on days 2 and 3 post-stroke, respectively. Moreover, Panayiotou et al., (1998) (377) reported a standing-induced MAP increase of 3mmHg and 4mmHg on day 1 and day 7 post-stroke, respectively.

Lastly, an exploratory analysis was conducted to assess the relationship between CBv changes and 3-month clinical outcomes using logistics regression analysis. This study's secondary hypothesis was that the magnitude of CBv decline would predict three-month clinical outcomes. However, this hypothesis was not supported by the data. Binary logistic regression demonstrated no significant association between haemodynamic variables (CBv, HR, MAP) and poor outcomes (e.g., modified Rankin Scale >2, falls, or death). Notably, this exploratory analysis was underpowered.

Strengths and limitations

The key strength of this study is that it provides novel insights into the cerebral haemodynamic response to standing during the acute phase of stroke, using an ecologically valid mobilisation protocol. However, embedding data collection into usual care therapy sessions precluded the use of a crossover design. Implementing a crossover design would have enabled systematic measurement of CBv responses in each posture relative to supine, without the confounding influence of the preceding mobilisation stage.

There are also several methodological limitations to consider. The absence of beat-to-beat blood pressure monitoring precluded the assessment of cerebral autoregulation which is a more sensitive measure of cerebrovascular function. Instead, CBv measurements were averaged over 1.5- to 3-minute intervals, which potentially obscured subtle, transient changes in cerebral haemodynamics. Given that both baroreflex-mediated blood pressure recovery and dynamic cerebral autoregulation operate over the first few seconds following standing (378,379), the inability to capture these rapid transitions limits mechanistic interpretation in the current study. In addition, end-tidal CO₂ was not measured, which prevented the ability to account for the

influence of arterial CO₂ on cerebrovascular responses. Another limitation is that middle cerebral artery CBv is a proxy for global CBF, and it is unclear if CBv responses reflect changes at a microvascular level (e.g., perfusion of penumbral tissue).

The meaningfulness of the observed haemodynamic responses warrants consideration beyond statistical significance and effect sizes. No published reliability data exist for TCD during postural transitions in acute stroke, which makes it difficult to contextualise this study's findings. Separating biological variability from instrument noise during active mobilisation is inherently challenging, as the postural transition stimulus will elicit inter-individual variation in haemodynamic responses due to varying stroke severity and cerebrovascular function, and the effort and technique of mobilisation. The use of a fixed headframe throughout each session minimises operator-dependent signal variability, which increases confidence that observed changes reflect physiological responses rather than probe displacement artefact. In the absence of published reliability data, the plausibility of the observed changes can be interpreted by assessing the consistency of individual responses. For ipsilesional MCAv, between 71% and 83% of participants exhibited reductions across all significant pairwise comparisons, with the highest consistency observed for stand versus supine and sit versus supine (83% in both cases). Contralesional MCAv exhibited similar consistency for the stand versus sit comparison (83%). MAP significantly increased during standing in 20/26 participants (77%), mirroring the response observed for sit versus supine (77%). The opposing directional responses of MCAv and MAP, whereby cerebral blood velocity fell as arterial pressure rose, indicate a plausible orthostatic stress response and are therefore unlikely to reflect measurement artefact. Whether smaller changes of 1–2 cm/s are as physiologically relevant or clinically meaningful as the larger observed differences of 3–4 cm/s is uncertain, and the broader question of clinical significance is cannot be answered using the present data.

This study was powered to detect a small-to-medium effect (Cohen's $f = 0.20$), yet the observed effects were generally medium-to-large, indicating that the sample size was adequate to detect the primary outcome of CBv. However, the logistic regression analysis which assessed relationships between CBv and clinical outcomes, was exploratory and underpowered. Given the small sample size, and low number of poor outcomes (mRS >2, $n=9$) the regression results should be interpreted with caution.

Based on the ‘10 events per predictor variable’ rule of thumb (380), and including four predictor variables (bilateral CBv, age, and stroke severity), at least 40 events are required for adequate statistical power. Assuming a 41.3% 90-day poor outcome rate (381), this would require a sample size of at least 97 participants ($40/0.413$) to provide sufficient events for a fully powered analysis.

Future research should therefore incorporate a larger sample size, together with beat-to-beat measures of CBv and blood pressure and concurrent monitoring of end-tidal CO₂, to better evaluate the prognostic value of cerebral haemodynamics post-stroke. Moreover, if examining dynamic cerebral autoregulation during orthostatic stress, the precise detection of stand initiation should be incorporated, as demonstrated by Whitaker et al., (2022, 2023) (378,382) using a novel force sensor.

Conclusion

This study offers novel insights into cerebral haemodynamic responses to upright positioning in acute stroke patients, using an ecologically valid experimental protocol involving routine mobilisation. Statistically significant reductions in CBv were observed during standing compared to supine, 30°, and sitting postures. Standing induced a progressive decline in CBv over three minutes reaching -10.9% and -8.32% in the ipsilesional and contralesional hemispheres, respectively. Systemic compensatory responses, including a 14 bpm increase in heart rate and a 6 mmHg rise in mean arterial pressure during standing reflect adaptive mechanisms to offset CBv reductions. Despite thorough screening, mild orthostatic symptoms occurred in 11.5% of patients, although these were mild and transient. While CBv changes did not predict three-month outcomes in this study, they highlight a physiological mechanism that may contribute to poorer recovery associated with earlier mobilisation as reported in the large-scale phase III AVERT trial (14). Current guidelines recommend the implementation of early mobilisation to promote post-stroke recovery, but these guidelines overlook the risk of cerebral hypoperfusion. The current findings reveal that upright positioning may lower cerebral perfusion in acute stroke, highlighting the need for greater caution when implementing early mobilisation.

Chapter 5 – The Feasibility of Aerobic Exercise Training in Acute Ischaemic Stroke

Background

Aerobic exercise is a core recommendation of stroke rehabilitation guidelines throughout the world (8,63,81,82,84,383–385). The rationale to implement aerobic exercise is to counteract deconditioning, enhance physical and cognitive function, support participation in therapy and everyday activities, and reduce the risk of secondary cardiovascular events. Most guidelines state that aerobic exercise should begin once a patient is medically stable. However, these recommendations appear to be based on trials conducted after the acute phase of stroke (>7 days post-stroke) (9,384,386).

The few studies which have initiated aerobic exercise interventions in the acute phase of stroke have reported mixed results (reviewed in Chapter 2). One study reported functional improvements in response to a 5-day light-to moderate-intensity (50–70% HRmax for 20 mins per session) upright cycling intervention, with no adverse events in acute stroke patients with hemiparesis (134). This intervention was initiated 3-7 days post-stroke, but stroke severity was not reported. In addition, information about the attained exercise dose was missing, including what proportion of cycling exercise was passive versus active. In contrast, Sandberg et al., (2020) (133) implemented a 3-week (5 days per week) light-intensity (>50% HRmax) in-bed cycling ergometer intervention and found no benefit in comparison to usual care. This study recruited patients with moderate-to-severe stroke (modified Rankin Scale [mRS]: 4 ± 1), and similarly, lacked reporting on attained exercise dose. Similar to the study conducted by da Rosa Pinheiro et al., (2021) (134), Sandberg et al., (2020) (133) did not report what proportion of exercise sessions were passive versus active. In the only other study which recruited acute stroke patients (mild stroke: mRS ≤ 2), Strommen et al., (2016) (135), demonstrated that twice daily moderate-intensity (>50% HRR) treadmill exercise, initiated 41.5 ± 14 hours after stroke provoked dizziness and exhaustion in several sessions, raising concerns about the safety and tolerability of treadmill exercise early after stroke.

The PHYS-STROKE trial adds to these concerns (140). This treadmill-based aerobic exercise programme, consisting of moderate-intensity sessions (50–60% HRR) delivered five times per week for four weeks (20 sessions), initiated at a median of 30 days post-stroke (IQR 17–39), was associated with increased rates of falls, recurrent stroke, and hospital admissions in patients with moderate stroke deficits (median NIHSS = 8). A possible contributing mechanism is orthostatic stress; cerebral autoregulation can be impaired for weeks after stroke (52–56,56–58), meaning that ambulatory exercise may compromise perfusion of vulnerable brain tissue and could exacerbate gait or balance impairments. Mechanistic evidence presented in Chapter 4 of this thesis supports this theory, demonstrating that in acute stroke patients, standing up reduces cerebral blood velocity (a proxy for blood flow), with a more pronounced decline in the ipsilesional hemisphere.

In-bed recumbent cycling offers a potentially more suitable mode of aerobic exercise training for acute stroke patients, particularly those who have severe neurological deficits. In-bed exercise bikes enable engagement of large lower-limb muscle groups while patients remain in a supported position, thereby reducing orthostatic stress and eliminating fall risk. This accessible form of rehabilitation may help attenuate the rapid declines in muscle mass, strength, and cardiovascular fitness that often occur within the first days after stroke and contribute to long-term disability (161,162,263,384). This is particularly important for patients with more severe stroke, who are unable to walk and spend most of their day physically inactive (115,116). In addition, pre-clinical evidence suggests that aerobic exercise initiated in the acute phase of stroke promotes neuroprotection and neuroplasticity (9,13,85) (reviewed in Chapters 2 and 6), however, these promising findings have yet to be translated into clinical practice.

Although aerobic exercise is already recommended by stroke rehabilitation guidelines, considerable uncertainty remains regarding its safety, acceptability, optimal mode, dose, and timing of initiation in the acute phase of stroke (9,12). A feasibility study is therefore a necessary first step before progressing to a definitive phase III trial. Importantly, the current evidence base is derived predominantly from studies in ischaemic stroke (see Table 2.1), which has a markedly different aetiology and

haemodynamic risk profile compared with haemorrhagic stroke. To minimise heterogeneity, this study therefore focused exclusively on ischaemic stroke.

Methods

Study design

Phase II, single-centre, two-arm, parallel group, randomised, controlled feasibility trial.

Study setting

The study was conducted across two Sheffield Teaching Hospitals NHS Foundation Trust sites: 1) the Royal Hallamshire Hospital (RHH) hyperacute stroke unit (HASU), acute stroke unit (ASU) and the neurology day care unit; and 2) Stroke Pathway Assessment and Rehabilitation Centre.

Study aims and objectives

Aim 1: To assess the feasibility of conducting a randomised controlled trial.

Objectives:

- 1a)** Assess the recruitment/consent and dropout rates
- 1b)** Assess the completeness of planned data collection

Aim 2: To assess the acceptability and feasibility of the intervention.

Objectives:

- 2a)** Assess the safety of the intervention through recording of adverse events.
- 2b)** Determine the intervention fidelity by assessing the extent to which participants complete the prescribed exercise components (e.g., exercise intensity, duration and frequency).
- 2c)** Determine the retrospective acceptability of the intervention from the participant perspective using Likert scales and qualitative interviews.

2d) Determine the retrospective acceptability of the intervention from the perspective of healthcare practitioners using qualitative interviews.

Aim 3: To identify potential primary outcome measures for a definitive RCT.

Objective:

3a) Determine effect signals for potential primary outcome measures. An effect signal reflects the efficacy of the intervention (difference between means of the groups) relative to the 'noise' (inter-individual variability) in the measurement and to inform the selection of primary outcome for a subsequent definitive RCT.

Participant eligibility

Participants were recruited according to the predefined inclusion and exclusion criteria outlined below. This aerobic exercise study was limited to individuals with ischaemic stroke, irrespective of infarct territory. The rationale for restricting inclusion to ischaemic stroke was that exercise-induced increases in perfusion to hypoperfused tissue may support recovery processes. The intervention was therefore considered potentially applicable across all ischaemic stroke presentations. In contrast, exercise-induced elevations in cerebral blood flow and mean arterial pressure raise distinct safety concerns for haemorrhagic stroke patients, namely the potential risk of recurrent bleeding. Given the relatively limited evidence base for aerobic exercise in haemorrhagic stroke, individuals with haemorrhagic stroke were not included in this study.

Inclusion criteria

- Adult (age >18 years) patients diagnosed with acute ischaemic stroke.
- 1-7 days post-stroke.
- Medically stable, assessed by a stroke physician.
- Sufficient English language comprehension and cognitive ability to understand the study protocol, follow instructions, complete questionnaires and give informed consent.
- Ability to mobilise lower body limbs in a cyclical manner (at least one leg).

Exclusion criteria

- Haemorrhagic stroke.
- <1 day or >7 days after onset of stroke symptoms.
- Clinically unstable, assessed by stroke physician.
- Disability preventing unipedal cycling.
- New York Heart Failure Classification stage III/IV.
- Terminal illness (life expectancy <6 months).
- Resting blood pressure >180/110 mmHg.
- Uncontrolled arrhythmia causing symptoms or haemodynamic compromise.
- Unstable angina.
- Uncontrolled diabetes mellitus.
- Acute deep vein thrombosis, pulmonary embolism or pulmonary infection.
- Already participating in a clinical research trial.
- Pain during mobilisation of lower limbs.
- Lower-limb spasticity or contracture which impairs ability to cycle.
- Absolute contraindications to aerobic exercise (See Table A2 in Appendix 2)

Sample size

A minimum of 24 participants (12 per arm) is recommended for feasibility trials (387). Adjusting for a potential 20% attrition rate (388), the target sample size was 30 (15 per arm).

Screening and recruitment

Patients were screened by a healthcare professional during daily ward rounds. Eligibility was confirmed by a stroke consultant. A researcher provided eligible patients with a participant information sheet and answered patients' questions about the study. Where appropriate, aphasia-friendly documents were used, and a speech and language therapist assisted with communication. All participants provided informed consent. If participants were unable to provide a written signature due to a motor impairment, a healthcare professional independent to the study signed on their behalf.

Randomisation

A web-based permuted block randomisation procedure (sealedenvelope.com) was used to allocate participants into each study arm: 1) usual care; 2) aerobic exercise training plus usual care. Participants were stratified using the National Institutes of Health Stroke Scale (NIHSS): 1) mild to moderate stroke (NIHSS 0-15); and 2) moderate to severe stroke (NIHSS >15) measured after reperfusion therapy or at a similar timepoint if not eligible for reperfusion therapy. Block sizes of either 4 or 6 were randomly allocated and block size was masked from research team members.

Usual care

Participants randomised to the control group received usual care according to guidance from the National Institute for Health and Care Excellence (389). Briefly, these guidelines (which have now been superseded) recommended that patients complete at least 45 minutes of each appropriate therapy per day (physiotherapy, occupational therapy and/or speech and language therapy) for five days per week. In addition, patients were encouraged to engage in mobilisation (out-of-bed sitting, standing or walking) within the first 48 hours of stroke onset, or if physically able, as soon as possible after stroke.

Aerobic exercise intervention

Exercise bike

A bedside cycle ergometer (MOTomed Letto 2, Reck, Betzenweiler, Germany) was positioned at the foot of each participant's hospital bed. Both the bed and the cycle ergometer were positioned at their lowest height which orientates the lower limbs at approximately chest height. The bed backrest angle was elevated to 30° and participants were positioned so that the lumbar spine was supported by the bed backrest. Participants' feet were inserted onto the foot pedals containing heel cups to prevent the feet from slipping downwards. Support frames were positioned underneath the shank of each lower leg to prevent knee hyperextension. Flexible rubber straps were fastened around the feet and lower legs for stability. The foot pedals and support frames fixed the

lower limbs in a comfortable position, enabling a smooth cycling motion in the sagittal plane. The knee angle at the end of the pedal stroke was approximately 25°.

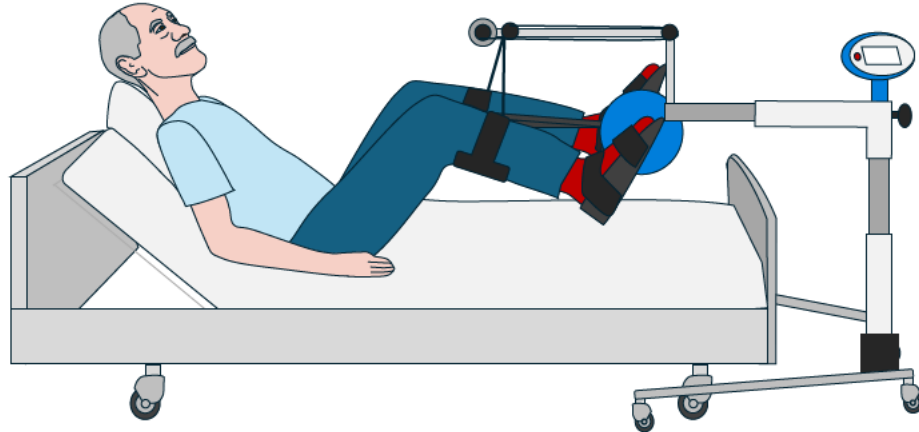


Figure 5.1 Diagram of recumbent cycle ergometer (Letto 2, MOTomed, Reck, Betzenweiler, Germany). Image created by Nik Kudiersky.

Exercise intervention

The aerobic exercise intervention was designed based on a balance between pre-clinical evidence, and feedback from stroke survivors and stroke therapists (see PPI section in Appendix 4). The exercise protocol began with a 5-minute passive cycling period (20 revolutions per minute [rpm]), during which the participant was relaxed (no exertion), and the bike rotated the participant's legs. Subsequently, the participant completed a 5-minute light- to moderate-intensity active warm-up. The assistive motor was deactivated as soon as participants began cycling. Starting in the lowest gear, the participant was instructed to cycle at a self-selected cadence aiming for an intensity equivalent to 'light' (11/20) on the RPE scale (214). Throughout the warm-up, the researcher gradually increased the cycle gear so that the target RPE of 13 ('somewhat hard') was achieved by the end of the five-minute warm-up.

The warm-up was followed by the conditioning phase, where participants were instructed to maintain a consistent cadence ($\pm 10\%$) for five minutes, aiming to sustain an intensity equivalent to 'somewhat hard' (13/20 RPE), and were encouraged to be

slightly out of breath whilst being able to maintain a conversation (233). This RPE score corresponds with the first ventilatory threshold (approximate lower limit of moderate-intensity exercise domain). Participants were asked to avoid ‘hard’ exercise corresponding to an RPE score of 15/20, and to avoid exercise workloads that elicit heavy breathing where speech is difficult (i.e., above the respiratory compensation point) (233). Sixty percent of heart rate reserve was used as an objective upper exercise intensity limit to minimise the likelihood of participants exercising in the vigorous-intensity domain (79,192). The five-minute moderate-intensity bouts were interspersed with one-minute passive rest periods (20 rpm). RPE was measured in the last 15 seconds of the warm-up and each 5-minute conditioning bout. To ensure that the intervention was tolerable, the cycling gear (resistance) was adjusted according to the participant’s level of function, fatigue and proximity to the target intensity (RPE 13/20). After the conditioning phase, the participant undertook a graduated 5-minute cool-down and then was instructed to relax while a final 5-minute passive cycling recovery phase was completed.

The next working day (Monday to Friday) after completing the first exercise session, participants were encouraged to complete a single aerobic exercise session per day for four days (five exercise sessions in total). The workload that elicited an RPE of 13 (‘somewhat hard’) for each session was used to guide the workload for subsequent sessions. The number of five-minute conditioning bouts increased by one bout per session. The first session contained two bouts (total = 10 minutes), and the fifth session contained six bouts (total = 30 minutes). This progressive design was developed with input from researchers, healthcare practitioners, and people affected by stroke (see PPI section in Appendix 4)

To minimise distractions, most performance metrics available on the MOTomed interface (e.g., gear, left–right symmetry, distance) were concealed from participants, with cadence (rpm) being the only parameter displayed.

Heart rate calculations

Maximum heart rate was estimated using population-specific equations (203,390) displayed in Figure 5.2, in accordance with guidance from the Association of Chartered Physiotherapists in Cardiovascular Rehabilitation (2023) (391). Heart rate reserve (HRR) was calculated using the Karvonen method (197), which is the difference between resting heart rate and predicted maximum heart rate. Resting heart rate was measured after ten minutes of rest while in their hospital bed with a headrest angle of 30 degrees. Additionally, participants' routine ECG reports were checked (if available). The lowest recorded resting heart rate (directly measured or from patient's ECG report) was used for subsequent calculations. Sixty percent of HRR was calculated as follows: $(\text{HRR} \times 0.6) + \text{resting heart rate}$.

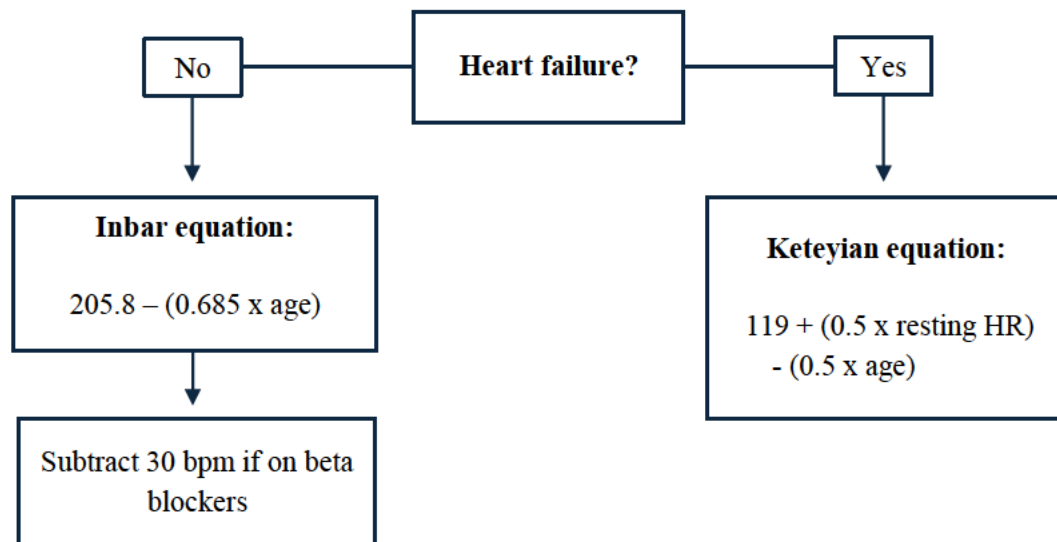


Figure 5.2 Flowchart of heart rate calculation methods. *bpm* = beats per minute.

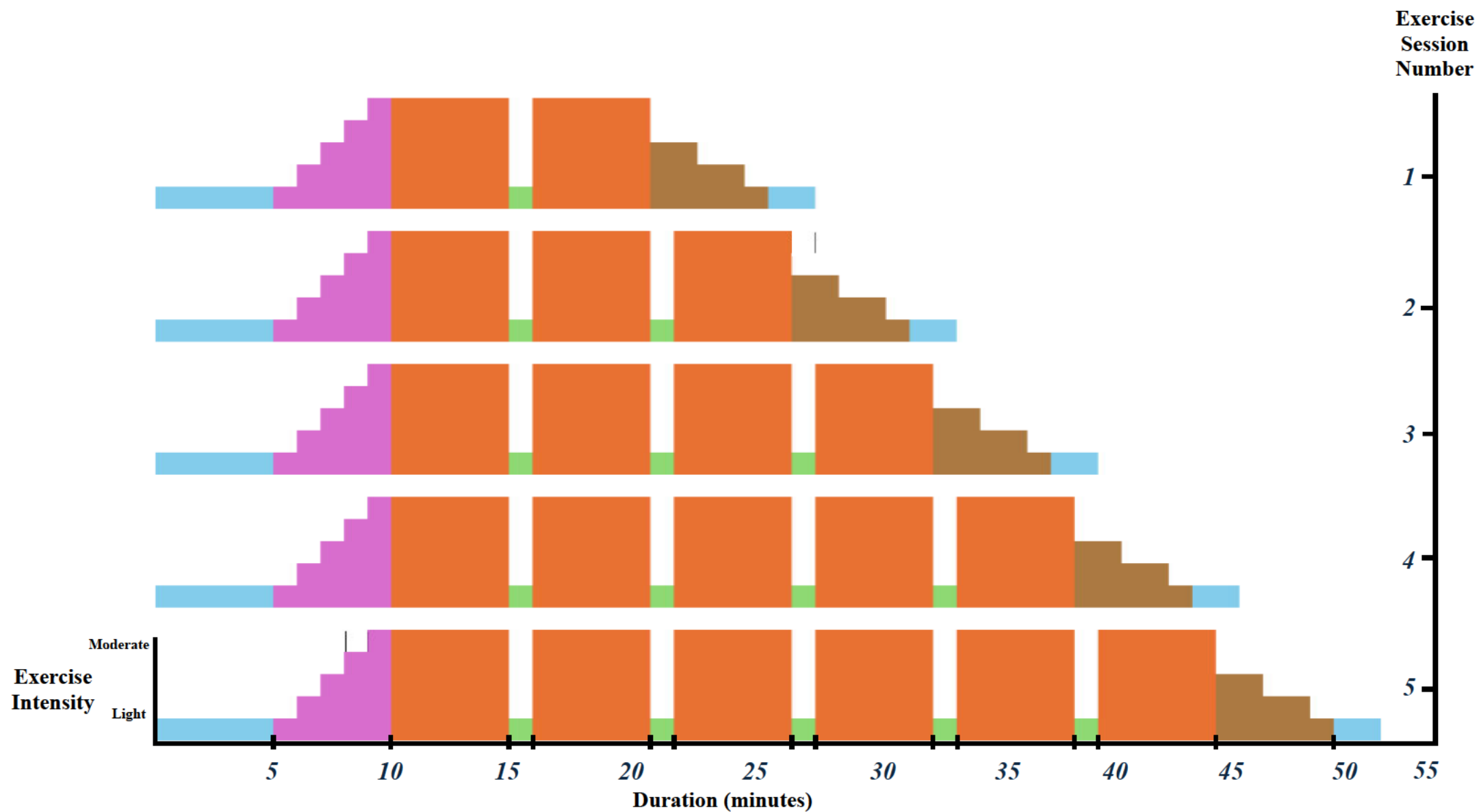


Figure 5.3 Schematic of the five-session, light- to moderate-intensity aerobic exercise intervention. Blue = Passive rest (20rpm), Pink = Graduated warm-up, Orange = Moderate-intensity active exercise, Green = Passive rest (20 rpm), Brown = Graduated cooldown.

Safety monitoring

Patients were supervised during all exercise sessions by an experienced clinical exercise physiologist (NK). Signs and symptoms of adverse responses, such as chest pain or pallor were monitored in accordance with the study's termination criteria (Table 5.1). An upper heart rate limit (60% HRR) was calculated before each exercise session, and patients' work rate was adjusted to avoid exceeding this threshold. Blood pressure was measured at the brachial artery while participants rested in bed at a 30° backrest angle and during exercise, using a clinically validated oscillometric monitor (DINAMAP, Carescape V100, GE Healthcare, Buckinghamshire, UK) (256).

Table 5.1. Aerobic exercise termination criteria

Termination criteria
†Cerebral blood velocity 30% below baseline
Chest pain suggestive of ischaemia
Fall in systolic blood pressure >20 mmHg from the highest value during exercise
>225 mmHg systolic blood pressure
>130 mmHg diastolic blood pressure
Hypotension (<100 mmHg systolic)
Severe desaturation: SpO ₂ ≤ 80% when accompanied by symptoms and signs of severe hypoxaemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory failure

Note. † = Study Doctor's clinical judgement, only applicable if using transcranial Doppler ultrasound.

Exercise dose monitoring

The RPE scale, Talk Test and heart rate monitors were used to determine exercise intensity. Accelerometers (activPAL) were used to assess the dose of each session and the whole intervention (i.e., external load).

Heart Rate

Heart rate was measured continuously before, during and after each exercise session via an elasticated fabric chest band containing ECG electrodes (H10, Polar Electro, Kempele, Finland), positioned directly inferior to the xyphoid process. This device has been validated against an ECG Holter monitor (255). Heart rate was continuously measured in beats per minute at a sampling rate of 1 Hz. The heart rate monitor was synced with the Polar Flow mobile application (Polar Flow, Polar Electro, Kempele, Finland). Deidentified heart rate data were uploaded to a cloud platform (Polar Flow, Polar Electro, Kempele, Finland), and downloaded in Microsoft Excel (Microsoft, Redmond, Washington, USA) CSV format to be analysed offline.

Rating of Perceived Exertion

The Borg 6-20 RPE scale was used to assess the perceived exertion of exercise throughout each exercise session (214). Participants were asked to rate their perceived exertion using either a number or a corresponding descriptor. RPE was recorded in the last 15 seconds of the five-minute intervals including the warm-up, conditioning phase, and the cooldown.

Talk Test

A pragmatic approach was used to assess participants' breathing responses and ability to talk (233). If participants were able to talk easily without being out of breath, they were encouraged to exercise at a higher cadence or resistance. Conversely, if participants were unable to speak due to heavy breathing, they were encouraged to cycle at a slower cadence or lower resistance. For participants with expressive aphasia, conversational ability was not evaluated. However, if they exhibited signs of laboured breathing, they were guided to decrease cadence or resistance.

Accelerometer

The activPAL accelerometer (PAL Technologies Ltd., Glasgow, UK) was fitted at the baseline assessment and removed the day after the intervention period (usual care group and intervention group). The device was attached to the unaffected leg with a waterproof Tegaderm dressing, positioned centrally at the midpoint between the anterior superior iliac spine and the superior border of the patella (Figure 5.4). This provided an objective measure of exercise dose by quantifying accumulated cycling repetitions and ambulatory activity (step count) during the intervention period.

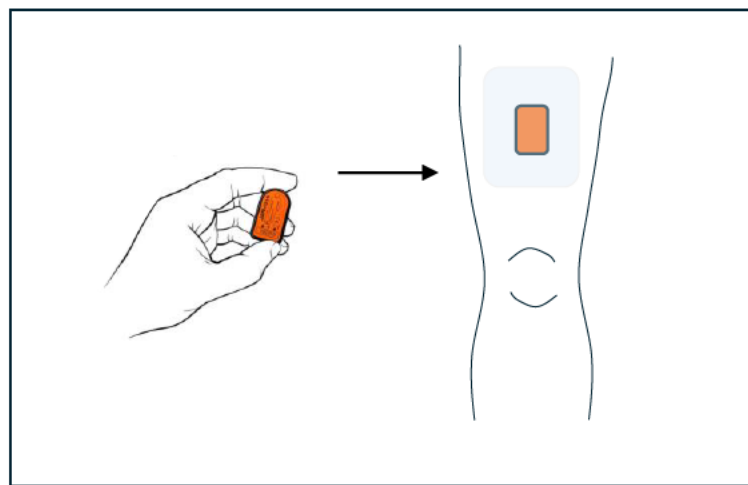


Figure 5.4 Diagram of thigh-mounted accelerometer (activPAL, PAL Technologies, Glasgow, UK).

Outcome measures

Feasibility

Feasibility outcomes were split into two categories: 1) study procedures; and 2) intervention delivery.

Table 5.2. Feasibility outcomes related to the study procedures

Outcome	Description
Eligibility rate	Percentage of screened patients who were eligible.
Recruitment rate	Number of participants recruited per month during the recruitment period.
Consent rate	Percentage of eligible patients who consented to participate.
Dropout rate	Percentage of individuals who discontinued participation after the study had commenced (reasons recorded).
Completeness of data	Percentage of planned measurements completed and recorded.

Table 5.3. Feasibility outcomes related to the delivery of the intervention

Outcome	Description
Participant fidelity	Adherence to exercise protocol including: • % of planned session duration completed • % of target exercise intensity achieved per session • % of total planned sessions completed
Safety	Number and severity of adverse events related to the intervention.
Acceptability of intervention and study procedures	• Cycling comfort assessed via Likert scale (patients only). • Qualitative interview (patients and therapists).

Progression criteria

Progression to a definitive trial was considered against the following a priori success criteria:

- Recruitment rate: ≥ 2 participants per month (30 participants recruited in 18 months)
- Safety - The following traffic light-style system was used:
 - Red: >10 adverse events related to the intervention – Do not proceed.
 - Amber: 5-10 adverse events related to the intervention – Review and revise protocol.
 - Green: <5 adverse events related to the intervention – Proceed.
- Acceptability: average comfort score $>3/5$ Likert scale (1= very uncomfortable, 2= uncomfortable, 3= neutral, 4= comfortable, 5= very comfortable).
- Completeness of data: $>80\%$ of planned measurements recorded.
- Identification of an appropriate primary outcome measure.

Assessment timepoints

Short-term preliminary efficacy

Muscle ultrasound structure and handgrip strength were evaluated at baseline and approximately 7-10 days later to assess the short-term effects of the intervention on hospital-associated deconditioning.

Long-term preliminary efficacy (90 days post-stroke)

Additional outcome measures, detailed in Table 5.4 below, were assessed at baseline and ~90 days post-stroke to evaluate longer-term preliminary efficacy. The rationale and methods for these outcome measures are described in detail within the Methodology chapter.

Table 5.4. 90-day preliminary efficacy outcome measures

Outcome Measure	Assessment
Disability/Independence	Modified Rankin Scale and Barthel Index
Upper limb function	Handgrip strength
Lower limb function	Short Physical Performance Battery
Walk speed	10-metre walk test
Anxiety and depression	Hospital Anxiety and Depression Scale
Chronic fatigue	Fatigue Severity Scale
Cognitive function	Montreal Cognitive Assessment
Quality of life	EuroQoL Quality of Life Index (3-Level)

Quadriceps muscle architecture

Quadricep muscle structure was assessed at baseline and after the intervention period in both groups (approximately 7-10 days after baseline) using a portable B-Mode ultrasound with a linear transducer and 4cm field of view (Sonon 300L, Healcerion Co., Seoul, Korea). The ultrasound frequency was set at 10MHz for all assessments. All participants were resting in a semi-recumbent position in their hospital bed with a 30-degree back rest. A water-soluble ultrasound gel was applied to the transducer to optimise image clarity. Minimal pressure was applied to the skin to avoid muscle distortion. The regions of interest were the rectus femoris and the vastus lateralis muscles (transducer positioning described below).

Rectus femoris

To measure the rectus femoris muscle, the transducer was positioned parallel to the transverse axis of the femur, at the central line of the anterior thigh, at 50% of the distance between the superior border of the patella and the anterior superior iliac spine (392).

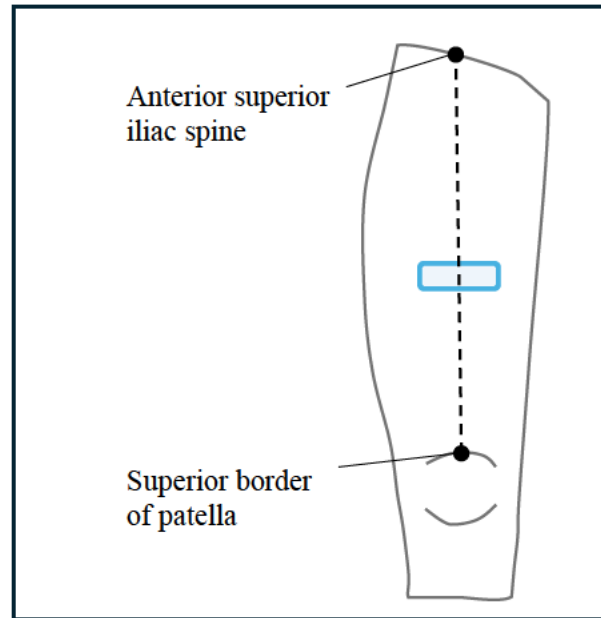


Figure 5.5 Ultrasound transducer positioning for rectus femoris measurement.

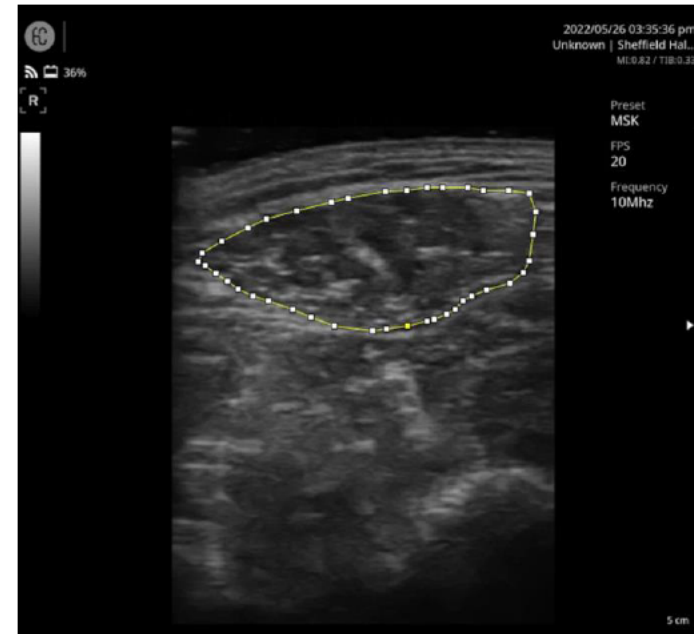


Figure 5.6 Ultrasound transverse view of the rectus femoris muscle with a superimposed border, manually traced using ImageJ software.

Vastus lateralis

To assess vastus lateralis architecture, the transducer was positioned parallel to the longitudinal axis of the femur, at 65% of the distance from the greater trochanter to the lateral epicondyle of the knee (393).

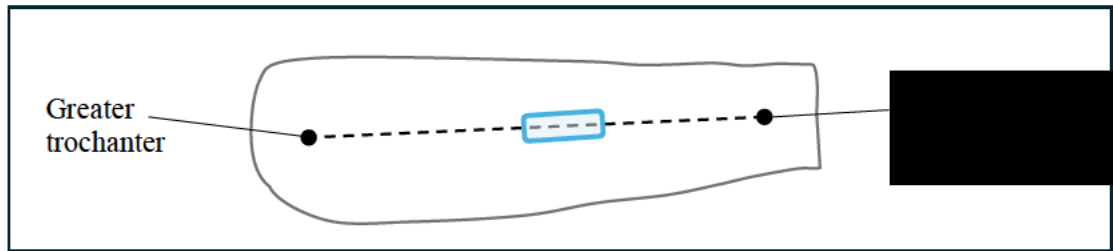


Figure 5.7 Ultrasound transducer positioning for vastus lateralis measurement.



Figure 5.8 Ultrasound longitudinal view of the vastus lateralis muscle with a superimposed yellow line representing muscle thickness; superimposed white lines represent: (A) superficial aponeurosis; (B) deep aponeurosis; and (C) pennation angle. Analysis performed using ImageJ software.

Image capture and analysis

Live video output was transmitted to a mobile application (SONON Ultrasound App, Version M1.00.18, Healcerion Co., Seoul, Korea) installed on a digital tablet (iPad, Apple, California, USA) via Wi-Fi. Still images were saved in the mobile application and exported to a desktop computer. Images were then imported into ImageJ (Version 1.54m, National Institutes of Health, Maryland, USA) for analysis. ImageJ enables accurate measurement of muscle thickness, cross-sectional area and pennation angle by scaling the image pixel size to a known distance. For muscle thickness, a straight line was superimposed over the region of interest, and three measures were averaged. For cross-sectional area, a multi-point line was superimposed around the border of the muscle belly. Occasionally, participants' rectus femoris muscle was wider than the transducer, therefore multiple images were taken across the muscle width and 'knitted' together using photoshop software ensuring that anatomical landmarks were aligned (e.g., central aponeurosis and muscle border). For pennation angle, the angle of two intersecting lines was measured: one line over the deep aponeurosis, and one over a clearly visible muscle fascicle. The muscle ultrasound analysis was blinded, conducted by an expert in muscle physiology (TMW).

Handgrip strength

Handgrip strength was assessed at baseline and after the intervention period in both groups (approximately 7-10 days after baseline) using a digital handgrip dynamometer (TKK Model 5401; Takei, Tokyo, Japan). To minimise variability, the elbow was maintained at a 90-degree angle, and grip position was adjusted to an appropriate setting, which was recorded and replicated in subsequent assessments. Whilst it has been reported that full elbow extension is the most accurate measure of maximal strength (394), a 90-degree elbow flexion angle is more practical for acute stroke patients as the weight of the device and arm can be supported by their hospital bed or chair's arm rest. Participants were seated with their back supported either in their hospital bed or a bedside chair with their feet flat on the floor. Participants were instructed to squeeze the dynamometer with maximal effort and were asked to relax once the force reading had stopped increasing. Participants were given verbal encouragement in a consistent manner during all assessments. Three measurements

were taken for both hands, and the highest value was recorded for each hand. To minimise fatigue, 30-second rest intervals were implemented between efforts, which were alternated between hands.

Data analysis

Data are summarised using descriptive statistics. Normally distributed data are presented as means and standard deviations, whereas non-normally distributed data are reported as medians and interquartile ranges. Categorical variables are presented as frequencies. The primary statistical method for assessing preliminary efficacy was ANCOVA, comparing between-group differences at follow-up, adjusting for age, stroke severity (NIHSS) and baseline scores (unless comparing change scores). Levene's test was used to assess homogeneity of variances of ANCOVA residuals and raw data between groups. Normality of data distribution was assessed using Shapiro-Wilk tests and visual inspection of histograms. ANCOVA was used for normally distributed data. If normality was violated and persisted after transformations (e.g., logarithmic), a bootstrapped one-way ANCOVA was conducted (1000 samples, 95% CIs). When ANCOVA was not appropriate due to missing data (≤ 5 data sets available per group) or unequal variances (despite transformations), Welch's ANOVA was used. Cohen's *d* effect sizes or omega squared statistics were reported alongside p-values to highlight practical significance. The alpha level was set at 0.05 to determine statistical significance. Qualitative data were analysed using thematic analysis, guided by the Theoretical Framework of Acceptability (173). Qualitative findings are presented in Chapter 7.

Blinding and peer review

It was not possible to blind participants or on-site research team members to group allocation due to the nature of the aerobic exercise intervention. Unblinded assessments were conducted by one of two research team members (NK & AA) using standardised protocols to minimise bias. Muscle ultrasound images were analysed by one research team member (TMW), who was blinded to group allocation. Quantitative analyses were conducted by one research team member (NK). An independent statistician (NT) reviewed the data analysis plan and checked a sample of analyses outputs for accuracy.

Results

Recruitment

Screening

A researcher (NK) attended daily ward rounds, and a senior physiotherapist highlighted potentially eligible patients. Subsequently, eligibility was confirmed by a stroke consultant. Screening occurred approximately three days per week during the 13-month recruitment period. However, screening paused if more than two patients were already enrolled due to limited study capacity. It was not feasible to quantify the number of patients who were screened due to the dynamic, fast-paced nature of ward rounds. Eligibility rate was therefore retrospectively estimated using hospital admission data.

Estimated eligibility rate

During the 13-month recruitment period, 1537 patients were admitted to the Royal Hallamshire Hospital's acute stroke ward with a stroke diagnosis. Of these patients, 1392 (91%) were diagnosed with ischaemic stroke, and 139 (9.0%) with haemorrhagic stroke. Among the ischaemic stroke patients, 763 (54.8%) had a short length of stay (LOS; <7 days), 191 (12.4%) had an unrecorded LOS, and 438 (28.5%) had a LOS of at least seven days. Of the patients who had a LOS of >7 days, 99 developed pneumonia, 40 had a urinary tract infection, 24 had a dementia diagnosis, and four experienced a cerebral haemorrhage due to thrombolysis during their admission to the acute stroke ward. After excluding these 167 patients, 271 remained potentially eligible, representing 17.6% of all admitted patients (271/1537). Additional exclusion criteria, such as medical instability (e.g., severe hypertension) and severe cognitive impairment, were not available in hospital admission records. The estimated 17.6% eligibility rate is therefore likely to be overestimated.

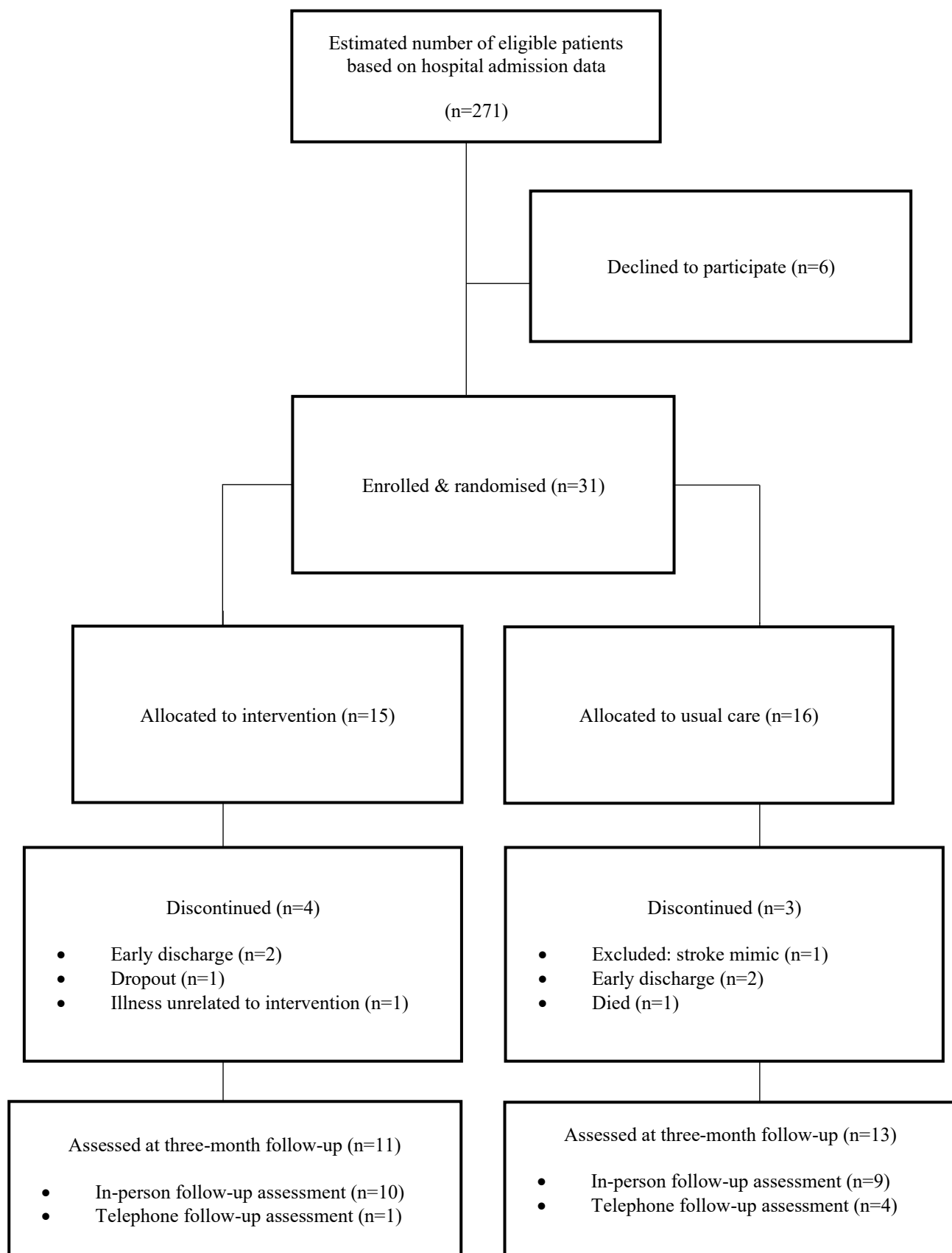


Figure 5.9 CONSORT flow chart.

Table 5.5. Baseline characteristics of all enrolled participants (n=30)

	Control group (n=15)	Intervention group (n=15)
Age (years), median (IQR)	84 (76-87)	65 (62-75)
Sex, n (%)		
Female	5 (33)	5 (33)
Male	10 (67)	10 (67)
Ethnicity, n (%)		
White	14 (93)	14 (93)
Asian	0 (0)	1 (7)
Black	1 (7)	0 (0)
Mixed ethnic groups	0 (0)	0 (0)
Other ethnic group	0 (0)	0 (0)
Anthropometrics, mean (SD)		
Body mass index (kg/m ²)	25.5 (5.4)	29.4 (6.6)
Stroke history		
NIHSS score (0-42), median (IQR)	6 (3.5-12.5)	9 (4.5-12.5)
Mild (0-7)	8 (53)	6 (40)
Moderate (8-15)	6 (40)	6 (40)
Moderate-to-severe (16-42)	1 (7)	3 (20)
Successful reperfusion therapy, n (%)	2 (13)	1 (7)
Prior stroke, TIA or cerebral disease n (%)	9 (60)	7 (47)
Comorbidities / risk factors, n (%)		
Ischaemic heart disease	0 (0)	3 (20)
Heart failure	0 (0)	2 (13)
Type II diabetes	6 (40)	3 (20)
Atrial fibrillation	2 (13)	1 (7)
COPD	2 (13)	3 (20)
Smoker	2 (13)	2 (13)
Independent pre-stroke, n (%)	15 (100)	15 (100)
Time to randomisation (days post-stroke), mean (SD)	3.5 (1.8)	3.8 (1.8)

Note. *IQR* = interquartile range; *NIHSS* = National Institutes of Health Stroke Scale; *TIA* = transient ischaemic attack; *COPD* = chronic obstructive pulmonary disease.

Table 5.6. Baseline characteristics of participants who completed the three-month assessment (n = 25)

	Control group (n=14)	Intervention group (n=11)
Age (years), median (IQR)	83 (75-87)	67 (63-75)
Sex, n (%)		
Female	4 (29)	3 (21)
Male	10 (71)	11 (79)
Ethnicity, n (%)		
White	14 (100)	10 (91)
Asian	0 (0)	0 (0)
Black	0 (0)	1 (9)
Mixed ethnic groups	0 (0)	0 (0)
Other ethnic group	0 (0)	0 (0)
Anthropometrics, mean (SD)		
Body mass index (kg/m ²)	25.8 (5.4)	30 (7.5)
Stroke history		
NIHSS score, median (IQR)	7 (4.5-12.8)	9 (4.5-13.5)
Mild (0-7)	7 (50)	5 (45)
Moderate (8-15)	6 (43)	3 (27)
Moderate-to-severe (16-42)	1 (7)	3 (27)
Successful reperfusion therapy, n (%)	2 (14)	1 (9)
Prior stroke, TIA or cerebral disease, n (%)	8 (53)	4 (36)
Comorbidities / risk factors, n (%)		
Ischaemic heart disease	0 (0)	1 (9)
Heart failure	0 (0)	2 (18)
Type 2 diabetes	6 (43)	2 (18)
Atrial fibrillation	2 (14)	1 (9)
COPD	1 (7)	1 (9)
Smoker	2 (14)	2 (18)
Independent pre-stroke, n (%)	14 (100)	11 (100)
Time to randomisation (days post-stroke), mean (SD)	3.6 (1.8)	4.1 (1.9)

Note. IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease.

Recruitment rate

31 patients were enrolled in this study over 13 months (19th April 2021 to 18th May 2022), yielding a recruitment rate of 2.4 participants per month.

Consent rate

Thirty-seven eligible patients were asked to participate. Of these, 31 consented to take part in this study (84% consent rate). One control group participant was subsequently re-diagnosed as a stroke mimic and was therefore excluded (before baseline assessments). Six patients (16%) declined to participate, providing the following reasons: (1) concerns that exercise may exacerbate a surgical wound in the groin and a pressure headache; (2) feeling overwhelmed by life circumstances and prioritising returning home; (3) a general dislike for exercise; (4) a preference to delay exercise until after returning home; and (5) a perception of being too old (89 years) and viewing the study as too demanding. One participant did not provide a reason.

Attrition

Six out of 30 participants (20%) withdrew from the study. Reasons for attrition were: early hospital discharge (n=3; control, n=1; intervention, n=2), perceived study burden (n=1; intervention), medical withdrawal due to a urinary tract infection with fever, unrelated to the intervention (n=1; intervention), and death unrelated to the study (n=1; control). The overall attrition rate was 20% (6/30), with rates of 26.7% (4/15) for the intervention group and 13.3% (2/15) for the control group. After excluding dropouts due to early discharge, the overall attrition rate was 10% (3/30); 13.3% (2/15) for the intervention group and 6.7% (1/15) for the control group.

Completeness of data

Completeness of data is calculated as the percentage of outcome measure assessments conducted relative to the number of patients enrolled at each timepoint (see Table 5.7). Physical function and physiological outcome measures were prioritised, whereas psychometric measures were occasionally omitted due to patient fatigue or time constraints. Most participants were non-ambulatory which limited the ability to assess lower limb function. Moreover, although it was expected that cognitive assessments would be conducted as part of usual care for all patients, this was only carried out for selected patients by occupational therapists, resulting in missing data. Lastly, four control group participants and one intervention group participant opted for a brief

telephone follow-up assessment instead of a face-to-face appointment, which precluded assessment of physical function and psychometric outcomes. Only the modified Rankin Scale and Barthel Index assessments were conducted during telephone follow-up appointments.

Table 5.7. Completeness of data for study outcome measures

Assessment	Control group		Intervention group	
	Baseline (n=15)	3-month follow-up (n=13)*	Baseline (n=15)	3-month follow-up (n=11)
Disability (modified Rankin Scale)	15 (100%)	14 (100%)	15 (100%)	11 (100%)
Independence (Barthel Index)	15 (100%)	13 (100%)	15 (100%)	11 (100%)
Short Physical Performance Battery	13 (87%)	10 (77%)	11 (73%)	10 (91%)
10 metre walk speed (normal pace)	3 (20%)	4 (62%)	1 (7%)	9 (82%)
Handgrip strength (both hands)	14 (93%)	8 (62%)	11 (73%)	10 (91%)
Quality of life (EQ5D-3L)	12 (80%)	9 (69%)	8 (53%)	10 (91%)
Mood (Hospital Depression and Anxiety Scale)	8 (53%)	5 (38%)	6 (40%)	7 (64%)
Fatigue (Fatigue Severity Scale)	8 (53%)	4 (31%)	6 (40%)	8 (73%)
Cognitive function (Montreal Cognitive Assessment)	3 (20%)	4 (31%)	5 (33%)	6 (55%)
Optimism (Revised Life Orientation Test)	7 (47%)	3 (23%)	6 (40%)	8 (73%)

Note. *Control group baseline sample size for mRS data was n=14 (one participant died).

In addition to the abovementioned 3-month outcome measures (Table 5.7), hand grip strength and quadriceps muscle structure were measured at baseline and approximately 7-10 days after the intervention period to determine the short-term effects of the intervention on hospital-associated deconditioning. Follow-up muscle ultrasound assessments were completed for 91% (10/11) of the intervention group and 79% (11/13) of the control group. In addition, follow-up hand grip strength assessments were completed for 100% (11/11) of the intervention group and 64% (9/13) of the control group. The reasons for missing hand grip strength assessment data were: early discharge (n=3), dropout (n=2), and illness (n=1).

Intervention acceptability

Thirteen participants (87%) rated the exercise bike as 'comfortable' (4/5 on the comfort Likert scale), and two participants (13%) rated the bike as very comfortable (5/5 on the comfort Likert scale). Intervention acceptability is assessed in more detail in Chapter 7.

Exercise dose

External load

External load is the amount of work completed by an individual, independent of the perceived exertion or physiological response (e.g., heart rate) (395). Figures 5.10 and 5.11 display external load metrics measured via accelerometry and the exercise bike, respectively. Figure 5.10 exhibits the mean number of repetitions (legs combined) performed by a sub-sample of participants (n=8) in each exercise session. One step is recorded when a single leg moves from a flexed to an extended position. A limitation of measuring step count while using an exercise bike is inability to determine the contribution of each leg to the recorded step count. Whilst the cycle ergometer has a symmetry function which displays the proportion of force being exerted by each leg, our preliminary testing with healthy adults found this function to be unreliable. Nevertheless, all participants had sufficient motor function to rotate the cycle crank with both legs.

Figure 5.11 displays the peak cycling gear (mean $\pm$ standard deviation) achieved by participants per exercise session. Both external load figures demonstrate a gradual progression in exercise dose performed per session. Whilst the repetition count declines slightly in session 4, cycling resistance increases incrementally session by session, indicating that a slower cycling cadence is offset by a higher cycling resistance. The gradual progression in external load aligns with trends in RPE and HR data reported in the sections below.

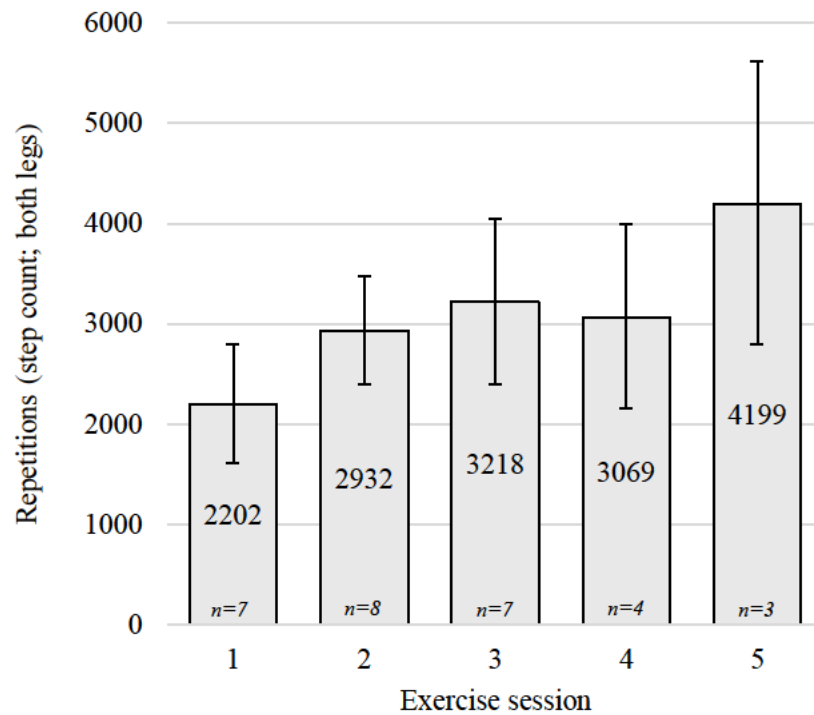


Figure 5.10 Self-paced cycling repetitions (step count) measured using an activPAL thigh-mounted accelerometer including warm-up and conditioning bouts (steps recorded during passive periods were removed from total). Data are presented as group means $\pm$ standard deviation. Data are missing for several participants due to device battery depletion, device reading errors, or non-participation (e.g., early discharge).

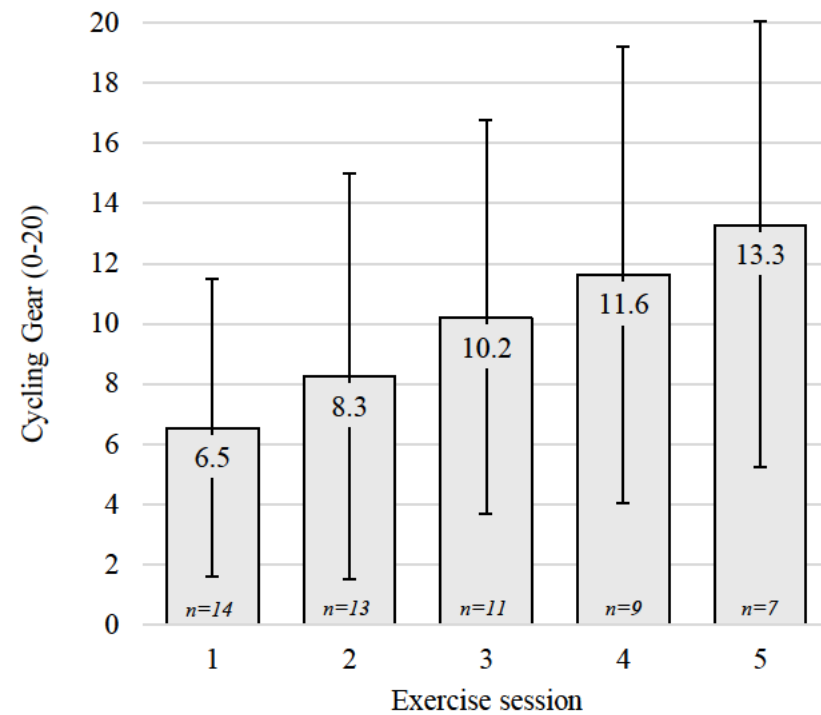


Figure 5.11 Maximum gear achieved by each participant, averaged across each exercise session. Data are presented as group means $\pm$ standard deviation. Cycle gears range from 0 to 20. Watts data are unavailable.

Exercise intensity

Rating of Perceived Exertion

Rating of perceived exertion (RPE) was recorded at the end of each five-minute segment (warm-up or conditioning bout). To visualise trends in RPE scores reported within and between exercise sessions, RPE scores are grouped into light (RPE 11 & 12), moderate (i.e., somewhat hard; RPE 13 & 14) and vigorous (i.e., hard; RPE 15 & 16) exercise intensity domains (see Figure 5.12)

Warm-up

The objective of the warm-up was to gradually increase exercise intensity from light to moderate, aiming to reach an RPE of 13/20 (somewhat hard) at the end of the warm-up. The graduated warm-up was intended to be performed at a lighter intensity than the conditioning exercise bouts, and this is reflected by the higher proportion of 11 and 12 RPE scores during the warm-up. There is a notable trend whereby the warm-up exercise intensity gradually increases for each session, represented by a declining proportion of 11 and 12 RPE scores with a corresponding increase in 13 and 14 RPE scores.

Conditioning phase

The target exercise intensity was 13 RPE for each 5-minute exercise interval within the conditioning phase of each session. This target was achieved for most exercise intervals across the intervention, with proportions of 13 and 14 (moderate) scores ranging from 75% to 100%. In addition, 8-20% of conditioning exercise intervals had 11 or 12 (light) RPE scores whereas 8-25% were rated as 15 or 16 (vigorous) RPE. Similar to the observed increase in warm-up intensity, the perceived exertion of each conditioning phase tended to increase with each session, with higher proportions of 15 and 16 RPE scores reported in sessions 3-5, particularly in the latter intervals of each exercise session. The increased proportion of 15 and 16 RPE scores reported in session 4 aligns with the rating of fatigue scores and haemodynamic data presented in Table 5.10, as post-exercise fatigue scores, peak %HRR and mean arterial pressure were highest in this session.

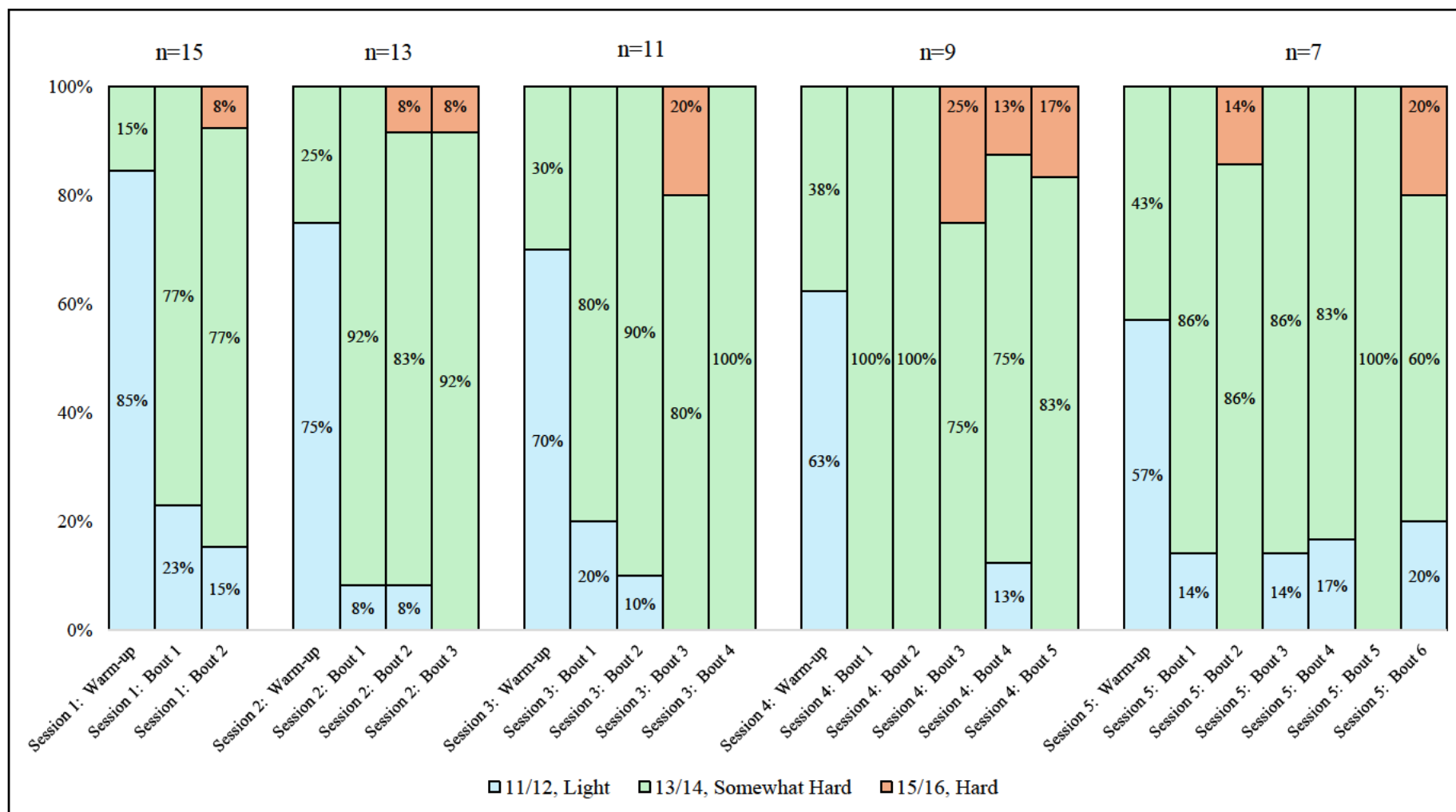


Figure 5.12 Proportion of RPE scores reported by all participants for each exercise session segment. Light blue = light (11/12); green = somewhat hard / moderate (13/14); orange = hard (15/16). *Note.* Bout is synonymous with interval.

Rating of fatigue: pre-post aerobic exercise

Rating of fatigue was assessed before and immediately after each exercise session (Figure 5.13). The scale spans from 0 (no fatigue at all), 2-3 (a little fatigue), 5 (moderately fatigued), 7-8 (very fatigued), to 10 (total fatigue or exhaustion). Approximately half of participants reported increased fatigue (orange lines), while the other half reported reduced fatigue (green lines) in sessions 1-3. A small proportion of participants reported no change in fatigue after exercise (purple lines). However, in session 4, there was a more consistent pattern of increased fatigue following exercise. In session 4, the group mean fatigue score was 5.5 (moderately fatigued to very fatigued) compared to other sessions where the group mean was typically 3-4/10 (a little fatigued to moderately fatigued). This is consistent with the higher group-level RPE and HR data observed in session 4. Session 5 exhibited similar variability to sessions 1-3. An interesting observation is that patients with the highest fatigue scores in sessions 1-3 reported reduced fatigue following exercise.

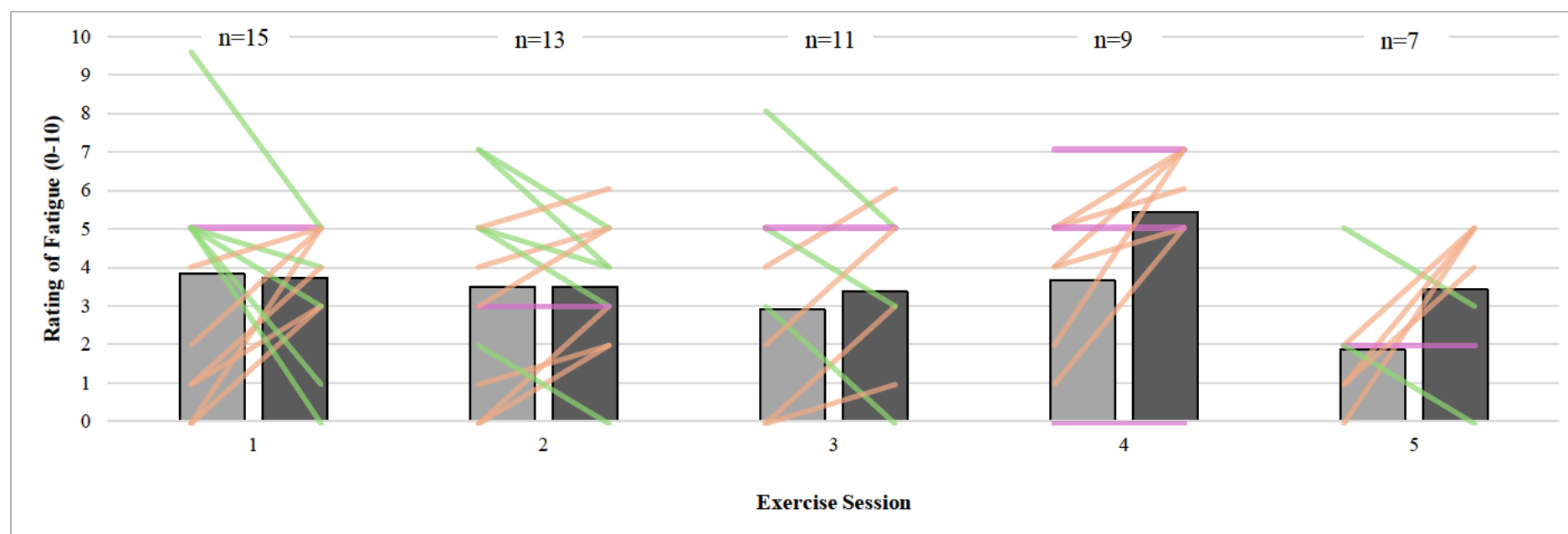
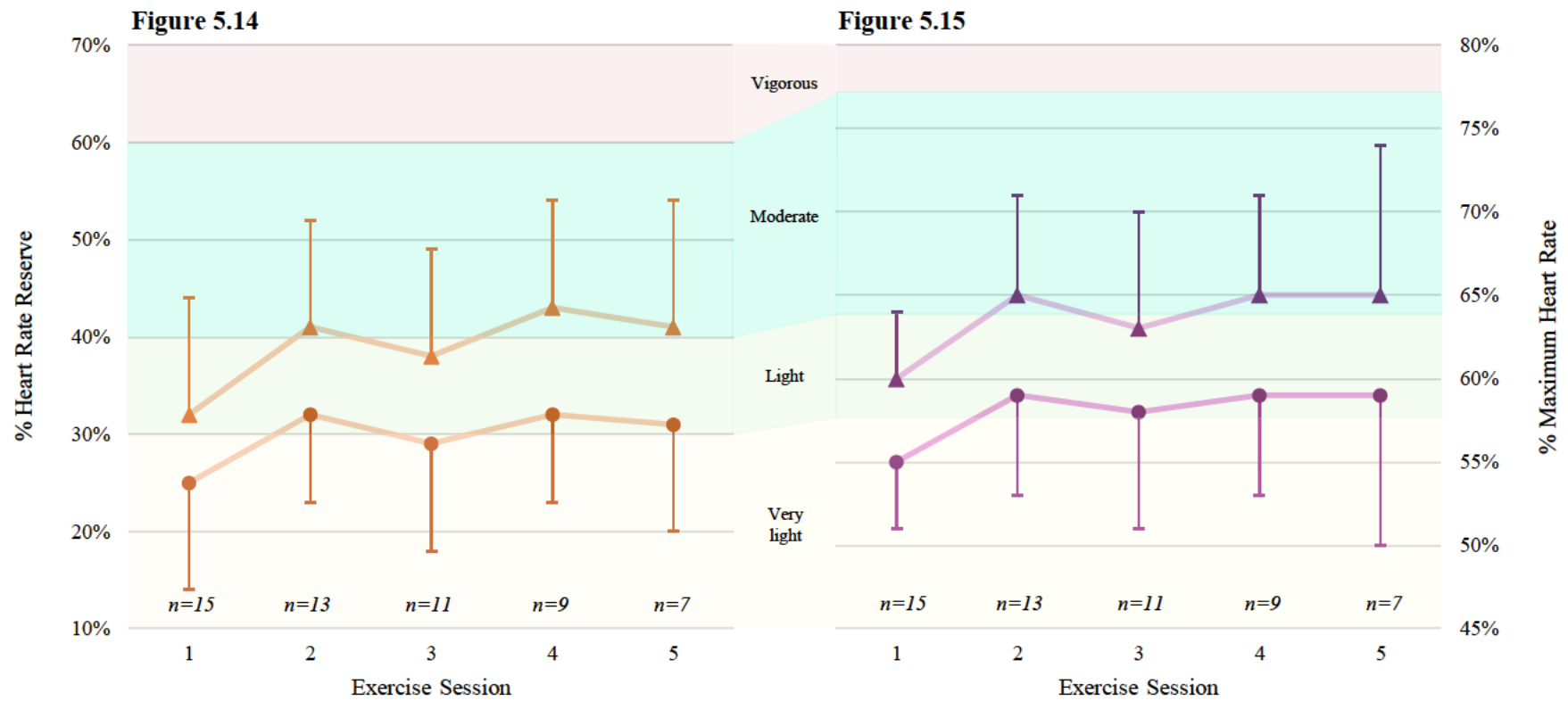


Figure 5.13 Rating of fatigue scores recorded before and immediately after exercise sessions. Light grey bar = pre-exercise group mean; dark grey bar = post-exercise group mean; green line = reduced fatigue; orange line = increased fatigue; purple line = no change.

Heart rate responses

Mean session and peak session heart rate (HR) data are displayed in Figures 5.14 and 5.15, presented as both %HRR and %HRmax with ACSM exercise intensity domains superimposed on each graph (coloured bands). The lower HR responses in session 1 align with lower RPE scores presented above. Additionally, session 4 elicited the highest overall HR responses, which corresponds with a higher proportion of 15/16 RPE scores as noted above. However, there is a large degree of variability in HR responses, with standard deviations ranging between 9-12% for %HRR and 4-9% for %HRmax. This variability is explored in further detail in the next section.



Figures 5.14 and 5.15 display %HRR (orange) and %HRmax (purple) data, respectively averaged across each session. To enhance visual clarity, only positive error bars are shown for peak HR values (triangles), and only negative error bars are shown for mean HR values (circles). ACSM exercise intensity domains are superimposed to provide context: yellow = very light; green = light; turquoise = moderate; red = vigorous.

Whilst RPE scores were mostly consistent between participants, HR responses were highly variable. Figure 5.16 displays each participant's mean and peak %HRR, calculated as means ($\pm$ SD) for all exercise sessions completed by each participant during the intervention. Most mean %HRR values range from 20% to 40% (light intensity), and most peak %HRR values are between 30% and 50% (light to moderate intensity). Mean %HRR values range from 8.5% to 54%, and peak %HRR values range from 14% to 79%. There are also notable outliers; Participant 20 only completed one exercise session (mean = 8.5% HRR; peak = 14% HRR) but subsequently dropped out of the study. Conversely, participant 22 exhibited a much higher HR response, with a mean of 54% HRR and a peak of 79% HRR which exceeded the planned upper HR threshold. As this participant consistently reported an RPE of 13 (indicating “somewhat hard” effort), this indicates a misunderstanding of the RPE scale and/or the target exercise intensity. This participant was discharged early (after two exercise sessions) and therefore withdrew from the study so could not provide feedback via interview.

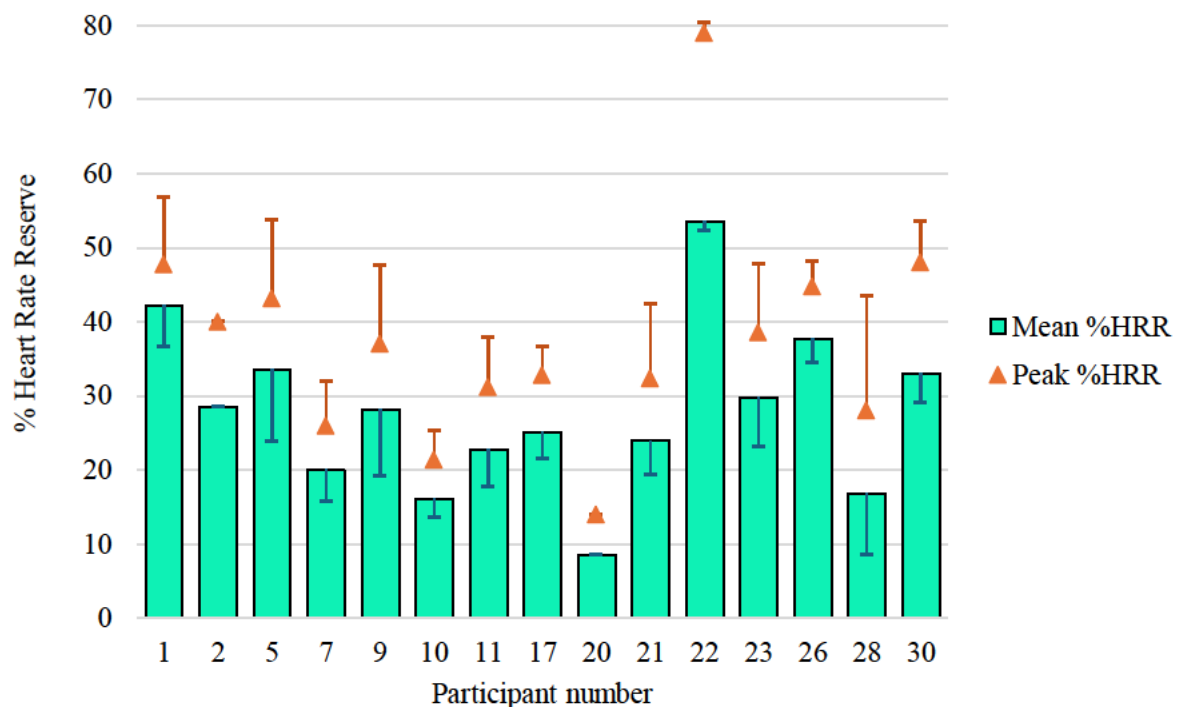


Figure 5.16 Mean (green bars) and peak (orange triangles) %HRR averaged over all exercise sessions completed by 15 participants. Error bars represent standard deviation of mean and peak %HRR averaged across sessions. To enhance visual clarity, only positive error bars are shown for peak %HRR, and only negative error bars are shown for mean %HRR.

Relationship between RPE and heart rate

Figure 5.17 is a boxplot of 225 individual %HRR values derived from averaging each 5-minute interval across all 55 exercise sessions. Each %HRR value was paired with an RPE score which was collected at the end of each five-minute interval. The boxplot illustrates that %HRR rises in line with RPE score, from approximately 20% HRR at RPE 11 (fairly light) to 34% HRR at RPE 15 (hard). However, there is substantial variability in %HRR at each RPE score, with interquartile ranges spanning ~15–20 percentage points and wide discrepancies between minimum and maximum values (e.g., 8% to 58% at RPE 13).

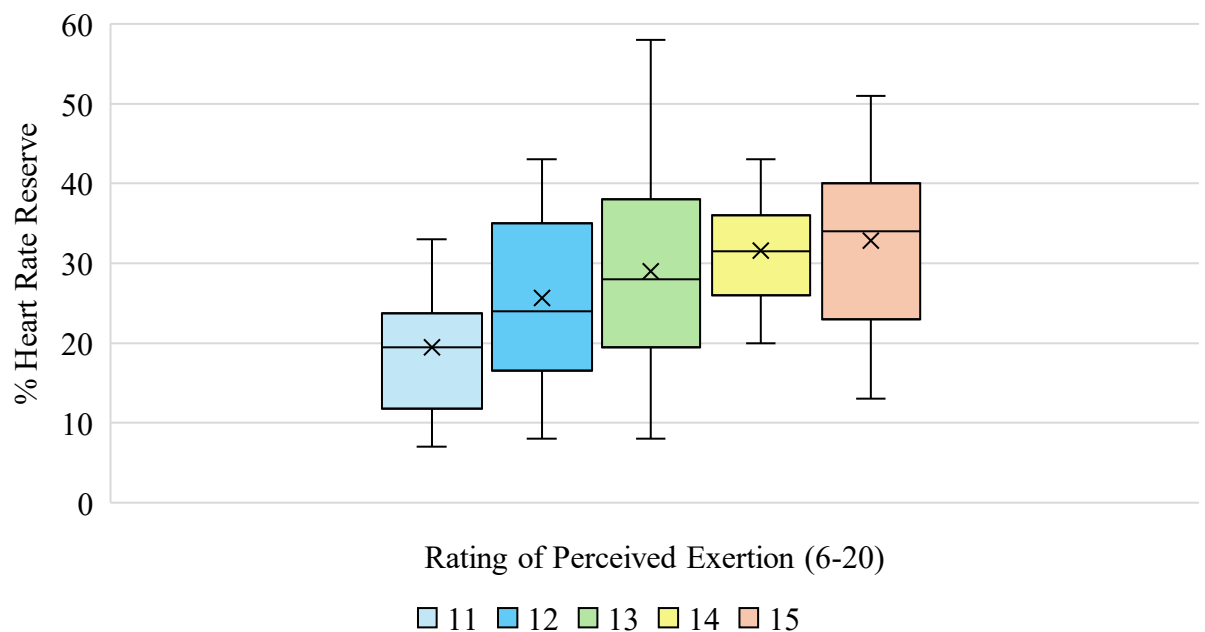


Figure 5.17 Boxplot of percentage heart rate reserve values categorised by RPE score (225 data points).

These findings indicate that while RPE scores broadly reflect changes in %HRR, the considerable between-participant variability suggests that relying solely on RPE to prescribe or monitor exercise intensity may be unreliable for acute stroke patients. Conversely, using %HRR alone to guide intensity may result in a wide range of RPE scores, indicating that heart rate-based targets may also be unreliable. In this study, exercise intensity was guided by the RPE scale alongside the Talk Test. HR monitoring was used solely as a safety precaution, with an upper limit of 60% HRR, adjusted for beta-blockers and heart failure where applicable. Given the challenges associated with both subjective and objective exercise intensity measures, a combined approach

integrating multiple methods, including RPE, the Talk Test and HR, may provide a more pragmatic approach for prescribing and monitoring exercise intensity in this population.

Blood pressure response to exercise

To examine the relationship between exercise intensity and blood pressure responses, peak %HRR and the corresponding change in systolic blood pressure (SBP; peak minus rest) were analysed using linear regression across all 55 exercise sessions (Figure 5.18). This analysis revealed considerable variability in SBP responses across %HRR values. A linear regression of the full dataset displayed a positive but non-significant correlation ($p=0.058$).

Notably, one participant (red circle marker; Figures 5.18 and 5.19 below) exhibited an exaggerated SBP increase of 83 mmHg (resting SBP: 108mmHg; peak SBP: 191 mmHg), possibly due to autonomic dysfunction associated with a lateral medullary stroke (366). After removing this outlier, the correlation between %HRR and change in SBP became significant, with a moderate positive relationship (multiple $R=0.32$, $p=0.018$). Despite statistical significance, the regression model demonstrated weak predictive power ($R^2=0.10$) and a standard error of 11.5 mmHg.

Another noteworthy finding is that one participant (pink triangle marker) had a SBP rise of 70 mmHg at an intensity of 29% HRR, yet when exercising at the same intensity in another session, their SBP only rose by 16mmHg. There is no obvious explanation for this variability apart from possible baroreflex dysfunction associated with old age (91 years old) (396). Of note, these two anomalous SBP responses are comparable to what would be observed in an exercise test to volitional exhaustion (397). However, both SBP values remained within a pre-defined safety limit (<225 mmHg). The reader is also directed to Figure 5.19 and Table 5.8 which display individual participants' SBP responses and along with their clinical characteristics. Collectively, these findings suggest the BP response to light- and moderate-intensity exercise is highly variable in acute stroke patients, and that %HRR alone is a poor predictor of BP. This demonstrates the importance of combining HR and BP monitoring during exercise in acute stroke populations.

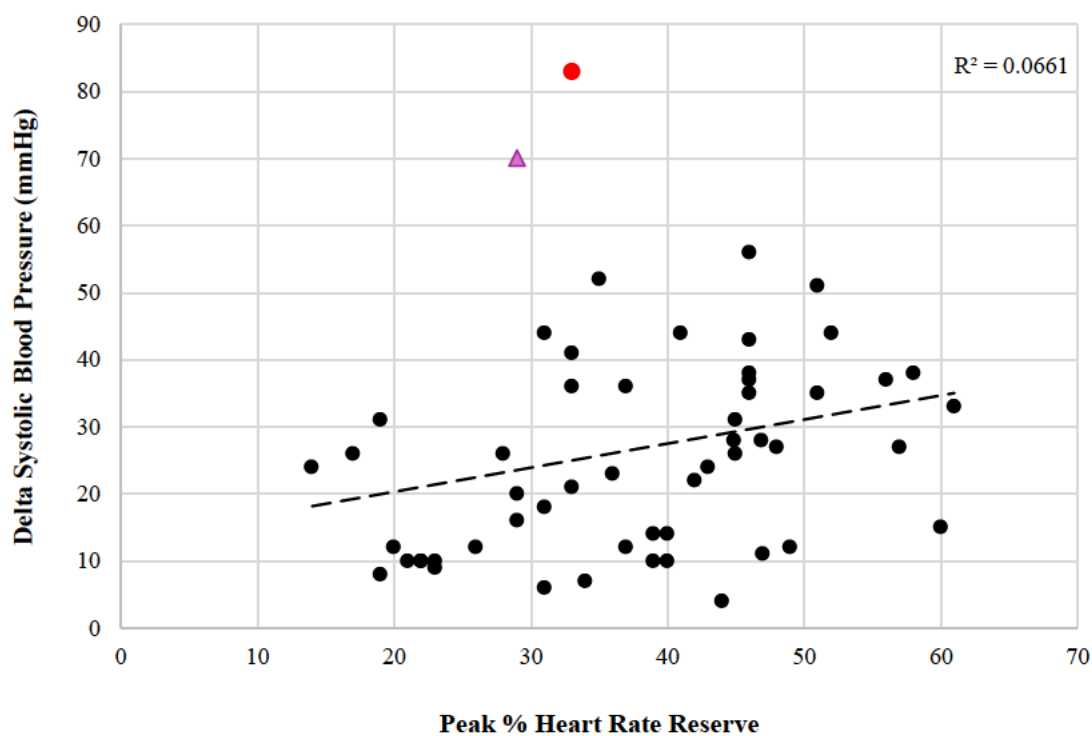


Figure 5.18 Relationship between peak % heart rate reserve and delta systolic blood pressure (mmHg).

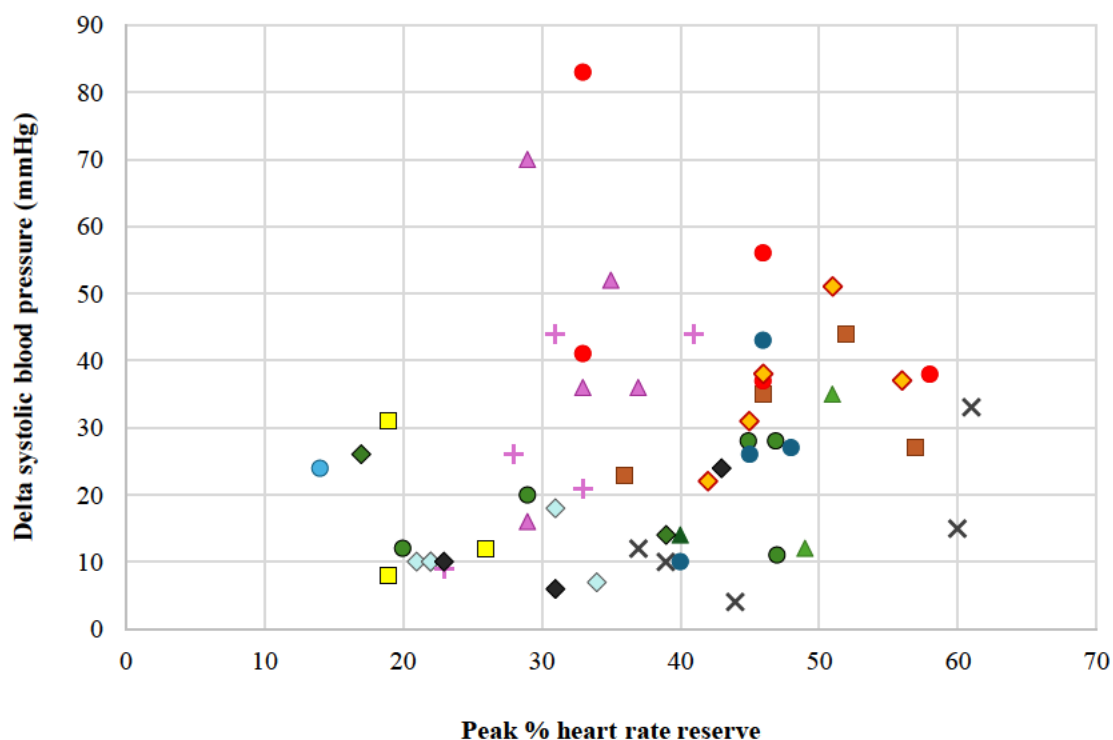


Figure 5.19 Scatterplot displaying the relationship between peak session %HRR and corresponding peak change in systolic blood pressure (mmHg). Each datapoint represents a single exercise session. Each marker style represents one participant. Participant characteristics for each marker are described in Table 5.8 below.

Table 5.8. Clinical characteristics of intervention group (n=15)

Marker	Age on admission (years)	Sex	NIHSS on admission	Cardiovascular comorbidities	Antihypertensive medication
■	65	Male	16	T2DM, hyperlipidaemia	None
◆	18	Male	0	Vasculitis	None
●	62	Male	6	Paroxysmal atrial fibrillation and hypertension	Bisoprolol
◇	75	Male	9	Hypertension; history of thrombophlebitis and venous thromboembolism	None
●	67	Male	2	Mild heart failure; history of myocardial infarctions (four events)	Amlodipine & bisoprolol
■	73	Female	9	T2DM	None
+	66	Male	21	Hypertension	None
▲	90	Female	6	None	None
●	62	Female	9	History of myocardial infarction (1 event)	None
◆	79	Male	1	None	Felodipine
▲	80	Male	10	T2DM; history of myocardial infarction (1 event)	Bisoprolol
×	41	Female	11	Mild heart failure; hypertension	Propranolol
●	62	Male	22	None	None
◆	63	Female	14	History of venous thromboembolism	None
◇	56	Male	3	None	None

Note. T2DM = Type two diabetes mellitus.

Usual care therapy dose

Therapy notes obtained from medical records provided a concise overview of therapy content. However, records were variable, and the intensity of therapy (e.g., patients' perceived exertion or heart rate) and duration of active therapy (excluding rest) were not recorded. Consequently, it was not possible to undertake a detailed analysis of usual care therapy dose. With this limitation in mind, it is assumed that all participants received the same amount of daily therapy on five days per week. Additionally, ambulatory activity (step count) was quantified using a thigh-mounted accelerometer over a five-day period. It is noteworthy that of the participants who wore accelerometers, a larger proportion of control group participants could walk unassisted (Table 5.9). Daily ambulatory step counts are displayed in Table 5.9.

Table 5.9. Ambulatory activity (step count) measured using a thigh-mounted accelerometer

		Day 1	Day 2	Day 3	Day 4	Day 5
Intervention group	Sample, n	12	11	9	9	7
	Step count, mean $\pm$ SD	131 $\pm$ 369	288 $\pm$ 743	181 $\pm$ 293	396 $\pm$ 742	112 $\pm$ 117
	Able to walk unassisted, n (%)	1 (8)	1 (9)	0 (0)	0 (0)	0 (0)
Control group	Sample, n	13	13	13	12	12
	Step count, mean $\pm$ SD	174 $\pm$ 241	186 $\pm$ 301	221 $\pm$ 299	258 $\pm$ 359	382 $\pm$ 488
	Able to walk unassisted, n (%)	5 (38)	5 (38)	5 (38)	4 (33)	4 (33)

Comparison between usual care and the intervention

In addition to measuring ambulatory step count, the thigh-mounted accelerometer was capable of detecting cycling repetitions, with a single repetition defined as a sequence of extension and flexion of the lower limb joints (single leg). Compared to usual care step count (mean = 222 steps), the cycling exercise intervention enabled a 14-fold increase in step count (mean = 3124 cycling repetitions) over the intervention period ($3124 \div 222 = 14.1$). Total cycling repetitions are reported in Table 5.9 (above) and Table 5.10 (below).

Table 5.10. Summary of exercise dose characteristics and physiological responses for each session (mean $\pm$ SD)

	Session 1 n=15	Session 2 n=13	Session 3 n=11	Session 4 n=9	Session 5 n=7
Total exercise session duration, including warm-up/cooldown and rest periods (minutes)	21 $\pm$ 0	27 $\pm$ 11	32.5 $\pm$ 1.8	36.3 $\pm$ 4.1	41.6 $\pm$ 5.9
Number of 5-minute conditioning intervals completed (excluding warm-up/cooldown)	2 $\pm$ 0	3 $\pm$ 0	3.9 $\pm$ 0.3	4.5 $\pm$ 0.7	5.3 $\pm$ 1.3
% of sessions where all conditioning intervals were completed	100	100	91	78	71
Duration of conditioning exercise (minutes)	10 $\pm$ 0	15 $\pm$ 0	19.5 $\pm$ 1.5	22.7 $\pm$ 3.4	26.3 $\pm$ 5.2
Repetitions (total step count; both legs) including active warm-up and conditioning intervals	2202 $\pm$ 592	2932 $\pm$ 538	3218 $\pm$ 824	3069 $\pm$ 917	4199 $\pm$ 1411
Conditioning phase mean heart rate (beats/min)	83 $\pm$ 9	86 $\pm$ 9	85 $\pm$ 9	86 $\pm$ 10	82 $\pm$ 4
Conditioning phase mean % heart rate reserve*	25 $\pm$ 11	32 $\pm$ 9	29 $\pm$ 11	32 $\pm$ 9	31 $\pm$ 11

	Session 1 n=15	Session 2 n=13	Session 3 n=11	Session 4 n=9	Session 5 n=7
Conditioning phase mean % age-predicted HRmax	55 ± 4	59 ± 6	58 ± 7	59 ± 6	59 ± 9
Peak session heart rate (beats/min)	88 ± 10	95 ± 11	92 ± 11	93 ± 12	91 ± 7
Peak session % heart rate reserve*	32 ± 12	41 ± 11	38 ± 11	43 ± 11	41 ± 13
Peak session % age-predicted HRmax	60 ± 4	65 ± 7	63 ± 7	65 ± 8	65 ± 9
Peak session rating of perceived exertion (6-20 Borg scale)	13 ± 1	13 ± 1	14 ± 1	14 ± 1	14 ± 1
Pre-exercise rating of fatigue (0-10)	3.8 ± 2.6	3.5 ± 2.4	2.9 ± 2.7	3.7 ± 2.2	1.9 ± 3.4
Post-exercise rating of fatigue (0-10)	3.7 ± 1.6	3.5 ± 1.7	3.4 ± 1.8	5.4 ± 2.2	3.4 ± 1.9
Pre-exercise resting systolic blood pressure (mmHg)	133 ± 24	129 ± 22	125 ± 23	125 ± 14	123 ± 25

	Session 1 n=15	Session 2 n=13	Session 3 n=11	Session 4 n=9	Session 5 n=7
Pre-exercise resting diastolic blood pressure (mmHg)	77 ± 11	71 ± 25	75 ± 11	78 ± 7	79 ± 13
Pre-exercise resting mean arterial pressure (mmHg)	96 ± 14	90 ± 21	92 ± 14	94 ± 8	94 ± 14
Mean exercise session systolic blood pressure (mmHg)	142 ± 26	141 ± 21	140 ± 17	151 ± 16	139 ± 14
Mean exercise session diastolic blood pressure (mmHg)	82 ± 16	82 ± 13	80 ± 10	88 ± 10	83 ± 9
Mean exercise session mean arterial pressure (mmHg)	102 ± 18	101 ± 14	100 ± 11	109 ± 11	102 ± 10
Peak exercise session systolic blood pressure (mmHg)	148 ± 27	149 ± 24	151 ± 20	162 ± 21	151 ± 16
Peak exercise session diastolic blood pressure (mmHg)	84 ± 15	82 ± 18	82 ± 15	90 ± 13	87 ± 9
Peak exercise session mean arterial pressure (mmHg)	105 ± 18	104 ± 15	105 ± 15	114 ± 15	108 ± 10

Note. Total exercise session includes warm-up, passive cycling (rest) between conditioning exercise intervals and cooldown. Conditioning exercise refers only to the moderate-intensity intervals excluding the warm-up, cooldown, and passive cycling. Mean heart rate values are derived from conditioning exercise periods. Peak refers to the highest measured value.

Fidelity to the intervention

Seventy-five exercise sessions (5 per participant) were planned, and 55 (73%) were delivered. Sessions were missed due to early discharge from hospital (12 sessions, n=5), study dropout (4 sessions, n=1), illness-related exclusion (3 sessions, n=1), and fatigue (1 session, n=1). The mean (SD) number of exercise sessions completed per participant was 3.9 ± 1.4 for the full intervention group cohort (n=15). Of the 11 intervention group participants who had a three-month follow-up assessment, the mean number of exercise sessions completed were 4.5 ± 0.8 . Completion of prescribed exercise intervals per session gradually declined as the intervention progressed, possibly due to increased exertion as the number of exercise bouts increased (session 1: 100% interval completion, peak RPE 13 ± 1 ; session 5: 71% interval completion, peak RPE 14 ± 1). Despite a gradual decline in interval completion rate, the mean conditioning exercise duration (excluding warm-up) increased as planned, progressing from 10 ± 0 minutes in session 1 to 26.3 ± 5.2 minutes in session 5.

Safety

No adverse events occurred during or on the same day as any exercise sessions. All adverse events which may have prolonged hospitalisation or required hospital readmission, occurring up to three months post-stroke, are reported below which were reviewed by the Study Doctor (AA).

1) Death (n=1)

One control group participant died while in hospital (51 days post-admission). The primary contributing factors were post-stroke seizures and neurological deterioration. A clinical decision was made to implement end-of-life care. This event was unrelated to participation in the study.

2) Secondary stroke (n=2)

One control group participant experienced a secondary stroke and an associated fall five days after hospital admission. This adverse event was unrelated to their participation in the study. The participant was discharged seven days later, independently mobile with the aid of a walking stick.

One intervention group participant, who was discharged early after two exercise sessions, experienced an adverse reaction to antibiotics and worsening stroke symptoms 12 days after discharge. The participant was subsequently diagnosed with new multi-territory infarcts. Given the 12-day interval and the drug-related aetiology, this event was determined to be unrelated to the intervention.

3) Migraine with functional stroke symptoms (n=1)

One intervention group participant was readmitted 13 days after completing the full intervention with a migraine and functional stroke symptoms. No evidence of a new stroke was found, and the adverse event was deemed to be unrelated to the intervention due to the 13-day interval between the final exercise session and hospital readmission.

4) Urinary tract infection (n=1)

One intervention group participant developed a urinary tract infection with fever, requiring temporary oxygen supplementation. This occurred the day after completing a very light-intensity exercise session (mean 11% HRR). Although initially suspected to be a pulmonary embolism based on the participant's medical history and existing cough, the final diagnosis was a urinary tract infection, and the cough was attributed to smoking. Treatment included antibiotics and anticoagulants. The participant was withdrawn, as fever and oxygen supplementation contraindicated further exercise. This adverse event was considered unrelated to the intervention.

Preliminary efficacy

Early changes in physical function and muscle structure (pre-post intervention)

This section assesses the effects of the intervention compared to usual care on quadriceps muscle structure and handgrip strength in the first two weeks post-stroke. Due to logistical challenges, such as patient transfers to other sites or weekend breaks, ultrasound and handgrip strength assessments were occasionally delayed. To address variations in follow-up timing, muscle ultrasound and handgrip strength data were expressed as daily rates of change, calculated by dividing differences by the number of days between assessments. Limbs were categorised as 'stroke-affected' if they were

contralateral to the stroke lesion (i.e., opposite side), and as ‘unaffected’ if they were ipsilateral to the stroke lesion (i.e., same side). While not all participants presented with hemiparesis or hemiplegia, this classification was applied to all participants for consistency.

Quadricep muscle structure

Portable ultrasound was used to assess daily percentage changes in rectus femoris cross-sectional area (CSA) and vastus lateralis thickness, as well as absolute daily changes in vastus lateralis pennation angle (degrees per day). The mean period between baseline and follow-up was 7.2 days (± 3.6 , range 3-16 days) for the intervention group and 6.82 days (± 1.5 , range 4-9 days) for the control group. One-way ANCOVAs were used to compare differences in change scores between groups, adjusting for age and baseline stroke severity (NIHSS). Due to unequal between-group variances, a Welch’s ANOVA was used to compare between-group differences for vastus lateralis thickness in the stroke-affected leg. For vastus lateralis pennation angle, only descriptive statistics are presented as unclear ultrasound images resulted in missing data.

Rectus femoris cross-sectional area

In the stroke-affected leg, rectus femoris CSA loss was mitigated in the intervention group ($-0.53\% \pm 1.28\%$ per day) versus the control group ($-1.89\% \pm 1.39\%$ per day). Although not statistically significant ($p=0.25$), the difference had a large effect size (Cohen’s $d = 0.92$). The adjusted mean between-group difference in rectus femoris CSA loss was 1.21% per day (95% CI -3.41 to 0.99), favouring the intervention group. Over a period of seven days, this translates to an 8.47% between-group difference in rectus femoris CSA. 100% (8/8) of the control group experienced rectus femoris atrophy. Conversely, 38% (3/8) of the intervention group experienced rectus femoris muscle growth.

In the unaffected leg, the intervention group had significantly less rectus femoris CSA loss (-0.10% , SD $\pm 1.18\%$ per day) than the control group (-1.36% , SD $\pm 1.25\%$ per day; $p=0.048$), with a large effect size (Cohen’s $d = 1.26$). The adjusted mean between-group difference in rectus femoris CSA loss was 1.60% per day (95% CI -3.18 to -0.02), favouring the intervention group. Across a seven-day period, this translates to a

between-group difference of 11.20% rectus femoris CSA loss. 88% (8/9) of the control group experienced rectus femoris muscle atrophy in the unaffected leg. In contrast, 75% (6/8) of the intervention group exhibited rectus femoris muscle growth in the unaffected leg. Rectus femoris CSA changes scores are presented in Figures 5.20 and 5.21.

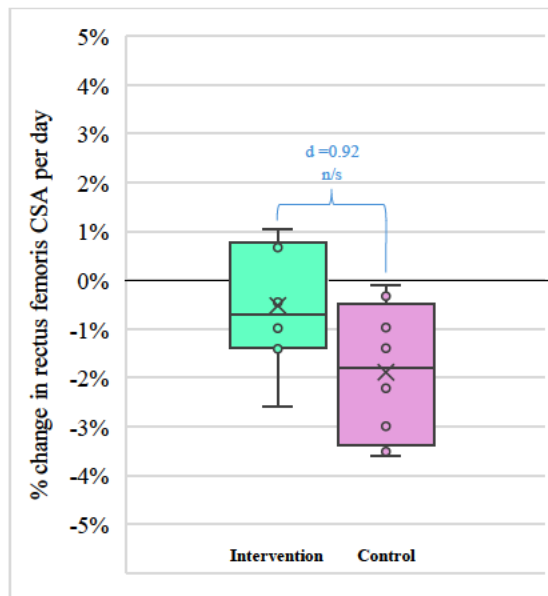


Figure 5.20 Boxplot of daily percentage change in rectus femoris cross-sectional area in *stroke-affected leg* (unadjusted data). Green, intervention group (n=8); purple, control group (n=8). n/s, ANCOVA: $p>0.05$.

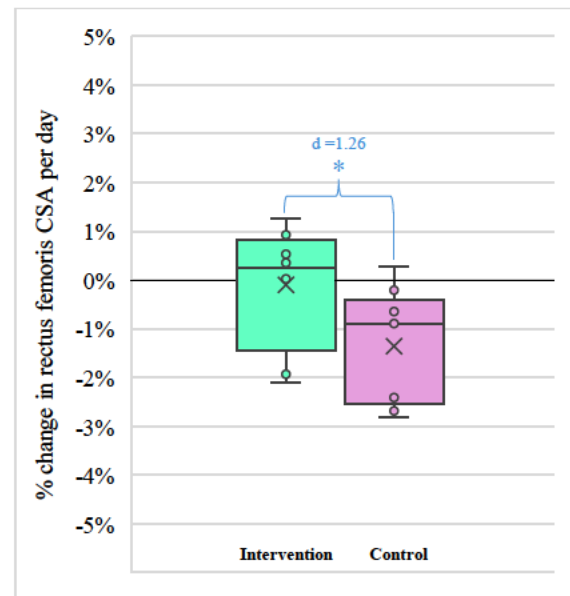


Figure 5.21 Boxplot of daily percentage change in rectus femoris cross-sectional area in the *unaffected leg* (unadjusted data). Green, intervention group (n=8); purple, control group (n=9). *, ANCOVA: $p<0.05$.

Vastus lateralis thickness

There were no statistically significant between-group differences for changes in vastus lateralis muscle thickness, for both the stroke-affected ($p=0.49$, $d=-0.32$) and unaffected legs ($p=0.07$, $d=-1.00$). However, it is noteworthy that there was a large effect size for the between-group comparison for the unaffected leg, which indicates that the control group ($-0.16\% \pm 1.75\%$ per day) may have had less vastus lateralis muscle atrophy than the intervention group ($-1.84\% \pm 1.60\%$ per day). Vastus lateralis muscle thickness changes scores are presented in Figures 5.22 and 5.23.

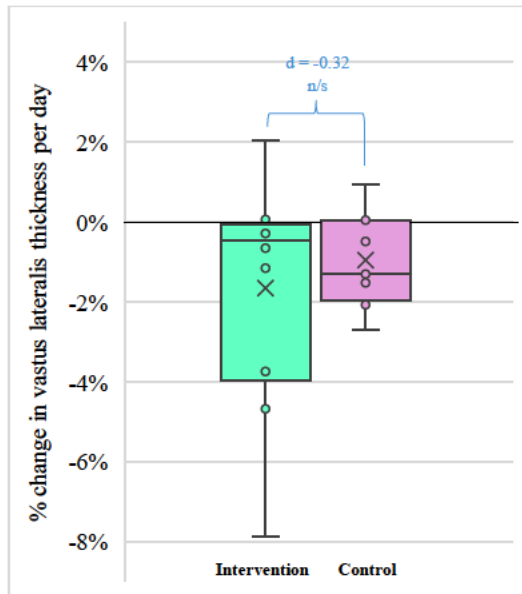


Figure 5.22 Boxplot of daily percentage change in vastus lateralis thickness in the *stroke-affected leg* (unadjusted data). Green, intervention group (n=10); purple, control group (n=11). n/s = Welch's F: $p > 0.05$.

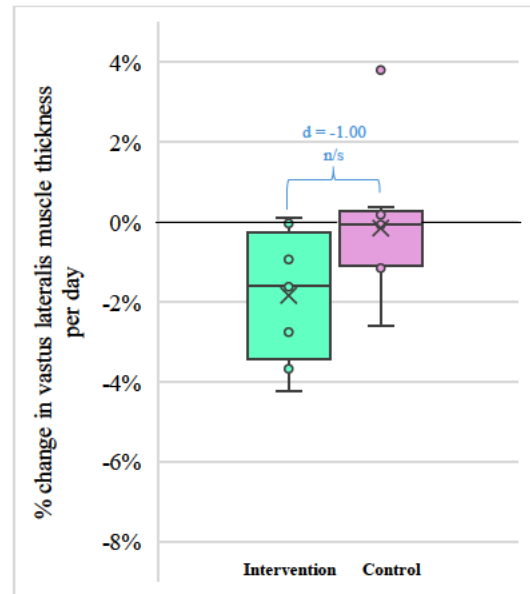


Figure 5.23 Boxplot of daily percentage change in vastus lateralis thickness in the *unaffected leg* (unadjusted data). Green, intervention group (n=8); purple, control group (n=9). n/s $p > 0.05$.

Vastus lateralis pennation angle

Due to small sample sizes and high variability, inferential statistical analyses were not suitable to assess vastus lateralis pennation angle, therefore only descriptive statistics are presented (see Figures 5.24 and 5.25). In the stroke-affected leg there was a slight between-group difference in vastus lateralis pennation angle (intervention group [n=8]: -0.24° per day ± 0.39 ; control group [n=3]: $+0.05^\circ$ per day ± 0.17). One participant in the intervention group had a more pronounced reduction in pennation angle (-1.08° per day), which skews the between group mean difference.

In the unaffected leg, group means for vastus lateralis pennation angle changes were similar (intervention group: -0.86° per day ± 1.92 ; control group: -1.03° per day ± 0.19). However, the intervention group (n=6) exhibited considerable variability, with values ranging from -3.07° to $+2.45^\circ$ per day. The control group (n=2) had less variation, with two similar values of -0.89° and -1.16° per day. The small and unbalanced sample sizes, and variable results, limit meaningful between-group comparisons.

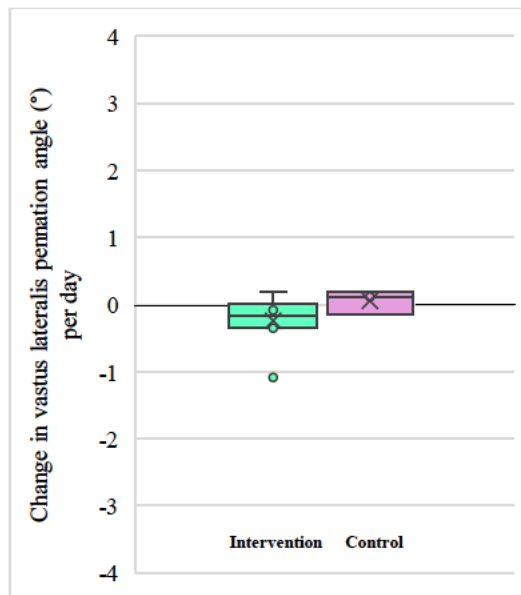


Figure 5.24 Boxplot of daily change in vastus lateralis pennation angle in the *stroke-affected leg* (unadjusted data). Green, intervention group (n=6); purple, control group (n=2).

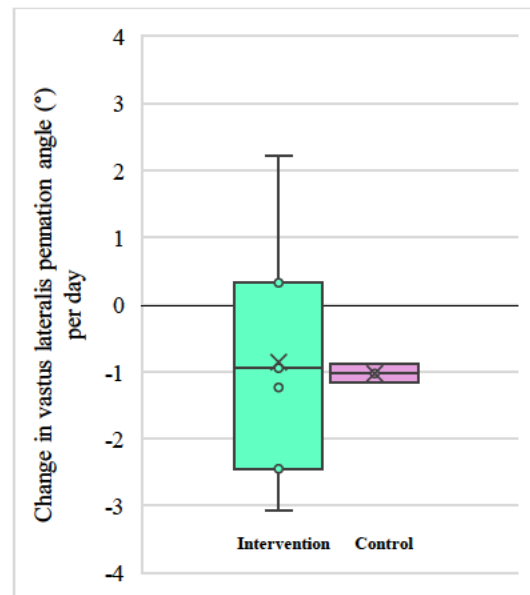


Figure 5.25 Boxplot of daily change in vastus lateralis pennation angle in the *unaffected leg* (unadjusted data). Green, intervention group (n=8); purple, control group (n=3).

Muscle ultrasound summary

In-bed cycling implemented early after stroke appears to mitigate rectus femoris muscle loss in both the stroke-affected and unaffected legs compared to usual care. Notably, some intervention group participants exhibited rectus femoris muscle growth while most control group participants experienced atrophy. This may be explained by the bi-articular function of the rectus femoris, which crosses both the hip and knee joints (398). As a hip flexor and knee extensor, the rectus femoris is likely to be active during both the up-stroke (hip flexion) and down-stroke (knee extension) phases of cycling, providing more opportunity for muscle activation. In contrast, the vastus lateralis, which functions solely as a knee extensor, would have been engaged during the downstroke only. No clear differences were observed in vastus lateralis thickness, although there is a trend indicating reduced vastus lateralis atrophy in the control group's unaffected leg, which could be explained by the fact that more control group participants could walk unassisted, and that these participants may have engaged in compensatory walking movements placing greater load through the unaffected leg. Vastus lateralis pennation angle analysis was limited by missing data and high variability. Overall, these findings suggest in-bed cycling has positive effects on rectus femoris muscle mass in acute stroke, but not vastus lateralis muscle architecture.

Handgrip strength

The mean period between baseline and follow-up assessments was 7.3 ± 3.4 days (range 3–16 days) for the intervention group and 7.0 ± 1.4 days (range 4–9 days) for the control group. At follow-up, the mean between-hand strength deficit was $77.0\% \pm 35.1\%$ for the control group and $50.3\% \pm 40.8\%$ for the intervention group. Between group differences were assessed by comparing change scores using ANCOVA, adjusting for age and baseline stroke severity (reported below).

Handgrip strength of the stroke-affected hand

A one-way ANCOVA revealed no significant between-group difference in handgrip strength in the stroke-affected hand, with a small effect size ($F [1, 14] = 0.157$, $p=0.698$, Cohen's $d = 0.21$). The intervention group ($n=11$) had a mean increase in handgrip strength of 0.01 kg per day (± 0.50 kg), whereas the control group ($n=7$) experienced a mean decrease of -0.09 kg per day (± 0.51 kg). The between-group mean difference in handgrip strength change score was 0.08 kg per day, equating to 0.56 kg over a seven-day period, favouring the intervention group. There was also notable variability amongst participants; 36% (4/11) of the intervention group and 20% (2/10) in the control group experienced increases in strength, 36% (4/11) scored zero on both assessments (floor effect), and the remaining participants exhibited a decline in strength.

Handgrip strength of the unaffected hand

A one-way ANCOVA revealed no significant between-group difference in handgrip strength in the unaffected hand, with a small effect size ($F [1, 14] = 0.120$, $p=0.73$, Cohen's $d = 0.19$). The intervention group ($n=11$) had a mean increase in handgrip strength of 0.01 kg per day (± 0.79 kg), and the control group ($n=7$) experienced a mean increase of 0.31 kg per day (± 0.50 kg). The between-group mean difference in handgrip strength change was 0.30 kg per day, which translates to 2.09 kg over a 7-day period, favouring the control group.

$d = 0.19$
n/s

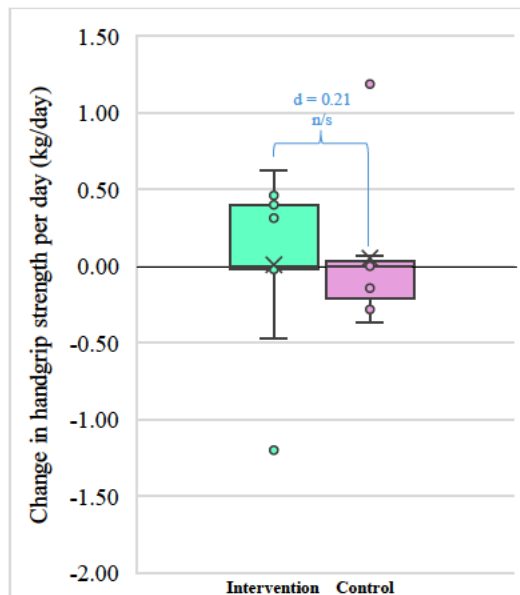


Figure 5.26 Boxplot of daily change in handgrip strength in the *stroke-affected hand* (unadjusted data). Green, intervention group (n=11); purple, control group (n=9).

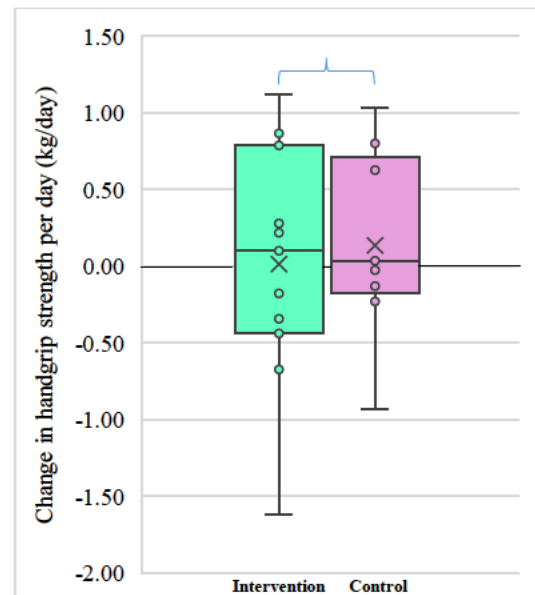


Figure 5.27 Boxplot of daily change in handgrip strength in the *unaffected hand* (unadjusted data). Green, intervention group (n=11); purple, control group (n=9).

Handgrip strength summary

No significant between-group differences were observed in handgrip strength for either the stroke-affected or unaffected hand (both small effect sizes). The intervention group exhibited a slight increase in stroke-affected handgrip strength (0.01 kg/day) compared to a mean minor decrease in the control group (-0.09 kg/day), yielding a between-group difference of 0.56 kg over 7 days. Conversely, handgrip strength in the unaffected hand increased to a larger extent the control group (0.31 kg/day) compared to the intervention group (0.01 kg/day), equating to a 2.09 kg difference over 7 days.

Long-term preliminary efficacy (90 days post-stroke)

To assess the longer-term preliminary efficacy of the intervention, numerous physical function and psychometric outcome measures were assessed at baseline and three months after stroke onset. A detailed summary of statistical results is presented in Tables 5.11 and 5.12 below.

Disability

After adjusting for baseline age and NIHSS score, the intervention group's three-month modified Rankin Scale score was significantly lower than the control group (large effect size). This result remained significant ($p=0.008$) following a sensitivity analysis where one control group participant who died was removed from the analysis, resulting in a between-group difference of 1.5 points, suggesting that the intervention reduced disability (adjusted mRS scores: 2 vs. 3.5). For context, the intervention group's adjusted mean mRS score was 2 which reflects a minor disability, whereas the control group's adjusted mean mRS score was 3.5 which is midway between moderate and moderately severe disability (399).

Independence

After adjusting for baseline age and NIHSS score, the three-month Barthel Index score was significantly higher in the intervention group ($p<0.001$), with a mean difference of 43 points (adjusted Barthel Index scores: 100 vs. 57) and a large effect size, indicating that the intervention improved independence. This between-group difference far exceeds the minimally clinically important difference of 9 points (0-100 scale) (400).

Physical function

All other measures of physical function, including the Short Physical Performance Battery, handgrip strength, and 10-metre walk speed, were not significantly different between groups (effect sizes ranging from negligible to medium; $p \geq 0.05$). Notably, the intervention group's mean 10-metre walk duration was nine seconds slower than the control group on average ($p=0.15$; negligible effect size). Despite a slower overall group-level walking speed, all intervention group participants (11/11, 100%) walked independently at follow-up, including those using walking aids, compared to 64% of the control group (9/14). In contrast, at baseline only 13% of intervention group participants were able to walk unassisted compared with 33% of the control group. The inclusion of individuals who had more severe initial impairments who regained walking ability likely led to the slower group-level walking speed in the intervention group. For instance, one participant who had a baseline MRC leg muscle power score of 1 (trace

contraction; (401) assessed by a physiotherapist) completed five exercise sessions and, three-months later walked 10 meters with a cane in 66 seconds. Although this is a very slow walking speed, this participant had fully regained independence which is a clinically meaningful outcome.

Physical activity level

Physical activity level (GPAQ), measured 3-months post-stroke, was not statistically different between groups ($p=0.56$) (adjusted for baseline NIHSS), indicating that post-discharge physical activity levels are unlikely to have contributed to the between-group differences in post-stroke recovery, and that the intervention did not influence physical activity levels outside of the hospital setting. Although not statistically significant, the intervention group had a mean GPAQ score of 55 MET-mins/week, whereas the control group had a GPAQ score of 115 MET-mins/week at the 3-month follow-up (small effect size). For context, these values are only 11-23% of the minimum recommended physical activity levels for good health (500 MET-mins/week) (402). With regards to pre-stroke physical activity levels, the intervention group was slightly more active (202 MET-mins/week, SD = 260) than the control group (M = 178 MET-mins/week, SD = 370), but the difference was not statistically significant ($p = 0.88$; small effect size). These findings suggest that pre-stroke physical activity levels are unlikely to have confounded this study's preliminary efficacy results.

Psychometric assessments

Most psychometric outcomes assessed at three months post-stroke did not significantly differ between the intervention and control groups, with effect sizes ranging from negligible to moderate. Notably, the intervention group reported higher scores on the quality-of-life visual analogue scale, with a corresponding large effect size ($p = 0.06$). This finding aligns with observed improvements in independence (Barthel Index) and functional ability (modified Rankin Scale). Statistical comparisons for psychometric outcomes are summarised in Tables 5.11 and 5.12.

Table 5.11. Descriptive statistics for baseline and adjusted follow-up outcome measures assessed by ANCOVA

Outcome Measure (Unit/Scale)	Baseline Score, Mean (SD)		3-Month Follow-Up Score, Adjusted Mean (SE)		Adj. Mean Difference (95% CI)	ANCOVA	P	Cohen's d	Effect Size Interpretation	Favouring
	Control	Intervention	Control	Intervention						
Modified Rankin Scale ^B (0-6)	3.64 (0.50)	4.00 (0.00)	3.46 (0.30)	1.96 (0.35)	-1.51 (-2.57, -0.45)	F (1,20) = 8.84	0.008*	-1.29	Large	Intervention
	n=14	n=11	n=14	n=11						
Modified Rankin Scale (sensitivity analysis) ^B (0-6)	3.61 (0.51)	4.00 (0.00)	3.27 (0.29)	1.96 (0.32)	-1.31 (-2.30, -0.32)	F (1,19) = 7.55	0.013*	-1.21	Large	Intervention
	n=13	n=11	n=13	n=11						
Barthel Index (0- 100)	47.86 (29.53)	32.73 (16.49)	57.36 (6.08)	99.94 (6.71)	42.59 (22.02, 63.15)	F (1,19) = 18.79	<0.001*	1.91	Large	Intervention
	n=14	n=11	n=13	n=11						
Short physical performance battery ^B (0-12)	1.23 (2.42)	1.27 (2.87)	1.96 (0.93)	3.94 (0.87)	1.99 (-0.89, 4.86)	F (1,15.01) = 2.19	0.155	0.50	Medium	Intervention
	n=13	n=11	n=10	n=10						
Handgrip strength (kg) – Stroke- affected hand	12.56 (9.73)	18.06 (18.77)	17.16 (4.10)	16.28 (5.21)	-0.88 (-13.70, 15.46)	F (1,14) = 0.02	0.899	0.06	Small	Intervention
	n=14	n=14	n=7	n=11						
Handgrip strength (kg) – Unaffected hand	19.50 (10.05)	25.38 (13.28)	22.93 (3.48)	22.60 (4.42)	0.33 (-12.05, 12.71)	F (1,14) = 0.00	0.955	0.00	Small	Intervention
	n=14	n=14	n=7	n=11						
Physical activity level (MET-mins/week)	178.29 (369.79)	202.44 (269.01)	113.87 (71.14)	56.54 (62.54)	-57.33 (-264.49, 149.83)	F (1,13) = 0.36	0.560	0.08	Small	Control
	n=7	n=9	n=7	n=9						
Quality of life (EQ- 5D-3L) index (-0.594 to 1)	0.36 (0.42)	0.28 (0.36)	0.38(0.08)	0.60 (0.08)	0.23 (-0.12, 0.47)	F (1,15) = 4.01	0.064	0.91	Large	Intervention
	n=12	n=8	n=9	n=10						
Quality of life (EQ- 5D-3L) visual analogue scale (0 to 100)	57.92 (14.22)	43.75 (18.66)	61.66 (5.38)	60.51 (5.09)	-1.16 (-17.53, 15.22)	F (1,15) = 0.02	0.882	0.07	Small	Control
	n=12	n=8	n=9	n=10						

Note. Sensitivity analysis (one control group participant removed who died). ^B= Bootstrapped ANCOVA

Table 5.12. Descriptive statistics for baseline and adjusted follow-up outcome measures assessed by Welch's ANOVA

Dependent Variable	Scale Range / Unit	Baseline Score, Mean (SD)		Follow-Up Score, Mean (SD)		Mean Difference Between Follow-Up Scores	Welch's ANOVA	p	ω^2	Effect Size Interpretation	Favouring
		Control	Intervention	Control	Intervention						
Cognitive function (MoCA)	0 to 100%*	77.78	73.52	85.00 (11.06)	91.67 (0.69)	6.67	F (1, 8) = 1.41	0.27	0.05	Small	Intervention
		n=3	n=5	n=4	n=6						
Optimism (R-LOT)	0 to 24	15.14 (4.63)	17.33 (2.73)	13.33 (1.15)	13.00 (1.49)	-0.33	F (1, 8.85) = 0.04	0.84	0.00	Negligible	N/A
		n=7	n=6	n=3	n=8						
Anxiety (HADS)	0 to 21	5.38 (2.87)	5.67 (2.80)	5.40 (4.72)	4.43 (2.51)	-0.97	F (1, 5.62) = 0.18	0.69	0.00	Negligible	N/A
		n=8	n=6	n=5	n=7						
Depression (HADS)	0 to 21	7.38 (4.00)	7.00 (3.29)	5.20 (2.77)	5.14 (3.39)	-0.06	F (1, 9.71) = 0.00	0.98	0.00	Negligible	N/A
		n=8	n=6	n=5	n=7						
Fatigue (FSS)	9 to 63	34.00 (19.04)	37.67 (16.02)	37.50 (20.11)	33.75 (13.42)	-3.75	F (1, 4.39) = 0.11	0.75	0.00	Negligible	N/A
		n=7	n=6	n=4	n=8						
10-metre walk time	Seconds	15.91 (3.54)	15.31 (2.98)	11.89 (1.06)	21.17 (17.57)	9.28	F (1, 8.13) = 2.49	0.15	0.00	Negligible	N/A
		n=3	n=2	n=4	n=9						

Note. *MoCA scores were converted to percentages to account for visual impairment. Normal scale range = 0-30; visually impaired scale range = 0-22; ω^2 = Omega squared (effect size for ANOVA).

Discussion

This phase II randomised controlled feasibility trial evaluated the feasibility, safety, acceptability, and preliminary efficacy of a recumbent cycling intervention initiated 1–7 days post-ischaemic stroke, compared to usual care.

Feasibility and recruitment

The trial successfully met its recruitment target, achieving a high consent rate of 84% and enrolling 31 participants over 13 months (2.4 participants per month), surpassing the *a priori* target of ≥ 2 participants per month. This target was based on a previous systematic review of stroke rehabilitation trials which concluded that the average recruitment rate was 1.5 participants per single site (403). The estimated eligibility rate (17.6%) suggests that only a relatively small subset of ischaemic stroke patients may be suitable for early aerobic exercise interventions, primarily due to short hospital stays, which is a common issue in stroke rehabilitation research (404). The attrition rate (20%) aligned with the anticipated value (20%) (388), with early hospital discharge being the primary reason for withdrawal. Future studies should consider multi-site designs, allowing patients to continue participation after transferring to another acute stroke unit or secondary rehabilitation facility. Completeness of data was varied across outcome measures, largely influenced by the study's primary focus on physical function, meaning that psychometric assessments were occasionally omitted to minimise patient burden or due to time constraints. The *a priori* success criterion for data completeness was defined as $>80\%$ of planned measurements recorded. Disability outcomes (Barthel Index and mRS) were the most consistently measured, with no missing data. Future decisions regarding additional outcome measures will depend on study priorities.

Intervention acceptability and fidelity

The intervention was highly acceptable, with 87% of participants rating the exercise bike as 'comfortable' and 13% as 'very comfortable' on a 5-point Likert scale, meeting the *a priori* acceptability criterion. Qualitative acceptability data is discussed in Chapter 7. Intervention fidelity was reasonable, with 73% of planned sessions delivered (55/75), with missed sessions primarily due to early hospital discharge (12 sessions missed). The

completion rate, defined as the percentage of prescribed exercise intervals completed per session, gradually declined as the total session duration increased, reducing from 100% in session 1 to 71% in session 5. Despite declining completion rates, the mean active exercise duration increased as planned, from 10 ± 0 minutes in session 1 to 26.3 ± 5.2 minutes in session 5. No *a priori* success criteria for intervention fidelity were established.

The exercise intensity target was an RPE score of 13/20 (somewhat hard), which according to the ACSM (2021) (79), corresponds to moderate intensity. This target was met for over 75% of exercise intervals (measured every 5 minutes) for each session, with a smaller proportion of intervals perceived as light (8-23%) and hard (8-25%) across the intervention. There was a greater proportion of RPE 15/16 scores (hard) in the latter bouts of sessions 4 and 5. This may explain the declining session completion rate discussed above. Mean heart rate responses typically ranged from 20–40% HRR (light intensity) and peak responses from 30–50% HRR (light to moderate intensity). However, there was a mismatch between subjective exercise intensity and HRR-derived intensity domains defined by the ACSM. The divergence between heart rate and RPE metrics aligns with prior research involving subacute stroke populations (224–226). Several factors may contribute to this mismatch, including differences in exercise experience, familiarity with the RPE scale, neuromuscular impairments, and cognitive impairment, as discussed in the Methodology chapter. Participants' experience of using the RPE scale is described in Chapter 7. Another potential explanation for the divergence between RPE and HR responses is that the ACSM %HRR intensity domains are not based on recumbent cycling, which elicits a 10-15 bpm lower HR response compared to work-matched upright cycling (207,208). While RPE scores remained relatively consistent across sessions, there was marked variability in heart rate and blood pressure responses. Despite this, rigorous physiological monitoring ensured that haemodynamic fluctuations remained within safe limits.

Safety

Prior studies tend to lack information about the exercise intensity attained by participants, which hinders the interpretation of safety outcomes. The current study adds value through detailed reporting of exercise dose and physiological responses. Peak

SBP values ranged from 148 ± 27 to 162 ± 21 mmHg across exercise sessions, and no participants exceeded upper BP safety thresholds. Importantly, BP values varied significantly across a wide range of %HRR values, highlighting the importance of BP monitoring during exercise sessions. No adverse events were reported during any exercise sessions, satisfying the *a priori* safety criterion. The absence of exercise-related adverse events is a key outcome, which aligns with previous seated ergometry aerobic exercise interventions in the acute (133,134) and early subacute phases of stroke studies (reviewed in Chapter 2).

The current study's intervention safety profile contrasts with Strommen et al., (135) who observed dizziness in 8.5% of treadmill sessions (intervention initiation: mean 42 hours post-stroke), and the PHYS-STROKE trial (140) which found that a bodyweight supported treadmill training intervention initiated 30 days (IQR 17-39 days) was associated with an increased risk of adverse events including falls and recurrent strokes. These differences may stem from variations in exercise mode, dose, and associated exposure to orthostatic stress in the early post-stroke period. Strømme et al., (2016) (135) implemented two daily treadmill sessions, totalling 10 sessions over five days. Similarly, the PHYS-STROKE trial delivered an intensive exercise programme, involving five treadmill sessions per week for four weeks (20 sessions in total) (140). In contrast, the current study's intervention comprised five recumbent cycling sessions, typically spread over seven days due to weekend breaks. Besides differences in dose, the current study's use of recumbent cycling is likely to have minimised orthostatic stress compared to treadmill training, reducing the risk of cerebral hypoperfusion. The cerebral haemodynamic response to recumbent cycling is investigated in Chapter 6.

Preliminary efficacy

The intervention's preliminary efficacy was assessed in the short term (7–10 days after baseline) for muscle structure and handgrip strength, and in the longer term (three months post-stroke) for disability, independence, physical function, and psychometric outcome measures.

Short-term efficacy (7–10 days)

Prior research has demonstrated that the expected decline in quadricep muscle structure (thickness or CSA) over the first two weeks of hospital admission is -0.93% to 1.83% per day in the stroke-affected leg, and -0.86% to -1.33% per day in the unaffected leg (161,162,263,335). In the present study, the intervention mitigated rectus femoris muscle atrophy bilaterally, with large-effect sizes for the unaffected leg ($d=1.26$) and stroke-affected leg ($d=0.92$). Rectus femoris muscle growth was observed in the unaffected leg in 75% of the intervention group, compared to atrophy in most control group participants. Similarly, 38% of the intervention group exhibited rectus femoris muscle growth in stroke-affected leg, whereas 89% of the control group's rectus femoris CSA declined. The control group's mean rectus femoris CSA change was -1.89%/day in the stroke-affected leg, and -1.36% per day in the unaffected leg. In contrast, the intervention appears to have preserved rectus femoris muscle structure (stroke-affected leg: -0.53%/day; unaffected leg: -0.10% per day). These outcomes may be explained by the anatomical and functional characteristics of the rectus femoris, which is a biarticular muscle acting as both a hip flexor and knee extensor. During cycling, the rectus femoris is likely engaged during both the up-stroke (hip flexion) and the downstroke (knee extension). The relatively high dose of cycling exercise (~2-4 thousand reps per session) is likely to have engaged the rectus femoris to a greater extent than usual care activities, contributing to its preservation or growth relative to the control group.

This corroborates findings from da Rosa Pinheiro (134) who reported that lower limb muscle strength improved in response to a 5-day upright cycling intervention initiated 3-7 days after ischaemic stroke onset. Although we did not assess lower limb muscle force, muscle CSA correlates with strength (261,262). The intervention appears to have had no effect on vastus lateralis structure as reductions were similar to normative values (stroke-affected leg: -1.66%/day; unaffected leg: -1.84%/day). However, the control group had preserved vastus lateralis structure in the unaffected leg (-0.16%/day), possibly attributed to increased compensatory walking activity, as a higher proportion of control participants were able to walk unassisted at baseline (38% vs. 0%). Future trials should consider including baseline functional capacity as a stratification factor to avoid this group imbalance. Interpreting changes in vastus lateralis pennation angle changes was limited by missing data due to poor image clarity.

Handgrip strength did not significantly differ between groups. Numerically, the control group had a greater increase in handgrip strength in the unaffected hand (control group: 0.31 kg/day; intervention group: 0.01 kg/day), equating to 2.09 kg over 7 days. However, this is unlikely to be clinically meaningful due to the lack of statistical significance and small effect size. Normative comparisons are challenging due to the wide variation in stroke-induced motor deficits. The reported normative between-hand strength differences are approximately 60% two weeks post-stroke (326). In the current study, the mean between-hand strength deficit measured the 7-day follow-up (approximately 10 days post-stroke), was $77.0\% \pm 35.1\%$ for the control group and $50.3\% \pm 40.8\%$ for the intervention group.

Longer-term efficacy (three months)

This study has demonstrated that a 5-session, light-to moderate-intensity, recumbent cycling, aerobic exercise training intervention initiated in the acute phase of stroke (1-7 days post-stroke) may improve three-month mRS (2 vs. 3.5) and Barthel Index scores (100 vs. 57) adjusted for age and baseline NIHSS. Only three other studies have evaluated aerobic exercise training in the acute phase of stroke (133–135) with equivocal results including short-term improvements in lower-limb function (upright cycling (134)), null effects (recumbent cycling (133)) and poor exercise tolerance (dizziness and exhaustion; treadmill training (135)). Only one of these studies assessed three-month outcomes, revealing that aerobic exercise training (recumbent cycling, RPE 11-13, 5x/week, 3weeks, initiated 3-5 days post-stroke) did not influence mRS or Barthel Index scores. A potential explanation for this discrepancy is that the current study involved predominantly active cycling, whereas Sandberg et al., (2020) (133) permitted passive cycling which likely resulted in a lower exercise intensity (HR responses and duration of active cycling not reported). The significant improvements in mRS and Barthel Index scores identified in the current study may reflect reduced neurological deficits, which aligns with preclinical studies which have demonstrated that early-initiated aerobic exercise promotes neuroprotection and neuroplasticity (13,85). Quality of life scores were higher in the intervention group (large effect size), which aligns with improvements in disability and independence scores. Importantly, this study cannot rule out the possibility that differences in recovery profiles are due to

differences in spontaneous recovery processes which may have occurred without intervention. A larger study is needed to elucidate this.

It is noteworthy that despite more severe baseline walking impairments, all intervention group participants (100%) could walk independently at follow-up, compared to only 64% of the control group. These functional improvements align with findings from other aerobic exercise interventions initiated during the early subacute phase of stroke (7–30 days post-stroke) (reviewed in Chapter 2), which have reported improvements in cardiorespiratory fitness (138,144), walking endurance (136–138,144), gait speed (137,144), and stair climbing ability (146). Overall, the intervention group had a slower overall walking speed at three months post-stroke (control: 0.81 m/s vs. intervention: 0.61 m/s), although this lacked statistical significance. This is likely a result of assessing more people who regained walking ability in the intervention group, highlighting the limitations of using walking speed as an outcome measure in acute stroke trials.

Other physical function measures were not different between groups, possibly due to the small sample sizes and variable results. Pre- and post-stroke physical activity levels (GPAQ) were similar between groups, indicating that physical activity levels did not confound the results. Apart from quality of life, differences in other psychometric outcomes—including cognitive function, fatigue, mood and optimism—were negligible. However, interpretation of several psychometric outcomes is limited by missing data, as these assessments were sometimes deprioritised due to time constraints and patient fatigue.

Clinical implications and research recommendations

This clinical trial confirms the feasibility and safety of recumbent cycling as an acute stroke rehabilitation intervention. This work offers reassuring safety evidence and practical guidance for exercise prescription in acute stroke. The findings also provide support to clinical guidelines which currently recommend initiating aerobic exercise as soon as patients are medically stable, despite limited prior evidence. The recumbent exercise bike's accessibility for non-ambulatory inpatients makes it a practical adjunct to usual care, especially for patients with motor impairments who may otherwise be excluded from aerobic exercise interventions.

This study provides preliminary evidence that light-to moderate-intensity recumbent aerobic exercise training is beneficial for stroke recovery. Reductions in muscle atrophy and improvements in disability, independence, and quality of life highlight the intervention's potential to counteract hospital-associated deconditioning and enhance neurological recovery. The 14-fold increase in lower-limb motor activity compared to usual care indicates that the intervention could be a time-efficient way to promote massed practice of lower limb motor activity (405).

The variability in acute physiological responses to aerobic exercise demonstrates the need for combined subjective (RPE and Talk Test), and objective (heart rate and blood pressure measures) monitoring to achieve a safe and sufficiently challenging exercise dose. Whilst this study highlights the safety of light-to moderate-intensity recumbent aerobic exercise training, the current UK clinical guidelines recommend an exercise intensity of at least 70% of maximum HR, without consideration of exercise posture, blood pressure responses and cerebral haemodynamics (63). Further research is required to determine the optimal aerobic exercise intensity and posture in early stroke rehabilitation programmes, particularly in the acute phase when cerebral autoregulation may be compromised (31,52–54,118).

Strengths and limitations

This study has several strengths. It is one of the first investigations of recumbent cycling in the acute phase of stroke and, importantly, included detailed monitoring and reporting of exercise dose. Rigorous reporting of exercise dose characteristics and physiological responses provides a clear picture of intervention safety, enables replication, and offers guidance for clinical practice. In addition, the use of thigh-mounted accelerometers enabled an objective comparison of physical activity dose with usual care. Further, the combination of physiological and functional measures with detailed exercise dose reporting provides mechanistic insight into the impact of aerobic exercise. Finally, this study was guided by the MRC framework, which ensured a systematic assessment of intervention feasibility.

This study also has several limitations that should be acknowledged. The small sample size (n=30) and single-centre design limit generalisability. A larger, multi-centre trial spanning acute wards and inpatient rehabilitation centres is needed to confirm preliminary efficacy findings. In the present study, stratification was based only on stroke severity (NIHSS). Although ANCOVAs adjusted for age, future trials should consider employing ‘minimisation’ to balance groups using multiple prognostic factors (406). Motor impairments prevented many participants from participating in baseline lower-limb physical function tests, questioning the suitability of these outcome measures in the acute stroke trials. In addition, missing data for psychometric measures in the current study highlights the need to refine the assessment battery, considering time constraints and patient burden. The lack of blinding for participants and assessors increases the risks of bias, though efforts were made to minimise bias through standardised protocols and a blinded muscle ultrasound analysis. Future studies should utilise blinded assessments where possible. Lastly, the inability to quantify usual care therapy dose hinders between-group comparisons, highlighting the need for standardised therapy reporting (407) which could be enhanced with the use of wearable activity monitors (408).

Conclusion

This feasibility study establishes that a light-to-moderate-intensity 5-session recumbent cycling intervention, initiated 1–7 days post-ischaemic stroke is safe, acceptable, and feasible within a UK hospital setting. This study was designed with input from people with lived experience of stroke, with an emphasis on inclusivity, specifically accommodating non-ambulatory patients. Preliminary efficacy findings indicate reductions in disability, improvements in independence, and preservation of rectus femoris muscle mass, offering a promising strategy to mitigate hospital-associated deconditioning and enhance post-stroke recovery. This study provides reassurance and practical guidance for stroke therapists to implement aerobic exercise in the acute stroke setting. The study’s success in meeting progression criteria justifies conducting a definitive RCT.

A future trial should adopt a multi-centre design, including acute wards and secondary rehabilitation centres to maximise recruitment and retention, intervention completion,

and generalisability. Prognostic factors should be balanced through minimisation. The modified Rankin Scale or Barthel Index should be prioritised as primary outcomes due to their low burden, large effect sizes, and clinical relevance. To help isolate the effects of the intervention, improved reporting of usual care therapy dose and unsupervised activities is needed. Lastly, studies incorporating more detailed mechanistic investigations, such as respiratory gas analysis and neuroimaging, are required to elucidate dose-response effects and identify potential mechanisms driving neuroprotection and neuroplasticity.

Mechanistic investigations are presented in Chapter 6, examining haemodynamic and neurotrophic responses to exercise. Additionally, a comprehensive exploration of the intervention's acceptability is provided in Chapter 7, incorporating perspectives from both patient participants and therapists.

Chapter 6 – The Acute Cerebral Haemodynamic and Neurotrophic Effects of Aerobic Exercise in the Early Subacute Phase of Stroke

Background

Ischaemic stroke is a leading cause of complex disability worldwide (2). Advances in reperfusion therapies have improved outcomes for some patients, but around 90% are ineligible due to late presentation, contraindications, or lack of provision (64).

Furthermore, hyperacute and acute stroke clinical trials have yet to identify alternative interventions that improve post-stroke recovery (67,74). Whilst it is established that penumbral tissue can only be salvaged in the first 24-48 hours post-stroke (17), a secondary cascade of pathological events occurs which may result in delayed lesion expansion over a several days (409,410). This evolving injury phase represents an important therapeutic target for tissue preservation.

Importantly, this window overlaps with the emergence of a heightened state of neuroplasticity that persists for several weeks after stroke, whereby growth promoting genes are upregulated and cortical reorganisation is heightened (11,112). Although the exact timeframe is not clearly defined, and likely varies between patients, evidence from pre-clinical models (11,85,112,114) and corticospinal excitability assessments in stroke patients (110) suggest that the first 2-4 weeks post-stroke are an optimal window to influence neuroplasticity through rehabilitation interventions.

The processes of tissue repair and neuroplasticity after stroke are governed by numerous overlapping mechanisms. Central to these processes is the neurovascular unit—an integrated system of neuronal, glial, vascular, and immune cells. Evidence suggests that aerobic exercise exerts beneficial effects on the neurovascular unit, through two primary stimuli: (1) acute elevations in cerebral blood flow (CBF); and (2) the activity-dependent release of brain-derived neurotrophic factor (BDNF) (411).

The effects of aerobic exercise on the neurovascular unit in stroke recovery

Aerobic exercise engages multiple brain regions that coordinate motor activity and sustain homeostasis (248). This widespread neuronal activation increases synaptic glutamate release which is sensed by adjacent astrocytes. In response, astrocytes release vasoactive messengers that act on pericytes or smooth muscle cells to trigger vasodilation (412), which increases regional CBF—a process known as neurovascular coupling (374). The engagement of neuronal and glial cells also stimulates release of BDNF into the local environment (413). Moreover, increased perfusion exerts shear stress on endothelial cells, stimulating angiogenesis signalling, and bidirectional release of BDNF into the bloodstream and into surrounding tissue (414).

Repeated elevations in CBF and BDNF released during aerobic exercise training drive structural and functional adaptations across the neurovascular unit, which in the context of acute stroke, may mitigate stroke lesion expansion and support post-stroke neuroplasticity (13,85). Aerobic exercise training enhances astrocyte growth, resulting in an increased complexity of endfeet processes (415), enhanced vascular coverage and reinforced blood–brain barrier integrity (47,416). Aerobic exercise training also increases glutamate uptake which protects against excitotoxicity (417). In addition, aquaporin-4 channel expression and function improve in response to aerobic exercise training, facilitating glymphatic clearance of waste products (418). The vasculature adapts to aerobic exercise training through angiogenesis which improves cerebral perfusion (419,420). In neurons, aerobic training upregulates BDNF mRNA and protein expression in key areas such as the hippocampus and motor cortex—supporting long-term potentiation, synaptic plasticity, and neurogenesis (13). Finally, aerobic exercise training can stimulate microglia to shift from a pro-inflammatory state toward a more neuroprotective phenotype, which supports synaptic remodelling and clearance of debris (416).

Acute cerebral haemodynamic and neurotrophic responses to aerobic exercise

The current mechanistic understanding of how aerobic exercise acutely affects the neurovascular unit is largely derived from pre-clinical studies which employ invasive imaging methods (421–423). In contrast, clinical research relies on non-invasive

proxies, such as transcranial Doppler ultrasound to assess cerebral haemodynamics (374), and blood-borne BDNF to estimate central neurotrophic responses (287). Although a small number of clinical trials have initiated aerobic exercise interventions within the first seven days post-stroke, and a greater number conducted within the first month post-stroke (reviewed in Chapter 5), these studies lack mechanistic investigations. The following literature review synthesises evidence on the cerebral haemodynamic and neurotrophic responses to aerobic exercise, drawing on data from healthy and clinical populations including individuals in the later stages of stroke recovery.

Acute cerebral and systemic haemodynamic responses to aerobic exercise

Aerobic exercise significantly increases metabolic demand across multiple organ systems, requiring precise distribution of blood flow to support oxygen and nutrient delivery and facilitate removal of metabolic waste products. Within the brain, increases in neuronal activity are matched to regional perfusion primarily through neurovascular coupling, whereby active neural tissue signals local neurovascular cells to permit increased blood flow. Cerebral blood flow is also influenced by carbon dioxide-mediated cerebrovascular reactivity, which adjusts global vascular tone in response to changes in arterial CO₂, and by endothelium dependent signalling, which modulates vessel diameter in response to changes in shear stress. Additionally, cerebral autoregulation preserves relatively stable cerebral blood flow despite changes in perfusion pressure by modulating cerebrovascular resistance. This is achieved primarily through myogenic responses of cerebral resistance vessels, which constrict when perfusion pressure rises and dilate when it falls.

Local cerebrovascular mechanisms alone, however, cannot fully buffer changes blood pressure that occur during exercise. Maintenance of cerebral and systemic haemodynamics also depends on precise autonomic regulation of arterial blood pressure, cardiac output, and systemic vascular tone. Stretch sensitive baroreceptors in the carotid sinus and aortic arch continuously sense changes in arterial pressure. When blood pressure rises or falls, these receptors detect the change within a single heartbeat and trigger near instantaneous autonomic adjustments in heart rate, cardiac contractility, and peripheral vascular resistance. During exercise, the baroreflex is reset to operate

around a higher pressure so that arterial pressure can rise appropriately with metabolic demand but still remains under effective beat to beat control, preventing excessive blood pressure fluctuations.

Active skeletal muscle also contributes to blood flow distribution through neural and mechanical mechanisms. Mechanical and metabolic sensors within contracting muscle detect changes in contraction and the accumulation of metabolic by products, and relay this information to the autonomic nervous system, increasing cardiovascular drive and enhancing blood flow delivery to active tissue as metabolic demand changes (424). In addition, during rhythmic contraction, the skeletal muscle pump enhances venous return to the heart and lungs, supporting cardiac output and promoting transport of metabolic byproducts for elimination through pulmonary gas exchange (425,426). Together, these peripheral mechanisms support perfusion of active muscle, return of venous blood, clearance of waste products and maintenance of arterial pressure.

Transcranial Doppler measurement of cerebral haemodynamic response to aerobic exercise in healthy populations

The cerebral haemodynamic response to aerobic exercise is most commonly assessed using transcranial Doppler (TCD) ultrasound (250,427). The cumulative evidence—derived from healthy populations—demonstrates a biphasic middle cerebral artery blood velocity (MCAv) response to incremental exercise to exhaustion. Middle cerebral artery CBv rises by ~10–30% above baseline during light-to-moderate intensities, peaking near the respiratory compensation point (RCP), then falls toward or below baseline as exercise progresses into the vigorous-intensity domain (250). After the RCP, hyperventilation lowers arterial CO₂, inducing cerebral vasoconstriction that reduces MCAv despite further increases in effort. In contrast, posterior cerebral artery and vertebral artery blood velocities continue to rise beyond the RCP (250), indicating increased activation of the cerebellum and brainstem regions involved in motor coordination and autonomic control (248).

There is limited evidence on the acute cerebral haemodynamic response to aerobic exercise in stroke populations, and investigations have primarily involved chronic stroke patients (>6 months post-stroke) (428–430), with one including patients at both three and six months post-stroke (431). Three studies have assessed responses to steady-state moderate-intensity cycling bouts (45–60% HRR) lasting between 6 and 20 minutes (428,429,431). In addition, one study assessed MCAv responses to vigorous-intensity interval exercise (10 × 1-minute intervals at 70% peak power output interspersed with 1-minute rest periods on a cycle ergometer) (430). Across these studies there is a broadly consistent pattern, where MCAv peaks within the first 2–5 minutes of exercise, followed by either gradual decline despite maintenance of exercise intensity.

Another notable finding is that some stroke patients appear to have a blunted MCAv response to aerobic exercise compared to controls. Using a six-minute cycling exercise bout at 45–55% HRR, Billinger et al., (2021) (431), identified that responders exhibited a ~15% increase in CBv (from 54 to 62 cm/s), peaking at approximately three minutes, before gradually declining, whereas non-responders had no elevation in CBv. The only differences in cohort characteristics were estimated cardiorespiratory fitness and six-minute walk test distance, suggesting that aerobic fitness influences MCAv dynamics.

This finding aligns with Kempf et al., (2019) (428) who also identified a blunted CBv response in a chronic stroke cohort compared with controls during six minutes of moderate-intensity recumbent stepper exercise (45–55% HRR). In the stroke cohort, peak CBv increases were +4.5 cm/s (+11 %) in the ipsilesional hemisphere and +6.4 cm/s (+11 %) in the contralesional hemisphere, compared with +10.9 cm/s (+21 %) in controls.

In contrast, Robertson et al., (2019) (429) reported that 20 minutes of moderate-intensity cycling exercise (45–60 % HRR) elicited an early MCAv peak of +15% in the stroke group and a similar 16% peak in controls, both occurring approximately two minutes after a 3-minute warm-up (absolute CBv values not reported). In both groups, MCAv gradually declined toward baseline over the remainder of the 20-minute exercise bout.

The discrepancy between Robertson's (429) and Kempf's (428) findings may relate to differences in attained exercise intensity between groups despite attempts to standardise this. Robertson et al., (2019) (429) reported that stroke participants exercised at significantly higher heart rates than controls, whereas Kempf et al., (2019) (428) reported that the stroke group had lower heart rate responses than controls. In both studies, ~50% of stroke participants were prescribed beta-blockers, suggesting medication did not account for the divergent results. Discrepancies may also reflect varying impairments in cerebrovascular function or baroreflex sensitivity amongst patients.

The only study to assess vigorous-intensity exercise post-stroke (430) reported a similar biphasic haemodynamic pattern with peak MCAv occurring within three minutes of exercise onset and a gradual decline thereafter. In addition, the MCAv trajectory closely tracked changes in end-tidal CO₂, consistent with studies using incremental exercise tests to exhaustion (250). Peak MCAv values (estimated from figures) were ~60 cm/s (+21% from a baseline of ~50 cm/s) in controls and ~50 cm/s (+17% from a baseline of ~42 cm/s) in the stroke group. Although absolute velocities were lower in the stroke cohort, the relative percentage increase appeared to be similar between groups.

Collectively, the available evidence indicates that people with stroke have an MCAv increase of approximately 4 to 7 cm/s (+11% to +16 %) during moderate-intensity exercise, and one study has reported an increase of +8 cm/s (+17%) during vigorous-intensity interval exercise. The peak CBv response typically occurs within the first 3-5 minutes of exercise and gradually declines toward baseline thereafter or stabilises above baseline. In addition, there is emerging evidence that some stroke patients have a blunted response, although this is not a consistent finding (429). The discrepancies in CBv responses between stroke and control groups are potentially explained by differences in neurovascular function or unmatched exercise intensities.

Acute neurotrophic response to aerobic exercise

Brain-derived neurotrophic (BDNF) is a key growth factor which regulates neuroprotection and neuroplasticity. Aerobic exercise increases the production of BDNF and its release into the blood through numerous mechanisms (discussed above). The

evidence base relating to acute neurotrophic responses to aerobic exercise measured in healthy adults, and people with neurological conditions including chronic stroke is summarised below.

Serum BDNF

A meta-analysis (274) of ten studies of healthy cohorts, and one study with obese adults, concluded that vigorous-intensity exercise acutely increased serum BDNF by an average of 8.35 ng/mL, equating to an approximate 40% increase above normal resting values (432). In contrast, light-intensity exercise had no effect on BDNF. Whilst the overall pooled data indicated an intensity dependent effect, the BDNF response to vigorous-intensity exercise was not significantly different to moderate-intensity exercise.

A closer examination of the studies included in this review suggests that differences in exercise protocols and intensity criteria may have obscured comparisons between moderate- and vigorous-intensity exercise. In three studies which found no difference between moderate and vigorous-intensity exercise responses, intensity was prescribed as a fixed percentage of maximal oxygen consumption ($\dot{V}O_{2\max}$), which may have elicited different metabolic stimuli across participants. In other words, some protocols classified as moderate intensity may have reached vigorous intensity, inducing greater sympathetic activation and, in turn, platelet-mediated BDNF release (and vice versa).

Máderová et al., (2019) (282) reported that in sedentary elderly individuals, a single 40-minute bout of cycling at 65–75% of maximum heart rate (HR_{max}; moderate intensity) induced a 15.6% rise in serum BDNF (pre: 19.2 ng/mL vs. post: 22.2 ng/mL)

Roh et al., (2017) (293) reported that serum BDNF increased significantly from rest after both moderate-intensity cycling at 65% $\dot{V}O_{2\max}$ for 35 minutes (+5.6 ng/mL, +23.3%) and vigorous-intensity cycling at 85% $\dot{V}O_{2\max}$ for 28 minutes (+6.6 ng/mL, +26.6%), but not light-intensity cycling at 50% $\dot{V}O_{2\max}$ for 43 minutes in healthy adults. In addition, BDNF responses were not different between moderate- and vigorous-intensity exercise conditions.

Inoue et al., (2020) (292) reported similar findings with significant increases in BDNF after both 40 minutes of continuous cycling at 65% $\dot{V}O_{2\max}$ (+1.9 ng/mL, +30.6%) and 20 minutes of vigorous-intensity intervals (10 intervals at 100% $\dot{V}O_{2\max}$ interspersed with 1-minute rest periods; +2.3 ng/mL, +23.5%) but no difference between moderate or high intensity exercise protocols. This study compared two separate groups of obese men, and did not use a crossover design, which introduces confounding factors.

Saucedo et al., (2015) (294) also demonstrated that serum BDNF increases after both 20 minutes of moderate-intensity continuous cycling at 70% $\dot{V}O_{2\max}$ (+1.54 ng/mL, +23.8%) and 20 minutes of vigorous-intensity intervals (10 intervals at 90% $\dot{V}O_{2\max}$ interspersed with 1-minute rest periods; +2.26 ng/mL, +37.7%), but that responses to vigorous-intensity exercise were greater than moderate-intensity.

The most robust intensity-dependent response was reported in a study in which exercise bouts lasted for 60 minutes or until exhaustion; Antunes et al., (2020) (291) found that both moderate-intensity (midpoint between the first ventilatory threshold and RCP; +4.62 ng/mL, +16.4%) and vigorous-intensity exercise (midpoint between the RCP and peak power output; +16.87 ng/mL, +63.2%) increased BDNF whereas light-intensity exercise did not (90% of work rate at first ventilatory threshold; +1.46 ng/mL, +4.4%). In addition, vigorous-intensity exercise produced a significantly greater BDNF response than moderate-intensity exercise. The use of metabolic thresholds to set exercise intensity in this study likely enabled more precise control over metabolic stress, reducing inter-individual variability compared with fixed % $\dot{V}O_{2\max}$ approaches.

Collectively these data suggest that vigorous-intensity exercise protocols elicit the greatest BDNF response, but longer duration moderate-intensity protocols lasting at least 35 minutes can also elicit similar responses.

Regarding stroke populations, a recent meta-analysis of single-session aerobic exercise protocols demonstrated an overall acute effect aerobic exercise on circulating serum BDNF, largely driven by vigorous-intensity exercise protocols (273). Of the five studies conducted in the chronic phase of stroke, both light-intensity exercise (25-mins at 50-63% HRmax or 20-mins at comfortable walking speed) and moderate-intensity aerobic exercise (5-mins below 70% maximum HR, 25-mins at 45±5% HRR or 45-mins at

64%–74% maximum HR) did not affect serum BDNF, whereas vigorous-intensity exercise (20-30 mins at >60 HRR up to maximal effort) elicited a large, statistically significant increase in serum BDNF (+2.49 ng/mL). This BDNF response to vigorous-intensity exercise equates to an approximate 21% increase relative to a baseline serum BDNF concentration of ~13 ng/mL reported in acute stroke studies (286).

Although this intensity-dependent trend is consistent with healthy populations, there was one anomalous study. Charalambous et al., (2018) (433) reported that across two different exercise modes (treadmill and total body ergometer), vigorous-intensity exercise resulted in a BDNF decrease of ~1.6 ng/mL. This may be explained by the fact that vigorous intensity was defined as 13-15 RPE and 70-85% HRmax. These RPE and HR ranges span both the moderate-intensity and vigorous-intensity exercise domains (ACSM). Secondly, the exercise bouts only last 5 minutes, whereas other protocols in other studies lasted at least 20 minutes. It is possible that 5 minutes of moderate-to-vigorous-intensity exercise is not a sufficient stimulus to acutely increase serum BDNF concentrations.

Plasma BDNF

Few studies have examined the acute plasma BDNF response to aerobic exercise, and investigations involving stroke patients are lacking. The current evidence demonstrates an intensity-dependent rise in plasma BDNF measured immediately after exercise, with high variability reported across studies. In a landmark study using jugular venous samples from healthy adults (272), plasma BDNF rose from 442 pg/mL at rest to 1172 pg/mL immediately after four hours of moderate-intensity rowing exercise (~165% increase), coupled with an increase in arterio-venous BDNF difference, demonstrating increased BDNF release from the brain. However, this prolonged exercise protocol is likely to be unachievable for untrained individuals. In contrast, shorter duration, moderate-intensity exercise protocols appear to elicit less pronounced changes in BDNF.

In a recent study where healthy adults performed a 45-minute run at $91 \pm 4\%$ of HRmax (vigorous intensity), plasma BDNF increased by ~140% (from 673 pg/mL at rest to 1557 pg/mL post-exercise) (279).

In contrast, Máderová et al., (2019) (282) reported that in sedentary elderly individuals, a single 40-minute bout of cycling at 65–75% of HRmax (moderate intensity) did not influence plasma BDNF (pre: 6.6 ng/mL vs. post: 6.9 ng/mL) despite inducing a rise in serum BDNF (reported above) highlighting differences in BDNF responses between blood compartments, and the potential influence of platelet-derived BDNF on serum measurements.

Gold et al., (2003) (295) reported that 30 minutes of cycling at 60% $\dot{V}O_{2\max}$ increased plasma BDNF by ~35% in people with multiple sclerosis (from ~4.5 to ~6 ng/mL) and ~48% in healthy controls (from ~4.7 to ~6.8 ng/mL) (values estimated from figures).

Gustafsson et al., (2009) (296) investigated sex-specific plasma BDNF responses to graded exercise in patients with major depressive disorder (MDD) compared to age- and sex-matched healthy controls. All participants completed a six-minute sub-maximal cycling bout at ~70% of age-predicted HRmax (moderate intensity) followed by an incremental maximal exercise test. In male MDD patients, plasma BDNF increased significantly from 487 pg/mL at rest to 810 pg/mL (+66%) during sub-maximal exercise and to 1627 pg/mL (+234%) measured immediately after the maximal exercise test. Male controls exhibited a large, significant rise only after maximal exertion, from 223 pg/mL at rest to 1111 pg/mL (+398%). In female MDD patients, BDNF also increased significantly after maximal exertion, from 367 pg/mL at rest to 642 pg/mL (+75%), with no significant change during the sub-maximal exercise bout. Lastly, female controls exhibited large increases at both sub-maximal (+143%) and maximal (+266%) workloads, but neither reached statistical significance.

It is noteworthy that only two of the above-mentioned studies used a two-step centrifuge protocol to minimise platelet contamination (272,279). Since platelets store more than 90% of circulating BDNF (278), even minor contamination can markedly inflate plasma concentrations.

Summary

In summary, aerobic exercise initiated early after stroke has been demonstrated to promote neuroprotection and neuroplasticity in animal models of acute stroke. Aerobic exercise is known to stimulate acute increases in cerebral perfusion and BDNF secretion, and these processes may be important for post-stroke recovery. There is currently a lack of clinical evidence on the cerebral haemodynamic and neurotrophic responses to aerobic exercise in the first few weeks after stroke onset. The available human evidence—derived from various populations including chronic stroke—indicates that both cerebral haemodynamic and circulating BDNF responses are transient and intensity-dependent, with vigorous-intensity exercise generally eliciting the largest increases. There is, however, notable variability in BDNF responses between studies, likely reflecting variations in blood sample preparation, assay methods, participant characteristics, and exercise dose. Similarly, variability in cerebral haemodynamic responses may reflect differences in haemodynamic control mechanisms, including cerebral autoregulation, baroreflex sensitivity, CO₂ reactivity, and neurovascular coupling, which may be disrupted to varying degrees following stroke.

Study rationale

Contemporary stroke rehabilitation guidelines recommend that stroke patients should participate in aerobic exercise as soon as they are medically stable. However, there is a lack of evidence supporting aerobic exercise in the first few weeks after stroke onset (9). This PhD thesis has demonstrated that light- to moderate-intensity aerobic exercise training, using a recumbent exercise bike, is safe to initiate in the acute phase of stroke. In addition, preliminary findings suggest that this intervention may improve post-stroke recovery. The current study seeks to elucidate the haemodynamic and neurotrophic responses to aerobic exercise in the early post-stroke period. Both are key to understanding the mechanisms underlying exercise-induced improvements in stroke recovery observed in animal models of stroke, as well as the preliminary efficacy results presented in Chapter 5. Determining the cerebral haemodynamic response to aerobic exercise is also important in understanding its safety profile during a period when haemodynamic regulation may be in an impaired state.

Methods

Study design

This study employed a repeated-measures design to investigate the acute effects of a single bout of aerobic exercise on cerebral haemodynamics and peripheral BDNF concentrations in participants within 14 days of ischaemic stroke. To assess whether prior exercise sessions may have influenced resting values, an exploratory between-group comparison examined differences in resting peripheral BDNF concentrations between the exercise and non-exercise control groups. Further exploratory analyses examined associations between predictor variables and physiological responses. This is a mechanistic sub-study embedded within a broader feasibility trial; full details of the feasibility study design, recruitment procedures, and eligibility criteria are provided in Chapter 5.

Transcranial Doppler ultrasonography

Middle cerebral artery mean blood velocity was continuously recorded at rest and during exercise using bilateral 2-MHz pulsed-wave transcranial Doppler ultrasound (TCD) probes (Viasys Sonara, Viasys Healthcare Inc., USA). Probe placement is described in Chapter 3. Probes were secured with an adjustable headset to ensure signal stability throughout the session. MCAv was calculated using the following equation:

$$\text{MCAv (cm/s)} = (\text{Peak Systolic Velocity} + [2 \times \text{End Diastolic Velocity}]) / 3$$

Data were recorded continuously and exported for offline analysis. Beat-to-beat changes in MCAv of >10 cm/s, indicative of signal dropout or movement artefact, were removed in accordance with previously published criteria (431).

To aid interpretation of individual responses, a detailed summary of participant-level clinical and haemodynamic characteristics is provided in Table 6.3. Reported variables include demographic information (age, sex), stroke severity (NIHSS score on admission), stroke territory, cardiovascular comorbidities, and anti-hypertensive medications. Exercise responses are reported as percentage heart rate reserve (%HRR), change in mean arterial pressure (Δ MAP), and change in rate–pressure product (Δ RPP).

Blood sampling

Venous blood samples were collected at two time points:

- 1) Baseline (pre-exercise): After at least 30 minutes of rest, at least one hour prior to commencing the exercise session.
- 2) Post-exercise: Within five minutes of exercise cessation, during the cooldown period.

Venepuncture was performed at the antecubital fossa using a butterfly needle, with one 5 mL serum separator tube and two 4 mL EDTA vacutainers collected per time point.

Blood processing and BDNF analysis

Enzyme-linked immunosorbent assay

Brain-derived neurotrophic factor (BDNF) was quantified using the Biosensis Rapid™ BDNF ELISA kit (Cat #: BEK-2211-2P, Biosensis Pty Ltd., SA, Australia), following the manufacturer's instructions (284). Serial dilutions were used to ensure values fell within the assay's detection range (7.8–500 pg/mL). Serum samples were diluted 1:75, and plasma BDNF samples were diluted 1:30. All samples were assayed in duplicate, and the mean concentration was reported. Calibration curves were constructed using serially diluted BDNF standards provided in the kit.

Serum BDNF

Serum separator tube samples were allowed to coagulate for 30 minutes at room temperature, then centrifuged for 10 minutes at 3800 rpm and subsequently aliquoted into cryovials and frozen at –20°C until batch analysis.

Platelet count adjustment

Higher-intensity exercise induces greater sympathetic activation, which can trigger thrombocytosis (an increase in platelet count) (276) as well as platelet activation (278,434). Given that platelets store over 90% of circulating BDNF (278), changes in platelet count can substantially influence measured serum BDNF concentrations. To account for changes in platelet count, blood samples were drawn into EDTA vacutainers

and subsequently full blood counts were performed by a hospital laboratory technician using automated haematology analyser. Serum BDNF was then normalised to platelet count.

Platelet-poor plasma BDNF

EDTA blood samples were centrifuged within 15 minutes of collection. Platelet-poor plasma was prepared using a two-step centrifugation protocol to minimise platelet contamination (283). The manufacturer's recommended protocol is an initial centrifugation at 1500 g for 15 minutes, followed by a second spin at 10,000 g for 10 minutes. However, the centrifuge available for this study (Clinispin Horizon 642e, Drucker Diagnostics, USA) operated at a fixed speed of 2000 rpm (~3800 g). Therefore, after an initial 10-minute centrifugation, plasma was carefully transferred via a Pasteur pipette into a fresh EDTA vacutainer and centrifuged again for 10 minutes at the same speed. The centrifuge lacked a soft acceleration/deceleration function, which has been identified as important for preserving platelet integrity (278).

Control group samples

To help interpret resting serum BDNF values, a control group was included comprising participants from the feasibility study who did not participate in the aerobic exercise intervention. However, as noted in Chapter 5, the control group was older (median age: 82 years [IQR 77–87]) than the intervention group (median age: 66 years [IQR 62–74]). Given the potential influence of age on BDNF concentrations, comparisons should be interpreted with caution. Comparisons with previously published studies are also limited by differences in analytical methods, assay protocols, and participant characteristics.

Aerobic exercise protocol

Middle cerebral artery blood velocity (MCAv) was measured immediately before and during a single aerobic exercise session. Brain-derived neurotrophic factor (BDNF) was measured before and immediately after the same exercise session. All participants were taking part in a broader multi-session aerobic exercise intervention (described in Chapter 5); however, this study was primarily designed to assess acute physiological

responses to a single bout of aerobic exercise. The exercise session was performed using a recumbent in-bed cycle ergometer (MOTomed Letto 2, Reck, Betzenweiler, Germany) and consisted of a 5-minute warm-up, followed by ~30 minutes of aerobic exercise comprising multiple 5-minute active cycling intervals interspersed with 1-minute passive rest periods (motor-assisted), concluding with a 5-minute cooldown.

Exercise intensity was guided by the Borg Rating of Perceived Exertion (RPE) scale (214), with a target of 13/20 (somewhat hard), which approximately corresponding to the first ventilatory threshold (boundary of light- to moderate-intensity). To minimise the likelihood of participants exercising in the vigorous-intensity domain, an upper intensity limit of 60% HRR was imposed. Participants were instructed to exercise at an intensity that elevated their breathing rate while still allowing them to maintain a conversation, but to avoid exercising at a level where speech became difficult due to heavy breathing (233). Cycling resistance and cadence were adjusted throughout the session to maintain the target intensity, taking into account each participant's RPE, breathing response and heart rate. Blood pressure and RPE were recorded during the final minute of each 5-minute exercise interval. Heart rate reserve (HRR) was calculated using the Karvonen method (197), as described in Chapter 5.

Data processing and statistical analyses

Middle cerebral artery blood velocity data were averaged over a three-minute baseline period at rest, excluding the minute immediately preceding exercise to minimise anticipatory effects (431). For inferential analyses, paired-sample t-tests were used to compare resting versus exercise MCAv, which was averaged across the entire active exercise period (from the warm-up to the final exercise bout).

Exploratory analyses were conducted to investigate relationships between systemic and cerebral haemodynamic responses. Middle cerebral artery blood velocity and %HRR were averaged over each five-minute interval including the warm-up and each active exercise period, yielding multiple data points per participant and enabling a linear mixed-effects model analysis. Blood pressure was measured during the final minute of each five-minute interval, and this BP datapoint was aligned with the average change in MCAv and %HRR values for that corresponding interval. As both heart rate and blood

pressure influence MCAv, rate pressure product ($RPP = HR \times SBP$) was also examined as an exploratory variable. Data are presented graphically to aid interpretation of group and individual responses, and to identify outliers.

Changes in BDNF concentrations were analysed using paired-sample t-tests comparing pre- and post-exercise values. Brain-derived neurotrophic factor values were corrected for platelet count by dividing by the number of circulating platelets. Additional exploratory Pearson correlation analyses were used to assess relationships between exercise intensity (%HRR) and changes in BDNF.

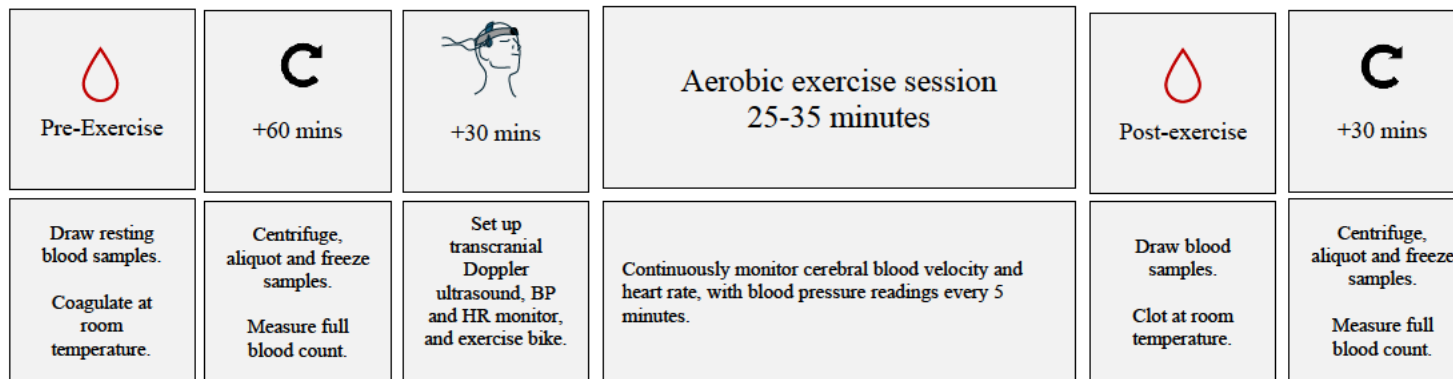
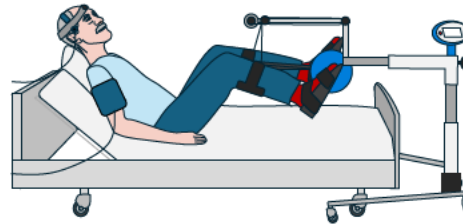


Figure 6.1 Experimental protocol. *BP* = blood pressure; *HR* = heart rate.

Results

Table 6.1. Participant characteristics for transcranial Doppler ultrasound analysis subgroup (n=8)

Characteristic	
Age (years), mean (SD)	65 (6)
Sex, n (%)	
Female	2 (25)
Male	6 (75)
Ethnicity, n (%)	
White	8 (100)
Asian	0 (0)
Black	0 (0)
Mixed ethnic groups	0 (0)
Other ethnic group	0 (0)
Anthropometrics, mean (SD)	
Stature (m)	1.69 (0.13)
Body mass (kg)	90.4 (20.2)
Body mass index (kg/m ²)	31.9 (7.8)
Stroke-related	
NIHSS score, median (IQR)	7.5 (5.3-13.5)
Mild (0-7), n (%)	4 (50)
Moderate (8-15), n (%)	2 (25)
Moderate-to-severe (16-42), n (%)	2 (25)
Prior stroke, TIA or cerebral disease, n (%)	2 (25)
Comorbidities / risk factors, n (%)	
Ischaemic heart disease	1 (13)
Heart failure	2 (25)
Type 2 diabetes	0 (0)
Atrial fibrillation	1 (13)
COPD	1 (13)
Hypertension	4 (50)
Resting blood pressure, mean (SD)	
Mean arterial pressure (mmHg)	106 (16)
Systolic blood pressure (mmHg)	124 (22)
Diastolic blood pressure (mmHg)	77 (9)
Anti-hypertensive medication, n (%)	4 (50)
Independent pre-stroke, n (%)	8 (100)
Days post-stroke, mean (SD)	9.9 (2.6)

Note. IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease. Due to signal loss, data were available for n = 7 (ipsilesional hemisphere) and n = 6 (contralesional hemisphere).

Exercise dose and systemic haemodynamic responses

For participants included in the transcranial Doppler assessment, the mean exercise duration was 30.6 minutes (SD = 4.6; range: 20–35 minutes). The mean exercise intensity was 30.2% HRR (SD = 9.9; range: 17.4–41.5% HRR; light- to moderate-intensity). When expressed relative to maximal heart rate (HRmax), the mean exercise intensity was 60.0% HRmax (SD = 7.3; range: 50.3–68.2%; light- to moderate-intensity). Mean arterial pressure during exercise was 106 ± 12 mmHg, with corresponding systolic and diastolic blood pressures of 147 ± 17 mmHg and 85 ± 11 mmHg, respectively. Group level MCAv and HR responses are reported in Figure 6.2. Individual exercise responses are reported in Figures 6.3 and 6.4, and Table 6.3. Participant's clinical characteristics are also provided in Table 6.3, including comorbidities, medications, stroke type and severity.

Resting versus exercise cerebral blood velocity

Middle cerebral artery blood velocity data were normally distributed in both the contralesional ($W = 0.856$, $p = 0.176$) and ipsilesional hemispheres ($W = 0.878$, $p = 0.220$), determined using Shapiro–Wilk tests. Paired sample t-tests were subsequently performed, which revealed a significant increase in MCAv during exercise in both hemispheres (ipsilesional: +11.27%; contralesional +10.08%) compared to rest (see Table 6.2 below). In addition, Figure 6.2 demonstrates that the peak increase in MCAv occurred 10–15 minutes after initiation of the warm-up, reaching +16.8% in the contralesional hemisphere and +15.3% in the ipsilesional hemisphere.

Cerebral haemodynamics

Table 6.2. Cerebral haemodynamics at rest and during exercise (session averages)

Variable	Rest		Exercise		Mean difference (cm/s)	Mean difference (%)	p	t	Cohen's d	Effect size
	Mean	(SD)	Mean	(SD)						
Ipsilesional MCAv (n=7)	35.77	(10.16)	39.80	(10.07)	4.03	11.27	0.007	2.50	0.94	Large
Contralesional MCAv (n=6)	34.58	(7.41)	38.06	(8.25)	3.49	10.08	0.013	2.57	1.05	Large

Note. Due to signal loss, data were available for n = 7 (ipsilesional hemisphere) and n = 6 (contralesional hemisphere).

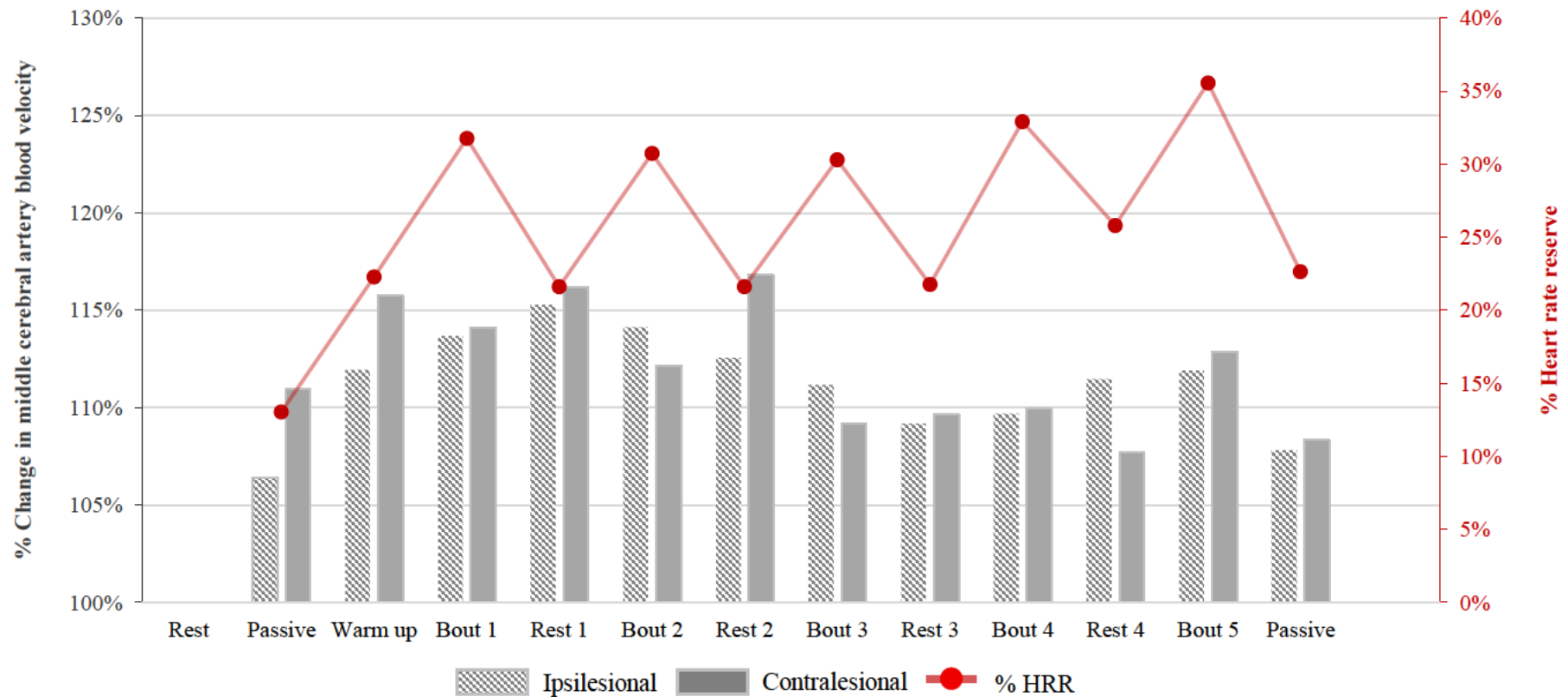


Figure 6.2 Mean exercise intensity (% heart rate reserve) and group-level (mean) cerebral blood velocity response to aerobic exercise session, grouped by 5-minute exercise bouts and with 1-minute rest periods. Solid grey bars = contralesional hemisphere; grey striped bar = ipsilesional hemisphere; red circles with adjoining line = % heart rate reserve. *HRR* = heart rate reserve.

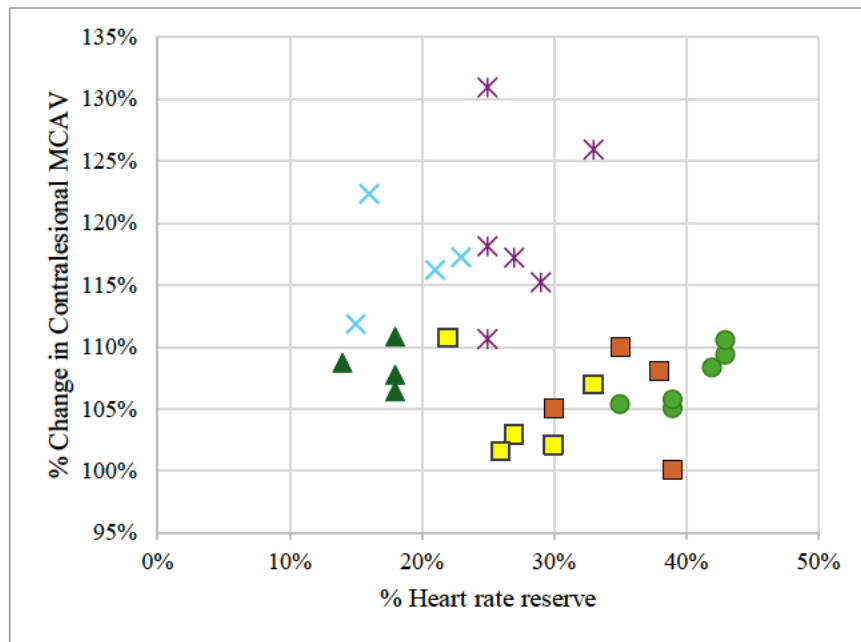


Figure 6.3 Contralateral hemisphere: individual participants' MCAv data averaged over 5-minute intervals, recorded during a single aerobic exercise session.

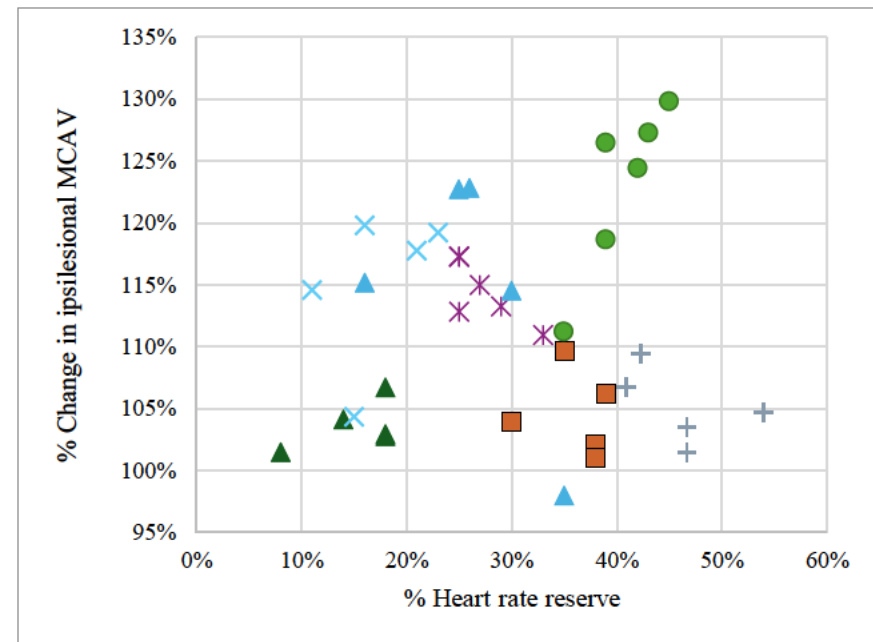


Figure 6.4 Ipsilesional hemisphere: individual participants' MCAv data averaged over 5-minute intervals, recorded during a single aerobic exercise session.

Table 6.3. Clinical characteristics of participants included in the transcranial Doppler assessment

Marker	PID	Age (years)	Sex	NIHSS on admission	Stroke territory	Cardiovascular comorbidities	Resting SBP/DBP (mmHg)	Anti-HTN medication	Exercise response (session average)					
									% HRR	Δ MAP (mmHg)	Δ Rate pressure product (AU)	Δ Contra-lesional MCAv (%)	Δ Ipsi-lesional MCAv (%)	MCAv hemisphere difference (%)
■	5	62	M	6	Right cerebellar	HTN; paroxysmal atrial fibrillation	121/82	Bisoprolol	36.0	13.7	3578.8	+5.8	+4.6	1.2
▲	7	75	M	9	Right multi-territory	HTN; history of thrombophlebitis & venous thromboembolism	133/71	Amlodipine & Doxazosin	17.0	4.2	2870.0	+8.4	+4.1	4.3
✱	9	67	M	2	Left cerebellar	Mild heart failure; history of myocardial infarctions (x4)	110/76	Amlodipine & bisoprolol	27.3	8.8	2900.7	+19.7	+14.4	5.3
+	23	41	F	11	Right PCA, multi-territory	HTN; mild heart failure	166/86	Propranolol	40.6	9.9	3771.0	NR	+4.5	N/A
✕	11	66	M	21	Right MCA	HTN	95/67	None	18.8	16.8	3342.0	+16.9	+15.3	1.6
●	26	62	M	22	Left MCA	None	135/82	None	40.2	15.7	5415.7	+7.4	+23.0	-15.6
▲	30	56	M	3	Left cerebellar	None	126/86	None	36.7	17.2	8121.7	NR	+12.7	N/A
■	17	90	F	6	Right PCA	None	108/62	None	28.0	9.3	2778.0	+4.8	NR	N/A

Note. AU = arbitrary unit; MAP = mean arterial pressure; MCA = middle cerebral artery; MCAv = middle cerebral artery blood velocity; HTN = hypertension; PID = participant ID; PCA = posterior cerebral artery; NR = not recorded; SBP = systolic blood pressure; DBP = diastolic blood pressure; N/A = not applicable.

Relationship between exercise intensity, systemic haemodynamics, and cerebral haemodynamics

Overview of linear mixed-effects models

Linear mixed-effects models were used to assess the relationship between percentage change in MCAv and four potential predictors: percentage heart rate reserve (%HRR), systolic blood pressure (SBP) change, mean arterial pressure (MAP) change, and rate-pressure product (RPP) change. A total of eight independent models were applied (four predictors per cerebral hemisphere), with participant ID included as a random intercept to account for repeated measurements (multiple 5-minute averages recorded within a single exercise session).

Assumption checks

Shapiro-Wilk checks revealed that contralesional MCAv change, MAP change, and %HRR deviated from normality. However, inspection of the residual-versus-fitted plots indicated that the residuals (model errors) were randomly scattered around the fitted values (model predictions). This suggests that the residuals were independent of the predicted values and that the assumption of homoscedasticity (constant variance) was met. Q-Q plots showed that the residuals followed a straight diagonal line, indicating that they were normally distributed.

Linear mixed-effects model results

For both hemispheres, none of the predictors had a statistically significant association with MCAv change in either hemisphere (all $p \geq 0.35$). Coefficients (β) were very small in magnitude, indicating negligible effect sizes. Marginal R^2 values (~ 0.28 – 0.33) indicate the proportion of variance in MCAv change explained by the predictors alone (fixed effects). Conditional R^2 values (~ 0.66 – 0.74) represent the total proportion of variance explained by both the predictors and consistent differences between participants (random effects). These R^2 values indicate that most of the explained variance ($>65\%$) in MCAv change, in both hemispheres, was due to individual participant differences rather than exercise intensity or associated systemic haemodynamic variables. Linear mixed-effects model results are displayed in Tables 6.4 and 6.5 below.

Table 6.4. Linear mixed-effects model results for percentage change in ipsilesional MCAv

Predictor	β	SE	t	p	Marginal R^2	Conditional R^2
SBP change	-3.92×10^{-4}	1.05×10^{-3}	-0.37	0.708	0.282	0.695
MAP change	1.86×10^{-3}	2.03×10^{-3}	0.92	0.358	0.305	0.658
RPP change	-1.01×10^{-7}	8.20×10^{-6}	-0.01	0.990	0.285	0.681
%HRR	-6.72×10^{-3}	1.57×10^{-1}	-0.04	0.966	0.285	0.681

Note. β = fixed-effect coefficient; SE = standard error; Marginal R^2 = variance explained by fixed effects; Conditional R^2 = variance explained by fixed and random effects.

Table 6.5. Linear mixed-effects model results for percentage change in contralesional MCAv.

Predictor	β	SE	t	p	Marginal R^2	Conditional R^2
SBP change	-9.32×10^{-5}	1.05×10^{-3}	-0.09	0.929	0.322	0.740
MAP change	-3.77×10^{-4}	1.07×10^{-3}	-0.35	0.725	0.328	0.735
RPP change	-2.99×10^{-6}	9.00×10^{-6}	-0.34	0.731	0.330	0.729
%HRR	-6.99×10^{-4}	2.20×10^{-3}	-0.32	0.751	0.325	0.742

Note. β = fixed-effect coefficient; SE = standard error; Marginal R^2 = variance explained by fixed effects; Conditional R^2 = variance explained by fixed and random effects.

The acute effects of aerobic exercise on peripheral brain-derived neurotrophic factor

Participant characteristics for the BDNF analysis subgroup are presented in Table 6.6.

Table 6.6. Participant characteristics for the BDNF analysis subgroup

Characteristic	Control group (n=9)	Exercise group (n=10)
Age (years), median (IQR)	82 (77-87)	66 (62-74)
Sex, n (%)		
Female	2 (22)	2 (20)
Male	7 (78)	8 (80)
Ethnicity, n (%)		
White	8 (89)	10 (100)
Asian	0 (0)	0 (0)
Black	1 (11)	0 (0)
Mixed ethnic groups	0 (0)	0 (0)
Other ethnic group	0 (0)	0 (0)
Anthropometrics, mean (SD)		
Stature (m)	1.74 (0.12)	1.71 (0.12)
Body mass (kg)	81.6 (24.2)	90.1 (18.0)
Body mass index (kg/m ²)	26.7 (5.9)	31.0 (7.1)
Stroke-related		
NIHSS score, median (IQR)	9 (6-13)	7.5 (3.8-14.8)
Mild (0-7), n (%)	5 (56)	5 (50)
Moderate (8-15), n (%)	2 (22)	2 (20)
Moderate-to-severe (16-42), n (%)	3 (33)	3 (30)
Prior stroke, TIA or cerebral disease, n (%)	4 (44)	3 (30)
Comorbidities / risk factors, n (%)		
Ischaemic heart disease	0 (0)	1 (10)
Heart failure	0 (0)	2 (20)
Type 2 diabetes	4 (44)	1 (10)
Atrial fibrillation	2 (22)	1 (10)
COPD	1 (11)	1 (10)
Smoker	1 (11)	2 (20)
Independent pre-stroke, n (%)	9 (100)	10 (100)
Days post-stroke, mean (SD)	10 (2.5)	9.7 (2.5)

Resting versus post-exercise serum BDNF

For participants included in the BDNF investigation, the mean exercise duration was 28.3 minutes (SD = 4.7; range: 20–35 minutes), and the mean exercise intensity corresponded to 33.3% HRR (SD = 9.5%; range: 20–45% HRR; light- to moderate-intensity). When expressed relative to maximal heart rate, the mean exercise intensity was 60.6% HRmax (SD = 5.7%; range: 50.9–68.2% HRmax; light- to moderate-intensity).

Normality of the post-exercise change scores in unadjusted and platelet-adjusted serum BDNF concentrations was assessed using Shapiro–Wilk tests. These indicated normal distribution for unadjusted serum BDNF, but non-normal distribution for platelet-adjusted serum BDNF. One outlier (Participant 7) was identified, with a change score far exceeding 2.5 standard deviations above the group mean. This outlier was removed (discussed below), then a sensitivity analysis was conducted. A Shapiro–Wilk test was repeated with the outlier removed, confirming a normally distributed platelet-adjusted dataset. For unadjusted serum BDNF concentrations, Shapiro–Wilk tests indicated normally distributed change scores both before and after removal of the outlier ($W = 0.877, p = 0.121$; and $W = 0.914, p = 0.346$, respectively). Paired-sample t-tests were used to compare resting and post-exercise serum BDNF concentrations (outlier removed), revealing no statistically significant differences for unadjusted ($p = 0.48$) and platelet-adjusted serum BDNF values ($p = 0.49$). Descriptive and inferential statistics for these comparisons are summarised in Table 6.7.

Table 6.7. Resting and post-exercise serum BDNF concentrations

Metric	Rest Mean (SD)	Post-exercise Mean (SD)	Mean Δ	SD of Δ	t	p	Cohen's d	Effect size
Unadjusted BDNF (ng/mL)	14.02 (8.38)	11.36 (6.07)	-2.67	10.70	0.75	0.45	-0.25	Small
Adjusted BDNF (ng/mL per 10^6 platelets)	0.052 (0.023)	0.043 (0.021)	-0.01	0.04	-0.73	0.49	-0.24	Small

Note. Data shown for $n = 9$ participants after removal of one outlier.

Variability in serum BDNF response to exercise

There was substantial between-participant variability in serum BDNF responses to exercise. Figures 6.5 and 6.6 display the individual responses overlaid on box and whisker plots of absolute scores (including the outlier). These figures show that 50% of participants experienced an increase, whereas 50% experienced a decrease in serum BDNF concentrations (unadjusted and platelet-adjusted) following exercise.

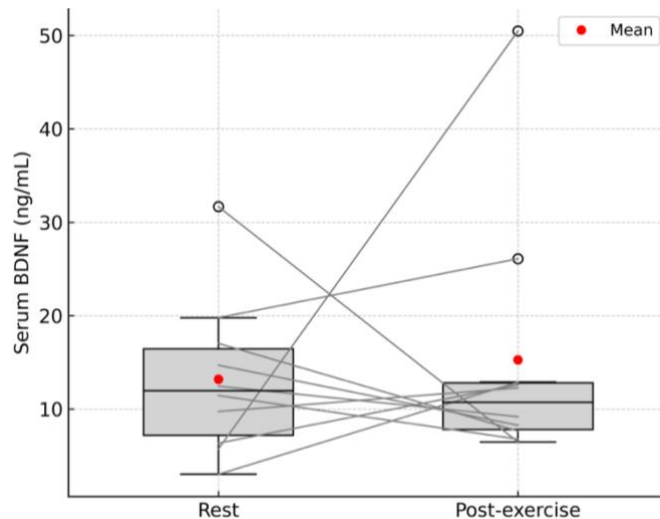


Figure 6.5

Box and whisker plot of *unadjusted serum BDNF* concentrations (ng/mL) at rest and post-exercise, with individual participant change lines ($n = 10$). Horizontal black lines indicate medians; red dots indicate group means, and paired lines display inter-individual variability in BDNF response.

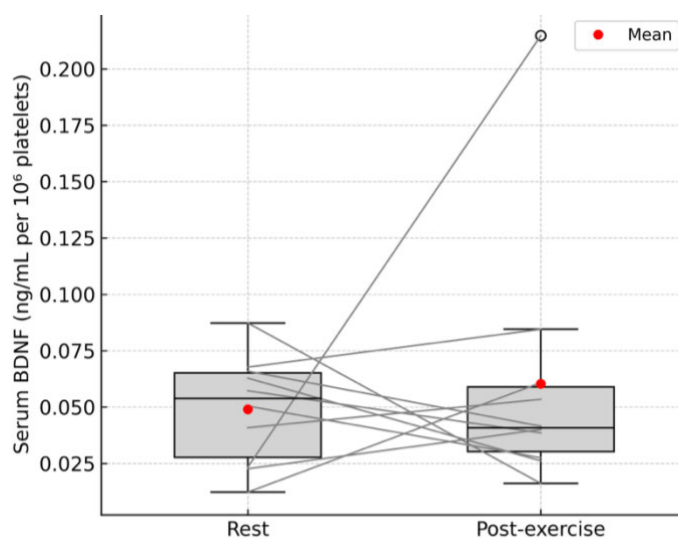


Figure 6.6 Box and whisker plot of *platelet-adjusted serum BDNF* concentrations (ng/mL) at rest and post-exercise, with individual participant change lines ($n = 10$). Horizontal black lines indicate medians; red dots indicate group means, and paired lines

display inter-individual variability in BDNF response. Values were adjusted to account for changes in platelet count.

Correlation between change in serum BDNF concentration and exercise intensity

Pearson's correlation coefficients were conducted (outlier removed) to assess the relationship between exercise intensity (%HRR) and changes in serum BDNF (Table 6.8). For unadjusted BDNF change scores, a moderate positive correlation was found ($r = 0.417$, $p = 0.264$, $R^2 = 0.116$), whereas platelet-adjusted change scores had a weak negative correlation with %HRR ($r = -0.198$, $p = 0.609$, $R^2 = 0.039$). In both cases, the correlations were not statistically significant. See scatterplots below (Figures 6.7 and 6.8) to visualise the relationships between %HRR and serum BDNF changes.

Table 6.8. Pearson's correlation coefficients between exercise intensity (%HRR) and changes in serum BDNF (unadjusted and platelet-adjusted)

Comparison	Pearson r	R^2	p	df
Unadjusted Δ BDNF vs %HRR	0.417	0.116	0.264	7
Adjusted Δ BDNF vs %HRR	-0.198	0.039	0.609	7

Note. df = degrees of freedom ($n-2$). Adjusted BDNF was corrected for platelet count (ng/mL per 10^6 platelets).

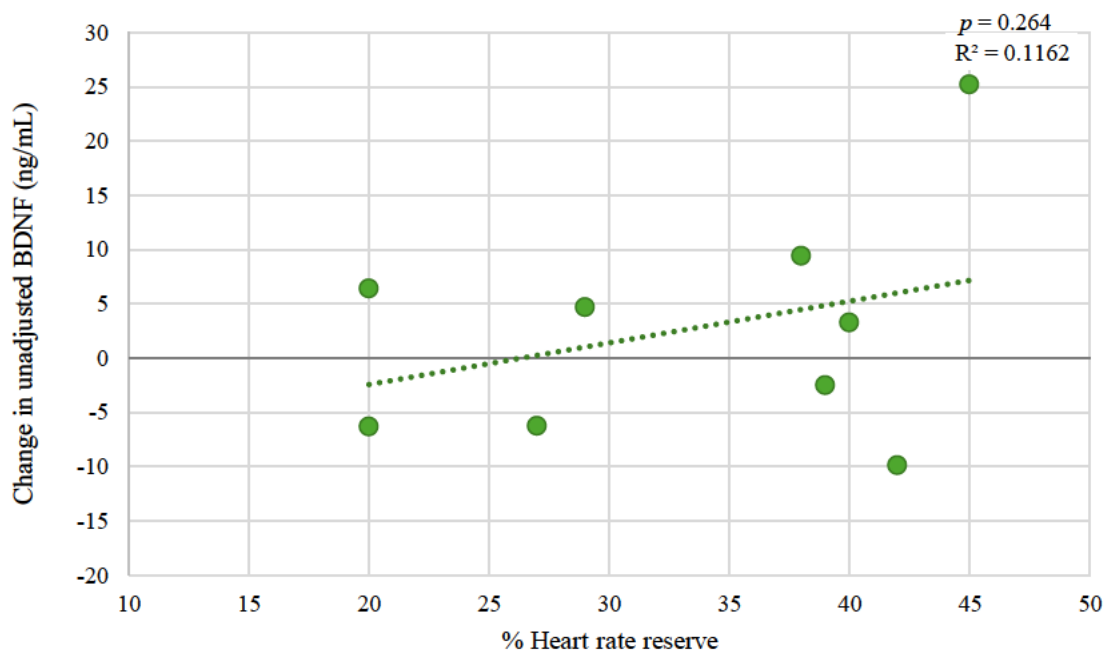


Figure 6.7 Scatterplot displaying the relationship between exercise intensity (%HRR) and the change in unadjusted serum BDNF (ng/mL); $n=9$.

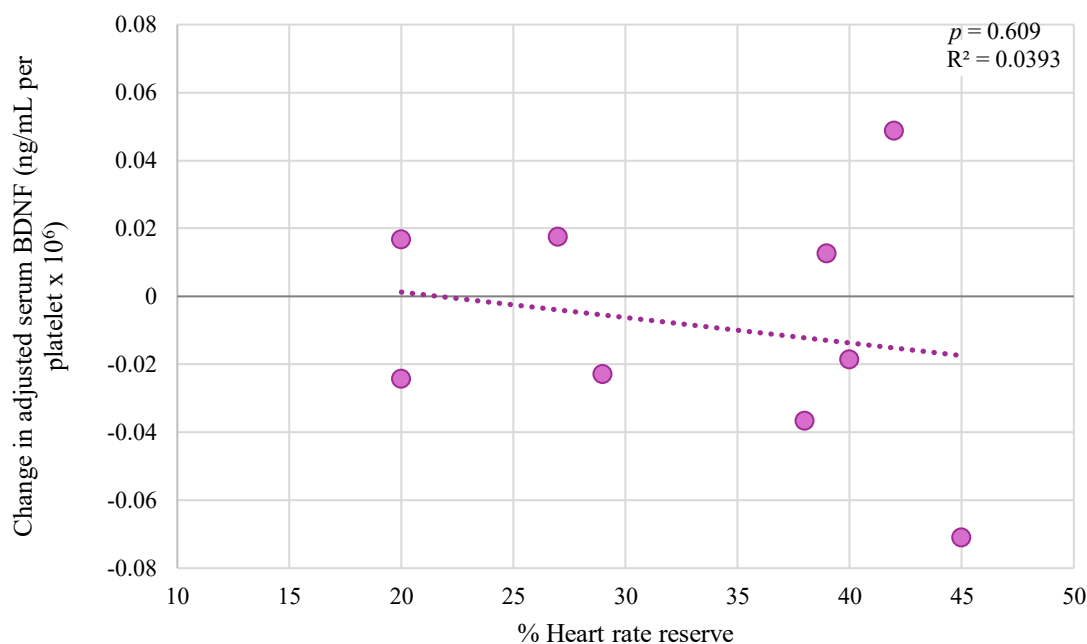


Figure 6.8 Scatterplot displaying the relationship between exercise intensity (%HRR) and the change in serum BDNF adjusted for platelet count (ng/mL per platelet x 10⁶); n=9.

Resting serum BDNF

To explore whether resting BDNF concentrations may have been influenced by participating in the multi-session exercise intervention (described in Chapter 5), resting serum BDNF values from the intervention group were compared with a control group drawn from the broader feasibility trial. In the days prior to blood collection, the intervention group had completed 3.2 ± 0.8 exercise sessions (light- to moderate-intensity). The Shapiro-Wilk tests revealed that both the control group ($W = 0.959$, $p = 0.789$) and exercise group ($W = 0.950$, $p = 0.687$) datasets were normally distributed. An independent samples t-test was subsequently performed which revealed no statistically significant difference ($t = -0.378$, $p = 0.710$) between the intervention group (13.19 ± 8.32 ng/mL) and control group (11.92 ± 6.05 ng/mL). The control group was older (median age: 82 years [IQR 77–87]) than the intervention group (median age: 66 years [IQR 62–74]). As increasing age is associated with lower resting serum BDNF (435), and only one sample per group was taken (single timepoint) this comparison should be interpreted cautiously.

The measured plasma BDNF concentrations were implausibly high. Typically, plasma BDNF levels are 0.5–1% of serum concentrations; however, in the present study, plasma BDNF values exceeded the corresponding serum values in 75% of participants. Several methodological factors may account for this. To obtain platelet-poor plasma, a two-step centrifugation protocol was used, requiring transfer of supernatant between vacutainers with a pipette (283). This handling step may have damaged platelets, which are a major source of BDNF. In addition, the centrifuge lacked soft acceleration and deceleration functions, potentially exposing platelets to excessive g-forces that could cause platelet activation and BDNF release (278). Although care was taken to avoid disturbing the buffy coat (intermediate layer between red blood cells and plasma which contains platelets), turbulence generated during plasma aspiration may have caused platelet contamination. In some cases, the buffy layer was not clearly visible, making it difficult to identify the boundary between plasma and other blood components. In such cases, minor pipetting errors could have resulted in platelet contamination, thereby compromising the plasma samples. Plasma BDNF data were excluded from inferential analyses; individual values are presented in Table 6.9 together with haematological measures.

Table 6.9. Haematological measures and plasma BDNF concentrations with plasma volume correction

PID	HCT Pre- exercise	HCT Post- exercise	Hb Pre- exercise	Hb Post- exercise	%Δ Plasma volume	Plasma BDNF Pre- Exercise (ng/mL)	Plasma BDNF Post- Exercise (ng/mL)	Plasma vol. adjusted BDNF Post- Exercise (ng/mL)
21	37%	31%	12.2	10.4	27.9	24.8	93.6	119.6
7	43%	41%	13.6	13.1	4.0	31.9	13.1	13.6
23	45%	47%	14.7	15.4	-4.5	19.1	16.4	15.7
17	35%	35%	11.9	11.9	0.0	78.3	9.1	9.1
5	46%	45%	15.2	15.4	-1.6	14.1	20.5	20.2
11	45%	45%	15.1	14.8	2.5	15.1	87.6	89.8
30	46%	47%	15.9	15.4	1.9	105.4	8.8	9.0
26	40%	41%	13.8	14.2	-2.4	6.5	15.4	15.1

Note. Values are shown for individual participants. *HCT* = haematocrit; *Hb* = haemoglobin; *BDNF* = brain-derived neurotrophic factor; *PID* = participant ID. Plasma volume correction was applied using the Dill and Costill method (1974).

Discussion

This study provides novel insight into cerebral haemodynamic and peripheral neurotrophic responses to a single bout of aerobic exercise (~30 minutes of light-to-moderate intensity recumbent cycling) performed 10 ± 3 days after ischaemic stroke. The following sections examine the study's findings in relation to existing literature and discuss their relevance for early stroke rehabilitation. The results are also interpreted within the broader context of this thesis, which has investigated the feasibility of aerobic exercise training in acute stroke, and the influence of posture on cerebral haemodynamics.

Cerebral haemodynamic responses

Aerobic exercise elicited a bilateral increase in MCAv of 10-11% averaged across the entire exercise session. Although exercise intensity was relatively stable throughout the exercise session, MCAv displayed a biphasic response, peaking at 15–17% above rest by 10–15 minutes of exercise onset, which then declined slightly and stabilised at around 8–12% above baseline for the second half of the session. The biphasic response in the current study is unlikely to reflect changes in arterial CO₂, as participants exercised at light-to-moderate intensity and were instructed to maintain an effort level that enabled comfortable conversation, which should have avoided hyperventilation-induced hypocapnia. This biphasic temporal profile is consistent with previous studies which demonstrate an early MCAv peak followed by a gradual decline (248,428–431) although other studies tend to exhibit an earlier peak within 2-5 minutes of exercise onset. For instance, Robertson et al., (2019) (429) reported that during steady-state moderate-intensity exercise, MCAv peaked within the first five minutes before progressively returning toward baseline in both chronic stroke survivors and age-matched controls. The delayed peak in the present study could be explained by the use of 5-minute exercise intervals interspersed with 1-minute recovery periods, which disrupted steady-state exercise and may have required more cognitive processing.

The specific brain regions involved in this biphasic response to cycling exercise have been characterised using positron emission tomography (PET) in healthy young adults

(248). In that study, participants performed 13 minutes of steady-state, moderate-intensity exercise. Global cerebral blood flow (CBF) peaked within the first three minutes and subsequently returned to baseline by the end of the session, despite a constant workload and minimal change in end-tidal CO₂ (5-6 mmHg). Regional analyses demonstrated that brain areas involved in motor planning and initiation (supplementary motor area) (436) and proprioceptive feedback and coordination (inferior cerebellum) (437) were highly active during exercise initiation, whereas other regions—including the primary sensorimotor cortex (involved in motor output and sensory integration) and the cerebellar vermis (involved in rhythmic coordination, bimanual motor learning, and cardiovascular regulation) (438,439)—remained active throughout the full exercise bout. The decline in CBF to the supplementary motor area, which is perfused by the MCA, suggests that cognitive processing demands decrease as the motor task becomes more familiar, providing a mechanistic explanation for the biphasic MCAv response measured during steady-state exercise using TCD. Supporting this theory, another PET study demonstrated that imagining cycling exercise (no actual leg movement) increased CBF in supplementary motor area by 13% (440). As described in Chapter 7, participants in the present study reported engaging in mental imagery during cycling, which may have contributed to the sustained elevation of MCAv observed here compared with previous studies reporting an earlier decline in MCAv.

One anomalous MCAv response was identified in the current study. While most participants demonstrated fairly symmetrical MCAv changes between hemispheres (interhemispheric difference range: 1.2% to 5.6%), one individual exhibited a 15.6% interhemispheric difference, with ipsilesional MCAv increasing by +23.0% compared with +7.4% in the contralesional hemisphere. Notably, this was the largest increase in ipsilateral MCAv amongst the study cohort. This individual had an MCA territory stroke, presented with the highest stroke severity of the cohort (NIHSS = 22), and had hemiparesis and expressive aphasia. Interestingly, this participant reported experiencing a dream-like state during exercise (see qualitative findings in Chapter 7). It is unknown if this delirious state was related to altered cerebral perfusion, and the clinical significance of this response is unclear. However, it is noteworthy that this participant exhibited a good recovery, regaining the ability to speak fluently, and progressing from requiring a hoist transfer to mobilising with a walking aid at three months post-stroke.

Another key finding is that MCAv changes were not predicted by exercise intensity or systemic haemodynamic measures including blood pressure and rate pressure product. This finding is consistent with other studies which report a divergence between MCAv responses and systemic haemodynamic responses during sustained sub-maximal exercise (248,429). Figures 6.3 and 6.4 (see Page 194) demonstrate the wide variability in MCAv responses between participants across a wide range of exercise intensities. Collectively, the current study's findings indicate that during light-to-moderate intensity recumbent cycling exercise, cerebral haemodynamic responses are independent of exercise workload and instead may be more strongly influenced by neurovascular coupling.

Neurotrophic responses

Aerobic exercise did not significantly affect serum BDNF levels in either the unadjusted or platelet-adjusted samples. This is likely attributable to the light-to-moderate exercise intensity used in the current study (mean 33% HRR, range 20-45% HRR). The null effect found in the present study is consistent with a recent meta-analysis in stroke populations, which concluded that only vigorous-intensity aerobic exercise protocols produced statistically significant increases in serum BDNF, while light- and moderate-intensity protocols did not (273). It is noteworthy that some healthy population studies have reported that moderate-intensity protocols elicit significant BDNF increases, however these were conducted at 65% $\dot{V}O_{2max}$, which equates to 75% HRmax (195), and is positioned at the boundary between moderate- and vigorous-intensity exercise domains (79). This was considerably higher intensity than the present study ($60.0\% \pm 7.3\%$ HRmax; range: 50.3–68.2%).

The current study intentionally avoided vigorous intensity as part of a broader feasibility trial assessing the safety, acceptability and preliminary efficacy of recumbent cycling exercise in acute stroke patients. The target intensity in this study was moderate, guided by the RPE scale (target 13/20; somewhat hard) (214) and the Talk Test (233). Participants were encouraged to exercise at an intensity where breathing rate was increased, but to avoid heavy or rapid breathing. The rationale for this approach is covered in detail in the Methodology chapter (Chapter 3).

While the use of subjective measures to guide exercise intensity likely led to variable heart rate responses between participants (mean session %HRR range: 20–45%), this presented an opportunity to explore potential intensity-dependent effects on BDNF. However, Pearson’s correlation coefficients revealed no significant association between exercise intensity and serum BDNF responses (unadjusted or platelet-adjusted). Given that the mean %HRR value was 33% which is classed as light intensity, and the maximum value of 45% HRR sits at the lower end of the moderate intensity domain, it is unsurprising that a dose-response effect was not identified. Nonetheless, it was relevant to examine the potential neurotrophic response in an acute stroke population, as this has not been previously reported. Although the null effect is consistent with previous findings in other populations, it still contributes mechanistic insight by indicating that light-to- moderate intensities may be insufficient to elicit a consistent peripheral BDNF response.

Although the primary aim of this study was to evaluate acute responses to aerobic exercise, it was a sub-study of a broader feasibility trial involving multiple aerobic exercise training sessions. To explore whether repeated exercise might influence resting BDNF concentrations, an exploratory cross-sectional analysis (single timepoint) was performed to compare resting BDNF levels between participants in the exercise arm and those receiving usual care. This analysis demonstrated no significant difference in serum BDNF levels between groups. This result is consistent with a recent meta-analysis by Ashcroft et al., (2022) (273) which concluded that light- and moderate-intensity aerobic exercise training does not significantly alter resting BDNF levels in stroke populations, whereas vigorous-intensity interventions elicited higher resting BDNF concentrations.

Plasma BDNF data were excluded from inferential analyses due to artefactually elevated concentrations. This was likely caused by platelet contamination during sample processing. Accordingly, plasma BDNF findings are not discussed further.

Strengths and limitations

A key strength of this study is that it is the first to examine both cerebral haemodynamics and BDNF responses to aerobic exercise in the early subacute phase of stroke (~10 days post-stroke). The comprehensive reporting of exercise intensity further enhances the mechanistic interpretation, including insights into inter-individual variability.

Several limitations should be acknowledged. As this was a sub-study of a broader feasibility trial, the small sample size limits mechanistic insights; this was compounded by data loss due to signal drop-out in TCD recordings and technical issues measuring plasma BDNF. Nonetheless, the large effect sizes observed for cerebral haemodynamic responses suggest that the study was adequately powered for this outcome. By contrast, serum BDNF concentrations were highly variable, and the null finding may reflect insufficient statistical power. A larger sample size may therefore be required to detect an acute effect of aerobic exercise on peripheral BDNF.

Second, TCD is a proxy for cerebral blood flow, and its accuracy relies on the assumption that the diameter of the insonated artery remains constant during exercise. This methodological limitation has been debated (241,441), as arterial CO₂ can influence vascular tone. However, the exercise protocol in the present study was light-to-moderate intensity, where arterial CO₂ changes are expected to be minor. Studies have reported that end-tidal CO₂ typically rises by only 3-8 mmHg at moderate intensity workloads, peaking at the respiratory compensation point (247,248). However, research suggests that larger CO₂ manipulations are required to increase MCA diameter. For example, Coverdale et al., (2014) (242) observed dilation with a +9 mmHg elevation in end-tidal CO₂, while Verbree et al., 2014 (245) reported significant effects only at +15 mmHg hypercapnia.

Third, respiratory gas analysis was planned for this study, but initial attempts to use a Hans-Rudolph facemask alongside a TCD headset was perceived as uncomfortable by participants, therefore this analysis was omitted. To strengthen future mechanistic investigations, a less-invasive technique such as nasal cannula to measure end-tidal CO₂ should be utilised. In addition, the use of an MRI scanner with an integrated exercise

bike could verify whether the MCA diameter changes during aerobic exercise, however, the feasibility of this approach for stroke inpatients is unknown.

Fourth, this study did not have access to a beat-to-beat blood pressure device. Instead, static blood pressure values obtained at the end of each five-minute interval were entered into the linear mixed-effects models to test if blood pressure predicted MCAv. However, this approach could not assess dynamic relationship between blood pressure and MCAv (118).

Fifth, exercise intensity was not standardised using objective physiologic measures (e.g., HR or $\dot{V}O_2$). The subjective methods used in this study (RPE scale and Talk Test) likely contributed to the variability in HR responses. Future mechanistic studies in the early post-stroke period should utilise objective exercise intensity measures to elucidate intensity-dependent effects.

Lastly, the influence of medications on BDNF concentrations was not explored. Evidence suggests that commonly prescribed medications including ibuprofen (pain relief) and clopidogrel (antiplatelet) diminish BDNF release from platelets. In contrast, anti-depressant drugs and ACE-inhibitors (antihypertensive) may increase circulating BDNF (442).

Conclusion

This mechanistic study demonstrates that light-to-moderate recumbent cycling exercise implemented early after stroke increases MCA blood velocity by approximately 10–11% across a 30-minute session. In addition, MCAv peaked at 15–17% above baseline within the first 10–15 minutes and stabilised at 8–12% above baseline thereafter. The biphasic pattern was independent of exercise intensity and blood pressure, suggesting that neurovascular coupling is the primary mechanism driving this response. Aerobic exercise did not influence circulating BDNF, and an exploratory comparison of resting BDNF levels in participants who completed multiple exercise sessions versus a control group revealed no difference between groups.

These findings complement the safety and preliminary efficacy data presented in Chapter 5. An increase in MCAv without adverse events suggests that recumbent cycling is a viable acute stroke rehabilitation option, particularly for patients who have difficulty engaging in conventional activities such as standing and walking. The intervention also shows promise as a method to promote neuroprotection and neuroplasticity, by potentially increasing perfusion to perilesional tissue. This mechanistic data may explain why the intervention group exhibited a superior post-stroke recovery, although a larger study with more detailed imaging methods would be required to confirm this hypothesis. Finally, although circulating BDNF did not increase, the increase in MCAv indicates elevated neural activity, which suggests that BDNF may have been upregulated within the brain even if not detectable in peripheral blood.

Chapter 7 – The Acceptability of Aerobic Exercise Training Initiated in the Acute Phase of Stroke

Background

International clinical guidelines recommend that aerobic exercise training should be a core component of stroke rehabilitation programmes (63,80–82,84) (see Table A1 in Appendix 1). These guidelines also advocate that aerobic exercise training should be initiated as soon as stroke patients are medically stable. However, the evidence underpinning these recommendations is derived from studies conducted in the subacute and chronic phases of stroke (9,386), whereas the safety and efficacy of initiating aerobic exercise in the acute phase of stroke is unclear.

Despite these recommendations, aerobic exercise is not routinely implemented in stroke rehabilitation settings. Surveys conducted in North America indicate that many stroke physiotherapists are ambivalent about implementing aerobic exercise. Therapists are faced with significant time and workforce constraints, leaving little room to implement alternative therapies beyond task-specific motor training (443–445). Prioritisation of functional training over aerobic exercise is also influenced by institutional targets, whereby functional training is incentivised but aerobic exercise is not (444). Further, many stroke rehabilitation services lack suitable exercise equipment (12), therefore people with severe motor impairments are more likely to be excluded from aerobic exercise interventions (445). Beyond resource constraints, therapists often report safety concerns about patients' cardiac health, and many therapists are unfamiliar with clinical exercise guidelines and lack knowledge in aerobic exercise prescription (443–445).

Several facilitators of aerobic exercise implementation have also been reported. Common themes are the need for multidisciplinary collaboration and a workforce culture that prioritises exercise (444). Therapists emphasise the importance of accurate equipment to monitor patients' physiological responses during exercise, and support from physicians to conduct pre-exercise screening. Access to expertise, such as colleagues working in cardiology and cardiac rehabilitation who can assist with pre-participation exercise testing, has also been identified as important. Moreover,

organisational factors such as leadership buy-in, efficient therapy scheduling, and provision of exercise equipment are all regarded as key facilitators. Lastly, there is a need to establish the cost-effectiveness of aerobic exercise training to justify its wider adoption (444).

Although there are several implementation barriers, stroke patients are largely in favour of aerobic exercise as an inpatient rehabilitation method. A Canadian survey (446) revealed that 83% of people with stroke believe that engaging in aerobic exercise is important after stroke, and almost all respondents (97%) believed that aerobic exercise improves post-stroke recovery. Additionally, 91% thought that aerobic exercise should be implemented as part of inpatient rehabilitation, and the median preferred timepoint to begin aerobic exercise was 1.3 days post-stroke. However, patients also reported engagement barriers including fear of falling (59% of respondents), and that physical (53% of respondents) or cognitive (63% of respondents) impairments may hinder participation (446).

Recently, Barzideh et al., (2025) (447) used behaviour change frameworks to explore stroke patients' views on participating in aerobic exercise within rehabilitation facilities. This study demonstrated that stroke patients generally believe that aerobic exercise will improve their recovery. Notably, patients trusted their stroke therapists and were highly compliant with prescribed exercise during their inpatient stay, regardless of the mode of activity (447). However, some patients also noted that feeling weak and fatigued, and having low confidence due to motor disabilities were key barriers to engaging in aerobic exercise.

Another recently published qualitative study conducted in Sweden revealed insight into patients' experiences participating in an aerobic exercise training programme within the subacute phase of stroke. This study reported that patients felt reassured that they were able to exercise without experiencing an adverse event (e.g., recurrent stroke), which increased their self-efficacy to engage in further aerobic exercise. In addition, despite initially fearing that the aerobic exercise would exacerbate their fatigue, the intervention had a positive impact on their energy levels (448).

When interpreting the evidence relating to the implementation of aerobic exercise in stroke rehabilitation programmes, it is important to highlight the current lack of data on the feasibility, safety and efficacy of aerobic exercise training initiated in the acute phase of stroke (discussed in Chapter 5). Despite this, clinical guidelines advocate the provision of aerobic exercise training as soon as patients are medically stable (63,80–82,84). The disconnect between evidence and clinical guidelines likely fuels uncertainty among stroke therapists. Moreover, the available evidence on patient and therapist perspectives on early post-stroke aerobic exercise predominantly stems from North America, highlighting the need to explore perspectives within the UK.

This PhD thesis aims to bridge these evidence gaps. The safety and preliminary efficacy of aerobic exercise initiated in the acute phase of stroke is evaluated in Chapter 5. The current study builds on Chapter 5 by exploring the experiences of stroke patients who participated in an aerobic exercise intervention during their inpatient stay using an accessible in-bed exercise bike. In addition, this study captures the perspectives of therapists working within the same acute stroke ward. By integrating these dual perspectives, this study offers a balanced insight into the acceptability of aerobic exercise in the acute stroke setting and the potential factors influencing its implementation.

Methods

Ethical considerations

This qualitative study was approved as part of a broader feasibility trial investigating the safety, feasibility, and acceptability of aerobic exercise training in acute stroke rehabilitation. Ethical approval for the overall study was granted by Bradford Leeds NHS Research Ethics Committee (IRAS: 280320; REC Reference: 20/YH/0285), and Sheffield Hallam University Research Ethics Committee (Converis: ER25055563). All participants provided informed consent prior to taking part in any study activities. Aphasia-friendly participant information was used where appropriate. Due to the small sample size and the potential for deductive disclosure, the single occupational therapist and therapy assistant, along with physiotherapists, were collectively referred to as ‘therapists’ in the qualitative analysis.

Clinical guideline context

Interviews were conducted in 2021-22, when the 2016 UK National Clinical Guideline for Stroke was in effect (449). These guidelines recommended that people with stroke should receive a minimum of 45 minutes of appropriate therapy per day, encompassing physiotherapy, occupational therapy, and/or speech and language therapy, tailored to individual needs. In addition, the 2016 guidelines include the following recommendations for aerobic exercise:

- People with stroke who are able to walk, with or without assistance, should undergo task-specific walking training with a cardiorespiratory and/or muscle strength focus at an intensity sufficient to improve endurance and walking speed.
- People with stroke, including those who use wheelchairs or have limited mobility, should be advised to engage in exercise aimed at improving aerobic fitness and/or muscle strength, unless contraindicated.

Although the 2016 guidelines did not specify a precise timeframe for initiating aerobic exercise, they noted that “both early and late after stroke, people benefit from time spent in task-specific, walking-orientated leg exercises which have a cardiorespiratory focus.”

Study design and participants

A qualitative design was employed to assess the acceptability of a five-session, in-bed cycling-based, aerobic exercise intervention delivered in a UK acute stroke unit (See Chapter 5 for detailed overview of methods). Semi-structured, one-to-one interviews were conducted with stroke patients (n=9) and a group of stroke therapists (n=6) comprising four physiotherapists, one occupational therapist, and one therapy assistant. Interviews with stroke patients focused on the acceptability of the intervention, and their experiences participating in the broader feasibility study (Chapter 5). Therapist interviews also explored the acceptability of the intervention, with a focus on perceived effectiveness and the feasibility of implementation. Convenience sampling was used to recruit both stroke patients and therapists.

Interview procedures

Semi-structured interview topic guides were designed for stroke patients taking part in the intervention and therapists working within the acute stroke ward (who could potentially deliver the intervention). Stroke patients were interviewed within seven days of participating in the intervention, whereas therapists were interviewed toward the end of the trial. All interviews were conducted in a quiet room, free from distractions. Interviews were conducted by the same researcher (NK), who also delivered the intervention, using open questions designed to encourage critical feedback. Interviews were recorded using a Dictaphone, and verbatim transcripts were generated by a professional transcription company. The interview topic guides are located in the Appendix 7.

Data analysis

Qualitative interview data were analysed using thematic analysis (174). In line with this PhD thesis' pragmatic orientation, a hybrid analytic approach was adopted, recognising that both theory-driven and data-driven insights can generate useful knowledge (450). The deductive approach using the Theoretical Framework of Acceptability (TFA) (173) ensured alignment with established constructs of acceptability, whereas inductive coding enabled the identification of salient patient and therapist experiences which may not be captured by the TFA framework. All transcripts were read in full to ensure familiarity with the data. Line-by-line coding was then conducted manually by NK, mapping onto the seven TFA domains. To ensure rigour and consistency, a subset of transcripts was independently coded by two other qualitative researchers (HH & RY). Coding discrepancies were discussed and resolved through consensus. A researcher reflexivity section is provided below.

Table 7.1. Theoretical Framework of Acceptability domains and descriptions

Domain	Description
Affective Attitude	Feelings about the intervention (e.g., enjoyment or dissatisfaction).
Burden	Effort required to participate in the intervention.
Ethicality	Alignment of the intervention with personal values and beliefs.
Intervention Coherence	Understanding of the intervention's components and how it works.
Opportunity Costs	Perceived trade-offs or sacrifices compared to alternative uses of time/resources.
Perceived Effectiveness	Belief in the intervention's ability to achieve its intended outcomes.
Self-Efficacy	Confidence in one's ability to engage with and complete the intervention.

Researcher reflexivity

I am a Research Fellow, PhD Student and registered Clinical Exercise Physiologist with research interests in designing and evaluating exercise interventions for clinical populations. My previous roles in public health involved delivering lifestyle education using behaviour change techniques, which gave me experience in asking open, non-leading questions, and being able to build a rapport with patients. In addition, I undertook training in interviewing techniques before collecting data. Collectively, these experiences enabled me to conduct interviews with a neutral stance. However, my educational and professional background, which have centred around the use of exercise to improve health and performance, may have shaped unconscious biases about the value of exercise in rehabilitation.

Although not acting in a clinical capacity, my role in delivering exercise sessions and conducting assessments (e.g., ultrasound and venepuncture) while wearing clinical uniform may have fostered a ‘clinician–patient’ relationship (451). Participants may have perceived me as supporting their recovery at a time when many were experiencing a significant loss of independence. Participants were also aware that the study formed part of my PhD, which may have created a sense of obligation to contribute. Through daily interactions during exercise sessions, I not only supported participants in achieving progress but also provided opportunities for social connection at a time that could otherwise feel very isolating. This was particularly relevant given that COVID-19 restrictions had limited visiting opportunities, potentially heightening feelings of loneliness. Taken together, this relational dynamic and the broader hospital context may have shaped how participants engaged with me and how they responded during interviews. For example, this may have led to a social desirability bias, whereby participants responded to interview questions in ways that they believed would be viewed favourably.

To mitigate these potential influences, I was transparent that the primary purpose of the study was to generate knowledge and refine the intervention for the benefit of future patients. I also emphasised to participants that, due to the novelty of the intervention, its risks and benefits were not yet fully understood, while reassuring them that they would be closely monitored throughout exercise sessions. By highlighting these unknowns, I aimed to facilitate a critical dialogue, encouraging participants to share both positive and negative feedback. In addition, by using open questions, probing for more in-depth responses, and employing reflections and summaries, I sought to obtain a rich account of participants’ experiences, and minimise ambiguities.

To enhance analytical rigour, a random sample of interview transcripts was independently coded by HH and RY. Both the organisation of deductive codes within the TFA domains and the positioning of inductive codes outside the TFA framework were reviewed by both researchers, and any discrepancies resolved through consensus discussions.

HH is a Senior Research Fellow specialising in physical activity interventions underpinned by behaviour change theories, participatory approaches, and human-

centred design. HH's expertise in interviewing methods and behavioural science provided valuable insight into the interpretation of participant accounts. RY is a Principal Research Fellow and Chartered Physiotherapist with expertise in neurological rehabilitation and exercise prescription, whose clinical background may predispose her to view exercise positively; however, her expertise in qualitative methodologies helped ensure that data were analysed with appropriate rigour. Both HH and RY contributed as independent coders and participated in consensus discussions, bringing different disciplinary perspectives that constructively challenged my interpretations. The independent coding and consensus discussions enhanced the credibility and trustworthiness of the findings.

Results

Nine out of the 15 intervention group participants were interviewed after participating in the intervention. Six participants were not interviewed for the following reasons: discharged from hospital (n=3); illness (n=1); withdrawal due to study burden (n=1); and expressive aphasia (n=1). Demographic and clinical characteristics of the interviewed stroke patients are presented in Table 7.2. Six therapists were interviewed toward the end of the feasibility trial, including four physiotherapists, one occupational therapist, and one therapy assistant. To protect therapists' anonymity, no demographic or professional information has been reported. All interviews lasted for between 20 to 40 minutes. Stroke patient participant characteristics are displayed in Table 7.2 below.

Table 7.2. Stroke patient participant characteristics (n=9)

Characteristic	Value
Age (years), median (IQR)	65 (62-73)
Sex, n (%)	
Female	3 (33)
Male	6 (67)
Ethnicity, n (%)	
White	9 (100)
Asian	0 (0)
Black	0 (0)
Mixed ethnic groups	0 (0)
Other ethnic group	0 (0)
Anthropometrics, mean (SD)	
Stature (m)	1.73 (0.11)
Body mass (kg)	88.2 (21.2)
Body mass index (kg/m ²)	29.4 (7.3)
Stroke severity (NIHSS score), mean (SD)	8.3 (6.7)
Mild (0-7), n (%)	5 (56)
Moderate (8-15), n (%)	2 (22)
Moderate-to-severe (16-42), n (%)	2 (22)
Prior stroke, TIA or cerebral disease n (%)	5 (56)
Comorbidities / risk factors, n (%)	
Myocardial infarction history	1 (11)
Mild heart failure	2 (22)
Type II diabetes	2 (22)
Smoker	1 (11)
Independent pre-stroke, n (%)	9 (100)
Timepoint of first exercise session (days post-stroke), mean (SD)	5.1 (1.8)
Number of exercise sessions completed, mean (SD)	4.3 (0.9)

Note. NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischaemic attack.

Affective attitude

This domain explores how patients and staff feel about the intervention.

Stroke patient perspectives

Stroke patients reported positive experiences about the aerobic exercise intervention, noting introduced structure, routine, and a sense of purpose to their inpatient stay, helping counteract the monotony of hospitalisation.

Participant 17: It made me feel that I was being useful, I wasn't just laid here waiting for the end.

Participant 30: It gave me something to look forward to doing and I know it was doing me good.

People with acute stroke valued the social and cognitive stimulation from participating in the study and engaging with the researcher.

Participant 21: ... for you to come along and give me something to concentrate on where I can be useful is what I'm trying to say, that was a good feeling...

Participant 5: It's always nice when someone comes, "Sorry, to wake you". I'm generally not asleep, I'm generally just closing my eyes because I can't see properly and I'm listening to the radio...I'm happy to see people.

Some stroke patients commented on the challenging nature of exercise sessions, framing the effort as an achievement which was motivating:

Participant 17: There was times when the back of your leg felt a bit tired and you thought, well that's the reason for doing it, so keep going.

Other stroke patients appreciated the encouragement and feedback provided by the researcher which increased their motivation to exercise.

Participant 30: I think whoever takes on that bike has got to be at one with you...I think when you're talking to somebody and saying come on you've got two minutes to go. Right, keep your speed at that...it kept it interesting. I was trying to look and keep my speed at between 70 and 80 and "you're doing good"...where you say "you're doing really well", it makes you go for it even more.

People with acute stroke also found the objective feedback about cycling distance, resistance and duration to be motivational.

Participant 23: I just wanted to go further, I just wanted to push more, and that's why I say can you turn it up [the cycling resistance], because I always wanted to try, better myself than what I did before.

After completing the intervention, one stroke patient expressed disappointment because he perceived the intervention as beneficial and this had been taken away.

Participant 05: Just that bit of time, just them five or six sessions what we've done. It's helped me in a lot of ways. Now there's really nothing to look forward to, now it's finished. At least if I was doing it once a day.

Therapist perspectives

Although therapists were not directly involved in the delivery of the intervention, they all observed some aerobic exercise sessions on the acute stroke ward. When asked about the intervention, their responses were mainly objective, focusing on evidence and practical considerations rather than using emotive language. As a result, therapist data were not included in the analysis of the affective attitude domain.

Perceived effectiveness

Perceived effectiveness refers to the extent to which the intervention is believed to achieve its intended outcomes. When recruiting participants to this study, stroke patients

were informed that the intervention may improve their recovery, but the safety and effectiveness of aerobic exercise are unknown. Stroke patients were asked open questions about the potential positive and negative effects of the intervention.

Perceived psychological effects

Beyond the psychological benefits mentioned in the affective attitude section (e.g., purpose and routine), stroke patients mentioned that taking part in the intervention enhanced their mood and induced a feeling of vitality.

Participant 30: It was good for my physical health, but really good for my mental health while being in hospital. Because I'd been down, it took my mind off everything and it's been really good to take part in it.

Participant 05: You feel good about yourself. I felt better. I felt like I'd given myself a shake, a stir. ...I feel like it was worthwhile doing, because it makes you physically feel more activated.

Therapists also noticed improvements in mood, which was perceived to have positive knock-on effects on motivation to engage in usual care therapy.

Therapist 1: The fact that they're moving is good. So by default they think it's really positive, which obviously has a really good knock-on effect on their general mood and then their ability or desire to want to engage in other therapy. Anyone who's happier is going to engage in stuff much better...low mood is one of the biggest factors that contribute to our patients declining.

Therapist 2: they're able to see their own progression, which then probably links in with helping to motivate them, which is always a big factor in rehab.

Perceived physical effects

There was a divergence in opinion amongst stroke patients and therapists about whether aerobic exercise would help or hinder motor recovery. One physiotherapist highlighted a general concern that therapists have about neurorehabilitation:

Therapist 3: Some therapists really don't like any movement that's not moved and controlled and perfectly aligned... the risk is that you're allowing them to over-use their good side and they're not encouraged to push and use their weak side because they haven't got the power or they can't.

This view was echoed by another therapist who questioned the suitability of aerobic exercise for motor recovery, expressing concerns about compensatory movements and suboptimal movement quality.

Therapist 4: We'd just have to be very much aware and choosing the patients appropriately so we're not reinforcing bad patterns of movement.

One therapist explicitly stated that aerobic exercise was not relevant for motor recovery, but acknowledged potential benefits to cardiorespiratory fitness.

Therapist 1: Ultimately, the goal is to get them out of this environment and get them home. If the bike is just improving physiological outcomes, exercise tolerance, ability to do those kind of things, that doesn't directly link to actual tangible functional things like walking, like their ability to sit up, or their ability to get in and out of bed themselves, which ultimately is what a patient wants.

In contrast, other therapists perceived that cycling-based aerobic exercise could be beneficial for motor recovery.

Therapist 5: For me most movement is good movement. There'll be a school of thought of like it needs to be good quality and efficient and effective and in a normal pattern...And I certainly would try and achieve that. But if a patient can move, help them move in a best quality. But stopping people moving because, or being too strict about that is not helpful in my opinion.

Therapist 2: I think this is more functional for patients than basic exercises...If I [a patient] can cycle, I've [the patient] got a better chance of walking, rather than doing knee extension exercises.

The therapist consensus was that priority is given to task-specific training which is perceived to be a more relevant rehabilitation method to improve motor recovery.

Therapist 5: My initial go-to thought wouldn't be about aerobic exercise. It would be about motor control and improving muscle function or power, or coordination.

Time and staffing shortages were frequently reported as significant barriers to incorporating aerobic exercise into stroke rehabilitation. Therapists emphasised that, given the prioritisation of task-specific training, robust evidence demonstrating the benefits of aerobic exercise was needed to justify its implementation. For instance, one therapist noted:

Therapist 4: If there's really good evidence base we're more likely to invest time into something like that.

However, another therapist highlighted that even with compelling evidence, additional staff would be needed:

Therapist 1: If there's evidence for it, then fine. But ultimately in practice, even if there was a massive amount of evidence, we would need extra bodies

Several stroke patients were convinced that the aerobic exercise intervention improved their motor function.

Participant 10: It were useful for me because of my foot, my leg being dead...I could tell the difference in my leg.

Participant 17: ...we walked round the corner and just to feel the movement of your legs on the floor, I thought oh that bike did me good.

Participant 09: It has helped me, because it's kept my legs going and my muscles going.

This sentiment was supported by one therapist who observed an improvement in one individual's motor function, but recognised that it would be difficult to determine causality due to the possibility of spontaneous recovery.

Therapist 5: There was one gentleman who fed back that after he'd had his sessions with the bike that he felt like actually he had got some return in activity back. And which again was then mirrored in like our assessment that there was. And whether that was just a chance thing because obviously there is some spontaneous recovery isn't there.

In summary, aerobic exercise was uplifting for most stroke patients and increased their motivation to engage in usual care therapy. Multiple stroke patients perceived that aerobic exercise training improved their motor function. However, there was a clear divide in opinion amongst therapists regarding the use of aerobic exercise in acute stroke rehabilitation. Some therapists suggested that aerobic exercise could hinder motor recovery, whilst others believed that it could be a valuable adjunct to usual care therapy. It was widely acknowledged by therapists that the primary goal was to help stroke patients regain sufficient motor function to be discharged from hospital, and task-specific training was the preferred therapy method to achieve this goal. In addition, it was highlighted that stronger research evidence and increased investment in staffing are needed to support the uptake of aerobic exercise in an acute stroke ward setting.

Intervention coherence

Intervention coherence reflects an individual's understanding of the intervention and how it might work (i.e., mechanisms of action). During the study recruitment process, stroke patients were given information about the aerobic exercise protocol, and how aerobic exercise may promote neuroprotection and neuroplasticity. More specifically, the participant information sheet (PIS) highlighted that in animal studies, early-initiated aerobic exercise led to smaller brain lesions and improved neurological recovery. In addition, the PIS outlined that one potential mechanism which is thought to improve recovery is an acute increase in cerebral blood flow during aerobic exercise. Therapists

were also presented this information as part of a site initiation visit, and copies of the PIS were given to the therapy team. As this was a phase II feasibility study, it was emphasised to stroke patients and therapists that the evidence base is limited and the effects of aerobic exercise in the acute phase of stroke in clinical populations are unknown.

The intervention coherence section is split into two sections: 1) understanding of the intervention components (stroke patients only); and 2) understanding of the mechanisms of action (i.e., how the intervention might work [stroke patients and therapists]).

Patients' understanding of the intervention components

Session structure

Most stroke patients demonstrated a clear understanding of the intervention components, recognising that sessions involved five moderate-intensity interval training sessions, and that each sequential session gradually increased in duration. The use of five-minute exercise intervals, which the researcher referred to as 'hills', inadvertently encouraged some stroke patients to practice mental imagery which enhanced their motivation and evoked a competitive spirit.

Participant 05: The whole of your body is working really. I know it's your legs, but your mind's working because you're thinking about the hills...Last big push. Top of the mountain, let's get there.

Participant 30: Get up to the top of that hill, you can do it, kick it up a bit.

The brief one-minute rest periods in between exercise intervals were seen as a useful psychological and physical break which encouraged stroke patients to continue exercising.

Participant 17: You felt you'd had enough really and then you had this little rest and then oh come on let's go again.

Participant 21: So you had a minute when you can think, what's happening? Where am I up to? And reset yourself, it was a good reset period rather than rest. Mental reset. Physically it's not long enough to make a massive change, but mentally it was helpful.

Stroke patients also understood that the progressive duration of each exercise session was designed to gradually challenge them.

Participant 10: as each session went on it was getting that bit harder, because my legs were tired obviously but it was getting that bit harder. But I was prepared to try and do it, as much as I could.

Exercise intensity

Exercise intensity was guided using two subjective methods: the Rating of Perceived Exertion (RPE) scale (214) and the Talk Test (233). The RPE scale required stroke patients to select a number or a corresponding descriptor, on a scale from six (complete rest) to twenty (maximal exertion). The Talk Test complemented this by assessing changes in breathing patterns and how this affects the ability to talk comfortably. Stroke patients were asked to exercise at an intensity equivalent to 'somewhat hard' or 'moderate' (13 out of 20). In addition, stroke patients were asked to find an intensity where their breathing depth or rate is increased but they are still able to talk, and to avoid 'hard' exercise where it would be difficult to talk due to fast, heavy breathing. This was a collaborative process where the researcher encouraged stroke patients to gradually increase their exercise intensity (cycling resistance and/or cadence) until they felt sufficiently challenged.

Stroke patients generally understood the intensity guidance, though initial sessions involved a familiarisation process. For example, one individual described:

Participant 17: I think at first I wasn't quite sure, but I got the hang of what you were wanting... And at first I just thought it was, oh this is nice but gradually it did mean an effort and I thought that was the purpose.

Another stroke patient reflected how their perception of moderate intensity changed as the intervention progressed.

Participant 21 - After a few sessions you don't rely on someone else to make that explanation clearer...I'm now beginning to establish in my own mind what moderately difficult means without someone else trying to. Like how the heck could you explain to me what moderately hard means?

The Talk Test was seen as a more intuitive approach to gauge exercise intensity compared to the RPE scale, allowing real-time self-monitoring of effort.

Participant 05: The thing you said to me was that you could still carry on a conversation if you had to. And all the time I was doing it I was thinking yeah, I could do that. If you asked me questions now, I could answer them. I wouldn't be struggling to speak... Right, I'm feeling tired. Right, now I'm going to have a minute to recover, so I can keep going at this. I'm checking my breathing, my breathing's OK. Yeah, keep going, keep going.

Intervention coherence: understanding of the mechanisms of action (stroke patients and therapists)

People with acute stroke perceived that aerobic exercise was beneficial to help offset deconditioning and promote recovery.

Participant 9: it has helped me, because it's kept my legs going and me muscles going

*Participant 17: I wasn't just laid here waiting for the end...I **would** get better, my legs **would** walk, they'd **have** to walk and that was the aim (bolded to emphasise voice inflections).*

One stroke patient conveyed that aerobic exercise was a whole body and mind stimulus, differing from conventional physiotherapy which caused dizziness.

Participant 30: I've had a stroke, I'm dizzy trying to walk with physios, but that's different. It's a different exercise. The whole of your body is working really [when cycling]. I know it's your legs, but your mind's working because you're thinking about the hills.

As discussed in the perceived effectiveness section, therapists had mixed views on how the intervention might work. Some perceived that aerobic exercise is not relevant for motor recovery and that it could worsen neuromuscular deficits. Whereas other therapists thought that cycling exercise could contribute to the recovery of walking function, favouring a 'more movement is better' approach. Only one out of six therapists mentioned a potential physiological mechanism by which aerobic exercise could improve motor function. This therapist described the concept of priming—a preparatory activity that increases the excitability of the neuromotor system, which if paired with a functional task may enhance skill acquisition:

Therapist 5: after doing that recent MSc module, that was about aerobic exercise and the benefits of that in driving neuroplastic change. So seeing that, would be really interesting to me as could I use that as a primer to a session.

In summary, stroke patients demonstrated a clear understanding of the intervention components. They valued the interval training design, as it enabled the achievement of manageable goals facilitated by short rest periods. Exercise intensity was guided by the RPE scale and the Talk Test. These subjective tools allowed stroke patients to self-select an appropriate exercise intensity, aiming for "somewhat hard" or "moderate", where breathing effort is increased but carrying out a conversation is still possible. The use of the Talk Test was easier to grasp, whereas some stroke patients commented that using the RPE scale was initially challenging, requiring familiarisation. Participants described a collaborative process between themselves and the researcher to identify a suitable exercise workload. The intervention was generally seen by stroke patients as a way to mitigate deconditioning and support motor recovery through keeping physically active. However, therapists had mixed views—some questioned the relevance of aerobic exercise to motor recovery, whereas others believed that it could be beneficial.

A notable discrepancy was that one stroke patient described a dissociative, dream-like state during exercise. This individual had the highest stroke severity of the interviewed

cohort (baseline NIHSS = 21; mRS = 4), had successful reperfusion therapy (complete occlusion of the left middle cerebral artery, with a favourable core-penumbra mismatch ratio), and had a favourable recovery at three months post-stroke (able to walk with assistance, and regained fluent speech).

Participant 26: I was taken back into like a dream world when I was on the bike...I was on t' bike but I didn't seem to be on t' bike... I haven't got an explanation for it...It was like blank, being took somewhere if you like. Just like a spell.

Ethicality

Ethicality reflects the extent to which the intervention aligns with a participant's value system. A person's value system can be regarded as an ethical compass which drives their choices and behaviour (452). A person is more likely to engage in an intervention if it is a 'good fit' with their value system (173).

Interpreting the ethicality domain in this study is complex due to participants' recent experience of a life-altering, disabling event and confinement to a hospital ward. The abrupt transition from being highly independent to becoming a vulnerable inpatient reliant on medical care, can result in a loss of identity and personal agency (453). One's pre-stroke identity could be viewed as a manifestation of their personal values; therefore, participating in an intervention aimed at restoring pre-stroke function may closely align with a person's value system. This section only focuses on patients' perspectives, as therapists did not refer to ethicality during interviews.

The monotony of the hospital ward led to stroke patients feeling idle, lacking daily structure and goals. The aerobic exercise intervention was an escape from this, with some participants expressing a desperation and relief toward taking part in the intervention and making progress.

Participant 5: I just thought, I'm laid in bed all day. I can't get up, I can't do anything. I'd have done anything, any exercise at all.

Participant 10: I'll do anything to help get me legs and me arms back together.

Other stroke patients reflected how the exercise intervention reminded them of their younger selves which promoted enjoyment and rekindled a competitive spirit:

Participant 30: I thought, come on, we'll make it. It's from being younger, isn't it, playing football and doing sport at school and all that. You have a goal and you say, do this. Right, I'll do it. If you've done sports and that at school you understand and it's the same with that hill. Come on, get up to the top of that hill.

Participant 20: I loved it, it took me back to my childhood.

Lastly, taking part in research afforded stroke patients the opportunity to feel useful and help others, which may have aligned with altruistic values.

Participant 09: I thought if it were going to help anybody else, it'd be a good thing.

Participant 10: I felt good. I felt as though I'd done something. So I'd helped something and I'd done something for me as well.

Self-efficacy

Self-efficacy reflects the participant's confidence that they can perform the required behaviour. This domain explores the stroke patients' perceived ability to take part in aerobic exercise, as well as therapists' perceived ability to deliver aerobic exercise.

The exercise intervention involved the use of a specialised in-bed exercise bike designed for hospitalised people with neuromuscular deficits. This equipment enabled the inclusion of non-ambulatory stroke patients, and individuals who lacked sitting balance or had orthostatic issues such as vertigo. The accessible exercise equipment inspired confidence in stroke patients that they were capable of exercising.

Participant 01: When I first went in I thought, oh I've only got one leg... but it was just like normal...that was unbelievable.

Safety was identified as an important factor influencing stroke patients' self-efficacy. The close supervision instilled confidence that it was safe to exercise.

Participant 21: because you were at the side of me and I felt that if I was overdoing it you'd tell me and bring me back. So that's why I felt safe on it, I wasn't in danger of over exercising because you would have pulled me back, because you were checking my blood pressure and things like that and the heart rate.

Participant 30: It was nice to know that when you were thinking were your blood pressure all right, were your oxygen levels all right? Me as a smoker for 40 years, I've only just packed in smoking, I just wanted to see if my oxygen levels were all right.

From an intervention delivery perspective, therapists described the need for clear medical guidance on how to assess eligibility, monitor physiological responses, and know when to stop exercise (i.e., termination criteria).

Therapist 1: There would have to be some guidance from a medical point of view. The medics would have to decide whether the patient was appropriate or not... We'd have to put a procedure in place... If this happens at any point stop... It would have to be really a flow chart basically of what to do.

Therapists also discussed the requirement for further training on how to use the exercise bike to increase their own self-efficacy to effectively operate the device, and to promote the adoption of the exercise bike amongst the therapy team.

Therapist 2: Maybe you could have... a how-to [guide] with the bikes, so staff members are following a similar sort of pattern, rather than people just doing it and everyone's been slightly different, or knee angles or hip angles or whatever have been different.

Therapist 5: I don't think we made as much of it as we could. Maybe a few joint sessions with you might have just fuelled that sort of confidence for staff to use it.

In summary, the accessibility of the exercise bike enabled non-ambulatory stroke patients to engage in aerobic exercise training. This inclusive equipment normalised exercise which was empowering. Close supervision was pivotal to reassure stroke patients that it is safe to exercise, which instilled confidence and enhanced motivation. Therapists echoed the importance of close physiological monitoring and highlighted the need for guidance from their medical colleagues. In addition, therapists seemed willing to use the exercise bike but highlighted the need for further training to increase their self-efficacy.

Burden and opportunity cost

The burden domain within the Theoretical Framework of Acceptability indicates that increased effort is equivalent to increased burden. However, when interpreting the intervention 'burden', it is important to consider that the intention of this exercise intervention was to physically challenge participants. Opportunity cost refers to any activities, values or benefits that must be given up to participate. In the context of stroke rehabilitation, burden and opportunity cost are inextricably linked because increased effort can provoke fatigue which could impede participation in other therapy. Therefore, these two domains will be discussed in unison.

There were varying opinions amongst therapists about the effects of aerobic exercise on stroke patients' fatigue levels and ability to engage in usual care therapy. In one instance, a therapist expressed ambivalence, favouring a 'more is better' approach, but also raised concerns about inducing fatigue.

Therapist 5: It was great to see some of my patients that we'd be seeing later on that day and thinking oh great they've got an extra 30 minutes or 60 minutes of input...My concern I suppose would be that there would be fatigue. So if I was looking at balance exercises, standing and stepping or repetitive stuff like that, or gait practice, if I put them on the bike, would I fatigue them too much?

Another therapist expressed stronger views about the potential negative impact on fatigue levels.

Therapist 1: If somebody we know from a physio point of view can only manage 15/20 minutes in the gym, but then they've done that exact amount of time, or longer more likely with you, they're pretty much written off for the day in terms of what else they can receive.

Interestingly, only one stroke patient (1/15; 6.7%) displayed signs of excessive fatigue, which inhibited their ability to fully engage in usual care therapy. This was the same participant who experienced a dissociative, dream-like state during aerobic exercise.

Participant 26: I wasn't putting a hundred percent effort into it [usual care therapy], because I was so tired when I come out of your sessions.

Furthermore, one therapist reported that occasionally, stroke patients chose to prioritise aerobic exercise over usual care therapy to conserve their energy, suggesting that these individuals perceived that the intervention was more beneficial than routine physiotherapy.

Therapist 1: there have been one or two occasions where a patient has said no, you can't come and see me, I'm seeing [the Researcher] for the bike today, I'm going to save my energy.

In contrast, some stroke patients thought that aerobic exercise was a helpful activity to prepare for usual care therapy, which could indicate a priming effect (454).

Therapist 6: Some of them fed back that actually ...it's then maybe given them a bit of a warmup if they're doing something later on in the day.

Most stroke patients viewed their participation in the exercise intervention and overall study as a valuable time investment which made them feel useful and that they were making a positive contribution to their recovery. Stroke patients compared their

participation to an alternative hypothetical situation, where they would otherwise be lay in bed feeling idle.

Participant 17: I found probably I was a little bit more useful that I thought I was. I thought I'm not just laid here.

Participant 5: I was very happy when you told me I was going to be taking part in the exercise, just because I'm laying in bed and I need to be doing something.

Lastly, therapists described that it was occasionally difficult to see their patients due to a busy ward schedule of medical procedures, scans, family visits and intervention exercise sessions. Although the researcher arranged exercise session timings in cooperation with the therapy team each day, the dynamic nature of ward activities meant that therapists often needed to arrange therapy sessions on an ad-hoc basis, which the intervention occasionally interfered with.

Therapist 6: so if people have been having bloods taken in the morning and then with the nurses then they're on the bike and then we're kind of then having to constantly like go back and try and do whatever we need to do...it doesn't feel like that's detrimental; it just feels like just part of acute ward care.

In summary, most participants valued participating in the study and exercise intervention. Therapists were generally concerned that the intervention would induce fatigue and hinder engagement in routine therapy sessions. However, only one stroke patient (1/15; 6.7%) felt that the intervention reduced their ability to fully engage in routine therapy. It is also noteworthy that on one or two occasions, a participant prioritised the aerobic exercise intervention over routine therapy to preserve their energy. Further, some stroke patients and therapists felt that aerobic exercise improved engagement in usual care therapy. Lastly, there were occasional scheduling conflicts where therapists were unable to provide therapy sessions due to clashes with other events such as blood tests, imaging investigations, family visits and intervention exercise sessions. These interviews provide insight into the delicate balance between exertion and fatigue, and the requirement for clear communication between staff members to optimise stroke patients' therapy schedules.

Discussion

This qualitative study explored the acceptability of a research trial involving an aerobic exercise intervention initiated during the acute phase of stroke, incorporating perspectives of stroke patients and stroke therapists. This study addresses a gap in stroke rehabilitation research by focusing on the earliest stage of recovery—a period in which aerobic exercise is recommended by international guidelines but seldom implemented in practice. The following discussion contextualises these qualitative findings against relevant stroke rehabilitation literature and draws on data presented in other chapters within this thesis.

Enhancing agency and wellbeing through accessible aerobic exercise

Integration of aerobic exercise into stroke rehabilitation programmes is often hindered by barriers including: impaired mobility, health concerns, fear of falling, and limited access to specialised exercise equipment (12). This study's intervention was specifically designed to overcome these challenges. Participants valued the opportunity to engage in daily exercise which fostered a sense of agency, at a time when they had experienced a sudden loss of independence. The progressive nature of the intervention allowed stroke patients to set and achieve tangible goals, and enabled them to play an active role in their recovery. Additionally, the exercise sessions and other study activities provided psychological and social stimulation, which broke up the monotony of hospital routines.

Exercise intensity monitoring and perceived safety of aerobic exercise

Observational studies involving surveys of physiotherapists practicing in North America have reported concerns about cardiac risk and a need for training on how to safely prescribe aerobic exercise (12). In the current study, therapists did not specifically cite cardiovascular events as a concern but stressed the importance of medical oversight and well-defined eligibility and termination criteria to increase the safety of aerobic exercise. The current study included rigorous monitoring of blood pressure, heart rate, and peripheral oxygen saturation throughout each aerobic exercise session. Stroke patients consistently reported that real-time vital sign monitoring, conducted by a

trained researcher, fostered a sense of safety, which enhanced their self-efficacy and motivation to engage in exercise.

Regarding exercise intensity monitoring, some stroke patients initially faced challenges interpreting the RPE scale. This uncertainty may have contributed to discrepancies between RPE and heart rate measures, as described in Chapter 5. However, stroke patients became familiar with RPE scale over time, likening it to a calibration process. The Talk Test was perceived as a more intuitive method for gauging exercise intensity, offering clear cues that were easy to interpret (i.e., increased breathing rate but able to maintain a conversation).

The exertion-fatigue trade-off

Fatigue was a common concern amongst therapists, with many believing that aerobic exercise would cause excessive fatigue and hinder engagement in routine therapy. These concerns were not echoed by most stroke patients—most of whom framed exertion as an important achievement which contributed to their recovery; 93% of stroke patients perceived that aerobic exercise did not inhibit engagement in routine therapy. To the contrary, some stroke patients and therapists noticed that the intervention resulted in increased motivation to engage in routine therapy, driven by improvements mood and a greater sense of personal agency. Improved motivation to engage in therapy is a significant finding because prior research has identified that therapists' perceptions of patients' motivation influences whether, and to what extent, rehabilitation is offered to them (455).

There was one exception, however, where one stroke patient (1/5; 6.7%) reported that aerobic exercise caused excessive fatigue which impacted their ability to engage in routine therapy. This individual had pre- and post-exercise fatigue scores of 7/10 (very fatigued) in their prior session (session 4 out of 5). This individual also experienced an atypical dissociative, dream-like state during the cycling sessions and had the highest stroke severity in the interviewed cohort (NIHSS: 21; vs. group mean NIHSS: 8.3 ± 6.7). The underlying cause of this cognitive response is unclear but may be linked to stroke severity and associated inflammatory processes. Post-stroke fatigue in the acute phase of stroke is driven by inflammation, which disrupts neuronal function, blood flow regulation, and mitochondrial activity, collectively reducing energy reserves and

impairing energy replenishment (456). Inflammation can also impair sensory attenuation—the ability to filter out irrelevant sensory input—which could result in sensory or cognitive overload, manifesting as a dream-like state, and leading to increased sensations of fatigue (456). Interestingly, preclinical studies involving rodent models of stroke demonstrate that aerobic exercise reduces cerebral inflammation and promotes neurological recovery (457), possibly through enhanced waste clearance via the glymphatic system (418). The current study did not assess the effects of the intervention on inflammatory markers, which is a key limitation. Future research should investigate the acute effects of aerobic exercise on inflammation, cognitive function and acute fatigue, which may help elucidate the optimal aerobic exercise dose to clear inflammation whilst minimising fatigue.

Preliminary evidence of a priming effect

Several stroke patients reported perceived improvements in physical function shortly after the taking part in aerobic exercise sessions. These observations were supported by one therapist who noticed enhanced function during therapy sessions for one stroke patient. This therapist speculated that this could have been a priming effect, whereby aerobic exercise increases ipsilateral cortical excitability which may promote motor skill acquisition in subsequent therapy sessions (454,458).

Evidence indicates that cycling and walking are partially governed by the same neural network within the spinal cord, known as central pattern generators, which regulate rhythmical motor activity (459,460). Priming of this shared neural circuitry during cycling exercise may contribute to the restoration of walking function.

Despite having knowledge of the priming concept, the same therapist expressed ambivalence about aerobic exercise noting the fine balance between priming and exertion-induced fatigue. To test the hypothesis that aerobic exercise induces a priming effect, future studies should incorporate neurophysiological measures—such as EEG or transcranial magnetic stimulation-evoked motor potentials—to assess changes in cortical activity and excitability pre- and post-exercise.

Conflicting views about movement quality, motor recovery and maladaptation

Some therapists questioned the relevance of aerobic exercise for motor recovery. Their primary concern focused on the repetitive, ‘non-functional’ nature of cycling, and potential ‘overuse’ of the unaffected limb, which could reinforce compensatory movement patterns. This scepticism is grounded in longstanding neurorehabilitation principles such as Hebbian plasticity and the theory of learned non-use. Task-specific training is a widely practiced technique, which involves goal-directed, meaningful activities that closely mirror real-world functional tasks (461,462). In addition, the theory of learned non-use posits that disuse of the affected limb leads to dominance of the unaffected cerebral hemisphere, reinforcing compensatory movement patterns and hindering recovery of the impaired limb (463). These qualitative data build on previous work showing that aerobic exercise is often deprioritised in stroke rehabilitation because it is not considered functionally relevant (444), and also provides new insight into the rationale underlying some therapists’ concerns—namely, the perceived risk of maladaptive motor learning.

In contrast, other therapists recognised the value of aerobic exercise as an adjunct to increase daily therapy dose, improve cardiovascular health and improve motor function. In one therapist’s opinion, “all movement is good movement”, provided the equipment was set up correctly (i.e., lower limbs moving in sagittal plane). This view was supported by another therapist who believed that cycling exercise was more functionally relevant to walking than single joint exercises, such as knee extensions, which are a commonly prescribed exercise in stroke rehabilitation.

Neurophysiological considerations

The recumbent exercise bike used in the current study enabled a relatively high dose of bilateral lower-limb repetitions. Specifically, the intervention involved a 14-fold increase in step count (cycling repetitions) compared to usual care, measured using a thigh-mounted accelerometer (see Chapter 5). As noted above, a key concern raised by some therapists was that a high dose of cycling exercise may lead to overuse of the unaffected leg which may exacerbate the between-limb motor deficit. Without the use of electromyography or force sensors, we were unable to quantify the engagement of each leg during exercise sessions. Whilst it is not possible to confirm or refute

therapists' concerns, there are five lines of reasoning which suggest that aerobic exercise did not lead to maladaptation, described below.

1. Engagement of both legs

Ultrasound data from Chapter 5 demonstrate that in the intervention group, rectus femoris muscle atrophy was attenuated bilaterally, suggesting that cycling exercise effectively engaged both legs. An additional noteworthy finding from Chapter 5 was that the control group, which had a higher proportion of stroke patients who were ambulant at baseline, exhibited preserved muscle vastus lateralis thickness in the unaffected leg only. This suggests that the control group may have relied on compensatory walking strategies, which could have reinforced motor deficits. In contrast, cycling-based aerobic exercise appears to have encouraged more balanced limb engagement.

2. Limb alignment

The MOTomed Letto 2 is a recumbent exercise bike which has an adjustable pedal height and crank length, combined with secure foot shells and fixation straps over the feet and lower legs. These ergonomic features help maintain a plantigrade foot position and support limb movement within the sagittal plane. This minimises abnormal joint loading, thereby reducing the risk of maladaptation (464,465).

3. Central pattern generator activation

Both walking and cycling are governed by shared neural networks in the spinal cord known as central pattern generators, which produce rhythmic, coordinated motor patterns without requiring constant input from the brain. Engaging in cycling may train these neural networks, potentially facilitating the restoration of walking function (459,460).

4. Crossover between cycling exercise and walking function

The crossover between cycling-based training and improved walking function is

well-supported in the literature. Studies conducted in the early subacute phase of stroke (<30 days post-stroke) have reported that cycling-based aerobic exercise interventions result in improvements in walking speed and endurance in people with stroke (144,146).

5. *Functional outcomes*

The intervention group demonstrated superior three-month functional outcomes compared to the control group. These improved outcomes support the hypothesis that early-initiated aerobic exercise initiated in the acute phase of stroke may have neuroprotective effects and support neuroplasticity.

Strengths and limitations

The study's strengths include its in-depth exploration of participant perspectives, capturing nuanced experiences from both stroke patients directly involved in the intervention, and therapists who observed exercise sessions and oversaw the rehabilitation programmes for each participant. The use of a theory-driven framework enabled a systematic evaluation (173), and the additional use of inductive analysis provided further depth (174), resulting in a more comprehensive understanding of acceptability.

This study also has limitations. The small convenience samples from a single site limits generalisability, as findings may not reflect experiences in other stroke units or healthcare settings with differing resources or patient characteristics. The researcher's dual role in delivering the intervention and interviewing participants may have introduced social desirability bias from participants, or 'research allegiance' (466) where a researcher is invested in a particular intervention and believes this intervention is superior to others. To minimise these potential biases, several techniques were employed: open-ended questions were incorporated to allow participants to express views freely, and participants were explicitly encouraged to provide critical feedback, emphasising that constructive criticism would help improve the intervention. Additionally, the researcher received support from two expert qualitative researchers who sense-checked the interview process and data interpretation, ensuring

methodological rigor. Future qualitative research should incorporate larger, multi-site samples, independent interviewers, and blinded analysis to maximise generalisability and minimise bias.

The initial protocol for Study 4 planned to include interviews with usual care group participants about their study experiences, and three-month follow-up interviews with both intervention and usual care group participants about post-discharge rehabilitation experiences. However, these datasets were not pursued for analysis due to their limited relevance to the overarching research topic, which is focused on the feasibility of aerobic exercise training in the acute phase of stroke. The usual care group interviews were intended to provide insights into the acceptability of the study procedures, but yielded no unique findings compared to the intervention group's perspectives. The three-month follow-up interviews, which focused on post-discharge rehabilitation experiences, revealed minimal aerobic exercise engagement across both groups due to lack of knowledge and motivation. Excluding these datasets ensured a more focused thesis, enabling sufficient analytical depth about the intervention's feasibility, whilst avoiding an excessive word count. Excluded data were archived for potential future analysis.

Conclusion

This study contributes novel insights into the feasibility and acceptability of initiating aerobic exercise during the acute phase of stroke. The findings demonstrate that a structured, closely monitored aerobic exercise programme was highly acceptable to stroke patients, enhancing personal agency, motivation, and psychological wellbeing. Most participants perceived that aerobic exercise contributed to their motor recovery. The findings also suggest a potential priming effect, whereby aerobic activity may have stimulated neuroplasticity and supported skill acquisition; however, this effect was not quantifiable in the current study. Therapists expressed concerns about aerobic exercise causing excessive fatigue, yet this was only documented on one occasion across the 13-month study period. Divergent views were noted amongst therapists regarding movement quality and the risk of maladaptive compensation, revealing conflicting stroke rehabilitation philosophies. System-level barriers such as limited staffing, time

constraints, and the absence of clear medical guidance were also identified as factors limiting implementation.

One of the key uncertainties arising from this study was movement quality and its consequences for recovery, whether beneficial or maladaptive. While neuromuscular measures were outside the scope of the present qualitative work, related data from the broader feasibility trial within this thesis indicated superior three-month functional recovery in the intervention group compared to controls, suggesting that the intervention was not harmful and may have been beneficial for motor outcomes. To better understand the physiological mechanisms underpinning these observations, future studies should integrate neurophysiological assessments—such as TMS-evoked motor potentials, EMG, and lower-limb dynamometry—alongside qualitative inquiry to capture both neuromotor engagement and patient experience. Collectively, these findings provide valuable insight for the design of a larger, fully powered RCT aimed at evaluating the effectiveness, optimal dosing, and underlying mechanisms of early-initiated aerobic exercise after stroke.

Chapter 8 – General Discussion

This doctoral research programme aims to bridge important gaps in the stroke rehabilitation literature. It focuses on two rehabilitation methods that are widely recommended in clinical guidelines: early mobilisation and aerobic exercise training.

The rationale for including both of these distinct rehabilitation approaches within this PhD is multifaceted. In the stroke rehabilitation literature, early mobilisation and aerobic exercise are often conflated, yet they differ fundamentally in their physiological demands. Initiation of stroke rehabilitation early after stroke is grounded in preclinical evidence which demonstrates that early intervention leads to superior recovery from stroke. However, much of the preclinical evidence supporting early post-stroke rehabilitation stems from environmental enrichment paradigms which often include wheel running as part of the experimental conditions. As such, it is difficult to distinguish the effects of early ‘rehabilitation’ from aerobic exercise in these preclinical studies. In fact, studies have shown that aerobic exercise is the primary driver of neuroplasticity and neuroprotection, whereas removing rodents’ access to a running wheel blunts recovery.

In clinical practice, however, aerobic exercise is rarely delivered in the acute phase of stroke, despite being recommended in most guidelines. Moreover, translating the promising preclinical findings to the bedside is complicated by fundamental anatomical and physiological differences between species. For example, rodents are quadrupeds whose habitual head-down posture does not impose the same orthostatic stress that humans experience during upright activity. Neuroprotection and neuroplasticity both depend on adequate cerebral perfusion; thus, attempts to promote recovery through frequent and prolonged upright activity may be counterintuitive in early after stroke.

This dilemma has, in fact, been debated for decades. The term ‘positional cerebral ischaemia’ was coined as early as 1974 to describe the concern that upright activity might compromise cerebral blood flow (99). More recently, the large-scale AVERT trial added weight to these concerns, demonstrating that very early mobilisation (within 24 hours of stroke onset) was associated with worse outcomes compared to delayed

mobilisation (97). Concerns have also been raised about aerobic exercise. For instance, twice-daily treadmill training initiated just two days after stroke onset showed signs of potential harm, with patients experiencing exhaustion and dizziness-symptoms consistent with cerebral hypoperfusion (135).

In contrast, two studies involving cycling-based aerobic exercise intervention in the acute phase of stroke demonstrated a favourable safety profile (133,134), and one study reported improved recovery outcomes (134). However, interpretation of these findings is limited by incomplete reporting of the exercise dose—particularly the proportion of passive versus active cycling—which makes it difficult to evaluate the safety and efficacy of each intervention.

In summary, the evidence highlights potential benefits and risks surrounding early rehabilitation after stroke; Preclinical studies indicate that aerobic activity can drive neuroprotection and plasticity (13,85), yet clinical findings suggest that upright activity—whether that is early mobilisation or intensive treadmill training—may compromise cerebral perfusion when delivered too early (97). Recumbent cycling may offer a more suitable alternative for early post-stroke aerobic exercise, as it imposes less orthostatic stress. In light of these insights, the central research questions for this thesis were as follows:

1. How does early mobilisation affect cerebral haemodynamics, and does this relate to clinical outcomes?
2. Can recumbent aerobic exercise training be delivered safely and feasibly in the acute stroke setting, and does it show preliminary signals of efficacy?
3. What are the acute cerebral haemodynamic and neurotrophic responses to aerobic exercise early after stroke?
4. How do patients and staff perceive the acceptability of introducing aerobic exercise in the acute phase of stroke, and what are the implementation barriers?

To address these questions, the thesis was structured into a series of interlinked experimental chapters, each corresponding to one of the above questions. These included physiological investigations and a phase II feasibility trial of early aerobic exercise.

Study 1: The Acute Effect of Early Mobilisation on Cerebral Haemodynamics in Acute Stroke

The first research question was addressed by examining the cerebral haemodynamic responses to early mobilisation in acute stroke. Using transcranial Doppler ultrasound, this study demonstrated that moving to a standing position led to a sustained bilateral decline in cerebral blood velocity, with greater reductions in the ipsilesional hemisphere. This occurred despite compensatory increases in blood pressure and heart rate. This finding is consistent with earlier studies on upright positioning (including seated postures) and a recent investigation of standing involving acute stroke patients. The present work extends previous evidence by showing that cerebral blood velocity continues to decline into the third minute of standing. Such a sustained reduction may explain the orthostatic symptoms commonly observed during early mobilisation in clinical practice.

These results also provide mechanistic insight into why very early mobilisation might lead to poorer outcomes compared to delayed mobilisation. In the current study, the cerebral blood velocity responses to standing were not significantly associated with functional outcomes, though this secondary analysis was underpowered. Collectively, the evidence from Study 1 suggests that the risk of cerebral hypoperfusion should be carefully considered when prescribing frequent or prolonged upright activity in the acute phase of stroke.

Study 2: The Feasibility of Aerobic Exercise Training in Acute Ischaemic Stroke

The second research question was addressed by evaluating the feasibility and safety of a recumbent aerobic exercise intervention in the acute phase of stroke. In this phase II randomised feasibility trial, light-to-moderate intensity recumbent cycling was implemented within the first two weeks after stroke onset without any evidence of harm. Recruitment was successful at 2.4 participants per month, exceeding the pre-specified target of 2 per month. The overall attrition rate was 20%, primarily due to early hospital discharge rather than intervention intolerance. Excluding those who were discharged early, attrition was 10%. Patients reported that the exercise bike was comfortable, and the majority were able to complete their exercise sessions as intended.

There were also preliminary signs of efficacy: recumbent cycling attenuated rectus femoris muscle atrophy in both legs and was associated with more favourable disability outcomes at three months post-stroke compared to usual care. These findings suggest that the intervention may not only counteract hospital-associated deconditioning but may also contribute to improved neurological recovery. This encouraging preliminary evidence is consistent with preclinical studies in which early-initiated aerobic exercise enhanced recovery via neuroprotective and neuroplastic mechanisms. However, further research is required to confirm these effects and clarify the underlying neurovascular mechanisms.

A unique aspect of Study 2 was the detailed tracking of exercise dose and physiological responses. This revealed considerable variability in heart rate and blood pressure responses to exercise, despite rigorous attempts to standardise intensity. Indeed, cardiovascular responses differed widely both between participants and within individuals (at the same relative intensity), highlighting the complexity of exercise prescription in the acute stroke setting. Nevertheless, close monitoring ensured all responses remained within predefined safety thresholds, and no adverse events occurred.

These observations demonstrate the importance of combining subjective measures such as the Rating of Perceived Exertion scale and Talk Test with objective vital sign monitoring when prescribing exercise early after stroke. The favourable safety and acceptability profile of recumbent cycling in this trial contrasts with reports of poor exercise tolerance during early treadmill training, possibly because the recumbent position imposes less orthostatic stress than upright exercise.

Study 3: The Acute Cerebral Haemodynamic and Neurotrophic Effects of Aerobic Exercise in the Early Subacute Phase of Stroke

The third research question was addressed by examining the acute physiological responses to a single bout of aerobic exercise in the early subacute phase of stroke (approximately 10 days post-stroke). In this study, a light-to-moderate intensity recumbent cycling session elicited bilateral increases in cerebral blood velocity of roughly 10-11%. A characteristic biphasic pattern was observed: cerebral blood velocity peaked around 10-15 minutes into exercise, then stabilised above the baseline level for the remainder of the session. Notably, these cerebral haemodynamic responses varied considerably between individuals and were not predicted by exercise intensity or systemic haemodynamic changes (such as blood pressure). This suggests that the increase in cerebral perfusion was driven primarily by neurovascular coupling - the brain's localised response to neural activity - rather than by systemic blood pressure elevations.

These findings stand in contrast to the reductions in cerebral blood velocity observed during passive upright mobilisation in Study 1. They demonstrate that recumbent aerobic exercise can augment cerebral perfusion early after stroke without evidence of harm. The increase in cerebral blood velocity provides a plausible mechanistic explanation for the more favourable functional outcomes seen in the exercise group of Study 2, supporting the idea that repeated bouts of aerobic exercise may stimulate recovery processes via enhanced cerebral perfusion.

In this study, aerobic exercise did not elicit significant changes in serum brain-derived neurotrophic factor (BDNF) levels. Roughly half of the participants exhibited a post-

exercise increase in BDNF while the other half showed a decrease, and these variable responses appeared unrelated to exercise intensity. This null finding is consistent with prior meta-analyses indicating that only vigorous-intensity exercise consistently increases peripheral BDNF, whereas light-to-moderate intensity exercise often does not. An exploratory comparison of resting BDNF levels between the intervention and control groups similarly revealed no significant difference.

Taken together, these results suggest that while recumbent cycling can safely augment cerebral blood velocity, the intensity used in this feasibility study was insufficient to stimulate a detectable increase in peripheral BDNF. However, it remains unclear to what extent peripheral BDNF reflects changes within the brain. Notably, neurovascular coupling and BDNF release in the brain are closely linked; thus, the observed rise in cerebral perfusion may still have promoted neurotrophic processes that were not detected in peripheral blood samples.

Study 4: The Acceptability of Aerobic Exercise Training Initiated in the Acute Phase of Stroke

The fourth study explored how patients and healthcare staff perceived the implementation of structured aerobic exercise in the acute phase of stroke. Overall, the intervention proved to be highly acceptable to patients and was reported to confer psychological and functional benefits. Participants described the cycling sessions as a way to break the monotony of the hospital routine, and an opportunity to reintroduce goals, structure, and a sense of purpose. Stroke patients welcomed the opportunity to regain agency in their recovery: they noted improved mood and motivation and felt they were actively "doing something" beneficial to help their recovery. Some even likened the exercise challenge to past sporting activities, which rekindled their competitive spirit.

Patients and staff reported improvements in mood and engagement in standard care rehabilitation sessions. Patients also consistently reported feeling safe throughout exercise intervention, due to continuous supervision and vital sign monitoring, which gave them confidence to exercise despite their recent stroke.

Therapists' perspectives on early aerobic exercise were mixed, reflecting differing rehabilitation philosophies and concerns. On one hand, some clinicians questioned whether non-task-specific exercise like cycling would translate into better motor recovery. They worried that patients might overuse their non-paretic side or become too fatigued for subsequent therapy sessions. These therapists emphasised the primacy of task-specific training and high-quality movement patterns in stroke rehabilitation. On the other hand, other therapists acknowledged potential benefits of the cycling intervention: they noted that aerobic exercise could improve cardiovascular fitness, potentially serving as a useful priming activity for therapy, and increase overall therapy dosage. All therapists agreed that clear evidence is needed to justify integrating routine aerobic sessions into acute stroke care. They also expressed the need for well-defined protocols regarding pre-exercise screening, monitoring during exercise, and equipment which enables good limb alignment.

The preliminary outcomes from Study 2, together with patient feedback from this study, may provide therapists with reassurance that the intervention does not have adverse effects. Only one of the fifteen participants in the exercise group experienced excessive fatigue that interfered with their regular therapy, indicating that most patients can tolerate additional aerobic exercise sessions. In fact, several participants described feeling physically and mentally energised after their cycling sessions, and some even thought they performed better in subsequent physiotherapy sessions. This observation aligns with the concept of exercise-induced "priming" whereby an aerobic exercise bout can transiently enhance neuroplasticity and readiness for motor learning. Moreover, evidence from Study 2—which demonstrated attenuation of muscle atrophy in both legs—indicates that maladaptive compensation is unlikely to have occurred. Together, these insights indicate that introducing early aerobic exercise is both feasible and potentially beneficial, addressing initial safety concerns and laying the groundwork for a large-scale multi-site trial.

Chapter 9 – Future Directions and Clinical Implications

A logical next step is to conduct a multicentre phase III randomised controlled trial to establish the safety and effectiveness of aerobic exercise training initiated in the acute phase of stroke. A large-scale multisite design would provide the statistical power and external validity required to detect clinically meaningful effects across different healthcare settings. Randomisation should be stratified by prognostic factors known to influence recovery trajectories, including collateral circulation, corticospinal tract (CST) integrity, baseline stroke severity and functional status, and age (467–470). For example, a more complex collateral blood vessel network protects perilesional tissue (468), severe CST injury limits recovery potential (470), and the presence of motor evoked potentials (a proxy for CST) through transcranial magnetic stimulation is associated with more favourable outcomes (467).

The questions of when to begin and how long to continue aerobic exercise training after stroke remain unresolved. Preclinical evidence indicates that initiating exercise in the hyperacute phase can worsen injury (124,126,127). No clinical trials of aerobic exercise have targeted the hyperacute phase, and the only available evidence is derived from very early mobilisation (<24 hours post-stroke), which has been linked to poorer outcomes (14). However, these findings cannot be directly extrapolated to aerobic exercise, as these two interventions have distinct haemodynamic effects. Beyond the hyperacute phase, animal studies suggest that aerobic exercise interventions initiated within the acute phase (1–7 days post-stroke) that last for at least two weeks are most effective for promoting recovery (13,85). Moreover, delaying rehabilitation by two to four weeks has been shown to blunt recovery (114). In the present work, the intervention was initiated 1-7 days post-stroke and was restricted to five sessions. This was a pragmatic decision to minimise attrition caused by short hospital admission periods, and because only one exercise bike was available at a single site. It was therefore not possible to extend the intervention into secondary rehabilitation centres or community settings, nor to investigate the impact of longer-term aerobic exercise training on physiological or functional outcomes.

Future trials should span the stroke rehabilitation pathway to enable the enrolment of a larger proportion of patients, including those with shorter inpatient stays, and to

examine the effects of different intervention durations. This would enable direct comparisons between early and delayed initiation, shorter versus longer intervention durations (e.g., 7, 14, or 30 days), and enable dose–response analyses across the acute and subacute phases of stroke.

Exercise intensity is another unresolved topic. Current guidelines in the United Kingdom recommend training at intensities above 70% of maximum heart rate (63), which borders moderate-to-vigorous intensity. It is not yet clear whether this recommendation is safe or beneficial in the acute phase of stroke. The findings of this thesis indicate that light-to-moderate intensity exercise is sufficient to increase cerebral blood velocity, potentially supporting perfusion of vulnerable tissue while posing a lower haemodynamic risk than vigorous intensity. Vigorous-intensity exercise is recognised as safe and beneficial in the later stages of recovery (471,472) but due to the lack of evidence in the acute phase of stroke, caution is advised. Future trials should therefore compare the safety and efficacy of light-, moderate-, and vigorous-intensity aerobic exercise in the acute and early subacute phases of stroke (<30 days post-stroke).

Rehabilitation posture is also a critical consideration. The present work demonstrates that upright activity (mobilisation) reduces cerebral blood velocity, raising concerns that mobilisation may compromise cerebral perfusion in the acute phase of stroke. This finding is consistent with wider evidence that very early mobilisation can be detrimental (14), and that treadmill training in the acute phase of stroke can provoke dizziness and exhaustion (135). In contrast, seated interventions appear to be better tolerated and may offer a safer means of delivering aerobic exercise in the early phases of stroke recovery (133,134). Future research should therefore compare exercise modes, assessing not only efficacy but also tolerability and safety (including haemodynamic responses), in order to determine the most appropriate interventions for patients across the different phases of stroke. In addition, early mobilisation interventions require further investigation. Currently, clinicians base mobilisation decisions largely on the presence or absence of orthostatic symptoms; however, a key finding of this thesis is that many patients exhibited sustained cerebral blood velocity reductions without overt symptoms. This highlights the need for future studies to explore whether objective indicators of cerebral autoregulation could guide mobilisation interventions.

Future studies should incorporate detailed mechanistic investigations to explain how aerobic exercise affects the brain. For example, functional MRI can map connectivity changes within and between motor networks (473), perfusion MRI can quantify blood flow to peri-infarct regions (474), and PET imaging can determine tissue viability and neuroinflammation (475). A promising advance in imaging methods is the integration of cycle ergometers within MRI scanners. Specialised ergometers now allow patients to pedal during image acquisition, enabling real-time assessment of brain physiology during exercise (476). This approach provides a unique way of examining how aerobic exercise acutely affects cerebral perfusion and neural activity.

Defining the optimal initiation timepoint, intervention duration, exercise intensity and mode, with supporting mechanistic evidence, will be essential for establishing tailored exercise protocols that are both safe and effective. While definitive evidence requires larger trials, this PhD work can begin to guide clinical practice. It supports the introduction of light-to-moderate intensity, recumbent aerobic exercise in the acute phase of stroke. It also provides practical guidance on pre-exercise screening and exercise prescription, with a clear explanation of intervention components and the physiological responses to exertion. The preliminary efficacy results, which revealed signs of improved recovery and mitigated quadricep muscle atrophy in both legs, should also help to alleviate therapists' concerns about potential maladaptation resulting from repetitive use of the unaffected leg. Furthermore, feedback from patients suggests that aerobic exercise training enhances mood and motivation, supporting the case for its integration into early stroke rehabilitation.

Chapter 10 – Reflection

I began this PhD journey with limited knowledge of stroke pathology, cerebrovascular physiology, and stroke rehabilitation methods. However, I was able to draw on a strong background in exercise science, with a prior focus on cardiac rehabilitation, to approach research questions through a unique lens.

The fundamental concept that guided me at the start of this PhD was that ischaemic stroke is caused by disrupted blood supply, and restoring blood flow is central to treatment. If aerobic exercise increases cerebral blood flow, then perhaps it could play a protective role in the acute phase of stroke. As I examined the literature in greater depth, my scope and understanding began to broaden. Aerobic exercise has effects beyond perfusion; it can also stimulate neuroplasticity and counteract hospital-associated deconditioning. At the same time, I became aware of the practice of early mobilisation, which is widely implemented in stroke rehabilitation. I learnt that very early mobilisation was associated with poorer outcomes, despite aims to promote neuroplasticity and prevent immobility-related complications. This steep learning curve prompted me to reflect more critically on how different interventions act on the brain and body simultaneously, and about the scientific principles that underpin rehabilitation practices.

In reviewing the preclinical literature, particularly environmental enrichment studies, I recognised the limitations of experimental findings, and the challenges of translating them to human clinical practice. This shift in perspective was also influenced by my developing understanding of the neurovascular unit. Learning about the interdependence of neurons, glia, and blood vessels gave me a new way of thinking about stroke rehabilitation: not as a set of separate targets (perfusion, neuroplasticity, or skeletal muscle engagement), but as interlinked processes. In the acute phase of stroke, rehabilitation aims to stimulate neuroplasticity, yet this must be balanced against the risk of compromising cerebral perfusion and exacerbating injury. This dilemma not only shaped my interpretation of the literature but also guided my empirical work, leading me to design studies that could investigate acute and chronic responses to different stroke rehabilitation methods.

Transcranial Doppler ultrasound allowed me to observe acute changes in cerebral blood velocity, offering a window into how cerebral perfusion responds to different rehabilitation methods. Muscle ultrasound provided insight into structural adaptations of skeletal muscle in response to usual care and aerobic exercise training. Blood sampling and BDNF assays, despite their challenges, provided a way of exploring biomarkers of neuroplasticity. On their own, each of these methods could only provide partial answers, but together they allowed me to examine mechanisms across vascular, muscular, and neural domains. The intensive reading, writing, and hands-on data collection and analysis required to tackle these complex questions demanded substantial time and effort, ultimately prolonging my PhD.

Beyond these physiological questions, feasibility was a central theme of my PhD. I was embedded as a researcher within an acute stroke team, which gave me first-hand experience of the pressures faced by staff and the constraints of clinical environments including limited space and equipment. Combined with qualitative feedback from patients and therapists, this front-line insight sharpened my understanding of how a small-scale study could expand to a larger multi-site trial, and, ultimately, what might be realistic to implement in routine care. A key limitation of my research was that it was predominantly conducted at a single hospital. Many patients were not eligible to participate, often because they had transferred to another rehabilitation facility. Additionally, some participants were discharged earlier than anticipated, continuing their rehabilitation at another site which lacked accessible aerobic exercise equipment.

To help overcome this issue, I strove to improve the exercise provision infrastructure locally in Sheffield. I recently negotiated a free trial of a specialist exercise bike for a secondary stroke rehabilitation centre. Working closely with therapists, we explored ways to integrate its use into daily therapy schedules, and developed operating guidance along with a pragmatic exercise dose monitoring protocol. To evaluate this, I led a clinical audit with the support of three MSc physiotherapy students. We compared the average therapy time per patient before and after the bike's introduction. Access to the bike increased therapy time by 21% (median) per patient per day, and these data supported a successful charity grant application that funded the procurement of three exercise bikes.

I also recently co-led a service evaluation of a multidisciplinary stroke clinic focused on secondary prevention advice for patients six weeks post-stroke. Feedback highlighted that many patients were fearful about the risks of exercise, and required guidance. I subsequently joined the clinic team to provide exercise guidance and signpost patients to community exercise services. A key aim of this ongoing work is to create a smoother pathway from the hospital to the community, and prevent patients from falling through the net.

Furthermore, I recently became a registered Clinical Exercise Physiologist. This credential formalises my expertise and will enable me to work more closely with clinicians and patients. My overarching aim is to bridge the gap between research and practice, and develop safe and effective exercise programmes which are tailored to each patient, dependent on their stroke type, stage of recovery, cerebrovascular function, neurological deficits, and underlying comorbidities.

In addition to these valuable experiences in stroke rehabilitation research and practice, I have contributed to several other research programmes during my PhD. For the RICFAST2 project, my role is to conduct cardiopulmonary exercise testing (CPET), which has enhanced my understanding of exercise tolerance after stroke. For the PACE4S project, my role is to help design, deliver, and evaluate a community-based exercise intervention for stroke survivors. I have also worked on projects involving CPET for Long COVID and cardiac populations, a probiotics trial in multiple sclerosis, and, most recently, a service evaluation of a cancer prehabilitation and rehabilitation programme. These experiences have been highly beneficial for my academic and career development. They have strengthened my project management skills, and broadened my understanding of different pathologies and how lifestyle behaviours influence disease and recovery trajectories.

My learning throughout this PhD has been shaped by engaging with the stroke research community through online interactions and attendance at academic conferences. Networking has been instrumental in helping me stay abreast of the latest evidence and discover new topics. This engagement also led to my involvement in an international stroke research interest group, and culminated in a career highlight: presenting my PhD

research at a symposium in Basel, Switzerland, alongside eminent researchers, sharing a platform in front of an international audience.

This six-year journey has taken much longer than anticipated. My decision to pursue such a variety of projects has, at times, diverted focus away from my PhD. In addition, completing my thesis write-up alongside full-time employment has been a huge challenge, which without the support of my family and colleagues, would not have been possible. I am sincerely grateful for the ongoing opportunities to continuously learn and push the field of clinical exercise science forward.

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Appendices

Appendix 1 - Aerobic exercise recommendations within international clinical guidelines

Table A1. Summary of aerobic exercise recommendations within international clinical guidelines

Country, year	Initiation timepoint	Pre-participation screening	Frequency	Intensity	Session and intervention duration	Mode	Progression	Goal
UK, 2023 URL	Once medically stable, regardless of age, time since stroke and severity of impairment.	Screen for contraindications. Screening equipment (such as treadmills, ECG and blood pressure monitors) should be available. Six-minute walk test or shuttle test.	Cardiorespiratory training only: 3-5 days/week Mixed training: ≥3 days/week	Cardiorespiratory training only: >70% peak heart rate. Mixed training: 40-60% HRR	30-40 min/session, for 10-20 weeks. Encourage ongoing participation in exercise training.	Bodyweight support treadmills walking, static/recumbent cycling, seated exercise groups.	Not mentioned	Improve cardiorespiratory fitness and ability to engage in rehabilitation; reduce secondary stroke risk.
USA, 2020 URL	Once medically stable. When feasible, typically in the subacute phase.	Screen for contraindications. Symptom-limited or submaximal exercise stress test with ECG and blood pressure monitoring. If planned training intensity is at lower end of exercise intensities (e.g., <50 of predicted HRR) submaximal test (e.g., six-minute walk test or shuttle test) may be used.	≥3/week.	Individually tailored based on baseline fitness, neurological involvement, cardiac status, comorbidities, and programme goals. The American College of Sports Medicine recommends that inactive individuals “start low and go slow.”	≥20 minutes (in addition to 3-5 minutes of low-intensity warm-up and cool-down) for ≥8 weeks. For very deconditioned individuals, exercise may be delivered in multiple bouts of ≤5 minutes in a single session or throughout the day.	Any mode of exercise that activates a large muscle mass for a prolonged period.	Individualised gradual progression of frequency, duration, and intensity to minimise muscle soreness, fatigue, and injury. Duration should be increased by 5 to 10 minutes every 1 to 2 weeks for the first 4 to 6 weeks and intensity by 5% to 10% of heart rate reserve every 1 to 4 weeks. A gradual progression in the duration may be required, starting with bouts of 5 minutes or less and alternating intervals of rest or lower-intensity exercise.	Improve cardiorespiratory fitness; reduce cardiovascular and secondary stroke risk.
Australia and New Zealand, 2021	Once medically stable and passed screening.	Screen for contraindications. Graded exercise test with ECG may be included.	3-5 days/week.	40–70% $\dot{V}O_2$ reserve or HR reserve; 55–80% HR _{max} ; RPE 11–14 (6–20 scale).	20–60 min/session (or multiple 10-minute sessions) with an additional 5–10 min of warm-up and cool-down activities.	Large-muscle activities such as walking, arm or leg ergometry; functional activities.	Not mentioned.	Improve cardiorespiratory fitness and walking ability; reduce

URL	While an inpatient.				Encourage ongoing regular physical activity.			disability; reduce secondary stroke risk.
Canada, 2019 URL	Most individuals post-stroke who are medically stable should start a regular exercise program.	Screen for contraindications. Exercise stress test with ECG, blood pressure and symptom monitoring, particularly if patient has cardiac history. If planned training intensity is light (<40-45% of predicted HRR) submaximal test (e.g., six-minute walk test or shuttle test) may be adequate.	≥3/week.	Individually tailored.	≥20 minutes (excluding warm-up and cool-down) for ≥8 weeks. Encourage ongoing participation in exercise training.	Aerobic training involving large muscle groups.	Not mentioned.	Improve cardiorespiratory fitness and cognitive function.
Netherlands, 2014 URL	Not mentioned.	Screen for contraindications.	≥3/week.	40-70% $\dot{V}O_2$ max, 40-70% HRR, 50-80% HRmax, or a Borg RPE score of 11-14 (6-20 scale).	20-60 min/session, or multiple 10-minute sessions.	Major muscle groups: walking (overground or treadmill), arm and leg cycle ergometry, or stepping using a box.	Not mentioned.	Improve cardiorespiratory fitness, respiratory and cognitive function, ability to engage in daily activities; reduce risk of morbidity and mortality associated with cardiovascular disease.
China, 2020 URL	As soon as possible when clinically stable.	Not mentioned.	Daily. Does not specify type of training.	Individualised.	Does not specify type of training.	Not mentioned.	Appropriately increase intensity and repetitions. Does not specify type of training.	Improve cardiorespiratory fitness Improvement of

								extremity dysfunction.
India, 2019 URL	After discharge.	Submaximal exercise tolerance testing.	5 days/week.	60-80% peak heart rate. Start with low intensity exercise and gradually increase to moderate levels (sufficient to become slightly breathless).	≥30-min/day Encourage ongoing participation in exercise training.	Overground walking, arm or leg ergometry.	Not mentioned.	Secondary prevention
Brazil, 2022 URL	Once medically stable.	Exercise testing with blood pressure and cardiac monitoring.	3 days/week and lighter physical activities on other days.	Individualised.	>20 min/session for ≥8 weeks. Encourage ongoing participation in exercise training.	Exercises to activate a large group of muscles for a sufficient period to produce aerobic effort.	Not mentioned.	Improve cardiac, metabolic and musculoskeletal health, mood and physical function; mitigate deconditioning. Secondary prevention.
South Africa, 2019 URL	As soon as the person with stroke is medically safe and/or able to participate.	Not mentioned.	≥3 days/week.	Not mentioned.	Progressing as tolerated to ≥20 min/session for ≥8 weeks. Encourage ongoing participation in exercise training.	Aerobic training involving large muscle groups.	Progressing as tolerated to ≥20 min/session	Improve cardiorespiratory fitness; reduce secondary stroke risk.
World Health Organisation, 2023 URL	Not mentioned.	Not mentioned.	≥3 days/week.	Low, moderate, or vigorous intensity.	10-minute 4 days/week (if low to moderate-intensity) or 20-minute 2 days/week (if vigorous intensity) Intervention duration not mentioned.	Group circuit training.	Not mentioned.	Improve cardiorespiratory fitness and cognitive function; reduce secondary stroke risk.

Appendix 2 – Contraindications to aerobic exercise

Table A2. Contraindications to Aerobic Exercise

Absolute contraindications	Relative contraindications
Acute myocardial infarction (within 3–5 days)	Left main coronary stenosis or its equivalent
Resting ST segment displacement (>2 mm)	Moderate stenotic valvular heart disease
Significant aortic stenosis (aortic valve area <1.0 cm ²)	Tachyarrhythmia or bradyarrhythmia
Uncontrolled sinus tachycardia (HR >120 bpm)	High-degree atrioventricular block
Third degree (complete) atrioventricular block without pacemaker	Hypertrophic cardiomyopathy
Active endocarditis	Significant pulmonary hypertension
Unstable angina	Electrolyte abnormalities
Uncontrolled hypertension: resting systolic blood pressure (SBP) >180mmHg, or resting diastolic blood pressure (DBP) >110mmHg	Use of insulin or insulin secretagogues
Orthostatic systolic blood pressure drop of >20 mmHg with symptoms	Orthopaedic impairment
Syncope	Advanced or complicated pregnancy
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	
Acute myocarditis or pericarditis	
Uncontrolled heart failure	
Severe grade 3 rejection (cardiac transplantation recipients)	
Acute pulmonary embolus or pulmonary infarction	
Thrombosis of lower extremities	
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest <85%	
Respiratory failure	
Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)	
Uncontrolled diabetes mellitus	

Other metabolic conditions, e.g. acute thyroiditis, hypokalaemia, hyperkalaemia or hypovolaemia (until adequately treated)	
Acute systemic illness or fever	
Medically unstable	
Cognitive impairment leading to inability to cooperate	

Appendix 3 – Ethical approval

Appendix 3a) Ethical approval for Study 1

	Ymchwil Iechyd a Gofal Cymru Health and Care Research Wales	
Dr Simon Nichols Advanced Wellbeing Research Centre Sheffield Hallam University, Olympic Legacy Park 2 Old Hall Rd, Sheffield S9 3TUN/A		Email: approvals@hra.nhs.uk
08 June 2021		
Dear Dr Nichols		
HRA and Health and Care Research Wales (HCRW) Approval Letter		
Study title:	The effects of posture on cerebral blood flow velocity during the acute phase of stroke.	
IRAS project ID:	295752	
Protocol number:	N/A	
REC reference:	21/NW/0146	
Sponsor	Sheffield Hallam University	
I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.		
Please now work with participating NHS organisations to confirm capacity and capability, <u>in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.</u>		
How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?		
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.		
If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.		

Appendix 3b) Ethical approval for Studies 2, 3 & 4

(Feasibility study with mechanistic and qualitative sub-studies)



Dr Simon Nichols
Advanced Wellbeing Research Centre
Sheffield Hallam University, Olympic Legacy Park,
2 Old Hall Rd, Sheffield
S9 3TU



Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

26 November 2020

Dear Dr Nichols

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title:	The feasibility of aerobic exercise training in the acute phase of stroke; a single-centre randomised, controlled, feasibility trial.
IRAS project ID:	280320
Protocol number:	N/A
REC reference:	20/YH/0285
Sponsor	Sheffield Hallam University

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix 4 – Patient and public involvement

Appendix 4a) Patient and public involvement event advert

sheffield

stroke research

public involvement event

13th Jan
2020

Can you help us design a research study focused on
exercise early after stroke?

Please join us if you:

- have experienced a stroke
- have supported somebody who has had a stroke
- work in stroke care, rehabilitation or research

Your opinion is important to us.

What will it involve ?

Group activities and discussions to understand your thoughts about hospital-based exercise after stroke.

WHEN ? 13 th January 2020 13:00 – 15:00	WHERE ? Graves Health & Sports Centre, S8 8JR NCSEM upstairs meeting room	FOOD & DRINKS provided ----- TRAVEL cost support*
---	---	---

please confirm attendance: [REDACTED]

*travel cost support must be approved before event

Appendix 4b) Patient and public involvement event 1

Introduction

In January 2020, a patient and public involvement (PPI) was held to gather ideas from key stakeholders regarding the use of aerobic exercise training early after stroke. Attendees included five people affected by stroke, two physiotherapists, one stroke physician, one speech and language therapist, one community fitness instructor, two senior research fellows and two PhD students. To avoid a potential power hierarchy, people affected by stroke were invited to sit on a separate table to the healthcare professionals. Researchers played a passive role by facilitating discussions and scribing. Discussions were transcribed and themes were identified. Due to the small sample size, the following summary may not be generalisable to the wider population of people affected by stroke; As one participant highlighted, “We are just the tip of the iceberg”.

Aerobic exercise training in the acute phase of stroke

For people affected by stroke, there were mixed experiences of participating in hospital-based aerobic exercise training early after stroke. Three out of five individuals were bed rested for at least two weeks before beginning physiotherapy. Hospital-based exercises were typically skill- and strength-focused, but it was acknowledged that walking exercise had an aerobic exercise component. Other than walking, no other modes of exercise that elicited a cardiorespiratory stimulus were mentioned. From a patient perspective, the key barriers to participation in aerobic exercise (walking) were a lack of physiotherapist availability, physical disability, low confidence to walk unsupervised and conservative patient management.

From a healthcare professional perspective, it emerged that hospital-based aerobic exercise training is unconventional and is typically discouraged. Conventional physiotherapy focuses on improving quality of movement and symmetry. Furthermore, it was mentioned that stroke rehabilitation guidelines are very conservative, and there is a lack of evidence to warrant aerobic exercise early after stroke. There was a concern that facilitating walking early after stroke may reinforce learning of compensatory (poor quality) movement patterns. A key priority for physiotherapists is to help patients achieve sufficient functional capacity to enable discharge from hospital, and it was

suggested that the Bobath physiotherapy method (promotion of normal, energy efficient movement patterns) takes preference over other methods to achieve this goal. It was also emphasised that staff resources and gym availability are limited and that the physical environment of a hospital ward is not conducive to physical activity.

Concerns

From the perspective of people affected by stroke, the primary concern about aerobic exercise early after stroke was a fear of falling. Collectively, there was a desire to get up out of bed and get moving early after stroke, but confidence levels were low due to poor balance, coordination, strength and overall mobility. When accompanied by a physiotherapist, people felt reassured that they could practice walking in a safe environment. For example, one participant stated: “You know you won’t fall if you’re with a physio”. However, it was reiterated by the group that there weren’t enough physiotherapists to meet demand. Another major concern was the fear of exacerbating health, but the group emphasised that proper medical screening and approval from a doctor would overcome this issue. Lastly, there was a common concern that people felt very fatigued after stroke, and that even a small amount of aerobic exercise could make this worse.

Healthcare professionals expressed various concerns about prescribing aerobic exercise early after stroke. One person mentioned that there is “risk aversion” culture in the management of patients with acute stroke, therefore decisions tend to be conservative. There appeared to be a general concern that aerobic exercise may increase the risk of secondary stroke or a cardiovascular event and there was uncertainty about the effectiveness of aerobic exercise training. It was mentioned that the risks and benefits of aerobic exercise are not weighed against the risks and benefits of immobilisation (prolonged bed rest). The collective uncertainty amongst healthcare professionals can be summarised by the following statement: “We just don’t know what the risks of aerobic exercise are. There is a lack of evidence to guide practice”. It was suggested that closer attention would need to be paid to hydration and nutritional status when undertaking aerobic exercise. Another factor was the potential increased burden on staff to complete extra paperwork for negative outcomes (near misses). Lastly, a concern was raised about a potential lack of equipment available for physiological monitoring during aerobic exercise.

Perceived Benefits

People affected by stroke highlighted a variety of physical, psychological and emotional benefits associated with aerobic exercise using a power-assisted cycle ergometer.

People perceived that cycling exercise would help build strength and mobility, and would act as a preparatory exercise prior to walking. Hip hiking and circumduction are common post-stroke gait compensations; one person thought that flexion and extension of the hip joint during cycling exercise would improve hip mobility facilitate re-learning of a normal (non-compensatory) walking gait. It was also described that muscle weakness and stiffness after stroke are exacerbated by sedentary behaviour and that cycling would help the muscles “warm up” and “loosen off”, which would facilitate physical activity. It was recognised that cycling exercise would help prevent or mitigate deconditioning and the associated health risks. There was a consensus that cycling exercise would give a psychological and emotional “boost”. People felt that cycling exercise would have “positive effects on the brain” and “make you feel cognitively sharper”. It was also described that cycling exercise would “break up the boredom”, “give you something to look forward to”, and provide an opportunity to socially interact with somebody. Social interaction was highly valued, particularly with physiotherapists who were described as “relatable” and “familiar”. A change of environment/scenery (if taken to a different hospital area) was also appreciated. In addition, cycling exercise would introduce a form of routine, enable goal setting, bring a sense of achievement, and help improve short- and long-term motivation to be physically active. Lastly, it was described that cycling exercise would make you “feel more positive”, “independent” and “make you feel more like your old self”.

Healthcare professionals highlighted similar benefits. It was mentioned that cycling exercise would bring “a sense of doing something for yourself” and the achievement would elicit an endorphin release and emotional benefits. It was acknowledged that cycling exercise would prevent deconditioning of body composition, neurological function and cardiac function. It was also highlighted that cycling exercise may have a neurological benefit such as innervation which may be mediated by regular “firing” or activation of cerebral neural pathways. Other proposed key benefits include lower mortality risk and an increased chance of returning to work. Lastly, with regards to physical activity motivation, it was argued that cycling exercise would “help normalise physical activity. The sooner this happens, the better”.

Exercise training protocol

Exercise equipment

People affected by stroke were enthusiastic about the use of an in-bed cycle ergometer. Non-weight bearing exercise was attractive to the group as it eliminated the risk of falling. The portability of the cycle ergometer was also praised because it would save time and prevent the need for patients to be transferred into another bed. Lastly, the passive cycling mode was attractive because it would still enable people to be ‘mobilised’ and loosen off stiff muscles. Notable comments were “I would have looked forward to it”, “it would break up the boredom” and “it would give you something to look forward to”.

Healthcare professionals approved of in-bed cycle ergometer. However, rather than providing feedback, healthcare professionals spent this portion of the PPI event asking the researchers questions about the practicalities of operating the equipment and positioning the patient.

Timing of exercise initiation

People affected by stroke had no concerns about exercising in the acute phase, provided that they were “given the green light from the doctor”. Emphasis was placed on a thorough medical screening to rule out exercise contraindications. The group agreed that an early start to rehabilitation would provide a psychological boost. One person stated, “I would be itching to get started on rehab as soon as possible” and another person said that “Proactive patients would be keen to get started early”. However, it was suggested that lots of patients would be apathetic towards the idea or would need to be convinced to participate.

The healthcare professionals discussion revolved around the feasibility of participant recruitment within the acute phase. The importance of aphasia severity was emphasised. For people with aphasia, typical participant information sheets may not be accessible in the acute phase. However, it was noted that aphasia-friendly documents would facilitate recruitment. Participants questioned the feasibility of recruiting severely disabled people

less than seven days after stroke. It was suggested that the recruitment timeframe should be extended for this population.

Exercise components

People affected by stroke expressed that 30 minutes of moderate-intensity cycling exercise may be “too much” or “too difficult” in the first week after stroke. Ideas for protocol modification were given including, “Why not try three lots of 10 minutes instead?” and “Participants could work their way up to 30 minutes”. Exercise progression was viewed as a valuable goal to strive for. Another common theme that emerged was the need for protocol flexibility and individualisation. It was mentioned that fatigue levels fluctuate on a day-to-day basis, and this would affect patients’ ability to participate, therefore the exercise intensity and/or duration would need to be adapted accordingly.

The healthcare professionals echoed the concern that the protocol may be “too challenging” or “quite long to start with”. Protocol individualisation was considered to be important, with one person stating that “15 minutes one day may feel different to the next”. Suggestions for protocol modification were “start with interval training then progress to continuous” and to have either “two 10-minute sessions per day” or “two times per day but shorter duration per session e.g. two 15-minute sessions”. Logistically speaking, two sessions per day was described as a “faff” due to the overall time spent setting up, packing away and completing administration tasks. One person questioned if the exercise session would be supplementary to usual physiotherapy. It was mentioned that if a patient was too fatigued to exercise on one day, the training programme duration should be extended accordingly. Exercise sessions conducted once per day for five days was deemed as achievable. The proposed intervention duration was ‘until discharge’, but the group advised that this would be logistically challenging because length of stay varies from days to weeks. This variability would make it difficult to carry out statistical analyses, therefore a duration of five days was considered to be optimal for a study.

Appendix 4c) Patient and public involvement event 2

Sheffield Teaching Hospitals 
NHS Foundation Trust

Stroke & Aphasia Patient & Public Involvement Group
12th October 2020

Researcher: Nikolaus Kudiershy
Project title: Cycling Exercise in Acute Stroke

Key points from the panel:

Day 1

- Exercise self-efficacy is difficult term to understand, please use an alternative term.
- Please consider speech/ language issues such as: jargon/ complex language, patients may say yes when they mean no
- Suggested creating a video to help participant understand the study information
- In general showing as well as explaining (demonstration) is really helpful
- The link between hand strength and cycling is not clear
- Those on early intervention after stroke may not realise the implications of exercise further down the line in their recovery.

Day 2

- Put the timelines for exercise tests on slides
- Heart rate information, please indicate that heart rate will be faster & blood pressure higher but that it will be within safe parameters which have been assessed by a medical doctor – this will help reassure patients and limit anxieties
- Reassure patients that if any issues occur all tests will be stopped immediately, you are being protected, your health is the priority.
- Probes on the head, this isn't shown in some pictures, ensure that the images are consistent through-out.

Day 6

- Very patient intensive, invasive and time intensive. 30 minutes seems a long time to do bike exercise – some patients may only be able to exercise for 2 minutes.
- How will you keep patients kept involved and consistent as will be a very tiring time for the patients - If tests done at a set time each day, could encourage a family member to support throughout? Also consistency/ continuity of having same researcher is important
- Patients may not appreciate the importance of the intervention whilst the family members will be able to understand the long-term benefits – use family or next of kin to assist in encouraging patients.
- It's too much information to take in from day 1 for patients, patients will need constant reminders & reinforcing of information will be required – family can be key to assisting with this.

General

- Positive feedback that this is important research
- Flagging up the need for any post-stroke exercise information to be accessible/ aphasia-friendly

Please provide us with feedback so we can continue to develop the PPI panel:

Appendix 4d) Patient and public involvement event 3

Public Involvement in Research Group – Lay Summary Template

Project Title: The effects of standing on cerebral blood flow velocity in acute stroke

Lay Summary:

In the first few days after a stroke, some people will be encouraged by their healthcare team to get out of their hospital bed and stand up. This is called early mobilisation. It is thought that early mobilisation helps improve recovery after stroke. Sometimes when people stand up, they feel light headed. This may be caused by low blood pressure and a reduction in blood flow to the brain. We can measure brain blood flow using ultrasound. In this study, we want to measure how brain blood flow changes when people stand up. We will attach an ultrasound device to each participant's head using a cushioned headset. We will also attach a blood pressure monitor to each participant's upper arm. We will measure brain blood flow and arm blood pressure while people are lying flat, sitting, and standing. The study will last for no more than 30 minutes.

Background – why is the study important?

After a stroke, the blood vessels in the brain are damaged. This means that they are not able to control blood flow within the brain properly. The brain needs a constant supply of blood to stay healthy and to repair itself from injury after stroke. If brain blood flow reduces too much, this might damage the brain. Moving from a sitting to a standing position can cause blood to move away from the brain toward the legs. When the blood vessels throughout the body and brain are working properly (not injured), blood is quickly returned to the brain after standing up. However, we do not know what happens when people stand up early after stroke. Early mobilisation (standing up) is a common rehabilitation method used in hospitals. More research is needed to understand how early mobilisation affects blood flow in the brain.

The study

THE PROJECT/STUDY

We will measure brain blood flow and arm blood pressure when participants are lying down, sitting and standing. Brain blood flow will be assessed using a device called transcranial Doppler ultrasound, which is a non-invasive imaging tool that measures blood flow using sound waves. The ultrasound device will be fixed to each participant's head using a cushioned headset. Blood pressure will be assessed using a standard blood pressure cuff on the upper arm. At the start of the study, participants will be asked to lay flat on their back for 5 minutes. Then the researcher will raise the bed, and the participant will be asked to sit a reclined position for 3 minutes. Then the participant will be asked to sit fully upright at the edge of their bed for 3 minutes. Finally, the participants will be asked to stand up for 3 minutes. Brain blood flow will be recorded continuously during the visit. Blood pressure will be measured at the first and third minute of each position. The study should last for no more than 30 minutes,

Public Involvement in Research Group – Lay Summary Template

Project Title: The effects of standing on cerebral blood flow velocity in acute stroke

Lay Summary:

In the first few days after a stroke, some people will be encouraged by their healthcare team to get out of their hospital bed and stand up. This is called early mobilisation. It is thought that early mobilisation helps improve recovery after stroke. Sometimes when people stand up, they feel light headed. This may be caused by low blood pressure and a reduction in blood flow to the brain. We can measure brain blood flow using ultrasound. In this study, we want to measure how brain blood flow changes when people stand up. We will attach an ultrasound device to each participant's head using a cushioned headset. We will also attach a blood pressure monitor to each participant's upper arm. We will measure brain blood flow and arm blood pressure while people are lying flat, sitting, and standing. The study will last for no more than 30 minutes.

Background – why is the study important?

After a stroke, the blood vessels in the brain are damaged. This means that they are not able to control blood flow within the brain properly. The brain needs a constant supply of blood to stay healthy and to repair itself from injury after stroke. If brain blood flow reduces too much, this might damage the brain. Moving from a sitting to a standing position can cause blood to move away from the brain toward the legs. When the blood vessels throughout the body and brain are working properly (not injured), the brain can tolerate sudden changes in blood flow. However, we do not know what happens when people stand up early after stroke. Early mobilisation (standing up) is a common rehabilitation method used in hospitals. More research is needed to understand how early mobilisation affects blood flow in the brain.

The study

THE PROJECT/STUDY

We will measure brain blood flow and arm blood pressure when participants are lying down, sitting and standing. Brain blood flow will be assessed using a device called transcranial Doppler ultrasound, which is a non-invasive imaging tool that measures blood flow using sound waves. The ultrasound device will be fixed to each participant's head using a cushioned headset. Blood pressure will be assessed using a standard blood pressure cuff on the upper arm. At the start of the study, participants will be asked to lay flat on their back for 5 minutes. Then the researcher will raise the bed, and the

participant will be asked to sit a reclined position for 3 minutes. Then the participant will be asked to sit fully upright at the edge of their bed for 3 minutes. Finally, the participants will be asked to stand up for 3 minutes. Brain blood flow will be recorded continuously during the visit. Blood pressure will be measured at the first and third minute of each position. The study should last for no more than 30 minutes, including the time to set up and remove equipment. This research aims to see what happens to people's brain blood flow and arm blood pressure during a standard rehabilitation session which will be supervised by a member of the healthcare team. We will not ask participants to do activities outside of their normal rehabilitation sessions.

FUNDING

This research is being funded by a PhD budget.

WHAT OTHER RESEARCH STUDIES HAVE YOU FOUND?

Who, or what, will it affect?

What is your target population?

People who have had a recently stroke (24-96 hours after the stroke).

What are the potential benefits of the study to the participant?

Participants will help improve knowledge about how standing affects blood flow in the brain. This may lead to improvements in stroke rehabilitation which may improve people's recovery from stroke.

Are there any limitations to your study or difficulties and how are they going to be overcome?

The blood pressure cuff will be inflated 7 times over a period of 30 minutes. This might feel uncomfortable, but it should not cause any harm. Placing the arm cuff in the correct position will make it as comfortable as possible.

Questions for the Public Involvement in Research Group

1.	Is the participant information sheet and consent form easy to understand?
2.	Do the pictures help people to understand the study protocol? Could these be improved?
3.	Is there any important information missing from the participant information sheet and consent form?
4.	Please provide any general comments about the proposals or study that you would like to be shared with the researcher/s

PIRG member comments	General comments	Question responses
1		1. I found it easy to understand 2. I think so, diagrams are important for anyone with difficulty reading/making sense of written text. They seem clear enough to see, the contrast seems quite good. Contrast is always something to be mindful of , a common barrier people encounter in many aspects of life is poor contrast ,i.e., pastel colour on pastel colour. 3. I can't think of anything, but I don't know enough about stroke survivors to know what's important to them 4. I would feel well informed & happy to do this study if it was for me , & would feel ok to ask questions & give feedback
2		1. Yes. But sentence in participation information sheet ' Sometimes when people stand up, they feel lightheaded.' may read better if it was 'However, during early mobilisation some people feel lightheaded when they stand up'. Also, typeface used for consent form should be larger. 2. Yes, but they could be less robotic, eg 'softer' and human shape 3. Explanation of why brain measurement blood flow and arm pressure need to be done together. Will there be a specific time arranged for the test? It would be useful to know if this is the case or whether someone could turn up at any time 4. Participant information sheet – heading 'What if something goes wrong?' doesn't seem appropriate. Perhaps something like ' Any questions, concerns or wish to make a complaint?' may be better. Does the ultrasound make any noise and does the headset prevent patient hearing external sounds? The section on benefits is a bit vague, eg doesn't state what type of improvements it could lead to in both rehabilitation and recovery. Limitations section – it would be useful to explain that the blood pressure cuff may feel uncomfortable when inflated. More clarity around which 'people' will use information to do research would be helpful
3		1. Yes it is - the project is relatively simple and easy to understand for a non-medical person 2. The pictures are helpful - the project is not complex 3. For me there is the question as to whether the patient is well enough to undertake the assessment. It will need to be driven by the medical assessment. The forms as presented seem to be thorough enough to me

Appendix 5 – Participant information sheets

Appendix 5a) Participant information sheet for Study 1

(Yellow highlighted text indicates amendment made in response to HRA requests).

 Sheffield Teaching Hospitals NHS Foundation Trust Participant Information Sheet Study title: The effects of posture on cerebral blood flow velocity in acute stroke Chief Investigator: Dr Simon Nichols, Sheffield Hallam University Introduction We would like to invite you to take part in a brief research study which will last for approximately 30 minutes. Joining the study is entirely voluntary. Before you decide if you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully. After you have had some time to consider the information, one of our team will meet with you to answer any questions you may have. Please ask if there is anything that is not clear to you or if you would like more information. Why is the study being done? In the first few days after a stroke, some people will be encouraged by their healthcare team to get out of bed and stand up. This is called early mobilisation. It is thought that early mobilisation helps improve recovery after stroke. Sometimes when people stand up, they feel lightheaded. This may be caused by a reduction in blood flow to the brain. We can safely measure brain blood flow using ultrasound (sound waves). In this study, we want to measure how brain blood flow changes when people sit and stand up. This study is being conducted as part of an educational programme (involving one PhD student and one medical student), and is supervised by Dr Ali Ali (Stroke Consultant). Who is funding the study? This study is funded and sponsored by the College of Health, Wellbeing and Life Sciences at Sheffield Hallam University. Participant Information Sheet. V3 – 19.05.2021 STH: 21782 REC: 21/NW/0146 IRAS: 295752 1

What does the study involve?

This research will take place during one of your normal sessions with a physiotherapist or an occupational therapist. Before your therapy session starts, a researcher will visit you at your hospital bed to put an ultrasound headset on your head (image 1). This headset does not make any sound, and is cushioned, so it should feel comfortable. The researcher will also put a blood pressure cuff over your left arm (image 2) and an elasticated heart rate monitor around your chest. We want measure arm blood pressure and heart rate because they affect blood flow to the brain. It will take about 5 minutes to set up this equipment.



Image 1. Ultrasound headset.



Image 2. Arm blood pressure cuff.

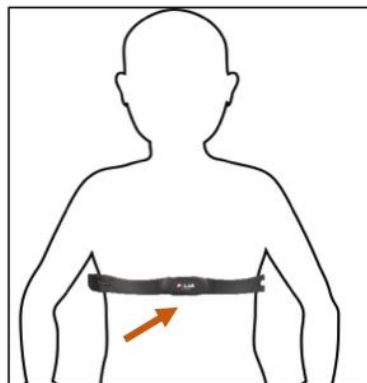


Image 3. Elasticated heart rate monitor worn under t-shirt.

The whole study will last for about **30 minutes**. We will measure your brain blood flow, heart rate, and arm blood pressure while you are in the following four different positions:

1. Lying flat for 5 minutes
2. Reclined sitting for 3 minutes
3. Sitting upright for 3 minutes
4. Standing for 3 minutes

The positions are described in more detail on the next pages. The ultrasound headset will be constantly recording and you will not feel anything other than slight compression on your head. The heart rate monitor will be constantly recording and should feel comfortable. The **blood pressure cuff will inflate 7 times** during this 30-minute study. Each cuff inflation will last for about 40-60 seconds. **This might feel uncomfortable, but it should not cause any harm.** The study is **voluntary** and you are free to stop at any time.

The **first position** will be lying flat (image 4). The researcher will lower the backrest on your bed until you are horizontal. You will be asked to relax for **5 minutes**.

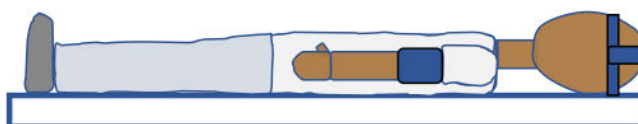


Image 4. Lying flat for 5 minutes.

The **second position** will be reclined sitting (image 5). The researcher will slowly raise the backrest on your bed until you are in a reclined position. You will be asked to relax for **3 minutes** in this position.

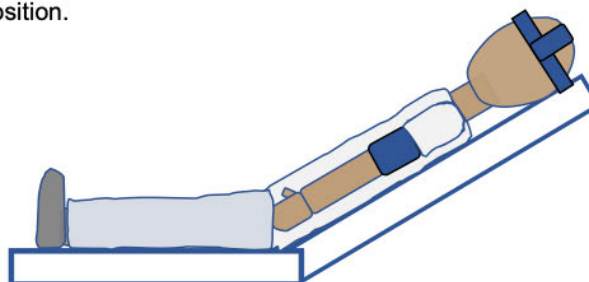


Image 5. Reclined sitting for 3 minutes.

The **third position** will be sitting upright (**image 6**). For this position, you will be asked to sit at the edge of your bed with your feet on the floor. A member of the healthcare team will be available to assist you. You will be asked to stay in this position for **3 minutes**.

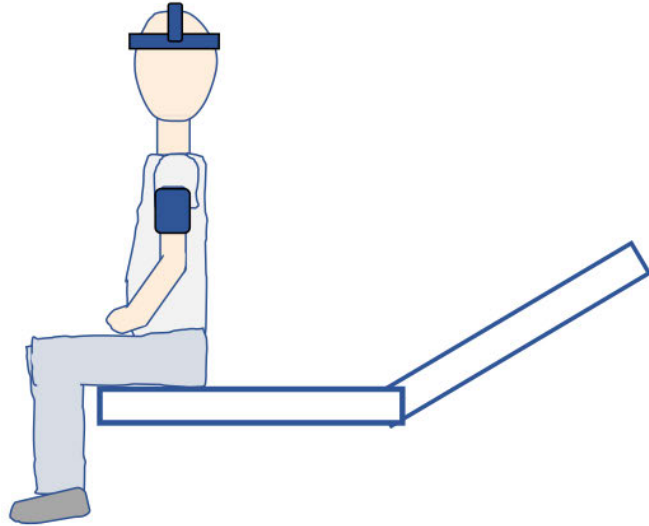


Image 6. Sitting upright for 3 minutes.

The **fourth position** will be standing (**image 7**). A member of the healthcare team will help you stand up. You will be asked to stay standing for **3 minutes**.



Image 7. Standing for 3 minutes.

You will then be asked to sit in a chair and relax while the researcher removes the equipment from your head, arm and chest. This will be the **end of the study**, and you will be able to continue with your normal activities with your healthcare team.

What are the possible benefits of taking part?

There are no direct benefits to you. However, your participation will help us understand how lying down, sitting, and standing, affect blood flow to the brain. This is important because lying down, sitting, and standing are part of your normal rehabilitation routine, and we don't know how these activities affect the blood flow to your brain. We think that when some people stand up, blood flow to their brain might drop. This might not help their recovery from a stroke. However, other people might not have a drop in blood flow to the brain when they stand up. This study might help healthcare professionals identify people who are more likely to have low brain blood flow when standing up. This information will help the healthcare team decide how soon and how often people should stand up after their stroke.

What are the possible disadvantages of taking part?

The blood pressure cuff will be inflated 7 times over a period of 30 minutes. This **might feel uncomfortable**, but it **should not cause any harm**.

When will I have the opportunity to discuss my participation?

You may discuss your participation at any time during the study. Participation is voluntary and you may withdraw at any time. If you choose not to take part, or to withdraw from the study, your medical care will not be affected in any way. If you decide that you no longer want to take part, or if you feel unwell at any point during the study, you are free to stop whenever you want.

Will my participation affect my medical care in any way?

No, your medical care will continue as normal.

Will I be reimbursed for expenses for taking part in the study?

There will be no payments for participating in this study.

How will we use information about you?

We will need to use information from your medical records for this research project.

This information will include your:

- Initials
- Name
- Age
- Sex
- Ethnicity
- Information about your stroke, treatments, therapies and health complications

Authorised people (researchers, NHS staff and auditors) will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that nobody can work out that you took part in the study. We may also contact you in the future to ask if you would like to take part in other research related to stroke rehabilitation. We will only contact you in the future if you give us permission by signing the relevant box on the consent form.

Will my taking part in this study be kept confidential?

Information about your medical condition and results of your assessments will be treated as strictly confidential. Your name, date of birth, telephone number and any other information that could be used to identify you will be removed from any physical or digital

documents or files. All data will be coded using a unique personal identifier (an anonymous code). If you would like a summary of the study results to be sent to you by post, we will keep a paper record of your name and contact details within a locked office at the Royal Hallamshire Hospital for a period of up to 2 years after the end of the study. This data will be destroyed after this point. All digital data containing your information will be transferred to a secure data storage platform hosted by Sheffield Hallam University. All research-related data which does not contain any personally identifiable information (e.g. name and address) will be securely archived for up to 10 years after the study has ended, after which it will be destroyed. Only the research team and authorised professionals will have access to your data. If you choose to stop participating in the study, you may request for your data to be withdrawn and destroyed **at any point until anonymisation of the final data has occurred.**

How will you use the study data?

The findings from this study may be published in scientific journals and presented at scientific conferences. The findings may help guide stroke rehabilitation practice in the future. If you would like to receive the results of the study when they are available, please tick the relevant box on the consent form and we will arrange for a summary to be sent to you by post.

Who are the researchers?

Study Role/Name	Details
Chief Investigator, Dr Simon Nichols	Senior Research Fellow, Sheffield Hallam University
Study Doctor, Dr Ali Ali	Consultant Stroke Physician, Royal Hallamshire Hospital
Co-Investigator, Dr Tom Maden-Wilkinson	Senior Research Fellow, Sheffield Hallam University
Co-Investigator, Dr Helen Humphreys	Research Fellow, Sheffield Hallam University
Co-Investigator, Mr Nik Kudiersky	PhD Student, Sheffield Hallam University
Co-Investigator, Mr Louie Marshall	Medical (MSc) Student, University of Sheffield

What if I have concerns, a complaint or want to know more about how my data will be used?

If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If you have any queries that the research team are unable to answer, or if you have a complaint, please find the relevant contact details below:

You should contact the Data Protection Officer if:

- you have a query about how your data is used by the University
- you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately)
- you would like to complain about how the University has used your personal data

DPO@shu.ac.uk

You should contact the Head of Research Ethics if:

- you have concerns with how the research was undertaken or how you were treated

Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT
Telephone: 0114 225 5555

Thank you for taking the time to consider participating in this study. Further information can be obtained from Dr Simon Nichols (Sheffield Hallam University, Collegiate Hall, Collegiate Campus, Sheffield, S10 2BP; e-mail [REDACTED]). **A member of the research team will return in 6 hours or more to answer any questions you may have about the study and to ask if you would like to participate in the study.**

Please use this box to write down any notes or questions about the study (optional).

Legal basis for research

Sheffield Hallam University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at: <https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research>. All University research is reviewed to ensure that participants are treated appropriately and their rights are respected. This study was approved by the Health Research Authority and NHS Research Ethics Committee (IRAS: 295752; REC reference: 21/NW/0146), and Sheffield Hallam University Research Ethics Committee (Converis: ER31600091).

Appendix 5b) Accessible participant information sheet for Study 1

(yellow highlighted text indicates amendment made in response to HRA requests).

The effects of posture on cerebral blood flow velocity in acute stroke Participant Information Sheet			 Sheffield Teaching Hospitals NHS Foundation Trust	
IRAS: 295752	STH: 21782	REC: 21/NW/0146	Version 2 – 19.05.2021	1

Introduction

You are **invited** to **take part** in a **research** study.



Do I have to take part?

No. This is a **voluntary** study.

It is **your choice**.

Why have I been asked to participate?

You recently had a **stroke**.

There was a **problem** with **blood flow** to your **brain**.



What will happen?

We will ask you to **lie flat** for **5 minutes**.

We will then **raise the bed**.

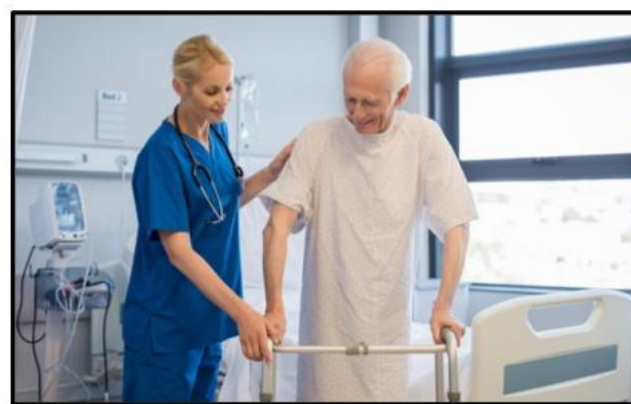
Then we will ask you to **sit back** for **3 minutes**.



What will happen?

We will ask you to **sit** at the **edge of the bed** for **3 minutes**.

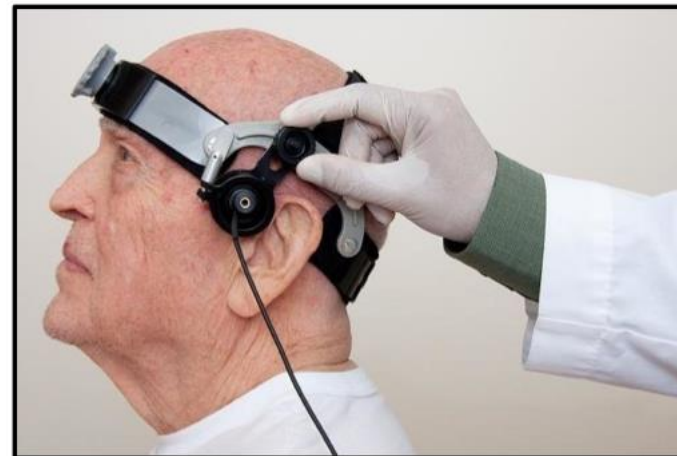
We will ask you to **stand up** for **3 minutes**.



What will happen?

We will **measure** the **blood flow** in your **brain**.

It does not hurt.



What will happen?

We will **measure blood pressure** in your arm.

It will **feel tight**.

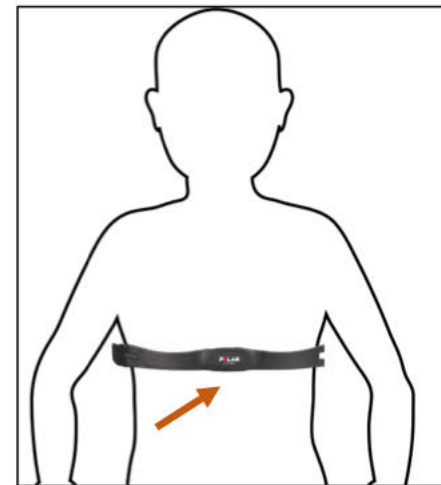


What will happen?

We will **measure heart rate** around your **chest**.

It will go **underneath** your **t-shirt**.

It should feel **comfortable**.



Will it change my treatment?

You will have the **same** hospital **treatment**.

10

What are the risks?

Standing is **safe**.

There is a small risk of feeling **dizzy**.

What are the benefits?

There are **no** direct **benefits** to you.

But you will help us **improve knowledge** about rehabilitation.

This **might help other people** with stroke.

How much time?

The study will be about **30 minutes** long.

Data

Your data will be **anonymised** (name removed).

Your data will be stored **securely** (protected).

Your data will be **destroyed** after 10 years.



What if something goes wrong?

You can **stop** participating at **any time**.

You can **ask** us **questions** at **any time**.

You can **complain if** you're **not happy**.

Contact details

Chief Investigator

Dr Simon Nichols

email:



Independent queries or complaints

Take some time to think about it.

Thank you.

You can **write questions** here if you want

[illegible]

**This document has been produced using the
Stroke Association Accessible Information Guidelines**

Retrieved from:

https://www.stroke.org.uk/sites/default/files/accessible_information_guidelines.pdf1_.pdf

Legal basis for research

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at <https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research>. However, all University research is reviewed to ensure that participants are treated appropriately, and their rights are respected.

This study was approved by the Sheffield Hallam University Research Ethics Committee (ER31600091) and NHS Research Ethics Committee (21/NW/0146).

Further information is available at:

<https://www.shu.ac.uk/research/ethics-integrity-and-practice>

Appendix 5c) Participant information sheet for Studies 2, 3 & 4

(Feasibility study with mechanistic and qualitative sub-studies)

Participant information sheet

Study title: The feasibility of aerobic exercise training early after stroke

Principal Investigator: Dr Simon Nichols, Sheffield Hallam University

Introduction

We would like to invite you to take part in our research study. Joining the study is entirely voluntary. Before you decide if you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with relatives or friends, if you wish. After you have had some time to read the information, one of our research team members will meet with you to go through the information sheet with you and answer any questions you may have. Please ask us if there is anything that is not clear to you or if you would like more information.

Why is the study being done?

A stroke happens when blood flow to the brain is reduced and part of the brain becomes injured. The brain controls our ability to think and do things by sending messages along nerves. After a stroke some of these nerves can become damaged. This may cause a physical or mental disability.

In animal studies, aerobic exercise (e.g. walking or jogging) training done early after stroke helps the brain heal and reduces disability. Some ways that aerobic exercise training may improve recovery is by increasing blood flow to the brain, reducing inflammation, and encouraging the damaged nerves to grow and repair. So far, no research has studied how starting aerobic exercise training in the first week after stroke affects recovery in humans.

Sometimes after a stroke, people have a disability which makes it difficult to exercise. In this study, we will use a **power-assisted bike that helps people to exercise in bed**, even if a person's leg(s) feel weak or numb. This study aims to see if it is feasible for people to do an aerobic exercise training programme early after stroke. This study is being conducted as part of a PhD (**educational**) programme.

What does the study involve?

The study will last for 7 days while you are in hospital. A researcher will also complete some assessments at a routine appointment with your doctor, 3 months after leaving hospital. At the start of the study, we will collect some personal and clinical details from you such as any medical conditions you have, medications, age, ethnicity and gender. During the study, the researchers will do some assessments to monitor your recovery. These assessments (listed on pages 8-12) will help us monitor the following:

- how you are feeling (e.g. mood)
- your thinking ability (e.g. memory, pattern recognition and reading)
- your physical ability (e.g. walking, hand grip strength and standing balance)
- how physically active you are
- how your muscle size changes
- how blood flow to your brain changes
- how the amount of a chemical in your blood (linked to brain repair) changes
- how long you stay in hospital

Important information

- You will be asked to join one of two groups. The choice of group is **random** (like flipping a coin) so **you won't be able to choose a group**. If you are selected for the **intervention group** you will take part in a cycling exercise programme, but this will not affect your usual care. If you are selected for the **usual care group**, you will **not** take part in the cycling exercise programme and you will continue to receive your normal care.
- Both groups will be asked to do some activities (see pages 8-12 for more detail). **10** of these **activities** will be part of your usual care including measures of physical and cognitive ability, fatigue, mood, and blood cholesterol. **51** of the **activities** are **for research** purposes and are **not normally performed** by the stroke team. Some activities will only take a couple of minutes (e.g. telling us how energetic or tired you feel) but others will take much longer (e.g. interview lasting up to 45 minutes).
- The time that you spend with the research team will range from **15 minutes** to **1 hour and 45 minutes per day**. On some days you will be asked to do some assessments that **might make you feel** physically or mentally **tired**. Some people might find this quite **demanding**, so we understand if you do not want to take part. If you **choose not** to take part, this **will not affect** the **care** that you receive.
- We will ask to take some **blood samples from your arm**. The **maximum** amount of blood taken over the entire study will be **24 millilitres** (about **5 teaspoons**).
- You will be asked to **avoid caffeine** (e.g. tea or coffee) on **two** of the study **days**. This can be replaced with decaf. However, this is optional/**voluntary**.

Cycling exercise (intervention group)

The aerobic exercise training programme will involve **one exercise session per day for five days**. On the first day, we will bring a cycling machine to your hospital bed and show you how to use it. The cycling machine is **specially designed** for use in a hospital ward. It has a **motor** which **helps you pedal**, which can be useful if your legs feel weaker than normal. Once you are comfortable and ready to start, we will ask you to cycle at a low intensity and gradually increase the cycling intensity to a moderate level. At a moderate intensity, you will feel **warmer** and your **breathing** will be slightly **faster** and **deeper**, which is **normal**. In the first exercise session you will do 10 minutes of moderate-intensity exercise. For the next 4 days, the amount of exercise will increase by 5 minutes per day. By day 5, you should be able to do 30 minutes of exercise.



Figure 1. Person using power-assisted bike in bed.

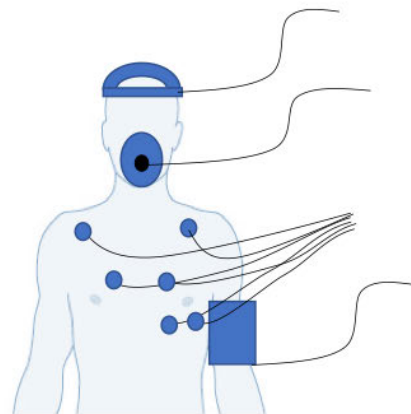


Figure 2. Example of equipment worn during cycling exercise **session 5 only** including headset, face mask, chest electrodes and arm cuff.

In **all 5 exercise sessions**, we will ask you to wear a **heart rate monitor** around your chest, a **blood pressure cuff** around your arm, and a **device on your fingertip** to measure your oxygen levels. You will be given a gown to wear, and a curtain will be drawn to **maintain your privacy**. If you would **prefer another member of staff** to attach the heart rate monitor, **please ask**. We will monitor you before, during and after exercise to see how your body responds to cycling exercise, and to **make sure that it is safe**.

Continued on next page.

In two of the exercise sessions, we will ask you to wear a comfortable **headset** to measure how the blood flow to your brain changes during exercise. **In one of the exercise sessions**, we will ask you to wear a flexible **mask** over your mouth and nose so that we can measure the air that you breathe out. You should **breathe as normal** whilst wearing this mask. See **page 6** for more **images of the equipment** that you will wear during the study. On the last exercise day, we will take some **blood samples** from your arm before and after exercise (**total = 24 mL or 5 teaspoons**). We will also collect details about any complications or problems you may experience during or after the study. **A member of the clinical team will always be available to help** if you feel unwell or experience any problems during the session.

As well as the exercise programme, you will be asked to do some **assessments** whilst in **hospital and 3 months later**, including questionnaires and physical function tests. We will also measure your physical activity levels and your thigh muscle size. You may also be asked to take part in **two interviews**, one in hospital and another 3 months later at a routine appointment with your doctor (see **page 5** for further information about **interviews**). A table summarising the study visits and **activities** for the **intervention group** is included on **pages 8-10**. It is important to note that some of the **assessments will be time consuming**, and **might feel tiring or uncomfortable**. However, we will do our best to be flexible around your arrangements, and we will aim to minimise fatigue and discomfort.

Please note that your follow-up appointments might be conducted by telephone or video call due to COVID-19 restrictions. If so, we may not do all of the assessments.

Usual care group

If you are selected for the usual care group, you will **not** be asked to do any cycling exercise. However, you will be asked to do some **assessments** whilst in **hospital and 3 months later**, including questionnaires and physical function tests. We will also measure your physical activity levels, your thigh muscle size, blood flow to your brain, and a chemical in your blood. We will take **12mL** (about **2.5 teaspoons**) of **blood** in total. You may also be asked to take part in **two interviews**, one whilst in hospital, and another 3 months later at a routine appointment with your doctor (see **page 5** for further information about **interviews**). A table summarising the study visits and activities for the **usual care group** is included on **pages 11-12**. **Images** of the **equipment** that you will wear can be found on **page 7**. It is important to note that some of the **assessments will be time consuming**, and **might feel tiring or uncomfortable**. However, we will do our best to be flexible around your arrangements, and we will aim to minimise fatigue and discomfort.

Please note that your follow-up appointments might be conducted by telephone or video call due to COVID-19 restrictions. If so, we may not do all of the assessments.

Physical activity monitor

If you are in either the intervention group or the usual care group, we may give you an activity monitor to wear on your wrist for two weeks. This will give us an idea of how your rehabilitation is progressing. If we give you one, **please wear** the activity monitor **as much as possible** for **two weeks**. It is **waterproof** so you can wear it while bathing and during water-based activities if you wish. You might prefer to take it off when sleeping or bathing, which is fine. The activity monitor is **insured** by Sheffield Hallam University. If you lose it, you **will not** need to pay any money to replace it. However, **please keep the activity monitor safe** so that your data is not lost, and so that other people can use the device in the future. You will be asked to bring the activity monitor to a 2-week follow-up appointment with your doctor. However, if COVID-19 restrictions are likely to prevent you from attending your appointment, you may not be given an activity monitor. If you have been given an activity monitor and cannot attend your appointment, we may send a pre-paid envelope to your address so that you can return it to us. If you need any help with this, please contact Mr Nik Kudiersky by e-mail: n.kudiersky@shu.ac.uk. We will give you a telephone call after a couple of weeks to see if you need any help.



Figure 3. Physical activity monitor worn on wrist after leaving hospital.

Interviews

We will ask **some participants** to take part in **two interviews**. These participants will be **randomly selected** (like flipping a coin) from both groups. The first interview will happen in hospital on day 7 of the study, lasting 30-45 minutes. The purpose of the first interview is to discuss participants' experience taking part in the study. This will be conducted by Mr Nik Kudiersky in a quiet, private area in the hospital. The second interview will happen 3 months after leaving hospital at a routine check-up that all patients will have with Dr Ali. This interview will last for 15-20 minutes, and will be conducted by Mr Nik Kudiersky. The second interview will focus on people's rehabilitation journey since leaving hospital. If you take part in an interview, your **voice** will be **recorded**. The interviews are voluntary, and if you feel upset at any point in the interviews, you may take a break or stop the interview early. We **will not video** record the interview. All data will be stored securely and will be anonymised. You may request for your data to be withdrawn and destroyed at any point until anonymisation of the final data has occurred.

Please note that the second interview might be conducted by telephone or video call due to COVID-19 restrictions.

Table 1. Intervention group equipment

Equipment	Images	When and for how long?
Small, lightweight activity monitor stuck on the front of one of your thighs with a waterproof dressing.		Fitted on day 1 and removed on day 7 (it will stay on your leg for 6 days).
Electrodes around your chest to measure your heart rate. A cuff around your upper arm to measure your blood pressure. A fingertip device that monitors the level of oxygen in your blood.	 	During 5 exercise sessions (study days 2-6) for 50-70 minutes per session.
An ultrasound headset to measure the blood flow to your brain.		During 2 exercise sessions (day 2 and day 6) for 50-70 minutes per session.
A face mask to measure the air that you breathe out.		During 1 exercise session (day 6) for 70 minutes.

Table 2. Usual care group equipment

Equipment	Images	When and for how long?
Small, lightweight activity monitor stuck on the front of one of your thighs with a waterproof dressing.		Fitted on day 1 and removed on until day 7 (it will stay on your leg for 6 days).
A cuff around your upper arm to measure your blood pressure.		Day 2 and day 6 for 15 minutes.
A fingertip device that monitors your heart rate and the level of oxygen in your blood.		
An ultrasound headset to measure the blood flow to your brain.		

Schedule of activities for the **intervention** group:

Visit	Timepoint	Study Activity	Duration
1	Day 1	• Consent. • Record relevant participant clinical and personal details. • Thigh muscle size measurement (ultrasound). • Attach activity monitor to thigh. • Cognitive assessment • Questionnaires (mood, fatigue and confidence). • Physical function tests (e.g. hand grip strength, and standing balance). • Measures of disability	105 minutes
2	Day 2	• Participant to avoid caffeine before study activities. • Exercise session 1. • Cerebral blood flow measurement (ultrasound). • Heart rate, blood pressure and oxygen level measurements. • Fatigue and physical exertion measurements.	50 minutes
3, 4 & 5	Days 3, 4 & 5	• Exercise sessions 2, 3 & 4. • Heart rate, blood pressure and oxygen level measurements. • Fatigue and physical exertion measurements.	45-55 minutes per day

Continued on next page. [Blue text](#) means that the activity is done as part of usual care.

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Continued. Schedule of activities for the **intervention** group:

6	Day 6	• Participant to avoid caffeine before study activities. • Exercise session 5. • Heart rate, blood pressure and oxygen level measurements. • Fatigue and physical exertion measurements. • Cerebral blood flow measurement. • Expired gas measurement. • Blood samples before and after exercise.	70 minutes
7	Day 7	• Remove activity monitor from thigh. • Thigh muscle size measurement (ultrasound). • Physical function tests (e.g. hand grip strength, and standing balance). • Measures of disability • Provide participant with wrist activity monitor. • Interview about the study.	105 minutes
8	2 weeks after discharge	• Routine appointment with doctor. • Participant returns wrist activity monitor.	N/A

Continued on next page. [Blue text](#) means that the activity is done as part of usual care.

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Continued. Schedule of activities for the **intervention group**:

9	3 months after discharge	• Routine appointment with doctor. • Thigh muscle size measurement (ultrasound). • Cognitive assessment • Questionnaires (mood, fatigue and confidence). • Physical function tests. • Interview about the study.	1.5 hours
Blue text means that the activity is done as part of usual care.			Total study duration = 9 hours 40 minutes

Schedule of activities for the **usual care** group:

Visit	Timepoint	Study Activity	Duration
1	Day 1	• Consent. • Record relevant participant clinical and personal details. • Thigh muscle size measurement (ultrasound). • Attach activity monitor to thigh. • Cognitive assessment • Questionnaires (mood, fatigue and confidence) • Physical function tests (e.g. hand grip strength and standing balance). • Measures of disability	105 minutes
2	Day 2	• Cerebral blood flow measurement at rest (ultrasound). • Participant to avoid caffeine before CBF measurement.	15 minutes
3	Day 6	• Cerebral blood flow measurement at rest (ultrasound). • Blood samples at rest. • Participant to avoid caffeine before CBF measurement and blood samples.	20 minutes

Continued on next page. [Blue text](#) means that the activity is done as part of usual care.

Continued. Schedule of activities for the **usual care group**:

4	Day 7	• Remove activity monitor from thigh. • Thigh muscle size measurement (ultrasound). • Physical function tests (e.g. hand grip strength, and standing balance). • Measures of disability • Provide participant with wrist activity monitor. • Interview about the study.	105 minutes
5	2 weeks after discharge	• Routine appointment with doctor. • Participant returns wrist activity monitor.	N/A
6	3 months after discharge	• Routine appointment with doctor. • Cognitive assessment. • Questionnaires (mood, fatigue and confidence). • Physical function tests (e.g. hand grip strength, and standing balance). • Interview about the study.	1.5 hours
Blue text means that the activity is done as part of usual care.			
			Total study duration = 5 hours 35 minutes

What are the possible benefits of taking part?

We are unsure if this exercise intervention will help your recovery at this stage. By participating in either the intervention group or usual care group, you will help improve our knowledge about how aerobic exercise can be used in stroke rehabilitation. This may help future patients who have had a stroke. By doing aerobic exercise, you may improve your fitness, prevent or slow down the loss of muscle strength and size, and improve your mood.

What are the possible disadvantages of taking part?

Previous studies have shown that aerobic exercise is safe for people to do in the first week after stroke. So far, 276 aerobic exercise sessions have been completed in the first week after stroke. 237 sessions (86%) involved walking, 32 sessions (12%) involved seated cycling or stepping, and 7 sessions (3%) involved sit-to-stand exercise. From these studies, we estimate that the risk of:

- Cardiovascular (e.g. heart or blood pressure problems), neurological, or musculoskeletal (e.g. muscle or joint injuries) complications is **less than 1%** (no adverse events have happened so far).
- Lower-limb pain is **less than 2%** (only occurred in treadmill exercise).
- Getting a blister or superficial wound on the foot is **1.1%** (only occurred in treadmill exercise).
- Dizziness is **less than 7%** (only occurred in treadmill exercise).

The risk estimates are also shown in the charts below where the **black** area indicates the chance of an **adverse event** happening and the **grey** area indicates the chance of **no adverse event** happening. The charts include data from studies that included *walking* and *cycling* exercise.



Figure 4. Charts showing the risk of adverse during aerobic exercise.

Possible disadvantages of taking part (continued)

Taking part in the study may feel inconvenient or burdensome for participants, but we will be as flexible as possible and work around your arrangements. Some of the study procedures might be physically uncomfortable such as having a blood sample taken. However, the researchers are well-trained to minimise discomfort. The questionnaires or interviews might make you feel emotional or uncomfortable at times. The researchers are well-trained in speaking to people who have had a stroke, and everything that you disclose will be kept confidential.

You are free to withdraw from this study if you find it too demanding on top of your other activities.

When will I have the opportunity to discuss my participation?

You may discuss your participation at any time during the study. Participation is voluntary and you may withdraw at any time. If you choose not to take part, or to withdraw from the study, your medical care will not be affected in any way.

Will my participation affect my medical care in any way?

No, your medical care, including any physiotherapy you are undergoing, can continue as normal even if you are taking part in this study.

Will I be reimbursed for expenses for taking part in the study?

If you are required to travel to an appointment that is not part of your routine care, we will reimburse your travel costs.

How will we use information about you?

We will need to use information from your medical records for this research project. This information will include your:

- **Initials**
- **Name**
- **Age**
- **Sex**
- **Ethnicity**
- **Contact details**
- **Information about your stroke, treatments, therapies and health complications**

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that nobody can work out that you took part in the study.

Will my taking part in this study be kept confidential?

Information about your medical condition and results of your assessments will be treated as strictly confidential. Your name, date of birth, telephone number and any other information that could be used to identify you will be removed from any physical or digital documents or files. All data will be coded using a unique personal identifier (an anonymous code). Any paper files containing your information will be stored in a file within a locked office at the Royal Hallamshire Hospital and will be securely archived for up to 10 years after the study has ended. All digital or audio data containing your information will be transferred to a secure data storage platform hosted by Sheffield Hallam University.

Blood samples will be stored confidentially and securely, and will be destroyed within 10 years of completing the study. Your GP will be informed by letter that you are taking part in the study. If any of your questionnaire or interview responses raise concern about your wellbeing, your GP will be informed. If any other information is released outside the study office this will be done in a coded form with your name and any other identifiable information removed from the records. All study data will be stored for a maximum period of 10 years, after which it will be destroyed. Only the research team and authorised professionals will have access to your data. If you choose to stop participating in the study, you may request for your data to be withdrawn and destroyed **at any point until anonymisation of the final data has occurred.**

How will you use the study data?

The findings from this study may be published in scientific journals and presented at scientific conferences. The findings may help guide stroke rehabilitation practice in the future. If you would like to receive the results of the study when they are available, please tick the relevant box on the consent form and we will arrange for a summary to be sent to you by post.

Who are the researchers?

Study Role/Name	Details
Principal Investigator, Dr Simon Nichols	Senior Research Fellow, Sheffield Hallam University
Study Doctor, Dr Ali Ali	Consultant Stroke Physician, Royal Hallamshire Hospital
Co-Investigator, Dr Tom Maden-Wilkinson	Senior Research Fellow, Sheffield Hallam University
Co-Investigator, Dr Helen Speake	Research Fellow, Sheffield Hallam University
Co-Investigator, Mr Nik Kudiersky	PhD Student, Sheffield Hallam University

Who is funding the study?

This study is funded by the College of Health, Wellbeing and Life Sciences at Sheffield Hallam University.

What if something goes wrong?

If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If you have any queries that the research team are unable to answer, or if you have a complaint, please find the relevant contact details below:

You should contact the Data Protection Officer if:

- you have a query about how your data is used by the University
- you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately)
- you would like to complain about how the University has used your personal data

DPO@shu.ac.uk

You should contact the Head of Research Ethics (██████████ Macaskill) if:

- you have concerns with how the research was undertaken or how you were treated

Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT
Telephone: ██████████

Legal basis for research

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at <https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notice/privacy-notice-for-research>. All University research is reviewed to ensure that participants are treated appropriately and their rights are respected. This study was approved by the Sheffield Hallam University Research Committee (Converis number: ER25055563). Further information is available at <https://www.shu.ac.uk/research/ethics-integrity-and-practice>

Use this box to write down any notes or questions about the study (optional).

[illegible]

Appendix 5d) Accessible participant information sheet for Studies 2, 3 & 4

(Feasibility study with mechanistic and qualitative sub-studies)

Aerobic exercise training in acute ischaemic stroke:

A feasibility study

Participant Information Sheet

IRAS number: 280320

Version 2 – 25.08.2020

Introduction

You are **invited** to **take part** in a **research** study.



Do I have to take part?

No. This is a **voluntary** study.

It is **your choice**.

Why have I been asked to participate?

You recently had a **stroke**.

There was a **problem** with **blood flow** to your **brain**.



What will I do?

You might be asked to **continue as normal**,
or ...

You might be asked to **exercise**.



Exercise makes your **heart beat** faster.

Exercise **increases blood** to the **brain**.

Exercise **may help** the **brain recover**.



Exercise

Exercise will be **on a bike**.

Exercise will be **once a day**.

Exercise will be for **five days**.



What will I do?

We will do some **tests**.

Tests will measure your **recovery** and **wellbeing**.



Will it change my treatment?

You will have the **same** hospital **treatment**.

What are the risks?

Studies show that exercise is **safe**.

There is a small risk of feeling **dizzy** or **tired**.

There is a small risk of having leg or foot **pain**.

What are the benefits?

You will help us **improve knowledge** about stroke rehab.

Exercise may **improve** your **fitness** and **mood**.

We **don't know** if exercise will help the brain.

How much time?

The study will be for **6 days**.

Some days we may meet for **10 minutes**.

Other days we may meet for up to **2 hours**.

Data

Your data will be **anonymised** (name removed).

Your data will be stored **securely**.

Your data will be **destroyed** after 10 years.



What if something goes wrong?

You can **stop** participating at **any time**.

You can **ask** us **questions** at **any time**.

You can **complain if** you're **not happy**.

Contact details

Principle Investigator

Dr Simon Nichols

email:

[REDACTED]

Independent queries or complaints

[REDACTED]

email:

[REDACTED]

telephone:

[REDACTED]

Take some time to think about it.

Thank you.

**This document has been produced using the
Stroke Association Accessible Information Guidelines**

Retrieved from:

https://www.stroke.org.uk/sites/default/files/accessible_information_guidelines.pdf1_.pdf

Legal basis for research

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at <https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research>. However, all University research is reviewed to ensure that participants are treated appropriately and their rights are respected. This study was approved by the Sheffield Hallam University Research Committee (Converis number ER25055563). Further information is available at <https://www.shu.ac.uk/research/ethics-integrity-and-practice>

Appendix 6 – Participant consent forms

Appendix 6a) Participant consent form for Study 1

Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Participant consent form

Study title: The effects of posture on cerebral blood flow velocity in acute stroke

Principal Investigator: Dr Simon Nichols

Please initial box

- 1) I confirm that I have read and understood the participant information sheet (version 2, dated 24.02.2021) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
- 2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
- 3) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, and from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical notes. ☐
- 4) I understand that some personally identifiable information (e.g. my name, address, date of birth and telephone number) will be collected but these data will be stored in a locked office in the hospital and will be kept separate from other data collected during the study. ☐
- 5) I would like to be sent a copy of the results in the post/via e-mail (optional). ☐
- 6) I agree to be contacted in the future about other study-related activities (optional). ☐
- 7) I agree to take part in the above study. ☐

Name of participant

Date

Signature

Name of witness
(For participants who cannot write)

Date

Signature

Name of person taking consent

Date

Signature

Participant Consent Form. Version 2 – 24.02.2021

IRAS: 295752

**The effects of posture
on cerebral blood flow velocity
in acute stroke**

Aphasia-friendly consent form

STH:

IRAS: 295752

Version: 1

Date: 03.02.2021

Informed consent checklist

Action	Please tick
Potential participant provided with appropriate participant information sheet.	
Potential participant provided with opportunity to ask questions and discuss the study.	

Recruiter name: _____

Recruiter signature: _____

Please choose **yes** or **no** for the statements below

You can draw a **circle**.



Yes



No

I have been given **information** to keep **about this study**.



Yes



No

The information has been **explained** to me.

I understand the information.



Yes



No

I have had the chance to **ask questions** about the study.

I am **happy with** the **answers** to my questions.



Yes



No

I understand that **I can stop** the study at any time.

I **do not** have to **give a reason**.

This will **not affect** the **care** I get from the **NHS**.



Yes



No

I understand that some of my personal details will be used, and stored securely (e.g. name, address).



Yes



No

I agree to be contacted in the future about
taking part in **other research.**



Yes



No

I want to be **sent** the **results** in the **post**.



Yes



No

I agree to take part in this study.



Yes



No

Name of person taking consent

Date

Signature

Name of participant

Date

Signature

**Name of witness
(for participant who cannot write)**

Date

Signature

Relationship of witness to patient:

Appendix 6c) Participant consent form for Studies 2, 3 & 4
(Feasibility study with mechanistic and qualitative sub-studies)

Royal Hallamshire Hospital
Glossop Road
Sheffield, S10 2JF

Participant Consent Form. Version 2 - 24.08.2020

Study title: Feasibility of aerobic exercise training in the acute phase of stroke

Principal Investigator: Dr Simon Nichols

Please initial box

- 1) I confirm that I have read and understood the participant information sheet (version 2 dated 24/08/20) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
- 2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
- 3) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, and from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
- 4) I agree to have blood samples taken during this study, and I consent for these blood samples to be analysed for current and future research purposes. ☐
- 5) I understand that some personally identifiable information (my name, address, date of birth and telephone number) will be collected but these data will be stored in a locked office in the hospital and will be kept separate from other data collected during the study. ☐
- 6) I consent to my General Practitioner being informed about my participation in the study and of any concerns about my medical condition which occur as a result of my participation. ☐
- 7) In the unlikely event that I lose capacity to participate in this study, I understand that the research team may retain tissue (e.g. blood samples) and personal data collected and continue to use it confidentially for the purposes described in the participant information sheet. ☐
- 8) I would like to be sent a copy of the results in the post (optional). ☐
- 9) I agree to be contacted in the future about other study-related activities (optional). ☐
- 10) I agree to take part in the above study. ☐

Name of participant

Date

Signature

Name of witness
(For patients who cannot write)

Date

Signature

Name of person taking consent

Date

Signature

Appendix 6d) Accessible participant consent form for Studies 2, 3 & 4

(Feasibility study with mechanistic and qualitative sub-studies)

ATAS Study
Aphasia-Friendly Consent Form

STH: 21298

IRAS: 280320

Version: 1

Date: 23.10.2020.

Informed consent checklist

Action	Please tick
Potential participant provided with appropriate participant information sheet.	
Potential participant given at least 24 hours to consider information.	
Potential participant provided with opportunity to ask questions and discuss the study.	

Recruiter name: _____

Recruiter signature: _____

Please choose **yes** or **no** for the statements below

You can draw a **circle**.



Yes



No

I have been given **information** to keep **about this study**.



Yes



No

The information has been **explained** to me.

I **understand** the information.



Yes



No

I have had the chance to **ask questions** about the study.

I am **happy with** the **answers** to my questions.



Yes



No

I understand that **I can stop** the study at any time.

I **do not** have to **give a reason**.

This will **not affect** the **care** I get from the **NHS**.



Yes



No

I agree to have blood samples taken
(no more than 5 teaspoons).



Yes



No

**I understand that my doctor will be told
that I am taking part in this study.**



Yes



No

I understand that some of my personal details will be used, and stored securely (e.g. name, address).



Yes



No

I agree to be contacted in the future about
taking part in **other research.**



Yes



No

I want to be **sent** the **results** in the **post**.



Yes



No

I agree to take part in the ATAS study.



Yes



No

Name of person taking consent

Date

Signature

Name of participant

Date

Signature

Name of witness
(for participant who cannot write
due to motor impairment)

Date

Signature

Relationship of witness to patient:

Appendix 6e) Healthcare professional participant consent for Study 4

Participant consent form (for healthcare professionals)

Study title: The feasibility of aerobic exercise training early after stroke

Principal Investigator: Dr Simon Nichols

Please initial box

1. I have read the participant information sheet (dated 06.11.2020, version 1) for this study and have had the details of the study explained to me. ☐
2. My questions about the study have been answered to my satisfaction and I understand that I may ask further questions at any point. ☐
3. I understand that I am free to stop participating in this study at any point, and may request for my data to be withdrawn and destroyed (as outlined in the participant information sheet) without having to give a reason. ☐
4. I agree to be interviewed and to have my voice recorded. ☐
5. I understand that I am free to decline to answer any particular questions in the interview without giving a reason. ☐
6. I agree to provide information to the researchers under the conditions of confidentiality set out in the participant information sheet. ☐
7. I wish to participate in the study under the conditions set out in the participant information sheet. ☐
8. I consent for my anonymised data to be used for research purposes related to this study. ☐
9. I would like to be sent a copy of the results in the post (insert address below). ☐

Name of participant: _____ **Date:** ____/____/____ **Signature:** _____

Participant's postal address (optional): _____

_____ **Post code:** _____

Name of person taking consent: _____ **Date:** ____/____/____ **Signature:** _____

Appendix 7 – Interview schedules

Interview Schedule

Table 1. Interview topics to be discussed with **usual care group** participants after the **inpatient phase** of the trial.

Topic	Question examples
Experience of the study	• Can you tell me about your overall experience of participating in this study? • What impact has participating in this study had on you? • Have you had any positive experiences (in addition to anything already mentioned)? • Have you had any negative experiences (in addition to anything already mentioned)? • If you were to go back in time, would you have done this again? Why is that? • Is there anything you would like to have been done differently?
Recruitment	• At the beginning of the study, we asked you to join the usual care group (no exercise). How do you feel about this? • How would you feel if we asked you to join the other group instead?
Time burden	• How do you feel about the amount of time you have spent participating in this study?
Exercise-related self-efficacy	• When you leave hospital, you'll be encouraged to do some physical exercise to help you recover from your stroke. This could be on your own or supervised. How confident do you feel in your ability to start exercising? • You might be encouraged to do some exercise that increases your heart rate and makes you breathe faster (e.g. walking or cycling in a gym). This could be at on your own or supervised. How confident would you feel doing this type of exercise when you leave hospital?
Optimism	• What are your main hopes and concerns about the rehabilitation journey ahead of you?

Interview Schedule. Version 2 – 03.11.2020

STH:21298

IRAS:280320

Table 2. Interview topics to be discussed with **intervention group** participants after the **inpatient phase** of the trial.

Topic	Question examples
Experience of the study	• Can you tell me about your overall experience of participating in this study? • What impact has participating in this study had on you? • Have you had any positive experiences (in addition to anything already mentioned)? • Have you had any negative experiences (in addition to anything already mentioned)? • If you were to go back in time, would you have done this again? Why is that? • Is there anything you would like to have been done differently?
Recruitment	• At the beginning of the study, we asked you to join the intervention group (exercise). How do you feel about this? • How would you feel if we asked you to join the other group instead?
Exercise mode	• How did you find the cycling exercise? • What are your thoughts about using the bike?
Exercise session duration	(Recap that exercise session duration progressed from 10 minutes to 30 minutes). • How do you feel about the length of the exercise at the start of the intervention (10 minutes)? • What do you think about the length of the exercise progressing from 10 to 30 minutes? • We used rest intervals (breaks) every 5 minutes. How was this? • How do you think it would be different if the exercise was continuous without recovery intervals?

Exercise intensity	(Recap that exercise intensity was guided by Rating of Perceived Exertion [RPE]). We asked you to exercise at a difficulty described as 'somewhat hard' or 13 out of 20 on the RPE scale. How did this feel?
Exercise session frequency	How did you find it exercising once a day?
Perceived effectiveness of exercise training intervention	What impact do you think that the exercise has had on you? This could be positive or negative.
Time burden	How do you feel about the amount of time you have spent participating in this study?
Exercise-related self-efficacy	- When you leave hospital, you'll be encouraged to do some physical exercise to help you recover from your stroke. This could be on your own or supervised. How confident do you feel in your ability to start exercising? - You might be encouraged to do some exercise that increases your heart rate and makes you breathe faster (e.g. walking or cycling in a gym). This could be at on your own or supervised. How confident would you feel doing this type of exercise when you leave hospital?
Optimism	What are your main hopes and concerns about the rehabilitation journey ahead of you?

Table 3. Interview topics to be discussed with **healthcare practitioners** after the **inpatient phase** of the trial.

Topic	Question examples
Attitude towards the exercise training intervention	• What are your thoughts about the exercise intervention? • Is there anything you would like to have been done differently?
Impact of the study on clinical practice	• What impact did the study have on you as a practitioner? This could be positive or negative.
Impact of the intervention on participants	• What impact did the exercise intervention have on the participants? This could be positive or negative.
Unintended consequences	• Have there been any unintended/ unexpected consequences of the study? • How do you feel about this?

Table 4. Interview topics to be discussed with **participants** that **dropped out** of the study **at any point**.

Topic	Question examples
Experience of the study	• Can you tell me about your overall experience of participating in this study? • What impact has participating in this study had on you? • Have you had any positive experiences (in addition to anything already mentioned)? • Have you had any negative experiences (in addition to anything already mentioned)? • Is there anything you would like to have been done differently?
Reason for dropout	• What are the main reasons that you dropped out of the study?

Table 5. Interview topics to be discussed with **usual care group** participants at the **3-month follow-up** appointment.

Topic	Question examples
Rehabilitation after being discharged from hospital.	• Try and think back to the first few days after leaving hospital, how did you feel about the rehabilitation journey ahead of you? • Can you tell me about the support that was offered to you to help with your rehabilitation? • Can you give me a summary about how your rehabilitation has gone over the last 3 months? What types of activities have you been doing? • What were the main things that helped you do your rehabilitation activities? • What were the main things that got in the way of doing your rehabilitation activities? • Since leaving hospital, have you done any aerobic exercise? That's exercise that makes you get out of breath and makes your heart beat faster, like walking, cycling in a gym, or water-based activities? Tell me more about that (duration/intensity/frequency). • (If no) Why is that? • (If no, but person expresses interest) What do you think would help you do aerobic exercise? • If you were to go back in time to when you first left hospital, is there anything you would like to have been done differently to improve your rehabilitation experience? • How do you feel about your health going forward? What are your priorities and/or concerns?

Table 6. Interview topics to be discussed with **intervention group** participants at the **3-month follow-up** appointment.

Topic	Question examples
Rehabilitation after being discharged from hospital.	• Try and think back to the first few days after leaving hospital, how did you feel about the rehabilitation journey ahead of you? • Can you tell me about the support that was offered to you to help with your rehabilitation? • Can you give me a summary about how your rehabilitation has gone over the last 3 months? What types of activities have you been doing? • What were the main things that helped you do your rehabilitation activities? • What were the main things that got in the way of doing your rehabilitation activities? • Since leaving hospital, have you done any aerobic exercise? That's exercise that makes you get out of breath and makes your heart beat faster, like walking, cycling in a gym, or water-based activities? Like you did in hospital. Tell me more about that (duration/intensity/frequency). • (If no) Why is that? • (If no, but person expresses interest) What do you think would help you do aerobic exercise? • What impact do you think the cycling exercise that you did in hospital has had on you? This could be physical, psychological/emotional? (Emphasise answers can be positive or negative). • If you were to go back in time to when you first left hospital, is there anything you would like to have been done differently to improve your rehabilitation experience? • How do you feel about your health going forward? What are your priorities and/or concerns?