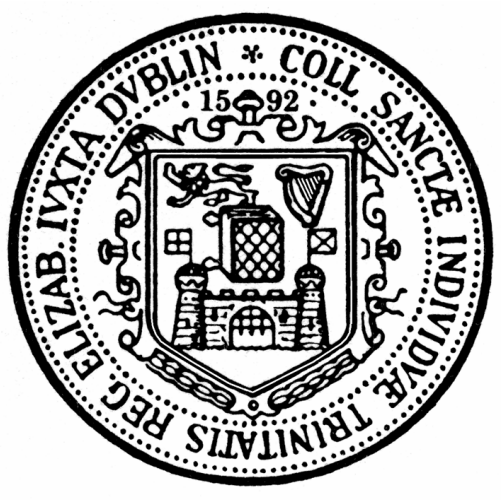

Trinity College Dublin, the University of Dublin

School of Medicine

Department of Medical Gerontology

2025

Orthostatic Hypotension and Cerebral Perfusion in Falls and Related Syncopal Disorders

A dissertation submitted In fulfilment of the requirements for the degree of Doctor of Philosophy

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Regius Rose Anne Kenny, Dr Ciarán Finucane, Prof Roman Romero-Ortuño, Prof Cónal Cunningham

Declaration

I declare that this thesis has not been previously submitted as an exercise for a degree at this or any other university.

I declare that it is entirely my own work under the direction and supervision of my supervisors, Regius Rose Anne Kenny and Dr Ciarán Finucane.

Part of this work was carried out in collaboration with Dr Laura Pérez-Denia as part of her PhD. Relevant sections will be acknowledged in the text.

I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

I consent to the examiners retaining a copy of the thesis beyond the examining period, should they so wish.

Signed: 

Paul Claffey

Date: 28th June 2024

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Lastly, I dedicate this work to my wonderful grandmother, Annie Claffey, who, in her 100th year, continues to inspire my journey through geriatric medicine. Her resilience and wisdom have been a guiding light, and I am privileged to honour her in this endeavour.

Paul Claffey

June 2024

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List of Abbreviations

ACA anterior cerebral artery

AD Alzheimer's disease

ALOC amnesia for loss of consciousness

ANS autonomic nervous system

ARB angiotensin II receptor blocker

AS active stand

ASL arterial spin labelling

ATC Anatomic Therapeutic Chemical

BBB blood-brain barrier

BP blood pressure

BMI body mass index

CA cerebral autoregulation

CAGE cut down, angry, guilty, eye-opener

CAPI computer aided personal interview

CBF cerebral blood flow

CBFv cerebral blood flow velocity

CBV cerebral blood volume

CEA carotid endarterectomy

CES-D centre for epidemiological studies - depression

CGA comprehensive geriatric assessment

CI 95% confidence interval

$CMRO_2$ cerebral metabolic rate of O_2

CNS central nervous system

CO cardiac output

CO_2 Carbon dioxide

CPB cardiopulmonary bypass

CPP cerebral perfusion pressure

CSM carotid sinus massage

CSS carotid sinus syncope

CT computed tomography

CV cardiovascular

CVLM caudal ventrolateral medulla

DBP diastolic blood pressure

DLB dementia with Lewy bodies

DPF differential pathlength factor

ECG electrocardiogram

ED emergency department

EEG electroencephalogram

ENS enteric nervous system

ESC European Society of Cardiology

FASU falls and syncope unit

HHb deoxygenated haemoglobin

HR heart rate

HUT head up tilt

ICP intracranial pressure

ICU intensive care unit

iOH initial orthostatic hypotension

LBNP lower body negative pressure

MAP mean arterial pressure

MCA middle cerebral artery

mmHg millimetres of Mercury

MMSE mini mental state examination

MOCA Montreal cognitive assessment

MRI magnetic resonance imaging

MSA multiple systems atrophy

MTT mean transit time

NART national adult reading test

NIRS near infrared spectroscopy

nm nanometres

NO nitric oxide

NTS nucleus tractus solitarius

NVC neurovascular coupling

O_2 Oxygen

O_2Hb oxygenated haemoglobin

OH orthostatic hypotension

OR odds ratio

$PaCO_2$ partial pressure of carbon dioxide

PaO_2 partial pressure of oxygen

PCA posterior cerebral artery

PCT perfusion computed tomography

PD Idiopathic Parkinson's disease

PET positron emission tomography

POCD postoperative cognitive dysfunction

PNES psychogenic non-epileptic seizures

PPS psychogenic pseudosyncope

PSNS parasympathetic nervous system

RAAS renin-angiotensin-aldosterone system

RCT randomised controlled trial

REC research ethics committee

RVLM rostral ventrolateral medulla

SBP systolic blood pressure

SCQ self-completion questionnaire

SH supine hypertension

SjO_2 jugular bulb venous O_2 saturation

SNRI serotonin norepinephrine reuptake inhibitor

SNS sympathetic nervous system

SPECT single photon emission CT

SPRINT Systolic Blood Pressure Intervention Trial

SRS spatially resolved spectroscopy

SSRI selective serotonin reuptake inhibitor

SV stroke volume

SVD small vessel disease

TBI traumatic brain injury

TCD transcranial doppler

TFA transfer function analysis

THb total haemoglobin concentration

TIA transient ischaemic attack

TILDA The Irish Longitudinal Study on Ageing

TLOC transient loss of consciousness

TPR total peripheral resistance

TSI tissue saturation index

TUG timed up and go

VVS vasovagal syncope

WMH white matter hyperintensities

XeCT Xenon enhanced computed tomography

Abstract

Falls, syncope and orthostatic dizziness are common reasons for hospital presentations and are highly prevalent among older adults, leading to significant morbidity, loss of independence and increased healthcare utilisation. These problems may indicate impairments in mechanisms regulating systemic blood pressure (BP) and cerebral blood flow (CBF).

Orthostatic Hypotension (OH) is defined by consensus statement as a sustained drop in systolic BP of at least 20 mmHg or in diastolic BP of at least 10 mmHg, within 3 minutes of standing. OH is associated with several adverse health outcomes including falls. Current practice involves measuring peripheral beat-to-beat BP and heart rate (HR) during active standing and head up tilt (HUT) – two potent physiological stressors to the cardiovascular system – providing valuable information for diagnosis and management. However, less is known about CBF during these stressors, particularly in older adults who may or may not report symptoms of cerebral hypoperfusion.

Near-Infrared Spectroscopy (NIRS) is a non-invasive technology that measures frontal lobe cerebral tissue oxygenation, known as tissue saturation index (TSI) – regarded as a suitable surrogate for CBF and can be applied during clinical orthostatic BP assessment.

The primary aim of this thesis is to investigate the relationship between CBF and OH in two cohorts: a clinical group of patients with falls, syncope and dizziness recruited from a specialised outpatient setting and a population group of participants from The Irish Longitudinal Study on Ageing (TILDA). The hypothesis was that OH would be associated with greater cerebral hypoperfusion upon standing and would explain symptoms of

orthostatic intolerance. Furthermore, it was hypothesised that degree of cerebral hypoperfusion would inform future falls risk.

Four hundred ninety-one patients attending a national referral clinic had concurrent TSI recorded alongside peripheral beat-to-beat BP during an active stand (AS). The prevalence of OH was 38.5%. OH patients experienced greater declines in TSI compared to those without. Mixed-effects linear regression models demonstrated a significant relationship between OH and TSI at the same timepoint (β -0.53, [95% confidence interval (CI) -0.59 - -0.46]; p<0.001), which persisted following adjustment for age, sex, baseline BP, cerebrovascular and cardiovascular disease, depression/ anxiety, diabetes, systolic BP, antihypertensives, and antidepressants (β -0.51, [CI -0.58 - -0.44]; p<0.001). TSI changes did not differ in those with symptomatic OH versus those with asymptomatic OH. Secondly, the TILDA population study of over 900 community-dwelling individuals aged ≥70 years found a 10% prevalence of OH, with two-thirds asymptomatic. Compared to those with symptomatic OH, participants with asymptomatic OH had a higher risk of unexplained falls (odds ratio (OR) 2.01 [CI 1.11, 3.65]; p=0.022) but not explained falls (OR 0.93 [CI 0.53, 1.62]; p=0.797) during follow-up. The third study revealed that those with OH and greater TSI drops on standing had the highest risk of future unexplained falls (OR 2.16 [CI 1.30 – 3.60]; p = 0.003). Finally, NIRS monitoring during HUT testing was shown to be a useful adjunct in the investigation and diagnosis of psychogenic pseudosyncope (PPS), an important form of apparent syncope.

These findings provide important clinical implications for the assessment of falls in older people with OH particularly those with asymptomatic OH and in those with marked

cerebral hypoperfusion on standing. NIRS-derived TSI measurements of CBF can identify those with OH at highest risk of future unexplained falls and aid in the diagnosis of PPS.

Lay Abstract

Falls, fainting and feeling dizzy when standing are common reasons older adults present to hospital. These issues can lead to serious health complications, loss of independence, and needing more medical care. Problems like these can indicate disruption to the way the body regulates blood pressure and blood flow to the brain.

Orthostatic Hypotension (OH), where blood pressure drops significantly when standing up is a particular challenge. This is common among older adults and is linked to falls. In the clinical setting, tests that measure blood pressure and heart rate when someone stands up or is tilted upright are carried out to understand these issues better. What happens to brain blood flow in people with OH during these tests is not fully understood, especially in older adults who report feeling dizzy or lightheaded.

Near-Infrared Spectroscopy (NIRS) is a way to measure oxygen levels in the brain without being invasive. This can help understand blood flow in the brain during tests for blood pressure problems.

The main aim of the work in this thesis is to assess how brain blood flow and OH interact with each other in older adults experiencing falls, fainting, or dizzy symptoms. This research involved two groups: one from a specialised clinic and another from a larger study on ageing (TILDA). The hypothesis is that OH leads to reduced brain blood flow upon standing, causing symptoms of dizziness, and that this reduction in blood flow could predict future falls.

The first clinic study, 491 patients had brain oxygen levels and blood pressure measured at same time during a standing test. OH was found in 38.5% of patients and those with

OH had lower levels of brain blood flow at the time of standing compared to those without OH.

The second TILDA study found that about one in ten older adults from the general population had severe OH, even though most (about two thirds) did not feel any symptoms. Those who did feel light-headed when standing did not necessarily have a bigger drop in blood pressure. Interestingly, those with no symptoms of OH were more likely to have future unexplained falls.

Thirdly, it was shown that In the TILDA cohort, those with severe OH and large brain blood flow drops on standing were at the highest risk of future unexplained falls.

Finally, this research also suggests that NIRS was a useful tool to show the absence of reduced blood flow to the brain in a condition called psychogenic pseudosyncope – a form of apparent fainting that can be challenging to diagnose.

Overall, the findings of this research can help clinicians better understand, assess and treat those who experience falls and other related conditions. For older adults with OH, this research allows identification of those at highest risk of future falls, namely those without dizzy symptoms and those found to have large drops in brain blood flow on standing.

Value of Research

This thesis demonstrates the successful incorporation of NIRS into the workflow of a falls and syncope unit. It highlights that it is feasible to integrate the technology into routine clinical practice.

This research shows that OH is associated with lower cerebral perfusion during the AS. In the future, this may facilitate risk stratification and inform important clinical decisions regarding therapy and management. Given the heterogeneity of patterns in the health of older persons, this may enable the personalised approach necessary to manage OH in this cohort.

This research confirms a common scenario observed in the clinical environment – namely that up to two thirds of older adults with severe OH are asymptomatic. It is shown that asymptomatic OH is just as important as symptomatic OH as a risk factor for future unexplained falls.

This research also shows that, when combined, those with severe OH and evidence of greater cerebral hypoperfusion on standing have a higher future risk of unexplained falls compared to either group alone.

The research carried out as part of this thesis also provides valuable insights into an often under recognised and under diagnosed cohort of patients with PPS. This research confirms that NIRS can be a useful adjunct to CBF assessment as it aids with biofeedback and diagnosis disclosure. This may inform future diagnostic guidelines.

Dissemination of Thesis

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Claffey P, Pérez-Denia L, Finucane C, Kenny RA, Briggs R. Cerebral Hypoperfusion and Future Falls Risk among Community Dwelling Older Adults with Orthostatic Hypotension.

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McNicholas T, **Claffey P**, O'Callaghan S, Briggs R, Newman L, Tobin K, Kenny RA, 343 Atrial Fibrillation, Orthostatic Hypotension and Cerebral Perfusion – Data from The Irish Longitudinal Study on Ageing, *Age and Ageing*, Volume 48, Issue Supplement_3, September 2019, Pages iii1–iii16, https://doi.org/10.1093/ageing/afz102.70
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Awards

Special Commendation, Department of Medical Gerontology, Trinity College Dublin, Postgraduate Research Day 2022

Gold Medal, Department of Medical Gerontology, Trinity College Dublin, Postgraduate Research Day 2023

Shortlisted Trinity Excellence in Teaching Award 2021

Structured PhD Credits

As part of the structured PhD programme, I completed the following modules:

CA7000 Research Integrity and Impact in an Open Scholarship Era (5 credits)

VP1017C Graduate Teaching and Learning (5 credits)

Chapter One – Introduction

1.1 Motivation for this thesis

The motivation behind embarking on this thesis stems from a desire to further the understanding of the role of cerebral hypoperfusion in falls, faints and dizziness – common phenomena encountered in clinical practice. As a researcher, my fascination with the complex interplay of these clinical problems has been fuelled by a desire to make a meaningful impact on healthcare outcomes, particularly in the context of falls in older people.

Given the increased longevity in the ageing population, the prevalence of falls and syncope in older people is expected to increase. This underscores the urgency to add to the literature in the hope of preventing associated significant morbidity and provide more effective preventive and therapeutic strategies.

Current clinical evaluation of patients presenting with falls, syncope and related disorders relies on measurements observed at the level of the peripheral vasculature with no direct observation of changes occurring in the brain. The limitations in our current understanding of the interplay between OH, CBF and the risk of falls have instilled a determination to bridge these knowledge gaps.

This research seeks to contribute not only to academic discourse but also to inform practical changes in the way clinicians assess and treat those patients who present with OH, falls or other symptoms suggestive of compromised CBF. By examining these connections, this thesis aspires to offer insights that can inform clinical decision-making, enhance risk stratification, and ultimately improve the quality of life of those we care for.

The ultimate goal is to translate research findings into tangible benefits for individuals at risk of OH related falls, aligning with a broader commitment to advancing knowledge and improving patient outcomes in this important clinical area.

1.2 Thesis Outline

Chapter 1 provides a brief introduction and outline of this thesis. **Chapter 2** will focus on a general introduction and background to falls and syncope. The overlap between the two will also be highlighted. The subject of CBF, perfusion and its physiological regulation will be discussed. The methods employed to measure CBF will be introduced with a particular emphasis on NIRS, its methodology and clinical applications. Finally the pathological consequences and clinical relevance of CBF dysregulation and hypoperfusion will be highlighted. Following an outline of the normal physiological response to standing, **Chapter 3** presents an introduction of OH and a review of its association with cerebral hypoperfusion. An examination of the impact the presence of symptoms has on this relationship is then presented. **Chapter 4** details the aims and research questions to be examined in this thesis. **Chapter 5** outlines the materials and methodology employed in the studies conducted as part of this thesis. **Chapters 6–9** outline each study undertaken as part of this work. **Chapter 6** examines the association of OH with cerebral hypoperfusion in a clinical cohort of patients presenting to a falls and syncope clinic. The influence of symptoms on cerebral perfusion changes in OH is also presented. **Chapter 7** outlines the relationship of symptomatic and asymptomatic OH and risk of future falls in a population cohort of community dwelling older adults. **Chapter 8** highlights the association between OH, cerebral hypoperfusion and future falls in a population cohort.

Chapter 9 details a case series of individuals diagnosed with psychogenic pseudosyncope on tilt testing. Concurrent measurement of cerebral oxygenation using NIRS demonstrated lack of cerebral perfusion change during events and aided diagnosis. **Chapter 10** provides a general discussion including strengths, limitations and future directions for this research.

'It takes a child one year to acquire independent movement and ten years to acquire independent mobility. An old person can lose both in a day' (9)

Professor Bernard Isaacs (1924–1995)

Chapter Two – Background

2.1 Falls

The World Health Organisation defines a fall as an "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level" and includes trips and slips occurring on one level or from a height (10). Falls can occur throughout the lifespan and are regarded as an inevitable consequence of upright posture and physical activity (11).

2.1.1 Prevalence of Falls

Falls are the most common cause of injury and associated morbidity and mortality in older people (12) occurring in a third of adults over 65 years annually (13). Of those, 10-20% will result in injury, presentation to hospital and/ or death (14). The prevalence of falls varies widely throughout regions of the world, from 15-40% (15) and depends on the setting. For instance, Rubenstein reports a three times greater incidence of falls among older persons in residential care facilities at 1.7 per bed per year than those occurring among community dwelling older people at 0.65 per person per year (14).

2.1.2 Burden of Falls

According to the Irish Major Trauma Audit 2021 (16), falls <2 metres, termed 'low falls', continue to be the most frequent cause of injury, with a large proportion (n=1,265, 89%) of patients aged ≥75 years having been injured in low-falls events. Home was the predominant place of injury for those aged over 55. Twenty-nine percent of those aged

75-84 and 34% of those ≥85 years died as a result of their injury while 12% were discharged to residential care. More than four out of every five deaths were attributable to falls, at 82%.

Falls are the single most common reason for older persons to attend the emergency department (ED) accounting for one third of all adult attendances (12, 17). Falls in older adults are more likely to be associated with more serious and severe injuries such as hip fractures compared to falls in younger people, and are more likely to lead to disability, hospital admission, institutionalisation and mortality (11, 18). In a prospective cohort study of 754 community-dwellers aged ≥70, 130 of whom had sustained serious falls over fourteen years follow up, 64% of participants reported little or no recovery of functional activity post fall (19). Moreover, 44-59% of participants who had no or mild-moderate disability pre fall did not recover to pre fall levels of function afterwards.

Falls also present substantial societal and economic sequelae. The Global Burden of Disease study reported nearly seventeen million years of life lost from falls in 2017 (15). In the developed world, health care expenditure related to falls is substantial costing over £2 billion in the United Kingdom (20) and approximately $50 billion in the United States (21). In the Irish context, a study undertaken by The Irish Centre for Social Gerontology estimated that in the absence of a national fall and fracture prevention strategy, fall-related injuries in older people would cost approximately €1587-€2043 million by 2030 (22).

Falls also impact confidence to maintain balance and increase an individual's fear of falling. A fear of falling typically leads to limited participation in activities which in turn

further reduces strength and flexibility, placing the individual at a further increased risk of falling and poorer quality of life (23).

2.1.3 Risk Factors for Falls

Risk factors for falls can be divided into intrinsic and extrinsic risk factors (24). Intrinsic factors are those related to the individual such as age or underlying condition. Extrinsic risk factors relate to outside environmental influences contributing to a fall such as uneven surfaces, lighting or footwear. These risk factors are not present in isolation, often occurring in combination to result in a fall. Therefore, most falls are considered multifactorial with many risk factors present to contribute to overall falls risk (25). Common risk factors for falls are outlined in the Table 2.1 below. The setting of where falls occur can offer insights into potential underlying risk factors. Specifically, indoor falls are often associated with frail individuals with multiple chronic conditions, whereas outdoor falls are more common among healthier, more mobile individuals who may encounter increased exposure to environmental hazards (26).

Table 2.1 Intrinsic and Extrinsic Risk Factors for Falls. Summarised from (11, 14, 24, 27)

Intrinsic Risk Factors	**Extrinsic Risk Factors**
Increasing Age	Poor Footwear
Female Gender	Environmental Hazards
Gait & Mobility Issues • Balance Disorders • Reduced Timed-Up and Go • Reduced Muscle Strength • Use of Walking Aid	
Foot Deformities	
Cognitive Difficulties • Delirium • Dementia	
Sensory Deficits • Vision problems • Dizziness/ Vestibular dysfunction • Hearing problems	
Psychosocial Factors • Depression • Fear of Falling • Social Isolation	
Previous History of Falls	
Impairment in Activities of Daily Living	
Medications • Benzodiazepines and Hypnotic/ Sedatives • Antidepressant Medications • Antipsychotic Medications • Antihypertensive Medications • Antiarrhythmic Medications • Dopaminergic Medications • Anticholinergic Medications • Diuretic Medications	
Autonomic Dysfunction • Orthostatic Hypotension • Urinary Incontinence • Parkinson's Disease	
Cardiovascular Disease	
Multimorbidity and Frailty	
Nutritional Status • Sarcopenia • Vitamin D Deficiency	

2.1.4 Unexplained Falls

Up to one fifth of older fallers have no obvious cause for their event and are classified as "unexplained" or "non accidental falls" (28) – not simply due to a slip or trip. The literature supports an association between unexplained falls and cardiovascular disorders such as OH, reflex syncope, carotid sinus syndrome (CSS) and cardiac arrhythmias (28, 29). A recent systematic review and meta-analysis by Bourke et al. (30) assessing the association between cardiovascular disorders and falls in older adults report the largest positive associations with falls over a 12 month interval were for stroke (OR 1.90, [CI 1.70–2.11]), peripheral arterial disease (OR 1.82, [CI 1.12–2.95]), atrial fibrillation (OR 1.52, [CI 1.27–1.82]), and OH (OR 1.39, [CI 1.18–1.64]). Bhangu et al, report that 71.4 % of a cohort of older people (n=50, mean age 67.9 years) who presented to the ED with unexplained falls were found to have a cardiac arrhythmia not present at presentation but detected over 9 months subsequently by implantable loop recorder (31). Therefore, the cause of unexplained falls warrants further investigation particularly cardiovascular assessment.

'Those who faint (literally 'loosen') frequently and severely without obvious cause die suddenly.'

Hippocrates of Kos (c. 460-377 B.C.E)

From Corpus Hippocraticum

''When a patient faints, symptoms improve when he is laid flat.'' (32)

Pierre Adolphe Piorry (1794-1879)

2.2 Syncope

Syncope is defined as transient loss of consciousness (TLOC) due to transient cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery (7).

Syncope represents a subgroup of disorders of TLOC. TLOC is defined as a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration (7). For this reason PPS is a form of TLOC and technically not syncope. (See Figure 2.1)

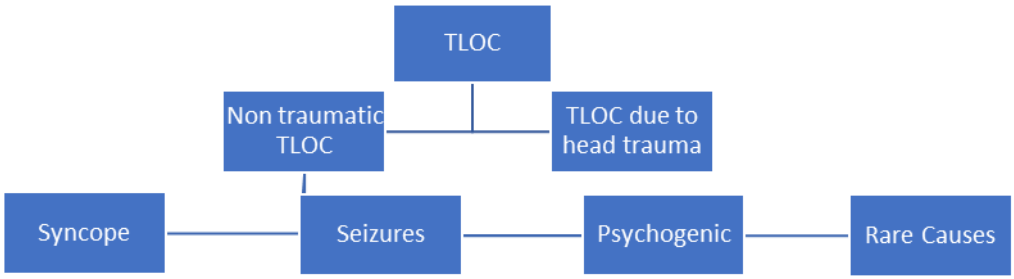

Figure 2.1 Syncope is a subgroup of TLOC disorders. Modified from (7).

2.2.1 Classification of Syncope

Syncope is classified into cardiogenic (secondary to structural heart disease or arrhythmia), orthostatic hypotension, or neurally mediated/ reflex syncope. Reflex syncope is the most common cause of syncope across all age groups (33) and incorporates carotid sinus syndrome and vasovagal syncope (VVS). VVS is regarded as the “simple faint” in common parlance. See Table 2.2 for classification of the causes of syncope.

Table 2.2 Classification of Syncope. Adapted from (7, 34).

Cardiac Syncope	Syncope due to OH	Reflex Syncope

Arrhythmia
- Sinus Node Dysfunction
- Atrioventricular Conduction Disease
- Supraventricular Tachycardia
- Ventricular Tachycardia
- Drug Induced Arrhythmia
	Primary Autonomic Failure
	- Pure Autonomic Failure
	- Idiopathic Parkinson's Disease
	- Parkinson's Plus Syndromes
	  - Multiple Systems Atrophy
	  - Lewy Body Dementia
		Vasovagal
		- Mediated by orthostatic or emotional stress

Structural Heart Disease
- Aortic Stenosis
- Hypertrophic Cardiomyopathy
- Atrial Myxoma
- Congenital Anomaly
- Prosthetic Valve Malfunction
	Secondary Autonomic Failure
	- Diabetes
	- Amyloidosis
	- Uraemia
	- Spinal Cord Injury
		Situational
		- Cough
		- Sneeze
		- Gastrointestinal Stimulation
		  - Swallow
		  - Defecation
		  - Visceral Pain
		- Micturition/ Post Micturition
		- Pain
		- Laughter
		- Post Prandial
		- Post Exercise

Other - Pulmonary Embolus - Aortic Dissection - Cardiac Tamponade - Pulmonary Hypertension	**Drug Induced Orthostatic Hypotension**	**Carotid Sinus Syndrome**
Vascular Steal Syndromes	**Volume Depletion** - Haemorrhage - GI losses - Addison's Disease - Intercurrent Febrile Illness - Hot Weather	
Multifactorial		

2.2.2 Prevalence

Syncope affects about 3.5% of the general population throughout the lifespan (35). Not all who experience a syncope episode will seek medical attention, therefore the exact incidence and prevalence of syncope is likely to reflect an under representation of true rates in the community and quoted studies vary widely. Indeed, Soteriades et al. (36) report that only 56 percent of participants with a syncopal episode reported seeing a doctor or visiting a hospital for evaluation. The Framingham Heart and Offspring studies of community dwellers reported an incidence rate of 6.2 per 1000 person years for first syncope episode and a 10 year cumulative incidence of 6% (36). The most frequently identified causes were vasovagal (21.2%), cardiac (9.5 %), orthostatic (9.4%) and 36.6%

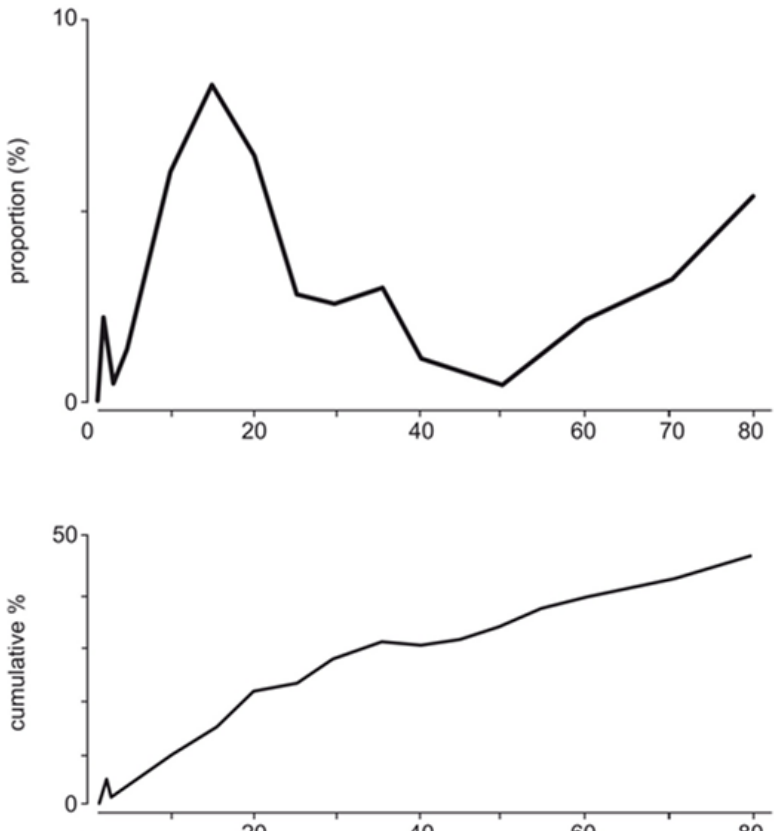

Figure 2.2 Bimodal age distribution of first syncope (top) and cumulative incidence (bottom) of age of first syncope in the general population. Adapted from (7).

for unexplained syncope. The distribution of age at first syncope would appear bimodal peaking at 15 years of age and then increasing with age after 65. (7, 36). (See Figure 2.2). Incidence rates are much higher in females than males (37, 38).

The presence of existing heart disease is an independent predictor for cardiogenic syncope and so increases sharply with age (39, 40) responsible for about a third of cases in the older patient (41).

2.2.3 Clinical Presentation

For most syncope presentations, there are three distinct phases to an episode: a prodrome or aura, loss of consciousness and a post-syncopal phase (42). A precipitating factor or situation is identifiable in most patients. Common precipitating factors include extreme emotional stress, anxiety, trauma, physical pain or anticipation of physical pain (e.g. prior to venepuncture for blood sampling), warm environment, air travel and prolonged standing. The commonest triggers in older individuals are prolonged standing and vasodilator medication. Some patients experience symptoms in specific situations such as micturition, defecation and coughing. Prodromal symptoms include extreme fatigue, weakness, diaphoresis, nausea, visual disturbance, visual and auditory hallucinations, dizziness, vertigo, headache, abdominal discomfort, dysarthria and paraesthesias (7, 42). One in three individuals with VVS report no warning prior to TLOC (43). Older patients may have poor recall for prodromal symptoms. The syncopal period is usually brief during which time some patients develop involuntary movements such as myoclonic jerks. Tonic clonic movements have also been observed (44). Thus, vasovagal syncope may masquerade as a seizure (42, 45). Recovery is usually rapid but older patients

can experience protracted symptoms such as confusion, disorientation, nausea, headache, dizziness and a general sense of ill health (41, 46).

2.2.4 Clinical Evaluation

International guidelines recommend an active stand (AS) test for the evaluation of both falls and syncope (7). This assessment will be discussed in greater detail later. The tests for reflex syncope consist of tilt testing and carotid sinus massage (in those over 40 years) (7). Confirmation of the diagnosis of VVS is based on the HUT test introduced into clinical practice by Kenny et al. (47) in 1986. The gold standard for the diagnosis of cardiogenic syncope is symptom rhythm correlation i.e. contemporaneous heart rate and rhythm recording during a syncopal event. Therefore a period of cardiac rhythm monitoring is required. Echocardiography is used to evaluate for structural abnormalities of the heart. Other specialised cardiac investigations include ambulatory BP monitoring, the exercise stress test, cardiac electrophysiology study and specialised cardiac magnetic resonance imaging (MRI).

2.2.5 Burden of Syncope

Cardiogenic syncope carries the highest risk for premature and cardiovascular death (36, 48) and is the predominant reason for admission to hospital for further evaluation (49). The Framingham Offspring Study found that survival of patients with reflex syncope is equivalent to those who had not suffered syncope (36). A 2 year longitudinal study conducted in Italy, found that in those over 65, the overall mortality rate for those with syncope was 17.2%, again highest for those with cardiac syncope compared to those

without. (21.7% vs 12.3%, p=0.03). There was no difference in mortality rates for reflex syncope (62.1% vs 66.2%, p=0.357) or unexplained syncope (10.8% vs 11.8%, p=0.397) (50).

Injurious syncope is not uncommon with 29.1% of 1253 consecutive patients attending the ED with TLOC reporting a trauma, in 59 cases (4.7%) severe (51). Syncope – particularly if recurrent and associated with subjects who experience fear of falling – has a significant association with poorer quality of life (52). Quality of life studies consistently identify functional impairment in syncope on par with other chronic diseases such as rheumatoid arthritis, chronic back pain and epilepsy (53-56).

There are also significant costs associated with syncope. Data mainly exists for emergency department presentations, investigations and hospital admissions. In 2005, a US study (57) reported that 2.4 billion dollars was spent per annum on syncope related hospital admissions while another (58) suggested a cost of $2517 for the investigation of one "faint" episode. British costs per patient have been estimated at £611 with the bulk of this allocated to hospital stay (59). Much of the costs incurred with syncope are likely related to unnecessary investigation and hospitalisation (60). This has led to efforts to establish dedicated syncope units with integrated pathways to provide timely access to investigations, remote monitoring and outpatient reviews to reduce inpatient bed use (49, 61). Where a high index of suspicion exists for cardiac syncope, there remains a low threshold for hospital admission which can ultimately be unnecessary (62-64).

2.2.6 Unexplained Syncope

Establishing the exact aetiology of syncope can be challenging. It is not uncommon for more than one predisposing disorder to coexist rendering precise diagnosis difficult. There is considerable variability in the literature on the success of establishing an aetiology for a syncopal episode. Rates of unexplained syncope vary from 14-40% (65-67) depending on the aggressiveness of diagnostic testing pursued, diagnostic criteria applied, patient population studied and exclusion of those with a seizure disorder.

Between 1-12% (68) of apparent syncope presentations are related to psychogenic pseudosyncope (PPS). This challenging diagnosis will be discussed in greater detail in Chapter 9 of this thesis.

2.3 Overlap between Falls and Syncope

There is considerable overlap between falls and syncope – particularly in older individuals. Falls associated with TLOC in older people have a higher risk of injury or fracture than non-TLOC events (27). Some traditional definitions of a fall excluded those with transient loss of consciousness or other cardiovascular abnormalities. In recent years this has been successfully challenged as a broader definition has been adopted in the recently published World Falls Guidelines (11, 69). Frequently, syncope can present atypically in older patients and therefore can be under recognised in acute care settings. The older patient is less likely to experience warning or prodromal symptoms prior to syncope and therefore will be at increased risk of perceiving these events as falls (70).

Witness accounts, which often reveal important relevant additional history to establish a diagnosis of syncope (71), are frequently unavailable in over 40-60% of events (70, 72).

Thus, these events can be attributed erroneously to falls by the patient and the inexperienced clinician.

Impaired cognition in older patients can mean that they are less likely to recall falls or the circumstances in which they occurred increasing the ambiguity surrounding the aetiology of events. Indeed, in a study of 304 community dwelling individuals over 60 with normal cognitive functioning (by MMSE), 32% of the 179 who had documented falls in the previous three months were unable to recall having fallen at all (73).

Amnesia for loss of consciousness (ALOC) has also been described in the literature and can cause syncope to present as a fall (74). ALOC has been observed in Carotid Sinus Syndrome (CSS), a subtype of reflex syncope diagnosed by carotid sinus massage (CSM). A study by Parry et al (75) found that those presenting with falls who were subsequently diagnosed with CSS were significantly more likely to have ALOC than those who presented with syncope (95% v 12%, $p<0.001$). The incidence of ALOC in CSS ranges from 18-27% (28, 76, 77). The prevalence of ALOC in vasovagal syncope in 159 individuals (mean age 55±22.5 years) diagnosed at tilt table testing was 28% and was higher in older individuals (78).

Injury sustained after a fall is very often the primary focus of medical attention and important risk modification opportunities may be overlooked (31). It is, therefore of utmost importance that the overlap between syncope and falls is appreciated in the investigation of all patients presenting with an unexplained fall i.e. one not due to simple slip, trip or accident (79). The updated ESC syncope guidelines (7) suggest that there is strong consensus that those presenting with unexplained falls should undergo the same

diagnostic work up as those presenting with unexplained syncope. (See Figure 2.3). In this way, the significant morbidity associated with unexplained falls may be reduced.

In order to fully understand the relationship between falls and syncope, it is important to consider the anatomy and physiology of key systems involved in the regulation of BP and CBF.

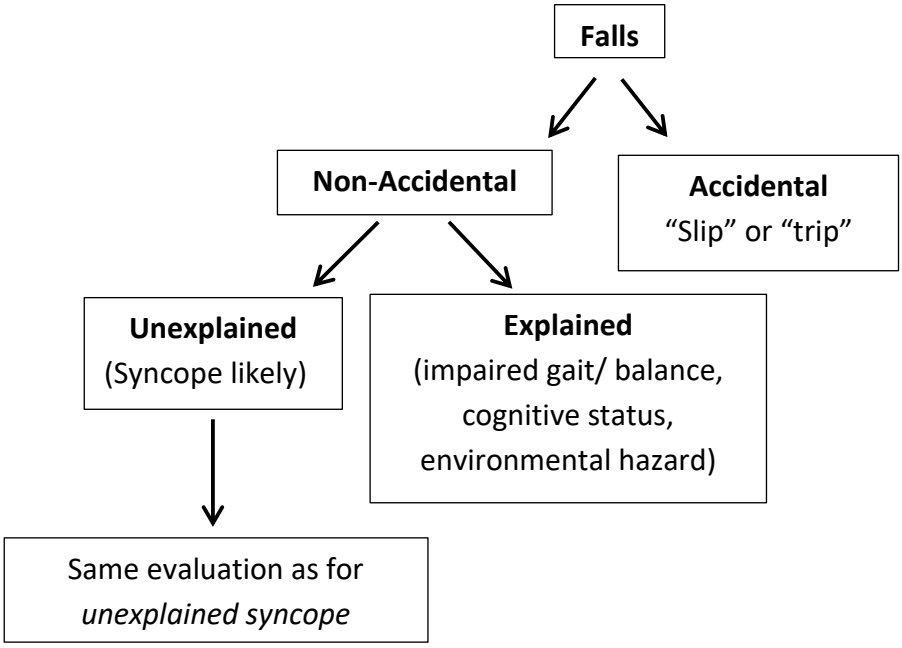

Figure 2.3 Suggested evaluation algorithm for falls according to European Society of Cardiology guidelines (7).

2.4 Autonomic Nervous System

The Autonomic Nervous System (ANS), a highly complex, largely involuntary system of interconnected neurons is responsible for the control of visceral functions, maintaining homeostasis and adapting to changing conditions in the external environment (80). The ANS is responsible for the innervation of all organs and tissues, except skeletal muscle and so can be implicated in almost all disease. It is the component of the peripheral nervous system that regulates involuntary physiologic processes including heart rate (HR), BP,

respiration, digestion and sexual arousal (81). It contains three anatomically distinct divisions: sympathetic, parasympathetic and enteric. The sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS) contain both afferent and efferent fibres that provide sensory input and motor output, respectively, to the central nervous system (CNS). (See Figure 2.4). The enteric nervous system (ENS) is an extensive, web like structure that is chiefly responsible for the reflex pathways for the regulation of digestive processes.

2.4.1 Anatomy of the ANS

Sympathetic neurons have their cell bodies located in the intermediolateral columns, or lateral horns, of the spinal cord. The presynaptic fibres exit the cord through anterior roots and enter the anterior rami of T1-L2 spinal nerves and onto the sympathetic trunks – the thoracolumbar division. From here, the fibres may ascend or descend the sympathetic trunk to a superior or inferior paravertebral ganglion, respectively, pass to adjacent anterior spinal nerve rami, or cross through the trunk without synapsing and continue through the abdominopelvic splanchnic nerve to reach prevertebral ganglia. Here, the pre and post ganglionic neurons synapse. There are three cervical, twelve thoracic, four lumbar and five sacral paravertebral ganglia. These convey afferent and efferent fibres between the CNS and the visceral effector organs as splanchnic nerves. Preganglionic neurons use acetylcholine for neurotransmission and the postganglionic neurons transmit noradrenaline (except for fibres to the sweat glands which use acetylcholine) (5).

Parasympathetic neurons leave the CNS via the oculomotor (CNIII), facial (CNVII), glossopharyngeal (CNIX) and vagus (CNX) cranial nerves as well as through the S2-4 nerve

roots – the craniosacral division. Apart from those in the head, all other presynaptic parasympathetic fibres synapse in a ganglion near or very close to the walls of the target organ. Postganglionic PSNS fibres release acetylcholine that acts on muscarinic or nicotinic receptors. The M1 like receptors mediate excitatory effects of acetylcholine while M2 receptors mediate inhibitory effects in response to acetylcholine.

The vagus nerve (CN X) deserves particular mention, making up approximately 75% of the PSNS providing input to most of the thoracic and abdominal viscera. The vagus nerve has four cell bodies in the medulla oblongata including:

- Dorsal nucleus: provides PSNS output to the viscera.
- Nucleus ambiguus: produces motor fibres and preganglionic neurons that innervate the heart including the sinoatrial node.
- Nucleus solitarius: receives afferents of taste sensation and afferents from viscera.
- Spinal trigeminal nucleus receives information of touch, pain and temperature of the outer ear, mucosa of the larynx and part of the dura.

Additionally, the vagus nerve conducts sensory information from baroreceptors of the carotid sinus and the aortic arch to the medulla. A schematic representation of the ANS can be found in Figure 2.4.

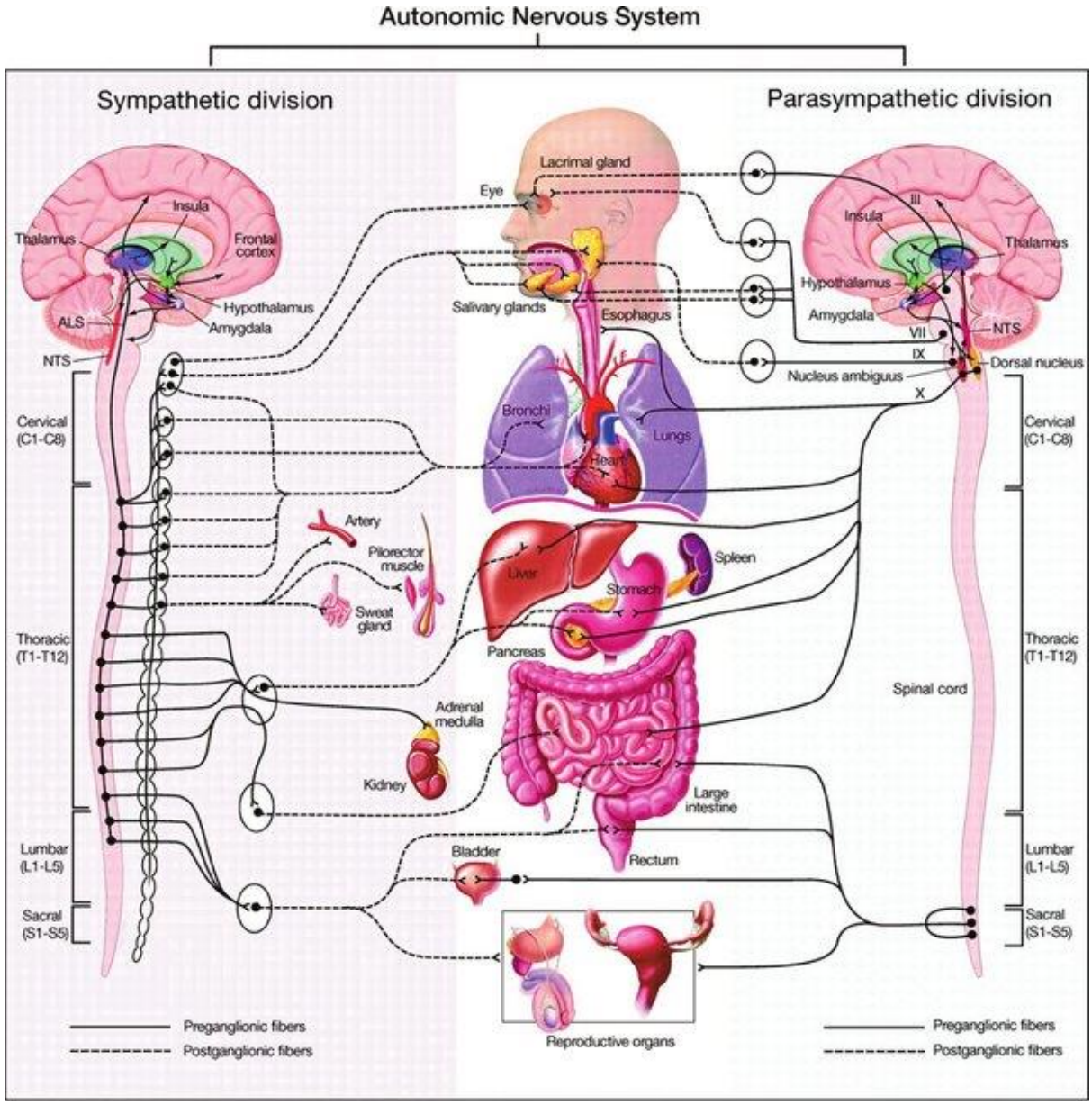

Figure 2.4 Schematic representation of the ANS – sympathetic and parasympathetic divisions and anatomical structure innervated by each. III, VII, IX, X represent numbered cranial nerves; ALS anterolateral system, NTS nucleus tractus solitarius – adapted from (5).

2.4.2 Function of the SNS and PSNS

The SNS increases its activity under conditions of physical or psychological stress via the "fight or flight" response (82). This reaction primarily regulates blood vessels. All resources for physical exertion are activated; HR and BP increase; cardiac contractility increases; blood flow to the skeletal muscles, heart and brain increases; the liver releases glucose; and the pupils dilate.

In contrast, when the PSNS system is activated, a person is in a "a rest or digest" state in which homeostatic functions are predominant and directed towards conserving and restoring energy. HR is slowed; BP falls; pupils constrict; peristalsis and glandular activity increase; sphincter muscles are relaxed; and the bladder wall is contracted.

The two divisions of the ANS rarely operate independently of each other and ANS responses generally represent the regulated interplay of both divisions. While considered antagonists of each other, producing opposite effects in most organs, each division of the ANS serves to complement each other in maintaining a stable internal environment. Autonomic responses usually occur without conscious control or awareness.

2.4.3 Higher Control of ANS

Higher control of the ANS is mediated by a group of extensively interconnected areas of the brain including the insular and medial prefrontal cortices, the amygdala, hypothalamus, preaqueductal grey matter, the pons, the nucleus tractus solitairius and the medullary intermediate reticular zone. In the hypothalamus the most important nucleus is the paraventricular nucleus which has direct influences on sympathetic and

parasympathetic outflow. Input is received from the caudalis nucleus (for SNS) and nucleus tractus solitarius (for PSNS) (82).

2.4.4 The Baroreflex

Arterial baroreceptors are specialised mechanoreceptors located in the carotid sinus and aortic arch and are capable of detecting changes in BP. The cardiopulmonary baroreceptors in thoracic veins and the heart sense changes in blood volume. Both arterial and cardiopulmonary baroreceptors inhibit efferent SNS neurons leading to vasodilation while only arterial baroreceptors are capable of influencing HR. The baroreflex is the physiological mechanism through which these receptors contribute to BP regulation and occurs within seconds (83).

Baroreceptors continuously signal to the nucleus solitarius via the vagus and glossopharyngeal nerves and are activated by stretch when BP, blood volume or both rises. To counter the rise, the baroreceptor reflex inhibits SNS signals to splanchnic, skeletal muscle and renal blood vessels causing vasodilation. A concomitant increase in PSNS signalling to the sinoatrial node slows the HR.

In response to hypotension, there is reduced firing from the baroreceptors, SNS neurons become activated, and vasoconstriction ensues. There is concomitant inhibition of PSNS neurons causing increased HR and restoration of BP.

2.4.5 Clinical relevance for this thesis

Due to the vast expanse of the connections of the ANS to the organ systems of the body, it stands to reason that when it becomes impaired or dysregulated, it can become implicated in a wide range of diseases. Autonomic neuropathy can affect any organ system. OH is the most common dysautonomia (81) and will be discussed in greater detail in Chapter 3.

In addition to the ANS, another important consideration in the maintenance of optimum brain health is the regulation of CBF.

"The cerebral perfusion is apparently regulated in such a way as to maintain scrupulously the normal chemical milieu of the brain...it seems likely that both mechanical and chemical factors are of importance for the autoregulation of CBF, the latter factor, however, having the final regulatory effect (6)".

Niels Alexander Lassen MD PhD (1926-1997)

2.5 Cerebral Blood Flow

In marked contrast to other organs and tissues, the metabolic activity of the brain is significant regardless of body activities or circumstances. Despite accounting for about two percent of the total body mass, the brain is responsible for about twenty percent of the body's basal metabolic rate (4, 84, 85). The brain is also unique in that, unlike other organs, it lacks readily available energy stores (86) and damage can occur in times of hypoperfusion and hyperperfusion (87). Therefore the brain depends on the continuous supply of blood flow at the right time and place and in the right amount to meet demand and sustain neurological function. Cerebral blood flow (CBF) is defined as the volume of arterial blood delivered to a unit mass of brain tissue per unit time. The standard unit of measurement is millilitres (ml) of blood per 100 grams (g) of brain tissue per minute (min). A typical CBF value for grey matter in humans is about 60ml/100g/min (88) with lower values for white matter (89). 60ml/100g/min corresponds to the delivery of 1ml of blood to 100g of brain tissue per second.

2.5.1 Cerebral Vasculature

Brain parenchyma is subdivided into the grey matter and white matter. Grey matter - known as the cerebral cortex – is a major component of the central nervous system (CNS) and is where neuronal cell bodies, glial cells, dendrites, unmyelinated axons and capillaries are found. The grey matter is responsible for initiating signalling, processing and cognition while the white matter modulates the distribution of action potentials and coordinates communication between brain regions. In contrast to cortical grey matter, white matter is made up of myelinated axons and glial cells.

2.5.1.1 Arterial Supply

The internal carotid arteries provide 80% of the cerebral blood supply where each side supplies an ipsilateral cerebral hemisphere. Both grey and white matter is perfused by the three major arteries: the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA), which are themselves branches of an anastomotic ring at the base of the brain known as the Circle of Willis. The ACA and MCA form the *anterior circulation* which arises from the internal carotid arteries. The PCA forms the *posterior circulation* and arises from the vertebral and basilar arteries. The ACA, MCA and PCA arteries course anteriorly, medially and posteriorly respectively from the Circle of Willis before branching into smaller mid- and end-arterioles. These arteriolar networks differ depending on whether they are supplying the grey or the white matter and this leads to regional variations in the way CBF is modulated within these areas.

Arterial Supply to the Grey Matter

The divisions of the major cerebral arteries extend across the cortex and branch into smaller mid and end arterioles, forming a rich network of anastomosis known as conducting arteries.

Some conducting arteries further subdivide to form pre-cortical arteries. Other conducting arteries extend along the surface of the cortex (as pial vessels) to form leptomeningeal arteries. They course distally to their respective source vessels, through the border zone regions of the brain and eventually form the leptomeningeal anastomosis from other major cerebral vessels thus connecting the two major arteries, the ACA and MCA. These anastomotic beds serve to protect the cortex and ensure that if single vessel

occlusion occurs downstream, flow redirection can occur through these anastomotic connections and allow cortical perfusion to be maintained. This is aided by extrinsic autonomic innervation to these vessels.

Arterial Supply to the White Matter

In contrast to the grey matter, white matter is supplied by non-anastomosing tortuous arterioles. They penetrate down from the cortical vessels superiorly and penetrate up from the proximal MCA inferiorly. In the posterior circulation they penetrate laterally from the basilar artery. Because they lack anastomosis networks, these vessels cannot compensate for vessel occlusion and are therefore more vulnerable to hypoperfusion. White matter arterioles are less richly innervated by autonomic neurons than grey matter and so may not have the capacity for autonomic control to facilitate changes in blood flow.

2.5.1.2 Venous Drainage

The venous drainage of the brain can be divided into two systems. The superficial or cortical system drains the cerebral cortex and subcortical white matter; and the deep or central system which drains the deeper white and grey matter. Both systems converge to drain into the internal jugular veins.

2.5.2 Regulation of Cerebral Blood Flow

Since the brain is enclosed within a rigid skull, high levels of intracranial pressure will result in increased cortical damage. Therefore tight regulation of CBF is essential to avoid excessive hypo and hyper perfusion. Control of CBF involves a spectrum of overlapping regulatory mechanisms that collectively facilitate optimal oxygen and nutrient delivery to individual brain cells. Mechanisms that influence CBF include arterial blood gases, central haemodynamics, cerebral metabolism and neural mechanisms including extrinsic autonomic and sensory nerves and intrinsic neurons in close association with the vasculature within the brain parenchyma. As mentioned earlier, it is the arterioles and capillaries of the cerebral microcirculation that regulate cerebrovascular resistance and greatly impact CBF.

In their review, Claassen et al. (4) propose that the mechanisms regulating CBF can be divided into four distinct responses: autoregulation, chemoregulation, neuronal regulation and endothelium-dependent regulation.

Some of these mechanisms are unique to the brain, explaining the generalised observation that the peripheral vasculature is a poor model or predictor for what is occurring at the cerebral level in health or disease – one of the primary motivations for embarking on this thesis.

2.5.3 Cerebral Autoregulation

To understand CBF regulation, one needs to consider Poiseuille's Law of flow dynamics which describes the relationship between the flow of a viscous fluid through a cylindrical

pipe (or blood vessel) and the numerous factors influencing that flow. The formula for Poiseuille's Law is:

$$Q = \frac{\Delta \mathrm{P} \pi r^4}{8 \eta L}$$

where:

- Q is the flow rate of the fluid,
- ΔP is the pressure difference across the ends of the pipe,
- r is the radius of the pipe,
- η is the viscosity of the fluid, and
- L is the length of the pipe.

Strictly speaking, CBF does not fulfil all the requirements of the law given that blood does not behave like a Newtonian fluid, especially in the microvasculature. Blood vessels are not rigid pipes and blood flow is not always laminar such as at branching points or curved sections of their course. However, Poiseuille's Law highlights that flow rate is directly proportional to the fourth power of the radius of the pipe, emphasising the significant impact that changes in vessel radius can have on blood flow.

Ohm's Law (or more correctly, Darcy's Law (90), its haemodynamic equivalent) allows for blood flow through a capillary bed to be expressed as the ratio between the pressure difference across that blood vessel and its vascular resistance. In other words, flow rate (Q) is equal to the pressure gradient (pressure difference at either end of vessel) (ΔP) divided by cerebrovascular resistance (R):

$$Q = \frac{\Delta P}{R}$$

For CBF, the main pressure driving this equation is cerebral perfusion pressure (CPP) which is defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP). Under conditions where ICP is constant, cerebral arterial BP can be substituted for CPP:

$$CBF = \frac{MAP}{R}$$

By combining these equations above, we gain an appreciation for the factors affecting CBF:

$$CBF = \frac{MAP}{R} = \frac{\Delta P \pi r^4}{8\eta L}$$

From this equation, it is apparent that – at least once steady state equilibrium is achieved – changes in perfusion pressure, changes in vessel radius (by vasodilation or vasoconstriction), and changes in blood viscosity all affect CBF.

Cerebral autoregulation (CA) is the homeostatic capacity of the cerebrovascular system to maintain a constant rate of CBF during changes in arterial BP and CPP (4, 85). This means that CBF is maintained by adjusting cerebrovascular resistance in the face of changes in BP and is mainly achieved by modulating arteriolar diameter. This phenomenon can be illustrated by Lassen's MAP-CBF autoregulation curve (6). (See Figure 2.5)

2.5.3.1 Changing Perspectives of the Cerebral Autoregulation Curve

Lassen's publication on CA in 1959 (6) is regarded as a landmark breakthrough in this field. He presented data from eleven different and distinctive clinical datasets and described

how varying BP across a range from 60-150mmHg maintained CBF and that below 60mmHg, CBF and BP became linearly related – the so called lower limit of CA.

However, while Lassen's work provided a solid foundation for understanding autoregulation, in the decades that followed, some criticisms and refinements have been suggested that have led to an evolution in our comprehension of CA.

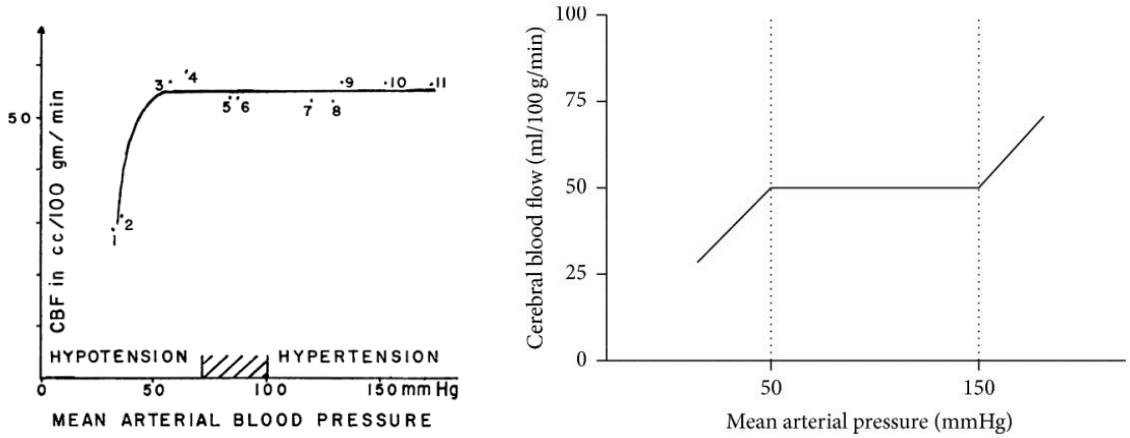

Figure 2.5 Lassen's MAP-CBF curve (6) (left). "Classic" MAP-CBF curve representation of static cerebral autoregulation (right).

Criticisms of Lassen's Curve

Firstly, Lassen constructed the curve using data extrapolated from eleven distinctive clinical datasets of individuals from seven prior published works. There were differences in how measurements were recorded in many of these previous works – and indeed one of the seven publications could not be traced and verified. Secondly, many of Lassen's eleven datasets contained individuals who were healthy, had systemic hypertension or medicated with vasoactive drugs. The heterogeneity of these groups may have led to confounding in the results. Thirdly, the original work did not account for the intra variability of BP within individuals often with only a single data point for BP or CBF taken

from each subject. Finally, Lassen's original curve (Figure 2.5 [left panel]) contained no data at higher BP values and so only inferred the existence of an upper autoregulatory limit which was identified in later years.

Evolution of Cerebral Autoregulation Curve

Notwithstanding the above criticisms, further research conducted in animal and mathematical models has provided evidence for the substantial autoregulatory capacity of the cerebral circulation to maintain *relative* stability in CBF in the face of changes to BP (4). It is possible that CA is more passive than previously described by Lassen. This means that the CBF-MAP curve in the autoregulation range is not perfect i.e. a flat plateau, but has a slight positive slope (85). It has also been suggested that the cerebral circulation is better at defending against acute hypertension than hypotension leading to a less steep gradient at higher BP levels than at lower BP levels (91-93). (See Figure 2.6)

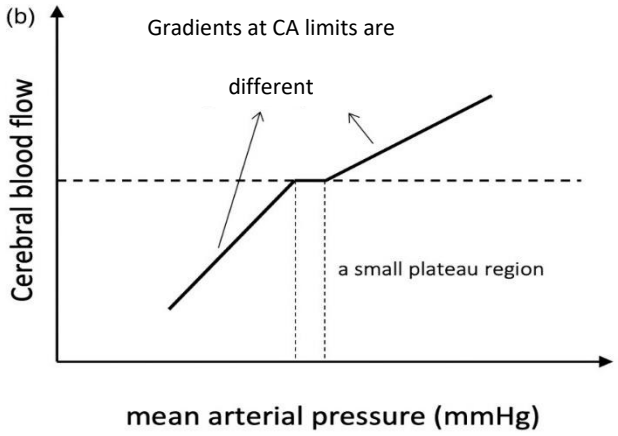

Figure 2.6 Contemporary representation of MAP-CBF curve. (Modified from (3))

In a recent review, Numan et al. (94) confirmed the ability of the cerebral vasculature to autoregulate CBF but only over a relatively small range of BP. They showed that the

cerebral circulation was more active in buffering against increases in BP than in reductions in BP. Tan (95) used oscillatory lower body negative pressure (LBNP) at varying frequencies in 43 healthy volunteers and demonstrated that the limits of autoregulation may not exist over as wide a range (only ~10mmHg) as Lassen had proposed but may in fact be dependent on the frequency at which fluctuations occur. The effectiveness of CA was significantly reduced as pressure fluctuations became faster. This has given rise to models of static and dynamic CA. (See Figure 2.7).

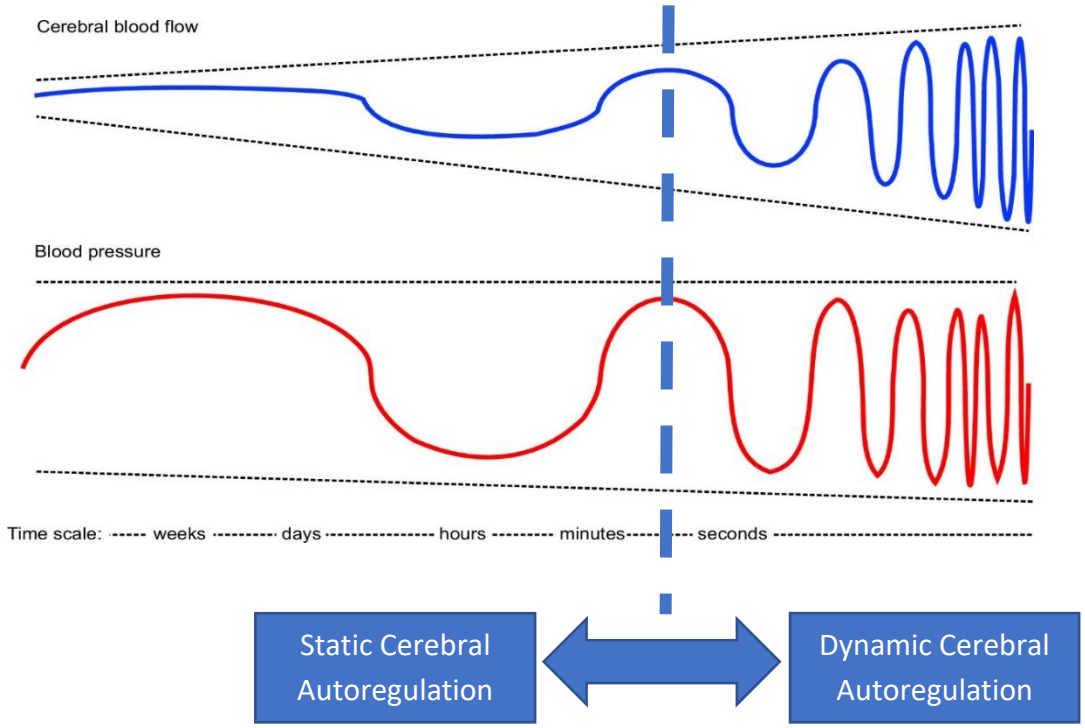

Figure 2.7 Models of static and dynamic cerebral autoregulation. (Modified from (4)) Note that there is less effective buffering of CBF changes during higher frequency oscillations in BP.

2.5.3.2 Static Autoregulation

Static CA has come to be represented by Lassen's traditional autoregulatory curve, where slow changes in BP (over minutes, hours, days and weeks) relate to CBF. In other words,

BP and CBF have reached a steady state level before they are measured. Due to this averaging, BP and CBF will have lost their short term variability.

2.5.3.3 Dynamic Autoregulation

The concept of dynamic CA accounts for how CBF is maintained during acute rapid fluctuations (over seconds to minutes) in MAP. Birch et al (96) showed that capacity to buffer changes in CBF was strongly dependent on the speed of BP changes i.e. the slower the change in BP, the smaller the impact on CBF. Where rapid fluctuations in BP occur, this buffering ability becomes reduced and CBF changes become larger up to a point where this buffering ability is lost completely. At this point, the relationship between BP and CBF is passive. Studies by Tan (95) and Giller (97) have found that the higher the frequency of fluctuations or oscillations in BP, the less capable the system is at buffering CBF. (See Figure 2.7).

Dynamic CA attempts to dampen the amplitude and delay the frequency of oscillations. This results in a *phase shift* between BP and CBF signals whereby CBF recovers before BP and a reduction in relative magnitude (*damping gain*) of CBF compared to BP. (See Figure

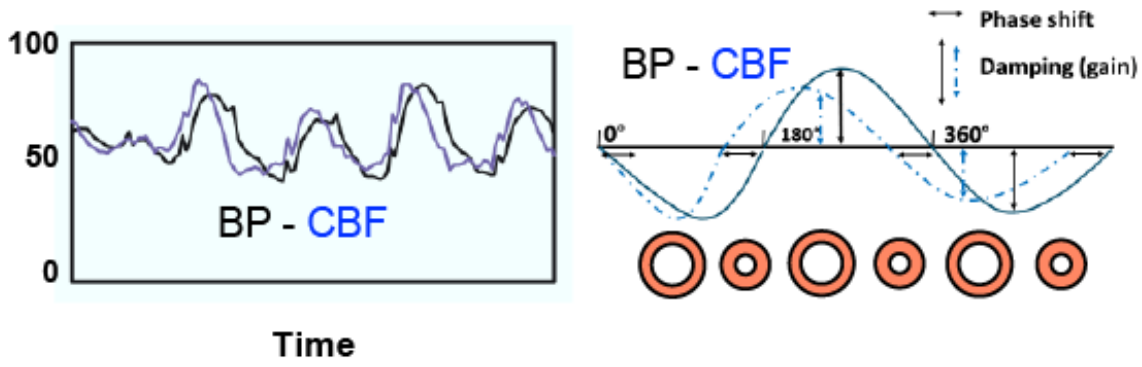

Figure 2.8 Demonstrating the phase shift and damping gain, key features of dynamic cerebral autoregulation. Adapted from (4)

2.8). For example, when dynamic CA is impaired, there is an increase in gain and decrease in phase as less buffering of BP fluctuations occurs. Importantly, CA is thought to have a latency of approximately 10 seconds which is too slow to adjust CBF during short episodes of arterial hypotension (42, 98).

Transcranial doppler (TCD) and NIRS modalities possess the high temporal resolution required to monitor CBF and when combined simultaneously with a non-invasive beat-to-beat BP recording device, dynamic CA can be evaluated. Dynamic CA has been assessed using transfer function analysis (TFA) during posture change (99), using thigh cuff release methods (100), during HUT (101, 102), and by LBNP techniques (103).

The ability of the cerebral circulation to maintain CBF and the speed at which dynamic CA responses occur have implications for many everyday lifestyle activities such as sitting, standing and physical exercise. Conditions like OH and syncope pose further challenges for autoregulation, and this will be highlighted in later chapters of this thesis.

2.5.3.4 Myogenic Tone

As stated above, attempts to maintain constant CBF in response to changing BP is achieved by altering the diameter of blood vessels in the cerebral vasculature – particularly pial and parenchymal arterioles. Myogenic tone is defined as the state of partial vasocontractility that occurs in an isolated blood vessel when maintained at constant pressure (104). Myogenic reactivity reflects changes in myogenic tone in response to changes in pressure. Increases in BP induce rises in wall tension leading to depolarization of muscle cells, an influx of calcium ions, which results in myogenic contraction, reductions in vessel diameter, vasoconstriction and increased vascular

resistance. The opposite occurs in response to BP reductions. This response of smooth muscle to changes in MAP is known as the Bayliss effect (105).

2.5.3.5 Neurogenic Control

CA may also be influenced by direct neural control via specific central pathways within the ANS, but this remains poorly defined and understood (4). It is hypothesised that the SNS directly influences the microcirculation in times of increased activity in order to protect against increases in CBF rather than to preserve CBF in the face of decreases in BP (105).

2.5.4 Chemoregulation

Chemoregulation deals with how CBF responds to changes in the concentrations of vasoactive substances, such as oxygen (O_2) and carbon dioxide (CO_2). CBF is highly sensitive to changes in the arterial partial pressure of CO_2 ($PaCO_2$) (91). Hypercapnia (an increase in $PaCO_2$) produces vasodilation, reductions in cerebrovascular resistance, and increases in CBF whereas hypocapnia (a decrease in $PaCO_2$) increases cerebrovascular resistance and reduces CBF. This response is known as cerebrovascular CO_2 reactivity or vasomotor reactivity and occurs in all large arteries, pial arteries, pial arterioles and parenchymal arterioles.

The diffusion of CO_2 across the blood brain barrier to maintain extracellular pH homeostasis is also felt to play a role in vasodilation mechanisms to regulate CBF (4).

In hypoxia, mostly when the partial pressure of O_2 (PaO_2) is below ~50mmHg, PaO_2 becomes a potent vasodilator of resistance vessels in the cerebral vasculature. However,

this response is mediated by the prevailing $PaCO_2$ (4, 91). The simultaneous presence of hypercapnia increases the vasodilatory response whereas the presence of hypocapnia decreases cerebrovascular sensitivity to hypoxia thereby attenuating the response on CBF (4, 91).

Adenosine and nitric oxide (NO) are also important mediators in chemoregulation of CBF (91).

2.5.5 Neuronal Regulation

Neuronal regulation involves the innervation of cerebral vessels by nerves, neurons and glial cells to facilitate modulation of CBF by inducing changes in local vessel diameter triggered by increases in neuronal activation and local demand (for oxygen or nutrients). This anatomical and local cerebral metabolic relationship between nerve cells and surrounding arteriolar networks is termed neurovascular coupling (NVC) (106). NVC, also termed functional hyperaemia, describes the increase in blood flow to neurally active regions. NVC takes place at the level of a neurovascular unit composed of neurones, astrocytes, endothelial cells of the blood-brain barrier (BBB), myocytes, pericytes and extracellular matrix components (107). NVC is the mechanism by which microscopic blood flow is regulated at a local level ensuring that the delivery of oxygen and nutrients fits the changes in neuronal activity (108). For example, NVC is activated in corresponding areas of the cerebral cortex in physiological situations such as reading, calculating or any other mental exercise. NVC regulates CBF via feedback and feed forward mechanisms. In the feedback model, toxic metabolic by-products of brain activity (such as CO_2, adenosine, lactate and other peptides) trigger increased CBF to that region by causing local

vasodilation. In the feedforward model, CBF is not driven by the tissue metabolic state but by the excess delivery of oxygen and glucose driven by neurovascular signalling pathways and increased synaptic neurotransmitter activity (potassium ions, nitric oxide (NO) and prostanoids) (86).

2.5.6 Endothelium-Dependent Regulation

Blood vessels are lined by a thin layer of endothelial cells in direct contact with blood as it flows. Vasoactive substances (NO, potassium ions, hydrogen peroxide, adenosine) are released by the endothelium in response to mechanical shear stress and activation of endothelial cell receptors to affect changes in vascular tone (4). Forming part of the neurovascular unit, the endothelium contributes to the NVC mechanisms discussed above.

As alluded to above, the endothelium is the site of the BBB (109) – a unique network of microvasculature that tightly regulates CNS homeostasis. It exerts precise control over the exchange of molecules, ions, and cells between the bloodstream and the CNS, and acts as a safeguard against toxins, pathogens, inflammation, injury, and diseases to protect the integrity of the CNS (110).

2.5.7 Integrative Regulation of Cerebral Blood Flow

Meticulous control of CBF involves a wide spectrum of overlapping and sometimes redundant regulatory mechanisms that work to ensure optimum oxygen and nutrient delivery. The cerebral vasculature possesses the capacity to adjust to alterations in the

microenvironment, varying metabolic requirements such as oxygen and glucose supply, and fluctuations in BP. This adaptation is a result of endothelium-mediated responses within the neurovascular unit, effectively regulating perfusion at the local, regional, and global levels (111). The regulation of CBF should not be viewed as being limited to a single mechanism occurring in isolation but as an integrative process. This regulation relies on the marked influence of gas exchange and cardiovascular function in addition to intracranial mediators of cerebrovascular resistance working simultaneously depending on the activity and demands of neurological function (91).

2.6 Measurement of Cerebral Blood Flow and Autoregulation

Since the early days of the Kety-Schmidt method described in 1948 (112), which exploited the principle that the rate of uptake and clearance of an inert diffusible gas – nitrous oxide inhalation in this case – is proportional to CBF, the technologies available to measure CBF and metabolism have evolved. Various techniques have been developed to measure CBF, both directly and indirectly, each with their own advantages and limitations.

Direct methods include Xenon enhanced computed tomography (XeCT), positron emission tomography (PET), single photon emission computed tomography (SPECT), perfusion computed tomography (PCT) and arterial spin labelling - magnetic resonance imaging (ASL-MRI).

Indirect methods comprise TCD ultrasound imaging and NIRS. Choice of modality depends on equipment availability, cost, ease of use, degree of invasiveness, resolution, accuracy and ability to quantify CBF. For instance, only TCD and NIRS can be used to measure real-time CBF during a dynamic manoeuvre like orthostasis.

Some modalities – in addition to being able to provide an assessment of global CBF – can facilitate measurement of regional CBF to localised regions of the brain. Regional CBF measurement is important to allow study of metabolic demand and function reflecting NVC within the region. The following sections in this chapter summarise the above modalities in greater detail with particular focus on NIRS.

2.6.1 Xenon Enhanced Computed Tomography

XeCT studies provide an absolute value of CBF in ml/100g/min. Following a baseline CT scan, a mixture of xenon and oxygen is inhaled, and scanning is repeated. Studies take approximately 30 minutes. CBF information is converted to produce a map of quantitative flow data that can be superimposed on the anatomical image of the brain (113). Head stabilisation is vital with the subject in the supine position as images are prone to movement artefact and degradation. Sometimes sedation is necessary (114). There is a risk of sedation, nausea, vomiting, dizziness and paraesthesia in the extremities. Rarely apnoea and seizures occur with the use of xenon.

2.6.2 Positron Emission Tomography

As well as providing measurement of CBF, PET can provide metabolic or functional information about the brain. PET uses small quantities of positron emitting radioactive isotopes attached to a natural compound such as glucose, ammonia or water which is used for CBF measurement. The isotope is administered intravenously, and as it decays, the emitted positrons collide with electrons resulting in the production of gamma rays which are then detected by scintillation monitors. The data retrieved is converted into

three-dimensional coloured maps of the brain with different brightness reflecting higher levels of functioning. PET has the advantage of being able to show rapidly occurring changes over seconds with good resolution. PET scans are increasingly used alongside CT scans to facilitate concurrent structural and metabolic correlation. The expense attached to the radioisotope preparation and their short half-life makes PET scanning expensive (114). Studies take approximately 10 minutes (113).

2.6.3 Single Photon Emission Computed Tomography

SPECT provides a measure of regional CBF and similar to PET, gives a semi quantitative relative measure of flow by comparing a region of interest with the comparable area on the opposite side of the brain. A radioisotope such as technetium-99 is injected intravenously and its uptake in brain cells is proportional to CBF. The resolution of SPECT images is poorer than PET but is less expensive with radioisotopes being more readily available.

2.6.4 Perfusion Computed Tomography

The advent of high speed spiral CT scanning technology has made PCT widely available. A non-contrast scan is first obtained followed by an intravenous injection of iodinated contrast. A second scan is rapidly obtained and measures the first pass of contrast material through the cerebral blood vessels. The measures obtained using this method include CBF, cerebral blood volume (CBV) and mean transit time (MTT) – which is the mean time taken for blood to pass between the MCA and venous sinus.

$$CBF = \frac{CBV}{MTT}$$

Regions of decreased haemodynamics are represented as regions of prolonged MTT and CT software provides maps to aid interpretation. Scanning time is quick and scans can also be combined with other CT techniques such as non-contrast CT and CT angiography. Indeed, these combined CT modalities are used for the emergent assessment of acute ischaemic stroke to determine the presence of salvageable brain tissue and eligibility for clot retrieval/ thrombectomy procedures. Disadvantages include high radiation dose and potential for allergy to the iodinated contrast. Contrast enhanced MRI perfusion techniques (e.g. dynamic susceptibility contrast enhanced MRI) are also available.

2.6.5 Arterial Spin Labelling MRI

ASL-MRI is a non-invasive imaging technique that unlike traditional contrast-enhanced MRI methods, relies on the manipulation of magnetically labelled arterial blood water as an endogenous contrast agent (115). This process involves magnetically labelling protons in the bloodstream, which then traverse the vascular system and enter the tissue of interest (116). By comparing images acquired with and without labelling, ASL allows for the quantitative assessment of regional cerebral blood flow, providing information about perfusion patterns in the brain. MRI equipment is relatively expensive, and the modality may not be suitable for those with pacemakers or other metal implants. Because of the lack of ionising radiation, multiple repeated studies can be obtained.

2.6.6 Transcranial Doppler Ultrasound

TCD, first described by Aaslid et al. in 1982 (117), is a non-invasive ultrasound technique and provides a measurement of cerebral blood flow velocity (CBFv) of the larger cerebral arteries – most commonly the left or right MCA.

The doppler probe (typically two megahertz) is placed over the appropriate transcranial acoustic window (the trans temporal window for the MCA) and when the signal encounters moving red cells, its frequency becomes altered. This change is detected by the device and is directly proportional to the velocity of blood flow in that vessel (118).

CBFv is regarded as a direct surrogate for CBF when the diameter of the vessel is assumed to be constant (119). However, given that both velocity and vessel diameter cannot be measured by TCD simultaneously (120), the validity of this assumption has been challenged. There have been divergent results from studies showing that certain magnitudes of change in levels of CO_2 concentration can influence vessel diameter (121). Therefore, caution should be taken when interpreting TCD measures as CBFv values may be underestimated in the presence of changing arterial gas concentrations.

Another limitation is that TCD is operator dependent and relies on the maintenance of an accurate and standardised angle of insonation (55-65 degrees) towards the blood vessel to obtain reliable and repeatable measures (113, 114). The insonation of cerebral arteries is technically challenging in older subjects due to temporal bone thickness and can be difficult to record during manoeuvres such as those involving change of posture (122). Indeed, about ten percent of individuals do not have an appropriate optical window for the probe to operate and this increases with age (114).

Despite these uncertainties, with strict protocol compliance, TCD demonstrates good inter-observer reproducibility (123, 124) and correlates well with SPECT, Xenon^{133} clearance techniques and functional MRI. TCD is widely used both in clinic and research settings due to its low cost, lack of need for radiation or contrast and useability at the subject's bedside.

“The results indicate that a "window" for effective transmission of near infrared light exists in biological materials and that haemoglobin-oxyhaemoglobin equilibrium, the blood volume, the redox state of cytochrome a,a3, and thereby oxygen sufficiency can be monitored noninvasively…” (125)

Frans Frederik Jöbsis PhD (1929-2020)

2.6.7 Near Infrared Spectroscopy

The remainder of this section provides an in depth discussion on the modality of NIRS given its relevance to the method of CBF assessment used in the studies conducted as part of this thesis.

NIRS is a non-invasive device used to measure relative changes in haemodynamic and metabolic activity within the brain. It was the seminal work of Frans Jöbsis in 1977 (125) on the use of photospectroscopy with near infrared wavelengths to measure cerebral oxygenation in cats that led to the further development of this field. Arterial blood is rich in oxygen and has a bright red colour while venous blood is dark red due to its lesser oxygen content. This physical observation is exploited by NIRS and its principles are based on two important observations: i) light in the near infrared spectrum (700-950 nanometres (nm)) can traverse biological tissue due to the relative transparency of tissue to light in this wavelength range and ii) several biological molecules (chromophores) have distinct absorption properties when exposed to light in the near infrared range (125).

Tissue chromophores include water, lipids, melanin, myoglobin, oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), and cytochrome oxidase. Each of these absorbers exhibits distinct absorption spectra, enabling their spectroscopic differentiation through the use of light at different wavelengths (126). NIRS utilises the Modified Beer Lambert Law (127) to calculate the concentration of a solute in a solution by relying on its interaction with absorbed light. This law states that the attenuation of light is directly proportional to three variables: chromophore concentration, the distance travelled by the light and the absorption coefficient of the chromophore at a given wavelength.

The NIRS probe is placed on the scalp over the cerebral tissue and consists of a light source and photodetectors. The photons emitted from the light source scatter in the tissue bed and those that are not absorbed are reflected back to the detector (128). By measuring the amount of light returned, the amount of absorption occurring within the chromophores in the tissue is calculated. In a complex medium like biological tissue, the Beer-Lambert Law is modified to account for the scattering of light (129, 130):

$$A = \alpha B d C + G$$

where:

- A is the attenuation of light measured in units of optical density,
- α is the specific absorption coefficient of the chromophore at a specific wavelength,
- B is the differential pathlength factor (DPF) – the mean path length photons travel before reaching the detector,
- d is the distance between the device light source and detector,
- C is the concentration of the chromophore in the tissue, and
- G is an additive term for losses due to scattering.

The main chromophores of interest are O_2Hb and HHb.

2.6.7.1 NIRS Methodologies

With technological evolution, several refinements and methodological advances have been made by the proprietors of different NIRS devices to calculate the physiologically relevant signals from the attenuation of light measurements. These include continuous

wave spectroscopy, frequency-domain spectroscopy, time-resolved spectroscopy and spatially resolved spectroscopy (SRS) (129, 131).

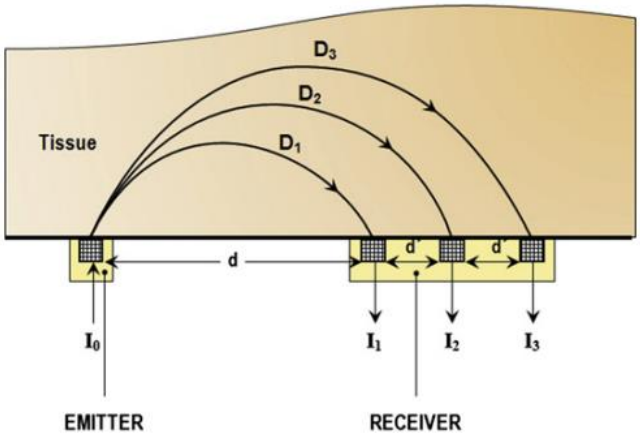

Figure 2.9 Spatially Resolved Spectroscopy illustrating three successfully detected signals (I_{1-3}) along with the possible photon paths (D1-D3) in different tissue layers. I_0 is the incident photon and d is the source-detector/ receiver distance. (Modified from (8))

In SRS – the approach used by the NIRS device utilised for the studies in this thesis – the attenuation of light is measured at multiple different source-detector distances. Combining this with an estimation of the wavelength dependency of light scattering, the relative proportions of O_2Hb and HHb can be derived (132). SRS enhances the contribution of deeper tissues while reducing the contribution of more superficial tissues (8). (See Figure 2.9). The SRS algorithm allows calculation of tissue oxygen saturation:

$$Tissue\ Oxygen\ Saturation = \frac{[O_2Hb]}{[O_2Hb] + [HHb]}$$

Tissue saturation index (TSI) is equal to tissue oxygen saturation expressed as a percentage:

$$TSI\ (\%) = \frac{[O_2Hb]}{[O_2Hb] + [HHb]}\ x\ 100$$

The precise determination of chromophore concentration is closely associated with the choice of light wavelengths directed into the tissue. Commercial devices commonly utilise wavelengths ranging from 700nm to 850nm, a range where the absorption spectra of O_2Hb and HHb exhibit maximal differentiation, and minimal interference occurs with the wavelength associated with water absorption (980nm) (131).

NIRS assesses tissue oxygen saturation, mirroring haemoglobin saturation across venous, capillary, and arterial blood within the tissue bed. In the cerebral cortex, the typical distribution of tissue haemoglobin averages around 70% venous and 30% arterial (133). This clarifies the reason why NIRS measurements consistently register lower values than arterial oxygen saturation measured by pulse oximetry. Pulse oximetry assesses only arterial blood by utilising the arterial pulsatile component of the signal. While TCD indirectly evaluates alterations in cerebral tissue perfusion by measuring blood flow velocity in the major cerebral arteries, NIRS directly assesses cerebral oxygenation at the cortical tissue level (134, 135).

The algorithms for the above methodologies are complex and contingent on certain assumptions. This can lead to some variability in the precise nature of reported outcome measurements in devices produced by different manufacturers making comparisons between them problematic. Indeed, some models use proprietary algorithms or modify algorithms with undeclared scaling factors (129).

Nevertheless, NIRS measures regional cerebral oxygenation saturation and reflects the interplay of oxygen supply and demand in cerebral tissue (136). The sum of O_2Hb and HHb yields the total haemoglobin concentration (THb) and as haemoglobin is confined to red blood cells and the vast majority of oxygen in blood is bound to haemoglobin, THb is

proportional to CBV. The concentration difference of O_2Hb and HHb is an indicator of the balance between oxygen supply and demand in the tissue and is determined by a number of factors including CBF, CBV, cerebral metabolic rate of O_2 ($CMRO_2$), capillary density and haematocrit. Cerebral oxygenation is not solely determined by CBF per se but is linked to CBF and provides a relative measurement of CBF assuming these other factors are not contributing significantly to their values (85).

NIRS derived regional cerebral oxygen saturation has been shown to correlate with jugular bulb venous saturation (SjO_2) (137). The SjO_2 – given that it measures oxygen saturation in blood on its return to the heart – helps establish the balance between CBF and the $CMRO_2$ which gives an indication of the use of O_2 by the brain (138). Therefore, in times of increased oxygen demand, the brain extracts a greater amount of oxygen resulting in decreased SjO_2. Conversely, when CBF exceeds metabolic requirements, SjO_2 will increase.

NIRS derived cerebral oxygenation has been found to correlate well with CBF as determined by Xenon clearance albeit in preterm infants (139). Estimates of cerebral oxygenation measured with NIRS correlated well with TCD CBFv over a wide range of BP in patients with autonomic failure (140).

2.6.7.2 Advantages of NIRS

In comparison with other techniques, NIRS devices are easy to apply and are relatively low in cost. The probe is usually placed on the forehead over the frontal lobe. NIRS is therefore applicable at the bedside and provides continuous non-invasive real time monitoring with higher temporal resolution than other techniques that use CT, MRI or PET (130). The

penetration depth of near infrared light can reach several centimetres allowing measurements from within the brain parenchyma (141). Typical depth sensitivity of most NIRS devices is approximately fifteen millimetres (131). This restricts measurements to the outer cerebral cortex.

2.6.7.3 Limitations of NIRS

The spatial resolution of NIRS is poorer than other modalities and devices have high signal to noise ratio and are prone to motion artefact (142). Motion artefacts arise primarily from head and skin movements during speech or facial expressions, as well as probe displacement (130, 142). A stable contact between the light source and skin is critical (131). In the studies carried out as part of this thesis, a bandage was used around the head to secure the probe in place and to prevent interference from ambient light (130). Given that near infrared light must travel through scalp, bone and CSF before reaching brain tissue, there are also concerns around contamination from extracranial tissues affecting cerebral oxygenation measurements. However the use of SRS techniques are suggested to reduce the influences of extracranial tissues (143) but do not eliminate them entirely (144). For optimal capture of cerebral tissue and to minimise extracerebral contamination, it is advisable to maintain a source-detector distance on the NIRS probe of at least 4.8cm (145).

The most significant limitation in the use of NIRS are question marks over its validity. The accurate measurement of DPF dominates this debate (130). DPF is influenced by factors such as age, tissue composition such as the presence of myelin, and anatomical differences such as individual head diameter. This variability makes it challenging to

establish a universal DPF value applicable to all subjects and critics argue that a more tissue-specific approach may be necessary to improve the accuracy of NIRS measurements (146). Devices using SRS do not rely on DPF values to calculate cerebral oxygenation levels. Therefore, when reading the literature, it is important to consider the particular NIRS device used within a given study as it may be challenging to make direct comparisons.

Consideration must also be given to other potential chromophores in the assessed tissue including water, melanin and bilirubin. While the contribution of water to NIRS values is considered low given that it exhibits its lowest absorption of light between 300-1000nm (127), a systematic review concluded that skin pigmentation (melanin) may lead to attenuated oxygenation readings (147). Nevertheless, the extent of this effect might vary depending on the particular NIRS platform used. A study investigating cerebral oxygenation levels in a group of liver transplantation patients found that bilirubin absorbed near-infrared light and lowered the measured cerebral oxygen saturation. However, while icterus interfered with NIRS values, changes in cerebral oxygenation were still visible (148). It is also worth noting that in individuals with anaemia (<6g/dL), cerebral oxygenation levels will yield an error of approximately fifteen percent (149). Various other patient-related factors that impact NIRS-derived values include patient agitation, skin conditions such as burns, infections, or scars, brain malformation, polycythaemia, and subcutaneous fat (137).

The algorithms used to calculate cerebral oxygenation tend to vary across different commercial devices making comparison between them challenging (131). Recently, Kleiser et al. (150) conducted an evaluation of multiple commercially available devices

using a phantom model in an attempt to enable comparison of absolute values obtained by the different devices.

TSI presents extensive intra and inter individual baseline variability with no establishment of a definitive range for normal values (129). Therefore there is no accepted threshold for recognising ischaemia or hypoxia (142). This has led to a reliance on trend analysis with attention paid to changes in measurements rather than to their absolute values. Recently, Newman et al. have published normative values for absolute TSI during supine rest (151) and change in TSI from baseline during orthostasis stratified by age and sex in the TILDA population cohort (152). This study used the PortaLite (Artinis Medical Systems, Elst, Netherlands) NIRS device.

Despite the aforementioned drawbacks, NIRS has moved beyond the research sphere with a number of commercial devices available for several clinical applications showing varying degrees of promise.

2.6.7.4 Clinical Applications of NIRS

Several clinical applications for NIRS have been developed to measure oxygenation levels in both cerebral and non-cerebral tissues.

Uses for NIRS to measure oxygenation in tissues such as somatic muscle to detect compartment syndrome (153, 154) or the early identification of shock in trauma (155) or sepsis (156) patients have been proposed. While NIRS has been proposed as a means to measure tissue oxygenation in non-cerebral tissues, the following summary is restricted to cerebral applications.

2.6.7.4.1 Neonatology

Given the thin scalp and skull of the newborn coupled with the desire to avoid radiation, perhaps it is not surprising that NIRS is increasingly used in the field of neonatology and paediatrics. Premature and low birth weight infants are predisposed to cerebral ischaemia as they are at significant risk of apnoea due to brain immaturity, intraventricular/ intraparenchymal haemorrhage and periventricular leukomalacia. Meek et al. (157) showed that low CBF detected by NIRS on the first day of life was a risk factor for severe intraventricular haemorrhage. The series of large multicentre SafeBoosC randomised controlled trials (RCT) (158-160) showed that it was feasible to use NIRS to detect cerebral hypoxia events in early preterm (<28 weeks gestation) infants enrolled within three hours of birth. This allowed clinicians to intervene and maintain oxygenation levels at 55-85% and significantly reduced hypoxic events (36.1%hrs versus 81.3%hrs, $p<0.001$). While the phase two trial showed an improvement in in early mortality and morbidity in the intervention NIRS monitoring arm, this was not statistically significant, and the results were not borne out in the later higher powered trials.

In the delivery room, Pichler and colleagues in their pilot RCT (161) used NIRS to guide the administration of supplemental oxygen to infants <34 weeks gestation over the first 15 minutes of life in an effort to improve survival without cerebral injury. The authors found a significant relative risk reduction (55.4%) of cerebral hypoxia in the NIRS monitored group compared with usual care (126.6%min versus 56.5%min, $p=0.028$). The extensive phase three trial (162) determined that NIRS monitoring did not lead to significantly higher survival without cerebral injury when compared to standard care alone. Although there was a 4.3% increase in survival without cerebral injury, the difference was not statistically significant.

Regarding hypoxic ischaemic encephalopathy which is associated with poor neurodevelopmental outcomes, the use of NIRS early in this group of newborns may facilitate better identification of those at risk of deterioration and allow individualised targeting of interventions such as therapeutic hypothermia (163).

2.6.7.4.2 Perioperative & Surgery Settings

The brain remains one of the least monitored organs in anaesthesia (141). Therefore the application of NIRS to measure brain metabolism, perfusion and functional integrity during surgery is attractive. When there is an imbalance between cerebral oxygen supply and demand, cerebral hypoxic injury results, leading to a range of disorders. Ideally, the use of cerebral oxygenation measurement can help prevent or minimise ischaemic injury before it becomes irreversible (164).

Cardiac Surgery

Clinicians have been actively searching for a dependable method to monitor the adequacy of brain perfusion, especially during cardiopulmonary bypass (CPB). This is particularly crucial due to the significant impact of neurological complications such as stroke, delirium, and cognitive impairment on patient outcomes (165). In a RCT involving 200 patients undergoing CPB, Murkin et al. (166) found that actively monitoring cerebral oxygenation using NIRS and treating decreases in values effectively prevented prolonged cerebral desaturations. This approach was associated with a shorter stay in the intensive care unit (ICU) ($p=0.029$) and a significantly reduced occurrence of major organ morbidity (including ventilation > 48 hours, stroke, myocardial infarction, return to theatre) and mortality

compared to the control group (p=0.048). However, the study was not powered to compare stroke rates between the two groups. Murkin's algorithm for treating and reversing cerebral desaturation (defined as abnormal when there was a 20% decline from baseline or an absolute decrease of at least 50%) was further validated by Deschamps et al. (167) in 2013. Measures included in the study to correct cerebral desaturation included verifying head position, increasing BP, ensuring adequate CPB flow, correcting $PaCO_2$, optimising haemoglobin by transfusion and/ or deepening anaesthesia.

Other observational studies (168-170) suggest an association between decreases in cerebral oxygenation from baseline and the development of post operative cognitive dysfunction (POCD) and delirium. These studies are not consistent, and limitations include their small sample size, the use of insufficient cognitive assessment and poor timing of testing early after surgery during which time there are many confounders to affect cognition.

Regarding stroke outcomes in cardiac surgery, a study conducted by Goldman et al. (171) found that stroke rates were significantly higher in a group without NIRS monitoring (n=10 [0.97%] versus n=25 [2.5%]; p <0.044). However, the study was retrospective in nature and failed to outline how cerebral desaturations were treated.

Based on findings from a Cochrane review (172) in 2018 regarding the active monitoring of brain oxygenation using NIRS during the perioperative period, there is only limited support to date for its use in adults to reduce the occurrence of short-term mild POCD and the length of stay in ICU. However, the observed difference is marginal, and the overall quality of the evidence is deemed to be low to moderate due to issues of bias, imprecision, and inconsistency across trials. The review concludes that there is insufficient

evidence to determine the effects of active cerebral NIRS monitoring on postoperative neurological injury. Additionally, the evidence suggests that active NIRS monitoring may result in little or no decrease in postoperative stroke, delirium, or mortality, but that this evidence is of low quality (173). Despite the presence of conflicting outcome data, the growing utilisation of NIRS in monitoring cerebral oxygenation during cardiac surgery can be attributed to its ease of use and modest cost (174).

Carotid artery surgery

NIRS has been used during carotid endarterectomy (CEA) surgery for carotid stenosis in an effort to minimise the risk of perioperative neurological complications such as stroke, rates of which can range 3-7.5% particularly during occlusion and clamping of the artery (175).

The placement of a shunt to maintain cerebral blood supply is itself associated with substantial risks of embolization and NIRS has been used to inform the decision regarding shunt placement in those where collateral blood supply is insufficient to perfuse the brain during the cross-clamp period. Several studies have used cerebral oxygenation changes to identify a threshold for critical cerebral ischaemia (141, 176, 177). Wang et al. (178) suggest a decrease in TSI of 12.3% be adopted as a reliable threshold for intraoperative hypoperfusion to guide shunt placement.

The occurrence of postoperative neurological complications following CEA may be linked to rebound increases in CBF following the surgical correction of carotid stenosis – so called post-CEA hyperperfusion syndrome. The impaired autoregulation resulting from chronic brain ischemia, coupled with a rapid restoration of regional perfusion, gives rise to a hyperperfusion syndrome characterized by symptoms such as headache, brain oedema,

seizures, and, in severe cases, intracerebral haemorrhage and death (179). A number of studies have attempted to use NIRS to predict those at risk of hyperperfusion post revascularisation (180, 181). In a cohort of 50 patients undergoing CEA, Ogasawara et al. (182) observed a notable association between TSI values immediately after de-clamping during CEA and changes in CBF, with a sensitivity and specificity of 100% and 86.4%, respectively, for identifying patients at risk of developing hyperperfusion syndrome when employing a cut-off value of 5%. Using this 5% cut-off point, cerebral oximetry demonstrated a positive predictive value of 50% and a negative predictive value of 100%.

Despite its limitations, it is evident that NIRS provides benefits over alternative techniques (such as TCD or electroencephalogram (EEG)), particularly in terms of simplicity. NIRS has served as the primary cerebral monitor during carotid endarterectomy (CEA) for over a decade (183).

Other surgery

Another area of emerging interest is the application of NIRS to study patients undergoing surgery requiring specialised positioning such as the beach chair, prone, Trendelenburg and reverse Trendelenburg positions as these techniques can predispose to periods of hypotension and hypoperfusion (129, 164).

A systematic review by Nielsen (184) concluded that following thoracic surgery, major orthopaedic, and abdominal surgery, the occurrence of POCD may be related to severe episodes of intraoperative cerebral desaturation.

2.6.7.4.3 Brain Injury & Critical Care

The use of NIRS has also been explored in head injury patients and in the neuro ICU (185). In traumatic brain injury (TBI), cerebral metabolic function and CA mechanisms become disordered leading to intracranial hypertension, impaired perfusion and secondary brain injury. Therefore, neuromonitoring is important to facilitate early recognition and management of secondary brain injury in critically ill patients (186). An observational study involving 18 patients with traumatic brain injury (TBI) revealed a correlation between the duration of cerebral desaturation below 60% and adverse outcomes, including mortality, intracranial hypertension, and compromised CPP (187). Another study found that NIRS derived oxygenation <60% was moderately accurate for predicting severe hypoxia but poor at detecting moderate hypoxia (188).

Another area of interest is the use of NIRS to detect areas of focal haemorrhage or vascular injury particularly prehospital or in low resource settings where CT imaging is unavailable. Out of 54 CT-confirmed haematoma cases in a cohort of 148 TBI patients, NIRS detected 48 with a sensitivity of 88.9%, specificity 77.7%, positive predictive value 69.6% and negative predicative value 62.8% (189). Detection rates improve further when haematomas are more superficial (190). Small lesions and bilateral lesions were difficult to detect given the poorer spatial resolution of NIRS to facilitate comparison with the contralateral region of interest. Yuksen and colleagues (191) suggest, however, that NIRS can be sensitive enough to inform decision making in selecting appropriate patients for transfer to neurosurgical centres.

Measurements of autoregulation obtained through NIRS show a correlation with invasive measures derived from intracranial pressure (ICP) (192, 193) potentially opening avenues for non-invasive personalised optimisation of cerebral haemodynamics in TBI (194).

Vasospasm and delayed cerebral ischaemia are important complications of subarachnoid haemorrhage which are often preceded by impaired CA (186, 194). Studies have evaluated the ability of NIRS to use reductions in cerebral oxygenation to predict vasospasm and delayed cerebral ischaemia (195, 196).

In seizures, convulsive activity which can be subclinical, is associated with rapid oscillations in tissue oxygen saturation detected by NIRS and therefore can be helpful in monitoring ventilated patients or assessing the response to anti-epileptic medication (197).

2.6.7.4.4 Ischaemic Stroke

The management of acute ischemic stroke centres on relieving cerebral artery occlusion through thrombolysis and/or endovascular thrombectomy. The objective is to restore CBF, to prevent infarct expansion and minimise haemorrhagic complications (194). In a proof of concept feasibility study, patients with stroke demonstrated a reduction in cerebral tissue oxygenation on the side of the ischaemic insult compared with the contralateral hemisphere (198). NIRS has been explored in the context of early revascularisation therapies to assess the effectiveness of treatment (194). Hametner et al. (199) found that a greater interhemispheric difference in TSI at the conclusion of the procedure is associated with higher mortality. Another more recent investigation

demonstrated that successful recanalisation of occluded vessels was associated with a significant reduction in the interhemispheric TSI difference (200).

In the early post stroke period, CA is impaired leaving vulnerable brain tissue around an infarct at risk of further ischaemia from hypoperfusion as well as from haemorrhage from hyper/ reperfusion injury. Attempts have been made to identify the lower and upper limits of autoregulation using NIRS derived indices and have found that time spent above the upper limit of CA led to worse functional outcomes at 90 days and with higher risk of haemorrhagic transformation (201).

2.6.7.4.6 Functional NIRS

Functional NIRS (fNIRS) is becoming an important research tool to assess functional activity and has been applied as both a monitoring and therapeutic tool in the field of neurorehabilitation (202). Functional NIRS may enable evaluation of NVC (194) (See section 2.5.5) in response to functional tasks such as hand movement, walking, or language (202, 203). The technology may also be used to develop brain-computer interfaces to restore function and improve activities of daily living in those with severe neurological disabilities (202, 204). Another application of fNIRS is that of language mapping for presurgical evaluations in those undergoing neurosurgery (205).

2.6.7.4.7 Syncope and other Autonomic dysfunction disorders

NIRS has been applied to the area of syncope, orthostatic intolerance, OH, and other autonomic disorders including postural tachycardia syndrome (206-216). Mol et al. (216)

demonstrated that NIRS derived cerebral oxygenation responses were sensitive to postural change and suggested its future clinical use in older adults with impaired BP control such as that seen in OH. A validity study conducted by Klop et al. (217) indicated that cerebral oxygenation measurements – particularly O_2Hb – correlated with postural BP dynamics especially in the initial phase post standing (first 30 seconds) and reflected changes occurring at a cerebral level in the latter phase (post 30 seconds). The authors also reported strong associations with CBFv derived from TCD but only when longer source detector distances were used. Kharraziha et al. (212) suggest that NIRS may help unravel the pathophysiological mechanisms underlying syncope and orthostatic intolerance and enhance the understanding of the relationship between haemodynamic changes and CA. They also suggest a role for NIRS in the clinical diagnosis and individualisation of treatment for syncope and orthostatic intolerance. The role of NIRS for CBF monitoring in syncope will be considered in greater detail in later sections of this thesis. (See Section 2.7.5). The following discussion, however, will explore important clinical factors that influence CBF.

2.7 Clinical Importance of Cerebral Blood Flow

Despite the meticulous and often redundant mechanisms underpinning the regulation of CA and maintenance of adequate CBF, many clinical disorders are associated with disruption and impairment of these mechanisms. Since older age is a prevalent risk factor for many of these conditions and constitutes a central focus of this thesis, the discussion commences with an exploration of the influence of ageing on the regulation of CBF.

2.7.1 Ageing and CBF

Age related changes in CBF (measured using different modalities) have been identified in healthy individuals throughout the lifespan. Both cross-sectional and longitudinal studies in individuals across the third to ninth decade of life showed that global CBF decreases by about 0.3-0.8ml/100g/min per year (<0.5% per year) (92, 218-220). Reasons for this may include reduced metabolism and/ or increases in cerebral atrophy (4).

Corresponding to this global CBF reduction, cerebrovascular resistance increases with age. This may be due to age related changes in the calibre of cerebral blood vessels (221) and/ or due to an increase in stiffness in the vasculature (222). Furthermore, age related reductions in the release of NO from the endothelium are suggested to contribute to reduced CBF in older people (223).

There is some disagreement in the literature regarding the effects of ageing on cerebrovascular CO_2 reactivity (4) but most studies have found that CA is preserved in healthy ageing (220, 224-226). Oudegeest-Sander et al. (224) investigated the dynamic responses of CBFv with TCD, and cerebral oxygenation using NIRS, in cognitively healthy individuals across three different age groups (young [aged 24±2 years], old [aged 66±1 years], and very old [aged 78±3 years]). The study confirmed the existence of an age-related decline in MCA CBFv with an increase in cerebrovascular resistance. However, it showed that the relative changes in CBF in response to sit-to-stand manoeuvres and changes in $paCO_2$ were maintained across all age groups. This observation suggests the preservation of dynamic autoregulation and CO_2 reactivity even with advancing age. Another more recent study with longitudinal follow up of 10.9 years showed subtle reductions in cerebrovascular CO_2 reactivity and preserved (or even improved) dynamic

CA with ageing in 28 healthy adults (227). Sorond et al. (228) compared 13 healthy young (mean age 30±7 years) and 13 healthy older subjects (mean age 73±4 years) using TCD during orthostasis (sit-to-stand) and found that while older participants showed larger changes in peripheral haemodynamic responses to standing, CBFv remained relatively unchanged. They also found regional differences between MCA and PCA territories in that CBFv in the PCA territory declined greater than in the MCA territory suggesting that the posterior circulation may be more vulnerable to hypoperfusion during standing.

In relation to other investigations using NIRS, Hallacoglu et al. (229) were first to suggest an age associated decline in cerebral tissue oxygenation – albeit reporting absolute NIRS values obtained from young (mean age 28±4 years) versus old (mean age 85±6 years) age groups. Kim et al. (99) observed a significantly smaller reduction in cerebral oxygenation among older adults compared to their younger counterparts during the initial phase of standing (sit-to-stand) and in the early steady state phase post stand. Conversely, Mehagnoul-Schipper et al. (122) demonstrated that during the post-standing period (supine-to-stand), healthy older adults experienced a significantly greater decline in cerebral oxygenation compared to a younger group in the absence of peripheral BP changes. Gatto et al. (230) reported a small but significant decrease in O_2Hb and an increase in HHb from supine to sitting position, which was similar between young (mean age 28±5 years) and older subjects (48±6 years). In a larger study of 60 healthy subjects (ages ranging 20-78 years) that used both NIRS and diffuse correlation spectroscopy, increasing age was associated with a larger decline in O_2Hb but not regional CBF or HHb during supine-to-stand manoeuvre (231). The variance in the methodologies employed for the standing manoeuvre may contribute to the apparent discrepancy in findings between these studies.

Contemporary hypotheses propose that maintaining or enhanced dynamic CA as one ages acts as a “reserve”, serving to offset the decline seen in other CBF physiological systems (232, 233). Another potential limitation of these “healthy ageing” studies is that they have unintentionally included individuals with prodromal or asymptomatic neurodegenerative diseases yet to become clinically apparent (4).

In addition to age related changes, it is worth noting that sex differences in cerebral haemodynamics have also been described – both in the resting supine state (151) and during orthostasis (231, 234). In a population cohort using NIRS, controlling for multiple covariates, Newman et al. (152) found that during orthostasis, males experienced larger declines in cerebral oxygenation compared to females and that females failed to stabilise TSI to baseline levels at any time post stand. Similar findings were reported in a large TCD study (235). In another TILDA study, CBF measured by MRI perfusion was found to be higher in females (236).

To summarise, while research involving healthy older adults suggests the preservation of CA with age, certain older people with reduced resting CBF, elevated cerebrovascular resistance, reduced NO production and diminished cerebrovascular reserve may manifest impairment in CA. Consequently, they may face an elevated risk of hypoperfusion during orthostatic stress events like changes in posture.

2.7.2 Hypertension and CBF

The cerebral vasculature is a major target of both structural and functional damage induced by hypertension (109). Hypertension is associated with arterial stiffening (237), the development of atherosclerosis and impairs the ability of endothelium to regulate CBF

by inhibiting the availability of NO induced vasodilation. It is also postulated that hypertension disrupts the BBB resulting in the reduction of synaptic signalling within the neurovascular unit and altered NVC (238, 239).

Understanding of the relationship between CBF and hypertension in static CA has evolved in recent years. Previously, it was felt that chronic hypertension would result in a shift of the autoregulation curve to the right. This shift would result in CBF being maintained stable at higher BPs leaving it more vulnerable to hypotension (238). This gave rise to concerns that attempts to lower BP would precipitate hypoperfusion and lead to problems like falls, dizziness, small vessel disease (SVD) and cognitive impairment. Chronic hypertension has been shown to reduce CBF (240, 241). However, it would seem that while hypertension does shift the autoregulatory range towards higher BPs, CA mechanisms are not impaired – at least for moderate hypertension (4, 238). A postulated example of how this is the case occurs when the CBF response to lowering of BP in hypertension is examined. Antihypertensive treatment appears to "rescue" CBF and reverse this rightward shift (109). CBF is maintained constant or even increased with antihypertensive treatment challenging the previously longstanding idea that lowering BP would lead to hypoperfusion in hypertensive patients. Lipsitz et al. (242) in their study of 598 community dwelling adults aged 70-97 (mean age 78.4±4 years) found that not only did the odds ratio of falls over one year decrease (OR 0.62 [CI 0.39-0.96]) in participants taking antihypertensives, but that TCD derived CBFv showed no difference (or in the case of calcium channel blockers an improvement in CBF) in those taking antihypertensives compared to those not taking these medications. Indeed, the authors reported that older people taking relatively large doses of calcium channel blockers and ace inhibitors had a lower risk of falls compared to those not taking these medications. The large RCT of 9361

individuals conducted by the Systolic Blood Pressure Intervention Trial (SPRINT) group also showed no increase in falls when BP was treated intensively to a SBP target of <120mmHg (243). An ASL MRI sub study (244) of the SPRINT participants (n= 547) showed that over four years follow-up there was a small but significant increase in whole brain and grey matter CBF in those whose hypertension was intensively treated. These results replicated those found in an earlier ASL MRI study (245) of 37 participants (mean age 75±4 years; mean SBP, >150 mmHg) randomised to standard versus intensive (<130/80mmHg) BP treatment which found increases in whole grey matter CBF in the intensive lowering group over a 3 month period. Both these studies measured CBF while supine and so reflected static CA rather than dynamic CA. The latter study did not include participants with stroke or SVD. A recent systematic review (246) concluded that antihypertensive treatment had no significant effect on global CBF and even suggested a trend towards improved CBF in older age groups. Indeed, recent work by Weijs et al (247) found that in fourteen frail hypertensive patients (mean age 80.3±5.2 years) treated intensively to a SBP target ≤140mmHg, there was no significant cerebral hypoperfusion, impaired CA or increased prevalence of initial OH – challenging the assumption that antihypertensive treatment in frail individuals should be avoided due to the risk of cerebral hypoperfusion or OH.

Some studies have examined the association of hypertension on dynamic CA. A small study by Lipsitz et al. (248) found that there was no difference in CBF fluctuations among groups of young (n=10), normotensive (n=10) and older hypertensive (n=10) individuals undergoing sit-to-stand. Zhang and colleagues (249) examined the CBF responses of the antihypertensive losartan/ hydrochlorothiazide on 30 subjects with varying degrees of mild and moderate hypertension over 1-2 weeks and again at 3-4 months. They assessed

dynamic CA using transfer function analysis (TFA) of TCD derived MCA CBFv and beat-to-beat BP measurements and found that static and dynamic CA are not compromised in subjects with mild and moderate hypertension. A larger study by Eames et al. (100) that used thigh cuff deflation to measure dynamic CA concluded that dynamic CA was preserved in hypertensive subjects compared to normotensive controls.

Severe elevation in BP such as that seen in malignant hypertension can have a profound impact on both static and dynamic CA. In malignant hypertension, levels of BP are so high, that this is beyond the upper limit of the CA curve (238) – resulting in the symptoms associated with raised ICP including altered mental state, headache, infarction or haemorrhage, papilloedema and retinal bleeding. In a study of 8 patients with malignant hypertension (MAP>140mmHg), treatment with sodium nitroprusside was associated with impairments in both static and dynamic CA (250). This implies that the magnitude of hypertensive change coupled with the duration of the period of raised BP are important influencers on adaptive responses of CA to hypertension and its treatment (4, 238).

The presence of hypertension increases the risk of OH (251), the CBF implications of which will be discussed later. Additionally supine hypertension – the paradoxical elevation in BP when lying flat – has been shown to be associated with impaired cerebral oxygenation responses to standing (252).

2.7.3 Stroke, White Matter Disease and CBF

When regional CBF falls below 20ml/100g/min, ischaemia ensues and infarction develops at levels <8ml/100g/min (253). Neurological symptoms develop and hypoxic tissue injury evolves within minutes to hours unless O_2 supply is restored (254). While the role of CBF

in acute stroke is complex and beyond the scope of this thesis, it suffices to say that stroke impairs CBF regulatory mechanisms including CA. The degree to which this occurs depends on the type, aetiology, severity, location, presence of comorbidities and whether acute interventions like thrombolysis or thrombectomy have been performed (4). While these mechanisms are impaired in the early period post stroke, there is evidence to suggest that both static and dynamic CA gradually improve with time and recovery, though at what point CA normalises if it all is unclear (255-258).

Hypoperfusion may provide the mechanism for a subtype of ischaemic stroke – so called haemodynamic or border zone or watershed infarction which account for about ten percent of all ischaemic strokes (253). As alluded to earlier, the structural anatomy of blood supply differs between the grey and white matter. The relative paucity of anastomotic networks in the white matter increases its vulnerability to hypoperfusion. Haemodynamic strokes occur at the border zone of these vascular territories. Border zone ischaemia is thought to be triggered by circumstances that induce hypotension or hypovolaemia leading to global hypoperfusion and arterial thromboembolism (259, 260). Anaemia, OH, exercise, transition from a cold to warm environment, post prandial hypotension and coughing can precipitate hypoperfusion leading to a stroke or transient ischaemic attack (TIA) (261). CBF is further compromised in those with co existent carotid stenosis or occlusion and are at greater risk of recurrence than those without (259). It is noteworthy that Ryan et al. (262) found that one in twenty patients with presyncope or syncope present with coexistent focal neurological/ TIA signs. Symptoms of OH have been shown to be an independent predictor of ischaemic stroke (263).

Impaired CA, reduced CBF and impaired anastomotic capacity may also be associated with the burden of white matter disease. Hypertension is a well-established risk factor for both ischaemic and haemorrhagic stroke and is associated with the development of SVD and white matter hyperintensities (WMH) (264, 265). In a systematic review, Shi and colleagues (266) found that CBF is lower in subjects with increasing WMH burden. However most studies were cross sectional in design so causation cannot be established. CA is particularly impaired in patients with severe SVD who have confluent WMH (267) and CBF is reduced in regions of high concentrations of WMH (268). Researchers from the PRESERVE RCT examined whether intensive BP lowering would reduce or worsen CBF in a group of 111 participants (mean age 68 years; 60% male) with severe SVD. An early sub study (269) showed no difference in change of CBF (measured by ASL MRI at baseline and three months) in the intensive treatment group compared to those on standard treatment. The main study concluded that after two years follow up, intensive BP lowering was not associated with the progression of WMH (270). In some participants however, the target BP was not reached. It should also be noted that the SPRINT-MIND sub study (244) (outlined above) found only weak correlations between CBF and the development of white matter lesion volumes over the four years of the study's follow up.

WMH, lacunar strokes, SVD and cerebral microbleeds compromise CBF by inducing vessel narrowing, disruption of the BBB, failure of endothelium dependent vasodilation and consequently are implicated in the development of cognitive impairment (109, 238).

2.7.4 Cognitive Impairment, Dementia and CBF

Hypertension and cerebrovascular disease are important risk factors for cognitive impairment and dementia – both Alzheimer's disease (AD) and vascular dementia (271). Substantial evidence exists to support an association between reduced cerebral perfusion and cognition. The majority of cross sectional studies carried out to date report lower CBF in those with cognitive decline. Hypoperfusion has been identified in the preclinical or prodromal phases of AD. Indeed associations have even been identified in those with subjective memory complaints (220). Chao and colleagues in a longitudinal study of 48 participants (mean age 76.3±7.2 years, 33% female) with mild cognitive impairment found that progression to dementia was associated with decreased perfusion in the right inferior parietal and right middle frontal lobes measured by ASL MRI (272) – regions implicated in AD neuropathology.

Regarding longitudinal associations, a recent systematic review and meta-analysis (273) found that global CBF reduced by approximately 1.32% per annum in line with declining cognition in probable AD patients – a decline 3-10 times higher than normal ageing. While a decline in CBF is observed in normal ageing (see 2.7.1 discussed above), additional changes in structure and function induced by a combination of hypertension, lifestyle factors and AD neurodegeneration may be responsible for the larger decline of CBF in these individuals (274).

Other studies suggest that abnormal amyloid protein deposition in AD pathology impairs NVC mechanisms. Nicolakakis et al. (275) suggest that in AD patients, vessels of the cortex become denervated and more constricted impairing function and leading to further cognitive decline. Amyloid-beta-42 impairs endothelial NO which further impacts

vasodilatory capacity resulting in reduced regional perfusion. Increased phosphorylation of tau protein and resultant neurofibrillary tangles seen in AD also disrupts synaptic signalling and neural activity (254). Further evidence for the link between CBF and cognition comes from studies on the pharmacological treatments used to treat AD. Acetylcholinesterase inhibitors such as donepezil and rivastigmine have been shown to increase CBF and improve cognitive function – albeit only modestly (254).

Weijs et al. (273) suggest that decreases in both global and regional CBF are linked to the progression of dementia most likely through neuropathological changes in specific brain areas such as the parietal, temporal and limbic lobes arguing that AD is responsible for hypoperfusion rather than vice versa. Reduced CBF may act as a biomarker for early detection of neurodegenerative pathology and progression to dementia in AD (4).

In line with the discussion on CA and hypertension above and in contrast to animal models, it appears that neither static nor dynamic CA is impaired in AD (4). A secondary analysis of data from the NILVAD trial (276) found that dynamic CA showed only minor non clinically relevant impairments in AD patients at 6 months but they did not progress further over subsequent 12 month follow up. There is also indirect evidence suggesting preserved CA in studies examining the effects of antihypertensive treatment on cognition and risk of dementia. A recent meta-analysis of longitudinal studies (277) involving 31,090 individuals over 7-22 years found that those taking any antihypertensive medication had a reduced risk for developing AD (hazard ratio 0.84, [CI 0.73-0.97], p=0.021) compared to those on no antihypertensive medication. Additionally, the aforementioned SPRINT MIND trial group (278) reported a reduced incidence of mild cognitive impairment in those treated intensively compared to those receiving standard BP lowering treatment.

Perhaps, because the trial was terminated early, the authors did not find a significant reduction in incident cases of dementia.

2.7.5 Syncope, Related Disorders and CBF

Syncope has been regarded as a disorder of (albeit temporary) baroreflex or peripheral BP failure rather than a failure of CA per se (279) though there is increasing evidence to suggest CA is altered in some forms of syncope. In cardiogenic syncope, the reduction in CBF is caused by reduced cardiac output. This leads to cerebral hypoperfusion as BP falls below the lower limit of autoregulation (280). Alterations in CA have been implicated in CSS patients versus asymptomatic controls (281). However, in reflex syncope, slow progressive reductions in BP are more efficiently buffered by CA mechanisms than fast changes with very fast changes not buffered at all (4).

Hypoperfusion is responsible for the symptoms during presyncope that herald the onset of syncope. The advent of TCD and NIRS is adding to our understanding of cerebral haemodynamics during syncope. Thomas et al. (103) in a study of 37 healthy subjects who underwent HUT and lower body negative pressure (LBNP) found that a drop in CBFv of 23-26cm/s or a decline in cerebral oxygenation of 5-7% correlated with presyncopal symptoms while Bachus et al. (213) suggested an absolute threshold for TSI of 60% for critical brain desaturation and TLOC. Another study by Krakow et al. (282) compared TCD and NIRS responses to HUT in 15 patients (mean age 51.2±17.7 years, 40% female) with a history of syncope due to orthostatic stress versus 20 healthy controls (mean age 54±18.9 years, 35% female) and found that while CBFv and TSI declined on tilting upright in all subjects, in patients with a history of orthostatic syncope, there was significantly more

pronounced decrease indicating cardiovascular and/ or cerebrovascular dysregulation. Presyncope symptoms only occurred once accompanied by a sudden and marked drop in TSI values below 60%. However, as discussed previously, absolute values must be interpreted with caution and may not be generalisable to other NIRS devices. In a study using diffuse correlation spectroscopy – a technique that uses near-infrared light to detect fluctuations in light scattering caused by red blood cell motion – Cheng et al. (283) report that a 50% change in TSI from baseline is a suitable threshold to separate presyncopal patients from controls. Additionally, it is interesting to note that Krakow et al. (282) reported that transcutaneous measurements of $paCO_2$ remained stable in both patients and controls during the fifteen minute HUT though no specific data are presented.

Global cerebral hypoperfusion is felt to occur in syncope but some studies highlight regional differences. In a SPECT study of paediatric patients with syncope, HUT was associated with diffuse and left hemispheric dominant hypoperfusion while subjects who went on to have TLOC had significantly lower perfusion in the right peri-insular, posterior parietal and temporal lobes (284). A further comparative SPECT study (285) of 35 adult patients with a history of syncope and 35 healthy controls found decreased regional CBF in the right anterior insular cortex, left parahippocampal gyrus, bilateral fusiform gyri, bilateral middle and inferior gyri, left lingual gyrus, bilateral precuneus and bilateral posterior lobes of the cerebellum in syncope patients compared to controls ($p<0.05$). The authors also found worse hypoperfusion at the right prefrontal cortex was associated with increased number of syncopal episodes. Interestingly, the insula is linked to emotion and the regulation of homeostasis. The right insular cortex is also known to exert SNS effects such as tachycardia and increased BP whereas the left insula induces mainly PSNS effects like bradycardia and reductions in BP and these higher ANS mechanisms may be

implicated in syncope (286). Franco Folino (280) suggests that hypoperfusion in the right insula represents the final trigger for TLOC in reflex syncope.

TCD and NIRS technologies enable real time evaluation of CBF and help to investigate whether cerebral hypoperfusion is merely a passive outcome of peripheral bradycardia and hypotension or if there is active involvement of CA in reflex syncope. The time scale through which CA acts is critical for reflex mediated syncope (287). For example, in the case of sudden asystole, BP will decrease below the lower limit of CA before that autoregulation has had time to exert its full effect. Conversely, when BP decreases gradually, autoregulation has a longer duration to counteract the impact of declining BP. Evidence from the literature on whether alterations to CA are implicated in syncope is conflicting – probably due to heterogeneity amongst syncope related conditions and due to the technical methodologies used to calculate and model CA measurements (288).

Schondorf et al. (101) used TFA of TCD derived measures during HUT to compare dynamic CA in 37 participants with reflex syncope versus that of 15 healthy controls. The authors reported that in the three minutes preceding TLOC, there were no differences in dynamic CA compared to controls. However, further studies suggest that CA plays an active role in the development of syncope. TCD studies (288-292) have demonstrated reduced CBFv and increases in cerebrovascular resistance resulting in paradoxical vasoconstriction in the period leading up to syncope instead of a reduction in cerebrovascular resistance in response to hypotension as would be expected. While this would suggest that alterations in CA are occurring in the lead up to syncope prior to peripheral BP changes, Lagi et al. (290) proposes that the vasoconstriction can be explained by hypocapnia due to hyperventilation just before syncope. Similar conclusions were reached by Krishnamurthy

and colleagues (293) who reported reduced CO_2 reactivity in the three minutes preceding presyncope on HUT. Critics, however, argue that while hypocapnia may increase the sensitivity to hypotension, the degree of hypocapnia is insufficient in isolation to trigger TLOC (294, 295). Dan et al. (291) found that paradoxical vasoconstriction occurred before decreases in peripheral BP leading to the conclusion that reflex syncope cannot be a hypotension-dependent reflex but an independent, early phenomenon beginning centrally at the cerebral level. An early NIRS study identified changes in cerebral oxygenation prior to BP and HR changes in a paediatric population (n=19) with reflex syncope during HUT (296). Carey et al. (102) calculated the autoregulation index during HUT in 17 patients with recurrent syncope and 17 healthy matched controls and reported that while there was no deterioration in dynamic CA in controls, dynamic CA deteriorated in presyncope and syncope and remained impaired for up to one minute after syncope when the patients returned to supine. Additionally, Szufladowicz et al. (209) investigated cerebral oxygenation responses using continuous wave NIRS in 42 of 69 subjects (mean age 35±17 years, 65% female) who experienced syncope while undergoing HUT and found that O_2Hb and THb began to decline about 1.3 minutes prior to the experience of presyncopal symptoms. A gradual decrease in O_2Hb was followed by a sudden drop in those in whom syncope was provoked. Declines in O_2Hb were observed to occur 3.3±2.8 minutes before syncope, while peripheral changes in BP and HR occurred 1.1±0.6 minutes before syncope ($p<0.0001$). The authors suggest that this time difference provides evidence that the syncope reflex begins in the brain rather than in the peripheral circulation. Smaller earlier studies using NIRS reported similar observations though no specific timings were described (297, 298). Colier et al. (297) suggests that this mismatch between oxygen demand and supply could be used to predict the onset of syncope before

changes in peripheral haemodynamic measurements could be detected. The more recent study by Bachus et al. (213) applied NIRS to 54 patients (mean age 55±19 years, 61% female) undergoing HUT for investigation of unexplained syncope. They found a gradual progressive fall in TSI from baseline up to one minute preceding a larger TSI drop coinciding with syncope despite preservation of MAP during the passive phase of the HUT. This two stage decline featuring a gradual decrease in CBF followed by rapid dramatic reduction associated with CA failure was also noted in a study using diffuse correlation spectroscopy by Cheng and colleagues (283).

Further studies to untangle the interplay between syncope and CA have utilised more complex mathematical modelling to account for the time dependent nature of physiological fluctuations occurring in syncope. Ocon et al. (295) studied 12 participants with syncope (mean age 17±1, 58% female) during ten minute HUT and used phase synchronisation techniques to analyse BP and CBFv responses. Approximately 2 minutes prior to TLOC, syncopal participants had a sudden rapid decrease in phase synchronisation (implying increased CA) between BP and CBFv followed by a prolonged increase in phase synchronisation – implying loss of CA shortly before TLOC and into the early recovery period. Another study conducted by Bari et al. (299) exploited a conditional joint entropy approach to examine HUT responses in 13 syncope subjects (mean age 28±9 years, 62% female) and 13 matched control subjects. This approach considered MAP and CBFv to operate within a closed loop and allowed the potential confounding effects of respiration to be conditioned out. The authors report impairments to both the baroreflex and CA in syncope subjects but that similar behaviour was not seen in the control group. Pernice et al. (300) performed linear parametric analysis of pairwise interactions between time series considering both time and frequency domains with variability in MAP and CBFv

during HUT and suggested the increased MAP-CBFv coupling seen in syncope patients during HUT is an indication of CA “under pressure” and “less efficient” rather than definitively impaired. In other words, orthostasis and HUT reduce the effectiveness of cerebrovascular control in patients already prone to syncope.

In functional syncope or PPS – the focus of Chapter 9 of this thesis – consciousness is only apparently lost and there is absence of global cerebral hypoperfusion. TCD has been used to demonstrate normal/ unchanged CBFv during HUT in 8 patients (mean age 53.6±19.9, 87.5% female) (301). Other studies have suggested the use of NIRS to confirm the absence of hypoperfusion during the apparent TLOC of PPS (206, 213).

2.7.6 Orthostatic Hypotension and CBF

As mentioned previously, OH is a frequent cause of syncope and so there is some overlap when discussing the role of CBF in OH between that already outlined above. Nevertheless, the role of cerebral hypoperfusion in OH is the primary focus of the literature review in the following chapter of this thesis.

"The one feature of outstanding interest and importance…is the extraordinary dependence of the systolic and diastolic blood pressures upon the influence of gravity, as exerted through alterations in the positions of the body from the horizontal." (302)

(Samuel Bradbury MD & Cary Eggleston MD, 1925)

Chapter Three – Orthostatic Hypotension and Review of Literature

3.1 Introduction

OH results from an unusually large decrease in BP upon standing and reflects a final common pathway for various conditions affecting BP regulation. Often considered a physical sign rather than a disease per se (303), OH can also be one of the first presenting clinical features in many neurodegenerative conditions (2). OH negatively affects quality of life, shortens life expectancy, leads to falls, and increases the risk for various cardiovascular and cerebrovascular conditions (1). Before discussing OH, it is important to understand the mechanisms involved in the normal response to upright posture.

3.2 Normal Response to Upright Posture

Standing is a common stressor to the homeostatic mechanisms regulating BP and CBF with the average person standing from a sitting or lying position up to seventy times per day (304). Orthostasis – from the Greek *orthos* (meaning upright) and *histanai* (meaning to stand) – is the normal physiological response to standing, a unique compensatory mechanism that distinguishes humans from other species (305). Humans are the only animals capable of maintaining erect posture for prolonged periods of time (306).

The circulating blood volume of an average adult human weighing 70kg is approximately five litres with about one quarter contained in the thorax. When an individual transitions from supine to an upright position, pooling of 500-1000ml of blood from the thorax into the lower extremities and splanchnic vasculature occurs. With standing, the muscles of the lower limbs are activated and subsequently vasodilate leading to an approximate 40%

reduction in TPR (307). Standing can result in a rapid 25% reduction in blood volume, with 50% of this decrease occurring within seconds. In addition to lower limb muscle activation, increases in intra-abdominal pressure contribute further to the BP drop on standing. With the legs and abdomen initially contracting during the standing transition, intraabdominal pressure rises, inducing a transient increase in venous return and increased pressure on the right atrium of the heart. This right atrial pressure increase leads to activation of the cardiopulmonary mechanoreceptors. This results in withdrawal of sympathetic vasoconstrictor tone, and lower vascular resistance for about 6-8 seconds (307).

Due to hydrostatic pressure effects, a further 10% of intravascular plasma shifts towards the interstitium within about 10-30 minutes of standing. Peripheral pooling of blood below the level of the heart and the movement of plasma into interstitial fluid contribute to reduced venous return and right ventricle filling pressure leading to a decrease in stroke volume (SV), cardiac output (CO), and subsequently, BP. BP reaches its lowest point approximately 7-9 seconds post transition (307). Indeed, it is estimated that CO drops by about a fifth which in the absence of compensatory mechanisms would compromise perfusion of vital organs above the heart (306).

To counteract the initial haemodynamic responses, compensatory mechanisms consisting of contributions from the baroreflex, the so-called “muscle pump”, and the renin-angiotensin system respond. The most important physiological system involved in homeostasis upon standing is the very short acting ANS feedback loops of the cardiac and arterial baroreflex. (See section 2.2.4 *The Baroreflex*). Cardiac mechanoreceptors, specifically vagal c-fibres, are present in cardiopulmonary vessels, while baroreceptors are situated in the carotid sinus and aortic arch. The cardiac mechanoreceptors and arterial

baroreceptors in response to a change in stretch reduce afferent impulses – via the glossopharyngeal and vagus nerves for the carotid and aortic baroreceptors respectively – to the nucleus tractus solitarius in the dorsal medial medulla. This diminished activity of baroreceptor afferents prompts an elevation in sympathetic activity directed towards the heart and blood vessels, accompanied by a reduction in parasympathetic (vagal) activity targeting the heart. The NTS mediates the increase in sympathetic efferent activity by relaying signals to the caudal ventrolateral medulla (CVLM), which then projects to the rostral ventrolateral medulla (RVLM). Sympathetic neurons originating from the RVLM extend projections to pre-ganglionic neurons located in the intermediolateral cell column of the spinal cord, which, in turn, synapse with post-ganglionic neurons within the sympathetic chain. These post-ganglionic sympathetic fibres form a network situated in the adventitial layer of blood vessels, releasing norepinephrine as their primary neurotransmitter leading to vasoconstriction and increased TPR. Furthermore, projections from the RVLM to the heart augment HR and myocardial contractility. Diminished vagal input to the sinoatrial node, facilitated by the neuroanatomical

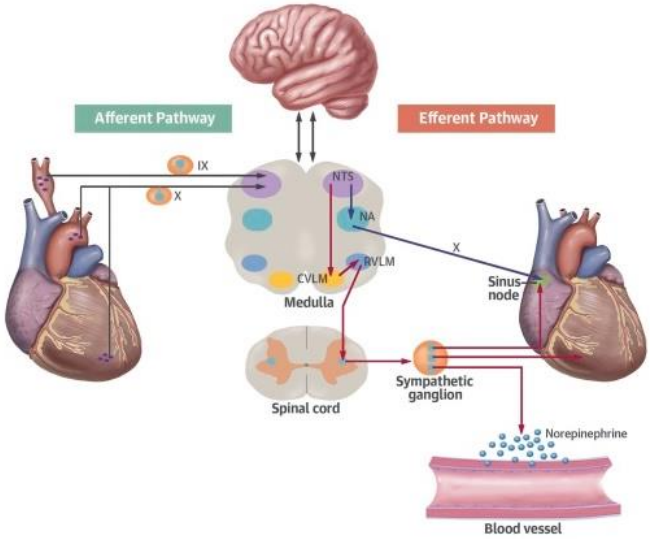

Figure 3.1 Neurophysiology of Normal Standing Adapted from (2).

connections between the NTS and pre-ganglionic parasympathetic neurons in the nucleus ambiguus, results in an increased HR. (See Figure 3.1). These adjustments collectively restore BP to baseline levels (2) typically within 30 seconds from the onset of the transition (307). (See Figure 3.2).

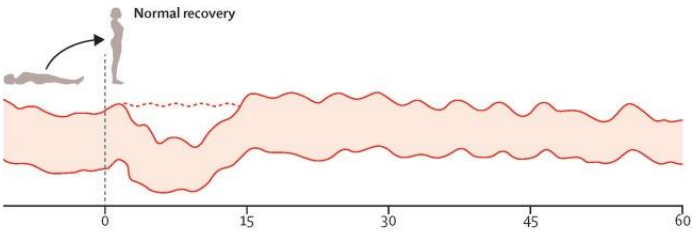

Figure 3.2 BP response to normal standing. Adapted from (1)

It is important to note that the shift in blood volume towards the lower extremities is counteracted by muscular contractions of the lower limbs, gluteal muscles and abdomen, increasing venous return by compressing capacitance vessels, reducing venous pooling and increasing TPR (306, 307) – the muscle pump response.

The other main system involved in the regulation of orthostasis is the renin-angiotensin-aldosterone system (RAAS) which typically acts over minutes to hours (306). The RAAS is activated in response to a transient drop in afferent arteriole perfusion pressure at the juxtaglomerular apparatus of the nephron caused by standing. Angiotensin II is a potent vasoconstrictor, and along with other peptides and active neuroamines such as aldosterone and vasopressin, is also involved in sodium and water reabsorption which acts to increase BP.

Typically, in healthy individuals upon standing, beat-to-beat BP measurements show a mild transient decrease in SBP and DBP and a compensatory increase in HR of about fifteen percent during the first 10 seconds, followed by a return to baseline values or

slightly higher SBP and DBP (306, 308). Figure 3.3 presents a visual synopsis of normal orthostatic responses.

OH occurs when these compensatory responses are insufficient or become overwhelmed, often due to failure of the arterial baroreflex. Impairment may occur at the sensing stretch receptors, in the afferent nerves to the brainstem, in the brain and central autonomic network, the efferent pre- and post-ganglionic neurons to effector organs, the ganglia themselves, or neurotransmitter production and transmission (309).

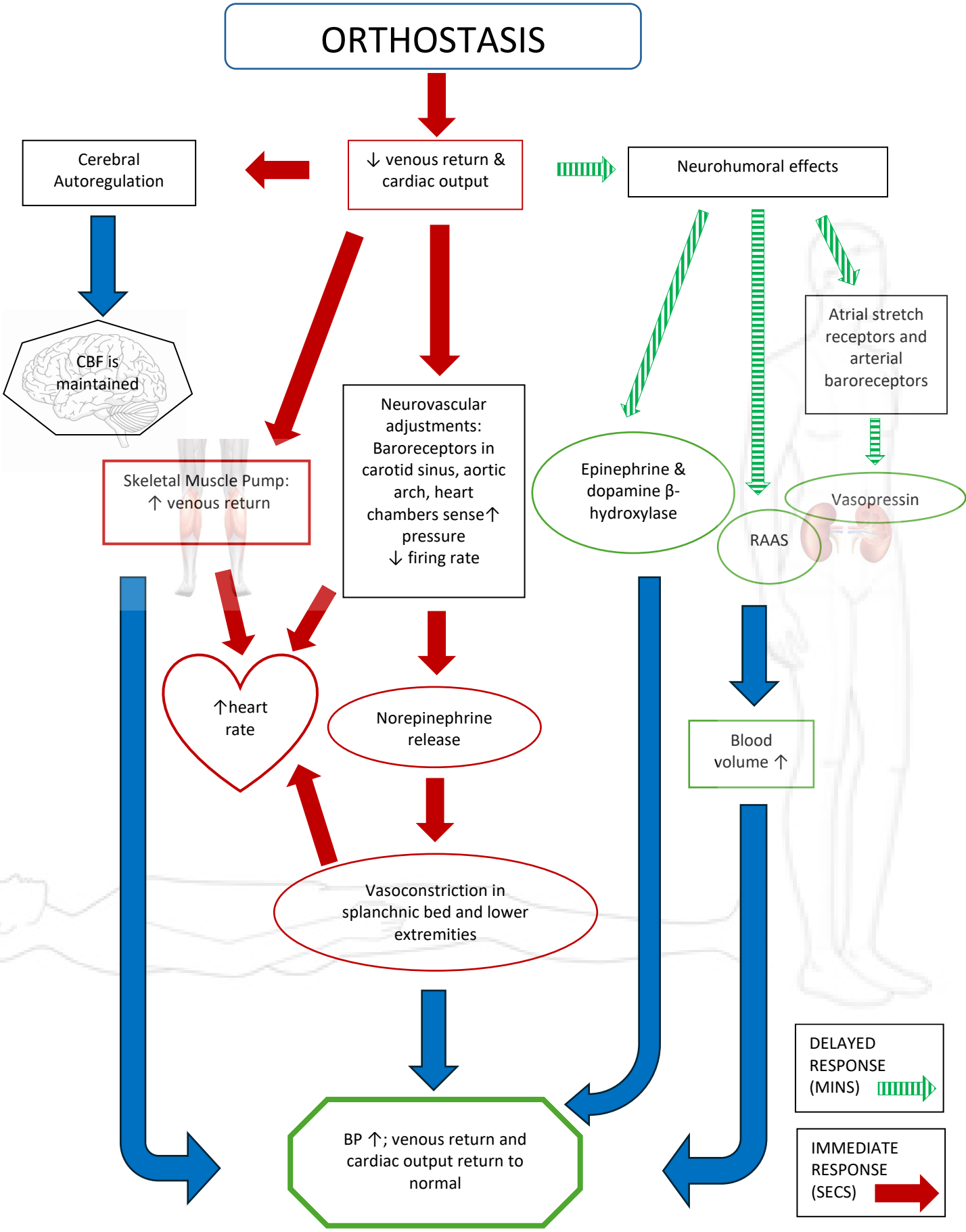

Figure 3.3 Schematic representation of the normal physiological response to orthostasis

3.3 Definitions of Orthostatic Hypotension

OH is defined by consensus statement as a sustained drop in SBP of at least 20mmHg or in DBP of at least 10mmHg, within 3 minutes of standing (310). There are a number of subtypes that have been defined based on the magnitude and timing of the BP response to orthostasis (98, 310, 311). Each can be symptomatic or asymptomatic.

3.3.1 Classical Orthostatic Hypotension

Classical OH has been defined as a sustained decrease of ≥20mmHg in SBP or ≥10mmHg in DBP between 60-180 seconds of standing. It also includes those with a sustained drop in SBP below 90mmHg. The prevalence of classical OH in the overall TILDA population is 6.9% (CI 5.9-7.8%) and increases with age to approximately 18-19 percent in those aged over 80 (311). In those with baseline hypertension, the drop may be ≥30mmHg in SBP or ≥15mmHg in DBP.

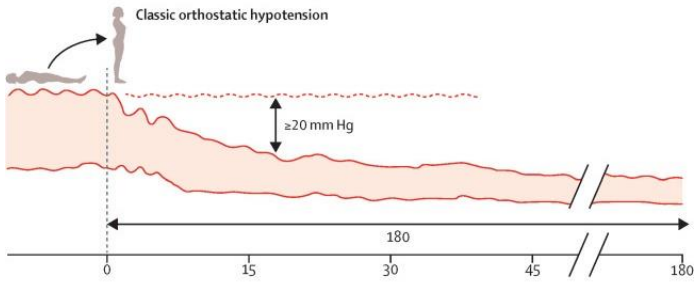

Figure 3.4 SBP pattern in Classical OH. Adapted from (1)

3.3.2 Initial Orthostatic Hypotension

Initial OH (iOH) has been defined as a transient decrease in SBP of >40 mmHg in SBP and/ or >20 mmHg in DBP within 15 seconds of standing – with complete recovery within 30 seconds usually accompanied by orthostatic symptoms. Initial OH can only be reliably detected by continuous beat-to-beat BP measurements (312, 313). The prevalence of iOH in the overall TILDA population is 32.9% with no age gradient evident (311).

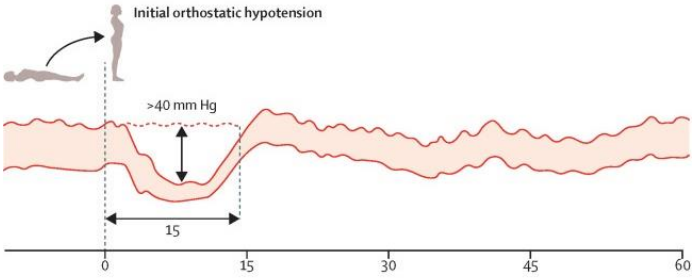

Figure 3.5 SBP response in iOH. Adapted from (1)

3.3.3 Delayed Recovery Orthostatic Hypotension

Delayed recovery OH is defined as the inability of SBP to recover to ≤20mmHg of supine baseline values at 30-40s after standing in the absence of sustained OH. SBP must recover within 3 minutes. The total prevalence of delayed recovery OH/ impaired BP stabilisation at 40 seconds in the TILDA population was 15.6% (CI 14.1-17.1%) and rose to 39-44% in those over 80 (311).

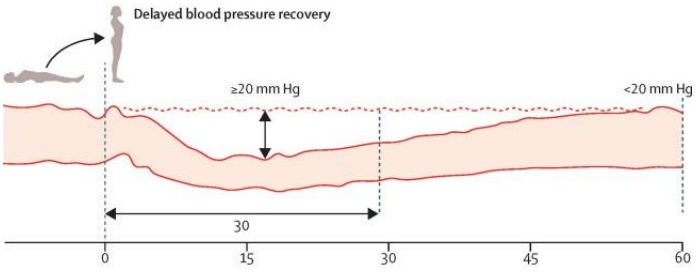

Figure 3.6 SBP response in Delayed Recovery OH. Adapted from (1)

3.3.4 Delayed Orthostatic Hypotension

Delayed OH occurs when the drop in BP occurs beyond 3 minutes. In clinical practice, this is detected during HUT rather than by AS. When compared with those who have classical OH pattern, patients with delayed OH have less severe impairments in other measures of sympathetic adrenergic function. Therefore, delayed OH is regarded as a milder or earlier manifestation of the disease that over time progresses to classical OH (2, 313).

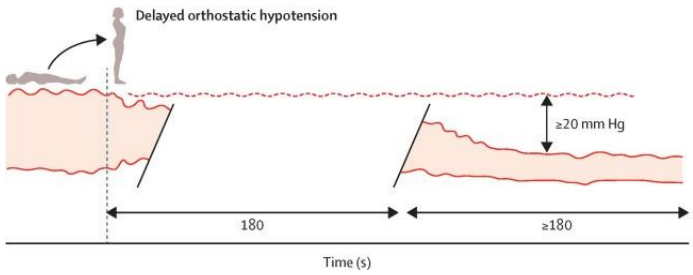

Figure 3. 7 SBP response in Delayed OH. Adapted from (1)

3.3.5 Orthostatic Hypertension

Orthostatic hypertension is the converse of classical OH and is defined as a sustained increase of ≥20mmHg in SBP or ≥10mmHg in DBP from 60-180 seconds post standing. It includes those where BP >140/90 standing where the patient is normotensive when supine.

3.3.6 Supine Hypertension

In patients with proven OH, supine hypertension (SH) is defined as SBP of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg, measured after at least 5 min of rest in the supine position. BP is normotensive or hypotensive upon standing (314).

3.4 Diagnosis and Measurement of Orthostatic Hypotension

There is no accepted time duration that constitutes a *sustained* drop in BP nor is there a gold standard method to detect it (313). Though in classical OH, the term *sustained* is regarded as not recovering at all within 3 minutes (311). Data from BP profiles in community dwellers within TILDA show that 95% of BP drops in older adults have stabilised within 30 seconds of standing (311) and those that failed to stabilise BP by 40 seconds post standing were associated with increased risk for future falls – both unexplained and injurious (315).

Orthostatic BP and HR measurements can either take place by standing at the bedside during the so called "active stand" or on HUT (7, 306, 316). The AS test involves measuring BP and HR while supine, on standing and then for a further three minutes after standing. While both manoeuvres challenge the cardiovascular system, the BP response to HUT differs from an AS. Finucane et al. (312) suggest that relative to a passive HUT, an AS by its nature exaggerates the transient reduction in BP, better mimicking real world activities of daily living. In addition, HUT is felt to be an inappropriate test for iOH as the sudden drop in BP may be missed as the bed is tilted upright whereas HUT is used throughout the literature to diagnose classical OH (316). Guidance suggests a period of 5-10 minutes supine rest prior to orthostatic BP measurement to allow sufficient time for BP stabilisation and the identification of supine hypertension (1, 312, 317, 318). Longer periods of supine rest are associated with larger initial BP drops upon standing (312, 319).

Lying-to-standing measurements are more likely to detect OH than sitting-to-standing measurements (1). Indeed sit-stand assessments were demonstrated to have very low

diagnostic accuracy for OH compared to those diagnosed using continuous beat-to-beat monitoring during 3 minute HUT (320).

Orthostatic BP assessments can be conducted using traditional sphygmomanometry, intermittent oscillometric or continuous beat-to-beat BP measuring methods. Wieling et al. (1) suggest oscillometric measurements of BP at 30 seconds, 1 minute, 2 minutes and 3 minutes after standing. Conventional BP measurement methods will detect classical OH but will not capture drops associated with iOH or delayed recovery OH. Continuous beat-to-beat BP measurement protocols, on the other hand, will detect iOH, delayed recovery OH and classical OH but must be extended – in practice often using HUT – to allow for sufficient time to detect delayed OH.

Furthermore, attention should be placed on patient preparation and the testing environment to minimise stimuli affecting the function of the ANS. Ideally, assessments should be undertaken in a quiet, dimly lit room, at a temperature 21-23^{o}C. To achieve more accurate results, patients should if possible be fasting and avoid caffeine, exercise, smoking and alcohol and have an empty bladder (312, 319). OH is highly variable over the course of the day. Since sensitivity of the active stand to detect OH is increased, Finucane et al. (312) suggest morning time testing is preferable.

Given the degree of older patients with impaired balance and musculoskeletal problems, it is important to consider the influence of standing time on orthostatic BP assessments. Recently, O'Connor et al. (321) have shown that the speed of transitioning from supine to standing is associated with the magnitude of cardiovascular and cerebrovascular response to orthostasis. Slower standers had a less pronounced decline in BP and cerebral

oxygenation while faster standing was associated with significantly higher HR on standing and a quicker recovery in HR after standing.

While 24 hour ambulatory BP measurement has no diagnostic role in OH, monitoring can be valuable in detecting the frequency of low BP episodes occurring over the course of the day (1). Readings while in bed can be used to detect supine hypertension or reverse nocturnal dipping patterns – both associated with increased cardiovascular risk – while readings after mealtimes can help diagnose post prandial hypotension (1, 313).

3.5 Prevalence of Orthostatic Hypotension

OH is common and its prevalence rises with age. This increase is attributed in part to the normal physiological decline in baroreceptor sensitivity seen in advancing age, and partly to the increased prevalence of autonomic neurodegenerative disease (2) as well as other diseases known to affect the ANS. Prevalence rates vary depending on the cohort, setting, method of measurement and definition of OH used. One study even reported a seasonal variation in the prevalence of OH with more hospital presentations due to OH among older people (n=502, mean age 81.6) during summer months, probably reflecting higher rates of dehydration secondary to increased temperatures (322).

A recent systematic review (323) found that OH affects about one in five community dwelling older adults over 60 and one in four of those in residential long term care. In midlife, OH affected five percent of individuals (n=12,661) aged 45-64 in the large US based prospective Atherosclerosis Risk in Communities study (324).

In chronic disease cohorts, OH affects up to one fifth of community dwelling individuals with diabetes (325). In synucleinopathies such as idiopathic Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple systems atrophy (MSA), OH is found in up to 50% of PD and DLB patients while approximately 80% of patients with MSA present with OH (1). OH prevalence increases with disease duration among this cohort.

3.6 Pathophysiology of Orthostatic Hypotension

OH results when baroreflex-mediated ANS and RAAS responses are inadequate to regulate BP upon assuming the upright position. These impaired responses occur either because baroreflex function itself is impaired or because blood volume is insufficient to support ventricular filling (326). Baroreflex dysfunction may arise from impairments at any site along the reflex arc, including the carotid sinus baroreceptors, afferent and central neural connections or efferent sympathetic nerve fibres, either due to primary or secondary autonomic system disorders (83, 327). (See Table 3.1).

3.7 Causes of Orthostatic Hypotension

Many causes of OH have been identified and these are divided into non-neurogenic and neurogenic causes (306, 328). (See Table 3.1).

Neurogenic OH arises from *structural* lesions of autonomic pathways, due to disorders affecting central or peripheral autonomic structures such as PD, multiple system atrophy (MSA), diabetes mellitus or advanced renal failure.

Non-neurogenic OH on the other hand is associated with disruption to the *function* of the ANS and is much more common in older people than neurogenic OH (317). Medications are often implicated in non-neurogenic OH particularly in older patients. Over 250 medications have been proposed to cause OH (313, 329). Age related alterations in pharmacokinetics are common, impacting the bioavailability and distribution of medications. Moreover, older individuals have increased vulnerability to OH due to the frequent coexistence of multiple predisposing factors including comorbidities, polypharmacy and frailty. Therefore, medication related OH may exacerbate other neurogenic and non-neurogenic causes, worsening symptoms and increasing complications (330, 331).

Table 3.1 Causes of Orthostatic Hypotension. ARB= angiotensin II receptor blockers; SSRI= selective serotonin reuptake inhibitors; SNRI= serotonin norepinephrine reuptake inhibitors Summarised from (2, 306, 326, 332)

Non-Neurogenic OH	**Neurogenic OH**
Medications	**Primary Neurogenic causes**
Cardiovascular drugs	Parkinson's disease
Nitrates	Dementia with Lewy bodies
α- blockers	Progressive supranuclear palsy
Diuretics	Multi systems atrophy
Calcium channel blockers	Pure autonomic failure
β-blockers	Familial dysautonomia
Clonidine	Dopamine β-hydroxylase deficiency
ACE-inhibitors/ ARBs	Autoimmune ganglionopathy
Psychoactive drugs	
Levodopa	**Secondary neurogenic causes**
Dopamine agonists	Neuropathies
Anti-psychotics	Diabetes mellitus
Tricyclic antidepressants	Alcoholic polyneuropathy
Benzodiazepines	Amyloidosis
Trazodone	Guillain-Barré Syndrome
Opioids	HIV/ AIDS
SSRI, SNRI	Paraneoplastic
Monoamine oxidase inhibitors	Renal failure/ post dialysis
Anti-cholinergics	Vitamin B12 deficiency
Phenothiazines	Folate deficiency
Phosphodiesterase 1 inhibitors	CNS disorders
Chemotherapeutic agents	Spinal cord injury
Secondary non-neurogenic causes	Syringomyelia
Hypovolaemia	Transverse myelitis
Dehydration	Spinal tumours
Haemorrhage & Anaemia	Tabes dorsalis
Adrenal insufficiency	Brain stem lesions
Diabetes insipidus	Stroke
Diarrhoea/ Vomiting	Multiple sclerosis
Salt-losing nephropathy	
Pregnancy	
Cardiac failure (reduced cardiac output)	
Venous pooling	
Prolonged lying/standing	
Post prandial hypotension	
Fever	
Heat exposure & Burns	
Severe varicosities	

3.8 Role of Symptoms in Orthostatic Hypotension

Orthostatic intolerance symptoms are thought to result from transient cerebral hypoperfusion in the presence of low BP upon standing (301, 333). In OH, symptoms characteristically manifest when SBP falls below 75-80mmHg (42, 334). Indeed, orthostatic symptoms correlate with the BP nadir upon standing rather than the degree of BP drop (334, 335). However, another study of 89 participants with OH (mean age 69.4±11.9 years) conducted by Freeman et al. (336) found that despite low SBP on orthostasis and large drops in SBP during HUT, the majority of patients were either asymptomatic or only mildly symptomatic. If symptoms were present, light-headedness was the most prevalent and severe symptom reported.

Typical symptoms of orthostatic intolerance usually include postural dizziness and light-headedness, visual disturbance, presyncope and syncope and can be relieved (if acted upon in time) by assumption of the supine position (337). Approximately 90% of symptomatic OH patients will complain of postural dizziness or light-headedness (338). Challenging the dogma that vertigo (a sensation of spinning or motion) was indicative of central or peripheral vestibular disorders, Low et al. reported that 37% of OH patients also presented with orthostatic vertigo. However, another study of fifty consecutive older patients over sixty compared with twenty age and sex matched controls found that a cardiovascular diagnosis to dizziness was predicted by the presence of syncope ($p<0.001$), when dizziness was described as “light-headedness” ($p<0.001$), the need to sit or lie down during symptoms ($p<0.001$), pallor with symptoms ($p<0.001$), symptom precipitation by prolonged standing ($p<0.05$), and whether patients had a coexisting cardiovascular diagnosis ($p<0.001$) (339). Additionally, given the high prevalence of OH and benign

paroxysmal positional vertigo in older patients, it is not uncommon for both conditions to coexist in clinical practice (340, 341).

The clinical presentation of OH can include more atypical symptoms. Indeed, patients are often vague regarding symptoms (1). For instance, they may report fatigue, cognitive dysfunction, leg weakness or leg pain, gait impairment (postural sway), abdominal discomfort or may be completely asymptomatic. Low et al. (338) reported that up to 72% of OH patients report non-specific symptoms such as fatigue, loss of concentration, visual disturbance and nausea during assessment. Pain in the shoulders and neck – so called "coat hanger pain" – and dyspnoea upon standing have also been reported (1). Another symptom unlikely to be reported by patients but often observed by witnesses is that of a slowing of cognition once the patient is upright. Van Dijk refers to this phenomenon as "an inability to act" where patients freeze in their position – not having the higher cortical function to decide to sit/ lie down (287).

These atypical symptoms may not therefore be considered in the absence of the more usual symptoms of dizziness or light-headedness. It is worth noting that because of the non-specific nature of symptoms, this may lead to an artificially high estimate of asymptomatic OH (316). Recognition of symptoms is important as it can allow the clinician to provide advice about how to remedy OH. Interestingly, in their study of people with dementia (n=154), Bengtsson-Lindberg et al. (342) report 74% of patients with AD, 59% of patients with mixed AD-vascular dementia and 51% of patients with DLB were asymptomatic of OH during an AS. In another study of active stands of heart failure patients (n=321), up to 50% of cases with abnormal responses were asymptomatic (343).

Approximately one to two thirds of OH patients report minimal or no symptoms despite the magnitude of their BP drop upon standing (334, 335). Arbogast and colleagues (335) termed this phenomenon “hypotension unawareness” and described it as paralleling the impaired awareness of hypoglycaemia observed in diabetes or the dyspnoea unawareness in those with chronic respiratory disease. Hypotensive unawareness is particularly common in patients with neurogenic OH and may partly explain the increased risk of falls seen in these patients (344). It may also account for the overlap between falls and syncope frequently encountered in clinical practice. (See Section 2.3 *Overlap Falls and Syncope*). If hypotensive unaware, patients might not take evasive action before a fall and might not recall the TLOC that pre-empted the fall. Several potential mechanisms have been put forward to account for this phenomenon (335-337, 344). Habituation and chronic exposure to low BP may impair sensory signal processing and integration within neural networks resulting in an inability to perceive symptoms. Global cerebral hypoperfusion may impair afferent neuronal signals and disrupt the ability to generate language to express symptoms. There may also be interindividual variations in autoregulatory mechanisms. A further hypothesis is that cerebral hypoperfusion occurs to the extent where ischaemic changes to the reticular activating system results in patients becoming inattentive to orthostatic intolerance symptoms. Tipton and Cheshire (344) attempted to compare symptom recognition in neurogenic OH patients with central neuropathology (as seen in MSA) versus those with peripheral neuropathology (as seen in peripheral autonomic neuropathy) to evaluate whether perception of symptoms was related to location of pathology. The authors found no statistically significant difference in the rates of symptom recognition (which were infrequent in both groups). The presence of symptoms correlated with lowest SBP detected during HUT ($p=0.016$) and suggested

that symptom unawareness was most likely explained by cerebral ischaemia induced by transient cerebral hypoperfusion rather than by degradation of afferent neuronal networks. Despite this, there is limited understanding regarding the anatomical basis for the conscious recognition of OH, and no information exists regarding the potential mechanisms underpinning the role of habituation.

The relevance of asymptomatic OH has not been fully elucidated, with little guidance regarding its natural history, clinical outcomes, or benefit of treatment (316). Despite this, current guidelines emphasise that diagnosis of OH can be established in the absence of symptoms and there is increasing evidence that asymptomatic patients remain at risk for many of the same negative health outcomes as those who are symptomatic (337).

3.9 Clinical Importance of Orthostatic Hypotension

OH is neither incidental nor benign and is associated with several negative health outcomes including cardiovascular disease (345). In addition to potential culprit medications, OH has also been associated with falls (346), fractures (347), cognitive impairment (348), impaired gait (349), depression (350), frailty (351) and death (352, 353).

3.9.1 Orthostasis in Health and Ageing

Several physiological changes that may affect the appropriate response to orthostasis are associated with ageing. Older people demonstrate impaired sensitivity of α-1 adrenergic receptors, attenuated HR responses, reduced baroreflex sensitivity and overall decline in ANS function (83, 98, 354). Additionally, age-related factors such as myocardial stiffness

and diastolic heart dysfunction precipitate SV reduction as a result of reduced preload upon standing. Arterial stiffness further impedes an adequate vasoconstrictive response (355). Dehydration is also common among older individuals due to decreased thirst responses and diminished kidney function, leading to reduced intravascular volume (356).

The TILDA group have provided age-related normative data for haemodynamic changes seen in orthostatic BP in a nationally representative population (311). Several age and sex differences were identified. In men, supine SBP increased whereas DBP decreased with age and there were no age related changes after standing. In women, supine SBP and minimum SBP after standing increased with age whereas DBP did not. Supine HR did not differ in men or women with age whereas peak HR after standing was attenuated with age.

These physiological alterations collectively result in reduced intravascular volume, reduced SV, and attenuated chronotropic and vasoconstrictive responses upon standing, thereby precipitating OH. Furthermore, older people have a higher prevalence of conditions that can cause OH, such as medication use and deconditioning, as well as diseases considered risk factors for OH (354). Consequently, OH in older adults can occur with or without ANS dysfunction and is often the culmination of multiple mechanisms and factors encompassing all subtypes of OH.

Many studies have been carried out evaluating the effects of age on the cerebral haemodynamic response to orthostasis in healthy individuals (99, 122). Mehagnoul-Schipper et al. (122) analysed NIRS derived measures of cerebral oxygenation during orthostasis between a young (n=10, range 22-45 years) and older (n=18, range 70-83 years) group of healthy volunteers free from cardiovascular and neurological disorders

and not medicated. They found that frontal lobe O_2Hb declined in older subjects after standing in the absence of decreases in orthostatic BP while no such changes were found in the younger subjects. The O_2Hb changes were small and not associated with symptoms of orthostatic intolerance. Conversely, in a similar study comparing young and old groups, Kim et al. (99) identified a less pronounced effect in cerebral oxygenation during orthostasis but the methodology involved a sit-to-stand rather than supine-to-stand test. A NIRS sensitivity study identified significant differences in cerebral oxygenation between standing up from supine versus standing up from sitting independent of BP drop (216).

Using data from the SYSTEMA cohort from Malmo, Sweden, Kharraziha et al. (357) found that cerebral oxygenation prior to syncope in older individuals with VVS and OH is lower compared to younger individuals independent of SBP. The authors also reported that advancing age was associated with lower minimum cerebral oxygenation levels in those with OH suggesting an age-related gradient of impairment in CA mechanisms that fails to compensate completely for postural changes in older VVS and OH patients. However this study did not control for multimorbidity or medication use.

3.9.2 Cardiovascular Disease, Mortality and OH

Several studies including the large Malmo Preventive Project (345) have suggested that OH is an independent predictor of cardiovascular risk and all-cause mortality (352, 353). A systematic review and meta-analysis conducted by Angelousi et al. (353) identified an association between OH and coronary disease, heart failure, and arrhythmias. The meta-analysis of seven studies showed that OH was associated with a 36% increased risk of overall mortality (pooled hazard ratio 1.36, [CI 1.13-1.63], $p<0.001$). The risk of

subsequent myocardial infarction is higher in OH associated with drops in DBP as opposed to drops in SBP (345). OH is associated with an increased rate of atrial fibrillation development (358). Another recent systematic review (359) synthesised the evidence underpinning an association of OH with increased arterial stiffness and reported a 40% increased risk of OH in those with evidence of arterial stiffness identified by pulse wave velocity measurement (OR 1.40, CI: 1.28-1.54). While it is known that independent of the presence of hypertension, arterial stiffness is associated with reduced baroreflex sensitivity (360), it is also postulated that transient hypoperfusion of the heart during OH contributes to cumulative microvascular ischaemia over time (361).

3.9.3 Hypertension and OH

OH affects about ten percent of those with hypertension (362). Conversely, hypertension is present in about 70% of patients with severe OH (363). OH and hypertension are both risk factors for important health outcomes such as cardiovascular disease, stroke, dementia, falls and syncope as well as mortality. The relationship between hypertension, OH and antihypertensive treatment is nuanced and complex.

3.9.3.1 Supine Hypertension – Orthostatic Hypotension

Supine hypertension is commonly seen in patients with ANS dysfunction and correlates with severity of OH. Donoghue et al. (364) found that OH and co-existent hypertension whether measured seated or supine was associated with recurrent, injurious and unexplained falls among TILDA participants. The management of supine hypertension and

OH presents a dilemma with the aim being to treat one without having a significant effect on the other.

3.9.3.2 Antihypertensive Treatment and OH

In recent years, several large studies have prompted a reconsideration of the presence of OH as a limiting factor for hypertension treatment, thus challenging the more traditional view that aggressive antihypertensive treatment worsened OH and its sequelae. For instance, in a study of 702 community dwelling older adults over 70, Gangavati et al (365). found that OH was more common in individuals with uncontrolled hypertension compared to those with controlled hypertension (19% versus 5%, $p<0.001$). Similarly, in another study with 4266 patients from the ACCORD trial (366), the presence of OH was not affected by whether participants were assigned to the intensive (SBP<120mmHg) or standard (SBP<140mmHg) BP group. In a subsequent study (367), OH rates were not different during follow up at baseline, one or four years post enrolment.

The SPRINT study (243) randomised 9361 participants with hypertension (28% ≥ 75 years) to either an intensive BP target of <120mmHg or standard target of <140mmHg. Over 12 months, the prevalence of OH in the intensive group was 16.6%, significantly lower than in the standard group (18.3%, $p=0.01$). However in those aged ≥75 years, there was no difference in the prevalence of OH in both groups (21% versus 21.8%, $p=0.53$). This finding while appearing beneficial continues to spark debate. Some have argued against aggressive antihypertensive treatment in older patients, highlighting inconsistencies between outcomes of clinical trials and the real world. For example, in the SPRINT cohort discussed above, eligibility criteria excluded those with diabetes, prior stroke, dementia,

symptomatic severe heart failure, those living in residential care and those who were hypotensive at baseline (<110mmHg on standing) – potentially excluding those with more severe OH from representation in the study. The study assessed for OH using oscillometric measurements post sit-stand manoeuvre. Intensive BP lowering was associated with an increased risk of hypotension and syncope but not injurious falls (368).

Observational studies consistently show that overly strict hypertension treatment may lead to OH and OH related falls (30, 369). Indeed, when the SPRINT inclusion criteria were applied to the TILDA cohort over a similar duration of follow up, the rates of injurious falls and syncope were five-fold higher than those reported in the standard treatment group of SPRINT let alone the intensively treated group suggesting limited applicability to older people in the real world (370). However, an analysis of those participants who developed OH post randomisation in SPRINT conducted by Juraschek et al. (361) found that OH was associated with hypotension related hospitalisations and ED visits, but not with a higher risk of cardiovascular events, syncope, falls, or acute renal failure – though again the same caveats apply. It is worth noting that an individual participant level meta-analysis pooling the results of 5 RCTs found that among 18,466 adults (mean age 64.5±9.9 years) more aggressive BP lowering strategies in fact lowered OH risk (OR 0.93 [CI 0.86-0.99]).

Given that OH in these large hypertension trials can only be regarded as mild – the mean SBP drop in patients with OH in SPRINT and ACCORD was only 19mmHg – one must be cognisant that recommendations derived from these trials may not apply to patients with more severe forms of OH (363). There is considerable heterogeneity in older people and undoubtedly an individualised and personalised approach to treatment of severe OH – especially neurogenic OH – is indicated.

Other considerations for hypertension trials in older people

The cardiovascular benefits of intensive BP control may come at the expense of clinically important drawbacks, particularly in older patients who typically present with higher risks of hypotension-related complications. It is worth noting that the evidence supporting an aggressive BP control strategy has largely stemmed from clinical trials involving relatively healthy individuals with only mild frailty. Frequently, studies exclude individuals who are frailer or those with OH and this limits the generalisability of findings from these trials to real-world geriatric populations though this is the focus of considerable debate (372).

Another important consideration is life expectancy and time to derive clinical benefit from an intensive BP lowering approach. Harms of treatment can occur immediately, but benefits take time to emerge. Chen and colleagues (373) carried out a secondary analysis of six large clinical trials (n=27414, mean age 70, 56.3% female) advocating an intensive BP lowering approach and calculated that on average, 34.4 (95% CI 22.7-59.8) months were needed to prevent one major adverse cardiovascular event per 100 patients. This has important clinical implications especially in those with limited life expectancy.

3.9.4 Stroke, Cerebrovascular Disease and OH

OH is associated with TIA (OR 1.68, [CI 1.12-2.51]) and the presence of carotid artery stenosis (OR 1.67, [CI 1.23-2.26]) (374). The "orthostatic TIA" is a recognised but uncommon phenomenon in patients with unilateral severe carotid stenosis. When coexistent with OH, the patient experiences myoclonic limb jerking activity upon orthostasis (262). Removal of offending medications or correction of the stenosis relieves the symptoms (375).

Eigenbrodt et al. (263) investigated 11,704 middle-aged patients free from stroke and clinically overt cardiovascular disease and found that during 7.9 years follow up, OH conferred a relative risk for incident stroke of 2.0 (CI 1.2-3.2). Symptoms of OH have also been shown to be an independent predictor of ischaemic stroke (263).

OH may also be associated with the development of WMH. A cross-sectional MRI TILDA sub study which controlled for important covariates, assessed the association between burden of WMH on MRI and OH on active stand, and reported a significant positive correlation with OH at the 30, 70, 90 and 110 second timepoints post stand (376). A further prospective longitudinal study, however, found that while OH was cross-sectionally associated with higher WMH volumes and higher prevalence of cerebral microbleeds, there was no significant association between OH and progression of WMH over 9 years follow up (377). The study contained relatively small numbers of individuals with OH and there was a high rate of attrition between follow up assessments.

3.9.5 Late Life Depression and OH

In recent years, given the role played by increased WMH and ANS dysfunction in both conditions, there has been increased attention to the relationship between depression and OH. Briggs et al. (378), in a systematic review reported a positive, albeit cross-sectional, association between OH and depression of later life. A subsequent well-controlled longitudinal study within TILDA found that symptomatic OH at 30 seconds (but not asymptomatic OH or iOH) predicted incident depression with an OR of 1.90 (CI, 1.15-3.15) (350).

It is noteworthy that medications used to treat late life depression have also been implicated in OH. The class of antidepressant medications, selective serotonin reuptake inhibitors, were associated with a two-fold increased risk (OR 2.11 [CI, 1.25-3.57]) of OH at 30 seconds post standing when compared to older people not taking these medications (379). Interestingly, no association was established for tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors, but the study contained small numbers of participants taking these medications and so was not powered to detect an association.

Regarding CBF in late life depression, a further population study by Briggs et al. (380) showed that TSI decreases on standing were greater among older adults with depression versus those without, independent of OH status or antidepressant use. Statistical significance was lost however when SBP was added to the model suggesting that overall hypotension may have accounted for this finding.

3.9.6 Cognitive Impairment, Dementia and OH

The relationship between BP and cognitive function is challenging to untangle, as cognitive decline and dementia are associated with both hyper- and hypotension. Waldstein et al. (381) have suggested a nonlinear, U-shaped correlation between BP and cognitive function, indicating that individuals with both high and low BP show poorer performance on cognitive assessments compared to those with BP levels in the middle range.

Despite the transience of cerebral and peripheral haemodynamic changes in OH, measurable deficits in cognition have been identified (348, 382-384). For instance, Frewen et al (382) found that both classic OH and OH with delayed recovery (when accompanied

with supine hypertension) in older adults was associated with lower cognitive performance on accumulated MMSE and MOCA tests compared to those without OH. A longitudinal study carried out in TILDA found that those with OH at 40 seconds as well as those with OH at 110 seconds post AS were associated with a decline in global cognitive performance assessed using MOCA at four years follow up (348). This association was present after controlling for appropriate confounders but appeared dependent on the presence of coexistent hypertension and was strongest in those who were middle aged. The prevalence of OH in dementia is consistently high and OH has been associated with an increased risk of progression from prodromal mild cognitive impairment to dementia (385).

However, many studies assessing the association of OH and impaired cognition have shown mixed results, and this may be due to the sensitivity of the cognitive assessments used in these studies and the short duration of follow up.

3.9.7 Syncope and OH

OH is believed to underlie 10–15% of syncope episodes (34). However, in older patients >75, OH has been implicated in the diagnosis of up to 30% of cases of syncope presenting to acute and outpatient geriatric units (386). As noted earlier, there is thought to be considerable overlap between falls and syncope. See Sections *2.2 Syncope* and *2.3 Overlap between Falls and Syncope* for further discussion.

3.9.8 Medications, Polypharmacy and OH

Pharmacological treatment is one of the main culprits for orthostatic BP dysfunction often resulting in iatrogenic, medication-induced OH (332). In older patients, drug induced OH represents the most common form of non-neurogenic OH. Medications may exacerbate other causes of OH thereby worsening symptoms and increasing the risk of complications (332).

Iatrogenic OH is more common in individuals taking more than one potentially culprit medication. In a retrospective chart review, Poon and Braun (303) found a significant correlation between the prevalence of OH and the number of concurrent potentially culprit medications – from 36% in those receiving no culprit drugs to 67% in those on three or more medications. Results from a cross-sectional analysis within the British Women's Heart and Health Study (387) report that the prevalence of OH was strongly associated with the number of antihypertensive (but not total number of) medications. The authors reported a greater than two-fold increased risk of OH (OR 2.24 [CI 1.47-3.4]; $p<0.001$) in those on three or more antihypertensive medications when compared to those not taking any medications.

OH is the most commonly reported cardiovascular adverse effect of psychoactive medications (332). Tricyclic antidepressants and second-generation antipsychotics (388) as well as trazodone (303) induce OH due to interactions with α-adrenergic receptor activity while the underlying mechanism underpinning the association between benzodiazepines and OH is unclear (331). Additionally, anti-Parkinson's treatments are known to induce OH independently of autonomic dysfunction through vasodilation and

reduced SNS outflow (332), thus increasing the complexity of balancing the therapeutic benefits afforded by these drugs with likelihood of falls in an already at risk PD population.

As alluded to above (*See Section 3.9.3.2 Antihypertensive Treatment and OH*), there are inconsistent studies on the association of antihypertensive medications and OH with some reporting a protective effect (371). However details on the classes of BP lowering medications used in these hypertension studies are often not examined.

Among antihypertensive medications, diuretics, nitrates and α-blockers show a stronger association with OH while beta-blockers may impair orthostatic BP response due to their negative inotropic or chronotropic effects (330). Canney et al. (389) found that there was a two-fold increased risk of iOH and a three-fold increased risk of sustained OH and OH with delayed recovery in hypertensive older adults taking beta-blocker monotherapy compared to untreated hypertensive individuals after multivariable adjustment. The authors did not report an association among RAAS inhibitors, calcium channel blockers or diuretics. Indeed, some studies have suggested a protective effect for RAAS inhibitors against OH and reduced CBF (242, 362, 365). (See Section 2.7.2 Hypertension and CBF).

3.9.9 Falls, Fractures, Impaired gait and OH

OH is considered a risk factor for falls potentially due to its interaction with cerebral hypoperfusion precipitating dizziness or its relationship with disorders such as syncope, WMH burden, impaired cognition or cardiovascular disease (390, 391). As mentioned above, medications are also known to increase falls risk and prevalence of OH.

While a clear theoretical relationship between OH and falls in older adults exists, earlier studies have reported inconsistent findings (390) perhaps due to the intermittent nature of OH or the absence of prodromal symptoms before a fall (392). However, with improved methodologies including beat-to-beat BP assessment, the relationship can be better characterised. In the TILDA study population, OH (and OH with delayed recovery) have been found to be independent risk factors for future falls, unexplained falls and injurious falls (315). A systematic review and meta-analysis of the literature supports a consistent positive association between falls and OH no matter the setting, study design, OH definition or BP measurement method used (OR 1.73 [CI 1.50-1.99], $p<0.001$) (346). Similar findings were reported in a more recent systematic review (30) with studies using beat-to-beat BP measurement demonstrating a stronger association than traditional sphygmomanometer based methods in addition to studies using a supine-to-stand rather than sit-to stand manoeuvre for OH assessment.

Sustaining a fracture is a profound independent risk factor for subsequent functional decline, mobility impairment and admission to residential long term care (393-395). Doyle et al. (347) showed that community dwelling adults with delayed recovery OH at 30 seconds conferred a greater than 4-fold likelihood of hip fracture in the subsequent 8 years. The authors also found that delayed recovery OH at 30 and 60 seconds was associated with a 2-fold higher likelihood of incident fracture (wrist, hip or vertebral) after controlling for important clinical and demographic covariates. Another Swedish study (396) analysed the risk of incident fracture following hospitalisation for unexplained syncope or OH and found that over a follow up period of approximately 18 years, 27% of subjects suffered subsequent fracture. The hazard ratio of incident fracture in the OH

group was 1.17 (CI 1.01-1.37; p=0.042). This study highlights the importance of the implementation of fracture prevention strategies when OH is detected.

OH has also been found to associate with impairment in gait. For instance, in TILDA, OH with delayed recovery at 30 seconds was associated with slower gait speed and shorter step length in adjusted models during single task walking in addition to increased double support phase during dual task walking (397). The interplay between the triad of OH, cognitive impairment and impaired mobility with risk of falls has been referred to as the "Bermuda triangle" of geriatric syndromes (398). In fully adjusted models, the combination of all three syndromes was associated with a >4-fold likelihood of unexplained falls (OR 4.36 [2.61–7.28]; p<0.001) and a two-fold higher likelihood of fracture (OR 2.51 [1.27–4.96]; p =0.008) when compared with participants who did not have any of the syndromes of the Bermuda triangle (399).

Some studies have used NIRS to analyse the role of changes in cerebral haemodynamics with postural instability (400, 401) and gait (402) – both important correlates for falls. Fitzgibbon-Collins et al. (401) reported a greater drop in TSI among older adults on standing to be significantly associated with increased postural instability in the first 20-60 seconds after standing. The authors identified two groups based on the degree to which TSI dropped on standing and found that the group with more compromised TSI had an increased risk of falling in the following six months (though this did not achieve statistical significance, p=0.091). O'Connor et al. (402) demonstrated that the rate at which TSI recovers after standing is associated with gait speed. Those with slower walking speeds had lower TSI levels while standing compared to those with faster walking speeds. Interestingly, the association was independent of the effects of OH at 30 seconds

suggesting that the association between gait speed and TSI may be independent of peripheral changes in SBP.

3.9.10 Frailty, Multimorbidity and OH

Frailty, which is distinct from ageing, refers to a state of increased vulnerability to stressors due to decreased physiological reserve and diminished resilience in various organ systems (403). It is a complex syndrome characterised by a decline in physical function, reduced strength and activity as well as increased susceptibility to illness, disability, and adverse health outcomes (404). Frail individuals are at higher risk of falls, hospitalisation, and mortality compared to their non-frail counterparts (405).

In orthostasis, frailty is associated with an inability to regulate BP after standing and with lower orthostatic HR and BP (406). Romero-Ortuño et al. (407) found that, on average, after 30 seconds of standing, non-frail subjects had recovered 98% of their baseline SBP while prefrail and frail had recovered 95% and 92% respectively.

Mol and colleagues (408), in a study of 168 geriatric outpatient attenders (mean age 81.4±7 years) found that orthostatic SBP drop rate rather than drop magnitude was associated with increasing frailty and number of falls. This would support the finding of a recent systematic review and metanalysis (351) which reported a 1.6 times higher likelihood of classic OH (OR 1.607 [95% CI 1.15-2.24]) in frail individuals with even higher odds for iOH (OR 3.08 [95% CI 1.50-6.36]).

Additionally, immobility and deconditioning (308) and more recently sarcopenia (409) – frequent correlates of frailty – have been implicated in OH. Indeed, sarcopenia could

potentially worsen the hypotensive impacts of medications that induce an escalation in venous pooling and/or muscle relaxation, such as vasodilators and benzodiazepines (331). Medications potentially predisposing to OH should be prescribed with caution in frail older people and the presence of OH should prompt medication review (332).

Frailty is often expressed by a count of morbidities, but little is known about its relationship with CBF and other cerebral haemodynamics. As part of her PhD using the same clinical dataset as that of this thesis, Pérez-Denia et al. (410) found that multimorbidity was associated with impaired cerebral oxygenation recovery after active standing independent of peripheral haemodynamic changes.

3.10 Literature Review of the association between OH and CBF

As mentioned, some studies have suggested that acute and prolonged hypotension upon standing may be linked to cerebral hypoperfusion. The following is a review of the literature pertaining to OH and cerebral hypoperfusion. A separate review on the relationship of symptomatic OH, asymptomatic OH and CBF then follows.

3.4.1 Search Strategy

A customised search strategy was conducted in Pubmed and Embase for articles published up to December 31st, 2023. A manual search of references of selected articles was also conducted to identify additional studies. Key search terms were “orthostatic,” “hypotension,” “cerebral blood flow,” and “perfusion.” Details of the search strategy for each database can be found in the appendix section of this thesis.

3.4.1.1 Inclusion and Exclusion criteria

Studies were included if published as a primary research paper in a peer-reviewed journal, involved participants with a mean age of 18 years or more, and examined the relationship between OH and CBF compared with an appropriate control group. Studies were included even if the sample comprised a specific disease population. Articles were excluded if they were reviews, case reports, abstracts only, medication trials and if they were not published in English.

3.4.1.2 Data Extraction

Data collected included study design and setting, study population, method for BP assessment, method for CBF assessment, information on definition of OH used and main findings of each study. As included studies were heterogenous in design and assessment methods, a descriptive approach was used to summarise characteristics and outcomes. (Table 3.2)

3.4.1.3 Search Strategy results

After removing duplicates, the initial combined search retrieved 4663 journal articles. Of these, 4561 were excluded after screening the title and abstract. Full texts were assessed for eligibility, of which 24 were included in this review. (See Figure 3.8).

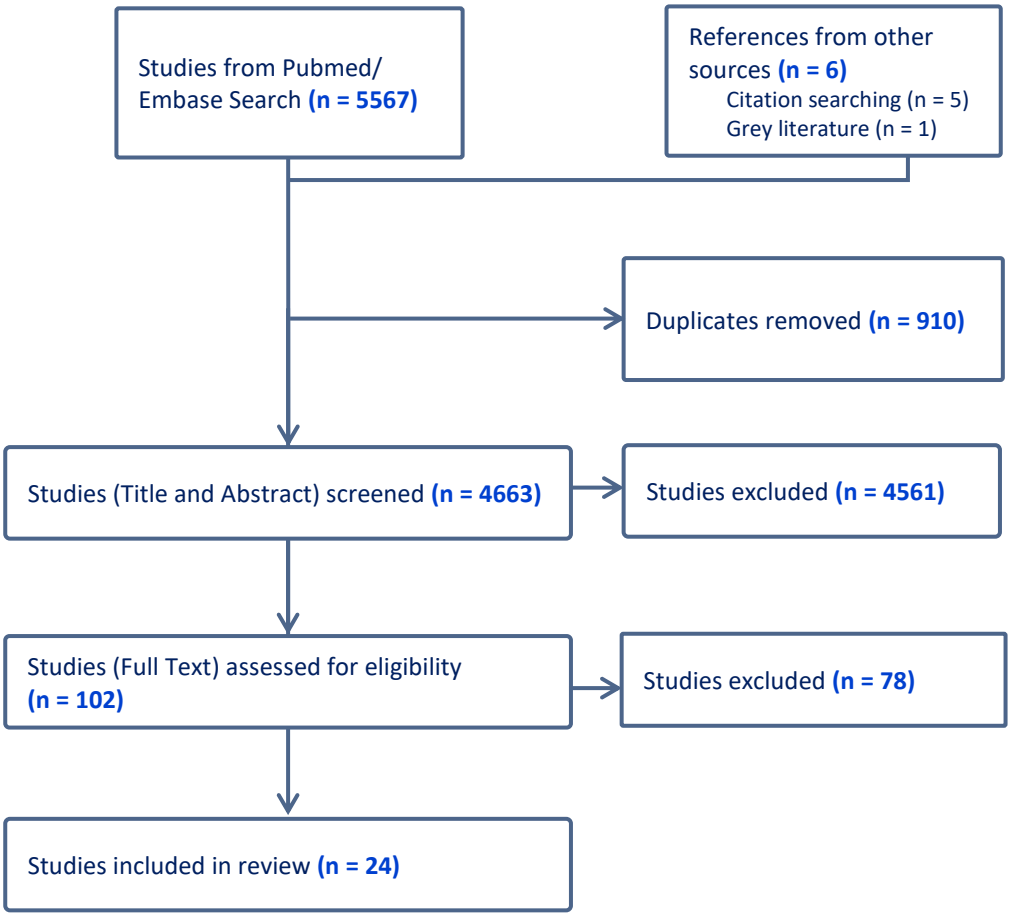

Figure 3.8 Data extraction flow chart for literature review

3.4.2 Studies examining the association of OH and CBF

The results of the literature search are presented in Table 3.2. Many of the studies recruited patient groups with various OH associated conditions. Seven studies (29.2%) were conducted on patients with diseases associated with autonomic failure including MSA while four (16.7%) studies were carried out among PD cohorts, three on dementia (AD and DLB) (12.5%), one in a diabetes cohort (4.2%) and one in participants undergoing rehabilitation post stroke (4.2%). In the remainder of the studies (8/24, 33%), OH was attributed to multiple causes or was otherwise unspecified. The comparison group was made up of healthy unaffected controls in 66.7% (16/24) while 29.2% (7/24) of studies used a non-OH group within the specified disease cohort to facilitate comparison. One study (411) sourced its controls from a group referred for investigation of acoustic neuroma.

Orthostatic BP assessment was by sit-to-stand in 8.3% (2/24), supine-to-stand in 25% (6/24) and HUT in 58.3% (14/24) while one study employed both active stand and HUT. One study employed a thigh cuff release method to simulate orthostasis. There was considerable variation among studies in the period of rest before orthostasis and the duration of upright posture.

BP measurement involved sphygmomanometer in 12.5% (3/24), oscillometric methods in 41.2% (10/24), while 29.2% (7/24) used continuous beat-to-beat measurement recordings. One study measured BP using left radial artery catheterisation while in the remainder (3/24, 12.5%) of studies, BP measurement method was not clearly stated. While seven studies (29.2%) adopted the consensus definition of OH within 3 minutes of

standing or tilt, the definition of what constituted OH differed between the rest of the studies.

Cerebral haemodynamic measurements were recorded using TCD in 29.2% (7/24) and NIRS in 16.7% (4/24) while two studies incorporated both. One TCD study also incorporated the intravenous Xenon washout technique while another single study used diffuse optical tomography, an adapted NIRS modality. Radiological methods utilised MRI perfusion (n=1), ASL MRI (n=2), PET-CT (n=1), SPECT (n=3) and Xenon inhalation techniques (n=2). One study used rheoencephalography (n=1).

The majority of included studies, (n=15, 62.5%), reported a positive association between the presence of OH and cerebral hypoperfusion. One study utilising SPECT (412) found a significant association between OH and decreased cerebral perfusion but only in AD patients and not in the healthy-OH group suggesting that AD may play a potential confounding role in the relationship. Additionally, the study was made up of an all-female cohort. Interestingly, the three studies utilising Xenon inhalation (413-415), one study using PET-CT (416) and one study using ASL MRI (417) failed to find a significant association between OH and lower CBF. This may be due to time delays between the orthostatic BP assessment and imaging acquisition. It is also noteworthy that the two studies (417, 418) that involved a sit-to-stand manoeuvre did not identify a significant association between OH and reduced CBF – though BP dropped enough to diagnose OH. Only one study (416) found that OH in early PD patients was associated with higher perfusion values on PET-CT compared to non-OH counterparts. The study authors speculate that this may be due to an early adaptive CA response in individuals with early

PD. Most of the studies contained small numbers and none attempted to control for possible confounders. No study evaluated a longitudinal association between OH and CBF.

Table 3.2 Studies examining the association between OH and CBF

Author/ Journal	Study Description/ Setting	Participants	Method for Assessment BP	Method for Assessment CBF	Definition of OH	Main Results
Hunt et al. 2006 (419)	Patients with pure autonomic failure and MSA (n=18)	n=18 OH patients (mean age 61[range 42-79]) n=10 normal volunteers (mean age 60 [46-68])	10 min rest HUT 10 min Beat-to-beat BP	NIRS (NIRO 300 spectrophotometer)	No details provided but all patients dropped MAP by mean 46.7mmHg (range 1-98mmHg)	During HUT, OH patients had substantial, though non-significant decreased TSI compared to controls. During HUT, OH patients had significant decrease O_2Hb compared to controls.
Suzuki et al. 2008 (215)	Patients (n=19) with MSA – all had OH	n=19 OH patients (mean age 66.6±8.3) n=10 healthy controls (mean age 66.5±8.5)	10 min supine rest HUT 10 min Oscillometric BP every 1 minute	NIRS (PSA III N)	SBP drop >20mmHg	No significant differences in changes in TSI, O_2Hb or HHb between the MSA (OH) groups versus controls.
Kim et al. 2019 (207)	Patients with symptoms of orthostatic intolerance were recruited and grouped according to HUT response.	n=7 OH patients (median age 72m(range 42-83)) n= 8 healthy controls (median age 67.5 (range 57-74))	Supine 20 min HUT 10-30min Beat-to-beat BP	Custom built 108 channel NIRS probe	SBP drop ≥20mmHg or DBP ≥10mmHg during HUT within 3minutes	OH group exhibited a large drop in O_2Hb, HHb and THb concentrations but only O_2Hb was statistically different compared to controls
Van Osch et al. 2005 (411)	OH patients (n=9) and Non OH control patients sourced from referral for acoustic neuroma	n=9 OH patients (mean age 80.7±4.6) n=8 controls (mean age 75±7)	HUT Intermittent oscillometric BP at 1, 2, 3 min during HUT	MRI perfusion	Consensus definition of OH	There was no significant difference in supine CBF of grey or white matter in OH versus controls. The lower the SBP on HUT, the higher the resting supine CBF on perfusion MRI

Harms et al. 2000 (140)	Patients with sympathetic failure (pure autonomic failure (n=8) and MSA (n=1))	n=9 OH patients (aged 37-70) n=9 age and sex matched controls	10 min rest supine Stand 5 min Beat-to-beat BP	NIRS O_2Hb and HHb TCD MCA CBFv	>20mmHg drop in SBP and >5mmHg in DBP at 1 min standing	MCA CBFv decreased significantly in patients versus controls. Patients had significantly larger drop in O_2Hb after standing versus controls.
Fuente Mora et al. 2017 (418)	Patients with familial dysautonomia – all with OH	n=25 OH patients (mean age 23±2) n=15 age and sex matched controls (mean age 25±2)	20 min rest seated Stand 5 min Beat-to-beat BP	TCD MCA CBFv	Consensus definition of OH	No significant difference in MCA CBFv after sit-stand in patients versus controls
Robertson et al. 2016 (420)	Cognitive and Movement Disorder clinic	n=15 LBD patients (mean age 76±7) n=15 SVD patients (mean age 76±7) matched for age sex and education.	15 min rest supine Stand 5 min Oscillometric BP at 1,3,5minutes	ASL MRI	>20mmHg drop in SBP 3 min standing	10/15 LBD patients had OH. There was a greater decline in CBF at the occipito-parietal region in OH patients
Kim et al. 2020 (421)	PD patients versus healthy controls	n=10 PD-OH (mean age 71.9±9.1) n=29 PD-No OH (mean age 68.7±9.2) n=7 healthy controls (mean age 68.1±4.5)	HUT as part of autonomic function test battery	Diffuse Optical Tomography	≥20mmHg drop in SBP or ≥10mmHg DBP within 3 minutes	PD-OH patients showed decreased O_2Hb and THb versus healthy controls.
Khandelwal et al 2011 (422)	Outpatient Autonomic Function Laboratory, New Delhi, India	n=15 OH patients (mean 41.8±12.9) n=15 age and sex matched healthy controls	Supine-stand within 3 seconds 5 min supine rest 5 min HUT Standard Mercury sphygmomanometer	Rheoencephalography	1996 Consensus criteria, American Autonomic Society/ American Academy of Neurology (423)	OH patients showed significant reduction in CBF at each timepoint (30seconds, 1min, 3min) compared to controls

Kharraziha et al 2022 (357)	SYSTEMA cohort at Skane University Malmo, Sweden	n=139 VVS on HUT (mean age 45.1±17.1) n=121 OH on HUT (mean age 61.4±19.2) n=82 negative HUT (mean age 44.5±18.2)	HUT as part of autonomic testing	NIRS (Fore-Sight absolute cerebral oximeter)	Sustained decrease SBP ≥20mmHg and/ or decrease DBP ≥10mmHg; or SBP<90mmHg	OH patients had a significantly lower minimum TSI and lower TSI at presyncope, and at 3mins and 10 mins during HUT compared to the VVS and negative HUT groups. This study also investigated the influence of age on the 3 outlined groups and found older patients with OH have lower cerebral tissue oxygenation compared with younger patients independent of concurrent SBP.
Yoo et al. 2021 (416)	n=73 (mean age 70.8±8.7) early stage drug naive PD patients attending neurology service, Seoul, Korea.	n=20 OH PD patients (mean age 73.8±7.1) n=53 Non OH PD patients (mean age 69.7±9.1)	Supine 20 min rest 20 min HUT Oscillometric BP measurements at 0, 3, 5, 10, 15, 20 minutes	PET-CT using ^{18}F-Florbetaben tracer	Decrease SBP ≥20mmHg and/ or decrease DBP ≥10mmHg at 3min or 5min during HUT	The OH PD patients demonstrated higher cerebral perfusion than non-OH counterparts – authors speculate that this may be explained as an early adaptive CA response to early PD.
Treger et al. 2006 (424)	Stroke Inpatient Rehabilitation Unit after diagnosis of first ischaemic stroke (n=13, mean age 58±11.7)	n=5 stroke and OH (mean age 59.87) n=8 stroke without OH (mean age 55.2)	6-7 min 7 stage HUT	TCD MCA CBFv Non continuous BP measurements at 1, 3,5,7 minutes	SBP drop ≥20mmHg during HUT	CBFv decrease was greater in OH group than non-OH group
Xing et al. 2022 (425)	PD patients, Neurology department, China	n=16 PD OH (mean age 63.7±7.7) n=74 PD No OH (mean age 57.7±11.1) n=20 age and sex matched healthy controls	10 min supine rest Active stand for 10 mins Beat-to-beat BP	TCD MCA CBFv	Definitions for Classical OH and Delayed OH	Used TFA to calculate CA parameters. PD-OH group had lower phase degree (impaired dynamic CA) than PD-No OH while supine. No significant differences between PD-OH versus healthy controls.

Lagi et al. 1994 (426)	Patients with Pure autonomic failure and MSA and with at least 2 syncopal episodes in preceding 6 months	n=12 OH patients (mean age 48.9 [range 26-72] n=12 healthy volunteers (mean age 48.8 [range 27-71])	Thigh cuff release Beat-to-beat BP	TCD MCA CBFv	Decreases SBP >50mmHg if normotensive. Decreases SBP >20mmHg if hypotensive	OH patients had greater drops in CBFv versus healthy controls. Variations in diastolic velocity and pulsatility index suggest impaired CA in OH
Novak et al. 1998 (427)	Neurogenic OH diagnosed with MSA, pure autonomic failure, diabetic neuropathy, idiopathic autonomic neuropathy	n=21 OH patients (mean age 61.76±2.4) n=14 age matched healthy controls	10 min supine rest HUT 5-10 minutes (mean duration 8±2.1 minutes) Beat-to-beat BP	TCD MCA CBFv	Decreases on HUT of ≥30mmHg SBP or ≥10mmHg DBP or ≥15mmHg in mean BP	In OH, CBFv and cerebrovascular resistance declined significantly during HUT compared to healthy controls indicating compromised perfusion. Used linear regression CBFv and SBP to calculate index of autoregulatory failure which identified 3 patterns: n=8 had impaired autoregulation with flat flow-BP curve, n=8 had intact CA but expanded range, n=5 had impaired CA with steep flow-BP curve.
Foster-Dingley et al. 2018 (417)	Participants (n=214)[mean age 81±4.1] from DANTE MRI sub study (all on antihypertensives and with mild cognitive impairment), Leiden	n=104 OH participants n=110 No OH participants	Seated rest 5 min 3 Oscillometric BP measurements within 3 minutes of standing	ASL MRI	≥20mmHg SBP and/ or ≥10mmHg in at least 1 of 3 standing measurements	There was no significant difference between CBF in OH versus no OH participants
Brooks et al. 1989 (415)	n=10 patients with autonomic failure; n=4 pure autonomic failure, n=4 with MSA, n=2 dopamine-beta-hydroxylase deficiency. All bar one had OH.	n=8 OH patients (range 23-78) n=4 normal controls (range 28-38)	Period of supine rest followed by HUT. Intermittent automated BP at 1-2 min intervals	Intravenous Xenon washout technique TCD MCA CBFv	No documented criteria	There was a negligible change in mean CBF (by Xenon clearance) in OH patients. However CBFv fell significantly.

Asahina et al. 2006 (428)	n=7 patients with OH secondary to MSA	n=7 OH patients (mean age 59±7) n=9 healthy controls (mean age 56±8)	Supine rest 15mins HUT 10 mins Arterial BP Left Radial Artery Catheter	TCD MCA CBFv NIRS (PSA III N device)	Fall of >30mmHg SBP and 15mmHg DBP on HUT for 3 min	There was no significant difference in mean CBFv between MSA and control groups. There was a significant reduction in cerebrovascular resistance in MSA group versus controls. There was no significant difference in TSI during HUT between OH patients and healthy controls.
Mankovsky et al 2003 (429)	Patients with type 1 or 2 diabetes attending German Diabetes Research Institute aged 18-70 divided into 3 groups based on cardiovascular autonomic neuropathy and OH status.	n=12 diabetics with no neuropathy, no OH (mean age 44.1±13.8) n=7 diabetics with neuropathy, no OH (mean age 46.4±13.8) n=8 diabetics with neuropathy and OH (mean age 47.3±12.7) n=12 healthy controls (mean age 42.6±9.7)	Supine rest 5min Active stand using oscillometric BP measurements at 1minute intervals	TCD MCA CBFv	Drop ≥27mmHg SBP during any of 5 BP readings during active standing	Mean CBFv was decreased significantly after standing in neuropathy and OH group compared to the other groups at 1minute post stand but were not statistically significant at 3minutes.
Passant et al. 1993 (414)	n=28 healthy women with and without OH (mean age 43)	n=7 OH participants n= 21 No OH participants	10 min supine rest 10 min HUT Oscillometric BP at 1, 3, 5, 10mins	133-Xenon inhalation method	Drop of at least 20mmHg SBP upon HUT	Non statistically significant greater prefrontal reduction in CBF in OH versus no OH groups.
Passant et al. 1995 (413)	n=18 Alzheimer's dementia patients with and without OH	n=13 AD and OH (mean age 72 [range 66-85]) n=5 AD and no OH (mean age 77 [72-83])	10 min supine rest 10 min HUT Oscillometric BP at 1, 3, 5, 10mins	133-Xenon inhalation method	Drop of at least 20mmHg SBP upon HUT	Non statistically significant greater decline in CBF in OH patients versus no OH patients

Hayashida et al. 1995 (430)	n=6 patients with OH compared with n=6 healthy controls	n=6 OH participants (mean age 60.3±9) n=6 No OH participants (mean age 55.5±6.2)	30 min supine rest Active stand for 5 mins Sphygmomanometer at 1 minute intervals	Technetium-99m-HMPAO SPECT at 1 min and 5min during stand	Drop of > 20mmHg SBP during stand before SPECT	OH group showed significant reduction in frontal CBF compared to normal controls.
Matsui et al. 2005 (431)	PD patients attending neurology outpatients, Sumitomo hospital , Japan	n=15 OH patients (mean age70.4±7) n=13 No OH patients (mean age 66.2±6.1)	10 min supine rest Active stand for 3 mins Intermittent automated BP at 0, 1, 2, 3 mins standing	3-dimensional stereotactic surface projection analysis of N-isopropyl-p-^{123}Iodine-iodoamphetamine SPECT	Drop of SBP >20mmHg at any time point post stand	Significantly decreased perfusion in bilateral medial frontal and bilateral anterior cingulate gyrus areas in OH group compared to no OH group
Siennicki-Lantz et al. 1999 (412)	Older women with AD in residential care versus healthy age matched community dwellers	n=4 AD patients with OH (median age 79.1 [range 76-83] n=8 AD patient without OH (median age 83 [range 82-90] n=9 No AD with OH (median age 82.6 [range 76-90] n=6 No AD, No OH (median age 81.8 [range 76-84])	8min HUT Sphygmomanometer 1 min before HUT, immediately after upright and each minute thereafter for 8 mins	99^{m}Tecnitium HMPAO SPECT	Drop of SBP ≥20mmHg at any time point after tilting	AD and OH patients had significantly lower CBF in frontal and parieto-frontal regions compared with AD no OH patients. No significant difference in CBF between controls with or without OH.

Table 3.3 Studies examining the association between symptomatic and asymptomatic OH and CBF

Author/ Year	Study Description/ Setting	Participants	BP Assessment	CBF Assessment	Definition of OH/ Symptom Assessment	Main Results
Novak P 2016. (301)	Retrospective single centre study including n=744 who underwent autonomic function testing for investigation of orthostatic intolerance symptoms (n=669) and unexplained TLOC (n=75)	n=102 normal response (mean age 48.7±16.7) n=96 compensated OH (no or mild symptoms) [mean age 56.9±17.5] n=60 uncompensated OH (severe symptoms) (mean age 57.7±17.6)	10 min rest supine HUT 10 min Intermittent oscillometric BP and continuous Beat-to-beat BP	TCD MCA CBFv	Relative drop of 80% in SBP or relative drop of 85% in mean SBP from supine within 3 minutes of HUT Self-report during HUT	Uncompensated (symptomatic) OH had significantly higher QASAT score during HUT compared to normal response suggesting greater declines in CBFv. There was no difference in QASAT score in compensated OH group (no or mild symptoms) compared to those with normal tilt response.
Park et al 2017 (432)	Movement Clinic of Parkinson's disease patients	a)n=23 (OH and symptoms) (mean age 68±8.8) b)n=22 (No OH and symptoms) (mean age 71.5±9.3) c)n=11 (No OH and no symptoms) (mean age 63.9±9.9) d)n=10 healthy controls (mean age 58.4±15.6)	10 min supine rest HUT 10 min Beat-to-beat	TCD CBFv	>20mmHg drop or >10mmHg DBP drop when standing Self-report of orthostatic dizziness during HUT	PD patients with orthostatic dizziness (a and b) showed lower CBFv than PD patients without symptoms

Harms et al 2000 (140)	Patients with sympathetic failure (pure autonomic failure (n=8) and MSA (n=1))	n=9 OH mean age 56.6 (range 37-70) -n=5 asymptomatic and n=4 symptomatic n=9 age and sex matched controls	10 min supine rest Stand 5min Beat-to-beat	NIRS O_2Hb and HHb TCD CBFv	>20mmHg in SBP and >5mmHg in DBP after 1 min standing Self-report dizziness during standing	Symptoms are associated with greater declines in BP ($p<0.05$), CBFv ($p<0.05$) and cerebral oxygenation (not significant) after standing versus asymptomatic patients.
Haubrich et al 2010 (433)	Outpatients with PD with OH (n=26) and non-PD OH (n=8)	n=18 asymptomatic PD OH (mean age 73±4) n=8 symptomatic PD OH (mean age 64±9) n=8 symptomatic non PD OH (mean age 66±20) n=25 healthy controls (mean age 66±9)	15 min supine rest HUT 10 min Beat-to-beat	TCD MCA CBFv PCA CBFv	1996 Consensus criteria, American Autonomic Society/ American Academy of Neurology Symptomatic = few episodes of presyncope or single episode of syncope in previous 8 weeks	Mean CBFv in MCA and PCA in symptomatic OH patients were significantly lower than asymptomatic OH.
Khandelwal et al 2011 (422)	Outpatients referred to Autonomic Function Laboratory, New Delhi, India	n=15 OH patients (mean 41.8±12.9) -subdivided into n=7 symptomatic and n=8 asymptomatic n=15 age and sex matched healthy controls	Supine-stand within 3 seconds 5 min supine rest 5 min HUT Standard mercury sphygmomanometer	Rheoencephalography	1996 Consensus criteria, American Autonomic Society/ American Academy of Neurology Symptoms defined on basis of “detailed history”	Symptomatic OH patients had greater max fall in CBF compared to asymptomatic counterparts

Xing et al. 2022 (425)	PD patients, Neurology department, China	n=16 PD OH (mean age 63.7±7.7) -subdivided into n=8 symptomatic and n=8 asymptomatic n=74 PD No OH (mean age 57.7±11.1) n=20 age and sex matched healthy controls	10 min supine rest Active stand for 10mins Beat-to-beat	TCD MCA CBFv	Classical OH and Delayed OH Symptomatic= Orthostatic Hypotension-Questionnaire Score >0	Used TFA to calculate CA parameters. In supine, symptomatic OH had higher normalised gain (impaired dynamic CA) versus asymptomatic. During stand, normalised gain significantly higher for symptomatic versus asymptomatic and controls
Gonzalez et al. 1991 (434)	Spinal cord injury patients (n=32) made up of complete and incomplete tetraplegia	n=10 asymptomatic OH (mean age 30±17) n=9 symptomatic OH (mean age 27±7)	15-20 mins supine rest HUT Oscillometric BP when tilt at 0, 30, 60, and 80 degrees	TCD MCA CBFv	No criteria documented Symptomatic = dizziness, nausea, blurred vision during HUT	Symptomatic OH at 80 degrees HUT had significantly greater decline in CBFv compared to asymptomatic patients.
Suzuki et al. 2008 (215)	Patients (n=19) with MSA – all had OH, symptoms = presyncope on HUT	n=19 OH patients (mean age 66.6±8.3) -subdivided into n=9 symptomatic OH (mean age62±11.8) and n=10 asymptomatic OH (67.4±6.6) n=10 healthy controls (mean age 66.5±8.5)	10 min supine rest HUT 10 min Oscillometric BP every 1 minute	NIRS (PSA III N)	SBP drop >20mmHg Patient report of “light-headedness, dizziness, blurred vision, white-out, grey-out or blackening” during HUT	Significantly greater TSI changes during HUT in symptomatic group versus asymptomatic and control group No significant differences in changes in O_2Hb or HHb across all groups

3.4.3 Studies examining Symptomatic and Asymptomatic OH and CBF

A further literature search was carried out to assess the role of symptoms on the relationship between OH and CBF. This second literature search yielded 8 studies for inclusion, four of which were also included from the initial review of OH and CBF, as they contained further subdivisions of OH patients into symptomatic and asymptomatic groups. Details are described in Table 3.3. Three studies (3/8, 37.5%) involved PD patients; two studies (2/8, 25%) involved patients with sympathetic failure including pure autonomic failure and MSA; one study (1/8, 12.5%) examined patients with OH post spinal cord injury while the rest (2/8, 25%) were recruited after referral for autonomic function assessment for various complaints. Six studies (75%) contained comparison groups made up of healthy controls.

Orthostatic BP assessment was by supine-to-stand in 25% (2/8) and HUT in 62.5% (5/8) while one study employed an active stand and HUT. Once again, the period of rest before orthostasis and the duration of upright posture varied across the studies.

BP measurement involved sphygmomanometer in 12.5% (1/8), oscillometric methods in 37.5% (3/8), while 50% (4/8) used continuous beat-to-beat measurement recordings. The definition of what constituted OH differed between studies While 50% adopted the consensus definition, one study (301) defined OH as a relative drop of 80% in SBP or relative drop of 85% in mean SBP from supine levels within 3 minutes of HUT. One study failed to record the criteria for definition used.

All studies relied on patient self-report of symptoms during orthostasis to define the symptomatic OH group in each study except for one study (425) which utilised the Orthostatic Hypotension-Questionnaire to record symptoms. This questionnaire is rated

0-10 and is based on subjective feelings as well as the impact symptoms have on daily activities.

The majority of studies recorded cerebral haemodynamic measurements using TCD (5/8, 62.5%) while one study used NIRS (1/8, 12.5%). A further study used both modalities. A final used rheoencephalography.

All included studies showed a positive association between the presence of symptomatic OH and altered cerebral haemodynamics after standing when compared to those with asymptomatic OH. However, in the study using both TCD and NIRS (140), a significant association was found in those monitored using TCD only as the relationship between symptomatic and asymptomatic OH using NIRS was non-significant. Xing et al. (425) used TFA of TCD derived measures to assess dynamic CA parameters between symptomatic and asymptomatic OH patients and found that normalised gain was significantly higher in the symptomatic group during standing versus the asymptomatic group indicating disrupted dynamic CA. In his study, Novak (301) attempted to characterise particular orthostatic syndromes based on HR, BP and CBF patterns and showed that orthostatic drop in CBFv was a better predictor of orthostatic symptoms than peripheral BP changes. Indeed, by incorporating CBF monitoring, Novak identified a novel syndrome termed orthostatic cerebral hypoperfusion syndrome which is characterised by pronounced hypoperfusion and symptoms of orthostatic intolerance despite no orthostatic drops in peripheral BP.

3.4.4 Summary of Literature Review

Most cross-sectional studies have demonstrated a consistent relationship between OH and reduced CBF. However, published data are small cross sectional studies with several methodological differences between them such as that used to measure orthostatic BP and CBF. The majority of studies used TCD and NIRS modalities to record cerebral haemodynamic measures. Cross-sectional studies cannot establish causality and will require further longitudinal studies to establish the direction of the association.

As well as OH itself, it also appears that symptoms in OH are related to significantly lower CBF metrics during orthostatic challenge. However, studies are small with no accepted objective measure to capture the variation in symptoms reported. Only one study using NIRS found a positive association.

Several factors exist that may mediate the observed cross-sectional association between OH and cerebral hypoperfusion among older adults, including impairments in ANS function, dynamic CA disruption and CBF dysregulation as well as the impact of chronic medical illness on BP and CBF. Further studies including longitudinal studies that robustly control for factors such as these are needed.

3.11 Management of Orthostatic Hypotension

Given the heterogeneity in clinical presentations of OH, management should be stepwise, and tailored to the individual (1). Comprehensive geriatric assessment (CGA) is a well-established beneficial multicomponent intervention to improve the care of older people. Because of its evidence on medication review, CGA is particularly suited to the adoption of a personalised approach to both prevent and improve OH (313). The goal of treatment centres on relieving symptoms of orthostatic intolerance, improving quality of life, mitigating future falls risk and preventing complications (435).

Management should begin with patient education and non-pharmacological approaches including cessation of culprit medications (7) and lifestyle measures such as standing up slowly (436), physical counterpressure manoeuvres (437), compression hosiery (2) and abdominal binders (317). In older patients with OH related to deconditioning, a graded exercise program starting with exercises in the reclining position like swimming or recumbent cycling may ameliorate symptoms (317). Maintaining adequate intravascular volume by the addition of salt to diet and/ or 2-3 litres fluid intake per day is also recommended (1, 306, 308). In a review of efficacy of non-pharmacological measures to treat OH, Newton and Frith found that bolus water drinking (480 ml of water within 5 minutes) was the most successful measure to improve postural BP after standing with a significant reduction in SBP drop but no significant improvement in symptoms (438). Eating smaller and more frequent meals may be of benefit in patients with chronic autonomic failure (439). Sleeping with the head of the bed elevated (15-20cm) may also be helpful, especially if there is supine hypertension (306, 435).

There is a lack of good quality evidence to support any of the agents commonly used to treat OH (313). Therefore, medications are suggested only in selected cases when non-pharmacological strategies do not improve symptoms satisfactorily (313). While midodrine is the only licensed drug for use in OH in Ireland, other medications often used in off label clinical practice include fludrocortisone, droxidopa and to a lesser extent pyridostigmine (354). Trials for other emerging drugs are ongoing and include atomoxetine and ampreloxetine (313).

The treatment of OH with concurrent supine hypertension is challenging as one can aggravate the other. Wieling et al. (1) suggests that when symptomatic, treatment of OH should be prioritised over moderate supine hypertension but, given the negative cardiovascular risks if severe, short acting antihypertensive medication may be considered at night. In a recent study, overnight continuous positive airway pressure therapy was proposed as a novel nonpharmacological method to treat supine hypertension while improving nocturia and daytime OH (440).

As mentioned in an earlier section (3.9.3.2 Antihypertensive Treatment and OH), there is emerging evidence that intensive BP-lowering strategies decrease the risk of OH. Juraschek et al. (371) in a meta-analysis of 5 RCTs using individual participant data from 18,466 adults with hypertension, found that assignment to a more intensive versus standard BP goal lowered the odds of OH (OR 0.93, [CI 0.80-0.98]). Mean age was 64.5±9.9 years, 38.9% female. Intensive BP goal varied among the 5 trials, from SBP <120mmHg in two trials, SBP <130mmHg in one trial, MAP≤92mmHg in another and SBP<150mmHg and DBP<85mmHg in the final trial. The authors suggest that the more aggressive BP treatment reduces OH by improving baroreflex function, reducing arterial stiffness and

decreasing left ventricular hypertrophy. The strict trial safety protocols – particularly with respect to titration of antihypertensive medications – coupled with the strict entry criteria to many of these trials may affect generalisability to the real world clinic environment and to older frailer populations.

3.12 Current Challenges and Gaps in Knowledge

3.12.1 OH and Cerebral Hypoperfusion

OH is implicated in a myriad of negative cardiovascular and cerebrovascular health outcomes. The literature suggests an association between OH and cerebral hypoperfusion, yet few studies have been conducted to investigate this. The studies that have are relatively small given the large interindividual variation in peripheral and cerebral haemodynamic measurements observed in these studies and none have controlled for potential confounding factors.

3.12.2 The relevance of symptoms in OH

OH varies greatly with time of day even in the same patient and may be symptomatic or not. As opposed to hypertension, which is most often asymptomatic but must be treated to avoid long term complications, management of OH is mainly guided by the presence of symptoms to improve immediate quality of life of the patient (306). The relevance of asymptomatic OH has not been fully elucidated, with little guidance regarding its natural history, clinical outcomes or benefit of treatment (316). There are no guidelines on clinical decision making in those with asymptomatic OH (441).

3.12.3 OH, Hypoperfusion and Falls Risk

OH is the commonest cause of falls and syncope in ageing. While the potential of NIRS in the assessment of falls and syncope has been acknowledged in the literature, there is a paucity of studies to date that have examined cerebral oxygenation during standing and falls risk.

3.12.4 Psychogenic pseudosyncope

PPS is a complex conversion disorder characterised by apparent syncope and felt to represent a significant cohort of those with unexplained syncope. Diagnosis relies on reproduction of symptoms during HUT with concurrent video EEG demonstrating lack of hypoperfusion. Many units do not have ready access to EEG to establish the diagnosis.

Chapter 4 will outline the aims and hypotheses of studies carried out as part of this thesis.

Chapter Four – Aims and Hypothesis of this Thesis

About a third of older adults experience a fall or syncope event each year (442, 443), resulting in significant morbidity, loss of independence and health care utilisation. Therefore, the diagnosis and prevention of these events is of particular importance. OH is a common cause of falls and syncope in older adults and is associated with early mortality, CV and cerebrovascular disease, cognitive impairment, impaired gait, frailty and depression. Impairments in CBF regulation resulting in cerebral hypoperfusion are also implicated in similar outcomes linked to adverse brain health outcomes including falls. Therefore, a better understanding of changes in CBF during orthostasis and OH may inform falls risk stratification and targeted management of at risk individuals.

The primary aim of this thesis is to investigate the relationship between CBF and OH in two cohorts: a clinical group of patients with falls, syncope and dizziness recruited from a specialised outpatient setting and a population group of participants from The Irish Longitudinal Study on Ageing (TILDA). The hypothesis is that OH is associated with greater cerebral hypoperfusion upon standing and accounts for symptoms of orthostatic intolerance. Furthermore, it is hypothesised that degree of cerebral hypoperfusion informs future falls risk.

4.1 Project Aims

1. Conduct a comprehensive review of the literature surrounding CBF and OH. (See chapters 2-3)
2. Identify key gaps or unresolved questions in the existing literature and attempt to address them. (See Chapter 3, Section 3.12)
3. Generate new insights, knowledge, or theories that contribute significantly to the advancement of the field. (See Chapters 6-10)
4. Publish findings in reputable academic journals and disseminate knowledge through conferences or other scholarly platforms. (See *Section Dissemination of thesis*)
5. Ultimately, make a meaningful and valuable contribution to improving the health of a cohort of patients that we review every day in clinical practice.

4.2 Research Questions

4.2.1 What is the relationship between OH and cerebral hypoperfusion (measured by NIRS) in a clinical cohort of patients?

OH is associated with a number of negative health outcomes. While the literature suggests an association between OH and cerebral hypoperfusion, few studies have been conducted to investigate this.

The author sought to investigate the association between OH and cerebral hypoperfusion in a real world cohort of patients presenting to a falls and syncope clinic.

The hypothesis tested in this study is that OH is associated with significantly greater cerebral hypoperfusion after standing compared to those without. (See Chapter 6)

4.2.2 What is the relationship between symptoms in OH and CBF?

Cerebral hypoperfusion in OH is felt to be responsible for the symptoms of orthostatic intolerance such as dizziness, light-headedness and unsteadiness upon standing. However, clinically, it is not uncommon for physicians to identify OH in asymptomatic individuals.

In this thesis, the author aims to outline the frequency of symptomatic and asymptomatic OH in a clinical cohort attending the falls and syncope unit and to investigate the relationship of symptoms in OH on changes in cerebral perfusion on standing.

The hypothesis here is that asymptomatic OH is common and that the presence of symptoms in OH is associated with a greater decrease in cerebral perfusion than their asymptomatic counterparts. (See Chapter 6)

4.2.3 What is the association between typical OH symptoms and orthostatic BP in a cohort of community-dwelling older people?

In a similar approach to the clinical cohort, the author seeks to investigate the frequency of typical OH symptoms, specifically dizziness and unsteadiness on rising from a chair and/or walking in the TILDA cohort of community dwelling older adults and whether such symptoms are related to changes in peripherally measured orthostatic BP.

The hypothesis is that in older adults, these typical symptoms of OH are not significantly associated with the degree of orthostatic BP drop and that a significant proportion of older people with OH demonstrated on active stand may be asymptomatic. (See Chapter 7)

4.2.4 Does asymptomatic OH confer an increased risk of future falls compared to participants with symptomatic OH?

In the clinic, OH is frequently detected in those presenting to hospital with unexplained falls. Given the longitudinal nature of TILDA, the author aims to investigate the relationship of asymptomatic and symptomatic OH on the future risk of unexplained falls.

The hypothesis tested here is that asymptomatic OH confers a higher risk of unexplained falls than symptomatic OH due to the absence of prodromal or warning symptoms. (See Chapter 7)

4.2.5 What is the relationship between OH and cerebral hypoperfusion in community dwelling older adults?

Here, in addition to the study above evaluating clinic attenders with a history of falls, dizziness and/ or syncope, the author seeks to investigate the association of OH and cerebral hypoperfusion in a separate cohort, namely community dwelling cohort of older adults.

Once again, the hypothesis here is that those with OH have a greater decline in CBF upon standing than those without OH. (See Chapter 8)

4.2.6 Is there a longitudinal association between the degree of cerebral hypoperfusion in OH with future falls?

Cerebral hypoperfusion is often proposed as the principal causative mechanism responsible for falls in those with OH. However, there is a paucity of research in this area to directly link cerebral hypoperfusion in OH to future falls risk. In this study, the author investigates the relationship between severity of cerebral hypoperfusion on standing in those with OH and the risk of future falls.

The hypothesis tested here is that those individuals with OH and greater degrees of cerebral hypoperfusion on standing have the highest risk of future falls. (See Chapter 8)

4.2.7 What is the clinical utility of NIRS in the evaluation of patients with psychogenic pseudosyncope?

The aim of this study is to examine the feasibility of using NIRS during HUT testing to confirm the lack of cerebral hypoperfusion contributing to symptoms during HUT testing thereby simplifying the diagnostic pathway. The hypothesis here is that in PPS, there is no cerebral hypoperfusion at time of apparent syncope during HUT. (See Chapter 9)

Figure 4.1 summarises, in graphical form, the research studies conducted as part of this thesis.

The following chapter will outline the materials and methods used in conducting the studies to test the above hypotheses as part of this thesis.

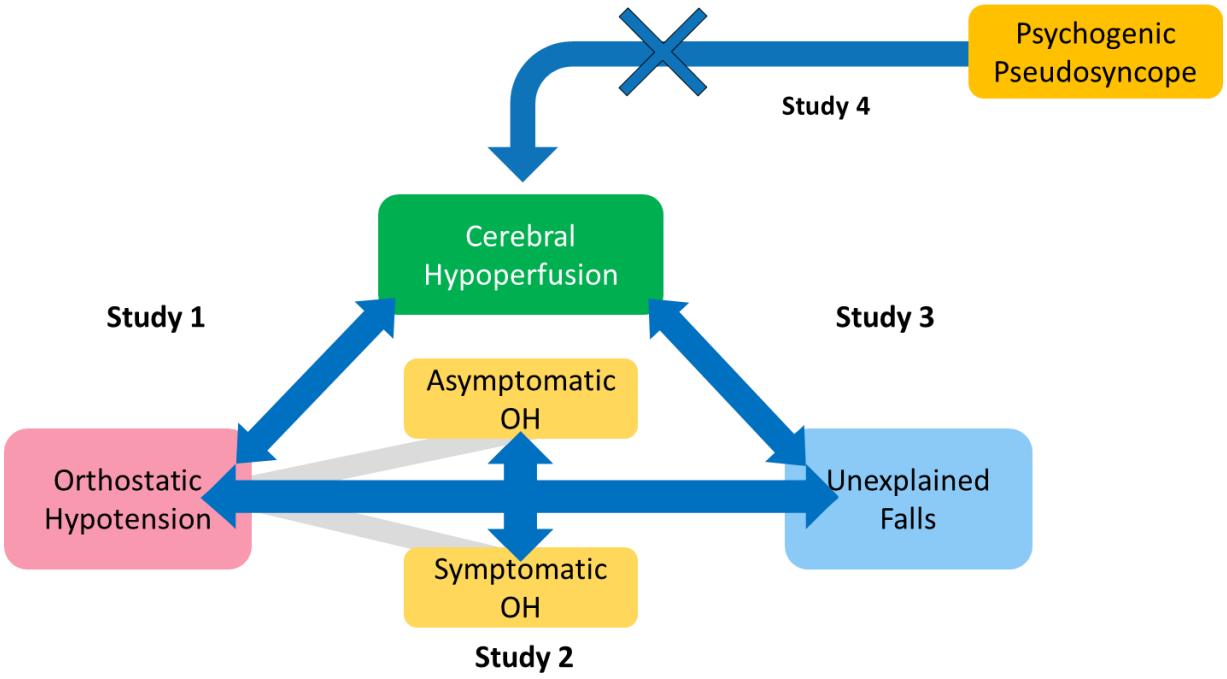

Figure 4.1 Figure outlining studies in this thesis

Chapter Five – Materials & Methods

Participants included in this project are either patients recruited from the Falls and Syncope Unit (FASU) at St. James's Hospital or participants from The Irish Longitudinal Study on Ageing (TILDA). In this chapter, details of each cohort will be discussed separately.

5.1 Clinical Sample

5.1.1 Ethics

Ethical approval was received from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08, CA,16). The collection of participants from St. James's Hospital required approval from the Research and Innovation office, which was also granted (Ref: 5149). A General Data Protection Regulation compliant patient information leaflet was created, with clear and simple explanations of the purpose and methodology of this work. A GDPR compliant informed consent form was also developed. Both documents (see Appendix) were approved by the St. James's Hospital Research and Innovation office.

The database used in this study was developed in collaboration with Dr Laura Pérez-Denia, a clinical bioengineer and at the time fellow PhD candidate in the discipline of Medical Gerontology at Trinity College Dublin. Informed consent was obtained from patients referred to the FASU by the clinic nurses or study researchers.

5.1.2 Sample Recruitment

5.1.2.1 Setting

The clinical sample was recruited from patients attending the FASU at St. James's Hospital. This dedicated syncope management unit is established since 2005 and is modelled as a rapid access, one site one stop day case facility (59, 61). The FASU is a large national referral centre for the evaluation of patients complaining of falls, syncope or dizziness either referred from the general practitioner, emergency department or other hospital consultant specialties in particular neurology and cardiology. The unit assesses up to six hundred new patients and 1200 review patients per annum and is led by several consultant geriatricians supported by senior specialist registrars and clinical nurse specialists. An integrated care pathway embedded within the emergency department has been established and can review patients directly at triage (49).

The main diagnoses established at FASU are listed in Table 5.1.

Table 5.1 Main diagnoses and definitions established at FASU

Diagnosis	**Definition**
Orthostatic Hypotension (OH)	A drop of at least 20mmHg in SBP and/or 10mmHg in DBP within three minutes of standing (423).
Carotid Sinus Syndrome (CSS)	50mmHg drop in SBP (vasodepressor) and/or a 3 second ventricular pause (cardioinhibitory), during carotid sinus massage (444).
Vasovagal Syncope (VVS)	Reproduction of prodromal symptoms or syncope induced by HUT associated with hypotension (vasodepressor) and/or bradycardia/asystole (cardioinhibitory) (445).
Cardiac arrhythmia	Supraventricular, ventricular or conduction disorder.
Structural Heart disease	Valvular or structural cardiac defect such as Aortic Stenosis or Hypertrophic Cardiomyopathy
Seizure	A seizure is characterised as an excessive asynchronous discharge of cerebral neurons leading to a clinical event.(446)
Psychogenic Events	Episode of unresponsiveness in the presence of normal blood pressure and heart rate during HUT and not consistent with normal seizure activity (447).
Vestibular/vertigo	Abnormality in surroundings and impairment of balance secondary to middle ear pathology
Falls (gait or otherwise related)	An event whereby the individual unexpectantly comes to rest on the ground or another level without any known loss of consciousness (448).

5.1.2.2 Participants

During their visits to FASU, patients were informed about the study by the reviewing nurse or clinician and invited to participate. The plain English patient information leaflet was provided, with patients given time to read and consider the decision to take part in the study, as well as the opportunity to ask any questions. If the patient agreed to participate, they were asked to sign the informed consent form. (See Appendix 2 for copies of the

patient information leaflet and consent form). They then underwent a standardised clinical testing protocol as described below.

5.1.2.3 Inclusion and Exclusion Criteria

All patients referred to the FASU aged over 16 years for investigation of falls, syncope or dizziness were invited to take part. Patients were excluded if:

- they had established cognitive impairment/ dementia and were unable to provide informed consent,
- they had contraindications to any of the diagnostic tests carried out in the clinic such as the AS or tilt table testing (e.g. pregnancy).

5.1.3 Data Collection

Detailed clinical information including medication history was obtained from each study participant using the clinic assessment proforma. Information regarding the nature, number and frequency of the patients' symptoms was gathered including:

- History and frequency of syncope
- History and frequency of falls (explained, injurious and unexplained)
- Details of witness account if present
- Frequency of presyncopal episodes
- Details of prodromal symptoms prior to syncope
- Details of symptoms in the recovery period
- Precipitating/ provoking factors
- Family history of syncope, sudden death or unexplained death

Any background clinical comorbidities were recorded and included the following covariates: anthropometrics (age (years), gender, weight (kg), height (m), body mass index (BMI, kg/m^2)), cardiovascular and cerebrovascular conditions (transient ischemic attack, stroke, carotid stenosis, hypertension, ischemic heart disease, angina, myocardial infarction, atrial fibrillation, other rhythm abnormalities, heart failure, diabetes, high cholesterol, other cardiovascular diseases), neurological disorders (mild cognitive impairment, Parkinson's disease, other neurodegenerative diseases, migraine, epilepsy), psychological disorders (depression or anxiety, other psychological diseases) and other disorders (benign paroxysmal positional vertigo or other vestibular disorders, obstructive sleep apnoea, chronic obstructive airway disease, and endocrine diseases). A recent (within last year) history of all-cause falls and syncope was also included. Behavioural health including smoking status (non-smoker, current smoker, or ex-smoker) and history of excess alcohol intake (>14 units/weeks for women, >21 units/weeks for men) was also recorded. A detailed medication record was taken at the time of testing and medications recorded using the ATC classification (449). Information from the FASU proforma for all participants were collected prospectively and transferred into a Microsoft Excel database daily. The database was updated when participants returned for follow up investigations and when a final diagnosis was reached.

5.1.4 Measurements in Clinical Sample

All participants were assessed as per European Society of Cardiology (ESC) guidelines on syncope (7). Each patient underwent recording of peripheral and central haemodynamic measurements during the AS.

5.1.4.1 The Active Stand – Experimental Methodology

Orthostatic BP was measured during an AS using a finometer (Finapres® Medical Systems, Amsterdam, The Netherlands). This device records finger plethysmography to provide non-invasive beat-to-beat estimates of brachial SBP, DBP, MAP and HR. The device uses the Modelflow™ algorithm to derive values of stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) from the BP waveforms recorded. A cuff was placed on the middle or proximal phalanx of a finger. The finger cuff size was selected according to the finger circumference. Oscillometric brachial BP measurements were obtained using a brachial arm cuff. Together with Physiocal™, these measurements were used for calibrating the finger measurements to brachial values. The height correction unit was placed on the finger cuff and the brachial cuff (which is placed at the level of the heart, at the fifth intercostal space in the mid-axillary line) to correct for hydrostatic differences. If considered appropriate by the nurse who was performing the test with the patient, the finometer arm was supported by a sling (312).

Cerebral oxygenation was monitored using a PortaLite NIRS probe (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands). The monitor was placed over the left side of the patient's forehead, approximately centred 3cm laterally and 3.5cm superior to the nasal bridge. This technology employs spatially resolved spectroscopy to derive [O_2Hb] and [HHb] in the cerebral tissue. Furthermore, values of TSI (units of %) are derived, calculated as the ratio of concentration of oxygenated haemoglobin to total haemoglobin concentration. (See *Section 2.3.2.Near-Infrared Spectroscopy* for more detailed information). An opaque bandage was wrapped around the head covering the sensor twice to protect it from environmental light contamination and minimise motion artefact.

Figure 5.1 Equipment set up for Active Stand.

5.1.4.2 The Active Stand – Protocol

Each participant underwent the AS as per accepted international guidelines (7, 312) with concurrent measurement of cerebral oxygenation. Each participant lay supine for five to ten minutes before starting the standing manoeuvre. Once the finometer and NIRS devices were attached, a marker was placed on the BP and NIRS tracings simultaneously to facilitate future synchronisation of the two recording files for the data analysis stage. Participants were asked to stand promptly and were aided by a nurse if necessary. The patient remained standing for 180 seconds while the BP and NIRS measurements were recorded. Participants were encouraged to stand quietly and when the test was completed, they were asked to report the occurrence of orthostatic symptoms (dizziness, unsteadiness and light-headedness) during the manoeuvre.

5.1.5 Head up tilt test

5.1.5.1 Equipment

A subset of participants underwent a tilt table test as part of their evaluation for unexplained syncope. The same finometer and NIRS devices as outlined above was also utilised for the HUT test. In addition, a three lead ECG was connected to the finometer, and a twelve lead continuous ECG was also attached separately. All emergency and resuscitative equipment including the cardiac arrest trolley were closely available.

5.1.5.2 HUT Protocol

The HUT test protocol used in this thesis was drug free and passive (450) i.e. no medications to provoke TLOC were administered. Patients were not required to fast prior to testing and took their medications as normal on the day of testing. The test was explained thoroughly by both the supervising doctor and clinical nurse specialist. They were advised to alert staff should they experience any symptoms which they recognised as reproductive of their previous syncope symptoms. Patients initially rested supine with both feet touching an end foot plate on the tilt table bed. The patient was secured with two horizontal Velcro straps; one above the waist level and the second across the lower legs just below the knees. All testing occurred in a quiet clinical environment in the testing bays of the FASU at an ambient temperature (21-23°C).

The finometer and NIRS devices were attached, calibrated and synchronised as outlined above. The automatic Physiocal™ function remained active to assess signal quality. The tilt bed was then tilted upright to 70 degrees with the patient's head resting on a pillow. The time of test commencement was noted and marked simultaneously on the finometer

and NIRS recordings. If the patient complained of symptoms familiar or otherwise, the time was marked on the recordings and the nature of symptoms was documented. The test continued for 40 minutes. The three chest electrodes and twelve lead ECG displayed continuous heart rate and rhythm monitoring throughout the test and immediately alerted the clinical staff to bradycardic, tachycardic or abnormal changes if present.

Once a marked BP drop was observed (<90 mmHg SBP) in the presence/ absence of symptoms, Physiocal™ was switched off to allow a continuous uninterrupted tracing during this phase. If BP recovered quickly Physiocal™ was switched back on but remained

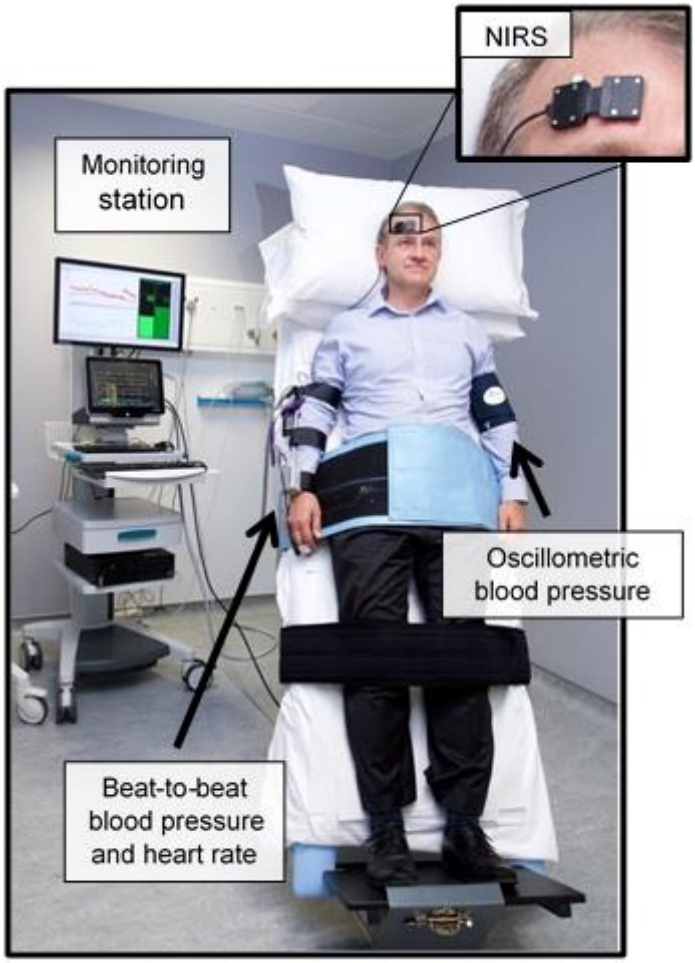

Figure 5.2 Actor demonstrating the clinical setup during a HUT test. Inset shows close-up detail of the NIRS device. For illustrative purposes, the overlying bandage to stabilise the NIRS device in place is omitted. Continuous beat-to-beat BP and HR are also monitored during the test.

off if hypotension persisted until the end of the test. If the hypotension was persistent, patients were asked to count backwards from 10-1. If LOC or apparent LOC occurred, the tilt table was returned to the supine position with legs elevated. Depending on the recording results and whether the patients' reported symptoms were deemed reproductive of their usual real world episodes, a syncope diagnosis was established. For example, if LOC was accompanied by a drop in BP or HR, a diagnosis of VVS was made. The HUT test was diagnostic for PPS when apparent TLOC occurred during testing in the absence of diagnostic HR, hypotensive BP or cerebral perfusion changes.

5.1.6 Data Management

All participant data were extracted to a database which was stored on a password protected encrypted server.

5.1.6.1 Feature Extraction and Data Analysis

This part of the methodology was completed in collaboration with Dr Laura Pérez-Denia as part of her PhD work. Custom code was developed in MATLAB (The Math Works, Inc., MATLAB Version 2020a, Natick, MA) to process physiological data collected. Only patients who had both finometer and NIRS data for both AS and HUT test were selected and synchronised using the synchronisation marks that had been placed at the time of testing. The start of the stand or tilt was identified from the height correction unit. Baseline values of SBP, DBP, HR, and TSI were calculated as the average value from -60 to -30 seconds prior to standing/ tilting. Additionally, for AS data, a five second moving average filter was applied to the raw data to obtain average values at 5, 10, 20, 30, 60, 90, 120 seconds for

each stand. For HUT test data, a five second averaging method was used to obtain average values for time of first reported symptom, onset of presyncope and time of TLOC – each of which had been marked on the recording.

Specific features used for the studies in this thesis are detailed in the methods section of each individual chapter.

5.2 Population Sample

5.2.1 The Irish Longitudinal Study on Ageing

TILDA is a large study of community-dwelling adults resident in the Republic of Ireland (451). It is a nationally representative prospective study and is the most comprehensive study of ageing carried out in Ireland to date. It collects information on aspects of health, social and economic circumstances from people aged over fifty in Ireland over a series of data collection "waves" occurring approximately every two years.

TILDA was designed following extensive international consultation, incorporating lessons learned in the conduct of similar studies in other countries and ensuring comparability of data with other well established international longitudinal studies of ageing (e.g., the English Longitudinal Study on Ageing , the Survey of Health, Ageing and Retirement in Europe and the Health and Retirement Survey in the US).

TILDA collects a wealth of physical, mental, social and financial information and is particularly rich in cardiovascular data.

5.2.2 Ethics

The TILDA study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All healthcare assessments were conducted by trained research nurses.

5.2.3 Sampling Methodology

Recruitment for the first wave of the TILDA study began in 2009, with a target population of those aged fifty and over living in the community in the Republic of Ireland, along with their partners (of any age). The sampling methodology chosen for the TILDA study to ensure a population representative cohort study was the RANSAM method (452), designed by the Economic and Social Research Institute of Ireland. This method employs a list of all residential postal addresses in the Republic of Ireland, compiled by the Irish postal service (An Post) and Ordnance Survey Ireland. The addresses are grouped into 1433 clusters, each containing 500-1500 addresses, which are stratified according to socio-economic status and geographic location. Of these, 640 clusters were selected with the probability of selection proportional to the number of individuals aged over fifty living within the cluster. Location of the clusters selected is depicted in Figure 5.3. Forty addresses were selected from each cluster and each selected address was visited by an interviewer who ascertained the eligibility of the address. Invitation letters were sent to each unique address (and hand delivered in the case of non-unique addresses). A home visit was carried out a week later to determine the eligibility of household members, who were invited to take part in the study. Successful interviews were obtained in 6279

households yielding a response rate of 62%. Participants with a history of physician diagnosed dementia were excluded from enrolment at wave 1.

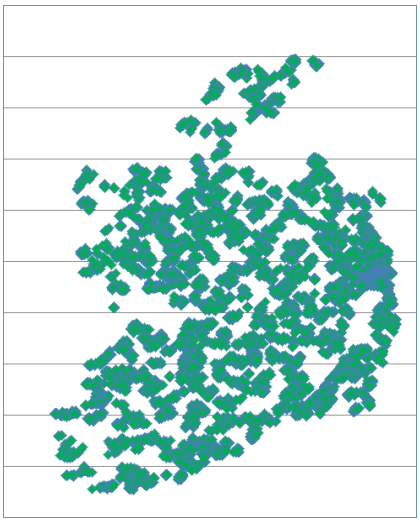

Figure 5.3 Location of clusters selected at random for inclusion in TILDA.

5.2.4 Data Collection

There are three components to data collection: (i) a computer-assisted personal interview (CAPI) administered by trained social interviewers in the participants' own homes; (ii) a self-completion questionnaire (SCQ) completed in the participants' own time; and (iii) a comprehensive health assessment delivered by trained research nurses in a dedicated health centre, or a modified version delivered in the participant's home(453). The CAPI and SCQ are included at each wave, while the health assessment is conducted at every second wave. Details of data captured in the SCQ and CAPI are summarised in Table 5.2. Detailed medication and supplement use is recorded during the interview and cross-checked with the Health Service Executive pharmacy database. The third component, the comprehensive health assessment was carried out at the TILDA health centre. Objective measurements taken are detailed in Table 5.3. Those unable or unwilling to attend were offered an in home assessment where an adapted series of measurements were obtained.

Table 5.2 Summary of data collected in TILDA CAPI and SCQ

Demographic Data - Education - Childhood Health - Migration History - Marital Status and Marriage History	**Physical Health** - Self-Rated Health - Limiting long-standing illness/ disability - Sensory Function - Cardiovascular disease - Non-cardiovascular chronic illness - Falls/ fear of falling/ steadiness - Chronic Pain - Incontinence - Medical screening
Social Circumstances - Transfers to (and from) children - Transfers to (and from) parents - (Instrumental) Activities of Daily Living - Helpers - Social Connectedness - Participation in Social/ Recreation Activities - Relationship quality ***(SCQ)***	**Mental Health** - Self-Reported Mental Health - Depression - Life satisfaction - Anxiety ***(SCQ)*** - Worry ***(SCQ)*** - Loneliness ***(SCQ)*** - Perceived stress ***(SCQ)*** - Stressful life events ***(SCQ)*** - Quality of life ***(SCQ)***
Employment and Lifelong Learning - Employment situation - Job history - Lifelong learning	**Cognitive Health** - Self-rated memory - Orientation - Word-list learning (immediate and delayed recall) - Verbal fluency - Prospective memory
Retirement and Expectations - Planning for retirement - Expectations	**Behavioural Health** - Smoking - Physical activity - Sleep - Alcohol ***(SCQ)***
Income and Assets - Sources of income - Assets	**Ageing Perceptions (SCQ)**
Transport - Transportation - Driving	**Health-care Utilisation**
Medications	

Table 5.3 Data Collected during TILDA Health Centre Assessment

Neuropsychological	**Cardiovascular**	**Mobility**	**Sensory**	**Anthropometric/ Other**
Mini Mental State Examination (MMSE)	Pulse wave velocity	Timed Up and Go (TUG)	Visual Acuity	Height
Montreal Cognitive Assessment (MOCA)	Seated and standing blood pressure	Repeated Chair stands	Contrast sensitivity	Weight
Sustained Attention to Response Task	Phasic blood pressure responses	GAITRite assessment	Macular pigment density	Waist and hip circumference
Picture memory	Heart rate variability		Retinal photographs	Grip strength
National Adult Reading Test (NART)	Cerebral perfusion		Multisensory integration	Heel ultrasound
Visual reasoning	ECG			Blood samples
Choice reaction time				Hair samples
Colour trail tests				Accelerometery (subset)
Depressive symptoms				MRI Brain (subset)
Anxiety symptoms				Dental assessment offered

5.2.5 Longitudinal Data

This thesis features data collected during the first (2009-2011), third (2014-2015), fourth (2016) and fifth (2018) waves of the TILDA study. Baseline interviews on 8504 participants took place between October 2009 and February 2011; 85% and 72% of these participants completed the SCQ and health assessment, respectively. The attrition rate between waves 1 and 3 was 15%, with 6,566 participants included at wave 3. Eighty-two percent and 85% of participants at wave 3 completed the health assessment and SCQ respectively (454). At wave 5, eighty-one percent and 86% of TILDA participants completed the CAPI and SCQ respectively (455).

5.2.6 Measurements in Population (TILDA) Sample

Specific measurements carried out during the TILDA health assessment pertinent to this thesis will now be discussed.

5.2.6.1 Orthostatic BP and NIRS Measurements

In the same way as in the clinical cohort outlined above, each participant who attended for health assessment at wave one and wave three underwent an active stand test using a similar standardised protocol. At wave 3, participants undergoing the AS had concurrent measurement of NIRS derived cerebral oxygenation with beat-to beat orthostatic BP. In TILDA, in order to remove discrete noise artefact from the data, a 10 second moving average filter (+/-5 seconds) as well as an 11-point median filter were applied. The beat to beat data was interpolated to 1 Hz and the NIRS data was down sampled to 1 Hz.

5.3 Statistical Methods

Unless otherwise stated, statistical analysis was carried out using Stata version 14.1 (Statacorp, Texas, USA).

For baseline descriptive characteristics, results are reported as means (with standard deviations) or medians (with interquartile ranges) as appropriate. Chi squared tests were used when comparing proportions between groups. When comparing two groups of continuous variables, a Student-T test or Mann Whitney U test was used depending on whether data was normally or non-normally distributed, respectively. Univariate and multivariate linear/ non-linear regression were used to study the association between continuous variables and categorical variables.

Linear Regression was used to model the relationship between a dependent variable and one or more independent variables. Logistic Regression was used for where the dependent variable was categorical and had two possible outcomes. Mixed effects or multilevel models were used to allow for the incorporation of both fixed effects (predictors that are constant across all levels) and random effects (predictors that vary across different levels) in the same model. These models provide insights into both within-group variations and between-group variations.

A p-value of ≤ 0.05 was considered statistically significant for all analyses in this thesis.

The following chapters 6-9 details the studies conducted as part of this thesis.

Chapter Six – Results

6.1 Paper One - Key Findings

- Nearly two-fifths of a clinical sample of 491 patients attending a specialised falls and syncope unit had OH on active standing.

- Of those with OH, over half (54.5%) were asymptomatic.

- Those with OH were demonstrated to have significantly lower frontal lobe cerebral perfusion upon standing than those without OH even after controlling for important potential confounders.

- There was no significant difference in TSI change from baseline on active stand among those with symptomatic OH compared to those without symptoms.

- OH may therefore disrupt CBF regulation mechanisms leading to associated negative brain health outcomes

- The high rates of asymptomatic OH detected in this study highlight the importance of objective orthostatic BP assessment in patients presenting with sequalae like falls and syncope.

Is Orthostatic Hypotension Associated with Altered Cerebral Perfusion During Active Standing?

6.2 Abstract

6.2.1 Introduction

OH is associated with poor health outcomes in later life including depression, cognitive impairment and falls. While it is hypothesised that OH compromises CBF regulation including CA leading to hypoperfusion, studies demonstrating this have been small and did not control for important covariates. This study investigated the association between OH and cerebral oxygenation during orthostasis using a non-invasive surrogate of cerebral perfusion, NIRS.

6.2.2 Methods

Four-hundred ninety-one participants (58% female, median age 65, IQR 38-92) attending a falls and syncope service underwent measurement of beat-to-beat BP (Finometer) and real-time frontal lobe oxygenation (% TSI: Tissue Saturation Index) using NIRS during the AS manoeuvre. We examined the association between OH and change in cerebral oxygenation (delta TSI) using mixed-effects linear regression, with adjustment for important clinical covariates.

6.2.3 Results

Nearly two-fifths of the sample (189/491,38.5%) met criteria for OH occurring between 30 and 120 seconds after standing.

Using mixed effects linear regression models, we observed a significant relationship between OH and TSI at the same timepoint (β -0.53, [CI -0.59 - -0.46]; p<0.001) which

persisted following adjustment for confounders including age, sex, baseline blood pressure, cerebrovascular and cardiovascular disease, depression/ anxiety, diabetes, systolic blood pressure, antihypertensives, and antidepressants (β -0.51, [-0.58 - -0.44]; p<0.001). Cerebral oxygenation levels differed for those with OH compared to those without. There was no significant difference in TSI changes in those with symptomatic OH compared to those without symptoms.

6.2.4 Conclusion

OH is independently associated with lower frontal lobe cerebral oxygenation. This association may indicate disruption to dynamic cerebral autoregulation and explain the significant link between OH and poor health outcomes.

6.3 Introduction

OH is defined by consensus statement as a drop in SBP of at least 20mmHg or a drop in DBP of at least 10mmHg within three minutes of standing (310). A recent meta-analysis reports varying prevalence rates of OH, affecting nearly one in five older persons living in the community to almost one in four persons living in long-term residential care facilities (323).

In recent years, longitudinal associations have been established between OH and negative health outcomes including all-cause mortality and cardiovascular disease (353). In addition to acting as a strong risk factor for future falls (346), OH is also associated with cognitive impairment (382-384), late life depression (350), impaired gait (349), and frailty (406). While these findings have been well-demonstrated epidemiologically, the mechanistic underpinnings are less clear. It is hypothesised that OH impairs or disrupts CBF and the resulting cerebral hypoperfusion provides the mechanistic link that over time leads to cerebral pathology.

CA refers to the ability to minimise variations in CBF during changes in systemic BP and can be static where steady-state measurements of CBF and BP have been achieved, or dynamic where there is a response to alter CBF in the face of more rapid changes in BP (4). The body's response to postural changes reflects dynamic cerebral autoregulation but due to the rapidity of BP alterations results in relative, time dependent buffering of changes in CBF. Maintenance of CBF is tightly regulated by multiple factors such as blood gases, neurovascular innervation, endothelial function, intracranial pressure, cerebral metabolism and neurovascular coupling (4, 91). The role of cerebral autoregulation in rapid OH associated cerebral perfusion changes is unclear although it is biologically

plausible that repeated hypotension and hypoperfusion would result in cerebral damage, thus indicating some attenuation of cerebral autoregulation or even cause impaired cerebral autoregulation.

OH is a manifestation of increased arterial stiffness, baroreceptor impairment and thus, ANS dysfunction when adaptive mechanisms typically observed in normal standing fail to compensate for venous pooling that occurs on assuming the upright posture (317). Symptoms of cerebral hypoperfusion such as falls, syncope and orthostatic intolerance occur when there is failure of dynamic autoregulatory mechanisms to buffer the rapid BP changes (over seconds to minutes) occurring during standing (4).

Our understanding of OH has evolved in recent years with the increasing availability of continuous non-invasive beat-to-beat BP measurements in the clinical setting. Several patterns of impaired BP recovery on standing have been described.(406) However, to date most lack a direct measurement of cerebral haemodynamics during orthostasis.

Near-infrared spectroscopy is a novel non-invasive technology first proposed by Jöbsis (125) in 1977 and increasingly available for assessment of real time cerebral oxygenation – a reliable surrogate for cerebral perfusion (185) reflecting available oxygen supply for cerebral tissues.

Previous work (140, 400, 401) using NIRS during orthostasis found that cerebral tissue oxygenation decreases in healthy individuals after standing and is associated with increased postural instability. This study sought to examine whether cerebral tissue oxygenation decreases more in OH patients compared to those without OH. In a clinical cohort referred to a specialist clinic for assessment of falls, syncope, and dizziness. The hypothesis tested is that those with OH have more marked cerebral hypoperfusion during

orthostasis than those without OH. Further, it was hypothesised that those with symptomatic OH would have significant differences in cerebral perfusion compared to those who were asymptomatic.

6.4 Methods

6.4.1 Study Sample & Setting

Consecutive patients referred to the FASU at St. James's Hospital, Dublin were recruited for participation in the current study, over a 9-month period. The FASU is a national referral centre located in a busy urban teaching hospital, which receives referrals from the ED, general practice and other secondary and tertiary services.

6.4.2 Ethical Approval

Ethical approval for this study was granted by the Joint Research Ethics Committee at Tallaght University Hospital/ St. James's Hospital. All participants provided informed written consent. All procedures adhered to the Declaration of Helsinki.

6.4.3 Clinic Measurements

Participants underwent clinical evaluation including detailed medical history, physical examination, 12-lead resting surface electrocardiogram (ECG) and AS.

6.4.3.1 Active Stand

Participants lay supine for 10 minutes prior to stand. They were then asked to stand unaided, if possible, in a timely manner. Clinic nurses aided if required. BP, HR and cerebral oxygenation (TSI) measurements were recorded at 10-second intervals, using five second moving averages around each time point. Immediately after standing, participants were asked to report presence of symptoms of orthostatic intolerance namely dizziness, light-headedness or unsteadiness. This informed the 'symptoms' variable.

6.4.3.2 Blood Pressure Measurements

During the active stand manoeuvre, continuous beat-to-beat BP and HR measurements were recorded using a finger plethysmography-based volume clamp approach (Finometer NOVA, Finapres Medical Systems, Amsterdam, The Netherlands).

Concurrently, continuous NIRS-derived regional cerebral oxygenation of the frontal lobe was also recorded using an optical sensor applied to the forehead 2.5 cm above the eyebrow (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands). A bandage was affixed around the head over the sensor to remove ambient lighting and exert comfortable pressure for effective contact between the probe and the subjects' skin.

NIRS reports TSI and is defined as the percentage ratio of oxygenated haemoglobin concentration ($[O_2Hb]$) to the total concentration of haemoglobin, i.e. oxygenated haemoglobin and deoxygenated haemoglobin.

6.4.3.3 Orthostatic Hypotension

Participants were classified as having OH if systolic BP at any timepoint from 30-120 seconds post standing was ≥ 20mmHg below baseline, or diastolic BP was ≥ 10 mmHg below baseline.

6.4.4 Covariates

A detailed medical history and clinical examination was conducted. Medical history included cardiovascular disease (defined as a known history of ischaemic heart disease, heart failure, atrial fibrillation or valvular disease), cerebrovascular disease (defined as a history of stroke or transient ischaemic attack), dyslipidaemia, diabetes, depression and anxiety. Depression and anxiety were defined as either physician diagnosed or by using anti-depressant or anxiolytic medications. Smoking status (non-smoker, current smoker, ex-smoker), alcohol excess (> 21 units/week for males and >14 units/week for females) was ascertained by self-report.

Current medications were coded using the Anatomical Therapeutic Chemical (ATC) classification (449). Polypharmacy was defined as those patients taking five or more medications. Culprit medications, known to influence orthostatic BP were defined as follows: antihypertensives (alpha-blockers (C02CA), diuretics (C03), calcium channel blockers (C08), angiotensin converting enzyme inhibitors/ angiotensin receptor blockers (C09), beta-blockers (C07)) and antidepressant medications (N06A), based on known impact on BP.

6.5 Statistical Analysis

Data was analysed using Stata version 14.1 (Statacorp, Texas, USA) while graphs were constructed in Microsoft Excel 2016 (Microsoft Corporation, Redmond Washington, USA). For baseline descriptive characteristics, results are reported as means (with standard deviations) or medians (with interquartile ranges) as appropriate. Between group univariate analysis was carried out using t-tests and Wilcoxon rank-sum tests. A p-value of ≤ 0.05 was considered statistically significant for all analysis in the current study.

To assess the relationship between OH at any timepoint from 30 to 120 seconds post-stand and cerebral perfusion, mixed-effects linear regression with random-effects for study participant (to take account of repeated measurements) were used. Change in TSI (ΔTSI) from baseline was the dependent variable, with OH as the independent variable. A time interaction was added to the models to account for changes with time after standing. The association was assessed unadjusted in the first instance (Model 1), followed by adjustment for age, sex and baseline SBP (Model 2) and further adjustment for important clinical covariates including cardiovascular disease, cerebrovascular disease, smoking, alcohol excess, polypharmacy, culprit medications (defined above), diabetes, dyslipidaemia, depression/anxiety and antidepressant medication (Model 3). To examine for multi-collinearity, variance inflation factors were computed and examined alongside residual-versus-fit plots. Results of linear mixed-effects models are reported as Beta-coefficients with corresponding 95% Confidence Intervals (CI).

The relationship between the presence of symptoms and OH on active standing and cerebral perfusion was assessed also using a mixed-effects linear regression model.

Change in TSI (ΔTSI) from baseline was the dependent variable, with symptomatic OH as the independent variable.

6.6 Results

6.6.1 Study Participants

491 patients were recruited (median age: 65, IQR: 38-92 years; 57.8%, 284/419 female). All were referred to the FASU for evaluation of falls, syncope or dizziness. Patient characteristics and descriptive statistics are detailed in Table 6.1.

Based on analysis of beat-to-beat BP, nearly two-fifths 38.5% (189/491) met criteria for OH at any timepoint between 30 to 120 seconds during standing. Those with OH were older (median age: 72; IQR: 56-88) with mean baseline SBP in the OH group 150.5mmHg versus 139.4mmHg in the non-OH group.

6.6.2 OH and cerebral perfusion during active stand

Overall, there was a significant association between concurrent OH and ΔTSI (β -0.53; [95% CI: -0.59, -0.46]; p<0.001) which persisted following adjustment for age, sex and baseline BP (Model 2) and for other important clinical confounders (Model 3; β -0.51; [-0.58, -0.44]; p<0.001) (Table 6.2). Figure 6.1 illustrates the mean SBP, DBP, HR and TSI obtained during active standing stratified by OH status.

*Table 6. 1 Baseline characteristics in clinical cohort. * denotes statistical significance*

		No OH (at any timepoint) v OH (at any timepoint 30-120s)		
	Total (n=491)	**No OH (n=302)**	**OH (n=189)**	**Statistic, p-value**
Age (median, IQR)	65, 38-92	58, 24-92	72, 56-88	z=-8.252, p<0.001*
Sex (female) (n,%)	284 (57.8%)	192 (63.6%)	92 (48.7%)	χ^2=10.582, p=0.001*
BMI (kg/h^2) (mean ± SD)	26.76 ± 5.51	26.86±5.8	26.6±5.02	t=0.52, p=0.603
Cerebrovascular Disease (n,%)	41 (8.4%)	13 (4.3%)	28 (14.8%)	χ^2=16.779, p<0.001*
Hypertension (n,%)	192 (39.1%)	101 (33.4%)	91 (48.1%)	χ^2=10.555, p=0.001*
Cardiovascular Disease (n,%)	156 (31.8%)	78 (25.8%)	78 (41.3%)	χ^2=12.788, p<0.001*
Diabetes (n,%)	49 (10.0%)	27 (8.9%)	22 (11.6%)	χ^2=0.943, p=0.331
Cholesterol (n,%)	178 (36.3%)	94 (31.1%)	84 (44.4%)	χ^2=8.923, p=0.003*
Depression/Anxiety (n,%)	112 (22.8%)	63 (20.9%)	49 (25.9%)	χ^2=1.694, p=0.193
Alcohol Misuse (n,%)	57 (11.6%)	27 (8.9%)	30 (15.9%)	χ^2=5.445, p=0.020*
Smoking Status - **Current (n,%)**	66 (13.4%)	41 (13.6%)	25 (13.2%)	χ^2=9.743, p=0.008*
- **Ex-Smoker (n,%)**	131 (26.7%)	66 (21.9%)	65 (36.0%)	
- **Non-Smoker (n,%)**	294 (59.9%)	195 (64.6%)	99 (52.4%)	
Polypharmacy (n,%)	200 (40.7%)	100 (33.1%)	100 (52.9%)	χ^2=18.873, p<0.001*
Antihypertensives (n,%)	179 (36.5%	96 (31.8%)	83 (43.9%)	χ^2=7.38, p=0.007*
Beta blockers (n,%)	97 (19.8%)	47 (15.6%)	50 (26.5%)	χ^2=8.67, p=0.003*
Antidepressants (n,%)	112 (22.8%)	62 (20.5%)	50 (26.5%)	χ^2=2.318, p=0.128
Baseline SBP (mmHg) (mean ± SD)	143.45 ± 22.82	139.36±19.87	150.47±25.74	t=-5.274, p<0.001*
Baseline DBP (mmHg) (mean ± SD)	82.67±13.38	81.81±12.69	84.13±14.4	t=-1.8312, p=0.068
Baseline HR (bpm) (mean ± SD)	73.59±11.69	74.08±11.54	72.76±11.93	t=1.1941, p=0.233
Baseline TSI (%) (mean ± SD)	66.7±5.71	67.19±5.37	65.91±6.14	t=2.4253, p=0.0157*
Nadir TSI (%) (mean ± SD)	64.52±6.29	65.04±5.65	63.68±7.16	t=2.347, p=0.0193*

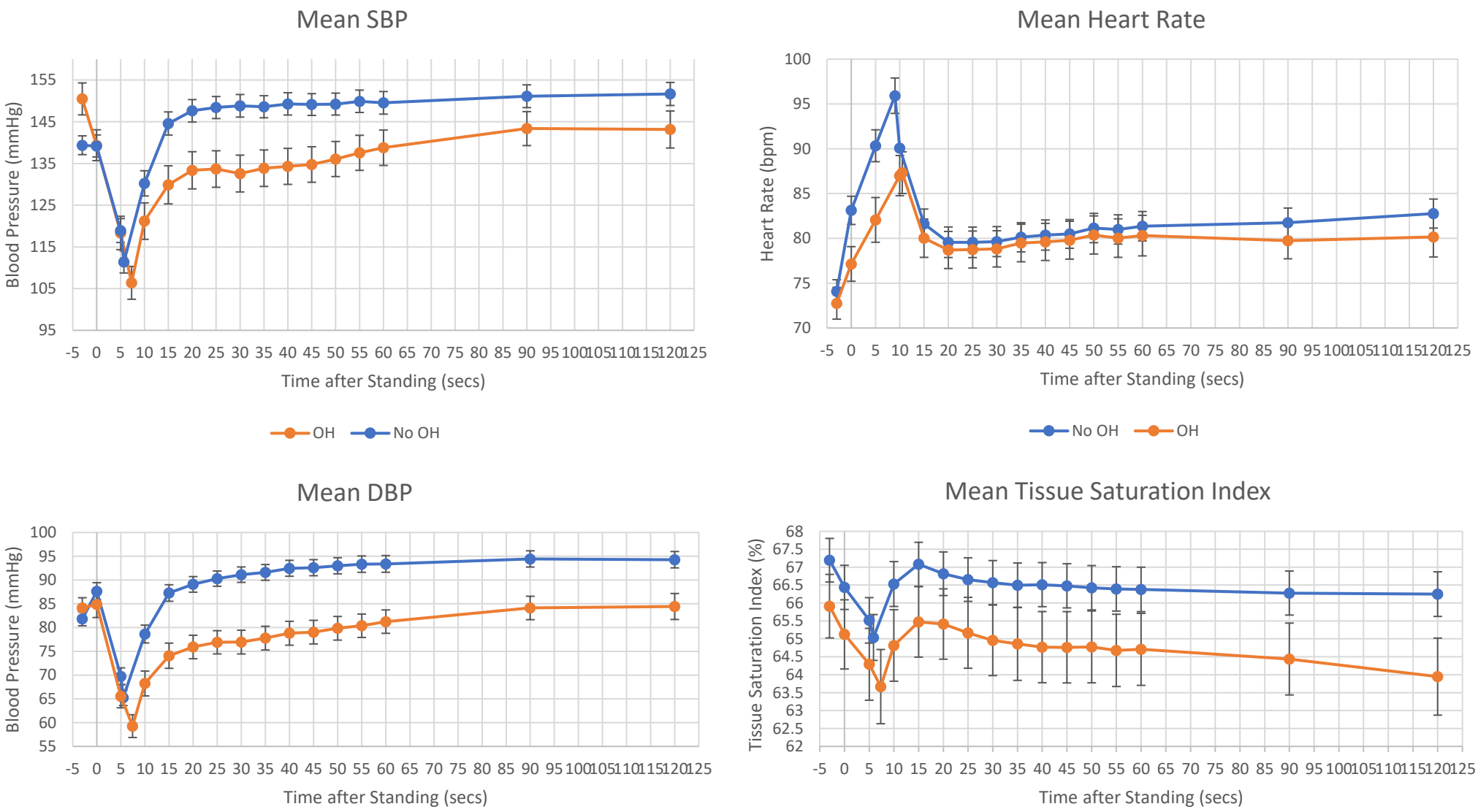

Figure 6. 1 Mean systolic BP (top left), diastolic BP (bottom left), heart rate (top right) and NIRS derived Tissue Saturation Index (bottom right) values obtained during standing shown for patients with no OH (blue line) and those with OH (gold line). Error bars denote 95% confidence intervals.

Table 6.2 Mixed-effects Linear regression models assessing the effect of OH over time (independent variable) on change in Tissue Saturation Index (ΔTSI) from baseline. Patients with any OH experienced a greater decline in TSI over time in comparison to those without OH. This association persisted after robust covariate adjustment. denotes statistical significance.*

	Model 1		**Model 2**		**Model 3**	
Predictor	**β-Coef. (95% CI)**	**p-value**	**β-Coef. (95% CI)**	**p-value**	**β-Coef. (95% CI)**	**p-value**
Any OH	-0.293 (-0.719, 0.133)	p=0.177	-0.291 (-0.761, 0.179)	p=0.224	-0.192 (-0.668, 0.283)	p=0.428
Time	-0.004 (-0.005, -0.003)	p<0.0001*	-0.004 (-0.005, -0.003)	p<0.0001*	-0.004 (-0.005, -0.003)	p<0.0001*
Time x Any OH	-0.003 (-0.004, -0.001)	p=0.0013*	-0.003 (-0.005, -0.001)	p=3.00E-04*	-0.003 (-0.005, -0.001)	p=6.00E-04*
Age			-0.006 (-0.017, 0.005)	p=0.2563	-0.003 (-0.015, 0.01)	p=0.6752
Gender			-0.59 (-0.994, -0.186)	p=0.0042*	-0.574 (-1.021, -0.127)	p=0.0119*
Baseline SBP			0.001 (-0.008, 0.01)	p=0.8435	0 (-0.009, 0.01)	p=0.9568
Cerebrovascular Disease					-0.406 (-0.911, 0.098)	p=0.1141
Cardiovascular Disease					-0.33 (-1.094, 0.434)	p=0.397
Smoking Status					0.372 (0.076, 0.668)	p=0.0137*
Alcohol Excess					-0.228 (-0.903, 0.446)	p=0.5067
Polypharmacy					0.01 (-0.518, 0.539)	p=0.9694
Diabetes					-0.254 (-0.948, 0.439)	p=0.4723
Cholesterol					0.073 (-0.411, 0.556)	p=0.7677
Depression/Anxiety					0.34 (-0.293, 0.972)	p=0.2923
Antihypertensives					0.345 (-0.132, 0.823)	p=0.1565
Betablockers					-0.424 (-0.983, 0.136)	p=0.1377
Antidepressants					-0.936 (-1.576, -0.296)	p=0.0041*

6.6.3 Symptomatic OH and cerebral perfusion during active stand

Information on the presence of symptoms on standing was recorded for 180 individuals with OH. Approximately 45.6% were symptomatic while 54.4% were asymptomatic of OH. Those with symptomatic OH were more likely to have a smoking history and have a history of depression or anxiety. (Table 6.3). Overall, there was no significant association between symptomatic OH and ΔTSI which persisted following adjustment for age, sex and baseline BP and for other important clinical confounders (β -0.026 [-0.875, 0.823]; p=0.952) (Table 6.4). Figure 6.2 illustrates the mean SBP, DBP, HR and TSI obtained during active standing stratified by OH symptom status.

*Table 6.3 Patient characteristics of those with symptomatic OH versus asymptomatic OH. * denotes statistical significance.*

	Asymptomatic OH (n=98)	**Symptomatic OH (n=82)**	**Statistic, p-value**
Age (median, IQR)	72, 57-87	71, 52-90	z=1.819, p=0.069
Sex (female) (n,%)	51 (52%)	37 (45.1%)	χ^2=0.855, p=0.355
BMI (kg/h^2) (mean ± SD)	26.2±4.97	27.2±5.1	t=-1.224, p=0.223
Cerebrovascular Disease (n,%)	14 (14.3%)	14 (17.1%)	χ^2=0.264, p=0.607
Hypertension (n,%)	46 (46.9%)	39 (47.6%)	χ^2=0.007, p=0.934
Baseline SBP (mmHg) (mean, SD)	151.6±22.12	149.37±28.67	t=-0.572, p=0.568
Cardiovascular Disease (n,%)	36 (36.7%)	37 (45.1%)	χ^2=1.303, p=0.254
Diabetes (n,%)	15 (15.3%)	6 (7.3%)	χ^2=2.765, p=0.096
Cholesterol (n,%)	42 (42.9%)	37 (45.1%)	χ^2=0.093, p=0.76
Depression/Anxiety (n,%)	15 (15.3%)	32 (39%)	χ^2=13.02, p<0.001*
Alcohol Misuse (n,%)	15 (15.3%)	15 (18.3%)	χ^2=0.287, p=0.592
Smoking Status - **Current (n,%)**	8 (8.2%)	17 (20.7%)	χ^2=6.535, p=0.038*
- **Ex-Smoker (n,%)**	33 (33.7%)	28 (34.1%)	
- **Non-Smoker (n,%)**	57 (58.2%)	37 (45.1%)	
Polypharmacy (n,%)	46 (46.9%)	50 (61%)	χ^2=3.534, p=0.06
Antihypertensives (n,%)	43 (43.9%)	37 (45.1%)	χ^2=0.028, p=0.867
Betablockers (n,%)	23 (23.5%)	23 (28%)	χ^2=0.492, p=0.483
Antidepressants (n,%)	21 (21.4%)	27 (32.9%)	χ^2=3.018, p=0.082

Table 6.4 Mixed-effects Linear regression models assessing the effect of symptomatic OH (independent variable) on change in Tissue Saturation Index (ΔTSI) from baseline. denotes statistical significance.*

	Change in TSI from Baseline (Dependent Variable)	
Predictor	**β-Coef. (95% CI)**	**p-value**
Symptomatic OH	-0.026 (-0.875, 0.823)	p=0.952
Age	-0.071 (-0.038, 0.024)	p=0.658
Gender	-0.653 (-1.591, 0.285)	p=0.172
Baseline SBP	-0.004 (-0.020, 0.013)	p=0.648
Cerebrovascular Disease	-0.29 (-1.499, 0.919)	p=0.638
Cardiovascular Disease	-1.111 (-2.079, -0.143)	p=0.024*
Smoking Status	0.628 (-0.003, 1.26)	p=0.051
Alcohol Excess	-0.016 (-1.213, 1.18)	p=0.978
Polypharmacy	-0.038 (-1.082, 1.006)	p=0.943
Diabetes	-0.365 (-1.7, 0.971)	p=0.592
Cholesterol	0.435 (-0.542, 1.411)	p=0.383
Depression/Anxiety	1.147 (-0.286, 2.581)	p=0.117
Antihypertensives	0.736 (-0.137, 1.609)	p=0.099
Betablockers	-0.875 (-1.876, 0.126)	p=0.087
Antidepressants	-2.155 (-3.522, -0.787)	p=0.002*

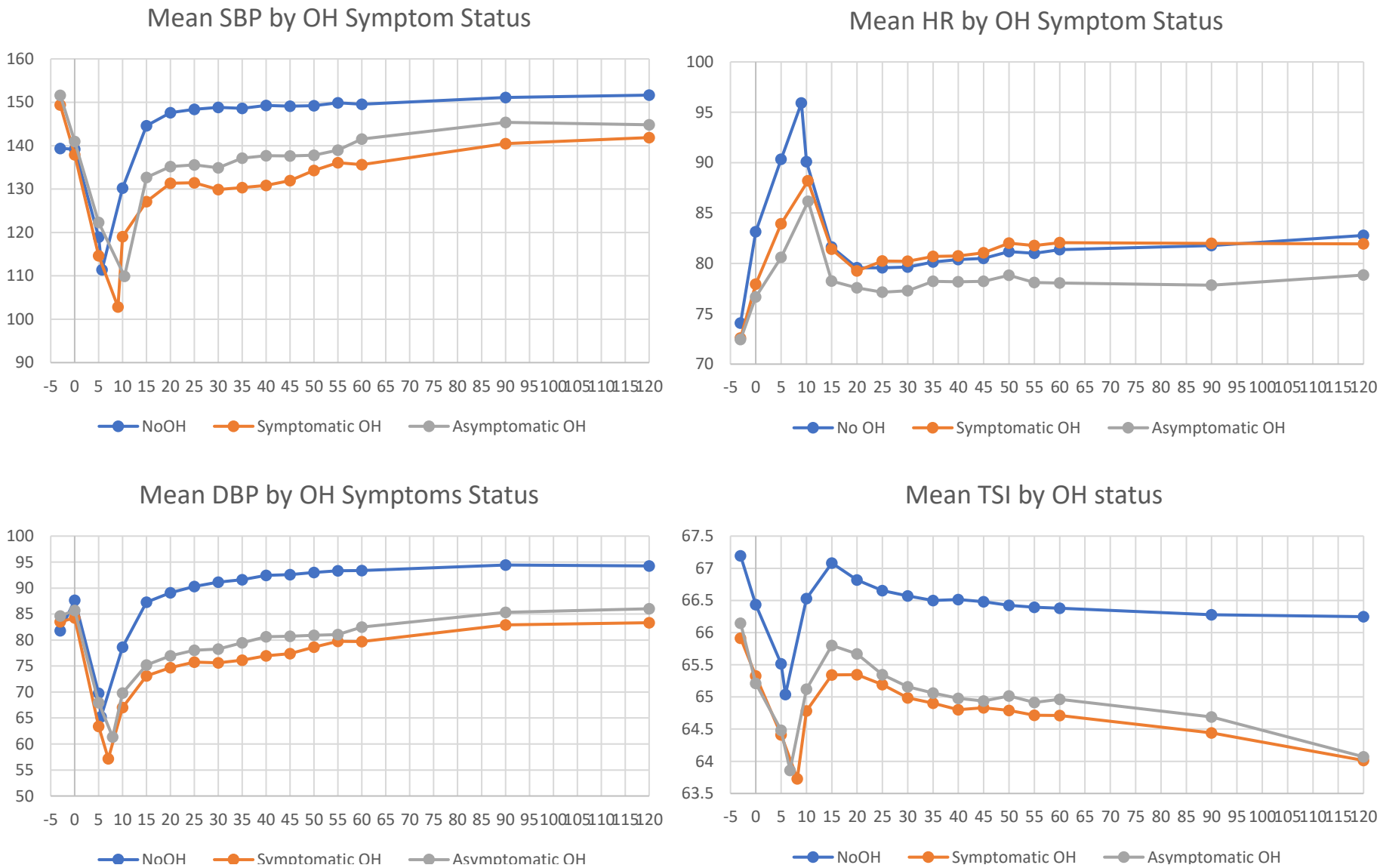

Figure 6.2 Mean systolic BP (top left), diastolic BP (bottom left), heart rate (top right) and NIRS derived Tissue Saturation Index values (bottom right) obtained during standing shown for patients with no OH (blue line) and those with symptomatic OH (gold line) and asymptomatic OH (grey line). Error bars not shown.

6.7 Discussion

This current study assessed the relationship between OH and CBF in 189 of 491 clinic attenders with history of falls, syncope and dizziness. By coupling continuous beat-to-beat BP measurement with concurrent measurement of cerebral oxygenation, a significant relationship between the presence of OH and more marked decreases in CBF was demonstrated. This association was demonstrated at multiple timepoints (from 30-120 seconds) and persisted after adjustment for demographic and clinical covariates. Further, there was no significant difference between NIRS detected changes in cerebral perfusion among those who were symptomatic compared to those without symptoms upon standing.

To our knowledge this is the largest study to date using novel NIRS technology in individuals referred for clinical evaluation of falls, syncope and dizziness to assess cerebral perfusion during active standing adjusting for important potential confounders. NIRS is safe, non-invasive and easily applicable in a busy clinical environment and in this case was coupled with continuous beat-to-beat peripheral BP and HR measurements.

Kim et al. (207) studied BP and cerebral oximetry responses to standing in seven OH subjects using the head up tilt test and found that the OH group exhibited a large drop in oxygenated haemoglobin compared to controls. The OH group did not show any recovery towards baseline levels for oxygenated or deoxygenated haemoglobin concentrations by the end of the tilt phase. Another study by Harms et al. (140) in nine OH patients found that OH was related to lower cerebral oxygenation and CBFv after standing. This current study confirms these findings and replicates them in a large clinical cohort, demonstrating the robust relationship between changes in orthostatic BP behaviour on standing and

altered cerebral perfusion. Fitzgibbon-Collins and colleagues (401) have shown a relationship between greater reductions in cerebral oxygenation post standing and increased postural instability. They argue that dizziness and increased falls risk might link directly to reduced oxygen delivery to the brain. This is likely to be further amplified in individuals with impaired orthostatic BP behaviour.

It is noteworthy that the differences in cerebral oxygenation in Figures 6.1 are in the order of 2-3%. This change would appear to be clinically relevant, given that a 5-10% TSI drop is associated with presyncope or loss of consciousness (456).

This study found no difference in TSI changes during AS in those with symptomatic OH compared to their asymptomatic counterparts. While other studies using TCD modalities have linked symptomatic OH with worse cerebral perfusion than those with asymptomatic OH (140, 425, 433), it is noteworthy that studies using NIRS have shown conflicting results (140, 215). A recent NIRS study in OH participants conducted by Klop and colleagues (457) (reporting O_2Hb rather than TSI) found a deeper oxygenation maximum drop during symptomatic supine-stand transitions compared to asymptomatic transitions but no difference between the groups in the recovery phase post stand.

The strengths of this study include the size of the population sample and the ability to adjust for important clinical covariates such as medical history and concomitant medication use. Many previous studies to date have used small sample sizes and older generations of NIRS devices and have assessed the response to orthostasis using passive tilting rather than the AS test. The active stand test is likely to better capture normal physiological responses (316) and offers an assessment of neurovascular responses to physiological challenge. This has the potential to improve our understanding of cerebral

haemodynamics in response to an everyday physiological challenge (standing) and offers a window of insight into the underlying pathophysiology by which OH could impair cerebral perfusion which may contribute to adverse brain health outcomes.

There are some limitations with this study which should be noted. This study only considered the effects of BP on CBF. It did not account for other variables that regulate cerebral blood flow like exercise, prior caffeine intake, mental stress, $PaCO_2$ or end tidal CO_2 which may not have remained stable during active standing.

Additionally, it is important to note that while NIRS does not measure CBF directly, NIRS is sensitive to detect postural changes in cerebral oxygenation (216). Cerebral oxygenation is determined by arterial blood oxygen concentration, cerebral oxygen consumption, oxygen-tissue diffusivity and CBF. It is assumed that if all other parameters are kept constant, changes in cerebral tissue oxygenation reflect changes in CBF (185). The changes in TSI in the frontal lobe detected by NIRS in the tissue under the probe may not be reflective of saturation levels in other areas of the cerebral circulation. It is also possible that the changes seen in the frontal lobe are as a result of an attempt to divert blood to other areas of the brain to preserve vital functions during OH.

Because the study is cross-sectional, it cannot establish causality. The relationship between OH and cerebral blood flow could be bidirectional. OH may be responsible for an acute drop in cerebral oxygenation resulting in symptoms of cerebral hypoperfusion like dizziness and falls (346). Alternatively, structural changes in the brain such as atrophy and white matter hyperintensities may lead to cerebral blood flow deficits upon standing. Cerebral hypoperfusion might induce behavioural changes that result in deconditioning, muscle loss, failure of the muscle pump and consequent OH.

Future work should focus on establishing a longitudinal relationship between OH and CBF and its impact on important clinical outcomes such as falls. Further research on the role symptoms of orthostatic intolerance plays on the relationship between OH and cerebral perfusion would be timely and welcome.

6.8 Conclusion

OH is a potentially serious and often under recognised phenomenon in older persons. This study highlights that the presence of OH is associated with lower cerebral oxygenation levels after standing even after adjustment for important covariates. These findings suggest that the ability of dynamic cerebral autoregulation to maintain, preserve or buffer cerebral oxygenation results in those with OH having larger differences in TSI in the periods after standing compared to non-OH individuals. This has implications for overall brain health and may help explain the link between OH and hypoperfusion symptoms or the development of impaired cognitive performance. Improving cerebral perfusion or rather preventing cerebral hypoperfusion may serve as an important target for treatment in OH, however further research is needed to tease out the underlying validity of this approach.

Chapter Seven - Results

7.1 Paper Two - Key Findings

- In total, 10% of a cohort of >900 community-dwelling people aged≥70years had OH demonstrated during active stand.

- Two-thirds of older people with OH did not report symptoms of light-headedness during an active stand.

- Participants who reported light-headedness during the active stand did not have a greater drop in BP after standing.

- Participants with asymptomatic OH had a higher risk of unexplained falls than those who reported symptoms.

- These findings have important clinical implications for the assessment of older people with OH and falls.

Asymptomatic Orthostatic Hypotension and Risk of Falls in Community-Dwelling Older People.

Claffey P, Pérez-Denia L, Lavan A, Kenny RA, Finucane C, Briggs R. Asymptomatic orthostatic hypotension and risk of falls in community-dwelling older people. Age and ageing. 2022 Dec;51(12):afac295.

7.2 Abstract

7.2.1 Introduction

Many older people with orthostatic hypotension (OH) may not report typical symptoms of dizziness, light-headedness, or unsteadiness. However, the relationships between orthostatic blood pressure (BP), OH and falls in the absence of typical symptoms are not yet established.

7.2.2 Methods

Continuous orthostatic BP was measured during the active stand using a finometer at Wave 1 of the Irish Longitudinal Study on Ageing in participants aged≥70 years.

OH, with and without dizziness, was defined as a sustained drop in systolic BP≥20 mmHg and/or drop in diastolic BP≥10 mmHg at 30, 60 and 90 seconds post-standing.

The association between symptoms of dizziness and orthostatic BP was assessed with multi-level mixed effects linear regression, while logistic regression models were used to assess the longitudinal relationship between OH and falls at 6-year follow-up (Waves 2-5).

7.2.3 Results

Almost 11% (n=934, mean age 75 years, 51% female) had OH, two-thirds of whom were asymptomatic. Dizziness was not associated with systolic BP drop at 30 (β=1.54 [−1.27, 4.36]; p=0.256), 60 (β=2.64 [−0.19, 5.47]; p=0.476) or 90 seconds (β=2.02 [−0.91, 4.95]; p=0.176) after standing in adjusted models. Asymptomatic OH was independently

associated with unexplained falls (OR 2.01 [1.11, 3.65]; p=0.022) but not explained falls (OR 0.93 [0.53, 1.62]; p=0.797) during follow-up.

7.2.4 Conclusions

Two thirds of older people with OH did not report typical symptoms of light-headedness. Reporting dizziness or unsteadiness after standing did not correlate with the degree of orthostatic BP drop or recovery. Participants with asymptomatic OH did however have a significantly higher risk of unexplained falls during follow-up, and these findings have important clinical implications for the assessment of older people with falls, particularly unexplained falls.

7.3 Background

Physiological regulation of blood pressure (BP) to achieve BP stabilisation after postural change is complex, with the primary short-term control mechanism involving stretch-dependent arterial baroreceptors, afferents of the autonomic nervous system (ANS) (458).

When we stand, blood pools in the legs, reducing venous return and causing a drop in systemic BP. This leads to a reduction in firing of baroreceptors located in the carotid sinus and aortic arch, resulting in increased sympathetic and reduced parasympathetic output. This, in turn, increases systemic vascular resistance and increases cardiac output, causing a rapid recovery of BP towards pre-standing value (459). Additional mechanisms involved in BP recovery after standing include the calf muscle pump (460) and activation of the sympathetic response by venous distension in the legs (461).

Normally, one would expect BP to have recovered to pre-standing values by 30-40 seconds after standing (311). Orthostatic hypotension (OH), characterised by delayed BP recovery after standing, is a clinical manifestation of failure of these BP stabilisation mechanisms. OH is defined as a sustained drop in systolic BP by at least 20 mmHg or diastolic BP by at least 10 mmHg within 3 minutes of standing. In classical or sustained OH, BP does not recover until beyond 40 seconds after standing, suggesting significant dysregulation of the baroreceptor- ANS reflex (214).

OH affects up to 1 in 5 community-dwelling older people (323) and is a significant risk factor for falls (390), cognitive decline (348), depression (350), and early mortality (352), particularly OH persisting across time points where time to recovery of BP is more prolonged (214).

While cerebral autoregulation can buffer long-term changes in cerebral perfusion to ensure steady cerebral blood flow, acute BP changes, such as when we change posture, are less-well buffered and can lead to cerebral hypoperfusion (4). This in turn leads to dizziness or light-headedness, which can act as a warning to sit down or lie down to prevent an impending fall or syncope. In some cases, however, cerebral hypoperfusion due to hypotension may not cause symptoms (462) and it is not uncommon clinically to see patients with severe OH who do not develop any symptoms of dizziness or light-headedness (336, 463).

The aim of this study therefore is to examine the link between typical OH symptoms, specifically dizziness and unsteadiness on rising from a chair and/or walking, and orthostatic BP in a cohort of community-dwelling older people. Our hypothesis is that in older adults these typical symptoms of OH would not be significantly associated with the degree of orthostatic BP drop and that a significant proportion of older people with OH demonstrated on the active stand may be asymptomatic. Further, we hypothesised that asymptomatic OH persisting from 30 to 90 seconds confers a higher risk of unexplained falls than symptomatic OH due to the absence of prodromal or warning symptoms.

7.4 Methods

7.4.1 Study Design

This study utilises data from The Irish Longitudinal Study on Ageing (TILDA), a large population-based nationally representative sample of community dwelling older adults aged ≥ 50 years. Waves of data collection are conducted at 2-yearly intervals, and we used data from Waves 1 to 4, collected between 2009 and 2016, in this study.

This study cross-sectionally compares orthostatic BP profiles measured during the active stand at Wave 1 in participants with OH with and without co-existing symptoms of dizziness, unsteadiness when standing or unsteadiness when walking. We further clarify the longitudinal relationship between OH with and without symptoms and falls, both explained and unexplained, during 6-year follow-up.

The TILDA study design has been outlined previously (454). Briefly, the first wave of data collection (Wave 1, 2009-2011) was conducted using a stratified clustered procedure to randomly sample postal addresses from the Irish Geo-Directory (a listing of all residential addresses in Ireland) to ensure the sample was population representative. There are three components to data collection: a computer-assisted personal interview carried out by social interviewers in the participants' own home; a self-completion questionnaire completed and returned by the participant; and a comprehensive centre-based health assessment or a modified home-based health assessment carried out by trained research nurses. Subsequent waves were conducted at 2-yearly intervals.

Participants were included in this study if they were aged ≥70 years at Wave 1 and underwent a health assessment including measurement of orthostatic BP by active stand.

Participants were excluded from participation in TILDA at Wave 1 if they had a pre-existing diagnosis of dementia.

7.4.2 Orthostatic Blood Pressure Measurement

Orthostatic BP was measured during an active stand test using a Finometer® Midi as described previously (311). Briefly, participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner (<5 seconds) and were aided by a research nurse to mobilize as necessary. Systolic BP, diastolic BP, and heart rate were monitored for a further 2 minutes after standing. Throughout the recording, subjects stood quietly. After the 2-minute period, subjects were asked to report occurrence of orthostatic symptoms (dizziness or light-headedness).

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing. Time-point values were 5-second moving averages, i.e., the 30 second time point was the average of 27.5 to 32.5 seconds. This represents 'Classical' or persistent OH rather than delayed BP recovery, which has been studied previously in the TILDA cohort (347, 350).

Symptomatic OH was defined as OH alongside symptoms of dizziness / light-headedness reported during the active stand. Asymptomatic OH was OH in the absence of these symptoms.

Delayed BP Recovery after standing was defined as a drop in systolic BP ≥20 mm Hg and/or drop in diastolic BP ≥10 mm Hg at 30 seconds after standing (347).

Other variables of interest derived from the active stand were the absolute systolic BP values for each timepoint after standing from baseline to 90 seconds, at 10-second intervals, as well as the magnitude of drop in systolic BP at 30, 60 and 90 seconds after standing (baseline systolic BP minus systolic BP at 30, 60 and 90 seconds, respectively).

Participants were also asked, 'When getting up from a chair, do you feel (1) very steady, (2) slightly steady, (3) slightly unsteady, (4) very unsteady? And 'When standing, do you feel (1) very steady, (2) slightly steady, (3) slightly unsteady, (4) very unsteady?'

7.4.3 Falls

At Waves 2-5, participants were asked 'Have you had any falls since the last interview?' This was used to derive the 'Falls' variable.

If they answered, 'yes' to this, participants were then asked, 'Were any of these falls non-accidental, i.e., with no apparent or obvious reason?' This was used to inform the 'Unexplained Falls' variable. Explained falls were therefore accidental falls, due to slips or trips.

7.4.4 Other Measures

Heart disease was defined as a self-reported history of heart attack, angina, congestive cardiac failure and/or arrhythmia. The Fried Frailty score was used to define frailty status as non-frail, pre-frail or frail (403). Cognitive impairment was defined as a Mini Mental State Examination score <25. Chronic disease burden was assessed by self-report of the following conditions: cancer, liver disease, kidney disease, thyroid, arthritis and lung

disease. This was intended to broadly capture chronic disease burden across different systems given the association between OH and chronic conditions (387). History of PD, prior stroke and diabetes were also collected by self-report.

7.4.5 Statistical Analysis

Data were analysed using Stata version 14.1 (Statacorp, Texas).

Baseline characteristics of the study sample by OH were presented descriptively using proportions and mean values with 95% CIs.

Multi-level mixed effects linear regression models with systolic BP during active stand as the dependent variable were used to compare orthostatic BP in participants with OH with and without symptoms of dizziness during the active stand. These models were fully adjusted for age, sex, heart disease, frailty status, cognitive impairment and chronic disease burden and presented in graphical format. Covariates were chosen a priori, based on their hypothesised role in modifying the relationship between symptoms and OH.

Linear regression models presenting β-coefficients (with 95% CIs) were used to analyse the association of dizziness during the active stand and unsteadiness while standing or rising from a chair with drop in systolic BP at 30, 60 and 90 seconds, respectively, as dependent variables. These models were adjusted for age, sex, heart disease, frailty status and chronic disease burden.

Logistic regression models with delayed BP recovery at 30 seconds and OH as dependent variables were used to estimate odds ratios (with 95% CIs) for the association with dizziness during the active stand and unsteadiness while standing or rising from a chair.

These models were also adjusted for age, sex, heart disease, frailty status and chronic disease burden.

Logistic regression models were used to obtain odds ratios with 95% CIs for the association between OH with and without symptoms at Wave 1 and falls (explained and unexplained) during follow-up. These models were also fully adjusted for age, sex, heart disease, frailty status, cognitive impairment, chronic disease burden and length of follow-up.

7.5 Results

Almost 11% (proportion 0.11 [95% CI 0.09 – 0.13]) of the study sample (n=934, mean age 75 years, 51% female) had OH. Two thirds of participants with OH were asymptomatic (proportion 0.64 [95% CI 0.54 – 0.73]).

Table 7.1 demonstrates the differences in baseline characteristics between those without OH and those with OH with and without symptoms. There were no significant differences between those with symptomatic and asymptomatic OH in terms of age, sex, heart disease, frailty status and chronic disease burden.

Figure 7.1 plots the systolic BP after standing during the active stand in the three study groups, adjusting for age, sex, heart disease, frailty status and chronic disease burden. There was no difference in systolic BP at any time point during the active stand between those with OH causing symptoms and those who were asymptomatic. There was also no significant difference between symptomatic and asymptomatic OH groups in lowest systolic BP reached during the active stand (85.5mmHg [95% CI 74.0 – 97.0] versus 88.6 mmHg [95% CI 82.2 – 95.0]; p = 0.6078).

As shown in Table 7.2, dizziness reported during the active stand was not significantly associated with drop in systolic BP at 30 seconds (β = 1.54 [95% CI -1.27 – 4.36]; p =0.256), 60 seconds (β = 2.64 [95% CI -0.19 – 5.47]; p = 0.067) or 90 seconds (β = 2.02 [95% CI -0.91 – 4.95]; p = 0.176) after standing in fully adjusted models. Unsteadiness when rising from a chair or when standing was also not significantly associated with the degree of systolic BP drop across timepoints during the AS.

Additionally, reporting dizziness during the active stand was not associated with delayed BP recovery at 30 seconds after standing (OR 1.22 [95% CI 0.91 – 1.65]; p = 0.197) or with

OH (OR 0.90 [95% CI 0.63 – 1.53]; p = 0.931) in fully adjusted models. Similarly, unsteadiness when rising from a chair or when standing was not associated with delayed BP recovery or OH. (See Table 7.3.)

Longitudinal analysis demonstrated that almost half (424/869; 49%) of the study sample had explained falls during follow-up, while almost one quarter (201/869; 23%) reported unexplained falls. Mean follow-up time was 6.3 (95% CI 6.1 – 6.5) years. Asymptomatic OH was independently associated with a higher likelihood of unexplained falls (OR 2.01 [95% CI 1.11 – 3.65]; p = 0.022) but not explained falls (OR 0.93 [95% CI 0.53 – 1.62]; p = 0.797) during follow-up in fully-adjusted models. (See Table 7.4) Symptomatic OH was not associated with a higher risk of either explained (OR 0.90 [95% CI 0.37 – 2.19]; p = 0.812) or unexplained (OR 0.86 [95% CI 0.34 – 2.17]; p = 0.754) falls during follow-up.

Of the cohort without OH (n=835), over one third (proportion 0.37 [95% CI 0.34 – 0.41]) reported dizziness or light-headedness during the active stand. There was no difference in likelihood of unexplained falls between those with (proportion 0.22 [95%CI 0.18 – 0.28]) and without (proportion 0.22 [95% CI 0.19 – 0.26]) dizziness/light-headedness in the non-OH group. Similarly, there was little or no difference in the likelihood of fracture by report of dizziness/light-headedness within the non-OH group (proportion 0.17 [95% CI 0.13 – 0.21] in those reporting dizziness compared with proportion 0.18 [95% CI 0.14–0.21] in those who did not report dizziness).

Table 7.1 Baseline Characteristics of Study Sample

	No OH N=835	**Asymptomatic OH N = 63**	**Symptomatic OH N = 36**
Mean age (Years), with 95% CI	74.7 (74.4 – 75.0)	76.5 (75.3 – 77.7)	75.1 (73.7 – 76.4)
Age Group (Prop. With 95% CI):			
- 70-74	0.56 (0.52 – 0.59)	0.44 (0.32-0.57)	0.53 (0.36-0.69)
- 75-79	0.31 (0.28-0.34)	0.30 (0.20-0.43)	0.28 (0.15-0.45)
- ≥80	0.13 (0.11-0.16)	0.25 (0.16-0.38)	0.19 (0.9-0.36)
Female Sex (Prop with 95% CI)	0.50 (0.46-0.53)	0.54 (0.41-0.66)	0.67 (0.49-0.81)
Heart Disease (Prop with 95% CI) A	0.25 (22-28)	0.27 (0.17-0.40)	0.17 (0.07-0.33)
Fried Frailty Status (Prop with 95% CI): B			
- Non-frail	0.58 (0.55-0.62)	0.59 (0.45-0.70)	0.64 (0.46-0.78)
- Pre-frail	0.38 (0.35-0.42)	0.38 (0.27-0.51)	0.31 (0.17-0.48)
- Frail	0.04 (0.03-0.05)	0.03 (0.01-0.12)	0.06 (0.01-0.21)
Cognitive Impairment (Prop with 95% CI): C	0.06 (0.05-0.08)	0.10 (0.04-0.20)	0.11 (0.04-0.27)
Mean Seated Systolic BP, mm Hg (95% CI): D	142.0 (140.6 – 143.3)	147.3 (142.3 – 152.2)	141.9 (134.8 – 148.9)
Antihypertensive Use (Prop with 95% CI): E	0.56 (0.52 – 0.59)	0.62 (0.49 – 0.73)	0.47 (0.31 – 0.64)
Antidepressant Use (Prop with 95% CI)	0.06 (0.05 – 0.08)	0.08 (0.03 – 0.18)	0.11 (0.04 – 0.27)
Chronic Disease Number (Prop with 95% CI): F			
- None	0.49 (0.46-0.53)	0.46 (0.34-0.59)	0.47 (0.31-0.64)
- One	0.41 (0.38-0.44)	0.48 (0.35-0.60)	0.39 (0.24-0.56)
- Two or more	0.10 (0.08-0.12)	0.06 (0.02-0.16)	0.14 (0.06-0.30)
Stroke	0.03 (0.02 – 0.04)	0.05 (0.01 – 0.14)	0.00 (0.00 – 0.00)
Diabetes	0.10 (0.08 – 0.12)	0.08 (0.03 – 0.18)	0.06 (0.01 – 0.21)
Parkinson's Disease	0.00 (0.00 – 0.01)	0.00 (0.00 – 0.00)	0.06 (0.01 – 0.21)

Notes: Data presented is mean values and proportions with 95% confidence intervals.

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured using finometer during active stand.

Symptomatic OH was defined as OH alongside symptoms of dizziness / light-headedness reported during the active stand. Asymptomatic OH was OH in the absence of these symptoms.

A Heart disease was defined as a self-reported history of heart attack, angina, congestive cardiac failure and/or arrhythmia; B Participants classified as non-frail, pre-frail or frail based on Fried Criteria (weight loss, exhaustion, grip strength, walking speed and physical activity); C Defined as a Mini-Mental State Examination Score <25; D Blood Pressure measured in seated position using Omron digital cuff, measured twice and average of 2 readings taken; E Prescribed medications with Anatomical Therapeutic Classification Codes C02, 03, 07, 08 and 09; F The self-reported number of the following conditions: cancer, liver disease, kidney disease, thyroid, arthritis, lung disease.

Table 7.2 Linear Regression Models with Systolic Blood Pressure Drop at 30, 60 and 90 seconds as dependent variables.

	SBP Drop at 30s		SBP Drop at 60s		SBP Drop at 90s	
	B-Coefficient (95% CI)	**p-value**	**B-Coefficient (95% CI)**	**p-value**	**B-Coefficient (95% CI)**	**p-value**
Dizzy during Active Stand						
- Unadjusted	1.27 (-1.56 – 4.10)	0.378	2.38 (-0.44 – 5.20)	0.098	1.70 (-1.21 – 4.62)	0.252
- Adjusted	1.54 (-1.27 – 4.36)	0.256	2.64 (-0.19 – 5.47)	0.067	2.02 (-0.91 – 4.95)	0.176
Unsteady Rising from Chair						
- Unadjusted	1.26 (-2.63 – 5.15)	0.526	1.09 (-2.79 – 4.97)	0.580	0.13 (-3.88 – 4.14)	0.948
- Adjusted	1.22 (-2.89 – 5.34)	0.545	1.26 (-2.88 – 5.41)	0.476	0.99 (-3.29 – 5.28)	0.650
Unsteady when Standing						
- Unadjusted	4.98 (-0.23 – 10.19)	0.061	3.11 (-2.09 – 8.31)	0.241	1.36 (-4.02 – 6.74)	0.620
- Adjusted	4.65 (-0.98 – 10.28)	0.105	3.40 (-2.27 – 9.07)	0.240	2.08 (-3.78 – 7.95)	0.486

Notes:

Linear regression models reporting β-coefficients and 95% confidence intervals with systolic blood pressure drop at 30, 60 and 90 seconds as dependent variables.

Systolic dop at specific time points is difference between pre-standing baseline systolic blood pressure and systolic blood pressure at 30, 60 and 90 seconds after standing as measured with finometer during active stand.

Abbreviations: SBP = systolic blood pressure; s = seconds; CI = Confidence Interval.

Analyses adjusted for age, sex, heart disease, Fried Frailty status, Diabetes, Parkinson's Disease, stroke and number of chronic diseases in adjusted models.

Dizziness during active stand, unsteadiness rising from a chair and unsteadiness when standing were elicited by self-report.

Table 7.3 Logistic Regression Models with Delayed Blood Pressure Recovery and Orthostatic Hypotension as dependent variables.

	Delayed BP Recovery at 30s		Orthostatic Hypotension	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Dizzy during Active Stand				
- Unadjusted	1.19 (0.88 – 1.59)	0.254	0.96 (0.62 – 1.48)	0.864
- Adjusted	1.22 (0.91 – 1.65)	0.197	0.98 (0.63 – 1.53)	0.931
Unsteady Rising from Chair				
- Unadjusted	1.32 (0.90 – 1.94)	0.158	1.59 (0.95 – 2.67)	0.080
- Adjusted	1.28 (0.84 – 1.96)	0.253	1.64 (0.91 – 2.94)	0.098
Unsteady when Standing				
- Unadjusted	1.47 (0.90 – 2.41)	0.123	0.98 (0.45 – 2.09)	0.950
- Adjusted	1.45 (0.83 – 2.54)	0.198	0.91 (0.38 – 2.17)	0.826

Notes:

Logistic regression models reporting odds ratios with 95% confidence intervals with delayed blood pressure recovery at 30 seconds and orthostatic hypotension as dependent variables.

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing. Delayed BP Recovery after standing was defined as a drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30 seconds after standing.

Abbreviations: SBP = systolic blood pressure; s = seconds; CI = Confidence Interval.

Analyses adjusted for age, sex, heart disease, Fried Frailty status, Diabetes, Parkinson's Disease, stroke and number of chronic diseases in adjusted models.

Dizziness during active stand, unsteadiness rising from a chair and unsteadiness when standing were elicited by self-report.

Table 7.4 Logistic Regression Model Reporting Odds Ratios with Unexplained Falls as Dependent Variable

	Odds Ratio (95% Confidence Interval)	**z**	**p-value**
OH: Ref= No OH			
- Asymptomatic	2.01 (1.11 – 3.65)	2.29	0.022
- Symptomatic	0.86 (0.34 – 2.17)	-0.31	0.754
Age: Ref = 70-74 years			
- 75-79 years	1.31 (0.90 – 1.89)	1.43	0.154
- ≥ 80 years	1.36 (0.83 – 2.23)	1.33	0.183
Female Sex	1.24 (0.88 – 1.76)	1.21	0.226
Heart Disease A	1.20 (0.82 – 1.77)	0.93	0.350
Frailty Status: Ref = Non-Frail B			
- Pre-frail	1.95 (1.37 – 2.77)	3.74	<0.001
- Frail	4.90 (2.13 – 11.27)	3.73	<0.001
Cognitive Impairment C	1.65 (0.72 – 3.76)	1.19	0.233
Chronic Disease Number: Ref = 0 D			
- 1 Chronic Disease	1.17 (0.81 – 1.68)	0.82	0.412
- ≥2 Chronic Diseases	1.43 (0.75 – 2.71)	1.09	0.277
Stroke	1.71 (0.68 – 4.31)	1.13	0.259
Diabetes	1.07 (0.57 – 1.99)	0.21	0.837
Parkinson's Disease	2.95 (0.51 – 16.91)	1.21	0.225
Follow-Up (Years)	1.22 (1.14 – 1.32)	5.32	<0.001

Notes:

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured using finometer during active stand. Symptomatic OH was defined as OH alongside symptoms of dizziness / light-headedness reported during the active stand. Asymptomatic OH was OH in the absence of these symptoms.

Abbreviations: OH + Orthostatic Hypotension; Ref = reference value.

A Heart disease was defined as a self-reported history of heart attack, angina, congestive cardiac failure and/or arrhythmia; B Participants classified as non-frail, pre-frail or frail based on Fried Criteria (weight loss, exhaustion, grip strength, walking speed and physical activity); C Defined as a Mini-Mental State Examination Score <25; D The self-reported number of the following conditions: cancer, liver disease, kidney disease, thyroid, arthritis, lung disease.

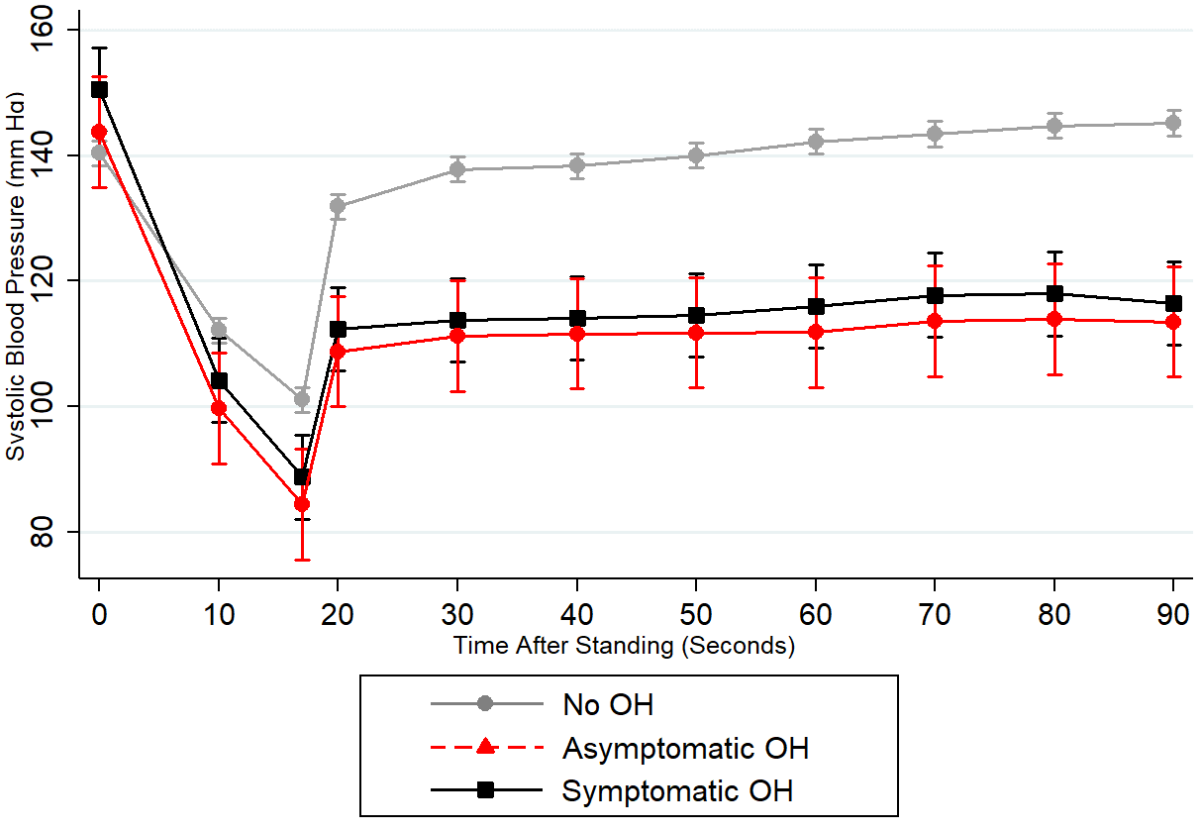

Figure 7.1 Systolic Blood Pressure during Active Stand by OH with and without symptoms of dizziness

Notes:

Graphical output from multi-level mixed effects linear regression models with systolic blood pressure (with 95% confidence intervals) during active stand as dependent variable to compare orthostatic BP in participants with OH with and without symptoms of dizziness during the active stand.

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured using finometer during active stand. Symptomatic OH was defined as OH alongside symptoms of dizziness / light-headedness reported during the active stand. Asymptomatic OH was OH in the absence of these symptoms.

Abbreviations: OH = Orthostatic Hypotension; CI = Confidence Interval.

Analyses adjusted for age, sex, heart disease, Fried Frailty status, diabetes, Parkinson's Disease, stroke and number of chronic diseases.

7.6 Discussion

This study demonstrates that over 10% of a cohort of more than 900 community-dwelling people aged ≥70 years had OH demonstrated during active stand, i.e., a sustained drop of 20 mmHg in systolic BP and/or 10 mmHg in diastolic BP at 30, 60 and 90 seconds after standing. Of those with OH, two thirds were asymptomatic and did not report dizziness during the AS.

There was no significant difference in terms of absolute BP parameters during the active stand in participants with OH who reported symptoms of dizziness compared to those without symptoms. Similarly, reporting dizziness during the AS was not associated with a greater drop in systolic BP at 30, 60 or 90 seconds or with binary variables reporting the presence / absence of delayed BP recovery and OH. Further, reporting unsteadiness when rising from a chair or when standing was also not associated with a greater orthostatic drop in systolic BP during the active stand or with OH.

Participants with asymptomatic OH did however have a significantly higher risk of unexplained falls during follow-up, while those with symptomatic OH did not. Asymptomatic OH did not increase the risk of explained falls during follow-up.

OH represents severe dysregulation of BP stabilisation mechanisms, and one might expect that this would be associated with significant symptoms of postural dizziness (435). While not yet well-defined, the concept of hypotensive unawareness in the setting of OH has been described in smaller studies previously, however. For example, almost 20% of a cohort of participants with OH due to autonomic failure did not report postural dizziness, while 88% endorsed non-specific symptoms such as weakness, lethargy or fatigue on changing posture (464). Further, less than half of participants with severe OH identified

during tilt table testing reported typical symptoms of postural dizziness, while one third were asymptomatic entirely (335).

This lack of awareness of hypotension has important implications clinically. Rather than presenting with falls in the context of postural dizziness, people with severe asymptomatic OH are more likely to present with falls without warning or prodrome, raising the suspicion of an arrhythmogenic cause for which the patient may undergo inappropriate testing (7). Absence of symptoms also makes it more difficult to identify OH as the primary cause of falls, especially when assessment involves less sensitive methods of orthostatic BP measurement such as lying/sitting to standing BP (320). Our findings also raise the issue of how older people with asymptomatic OH should be managed, as addressing postural BP drops in the absence of dizziness or light-headedness may prevent future falls and fracture. Importantly, studies have also shown previously that asymptomatic OH appears to confer similar risks in terms of non-falls related adverse events. For example, over one-third of patients with OH due to PD were asymptomatic, and asymptomatic OH was associated with similar impairments in physical functioning when compared with symptomatic OH in this cohort (465). Further, asymptomatic and symptomatic OH also appear to confer similar risk of cognitive decline in patients with PD (466).

There are several possible reasons why older people with OH do not exhibit typical dizzy symptoms. The sensation of dizziness is somewhat subjective and rather than feeling dizzy, light-headed or unsteady in the context of hypotension, older people may instead experience leg weakness or neck pain, which may actually represent 'typical' OH symptoms in this cohort and were not captured in this study (467). In any case, only 50–70% of acutely unwell older people present with so-called typical symptoms of their

underlying illness (468, 469). Further, as seen in problems with gait and balance (398), older people tend to compensate for gradual-onset conditions such as OH and may therefore have less awareness of symptoms or at least be less likely to report them as a problem. It has also been suggested that lack of awareness of hypotension in OH may be related to hypoperfusion-related changes in the reticular activating system, leading to inattention to the warning signs of dizziness or presyncope (344). Consistent with prior studies (470), this study also demonstrates a strong association between frailty status and unexplained falls, with a two- and fivefold increased likelihood of unexplained falls in those with pre-frailty and frailty, respectively. While OH was more prevalent in the cohort with frailty, there was no significant association with asymptomatic OH and frailty. The study was, however, not powered to detect this association, given the relatively low prevalence of frailty in the study sample.

There are some limitations of this study that should be noted. Variables including falls, heart disease and chronic diseases are based on self-report and may therefore be subject to recall bias. Linkage of TILDA data with healthcare services records pertaining to admissions with falls and fracture was unfortunately not possible. This applies equally across all groups in the study, however. At enrolment in TILDA, participants with a history of dementia were excluded, reducing the likelihood of cognitive impairment affecting recall. It is still possible that participants with undiagnosed dementia were included; however, although it should also be noted that there was no significant difference in the proportion of participants with cognitive impairment across the three study groups. Symptoms of OH were not measured using a standardised questionnaire, which may mean that less typical symptoms of OH and severity of dizziness/ light-headedness were not captured. Participants were, however, asked directly about symptoms during the

active stand, linking symptoms more closely to orthostatic BP changes. It was not feasible to administer a questionnaire during the active stand. We did not capture Initial OH in the study, as the focus was on delayed BP recovery rather than the large immediate BP drops seen in initial OH. Furthermore, we also only included BP measurements at 30, 60 and 90seconds post-standing. While this would capture all participants with classical OH, it would possibly omit those with delayed OH, which is also associated with falls and adverse outcomes (471). Strengths of the study include the continuous measurement of orthostatic BP with a finometer, the well described cohort of community-dwelling older people and the robust follow-up of 6 years.

7.7 Conclusion

In conclusion, this study demonstrates that two-thirds of older people with persistent OH identified during an active stand were asymptomatic and did not report dizziness or light-headedness. Participants with asymptomatic OH had a higher risk of unexplained falls than those who reported symptoms. These findings have important clinical implications for the assessment of older people with falls, particularly those without prodrome and unexplained falls, and for clinical trials assessing OH as reported symptoms correlate poorly with continuously measured orthostatic BP. Further work delineating the spectrum of symptoms in the setting of severe OH and determining how best to measure them is warranted.

Declarations

The authors have no conflicts of interest to declare.

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Chapter Eight – Results

8.1 Paper Three – Key Findings

- In total, one fifth of 2,478 community dwelling participants ≥55 years had OH demonstrated during active stand.

- Postural drop in TSI was significantly greater in participants with OH at 30, 60, and 90 seconds after standing compared to those with no OH.

- In fully adjusted models, those with OH and those with greater postural TSI drops were independently associated with future unexplained falls after 4 years.

- The combination of OH and co-existent greater hypoperfusion (TSI drops ≥75th centile) together were strongly associated with future unexplained falls while those with OH and no/ smaller TSI drops were not.

- TSI drops without OH did not confer a future risk of unexplained falls.

- These findings have important clinical implications for the assessment of older people with falls – particularly unexplained falls.

Cerebral Hypoperfusion and Future Falls Risk among Community Dwelling Older Adults with Orthostatic Hypotension.

8.2 Abstract

8.2.1 Introduction

Falls pose a significant health risk for older adults, affecting about a third of those over 65 annually, with 10-20% resulting in injury or hospitalisation. While most falls are multifactorial, unexplained falls often overlap with syncope. Orthostatic hypotension (OH), characterised by a significant drop in BP upon standing, is a potent risk factor for falls. Cerebral hypoperfusion is regarded as the mechanism by which OH contributes to falls risk. Despite this hypothesis little work has looked at the direct interaction between OH, cerebral perfusion and falls.

8.2.2 Methods

Real-time frontal lobe cerebral oxygenation by NIRS reporting TSI and continuous beat-to-beat orthostatic BP were measured in parallel (Finometer) during active standing among participants aged ≥55 at wave 3 of TILDA. OH was defined as a persisting drop in SBP ≥20mmHg and/or drop in DBP ≥10mmHg at 30, 60 or 90 seconds post standing. A drop in TSI from baseline ≥75th centile at 30 seconds informed the "greater TSI drop" variable in longitudinal analysis. Multilevel mixed effects linear regression models assessed the association between change in TSI from baseline and OH while multilevel logistic regression models assessed the longitudinal relationship between OH, cerebral perfusion and future unexplained falls at 4 years follow up (waves 4-5).

8.2.3 Results

One fifth of participants had OH and were more likely to be older and have cardiovascular disease. Drops in TSI from baseline after standing were significantly greater in those with OH at 30 (β=0.31 [CI 0.14-0.48]; p<0.001), 60 (β=0.41 [CI 0.23-0.59]; p<0.001), and 90 (0.46 [CI 0.26-0.64]; p<0.001) seconds in fully adjusted models. The combination of OH and greater TSI drops was strongly associated with future unexplained falls (OR 2.16 [CI 1.30-3.60]; p=0.003), while OH and lower TSI drops were not (OR 1.25 [CI 0.83-1.89]; p=0.288).

8.2.4 Conclusions

These findings confirm that OH and future falls risk is modified by co-existent significant cerebral hypoperfusion. This may have important clinical implications for the risk assessment of older people with falls, particularly those that are unexplained and may inform primary and secondary falls prevention strategies.

8.3 Background

Falls are the most common cause of injury and associated morbidity and mortality in older people (12) occurring in a third of adults over 65 years annually (13). Of those, 10-20% will result in injury, presentation to hospital and/ or death (14). Most falls are considered multifactorial though there is considerable overlap with other cardiovascular disorders such as syncope (7, 25) – particularly in older individuals where hypoperfusion is responsible for unexplained falls, those not due to a trip or a slip (79).

Standing is a common stressor to the mechanisms regulating BP and CBF with the average person standing from a sitting or lying position up to seventy times per day (304). Cerebral autoregulation (CA) is the homeostatic capacity of the cerebrovascular system to maintain a constant rate of CBF during changes in arterial BP and cerebral perfusion pressure (85). While research involving healthy older adults suggests the preservation of CA with age (4), certain older people demonstrate reduced resting CBF (220), elevated cerebrovascular resistance (221), reduced NO production (223) and diminished cerebrovascular reserve (233) and may manifest impairment in CA. Consequently, they may face an elevated risk of hypoperfusion during orthostatic stress events like changes in posture.

OH is defined as a sustained drop in SBP by at least 20mmHg and/ or 10mmHg DBP within three minutes of standing (310). In midlife, OH affects five percent of individuals (324) rising to approximately 18-19 percent in those aged over 80 (311). A recent systematic review (323) found that it affects about one in five community dwelling older adults over 60 and one in four of those in residential long term care. OH is linked to a myriad of poor health outcomes including impaired cognition (348, 381), depression (350), cardiovascular disease (353), early mortality (352) and is a well-established risk factor for falls (346).

Therefore, its assessment and management is emphasised in the recent World Guidelines for Falls Prevention (11).

The principal causative pathway proposed for falls in OH postulates that falls are the direct consequence of inadequate brain perfusion upon standing (391). However, there is a paucity of research in this area linking cerebral hypoperfusion in OH to future falls risk.

The aim of this study, therefore, is to investigate the association between declines in CBF on standing and OH in a cohort of community dwelling older people. The hypothesis is that those with OH would have significantly greater CBF drops than those without OH. Further, it was postulated that OH individuals with greater cerebral hypoperfusion on standing confers a higher risk of unexplained falls than those with smaller perfusion drops.

8.4 Methods

8.4.1 Study Design

This study examines the association between OH and frontal lobe cerebral perfusion in a large cohort of community-dwelling older people participating in the Irish Longitudinal Study on Ageing (TILDA). Further, we assess whether orthostatic changes in cerebral perfusion modify the association between OH and future unexplained falls.

The TILDA study design has been outlined previously (454). Briefly, there were three components to data collection: a computer-assisted personal interview carried out by social interviewers in the participants' own home; a self-completion questionnaire completed and returned by the participant; and a comprehensive centre-based health assessment or a modified home-based health assessment carried out by trained research nurses. Study waves were conducted at 2-yearly intervals. We analysed data from the third, fourth and fifth waves of TILDA collected between 2014 and 2018.

Participants were included in the cross-sectional analysis of this study if they were aged ≥ 55 years and underwent a complete health assessment at Wave 3 including measurement of orthostatic BP and frontal lobe perfusion by NIRS. For the longitudinal component of the study, follow-up was 4 years, with a minimum required follow-up time of 2 years (Wave 4).

8.4.2 Orthostatic Blood Pressure and Cerebral Perfusion

Real-time frontal lobe cerebral oxygenation was measured with a portable continuous wave near infrared spectroscopy (NIRS) system, using spatially resolved spectroscopy, as outlined previously (151, 380).

Changes in frontal lobe oxyhaemoglobin and deoxyhaemoglobin were measured continuously, to derive the Tissue Saturation Index (TSI) defined as (oxyhaemoglobin)/ (oxyhaemoglobin + deoxyhaemoglobin) and expressed as a percentage (8). Continuous orthostatic BP was measured in parallel with this by active stand using a Finometer® Midi as described previously (311).

Participants lay in the supine position for 10 minutes in a quiet room, before standing as quickly as possible and were aided in this by a research nurse as necessary. After standing, systolic BP, diastolic BP, heart rate, oxy- and deoxyhaemoglobin and TSI were monitored for a further 3 minutes. Throughout the recording, subjects stood quietly.

OH was defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mmHg at each of the 30, 60 and 90 second timepoints after standing. Smoothing was applied via a 10-second moving average filter (±5 seconds) and an 11-point median filter to remove discrete artefacts.

TSI was recorded continuously during the active stand but as OH is typically measured at 30, 60 and 90 seconds, we focused primarily on TSI at these time points in this study. A drop in TSI from baseline ≥75th centile at 30 seconds was used to inform the 'greater drop in TSI' variable for longitudinal analysis.

8.4.3 Falls

At waves 3, 4 and 5, participants were asked 'Have you had any falls since the last interview?' and if they answered "yes" to this, participants were then asked, 'Were any of

these falls non-accidental, i.e., with no apparent or obvious reason?' Answers from waves 4 and 5 were used to inform the 'Unexplained Falls' variable.

8.4.4 Other Measures

Alcohol excess was assessed with the Cut Down, Angry, Guilty, Eye Opener (CAGE) alcohol scale (472). Heart disease was defined as self-report of myocardial infarction, cardiac failure, or angina. Depressive symptoms were measured with the 8-item Centre for Epidemiological Studies Depression Scale (CES-D), with a score ≥9 indicating clinically significant symptoms (473). Cognitive impairment was measured with the Mini Mental State Examination (MMSE) Scale, with a score <25 indicating cognitive impairment (474).Parkinson's disease and history of stroke were elicited by self-report. Polypharmacy was defined as being prescribed ≥5 medications. Chronic disease burden was assessed as a count of the self-report of the following chronic diseases: cancer, liver disease, kidney disease, thyroid disease, arthritis and lung disease.

8.4.5 Statistical Analysis

Data were analysed using Stata 14 (Statacorp, Texas).

Baseline characteristics were presented as mean values (for continuous variables) or proportions (for binary variables) with 95% confidence intervals.

Multilevel regression models with change in TSI from baseline as the dependent variable were used to compare TSI data across specific time points after standing by orthostatic hypotension status. These models assess the effect of the two-way interaction between

OH and time on changes in TSI. Further, linear regression models, reporting β-coefficients with 95% confidence intervals, assessed the association between OH and changes in TSI at specific time points.

For the longitudinal analysis, logistic regression models reporting odds ratios with 95% confidence intervals were used to assess the relationship between OH, cerebral perfusion and future unexplained falls. Two-way interaction models involving OH and Greater drop in TSI (i.e., drop from baseline ≥75th centile) were used to assess how significant co-occurring cerebral perfusion deficits modified the association between OH and future unexplained falls.

All regression models were adjusted for age (in groups 55-64 years, 65-74 years and ≥75 years), sex, educational attainment (primary, secondary, and tertiary), CAGE Alcohol Score (<2, ≥2 or 'did not answer'), heart disease, prior stroke, Parkinson's disease, polypharmacy, depressive symptoms, cognitive impairment, and chronic disease burden (none, one or ≥2). Covariates were chosen a priori based on their likelihood of modifying the relationship between OH and cerebral perfusion measures. Longitudinal analysis was additionally adjusted for prior unexplained falls (i.e. those occurring between Waves 2 and 3).

8.4.6 Ethics

The TILDA study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki.

8.5 Results

8.5.1 Baseline Characteristics

One fifth of the 2,478 participants had OH (Proportion 0.20 [95% CI 0.18 – 0.22]). Participants with OH were older and more likely to be aged ≥ 75 years and have heart disease and polypharmacy. There were no significant differences between groups in terms of sex, educational attainment, alcohol excess, history of stroke, Parkinson's disease, chronic disease burden, cognitive impairment, and depression (Table 8.1).

Table 8.1 Baseline Characteristics by Orthostatic Hypotension

	No OH (n =1,983)	OH (n = 495)
Mean age (Years), with 95% CI	65.38 (65.07 – 65.68)	68.28 (67.61 – 68.95)
Age Group (Prop. With 95% CI)		
- **55-64 Years**	0.51 (0.49 – 0.53)	0.35 (0.30 – 0.39)
- **65 – 74 Years**	0.38 (0.36 – 0.40)	0.43 (0.39 – 0.48)
- **≥ 75 Years**	0.11 (0.10 – 0.13)	0.22 (0.19 – 0.26)
Female Sex (Prop with 95% CI)	0.53 (0.51 – 0.55)	0.50 (0.46 – 0.55)
Educational Attainment (Prop with 95% CI):		
- **Primary**	0.17 (0.15 – 0.18)	0.22 (0.18 – 0.25)
- **Secondary**	0.40 (0.38 – 0.42)	0.39 (0.35 – 0.44)
- **Tertiary**	0.43 (0.41 – 0.46)	0.39 (0.35 – 0.44)
CAGE Alcohol Score (Prop with 95% CI):		
- **<2**	0.78 (0.76 – 0.80)	0.78 (0.74 – 0.82)
- **≥2**	0.12 (0.11 – 0.14)	0.12 (0.10 – 0.16)
- **Did Not Answer**	0.10 (0.09 – 0.11)	0.09 (0.07 – 0.12)
Heart Disease (Prop with 95% CI) A	0.07 (0.06 – 0.08)	0.11 (0.08 – 0.14)
Depressive Symptoms (Prop with 95% CI) B	0.08 (0.07 – 0.09)	0.07 (0.04 – 0.09)
Parkinson's Disease (Prop with 95% CI)	0.00 (0.00 – 0.01)	0.01 (0.00 – 0.02)
Stroke (Prop with 9%% CI)	0.00 (0.00 – 0.01)	0.00 (0.00 – 0.01)
Cognitive Impairment (Prop with 95% CI) C	0.01 (0.01 – 0.02)	0.02 (0.01 – 0.03)
Polypharmacy (Prop with 95% CI) D	0.18 (0.17 – 0.20)	0.25 (0.22 – 0.29)
Chronic Disease Number (Prop with 95% CI) E	0.54 (0.52 – 0.56)	0.56 (0.52 – 0.61)
- None	0.37 (0.34 – 0.39)	0.33 (0.29 – 0.37)
- One	0.09 (0.08 – 0.10)	0.11 (0.08 – 0.14)
- Two or more		
Follow-Up Duration (Prop with 95% CI)		
- **Baseline Only**	0.04 (0.03 – 0.05)	0.05 (0.03 – 0.07)
- **2 years (Wave 4)**	0.08 (0.07 – 0.09)	0.10 (0.07 – 0.13)
- **4 years (Wave 5)**	0.88 (0.87 – 0.90)	0.85 (0.82 – 0.88)

Notes:

Abbreviations: CI = confidence interval; Prop = proportion; CAGE = Cut Down, Angry, Eye opener, Guilty Scale.

A Heart disease was defined as self-report of myocardial infarction, cardiac failure, or angina; B Depressive symptoms defined as 8-item Centre for Epidemiological Studies Depression Scale ≥9; C Cognitive impairment defined as Mini Mental State Examination Score <25; D Polypharmacy defined as prescribed 5 or more medications; E Chronic disease burden defined as self-report of the following chronic diseases: cancer, liver disease, kidney disease, thyroid disease, arthritis, lung disease.

Orthostatic Hypotension defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured by finometer during active stand.

8.5.2 Cerebral Perfusion Changes in Orthostatic Hypotension

As shown in Figure 8.1, multilevel models with TSI as the dependent variable across specific time points demonstrate that the drop from baseline TSI (i.e. the postural drop in the surrogate marker of cerebral perfusion) was significantly higher in participants with OH at 30, 60 and 90 seconds after standing in fully adjusted models.

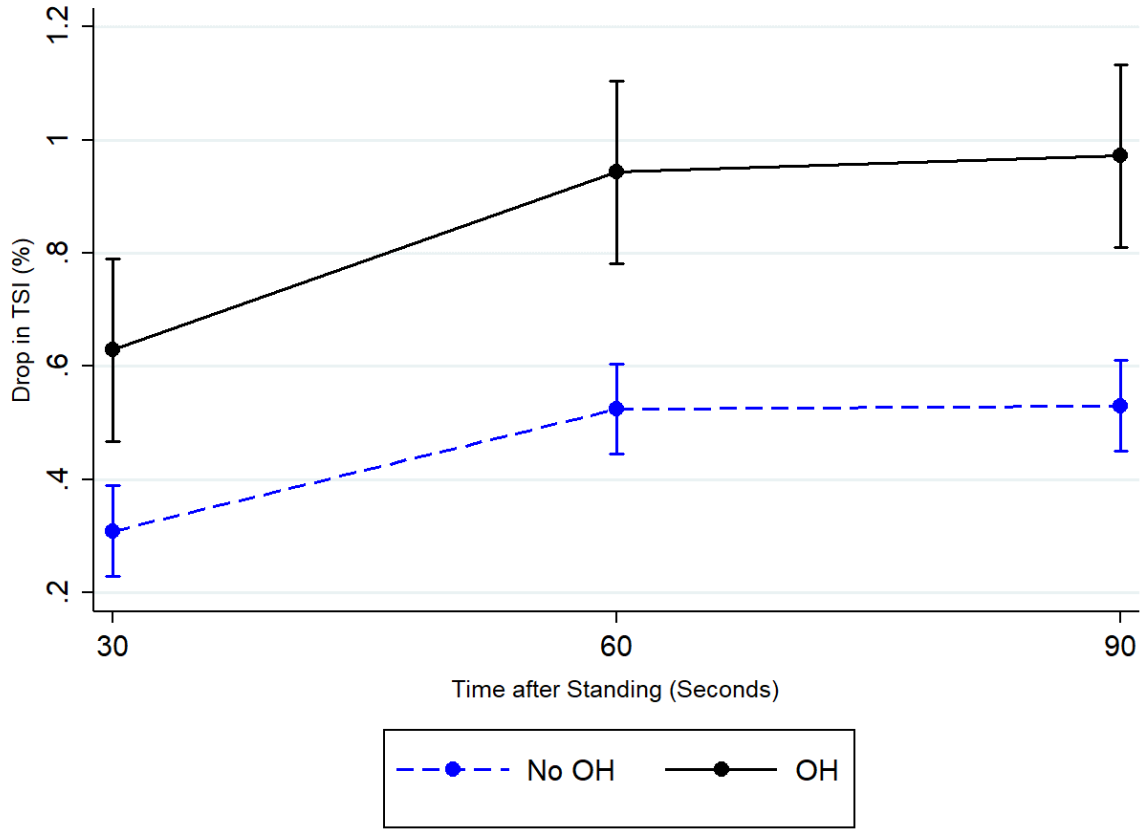


Figure 8. 1 Drop in Tissue Saturation Index after Standing by Orthostatic Hypotension

Notes:
Abbreviations: TSI = tissue saturation index; OH = orthostatic hypotension.
Output from multilevel modelling with change in TSI from baseline as dependant variable at specific time points during active stand, by orthostatic hypotension.
TSI defined as (oxyhaemoglobin)/ (oxyhaemoglobin + deoxyhaemoglobin) X 100 and measured during active stand with near-infrared spectroscopy. Orthostatic Hypotension defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured by finometer during active stand.
Analysis adjusted for age, sex, educational attainment, alcohol excess (measured with CAGE), heart disease (myocardial infarction, angina, cardiac failure), depressive symptoms (measured by CES-D) and cognitive impairment (Mini Mental State Examination Score <25) and chronic disease burden.

Linear regression models further demonstrated the significant independent association between OH and the drop in TSI from baseline at 30, 60 and 90 seconds after standing. (See Table 8.2.)

Table 8.2 Linear Regression Models with Drop in Tissue Saturation Index after Standing as Dependant variable and Orthostatic Hypotension as Predictor Variable

	TSI Drop at 30s		TSI Drop at 60s		TSI Drop at 90s	
Orthostatic Hypotension	**β-Coefficient (95%CI)**	**p-value**	**β-Coefficient (95%CI)**	**p-value**	**β-Coefficient (95%CI)**	**p-value**
- Unadjusted	0.31 (0.14 – 0.48)	<0.001	0.41 (0.23 – 0.59)	<0.001	0.44 (0.25 – 0.63)	<0.001
- Adjusted	0.31 (0.14 – 0.49)	<0.001	0.41 (0.23 – 0.59)	<0.001	0.46 (0.26 – 0.64)	<0.001

Notes:

Abbreviations: TSI = tissue saturation index; CI = confidence interval.

Output from linear regression models with change in TSI from baseline as dependant variable at specific time points during active stand, by orthostatic hypotension.

TSI defined as (oxyhaemoglobin)/ (oxyhaemoglobin + deoxyhaemoglobin) X 100 and measured during active stand with near-infrared spectroscopy. Orthostatic Hypotension defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured by finometer during active stand.

Analysis adjusted for age, sex, educational attainment, alcohol excess (measured with CAGE), heart disease (myocardial infarction, angina, cardiac failure), prior stroke, Parkinson's disease, polypharmacy (≥5 medications), depressive symptoms (measured by CES-D) and cognitive impairment (Mini Mental State Examination Score <25) and chronic disease burden.

8.5.3 Orthostatic Hypotension, Cerebral Perfusion and Future Unexplained Falls

Mean follow-up time was 3.66 (95% CI 3.63 – 3.70) years. Just over one tenth of participants (Proportion 0.11 [95% CI 0.10 – 0.12]) were lost to follow-up after the initial assessment in the study (TILDA Wave 3).

Almost one tenth (proportion 0.09 [95% CI 0.08 – 0.10]) of participants reported an unexplained fall during follow-up.

In fully-adjusted models, OH (OR 1.45 (95% CI 1.04 – 2.02); p = 0.027) and highest TSI Drop (OR 1.38 [95% CI 1.01 – 1.88]; p = 0.045) were independently associated with future unexplained falls, when analysed in separate regression models.

As shown in Table 8.3 and Figure 8.2, when analysed in a two-way interaction model, the combination of OH and high TSI Drop together are strongly associated with future unexplained falls (OR 2.16 [95% CI 1.30 – 3.60]; p = 0.003), while OH without a TSI Drop and a TSI drop without OH are not.

Table 8. 3 Logistic Regression with Future Unexplained Falls as Dependant Variable, analysing Two-Way Interaction between OH and Cerebral Perfusion During Active Stand

Dependant Variable: Unexplained Falls	**Odds Ratio with 95% confidence interval**	**p-value**
2-way interaction Model:		
- **No OH present and lower drop in Cerebral Perfusion**	*Reference Value*	
- **OH present, but lower drop in Cerebral Perfusion**	1.25 (0.83 – 1.89)	0.288
- **No OH present but greater drop in Cerebral Perfusion**	1.25 (0.85 – 1.83)	0.262
- **Both OH and greater drop in Cerebral Perfusion**	2.16 (1.30 – 3.60)	0.003
Age Category (Years):		
- **55-64**	*Reference Value*	
- **65-74**	1.53 (1.09 – 2.14)	0.014
- **≥75**	2.05 (1.33 – 3.17	0.001
Female Sex	1.12 (0.83 – 1.52)	0.463
Educational Attainment:		
- **Primary**	*Reference Value*	
- **Secondary**	0.87 (0.58 – 1.29)	0.482
- **Tertiary**	0.87 (0.58 – 1.30)	0.492
CAGE Alcohol Score:		
- **<2**	*Reference Value*	
- **≥2**	1.17 (0.74 – 1.85)	0.495
- **Did Not Answer**	1.19 (0.76 – 1.88))	0.443
Heart Disease A	1.15 (0.70 – 1.89)	0.592
Depressive Symptoms B	2.29 (1.47 – 3.55)	<0.001
Parkinson's Disease	0.73 (0.08 – 6.37)	0.775
Prior Stroke	5.71 (0.59 – 5.97)	0.132
Cognitive Impairment C	1.10 (0.35 – 3.46)	0.867
Polypharmacy D	1.47 (1.03 – 2.09)	0.033
Chronic Disease Number: E		
- **None**	*Reference Value*	
- **1**	1.16 (0.84 – 1.59)	0.368
- **≥2**	0.99 (0.60 – 1.65)	0.980
Prior Unexplained Falls F	3.58 (2.20 – 5382)	<0.001

Notes:

Abbreviations: OH = orthostatic hypotension.

A Heart disease was defined as self-report of myocardial infarction, cardiac failure, or angina; B Depressive symptoms defined as 8-item Centre for Epidemiological Studies Depression Scale ≥9; C Cognitive impairment defined as Mini Mental State Examination Score <25; D Polypharmacy was defined as 5 or more prescribed medications; E Chronic disease burden defined as self-report of the following chronic diseases: cancer, liver disease, kidney disease, thyroid disease, arthritis, lung disease. F Prior unexplained falls related to the 2 years between Waves 2 and 3, by self-report.

TSI defined as (oxyhaemoglobin)/ (oxyhaemoglobin + deoxyhaemoglobin) X 100 and measured during active stand with near-infrared spectroscopy. Greater drop in TSI defined as at/above 75th centile for drop in TSI from baseline at 30s after standing.

Orthostatic Hypotension defined as a persisting drop in systolic BP ≥20 mm Hg and/or drop in Diastolic BP ≥10 mm Hg at 30, 60 and 90 seconds after standing, measured by finometer during active stand.

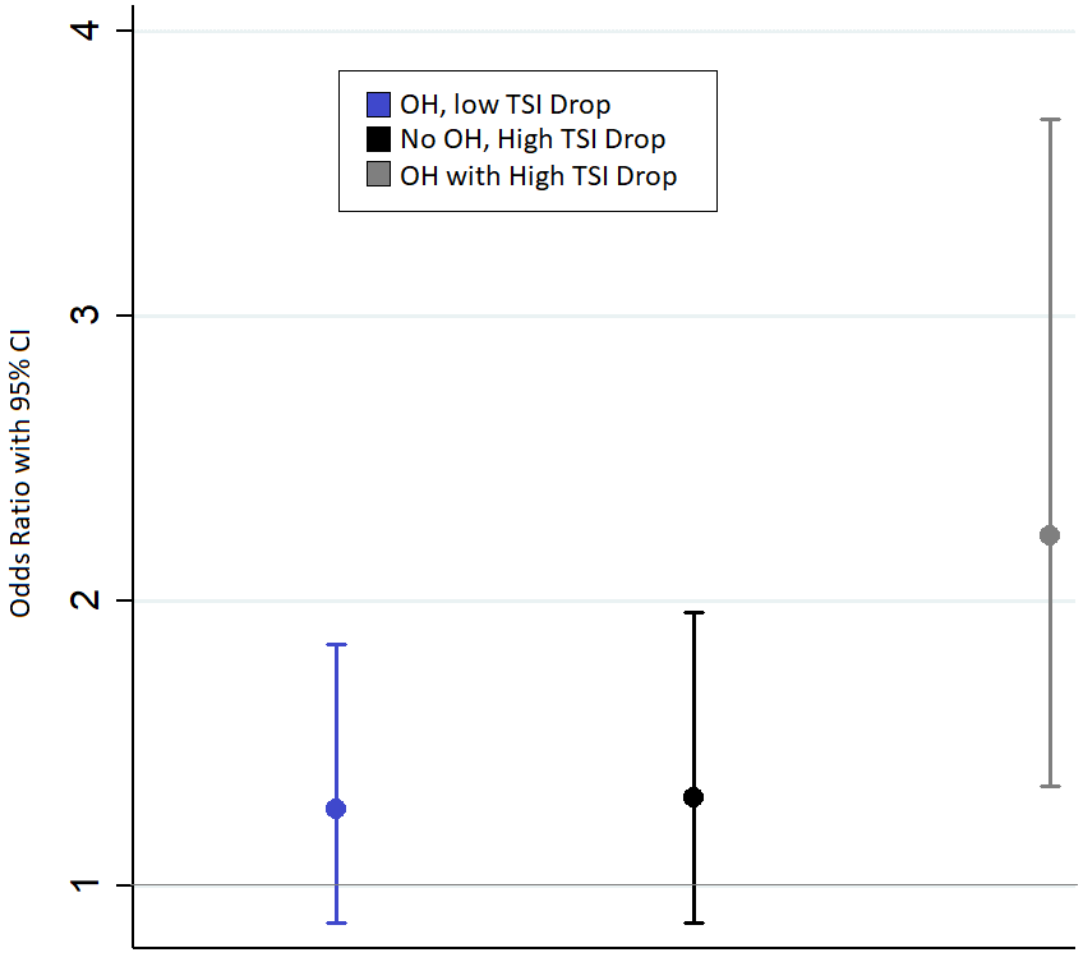


Figure 8.2 Two-Way Interaction Between OH and Cerebral Perfusion and Association with Future Unexplained Falls

Note: Abbreviations: OH = orthostatic hypotension; TSI = tissue saturation index; CI = confidence interval.

Output from logistic regression models with future unexplained falls as dependant variable, analysing two-way interaction between OH and Cerebral Perfusion (TSI) During Active Stand

TSI defined as (oxyhaemoglobin)/ (oxyhaemoglobin + deoxyhaemoglobin) X 100 and measured during active stand with near-infrared spectroscopy. High drop in TSI defined as at/above 75th centile for drop in TSI from baseline at 30s after standing.

Orthostatic Hypotension defined as a persisting drop in systolic BP ≥20 mmHg and/or drop in Diastolic BP ≥10 mmHg at 30, 60 and 90 seconds after standing, measured by finometer during active stand.

Analysis adjusted for age, sex, educational attainment, alcohol excess (measured with CAGE), heart disease (myocardial infarction, angina, cardiac failure), depressive symptoms (measured by CES-D) and cognitive impairment (Mini Mental State Examination Score <25) and chronic disease burden.

8.6 Discussion

This study demonstrates that community-dwelling older people with OH have a greater drop in cerebral perfusion, when measured by NIRS during active stand. OH is associated with greater drops in TSI, a marker of cerebral perfusion, when measured at 30, 60 and 90 seconds after standing in fully adjusted models.

This is consistent with findings of previous smaller studies (140, 212, 427) conducted using TCD and NIRS which found that OH was associated with reduced CBF indices.

Further, the co-existence of OH and a greater drop in TSI (≥75th centile) is independently associated with a 2-fold higher likelihood of future unexplained falls. OH in the absence of this greater drop in cerebral perfusion is not associated with future unexplained falls.

Despite the hypothesis that falls in OH are often related to cerebral perfusion deficits (391), little work has looked at the interaction between OH, cerebral perfusion and falls. A study involving 59 older nursing home residents identified that those with a history of falls within the preceding 12 months were more likely to have delayed blood pressure recovery after standing with a decline in CBFv measured by TCD ultrasound (475). Similarly, a study of orthostasis in 77 older adults found posture-related reductions in cerebral tissue oxygenation were associated with instability and a trend for increased falls risk (401). To the authors' knowledge, this is the first study to examine the interplay between OH, cerebral perfusion and future falls in a large cohort of community-dwelling older people.

These findings, therefore, have potentially important clinical implications. While OH has consistently been shown to increase the risk of future falls (315, 324, 476), this study demonstrates that OH is a marker of future unexplained falls only when associated with

significant contemporaneous drops in cerebral perfusion. Dynamic cerebral perfusion measures in addition to continuous orthostatic BP measurement, may therefore refine falls risk prediction in OH. This is important when we consider the complexities of treating OH to prevent falls, especially in the setting of co-existing hypertension (477, 478).

Prior work within the TILDA study has demonstrated how OH is one component of the 'Bermuda Triangle of Falls', alongside impairments in cognition and mobility, with each of the syndromes amplifying the effect of the other to increase falls risk (399). Given the associations with gait problems and cognitive impairment (479, 480), deficits in CBF may therefore act as the common pathway linking the three syndromes of this triangle. While rates of cognitive impairment within the TILDA study are relatively low, the link between cerebral perfusion and gait is well-established within the TILDA cohort (397, 402).

OH associated with larger drops in cerebral perfusion may therefore represent a more potent risk factor for future falls, partly due to the fact that perfusion deficits may signify failure of autoregulatory mechanisms (427) but also due to secondary effects of lower CBF including cognitive decline and mobility impairment (479, 480).

There are some limitations of this study which should be noted. Variables including falls, heart disease and chronic diseases are based on self-report and may therefore be subject to recall bias. However, at enrolment in TILDA participants with a history of dementia were excluded, reducing the likelihood of cognitive impairment affecting recall. Additionally, this study did not control for the influence of medications on the findings. Strengths of the study include the large, well-described cohort with state-of-the-art dynamic measures of orthostatic BP and cerebral perfusion and robust follow-up.

8.7 Conclusion

In conclusion, this study demonstrates that OH is independently associated with cerebral perfusion, measured by the portable NIRS device, during active stand. Importantly, the association between OH and future unexplained falls is modified by the co-occurrence of significant cerebral perfusion deficits as demonstrated by NIRS. This may have important clinical implications as it could help refine falls risk in the setting of OH and inform falls prevention strategies.

Chapter Nine – Results

9.1 Paper Four – Key Findings

- This is the first study to detail the benefit of application of cerebral oxygenation monitoring during HUT testing in the evaluation of transient loss of consciousness due to PPS in adult patients with unexplained recurrent events.

- This study describes a case series of eight patients with typical PPS semiology. Following diagnosis the number of events decreased.

- During HUT testing in all patients with PPS, peripheral haemodynamics including BP and HR increase at the time of apparent TLOC but TSI remains stable indicating the absence of cerebral hypoperfusion.

- In PPS, NIRS has the potential to benefit both clinician and patient by improving diagnostic accuracy, communication, and patient acceptance of this challenging diagnosis.

Near-infrared spectroscopy in evaluating psychogenic pseudosyncope – a novel diagnostic approach.

Claffey P, Pérez-Denia L, Rivasi G, Finucane C, Kenny RA. Near-infrared spectroscopy in evaluating psychogenic pseudosyncope-a novel diagnostic approach. *QJM*. 2020;113(4):239-244. doi:10.1093/qjmed/hcz257

9.2 Abstract

9.2.1 Introduction

PPS, a conversion disorder and syncope mimic, accounts for a large proportion of "unexplained syncope". PPS is diagnosed by reproduction of patients' symptoms during head-up tilt (HUT) testing. EEG, a time consuming and resource intensive technology, is used during HUT testing to demonstrate absence of cerebral hypoperfusion during TLOC. NIRS is a simple, non-invasive technology for continuous monitoring of cerebral perfusion. We present a series of patients for whom PPS diagnosis was supported by NIRS during a HUT test.

9.2.2 Methods

Eight consecutive patients with suspected PPS referred to a syncope unit underwent evaluation. During HUT testing, continuous beat-to-beat BP, HR and NIRS-derived TSI were measured. BP, HR and TSI at baseline, time of first symptom, presyncope and apparent TLOC were measured. Patients were given feedback and followed for symptom recurrence.

9.2.3 Results

Eight patients (6/8,75% female) aged 31 years (16-54) were studied with (5/8,63%) having comorbid psychiatric diagnoses, and (5/8,63%) presenting with frequent episodes of prolonged TLOC with eyes closed (6/8,75%). All patients experienced reproduction of typical events during HUT testing. Systolic BP(mmHg) increased from baseline (129.7(IQR 124.9-133.4)) at TLOC (153.0(IQR 146.7-159.0)) (p-value 0.012). HR (bpm) increased from

baseline 78(IQR 68.6-90.0) to 115.7(IQR 93.5-127.9) (p-value = 0.012). TSI (%) remained stable throughout, 71.4 (IQR 67.5-72.9) at baseline versus 71.0 (IQR 68.2-73.0) at TLOC (p-value =0.484).

9.2.4 Conclusions

NIRS provides a non-invasive surrogate of cerebral perfusion during HUT testing. We propose HUT testing incorporating NIRS monitoring in the diagnostic algorithm for patients with suspected PPS.

9.3 Introduction

Syncope is defined as TLOC due to cerebral hypoperfusion, characterised by a rapid onset, short duration, and spontaneous complete recovery (7). Psychogenic TLOC consists of two forms: one resembles epileptic seizures (psychogenic non-epileptic seizures, [PNES]) and one, without gross movements, resembles syncope (psychogenic pseudosyncope, [PPS]). PPS can be defined as an apparent TLOC occurring in the absence of impaired cerebral perfusion or function (68). PPS is associated with perceived poor physical health and significantly reduced quality of life (481).

In psychiatry, both PPS and PNES are classified as conversion disorders attributed to the physical manifestation of internal stressors (482, 483). There is a paucity of research regarding PPS compared to that of PNES, and much of what we know about PPS is adapted from PNES literature.

The prevalence of PPS varies according to clinical setting, ranging from 1%-12% of patients referred to specialist syncope clinics (68, 482, 484, 485). While patients with PNES are likely to be referred to neurologists, patients with PPS are more likely to be referred to cardiologists (483). However, PPS is under-reported (483, 486, 487), under-diagnosed and may account for a significant proportion of diagnoses which remain “unexplained” (482, 486).

In patients with suspected PPS, establishing and disclosing the diagnosis can be challenging (481, 488). These patients present to different specialists and undergo many investigations before a diagnosis of PPS is achieved (481, 488). This delay in diagnosis – as in most conversion disorders – compounds patients’ distress and leads to increased health care-associated costs (481, 488).

At present, PPS is diagnosed by reproduction of patients' symptoms during a head-up tilt (HUT) test without associated hypotension. New guidelines (7) advise concurrent electroencephalogram (EEG) monitoring during HUT testing if possible. Concurrent EEG monitoring demonstrates the absence of brain wave activity characteristic of cerebral hypoperfusion (7, 482, 485, 489). Such information is used to inform discussion with patients about diagnosis. However, EEG is time consuming and resource intensive (490). Many syncope units lack ready access to EEG and rely on demonstrating the absence of hypotension during symptoms to diagnose PPS.

Near-infrared spectroscopy (NIRS) is a non-invasive technology for continuous monitoring of tissue oxygen saturation, which has been validated as an accurate and reliable method for cerebral oxygenation assessment (491, 492). Cerebral TSI is a surrogate marker of CBF (128, 493) and is used perioperatively and in intensive care settings.

In this study, we present a series of patients for whom the diagnosis of PPS was supported by NIRS during TLOC on HUT testing. We propose use of NIRS in routine clinical assessment of suspected PPS.

9.4 Methods

9.4.1 Participants

Eight consecutive patients were referred for investigation of recurrent unexplained syncope to a dedicated syncope management unit. Patients were referred from the emergency department, primary care, cardiology and neurology.

9.4.2 Study Protocol and Patient Consent

This study protocol was approved by the hospital's research ethics committee. Written informed consent for the study was obtained from each participant.

9.4.3 Assessment

Patients underwent initial evaluation for syncope in accordance with the European Society of Cardiology guideline's recommendations (7) – including detailed medical history, physical examination, 12-lead resting surface electrocardiogram (ECG), active stand and HUT testing.

Blood pressure and NIRS set up was as follows: Continuous beat-to-beat BP and HR measurements were recorded using a finger plethysmography-based volume clamp approach (Finometer NOVA, Finapres Medical Systems, Amsterdam, The Netherlands). A three lead-ECG (Lead I, II, III) was also simultaneously recorded. Continuous NIRS-derived regional cerebral oxygenation of the frontal lobe was also recorded using an optical sensor applied to the forehead approximately 2.5 centimetres above the eyebrow (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands). (See Figure 1). A bandage was affixed

around the head over the sensor to remove ambient lighting and exert comfortable pressure for effective contact between the probe and the subjects' skin.

9.4.4 PPS Diagnostic Criteria

The clinical evaluation was diagnostic for PPS when apparent TLOC occurred during HUT testing in the absence of diagnostic HR, hypotensive BP or cerebral perfusion changes.

9.4.5 Patient Management

Patients were educated about the results of their assessment and the diagnosis of PPS was explained. Patients were referred to psychotherapy services for consideration of cognitive behavioural therapy. A repeat visit was offered to patients for follow up in the syncope unit after diagnosis.

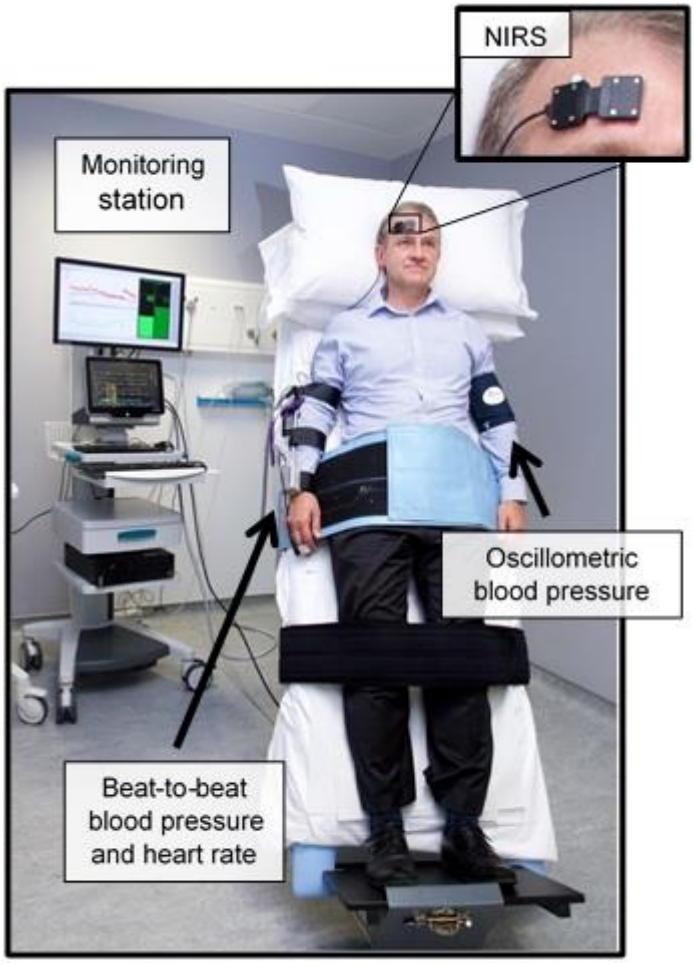


Figure 9.1 Actor demonstrating the clinical setup during a HUT test. Inset shows close-up detail of the NIRS device. For illustrative purposes, the overlying bandage to stabilise the NIRS device in place is omitted. Continuous beat-to-beat BP and HR are also monitored during the test.

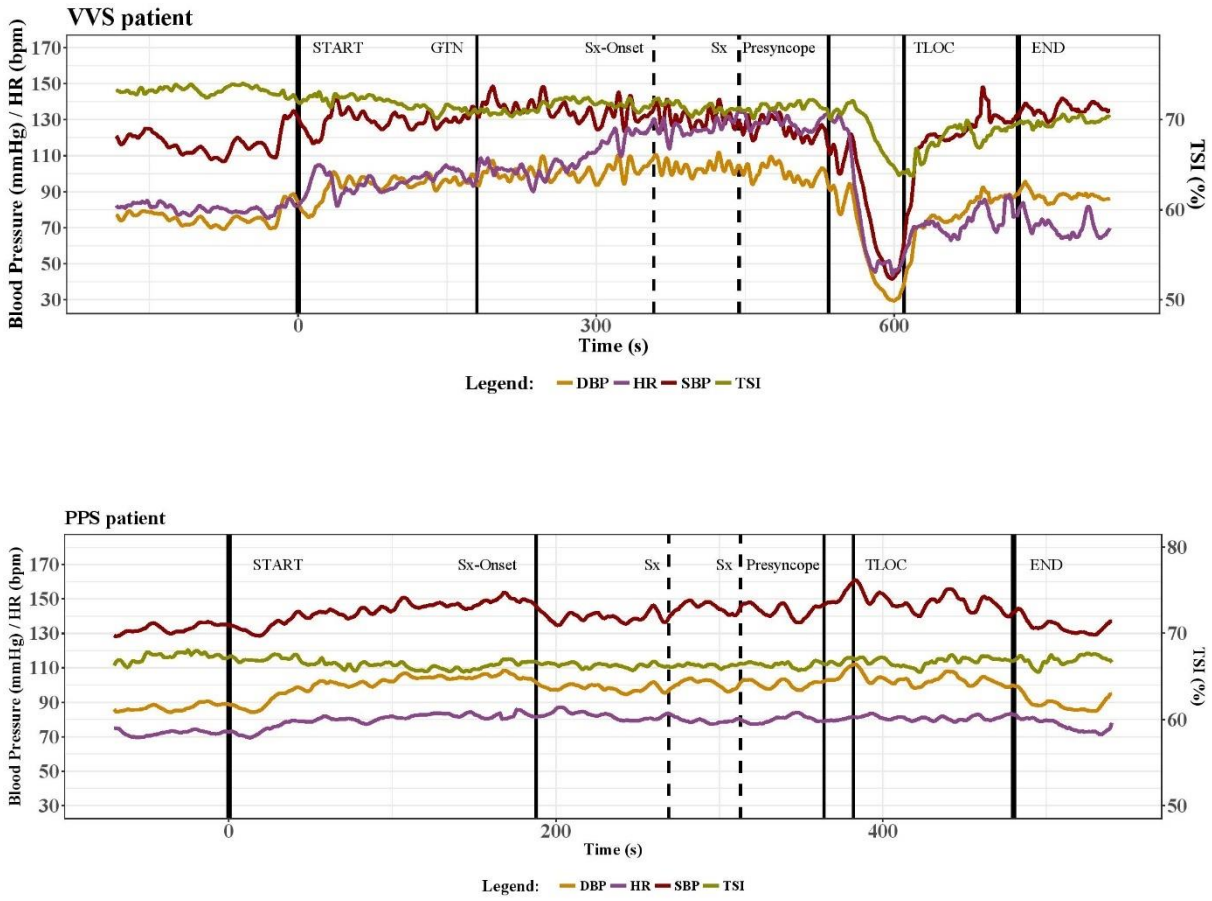


Figure 9.4 SBP, DBP, HR and TSI responses to HUT test for a patient experiencing PPS (Top) and Vasovagal Syncope (Bottom).

9.4.6 Data Analysis

Systolic (SBP) and diastolic (DBP) BP, HR and TSI signals were processed using custom developed software in MATLAB (MATLAB version R2010b. Natick, Massachusetts: The MathWorks Inc., 2010). TSI was defined as the percentage ratio of oxygenated haemoglobin concentration ([O_2Hb]) to the total concentration of haemoglobin, i.e. oxygenated haemoglobin and deoxygenated haemoglobin ([HHb]).

$$TSI\ (\%) = \frac{[O_2Hb]}{[O_2Hb] + [HHb]}\ x\ 100$$

Values for SBP, DBP, HR, and TSI were obtained at four time points: at baseline, at the onset of symptoms (first reported symptom), at presyncope (last reported symptom before TLOC) and at TLOC (exact moment of apparent loss of consciousness). Baseline values were derived as the average of TSI, SBP, DBP and HR values occurring -60 to -30 seconds prior to the start of the HUT test. During the HUT test, a 5-second moving average filter was applied to this data to remove unwanted noise. These averaged values were used to represent values at key time points: symptom onset, presyncope and TLOC.

9.4.7 Statistical Analysis

Patient characteristics are reported as medians and interquartile ranges. Absolute values of SBP, DBP, HR and TSI at baseline, symptom onset, presyncope and TLOC were compared using the non-parametric Friedman test suitable for small non-parametric samples. Wilcoxon signed-ranked tests were used to perform pairwise comparisons between these four time points. Statistical analysis was performed using SPSS (IBM Corp.

Released 2016. IBM SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corp).

Statistical significance was assumed at a p-value ≤ 0.05.

9.5 Results

The median age of our study population was 31 years (range 16-54). The majority (75%) were female. All patients were referred with a history of recurrent TLOC with median of 6 (IQR 2.75-10) events in the previous year. Events were present for 1.5 (IQR 0.625-3) years. Seven patients also reported presyncope (88%).

The clinical presentation, TLOC and follow up features of each patient are detailed in Table 9.1 and Table 9.2. No prior TLOC episode resulted in injury. All patients described prodromal symptoms prior to TLOC, and most events were witnessed. Three patients had a previous diagnosis of vasovagal syncope while five had comorbid psychiatric illness.

Seven patients attended the emergency department due to TLOC; six patients were hospitalised (length of stay 6.5 [IQR 4.5-10.75] days). Seven patients had normal cardiac and neurological investigations conducted prior to syncope unit referral. (Table 9.1). Following syncope unit visit, the number of TLOC events reduced after diagnosis over a follow up of 13.5 months.

During HUT testing, all patients experienced an apparent TLOC which they recognised as reproductive of their typical events. Figure 9.2 demonstrates a typical PPS patient HUT response together with a typical vasovagal syncope response for comparison. Group peripheral haemodynamics and cerebral oxygenation values observed during HUT testing are presented in Figure 9.3 (with numerical values displayed in Table 9.3). Time from baseline to first symptom onset, presyncope and TLOC was 4.2 (IQR 2.9-7.1), 12.5 (IQR 5.6-25.6) and 14.6 (IQR 6.2-26.5) minutes respectively. SBP increased from 129.7 (IQR 124.9-133.4) mmHg at baseline to 153.0 (IQR 146.7-159.0) mmHg at time of apparent TLOC (p-value = 0.012). DBP also increased from 78.0 (IQR 74.6-85.4) mmHg at baseline

to 109.9 (IQR 100.5-111.6) mmHg at time of apparent TLOC (p-value = 0.012). HR increased from 78 (IQR 68.6-90.0) bpm at baseline to 115.7 (IQR 93.5-127.9) bpm (p-value = 0.012). However, there was no significant change in TSI, which was stable throughout, 71.4% (IQR 67.5-72.9) at baseline versus 71.0% (IQR 68.2-73.0) at TLOC (p-value =0.484). Sensitivity analysis examining outlier effects indicated the same trend in the results.

Table 9. 1 Case Series Patient Characteristics and Diagnostic Investigations

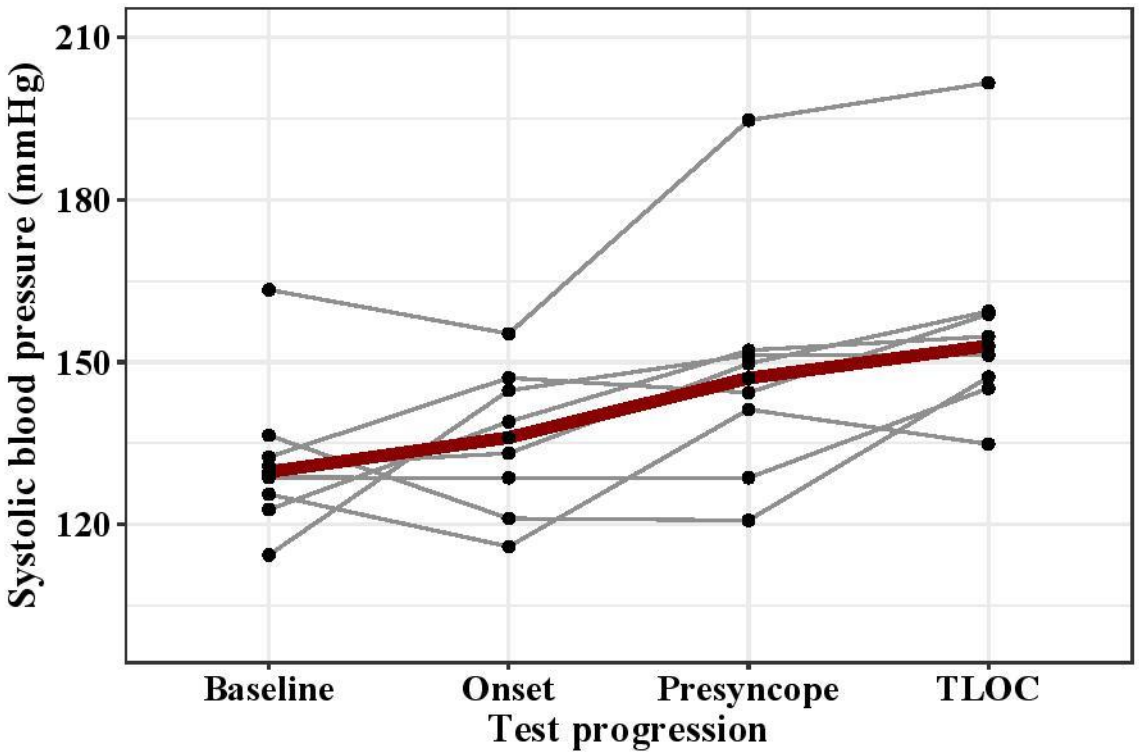
Patient	Gender M=Male F=Female	Age	Frequency of TLOC events prior to assessment	Clinical Features	Prior ED Attendance +/- Hospitalisation	Prior Investigations	Frequency of TLOC events at follow up
1	*F*	*34*	5 events	Prolonged TLOC Prodrome: warmth, diaphoretic, dizzy, leg numbness and right leg shaking	1 ED attendance	CT Brain Echocardiogram Heart Rhythm Monitor	Reviewed at 12 months: Nil further TLOC events
2	F	19	3 events per week	Prolonged TLOC Prodrome: Visual disturbance and limb shaking Eyes Closed	4 ED attendance 1 Hospitalisation (LOS 2days)	EEG Echocardiogram ABPM Heart Rhythm Monitor MRI Brain	Reviewed at 14 months: 2 TLOC events
3	F	54	3 events	Frequent presyncope, Prolonged TLOC Prodrome: dyspnoea, blurred vision, light-headedness Eyes closed		EST ABPM Echocardiogram	Reviewed at 10 months: Nil further TLOC events
4	F	16	2 events per day	Short duration TLOC Prodrome: warmth, dizzy, brain fog, Eyes closed	1 ED attendance 1 Hospitalisation (LOS 4 days)	Echocardiogram Heart Rhythm Monitor Cardiac MRI ABPM ILR	Reviewed at 14 months: Dizzy symptoms, nil further TLOC events
5	M	49	1 event per week	Short duration TLOC Prodrome: Neck pain, sweating, light-headedness, tremor, dyspnoea Eyes closed	2 ED attendances 1 Hospitalisation (LOS 12 days)	CT Brain EEG Hormone Panel MRI Brain	Reviewed at 14 months: 3 presyncope episodes, nil further TLOC events
6	F	22	1-2 events per month	Frequent presyncope, Short duration TLOC Prodrome: warmth, dizzy, vision disturbance Eyes closed	1 ED attendance	Heart Rhythm Monitor	Reviewed at 8 months: Nil further TLOC events
7	M	50	3 events	Prolonged TLOC, Prodrome: warmth, weak legs Eyes closed	2 ED attendances 2 Hospitalisations (LOS 7 & 6 days)	Cardiac Enzymes CT Brain EEG CXR EST Echocardiogram Heart Rhythm Monitor	Reviewed at 15 months: Nil further events
8	F	28	2 events	Daily dizziness, Prolonged TLOC Prodrome: light-headedness, paraesthesia, room spinning, nausea, chest pain, palpitations	2 ED attendances 1 Hospitalisation (LOS 13 days)	CT Brain Heart Rhythm Monitor EST	Reviewed at 13 months: Weekly dizzy symptoms, nil further TLOC events

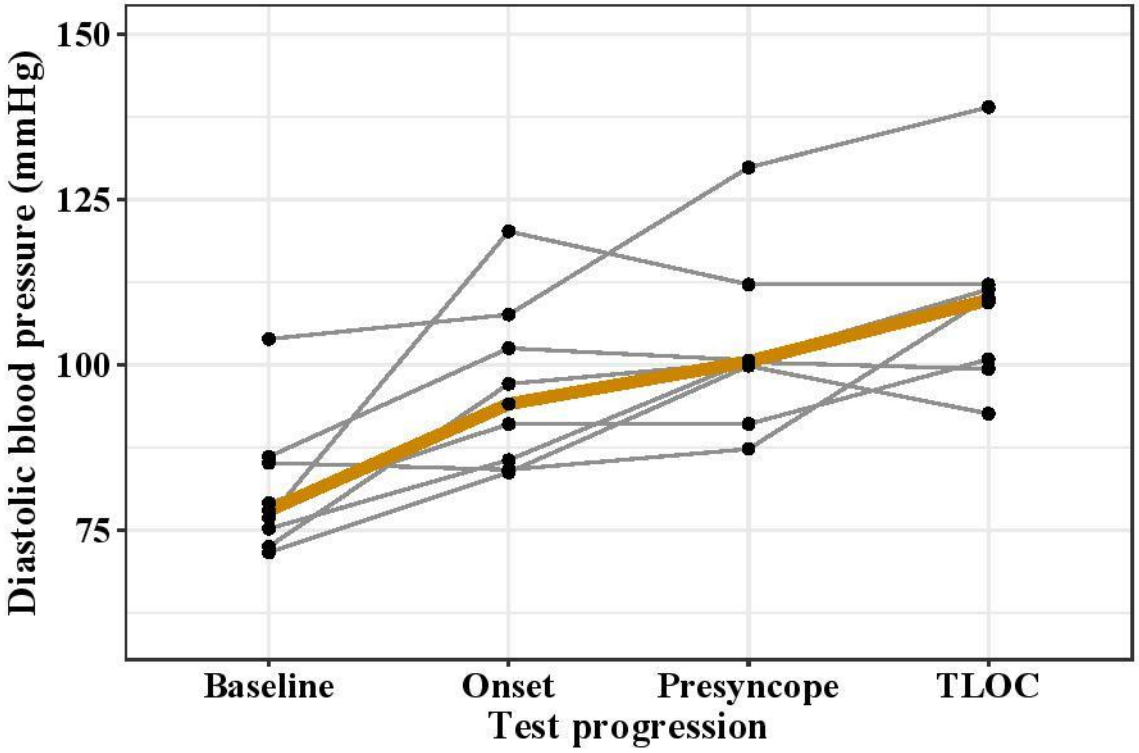
ED, emergency department; TLOC, transient loss of consciousness; LOS, length of stay; ABPM, ambulatory blood pressure monitoring; CT, computed tomography, EEG, electroencephalogram; MRI, magnetic resonance imaging; ILR, implantable loop recorder; EST, exercise stress test; Telemetry, inpatient cardiac monitoring

Table 9. 2 Baseline clinical features of the study sample.

	All patients (n=8)
Age (years), median (IQR)	31 (21.25-49.25)
Female, n (%)	6 (75)
BMI (kg/m^2), median (IQR)	24 (23.35-31.3)
Smoking status	
Current smoking, n (%)	2 (25)
Past Smoking, n (%)	2 (25)
Migraine, n (%)	2 (25)
Psychiatric Diagnosis, n (%)	5 (63)
Depression, n (%)	4 (50)
Anxiety, n (%)	3 (38)
Other Psychiatric Diseases, n (%)	2 (25)
Previous Diagnosis of VVS, n (%)	3 (38)
Fibromyalgia, n (%)	1 (13)
Hypermobility, n (%)	1 (13)
Alcohol Excess, n (%)	1 (13)
Associated Palpitations, n (%)	3 (38)
Associated Cardiac Symptoms, n (%)	2 (25)
Number of medications, median (IQR)	1 (0.75-5.5)
Antidepressants, n (%)	2 (25)
Antiepileptic medications, n (%)	2 (25)
Hypnotics, n (%)	2 (25)
Antipsychotic, n (%)	3 (38)

IQR= interquartile range; BMI = Body Mass Index; VVS = Vasovagal Syncope.


Systolic blood pressure (mmHg)
210
180
150
120
Baseline
Onset
Presyncope
TLOC
Test progression


Diastolic blood pressure (mmHg)
150
125
100
75
Baseline
Onset
Presyncope
TLOC
Test progression

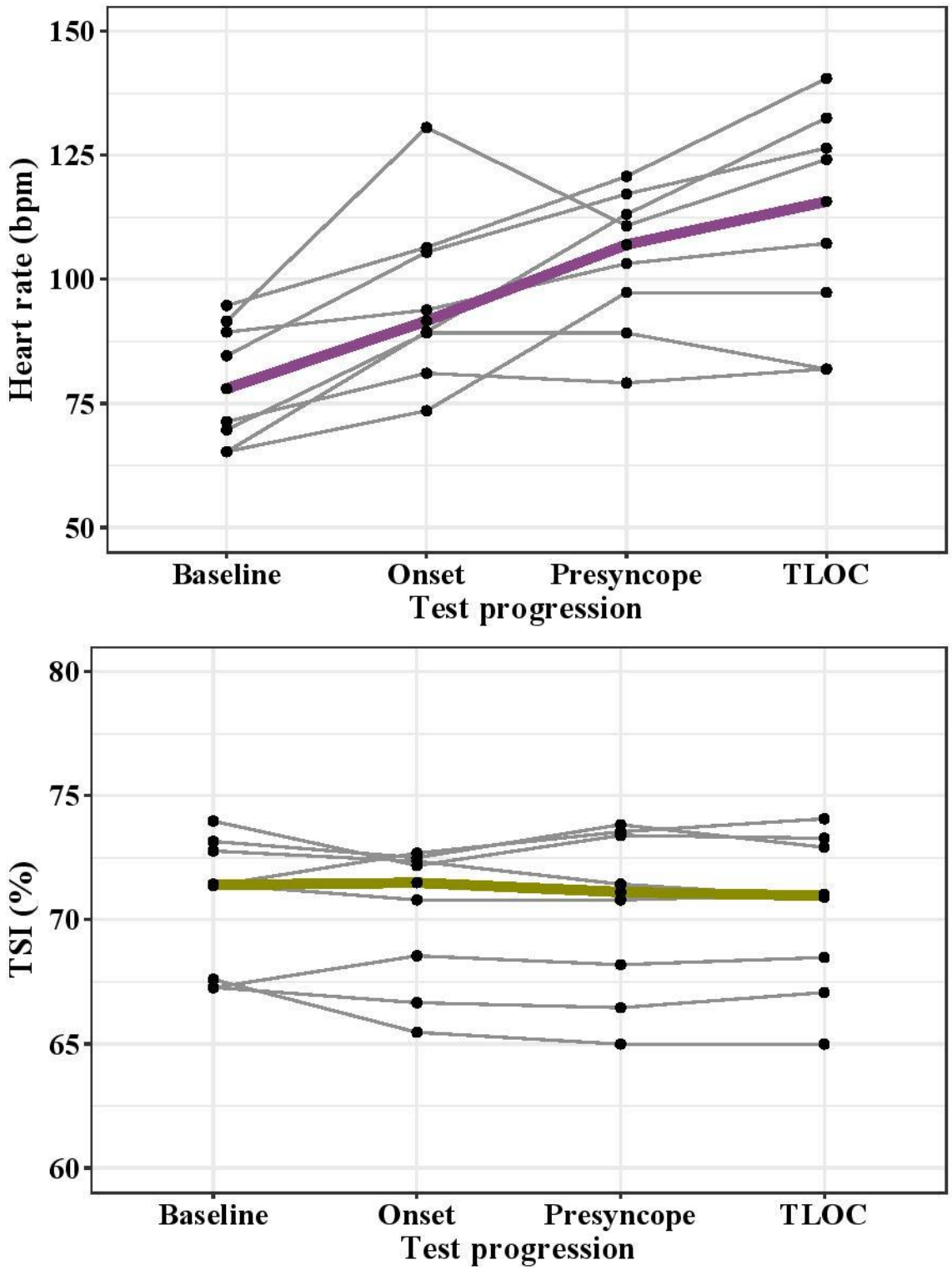


Figure 9.5 SBP, DBP, HR and TSI values for Baseline (prior to start of HUT test), Onset (first reported symptom), Presyncope (last reported symptom prior to apparent TLOC) and TLOC time points. Each thin grey line represents a single patient. The thick lines in each graph represent the group median value.

9.6 Discussion

This is the first study to detail the benefit of application of cerebral oxygenation monitoring during HUT testing in the evaluation of transient loss of consciousness due to PPS in adult patients with unexplained recurrent events.

In keeping with previous literature (485), our study demonstrates that peripheral haemodynamics including BP and HR increase at the time of apparent TLOC during HUT testing in patients with PPS. Our novel finding indicates that cerebral perfusion remains stable throughout despite positive symptom reproduction in PPS patients. Consistent with previous studies (7, 485), this PPS cohort were described with the typical clinical and semiological features of female preponderance, presence of other psychiatric diagnosis, frequent attack history, with prolonged TLOC and eyes closed at the time of their events.

A clinical suspicion of PPS is a recognised indication for tilt testing in ESC guidelines (7). Traditionally, the addition of concurrent video EEG monitoring during HUT has been utilised in the diagnosis of PPS (485, 494). Hypoperfusion produces characteristic EEG changes – either “slow” or “slow-flat-slow” wave patterns – which are not observed in PPS (45, 486). This information is used for biofeedback to patients. However, video EEG is not available in many syncope units, is expensive and requires experienced personnel to operate and interpret results, making its routine use complex (495). The likelihood of tilt testing provoking apparent TLOC is high with up to 90% of suspected PPS patients experiencing apparent TLOC and reproduction of symptoms during HUT (486). PPS patients are often labelled as “unexplained syncope” and have multiple emergency department presentations and hospitalisations with obvious cost implications. (481, 488).

Coupled with a detailed history of TLOC events, the use of continuous HR, BP and NIRS monitoring during HUT testing can provide a comprehensive assessment for peripheral and central haemodynamic changes before, during and after TLOC. The technology used – NIRS – is easy to apply and interpret. It has been validated for use in other settings such as anaesthesia, surgery and intensive care (141) for the monitoring of cerebral haemodynamics and more recently to document cerebral hypoperfusion during HUT induced syncope. (206, 209, 213, 482)

Patients in our study underwent cardiac and radiological investigations prior to attendance at the syncope unit. It is well recognised that patients with PPS often attend several specialists and undergo unnecessary investigations before a clear diagnosis is made. For many years, PPS was considered a diagnosis of exclusion (46, 496). We propose that NIRS can refine the assessment of patients with PPS minimising the need for excess investigations.

Patients who fail to believe the diagnosis of conversion disorder have a poorer prognosis (497). The additional availability of a real-time objective marker of cerebral perfusion provides further biofeedback to PPS patients beyond peripheral haemodynamic measures. This may assist them to accept the diagnosis and pursue further psychological or psychiatric assessment to gain better control over symptoms. Early establishment of the diagnosis is associated with decreased health care costs, health care utilisation and a reduction in subsequent events (481, 498).

9.7 Conclusion

NIRS is a convenient and readily available diagnostic tool for use in the assessment of syncope. In PPS, it accurately demonstrates the absence of cerebral hypoperfusion during patient events and has the potential to benefit both clinician and patient by improving diagnostic accuracy, communication, and patient acceptance of this challenging diagnosis.

Table 9 3 Absolute values from baseline to TLOC for systolic blood pressure, diastolic blood pressure, heart rate and tissue saturation index. (On = Onset, Pre-S = Presyncope, T = TLOC).

	Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)				Heart rate (bpm)				Tissue saturation index (%)			
ID	**Baseline, mean (SD)**	**On**	**Pre-S**	**TLOC**	**Baseline, mean (SD)**	**On**	**Pre-S**	**TLOC**	**Baseline, mean (SD)**	**On**	**Pre-S**	**TLOC**	**Baseline, mean (SD)**	**On**	**Pre-S**	**TLOC**
1	130.7 (3.9)	133.1	149.7	159.4	75.3 (2.7)	85.6	100.6	109.5	94.7 (2.8)	106.4	120.7	140.5	73.2 (0.3)	72.5	73.8	72.9
2	122.7 (3.9)	139.0	152.2	154.7	72.5 (5.8)	97.1	100.4	99.4	65.2 (9.4)	89.4	113.1	132.5	67.3 (0.7)	68.5	68.2	68.5
3	132.4 (3.1)	147.1	144.3	158.8	86.1 (2.4)	102.5	100.7	111.4	71.3 (2.1)	81.1	79.1	81.9	67.3 (0.4)	66.7	66.5	67.1
4	125.6 (4.7)	115.9	141.2	134.8	71.6 (4.3)	83.8	99.9	92.6	91.6 (5.8)	130.6	110.8	124.1	74.0 (0.3)	72.2	73.4	73.3
5	163.3 (8.1)	155.2	194.7	201.6	103.9 (4.3)	107.6	129.9	139.0	84.6 (3.5)	105.5	117.2	126.4	71.4 (0.4)	72.7	73.5	74.1
6	114.3 (2.5)	144.7	151.3	151.3	76.9 (3.2)	120.2	112.2	112.2	65.3 (10.1)	73.5	97.4	97.4	67.6 (0.3)	65.5	65.0	65.0
7	128.7 (3.8)	128.6	128.6	145.1	79.1 (2.7)	91.1	91.1	100.9	69.7 (5.4)	89.2	89.2	81.9	71.4 (0.4)	70.8	70.8	71.0
8	136.4 (3.2)	121.1	120.7	147.2	85.2 (2.7)	84.2	87.3	110.2	89.4 (2.8)	93.8	103.2	107.2	72.8 (0.3)	72.4	71.4	70.9
Median	129.7	136.1	147.0	153.0	78.0	94.1	100.5	109.9	78.0	91.6	107.0	115.7	71.4	71.5	71.1	71.0
1st Quartile	124.9	126.7	138.1	146.7	74.6	85.3	97.7	100.5	68.6	87.2	95.4	93.5	67.5	68.1	67.8	68.2
3rd Quartile	133.4	145.3	151.5	159.0	85.4	103.8	103.6	111.6	90.0	105.7	114.1	127.9	72.9	72.4	73.4	73.0

*Table 9.4 Results for the repeated measures comparison using Friedman test (bold) and Wilcoxon signed-ranks test (italics). SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TSI, tissue saturation index; IQR, interquartile range. * Significant (p-value ≤ 0.05)*

Variable	Comparison		P-value
SBP (mmHg)	**Between groups**	**Median (IQR)**	**0.003**
	Onset v Presyncope	136.1 (126.7-145.3) v 147.0 (138.1-151.5)	0.063
	Onset v TLOC	136.1 (126.7-145.3) v 153.0 (146.7-159.0)	0.012*
	Presyncope v TLOC	147.0 (138.1-151.5) v 153 .0(146.7-159.0)	0.043*
	Baseline v Onset	129.7 (124.9-163.3) v 136.1 (126.7-145.3)	0.575
	Baseline v Presyncope	129.7 (124.9-163.3) v 147.0 (138.1-151.5)	0.069
	Baseline v TLOC	129.7 (124.9-163.3) v 153.0 (146.7-159.0)	0.012*
DBP (mmHg)	**Between groups**		**0.001**
	Onset v Presyncope	94.1 (85.3-103.8) v 100.5 (97.7-103.6)	0.128
	Onset v TLOC	94.1 (85.3-103.8) v 109.0 (100.5-111.6)	0.025*
	Presyncope v TLOC	100.5 (97.7-103.6) v 109.0 (100.5-111.6)	0.063
	Baseline v Onset	78.0 (74.6-85.5) v 94.1 (85.3-103.8)	0.017*
	Baseline v Presyncope	78.0 (74.6-85.5) v 100.5 (97.7-103.6)	0.012*
	Baseline v TLOC	78.0 (74.6-85.5) v 109.0 (100.5-111.6)	0.012*
HR (bpm)	**Between groups**		**0.001**
	Onset v Presyncope	91.6 (87.2-105.7) v 107.0 (95.4-114.1)	0.176
	Onset v TLOC	91.6 (87.2-105.7) v 115.7 (93.5-127.9)	0.069
	Presyncope v TLOC	107.0 (95.4-114.1) v 115.7 (93.5-127.9)	0.063
	Baseline v Onset	78 (68.6-90.0) v 91.6 (87.2-105.7)	0.012*
	Baseline v Presyncope	78 (68.6-90.0) v 107.0 (95.4-114.1)	0.012*
	Baseline v TLOC	78 (68.6-90.0) v 115.7 (93.5-127.9)	0.012*
TSI (%)	**Between groups**		**0.435**
	Onset v Presyncope	71.5 (68.1-72.4) v 71.1 (67.8-73.4)	0.612
	Onset v TLOC	71.5 (68.1-72.4) v 71.0 (68.2-73.0)	0.575
	Presyncope v TLOC	71.1 (67.8-73.4) v 71.0 (68.2-73.0)	0.735
	Baseline v Onset	71.4 (67.5-72.9) v 71.5 (68.1-72.4)	0.327
	Baseline v Presyncope	71.4 (67.5-72.9) v 71.1 (67.8-73.4)	0.674
	Baseline v TLOC	71.4 (67.5-72.9) v 71.0 (68.2-73.0)	0.484

Chapter Ten – Discussion

The primary aim of this thesis was to investigate the association between OH, CBF (measured using NIRS) and falls risk in two cohorts: a clinical group recruited from a specialised outpatient setting and a population group of participants from The Irish Longitudinal Study on Ageing (TILDA).

In this chapter, the key findings of this research are summarised and discussed. Strengths and limitations are considered and the clinical implications of the findings along with topics for future research are highlighted.

10.1 Summary of Key Findings

Study 1 (Chapter 6) assessed the relationship between OH and CBF in 189 of 491 clinic attenders with a history of falls, syncope and dizziness. By coupling continuous beat-to-beat BP measurement with concurrent measurement of cerebral oxygenation, a significant relationship between the presence of OH and more marked changes in CBF upon standing was demonstrated. This association was demonstrated at multiple timepoints (from 30-120 seconds) and persisted after adjustment for demographic and clinical covariates. Additionally, the presence of symptomatic OH was not associated with greater cerebral oxygenation drops on standing compared with asymptomatic OH.

This is the largest study to date using novel NIRS technology in individuals referred for clinical evaluation of falls, syncope and dizziness to assess cerebral perfusion during active standing and that adjusts for important potential confounders.

Study 2 (Chapter 7) demonstrated that over 10% of a cohort of more than 900 community-dwelling people aged ≥70 years had severe OH demonstrated during AS, i.e., a sustained drop of 20mmHg in systolic BP and/or 10mmHg in diastolic BP at 30, 60 and 90 seconds after standing. Of those with OH, two thirds were asymptomatic and did not report dizziness during the AS.

There was no significant difference in terms of absolute BP parameters during the AS in participants with OH who reported symptoms of dizziness compared to those without symptoms. Similarly, reporting dizziness during the AS was not associated with a greater drop in SBP at 30, 60 or 90 seconds or with binary variables reporting the presence / absence of delayed BP recovery and OH. Further, reporting unsteadiness when rising from a chair or when standing was also not associated with a greater orthostatic drop in SBP during the AS or with OH.

Participants with asymptomatic OH did, however, have a 2-fold increased risk of unexplained falls during follow-up, while those with symptomatic OH did not.

Study 3 (Chapter 8) again confirmed what was shown in the clinical cohort in study 1 but in community-dwelling older participants in TILDA – namely, that those with severe OH have a greater drop in cerebral perfusion, when measured by NIRS during AS. OH was associated with greater drops in TSI, a marker of cerebral perfusion, when measured at 30, 60 and 90 seconds after standing in fully adjusted models.

Furthermore, the co-existence of OH and a greater drop in TSI (≥75th centile) is independently associated with a 2-fold higher likelihood of future unexplained falls. OH in the absence of this greater drop in cerebral perfusion is not associated with future unexplained falls.

Study 4 (Chapter 9) is the first study to detail the benefit of application of cerebral oxygenation monitoring during HUT testing in the evaluation of transient loss of consciousness due to PPS in adult patients with unexplained recurrent events.

This study showed that peripheral haemodynamics including BP and HR increase at the time of apparent TLOC during HUT testing in patients with PPS and that cerebral perfusion remains stable throughout despite positive symptom reproduction.

10.2 Orthostatic Hypotension and Reduced Cerebral Blood Flow

It was hypothesised that OH was associated with increased cerebral hypoperfusion during standing. This was demonstrated in study 1 among a clinical cohort of patients with OH at any timepoint 30-120 seconds post standing and in study 3 among community dwelling older adults with OH at multiple timepoints post stand.

These findings are supported by prior studies which have shown reduced CBF in OH patients using various measurement techniques including NIRS (140, 207, 357, 419, 420). However, these studies are relatively small involving specific disease cohorts and none controlled for potential confounding factors in their methodologies.

In addition to its association with advancing age, OH has been implicated in several adverse health outcomes including cardiovascular disease (353), cognitive impairment (382-384), late life depression (350), impaired gait (349), frailty (406), syncope (34), falls (346), fractures (347) and early mortality (353). (See Section 3.9 Clinical Importance of OH). This complex and multifactorial relationship between OH and negative outcomes may be at least partly explained by the stress of repetitive and persistent episodes of

hypotension over time resulting in relative regional cerebral ischaemia and chronic hypoperfusion. Given the latency of CA mechanisms to respond to short periods of arterial hypotension (42, 98), it is therefore suggested that those with OH will repeatedly experience a greater hypotensive load on standing resulting in recurrent episodes of cerebral hypoperfusion, leading to structural and functional changes at a neuronal level that results in cerebral pathology.

The findings of this thesis suggest that cerebral hypoperfusion – whether transient or persistent – may serve as a unifying pathway linking OH to its many associated negative health sequelae. Indeed, impaired cerebral haemodynamics have been implicated in declining cognition in AD patients (273), those with late life depression (380) and in those with postural instability (400, 401) and impaired gait (402). Further research examining this link will be critical to unravelling the broader implications of OH for older populations with these conditions.

OH is not a disease in and of itself but can be regarded as a physical manifestation of dysregulation in one or more of the regulatory mechanisms responsible for controlling BP and CBF responses to standing brought about by other conditions. These mechanisms include the baroreceptor reflex, vascular compliance, cerebral autoregulation, neurovascular coupling, maintenance of the BBB and neurohumoral responses. A failure in any or all of these systems may result in compromised CBF leading to dizziness, falls, the other long-term consequences such as cognitive impairment or late life depression. This is represented graphically in Figure 10.1.

Understanding the role of OH in cerebral hypoperfusion and the development of neurodegenerative sequelae is important as OH is potentially modifiable with appropriate

treatment and management. While these studies have identified cerebral hypoperfusion as a clear precipitant of OH, other important factors associated with cerebral hypoperfusion such as smoking and antidepressant use have also been identified. Additionally, other studies have suggested that alcohol intake (499), cognitive training (500), exercise (501) and medications such as antihypertensives (244) may also influence CBF.

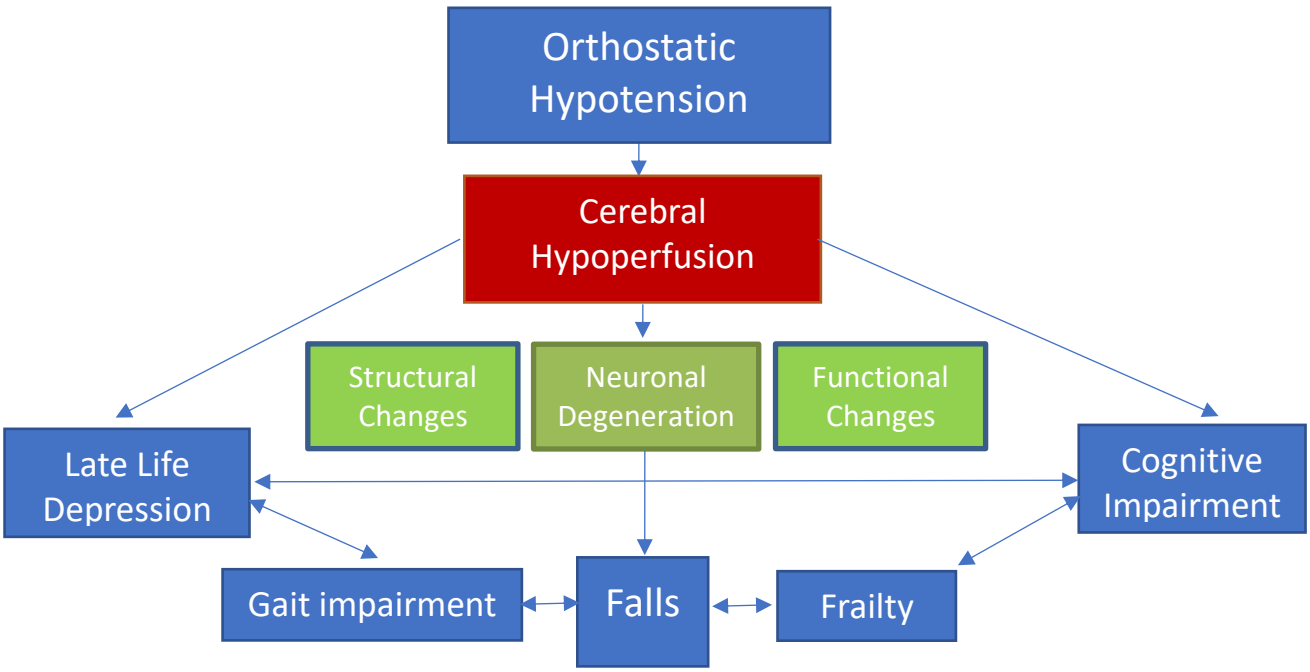


Figure 10. 1 How might OH contribute to falls?

10.3 Symptomatic and Asymptomatic OH

It was hypothesised that symptomatic OH was associated with greater cerebral hypoperfusion on standing than asymptomatic OH. However, the findings of study 1 (Chapter 6) suggest that there was no significant difference in TSI change from baseline upon standing in symptomatic OH compared with asymptomatic OH. Additionally, it was shown in study 2 (Chapter 7) that asymptomatic OH was more in important in terms of predicting future falls risk than those with symptomatic OH.

While studies using TCD modalities have linked symptomatic OH with worse cerebral perfusion than those with asymptomatic OH (140, 425, 433), it is noteworthy that studies using NIRS have shown conflicting results (140, 215). A recent NIRS study in OH participants conducted by Klop and colleagues (457) (reporting O_2Hb rather than TSI) found a deeper oxygenation maximum drop during symptomatic supine-stand transitions compared to asymptomatic transitions but no difference between the groups in the recovery phase post stand.

Furthermore, it was hypothesised that typical OH symptoms, specifically dizziness and unsteadiness on rising from a chair and/or walking in community dwelling older adults would not be related to changes in peripherally measured orthostatic BP and that a significant proportion of older people with OH demonstrated on active stand may be asymptomatic.

There are several possible reasons why older people with OH do not exhibit typical dizzy symptoms. The sensation of dizziness is somewhat subjective and often vague (1) and can vary widely within individuals frequently alternating between symptomatic and asymptomatic periods (457). Rather than feeling dizzy, light-headed or unsteady in the

context of hypotension, older people may instead experience leg weakness or neck pain, which may actually represent 'typical' OH symptoms in this cohort and were not captured in this study (467). In any case, only 50–70% of acutely unwell older people present with so-called typical symptoms of their underlying illness (468, 469). Also, as seen in problems with gait and balance (398), older people tend to compensate for gradual-onset conditions such as OH and may therefore have less awareness of symptoms or at least be less likely to report them as a problem. It has also been suggested that lack of awareness of hypotension in OH may be related to hypoperfusion-related changes in the reticular activating system, leading to inattention to the warning signs of dizziness or presyncope (344).

The results of study 1 and 2 suggest that between 50-66% of individuals with OH are asymptomatic. In clinical practice, the decision to treat OH pharmacologically is often geared towards lessening the symptomatic burden (334). The findings of this thesis suggest that relying on symptoms alone may not always be an accurate indicator of cerebral hypoperfusion in OH and that the management of asymptomatic OH presents the need for a nuanced consideration of the potential advantages and disadvantages of treatment.

Another hypothesis tested in this thesis was that asymptomatic OH confers a higher risk of unexplained falls than symptomatic OH due to the absence of prodromal or warning symptoms. The results of study 2 (See Chapter 7) detail that those with asymptomatic OH have a two-fold increased risk of future unexplained falls while those with symptomatic OH have not. Therefore, clinicians involved in the care of OH patients should not be reassured by the absence of symptoms in OH. Discovery of asymptomatic OH should

prompt the physician to consider future falls risk as well as added mindfulness towards the potential hypotensive effects of medications as they may be at greater risk for falls and subsequent injuries.

10.4 Orthostatic Hypotension, Cerebral Blood Flow and Future Falls

Cerebral hypoperfusion is often proposed as the principal causative mechanism responsible for falls in those with OH (391). The hypothesis tested in study 3 (Chapter 8) was that those individuals with OH and greater degrees of cerebral hypoperfusion on standing would have the highest risk of future falls.

Results of this study show that the co-existence of OH and a greater drop in TSI (≥75th centile) is independently associated with a 2-fold higher likelihood of future unexplained falls while OH in the absence of this greater drop in cerebral perfusion is not. This study confirms a novel finding – that degree of cerebral hypoperfusion on standing modifies falls risk in older individuals with OH.

Prior work within the TILDA study has demonstrated how OH is one component of the 'Bermuda Triangle of Falls', alongside impairments in cognition and mobility, with each of the syndromes amplifying the effect of the other to increase falls risk (399). Given the associations with gait problems and cognitive impairment (479, 480), deficits in CBF may therefore act as the common pathway linking the three syndromes of this triangle. While rates of cognitive impairment within the TILDA study are relatively low, the link between cerebral perfusion and gait is well-established within the TILDA cohort (397, 402). OH associated with larger drops in cerebral perfusion may therefore represent a more potent risk factor for future falls, partly due to the fact that perfusion deficits may signify

impairment or disruption to autoregulatory mechanisms (427) but also due to secondary effects of lower CBF including cognitive decline and mobility impairment (479, 480).

10.5 The role of NIRS in Psychogenic Pseudosyncope

The hypothesis of study 4 (Chapter 9) was that NIRS could be used to demonstrate the lack of cerebral hypoperfusion contributing to symptoms during HUT for patients with PPS. This study shows that, while peripheral haemodynamics including BP and HR increase at the time of apparent TLOC during HUT testing in keeping with previous literature (485), cerebral perfusion, measured using NIRS, remains stable throughout despite positive symptom reproduction in PPS patients.

PPS is a complex conversion disorder characterised by apparent syncope and felt to represent a significant cohort of those with unexplained syncope. Currently, diagnosis relies on reproduction of symptoms during HUT with concurrent video EEG demonstrating lack of hypoperfusion. However, video EEG is not available in many syncope units, is expensive and requires experienced personnel to operate and interpret results, making its routine use complex (495). The results of this study may negate the need for video EEG during HUT to make a PPS diagnosis.

For many years, PPS was considered a diagnosis of exclusion (46, 496) and it is well recognised that patients with PPS often attend several specialists and undergo unnecessary investigations before a clear diagnosis is made. Perhaps, it is for this reason that patients in this study underwent cardiac and radiological investigations prior to attendance at the syncope unit. Clear diagnostic pathways incorporating NIRS cerebral

perfusion measurement during events may refine the assessment of patients with PPS, minimising the need for excess investigations.

10.6 Clinical Relevance of Findings

10.6.1 Early Identification and Risk Stratification

Given the high prevalence of asymptomatic OH detected as part of this thesis, one argues for the screening for OH irrespective of symptoms in older patients and other high risk groups including those with PD and other Parkinson's-plus disorders. Measurement of orthostatic vital signs and not mere symptom assessment should be a routine component of the clinical assessment of patients with difficulty standing. Early identification of patients at risk of future falls may facilitate targeted and personalised interventions to prevent such adverse events.

The studies in this thesis highlight the added value of incorporating NIRS derived measurements into assessment for falls and syncope. While OH has consistently been shown to increase the risk of future falls (315, 324, 476), findings of study 3 demonstrate that OH is a marker of future unexplained falls only when associated with significant contemporaneous drops in cerebral perfusion. Dynamic cerebral perfusion measures in addition to continuous orthostatic BP measurement, may therefore refine falls risk prediction in OH and inform falls prevention strategies.

10.6.2 Hypotension Unawareness

Lack of awareness of hypotension has important implications clinically. Rather than presenting with falls in the context of postural dizziness, people with severe asymptomatic OH are more likely to present with falls without warning or prodrome, raising the suspicion of an arrhythmogenic cause for which the patient may undergo inappropriate testing (7).

Absence of symptoms also makes it more difficult to identify OH as the primary cause of falls, especially when assessment involves less sensitive methods of orthostatic BP measurement such as oscillometric or sitting to standing BP techniques (320).

Findings of this research also raise the issue of how older people with asymptomatic OH should be managed, as addressing postural BP drops in the absence of dizziness or light-headedness may prevent future falls and fracture as well as non-falls related adverse events such as gait impairment, late life depression and cognitive decline.

10.6.4 Hypertension Management in OH

The findings of this thesis are pertinent to the ongoing debate about intensive BP lowering strategies. Despite advancements, managing BP disorders such as hypertension and OH remains a critical challenge to brain health (363, 502). Individuals with both hypertension and OH face a unique treatment dilemma: OH increases the risk of falls, syncope and other adverse conditions while inadequate hypertension treatment is linked to cardiovascular disease, stroke and all-cause mortality. The conventional belief that antihypertensive treatments heighten the risk of OH has been questioned recently by the SPRINT (361) and ACCORD (366) trials, which suggest that targeting lower BP goals does not increase this

risk and may even be beneficial (244, 371). However, critics argue, as mentioned previously, that the stringent inclusion criteria and rigid protocols of these drug trials limit their applicability to real world older populations. Study 3 identified individuals with OH and more marked cerebral hypoperfusion as having the highest risk of future unexplained falls whereas those with milder drops were not at increased risk. This finding offers a potential strategy for selecting patients in the clinic who may benefit from more aggressive BP management. Further studies are needed, however, to validate this potential approach. Given the substantial heterogeneity in BP (311) and cerebral oxygenation (152) responses upon standing evident in the normal population, patients are likely to benefit from an individualised tailored treatment strategy.

10.6.5 Management of Patients with PPS

Management of PPS involves three stages, including diagnosis, communication of the diagnosis and treatment. An early diagnosis and shorter duration of symptoms are linked to a better outcome in conversion or functional neurological disorders (503) with decreased health care costs, health care utilisation and a reduction in subsequent events (481, 498). NIRS is easier to use than traditional EEG and can be successfully incorporated into the workflow of HUT assessments for PPS and hence may reduce time to diagnosis.

Patients who fail to believe their diagnosis of conversion disorder have a poorer prognosis (497). The additional availability of a real-time objective marker of cerebral perfusion can aid in the communication of the diagnosis and provides further biofeedback to PPS patients beyond peripheral haemodynamic measures. This may assist them to accept the

diagnosis and pursue further psychological or psychiatric assessment to gain better control over symptoms.

10.7 Strengths

The main strength of the studies in this thesis is that investigations were carried out in both a clinical real world environment with volunteering patients (Chapters 6 and 9) as well as part of a population cohort of research participants within TILDA (Chapters 7 and 8). The clinical database was carried out in collaboration with Dr Laura Pérez-Denia PhD, a biomedical engineer, who carried out complementary investigations as part of her PhD work. Data was collected prospectively in a large group of patients as they attended the FASU resulting in a unique cohort of individuals with orthostatic BP and NIRS responses in addition to demographic and clinical information.

As mentioned, a particular strength of the studies in Chapters 7-8 of this thesis is the use of the well described TILDA cohort of older people in Ireland. With follow up now over 10 years, TILDA contains a breadth of demographic, social and biological data including novel measures such as continuous orthostatic BP with concurrent NIRS cerebral oxygenation monitoring. The TILDA study is a large population-representative dataset allowing robust longitudinal analyses that can control for important potential confounders.

All studies in this thesis assessed OH by beat-to-beat BP measurement using a finometer during an AS. Cerebral oxygenation was measured using the same device across both cohorts also. This allows accurate characterisation of BP and cerebral oxygenation responses to standing.

10.8 Limitations

There are a number of limitations to the studies in this thesis which should be considered. While these research studies provide evidence for a cross sectional relationship between OH and cerebral hypoperfusion and are supported by other published work, they are observational in nature and cannot imply causation. The direction of the association would need to be confirmed in dedicated prospective randomised studies.

The clinical cohort may be open to selection bias since they were referred to the FASU for evaluation of falls, syncope and dizziness. Additionally, the underlying cause of OH in the participants within this thesis is not known. Studies 2 and 3 did not control for the influence of medications on the findings.

Variables including falls, heart disease and chronic diseases are based on self-report and may therefore be subject to recall bias. Linkage of TILDA data with healthcare services records pertaining to admissions with falls and fracture was unfortunately not possible. This applies equally across all groups in the study, however. At enrolment in TILDA and in the clinical cohort, participants with a history of dementia were excluded, reducing the likelihood of cognitive impairment affecting recall. It is still possible that participants with undiagnosed dementia were included; however, although it should also be noted that there was no significant difference in the proportion of participants with cognitive impairment across the groups in the studies.

Orthostatic BP measurements took place over two minutes rather than three and in studies 2 and 3 only included BP measurements at 30, 60 and 90 seconds post-standing. While this would capture all participants with classical OH, it would possibly omit those with delayed OH, which is also associated with falls and adverse outcomes (471).

Symptoms of OH were not measured using a standardised questionnaire, which may mean that less typical symptoms of OH and severity of dizziness/ light-headedness were not captured. Participants were, however, asked about symptoms directly after the AS, linking symptoms more closely to orthostatic BP changes. It was not feasible to administer a questionnaire during the AS.

The results of the studies within this thesis can only infer an effect on CA mechanisms underpinning CBF regulation as CA itself was not directly measured. Throughout the literature, there is no single method that can be considered a "gold standard" for quantifying CA particularly, dynamic CA (105). The cerebral autoregulatory index is one such frequently reported – albeit derived – measure from TCD recorded CBFv and beat-to-beat BP measurements. The autoregulatory index can be calculated by either the strength of correlation or transfer function between oscillations in BP and CBFv.

As mentioned in earlier chapters, regulation of CBF is determined not just by BP, but many other factors such as respiratory gaseous concentrations, myogenic tone and neuronal activity, none of which were captured in the studies of this thesis. For example, the possibility that respiratory variables such as $PaCO_2$ contributed to the presented findings remains. However, while relatively small changes in $PaCO_2$ and end tidal CO_2 have been reported during standing (279), it seems reasonable to speculate that such changes are unlikely to contribute considerably to the fall in CBF observed in the initial phase of standing (504).

Furthermore, the studies did not account for other variables that influence CBF like exercise, prior caffeine intake and mental stress which may not have remained stable during the AS.

The limitations of NIRS to measure cerebral oxygenation as a surrogate for CBF are discussed in *Section 2.6.7.3 Limitations of NIRS*. SRS NIRS was used throughout the studies in this thesis limiting the contribution of extracranial tissues to cerebral oxygenation levels. To further minimise the potential for extracranial contamination, only relative changes in TSI from baseline rather than absolute TSI levels were used in regression analyses. NIRS only measures cerebral oxygenation levels in the tissue directly beneath the probe and was placed on the forehead to measure frontal lobe CBF. Therefore, it is not known what is occurring in other areas of the cerebral circulation. For example, Sorond et al. (228) suggests that the PCA circulation may be more vulnerable to hypoperfusion. However, despite this, significant changes in frontal lobe cerebral oxygenation were detected in this research. It was not feasible to measure PCA cerebral oxygenation changes.

10.9 Future Directions

The research presented in this thesis has enhanced the understanding of the interplay between OH, cerebral hypoperfusion and falls, revealing several novel clinically relevant findings.

These findings have important clinical implications for the assessment of older people with falls, particularly those without prodrome and unexplained falls. In addition, there are consequences for clinical trials assessing OH as reported symptoms have been shown to correlate poorly with continuously measured orthostatic BP. The mechanisms underlying the threshold for symptoms of orthostatic intolerance and the reasons for hypotension unawareness remain unclear. Therefore, further work is needed to elucidate the natural history and spectrum of symptoms in the setting of severe OH and to determine the most effective methods for their measurement.

Further studies on the influence of medications particularly antihypertensive and psychoactive drugs on cerebral hypoperfusion in OH would be of interest.

The use of NIRS to measure cerebral oxygenation in the falls and syncope arena shows particular promise though some work to improve its validity remain. The research presented in this thesis highlights how NIRS can be successfully incorporated into the busy workflow of a FASU. Further work to integrate NIRS measurements with finometer derived peripheral haemodynamic measures on the same device would be welcome and would facilitate wider use of the technology.

It is hoped that the wealth of clinical and physiological data collected as part of this research may be used to develop decision support tools and machine learning algorithms

to aid clinicians in risk stratification and falls prediction in older adults presenting to the clinic.

Future studies should examine direct measures or indices of cerebral autoregulation to better understand its role in the pathophysiology of OH and syncope.

10.10 Conclusion

OH is prevalent among older people presenting with falls, syncope and dizziness and is associated with several adverse health outcomes. Cerebral hypoperfusion may represent one unifying common pathway in the development of such pathology in those with OH. While some individuals complain of symptoms of orthostatic intolerance, this thesis shows that the majority are asymptomatic. Asymptomatic OH is found to carry a higher risk of unexplained falls possibly due to lack of prodrome or warning signs. Those with OH combined with evidence of greater cerebral hypoperfusion are twice as likely to have future unexplained falls than those with milder perfusion drops on standing and suggests important clinical implications for the assessment and prevention of falls in older people.

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Appendices

1. Search Strategy for Literature Review

EMBASE

#1. 'brain blood flow'/exp

#2. ((‘Brain blood’ OR ‘cephalic blood’ OR ‘cerebral blood’ OR cerebrum) NEAR/2 flow):ti,ab

#3. #1 OR #2

#4. 'brain perfusion'/exp

#5. ((Cerebral OR brain) NEAR/2 (perfusion OR hypoperfusion OR hyperperfusion OR oxygenation)):ti,ab

#6. #4 OR #5

#7. 'abnormal blood pressure'/exp

#8. ((orthostatic OR postural OR depressed OR low OR elevated OR high OR abnormal OR decreas* OR increas*) NEAR/2 ‘blood pressure’):ti,ab

#9. (Hypotension OR hypertension):ti,ab

#10. ((Orthostatic OR postural) NEAR/2 hypotension):ti,ab

#11 #7 OR #8 OR #9 OR #10

#12. #3 AND #6 AND #11

Pubmed

("Brain/blood supply"[Mesh] OR "Cerebrovascular Circulation"[Mesh] OR Brain blood flow*[tiab] OR cephalic blood flow*[tiab] OR cerebral blood flow*[tiab] OR cerebrum blood flow*[tiab]) AND ((Cerebral[tiab] OR brain[tiab]) AND (perfusion[tiab] OR hypoperfusion[tiab] OR hyperperfusion[tiab] OR oxygenation[tiab])) AND ("Hypotension"[Mesh] OR orthostatic[tiab] OR postural[tiab] OR "Hypertension"[Mesh] OR Hypotension[tiab] OR hypertension[tiab] OR ((Depressed[tiab] OR low[tiab] OR elevated[tiab] OR high[tiab] OR abnormal[tiab] OR decreas*[tiab] OR increas*[tiab]) AND blood pressure[tiab]))

2. Patient Information Leaflet & Consent Forms

Falls & Syncope Service

St. James's Hospital, James's Street, Dublin 8

Ph: 4284105 or Fax 4284622

PARTICIPANT INFORMATION LEAFLET

HOSPITAL: St. James's Hospital

DEPARTMENT: Medicine for the Elderly

STUDY TITLE: Characterisation of Peripheral and Central Haemodynamic Measures in Patients Attending a Falls and Syncope Unit

NAME OF PRINCIPAL INVESTIGATORS:

Prof. Rose Anne Kenny (Principal Investigator), Dr. Ciarán Finucane, Dr. Paul Claffey, Ms. Laura Pérez-Denia

You are being invited to participate in a research study. Thank you for taking time to read this. Don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you.

WHAT IS THE PURPOSE OF THE STUDY?

Falls, dizziness and faints can sometimes be explained by changes in blood pressure, heart rate and blood flow to the brain. We wish to further understand the nature of these changes in people who have these symptoms.

WHY HAVE I BEEN CHOSEN TO PARTAKE IN THIS STUDY?

Your doctor has referred you to this clinic because you have been experiencing symptoms such as dizziness, falls or fainting (syncope). As part of your assessment in the clinic, you will have a number of measurements taken that try to explain your symptoms.

WHAT WILL HAPPEN IF I VOLUNTEER TO PARTICIAPTE?

If you agree to take part in the study, your clinical history and the results of your measurements will be entered into a coded database which will be used to look more closely at your blood pressure patterns in a more detailed way. This may improve our knowledge of the underlying conditions causing these symptoms. Because your information is coded, your personal details will not be readily identifiable. Your participation does not require you to attend for any further research investigations or hospital visits.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are no known clinical risks involved in participating in the study. There is a low risk that a connection to your identity could be made. However, great care will be taken to ensure the confidentiality of all data and the risk to participants of a breach of confidentiality is considered very low.

ARE THERE ANY BENIFITS INVOLVED IN PARTICIPATING?

The study will not provide you with any direct benefits and will also not interfere with your normal care. The study however may benefit other people in the future by helping us understand better how the relationship of blood pressure, heart rate and brain blood flow relate to falls, dizziness and faints.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

You don't have to take part in this study. It is entirely voluntary. If you decide not to take part, it won't affect your current or future medical care and will in no way affect your assessment and clinical management in St. James's Hospital. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it will not affect your current or future medical care. You do not have to give a reason for not taking part or for opting out.

WILL MY PARTICIPATION OR WITHDRAWAL HAVE ANY IMPACT ON MY ROUTINE CARE?

Your participation will not affect your routine care.

WILL MY PERSONAL DATA BE KEPT CONFIDENTIAL? HOW WILL MY DATA BE KEPT SAFE?

Your privacy is important to us. We take many steps to make sure that we protect your confidentiality and keep your data safe. Here are some examples of how we do this: Your information will be coded (pseudonymised) and stored on an encrypted password protected database in the Falls and Syncope Unit with access only to the research team. When the study is complete, the database will be fully and irreversibly anonymised. The research team are bound by a strict professional code of confidentiality. Details like your name or address will not be used in any way.

WHO IS THE PERSON RESPONSIBLE FOR MY DATA (THE DATA CONTROLLER)?
Professor Rose Anne Kenny and delegated members of the research team.

WHAT IS THE LEGAL BASIS FOR THE DATA COLLECTION?
Data will be collected as part of your usual health assessment and will be used for research purposes after you have provided informed consent. This research will conform to GDPR Regulations.

WHO ARE THE DATA PROCESSORS?
Professor Rose Anne Kenny and delegated members of the research team.

WILL I BE TOLD THE OUTCOME OF THE STUDY? WILL I BE TOLD THE RESULTS OF ANY TESTS OR INVESTIGATIONS PERFORMED AS PART OF THIS STUDY THAT RELATE TO ME?
The results of the study will be reported in medical journals and disclosed at medical conferences. No information which reveals your identity will be disclosed.

INDEMNITY
Your doctors are insured by the State Claims Insurance Service.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?
Mercer's Institute for Successful Ageing, St. James's Hospital

HAS THIS STUDY REVIEWED BY AN ETHICS COMMITTEE?
Yes, this study was approved by the Joint Research Ethics Committee of St. James's and Tallaght University Hospitals

CONTACT DETAILS

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MERCER'S INSTITUTE FOR SUCCESSFUL AGEING

Falls & Syncope Unit

St. James's Hospital, James's Street, Dublin 8 Ph: 4284105 or Fax 4284622

PATIENT CONSENT FORM – PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

I have read and understood the Participant Information Leaflet.	YES ☐	NO ☐
I have had the opportunity to ask questions and discuss the study.	YES ☐	NO ☐
I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study.	YES ☐	NO ☐
I understand that my clinical notes may be looked at by Prof Kenny and her team at St. James's Hospital where it is relevant to the research. I agree that these individuals can access my records. I understand that all information will be kept private and confidential and that my name will not be disclosed.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care.	YES ☐	NO ☐
I agree to take part in the study.	YES ☐	NO ☐

Participant's Signature: _____Date:_____

Apply Sticker Here

FASU Staff (print): _____

Staff Grade: _____

FASU Staff Signature: _____

Date: _____