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Department of Medical Gerontology

Clinical Decision Support for the Assessment of Syncope and Falls: Novel Applications of Cerebral Perfusion Measurement and Big Data Analytics

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work under the direction of my supervisors Dr. Ciarán Finucane and Professor Rose Anne Kenny.

This thesis was performed in collaboration with Dr. Paul Claffey, who contributed to study design, data collection, results interpretation and discussion of the studies presented.

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Laura Pérez Denia

25th of May 2022

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Glossary of Abbreviations

ACA	Anterior Cerebral Artery	GDPR	General Data Protection Regulation
AD	Alzheimer's Disease	GP	General Practitioner
ADLs	Activities of Daily Living	H ₂ O	Water
AI	Artificial Intelligence	Hb	Haemoglobin
AS	Active Stand	HbO ₂	Oxygenated Haemoglobin
ASL	Arterial Spin Labelling	HHb	Deoxygenated Haemoglobin
AUC	Area Under the Curve	HR	Heart Rate
BBS	Berg Balance Scale	HRV	Heart Rate Variability
BMI	Body Mass Index	HUT	Heat-up Tilt
BOLD	Blood Oxygenation Level Dependent	IMU	Inertial Mass Unit
BP	Blood Pressure	IOH	Initial Orthostatic Hypotension
BRS	Baroreflex Sensitivity	IQR	Interquartile Range
CA	Cerebral Autoregulation	LBNP	Lower Body Negative Pressure
CBF	Cerebral Blood Flow	LDA	Linear Discriminant Analysis
CBFV	CBF Velocity	LOG	Logistic Regression
CI	Confidence Interval	MAP	Mean Arterial Pressure
CMRO ₂	Cerebral Metabolic Rate of Oxygen	MCA	Middle Cerebral Artery
CO	Cardiac Output	MCAv	MCA Velocity
CO ₂	Carbon Dioxide	MFS	Morse Fall Scale
CSH	Carotid Sinus Hypersensitivity	ML	Machine Learning
CSM	Carotid Sinus Massage	MRI	Magnetic Resonance Imaging
CSS	Carotid Sinus Syndrome	MSA	Multiple System Atrophy
CVR	Cerebrovascular resistance	Mx	Mean Velocity Index
DBP	Diastolic BP	NIR	Near-Infrared
DLB	Dementia with Lewy Bodies	NIRS	Near-Infrared Spectroscopy
DPF	Differential Pathlength Factor	NN	Neural Network
ECG	Electrocardiogram	O ₂	Oxygen
ESC	European Society of Cardiology	OCHO	Orthostatic Cerebral Hypoperfusion Syndrome
FASU	Falls and Syncope Unit	OD	Optical Density
FDR	False Discovery Rate	OH	Orthostatic Hypotension
fNIRS	Functional NIRS	OHTN	Orthostatic Hypertension
FRAT	Falls Risk Assessment Tool	OLBNP	Oscillatory Lower Body Negative Pressure

OR	Odds Ratio	TCD	Transcranial Doppler
PaCO ₂	Partial Pressure of CO ₂	THx	Total Haemoglobin Reactivity Index
PAF	Pure Autonomic Failure	TILDA	The Irish Longitudinal Study on Ageing
PCA	Posterior Cerebral Artery	TLOC	Transient Loss of Consciousness
PD	Parkinson's Disease	TOI	Tissue Oxygenation Index
PET	Positron Emission Tomography	TOx	Tissue Reactivity Index
POMA	Performance-Oriented Mobility Assessment	TPR	Total Peripheral Resistance
POTS	Postural Orthostatic Tachycardia Syndrome	TSI	Tissue Saturation Index
PPS	Psychogenic Pseudosyncope	TUG	Timed Up and Go
PRx	Pressure Reactivity Index	UF	Unexplained Falls
QDA	Quadratic Discriminant Analysis	UFS	Unexplained Falls or Syncope
RF	Random Forest	VVS	Vasovagal Syncope
ROC	Receiver Operating Curve	XeCT	Xenon-Enhanced Computed Tomography
ROSE	Risk Stratification of Syncope	$\Delta[\text{HbO}_2]$	Changes in Concentration of Oxygenated Haemoglobin
RR	Risk Ratio	$\Delta[\text{HHb}]$	Changes in Concentration of Deoxygenated Haemoglobin
SBP	Systolic BP	$\Delta[\text{tHB}]$	Changes in Concentration of Total Haemoglobin
SD	Standard Deviation		
SPECT	Single-Photon Emission Computed Tomography		
SRS	Spatially Resolved Spectroscopy		
STRATIFY	St Thomas Risk Assessment Tool in Falling Elderly Inpatients		
SV	Stroke Volume		
SVM	Support Vector Machine		
SVMLin	Linear Support Vector Machine		
SVMRad	Radial Support Vector Machine		
TBI	Traumatic Brain Injury		

Thesis Summary

Syncope, defined as a transient loss of consciousness due to cerebral hypoperfusion, is common in both young and old, with syncope an attributable cause of unexplained falls (UF) in older adults. Both syncope and falls have significant negative physical and psychosocial consequences for an individual, with high associated healthcare costs (\$2.4 billion/year) at a societal level. Identification of causative and modifiable risk factors for syncope and falls is therefore paramount.

International guidelines recommend the Active Stand (AS) test with concurrent monitoring of continuous blood pressure (BP) and heart rate as part of a comprehensive clinical assessment. Despite the presumed causal role of cerebral hypoperfusion in syncope and UF, no direct measure of cerebral perfusion is currently used in clinical assessment. Near-infrared spectroscopy (NIRS) has emerged in recent years as a candidate tool for this purpose, enabling easy, continuous monitoring of cerebral oxygenation during dynamic testing.

In this thesis, four studies were developed to investigate the clinical utility of applying NIRS in this context, with the overarching goal of developing explainable AI/ML based clinical decision support tools to assist in the management of these complex patients. Firstly, NIRS was integrated into standard patient assessments, enabling the collection of cerebral oxygenation signals during the AS from a large cohort of consecutive patients attending a national Falls and Syncope Unit. This dataset was then integrated with population data from The Irish Longitudinal Study on Ageing (TILDA) resulting in a unique harmonised database of clinical information, and peripheral and cerebral circulation measures. A software framework was developed to automate signal processing, feature extraction, statistical analysis and fitting of artificial

intelligence/machine learning (AI/ML) models to this high dimensional data for predictive modelling.

Novel findings suggest that both age and sex strongly modulate cerebral oxygenation responses to standing. In young patients with syncope, peripheral cardiovascular hypersensitivity with unaltered cerebral oxygenation responses to an AS were observed, suggesting a peripheral origin of syncope, with no alterations in cerebral function evident. In older adults, multimorbidity/frailty was strongly associated with impairments in cerebral oxygenation independent of BP, suggesting that biological ageing is associated with repeated periods of hypoperfusion, increasing vulnerability of these individuals and potentially accelerating their rate of biological ageing. Lastly, novel explainable AI/ML models were developed for the first time, combining multimorbidity, BP and cerebral oxygenation to identify patients with UF and syncope with high accuracy (~75%), enabling the development of future clinical decision support tools to assist in the management of these patients. These explainable AI/ML models also provide novel insights into possible physiological mechanisms underlying syncope and UF, supporting the hypothesis that UF are central in origin, associated with more significant brain ageing and pathology, while syncope is likely present in those with younger intact brains with a peripheral origin. Overall, an independent future role for NIRS may be found in the assessment of brain ageing in older adults at risk of syncope and UF.

In conclusion, this work has furthered the scientific knowledge on orthostatic cerebral oxygenation in those with syncope and UF, while also highlighting the role of multimorbidity in these responses. Importantly, this thesis demonstrates the clinical value of using NIRS in the assessment of patients with syncope and falls. Additionally, it contributes to the development of a future AI/ML based clinical decision support tool

to assist clinicians in both community and specialised clinical settings, aiding in the early identification of patients at risk of falls and syncope. This tool has the potential to assist in the design of appropriate personalised interventions to prevent the occurrence of such episodes, and ultimately improving a patient's quality of life.

Lay Abstract

Fainting, which is defined as a temporary loss of consciousness due to low blood flow to the brain, is common in young and older adults. Additionally, one in three older adults fall at least once every year, with some of these falls being also related to reduced brain blood flow. In specialised clinical settings, falls and faints are investigated by measuring continuous heart rate (HR) and blood pressure (BP) while performing an active standing (AS) test, i.e., after the patient has been lying on a bed for 5-10 minutes, they stand up by themselves (or with help if necessary) and stay standing for 3 more minutes. However, even if falls and faints are related to the blood flow to the brain, this is not measured in standard practice during the AS test. Near-infrared spectroscopy (NIRS) is an emerging technology that allows the continuous measurement of brain oxygenation during the AS as a surrogate for brain blood flow in a non-invasive way. In this thesis, the role of NIRS in the assessment of patients with falls and faints during an AS test has been explored, with the overall goal of developing software that uses advanced methods of data analysis to help clinicians in the evaluation and management of these patients.

NIRS devices were incorporated in a falls and syncope specialist unit to collect brain oxygenation information during a patient's clinical visit, while they performed the AS test. HR, BP and other peripheral circulatory signals were also measured. These brain and peripheral signals, together with information regarding the medical history of patients, constituted a database that is unique in the world. Furthermore, this database was combined with an equivalent database of information from individuals living in the community participating in The Irish Longitudinal Study on Ageing (TILDA). Software was developed to allow the analysis of all these data, from extracting important signal features, to performing statistical analysis to understand the

relationship between brain oxygenation and clinical characteristics of patients. Advanced analysis methods known as artificial intelligence and machine learning (AI/ML) algorithms were implemented in this software.

The results from this thesis demonstrated that age and sex are important factors to consider when investigating brain oxygenation in patients with falls and faints. In young patients with faints, brain oxygenation demonstrated little differences when compared to healthy young volunteers, while their BP responses during the AS were exaggerated. These differences in BP indicate that their cardiovascular system is overly active, which might predispose them to fainting. In older adults, it was observed that with more accumulation of medical conditions a slower recovery in brain oxygenation after standing is present. These results suggest that frailer patients (with more medical conditions) might be more susceptible to short episodes of low brain blood flow, which might put them at risk of falls, faints and developing more medical conditions. Lastly, AI/ML algorithms were used to differentiate between patients with falls/faints and individuals from the community (TILDA) without falls/faints. These algorithms were successful in identifying patients with falls/faints (approximately 75% correctly identified), and represent the first step in the development of software that will help clinicians in the assessment of these patients.

To conclude, this thesis has provided new knowledge on the brain oxygenation responses to standing in patients with faints and falls. The role of medical conditions accumulation has also been highlighted, which might help identify patients at risk of low brain blood flow. AI/ML methods have proven successful in identifying patients with falls and faints. These results contribute to the future development of software that will help clinicians in identifying patients with high risk of future faint and falls,

therefore assisting in the prevention of these events and improving the quality of life of these patients.

Value of Research

The work presented in this thesis has multiple valuable impacts. Firstly, this thesis has demonstrated that NIRS can be successfully incorporated in a clinical setting, allowing for easy data collection in a large number of patients. This might motivate the future integration of NIRS in routine clinical practice, providing direct information about the circulation in the brain of patients. In particular, in the case of patients with falls and faints, the results from this thesis demonstrate that NIRS provides additional information to the BP and HR data already collected in standard practice.

Higher accumulation of medical conditions in older patients with falls and faints was demonstrated to be related to a slower recovery of brain oxygenation after standing. These findings can impact clinical practice by quickly identifying patients at a higher risk of low brain blood supply based on the information collected during clinical history taking.

Regarding the methodologies used in this thesis, some valuable research outputs can be highlighted. First, the most valuable information extracted from the signals were features from the initial response after standing (i.e., first 30 seconds), reinforcing the use of continuous beat-to-beat methods of BP and brain oxygenation measurement during the AS test. The use of AI/ML in combination of BP and brain oxygenation measures is novel, and encourages the development of more AI/ML models that can predict future falls and faints in other clinical and community populations. Additionally, the models developed are created using a method that allows understanding what is the importance of each of the components of the model, which represents relevant information for clinicians.

In conclusion, this thesis presents several novel contributions that will be valuable in the future development of a computer program to help clinicians in deciding what clinical strategy to follow to treat and manage patients. This program could be used in specialised falls and faints units, but could also be incorporated in broader community settings as a new screening tool to identify patients at risk and prevent the occurrence of future faints and falls.

Publications Arising from this Thesis

Journal Papers

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Chapter 1: Introduction

1.1 Motivation for this Thesis

Syncope, commonly known as a faint, is defined as a transient loss of consciousness (TLOC) due to cerebral hypoperfusion that resolves in a rapid and spontaneous manner [1]. In the general population, syncope has a crude cumulative rate of 18-40 per 1000 person-years [2], although it is greatly underrepresented in medical settings, with only 9.3 visits per 1000 person-years to a general practitioner (GP) [2]. The distribution of new syncopal episodes is bimodal [1]. A very high prevalence of first-time syncope is found in individuals aged 10-30 years, peaking at 15 years of age, with very few individuals fainting in the range 35-60 years [3] (see Figure 1.1). In young adults, some studies have reported that before the age of 24, 24% of men and 47% women have experienced at least one episode of syncope [4]. A second peak is found after 65 years, and incidence keeps increasing with age with a sharp increase after 70 years [5] (see Figure 1.2). Therefore, there are two main populations affected by syncope: young adults and older adults.

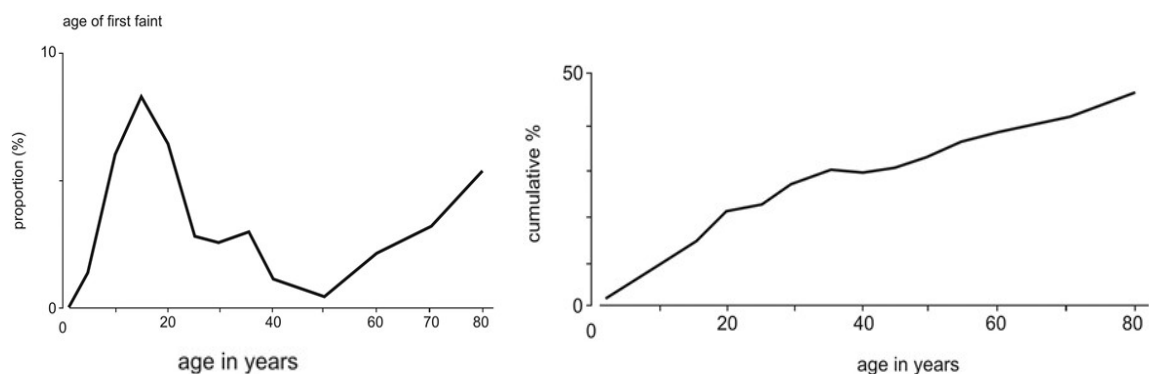


Figure 1.1. Demographics of syncope.
Proportion (left) and cumulative incidence (right) of first-time syncope in the general population for individuals aged ≤ 80 years [3].

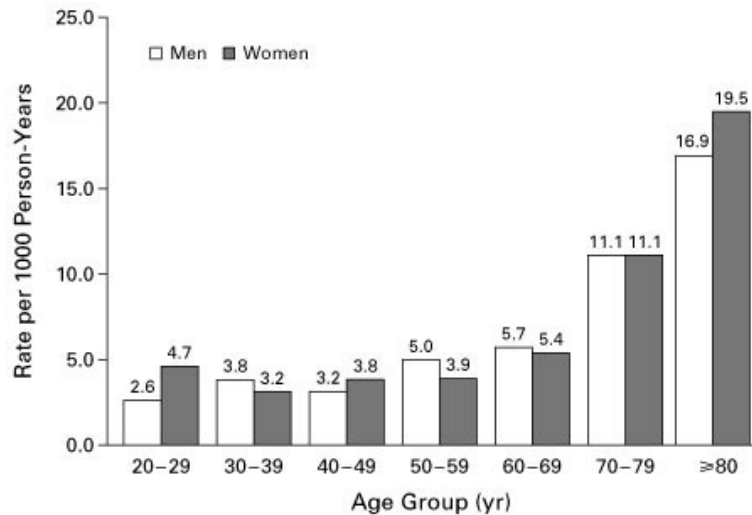


Figure 1.2. Incidence of syncope.

Incidence rate of syncope for 10 age periods for men and women (age range 20-96 years) [5].

The most common cause of syncope for all ages is vasovagal syncope (VVS), especially in the younger population [3]. While VVS is benign, it can severely impact the life of patients across physical, and psychosocial domains [3]. Furthermore, these patients are often misdiagnosed with epilepsy, leading to unnecessary stress and medical assessments [6, 7]. In patients with 6 or more accumulated syncopal episodes during their lifetime, the perception of health is negatively associated with the frequency of their episodes [8]. Quality of life indicators comprising areas such as physical functioning, social functioning, vitality or emotional status are all demonstrably reduced in syncope patients [9] especially in women, and in those with higher comorbidity accumulation and recurrence of syncope [9].

In the emergency department, 1-5% of the referrals are due to syncope, 50% of them leading to hospitalisation with more than 75% of these being unnecessary [1]. In the USA, the average cost of hospitalisation due to syncope was \$5400 in 2004, amounting to a total of \$2.4 billion/year [10]. A similar situation has been reported in

European countries, with an average cost of €2785 in Italy [11] and €11158 in Spain [12] for syncope-related admissions.

As previously stated, VVS is by far the most common form of syncope in young populations [3, 4]. While VVS is also the most common cause of syncope in older adults, other causes such as orthostatic hypotension or cardiac causes are also common in this population [3]. Furthermore, in older adults it is thought that syncope often presents as unexplained falls (UF) [13]. Amnesia for loss of consciousness combined with lack of eye witness accounts makes it hard to establish a clear separation between falls and syncope [13, 14]. For that reason, international guidelines for the management of syncope recommend that the investigation and management of UF (i.e., falls that cannot be attributed to a mechanical cause) follows a similar protocol as unexplained syncope [1].

One in three community dwelling adults over the age of 65 years experience at least one fall every year, with this proportion increasing to over 40% in adults over the age of 75 years [15]. Falls, even when non-injurious, have a huge impact on an individual's quality of life, contributing to the development of fear of falling, leading to decreased balance, confidence and anxiety [16]. Fear of falling develops in 21-85% of older adults after experiencing a fall, resulting in reduced physical and mental status, an increased risk of recurrent falls and a decline in quality of life [17]. Furthermore, one in four falls results in injury [18], including fractures (hip, wrist, pelvis, etc.) and other serious injuries such as head trauma, and joint dislocations [19]. In frailer patients these injuries can necessitate hospitalisation and nursing home admission [20]. In the worst cases, falls can lead to death, with over 35,000 older adults dying annually due to falls in the EU [21].

Falls represent a huge economic burden for healthcare systems [22], accounting for a significant proportion of GP visits, ambulance transportation, emergency department visits, hospital admission and stay, long term care and home care [20]. The average cost of a fall is estimated to be €9,730, although it is higher for women (€9,990) than men (€7,510), and increases with age, reaching a cost of up to €14,600 in older adults over the age of 85 years [20]. It has been demonstrated that falls prevention strategies are effective in 43% of falls [23], with some of these interventions including exercise, medication or home environment modifications [24]. Identifying those individuals at a higher risk of falls is therefore paramount. Another important factor to consider in the assessment of falls and syncope in older adults is frailty. Frailty can be defined as an increased vulnerability to stressors resulting from the accumulation of morbidities and health deficits, leading to an increased risk of adverse outcomes such as falls or disability [25]. Both falls and frailty are multifactorial, being the result of accumulated impairments in multiple systems [26] with frail older adults at an increased risk of falling [27].

International guidelines recommend an active stand (AS) test for the investigation and management of both falls and syncope [1]. The blood pressure (BP) and heart rate (HR) responses to AS testing yield biomarkers of cardiovascular function, autonomic control and syncope [28]. Impaired BP and HR responses are also risk factors for falls [29], morbidity [30], mortality [31, 32] and are associated with frailty [33] and accelerated brain ageing [34]. Symptoms of orthostatic intolerance are believed to be associated with cerebral hypoperfusion in some individual. Asymptomatic forms of orthostatic BP and HR impairments are common and may put patients at a higher risk of mortality and cardiovascular morbidity [35, 36]. Recent studies have also indicated that forms of symptomatic orthostatic intolerance due to

cerebral hypoperfusion also exist in the absence of clinically significant BP drops following standing [37]. Despite this evidence, cerebral perfusion is not monitored in standard clinical practice for the assessment of falls and syncope, and is only inferred from peripheral circulation, clinical history, and symptoms of orthostatic intolerance.

Near-infrared spectroscopy (NIRS) is emerging as a convenient tool that enables the measurement of cerebral oxygenation during dynamic manoeuvres such as the AS test. NIRS enables measurement of changes in concentration of oxyhaemoglobin ($\Delta[\text{HbO}_2]$) and deoxyhaemoglobin ($\Delta[\text{HHb}]$), as well as a tissue saturation index (TSI), as surrogates of perfusion [38, 39]. Very few studies have examined NIRS responses in a falls and syncope cohort, with a dearth of knowledge surrounding the spectrum and clinical importance of normal and abnormal NIRS responses in both young and old patients.

Cerebral oxygenation is known to decrease in young adults during syncope induced by head-up tilt (HUT) testing [40]. The HUT test is much more cumbersome and uncomfortable for the patient than the AS. Therefore, identifying biomarkers of syncope from AS testing would help in developing easier and more comfortable diagnosis and management strategies for these patients. Furthermore, haemodynamic responses to an AS test can help us understand the neurocardiovascular physiology of these individuals. In older adults, the literature surrounding cerebral circulation and adverse outcomes in this population is limited [41]. Furthermore, although it is known that orthostatic peripheral circulation is impaired with frailty [33, 42-44], little is known about the link between frailty and cerebral circulation during standing.

Recent advances in machine learning (ML) and artificial intelligence (AI) can facilitate tasks such as risk prediction for complex outcomes such as falls and syncope,

and detect novel and important patterns within large multimodal physiological databases. Despite the considerable amount of literature dedicated to the classification of fallers using ML approaches [45-47], to the best of the author's knowledge, none of these studies have used peripheral or cerebral circulation signals for this purpose. Furthermore, they have not considered UF and syncope as outcomes with the impact of frailty on these methodologies unexplored. ML has also been used for the prediction of syncope, although in the majority of cases studies have developed models to predict HUT responses, with very few studies focusing on a clinical diagnosis of VVS or cohorts of older adults.

This thesis aims to address the following challenges:

- 1) Characterising patterns of NIRS derived cerebral oxygenation in patients investigated for falls and syncope using the AS test
- 2) Relating the different patterns to clinical outcomes of the patients
- 3) Investigating the modulating effect of frailty in a subset of older patients

Modern AI/ML approaches are applied to determine what features are most appropriate for the identification of patients at risk of syncope and falls as well as creating models for future clinical decision support tools.

1.2 Thesis Outline

This thesis is structured according to the following outline. **Chapter 1** provides a general overview and rationale for this thesis. In **Chapter 2** a general background on falls and syncope assessment, and cerebral circulation physiology and measurement are presented. Emphasis is placed on the technical basis and limitations of NIRS given that it is the primary method used in this thesis. Furthermore, how different falls and syncope related factors and conditions are associated with cerebral and peripheral

responses to standing are reviewed. **Chapter 3** presents a systematic literature review on the use of ML for the classification of falls and syncope, and at the end of the chapter the main gaps identified in the literature are highlighted. **Chapter 4** details the primary research questions of this thesis. In **Chapter 5** the general methodologies developed during this thesis are discussed, including study design, ethical considerations, data collection and database harmonisation processes. Details of the analytical pipeline and software developed to facilitate study analysis are also provided. In **Chapter 6** age and sex associations with the cerebral oxygenation responses to standing are studied in a cohort of patients with falls and syncope, to establish whether these factors needed to be accounted for in the subsequent studies of this thesis. **Chapter 7** details a study investigating cerebral oxygenation responses to active standing in young patients with VVS in comparison to healthy controls. **Chapter 8** presents the results of a novel investigation of the relationships between multimorbidity and cerebral oxygenation responses in a cohort of older adults with falls and faints, and **Chapter 9** provides the results of the first study to apply AI/ML to classify individuals with syncope and UF using a novel harmonised dataset created during this thesis. Lastly, **Chapter 10** provides an overall discussion of the findings of the thesis, an overview of its strengths and limitations, and a discussion focussed on future directions. A set of **Appendices** provide details on additional papers published (or in review) co-authored in collaboration with local, national and international collaborators, as well as extended detail on the informed consent documents provided to patients, the software framework developed, the protocol used and the signal quality evaluation criteria implemented. Lastly, the supplemental material for Chapters 7-9 is presented.

Chapter 2: Background

This chapter provides a summary of background literature relevant to this thesis.

Initially, current standards of falls and syncope assessment in specialised clinics are presented. Subsequently, cerebral circulation anatomy, physiology and measurement is discussed with reference to falls and syncope assessment, with a focus on near-infrared spectroscopy, for which a review of the available methodologies and known limitations is provided. Lastly, the spectrum of peripheral and cerebral circulatory responses to the AS test encountered in health and disease are discussed.

2.1 Assessment of Falls and Syncope

This section presents an overview of how falls and syncope affect young and older adults, and highlights the value of Falls and Syncope dedicated services for the assessment and management of these patients. The Active Stand (AS) test is then described, with normal and impaired responses of this test considered.

2.1.1 Syncope in the Young

As discussed in the Introduction (Chapter 1), syncope is common in teenagers and young adults, with the median age for developing the first syncopal episode being 15 years [4]. In a group of 377 medical students (mean age 21 years), approximately 1 in 3 reported having had syncope at least once in their lives, with 24% and 47% of the men and women, respectively, reporting syncope before the age of 24 years [4]. A

similar prevalence was observed in university students and workers (mean age 22.4 years), with almost 30% of them reporting an episode of transient loss of consciousness (TLOC) in their lifetime [48]. They also observed a sex difference, with women being 2.4 times more likely to have a syncopal episode and having a higher prevalence of recurrent TLOCs. Some of the main factors that trigger these episodes are a warm environment, standing for prolonged periods of time, fasting, pain or emotion [4, 48]. The origin of these episodes is considered to be vasovagal (i.e., vasovagal syncope (VVS)) rather than cardiac in nature.

Psychogenic Pseudosyncope (PPS) has also been observed in young individuals (also rarely occurring in older adults), representing 1-12% of the patients seen in specialised falls and syncope units [49, 50]. Our recent work demonstrated that PPS is characterised by an apparent TLOC uncorrelated to neither drops in peripheral nor cerebral circulation [49]. These patients tend to have frequent episodes (can happen multiple times every month, week or even day), of long duration, and occurring in the presence of a witness, and are often related to psychiatric disorders [50]. Furthermore, these patients are often diagnosed with VVS, which has been shown to coexist with PPS in almost 50% of the patients [51], but can lead to a missed diagnosis of PPS, limiting the success of the subsequent prescribed management approaches.

For more details on our investigations on PPS refer to Appendix A – which provides details of a case series published as part of this thesis, entitled “*Near-infrared Spectroscopy in Evaluating Psychogenic Pseudosyncope—a Novel Diagnostic Approach*” [49].

2.1.2 Syncope and Falls in Older Adults

The world is ageing. In their 2019 revision of the World Population Prospects report by the United Nations, it was announced that, in 2018, for the first time in history, the population of older adults over the age of 65 years outnumbered that of children under the age of five [52]. It is estimated that by 2050 one in six people in the world will be aged 65 years or more, a proportion that becomes one in four in Europe and Northern America. Furthermore, by 2050, persons over the age of 80 years are expected to triple.

Falls are a major problem in the older population over the age of 65 years. One in three community-dwelling adults in this age cohort experience at least one fall per year [15]. With increasing age, falls become even more prevalent, with 40% of older adults over the age of 75 years falling at least once a year.

Falls have a negative impact on the quality of life of these patients through a range of negative health outcomes. Falls are associated with an increased risk of morbidity and mortality, and 5-10% of falls result in injury (bone fracture, head injury, skin laceration, etc) [53]. One of the most serious injuries are hip fractures, causing 25%-75% of individuals experiencing them not to recover to baseline level of mobility and daily activities [54]. Furthermore, injurious falls are associated with a higher risk of nursing home placement in community-dwelling adults [15]. In the United States, unintentional injuries have been identified as the seventh leading cause of death, with falls being the main factor causing these injuries [55], and patients developing a sustained hip fracture having a 20-30% higher mortality rate at 1 year follow-up [54].

Another consequence of falls that hugely impacts quality of life is fear of falling. This results from a combination of other fears such as fear of harm, functional

incapacity, loss of independence, pain, terminal physical decline and social embarrassment [56]. A meta-analysis of 21 studies analysing fear of falling in community-dwelling adults revealed that its prevalence ranged between 21-85%, and that one in two non-fallers also develops this fear [17].

Cardiovascular causes of falls are increasingly recognised especially in older adults [13]. In a study of unexplained falls (UF) presenting to the emergency department, 77% of the individuals had cardiovascular abnormalities such as orthostatic hypotension, carotid sinus hypersensitivity, VVS and arrhythmia [14]. While falls are defined as unexpected events in which an individual drops to the ground or to a lower level without losing consciousness [13], syncope is defined as a TLOC due to cerebral hypoperfusion that resolves in a rapid and spontaneous manner [1]. Patients with UF often lose consciousness (i.e., experience a syncope) without being aware of it [57]. Moreover, in a patient cohort of unexplained fallers and fainters, it was demonstrated that 28% had amnesia for loss of consciousness during head-up tilt (HUT) syncope provocation [58]. Another study of older adults presenting with symptoms of dizziness, syncope or UF, demonstrated that 30% of the patients who were diagnosed with carotid sinus syndrome had amnesia for loss of consciousness during carotid sinus massage [59]. The amnesia for loss of consciousness [60] combined with the lack of an eye witness in 60% of these cases [61] makes it challenging to distinguish between a fall and a syncopal event. These reports highlight that amnesia for loss of consciousness is a common presentation of UF and provide evidence that there is an overlap between falls and syncope [62]. As a result, The European Society of Cardiology (ESC) guidelines for the management of syncope recommend the management of UF (i.e., falls that cannot be attributed to a mechanical cause) to be the same as that of unexplained syncope [1].

2.1.3 Falls and Syncope Units

Physicians frequently encounter falls and syncope in an emergency department setting [63]. To reduce the burden of patients in this clinical setting, different models of falls and syncope units have been established across the globe [64, 65], with some reducing up to 80% of hospital admissions [66, 67]. In fact, the ESC recommends establishing falls and syncope units [1], which have been defined as:

“A facility featuring a standardized approach to the diagnosis and management of TLOC and related symptoms, with dedicated staff and access to appropriate diagnostics and therapies. The syncope unit should also take the lead in educating and training clinicians who encounter syncope.[64].”

Two of the primary cardiovascular tests performed in specialised falls and syncope services are the AS and the HUT tests [1]. The AS test, consisting of a resting period followed by a 3 minute stand, is indicated for the diagnosis of different manifestations of orthostatic intolerance such as Orthostatic Hypotension (OH), delayed OH, initial OH or Postural Orthostatic Tachycardia Syndrome (POTS) [1]. The HUT test consists of tilting a patient on a bed up to 70 degrees to provoke a syncopal episode or reproduce symptoms of orthostatic intolerance. It is recommended for some forms of orthostatic intolerance such as OH or POTS, as well as when VVS or PPS are suspected [1]. Furthermore, the educational role of HUT has been acknowledged in helping patients recognise and manage their symptoms [1].

Another important test is Carotid Sinus Massage (CSM), consisting of pressure applied to the neck at the level of the carotid bifurcation in order to stimulate the baroreflex [68]. CSM allows the identification of Carotid Sinus Hypersensitivity (CSH) and Carotid Sinus Syndrome (CSS) when a TLOC has suspected cardiac origin [69,

70]. A positive diagnosis of CSS is an indication for a cardiac pacemaker, which has been shown to reduce the number of falls (odds ratio: 0.23) after the intervention [70].

Given the focus of this thesis, the next section provides more detail about the protocol and responses obtained during an AS test.

2.1.4 The Active Stand Test

2.1.4.1 Active Stand Protocol

An AS test is a simple lying to standing manoeuvre. The word ‘active’ is used to emphasise that the patient has to actively move during the test, as opposed to other ‘passive’ tests such as the HUT test, which do not require an active involvement of the patient. Our group has published a practical guide in which the protocol is described in detail [71]. This guide recommends a lying duration of 5-10 minutes to allow haemodynamic stabilisation, as lower resting times can lead to unstable baselines and longer periods to larger drops in blood pressure (BP) upon standing [72]. A countdown can be used to indicate the subject when to stand. Patients are instructed to change posture as briskly as possible, which takes less than 3s in healthy young adults. However, older adults with mobility issues may require a longer time and, in many cases, assistance. Patients are then asked to remain standing for 3 minutes [1, 71]. Before the start of the test, patients are asked to minimise arm movement where devices are used to measure BP, and to remain silent unless symptoms are too severe. Event markers can be used to record the time of symptoms [71]. The testing environment is recommended to be quiet and maintained at a temperature of 21-23 °C, with the light dimmed. Controlling temperature is important, as warm environments can cause vasodilation and cold temperatures vasoconstriction, increasing and decreasing the probability of OH during standing, respectively [71].

2.1.4.1.1 Haemodynamics Monitoring during the Active Stand Test

In the late 60's, a revolutionary method to non-invasively measure blood pressure was developed by the Czech physiologist Jan Peñáz [73]. This is known as the volume clamp method (see Figure 2.1). This approach uses an inflatable finger cuff with an inbuilt photo-plethysmographic system, which transmits infrared light through the finger to measure the changes in the digital artery diameter. The principle of the method is to keep this diameter constant (hence the name 'volume clamp') at a point in which the arterial wall is unloaded. This is achieved when the transmural pressure, defined as the difference between extra-arterial and intra-arterial pressure ($p_{\text{transmural}} = p_{\text{extra-arterial}} - p_{\text{intra-arterial}}$), is zero [74]. First, the diameter corresponding to the unloaded vessel wall ($p_{\text{transmural}} = 0$) is found, and it is established as a reference set point. Then, the infrared plethysmograph monitors the diameter of the arterial finger, which naturally varies with the heartbeat, and a fast feedback loop maintains it unchanged at the reference set point by applying counterpressures on the finger with the pneumatic cuff. If the diameter is successfully maintained at the unloaded set point, then the transmural pressure is successfully kept at zero, and therefore $p_{\text{transmural}} = p_{\text{extra-arterial}} - p_{\text{intra-arterial}} = 0$. This implies that $p_{\text{extra-arterial}} = p_{\text{intra-arterial}}$, and thus, the pressure applied in the cuff (extra-arterial) equals the intra-arterial pressure in the finger.

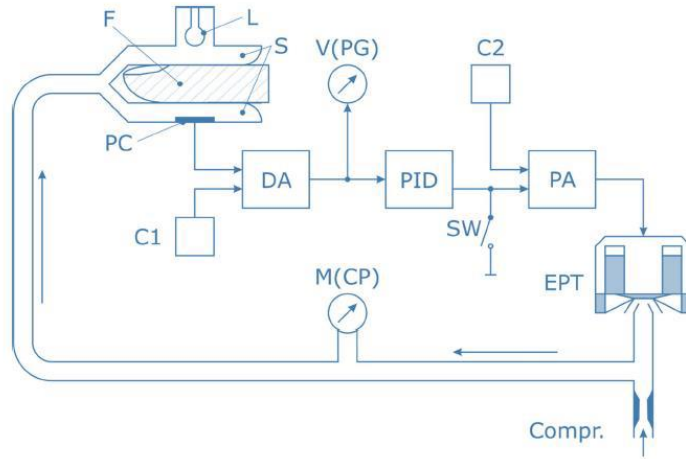


Figure 2.1. Finometer block diagram.

Block diagram representing the system developed by Peñáz, implemented in beat-to-beat continuous blood pressure devices. *F* = Finger, *L* = light source, *PC* = photo cell detector, *S* = pressure cuff, *C1* = *PC* signal average, *C2* = setpoint, *DA* = difference amplifier, *PID* = correcting network, *PA* = power amplifier, *SW* = switch between open and closed loop, *EPT* = electro-pneumatic transducer, *M(CP)* = pressure measured with manometer (image adapted from [74]).

Despite its ingenuity, this method still involves overcoming a complicated challenge: finding the set point. This is challenging because the set point is different for each individual and varies over time. It depends on a wide range of factors such as age, haematocrit content, arterial wall smooth muscle cells, temperature or pathology, amongst others [75]. To tackle this problem, in 1995, Wesseling et al. developed Physiocal, a criterion based on the arterial pressure-vessel diameter relationship variations with smooth muscle tone, in which a morphological feature of the plethysmograph signal is used to bring the vessel diameter back to the set-point by modifying the cuff pressure [75].

In order to obtain a blood pressure waveform as close as possible to that of central arteries, two more steps are required. First of all, a height correction unit is needed to account for the hydrostatic pressure difference resulting from the vertical distance difference between the finger and the heart [71]. Secondly, the distortion that the pressure waveform undergoes when travelling from the arm to the finger has been described by a transfer function. This is then used to create an inverse filter that allows

reconstructing the brachial blood pressure waveform from the recorded finger waveform [76].

Despite all the efforts in providing an accurate absolute measure of brachial blood pressure, the method is still not within the limits established by the AAMI standards, and its use is therefore not advised for monitoring absolute values [71, 76]. However, it has been extensively used and recommended for tracking dynamic changes in blood pressure [71], and can therefore be used to track changes from baseline during the AS test.

2.1.4.2 Normal Response to an Active Stand Test

Standing up from a lying position elicits a particular cardiovascular response in peripheral haemodynamics, which has been well described in the literature [28, 77]. Upon standing, there is a transient decrease in BP with a simultaneous increase in heart rate (HR). In the HR response, there is a first peak at 3s attributed to a reflex inhibition of vagal stimulation as a result of voluntary muscle contraction, followed by a larger and more progressive increase peaking at 12s. This second peak is a baroreflex-mediated mechanism and is a consequence of the drop in BP, which causes a decrease in baroreceptors activation. This leads to a further inhibition of the vagal outflow through the parasympathetic nervous system with a simultaneous sympathetic activation of the sinus in the heart, both effects resulting in an increase in HR [28].

Sympathetic activity also leads to increased peripheral vasoconstriction [28]. Regarding BP, standing causes a compression of veins in the legs and abdominal area, increasing venous return to the right atrium, which increases right atrial pressure. This effect, in combination with the already described increase in HR leads to an increase in cardiac output (CO). By looking at the physiological definition of BP, i.e., $BP = CO \times$

total peripheral resistance (TPR), it can be seen how, if CO increases, BP will only be maintained at a constant level if TPR decreases by the same amount. However, activation of muscles in the legs due to the active nature of the manoeuvre results in vasodilation, causing a decrease in TPR that exceeds the increase of CO - the net effect being a decrease in BP. The decrease in BP is therefore explained by an acute mismatch between the supply and demand of blood flow within the systemic system [77]. This drop in BP is only transient, with its nadir at approximately 10s after standing, recovering back to baseline by 20-30s in healthy individuals [28]. This recovery is achieved by the baroreflex-mediated HR above described, as well as vasoconstriction, which is achieved through sympathetic activation of resistance vessels [78]. Figure 2.2 shows a normal response in BP and HR to an AS test.

For a detailed discussion of this topic please refer to Appendix B – which provides details of a review article published as part of this thesis, entitled “*Systemic and cerebral circulatory adjustment within the first 60 s after active standing: An integrative physiological view*” [78].

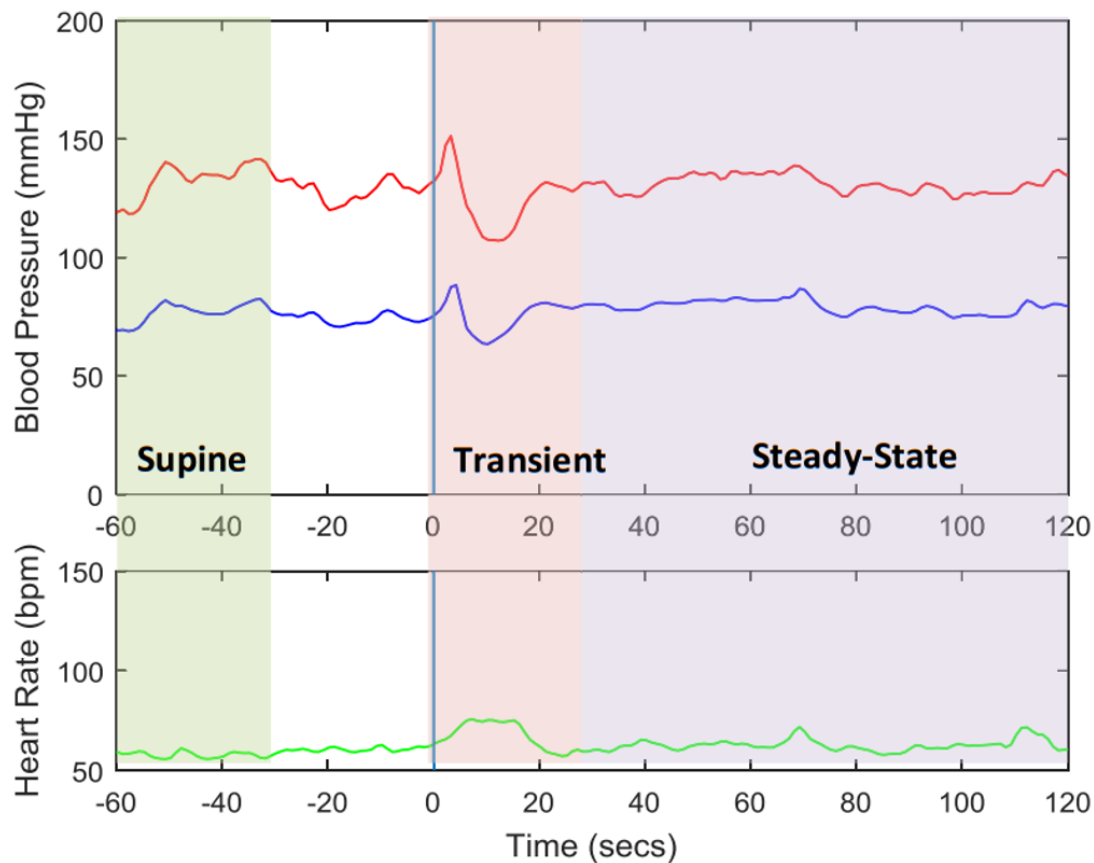


Figure 2.2. Normal responses to an Active Standing test.

Normal systolic (top, red) and diastolic blood pressure (top, blue), and heart rate (bottom, green) responses to an Active Stand test (image adapted from [71]).

2.1.4.3 Impaired Responses to an Active Stand Test

The previously described haemodynamic response to standing can be impaired as a result of ageing and disease. In this section the most commonly known impaired responses to an AS test are described, and the criteria used for their diagnosis using thresholds for systolic BP (SBP), diastolic BP (DBP) and HR [1] (graphs from [71]) are provided. The main responses are:

Classical Orthostatic Hypotension

(OH) (see Figure 2.3):

- In normotensive individuals: sustained drop from baseline ≥ 20 mmHg in SBP OR ≥ 10 mmHg in DBP from 60 to 180s after standing; OR a drop in SBP below 90 mmHg.
- In hypertension: sustained drop from baseline ≥ 30 mmHg in SBP OR ≥ 15 mmHg in DBP from 60 to 180s after standing.

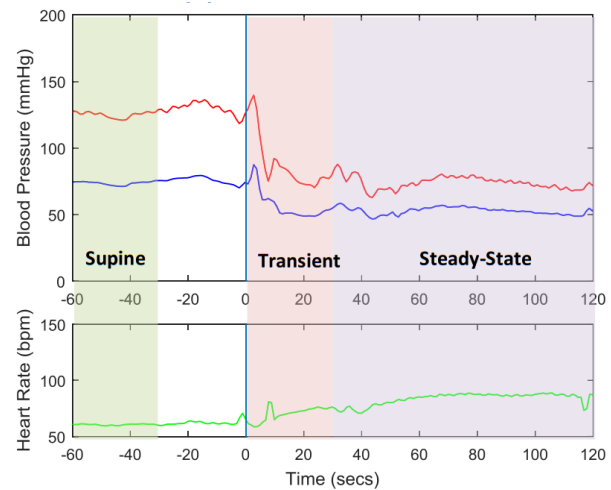


Figure 2.3. Active stand responses in classical orthostatic hypotension.

Responses to an Active Stand test in systolic (top, red) and diastolic blood pressure (top, blue), and heart rate (bottom, green) for a patient with Classical OH (image adapted from [71]).

Initial Orthostatic Hypotension

(IOH) (see Figure 2.4):

- Drop from baseline > 40 mmHg in SBP AND/OR > 20 mmHg in DBP within first 15s of standing
- In the absence of sustained OH or delayed recovery.

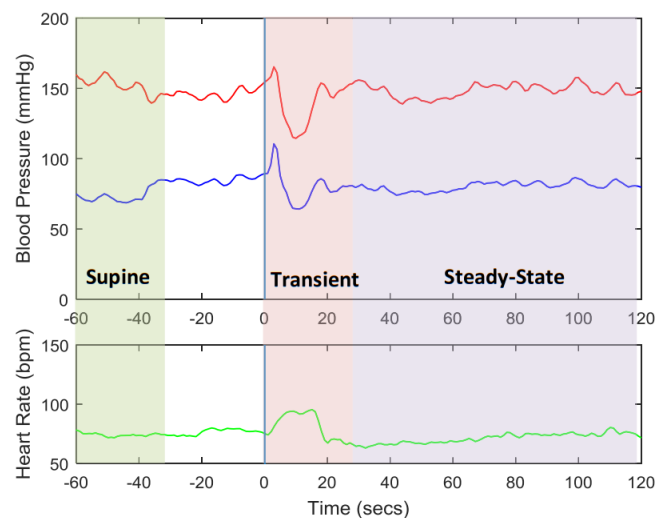


Figure 2.4. Active stand responses in initial orthostatic hypotension.

Responses to an Active Stand test in systolic (top, red) and diastolic blood pressure (top, blue), and heart rate (bottom, green) for a patient with IOH (image adapted from [71]).

Delayed recovery (see Figure 2.5):

- Drop from baseline ≥ 20 mmHg in SBP at 30-40s after standing.
- In the absence of sustained OH. A considerable delay is possible, but SBP must recover by 3 minutes of standing.

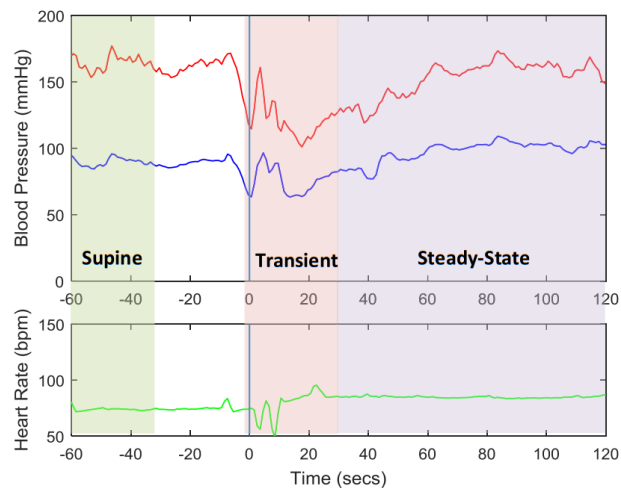


Figure 2.5. Active stand responses in delayed blood pressure recovery.

Responses to an Active Stand test in systolic (top, red) and diastolic blood pressure (top, blue), and heart rate (bottom, green) for a patient with delayed recovery (image adapted from [71]).

Orthostatic hypertension (OHTN) (see Figure 2.6):

- In hypertension: sustained increase from baseline ≥ 20 mmHg in SBP OR ≥ 10 mmHg in DBP from 60 to 180s after standing.
- In normotension: sustained increase from baseline above 140 mmHg in SBP OR above 90 mmHg in DBP from 60 to 180s after standing.

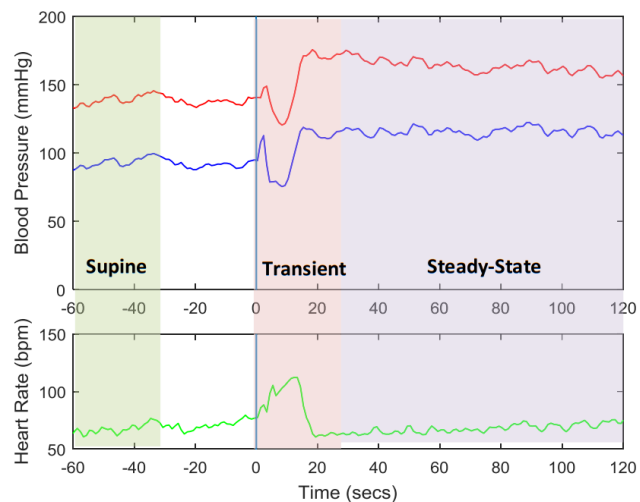


Figure 2.6. Active stand responses in orthostatic hypertension.
Responses to an Active Stand test in systolic (top, red) and diastolic blood pressure (top, blue), and heart rate (bottom, green) for a patient with OHTN (image adapted from [71]).

2.2 Cerebral Circulation

As detailed in the previous section, the AS test with concurrent monitoring of peripheral haemodynamics is part of the standard assessment of patients with syncope and falls [1]. However, despite syncope being defined as a TLOC due to cerebral hypoperfusion, and the known overlap between syncope and falls, no measures of cerebral circulation are used in standard clinical practice. This section provides an overview of the anatomy and physiology of cerebral circulation, its regulation in relation to blood pressure (i.e., cerebral autoregulation (CA)) and the available methods to monitor cerebral haemodynamics during AS testing.

2.2.1 Anatomy of Blood Supply and Drainage

Despite representing just a 2% of the total body weight, the brain accounts for 20% of the body's resting energy consumption [79, 80]. Energy supplies to the brain are met by adequate blood supply. Therefore, the brain is highly susceptible to injury in the case of decreased perfusion, which would lead to a dangerous decrease in oxygen and nutrients supply. Conversely, an increased perfusion could cause damage due to breakdowns in the blood-brain barrier, potentially leading to seizures, headaches, encephalopathy and stroke [81].

2.2.1.1 Arterial Supply

The brain is perfused by different head arteries; the internal carotid and vertebral arteries [82]. The former perfuse principally the cerebrum, while the vertebral arteries, after joining to form the basilar artery, are the main supply to the cerebellum and brain stem. The basilar artery and the internal carotid arteries anastomose to form the circle of Willis [82, 83], which guarantees sufficient oxygen delivery to the whole cerebral tissue even if one of the four main supplies is deficient. From the circle of Willis, three new

pairs of arteries arise: the anterior cerebral arteries (ACA), middle cerebral arteries (MCA) and posterior cerebral arteries (PCA) [83] (see Figure 2.7).

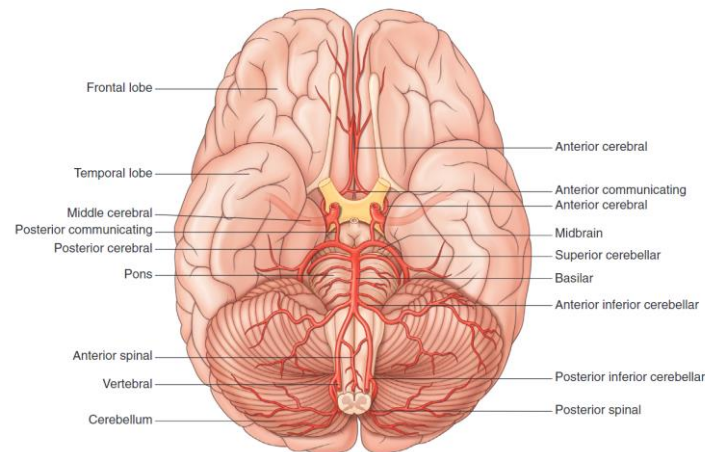


Figure 2.7. Cerebral arterial blood supply.
Arterial tree supplying blood to the brain, perspective from the base of the brain (image adapted from [84]).

Each artery irrigates a different region of the brain (see Figure 2.8). The prefrontal cortex is supplied by both the ACA and MCA [83, 85]. While the lateral and anterior regions of the prefrontal cortex are mostly supplied by the MCA, the superior and medial regions are supplied by the ACA. Borderzone regions between the areas served by the ACA and the MCA also exist [86]. Because they correspond to the most distal regions of each arterial supply, borderzones are particularly susceptible to ischemia. In pathological situations, ischemia in those zones can cause watershed infarcts [86], which are attributed to 10% of all brain infarcts [87].

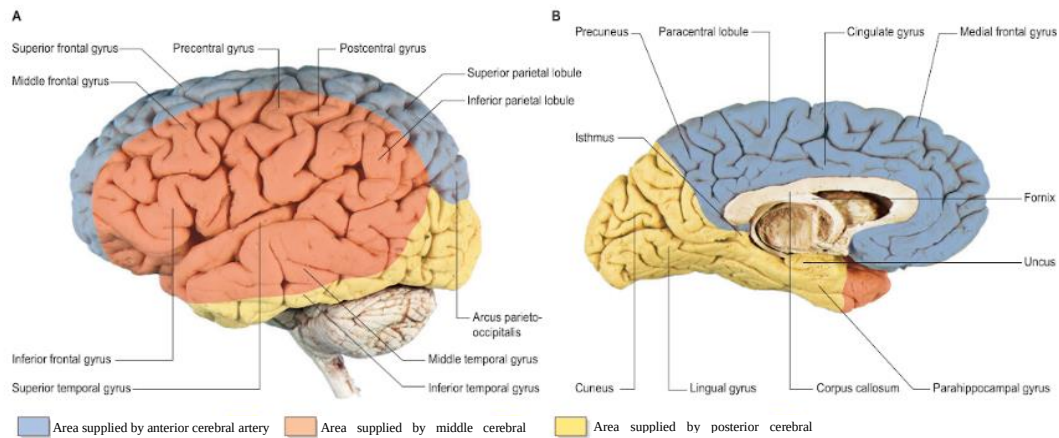


Figure 2.8. Regions of cerebral blood supply for different cerebral arteries.
Areas supplied by the anterior, middle and posterior cerebral arteries from a lateral (A) and medial (B) surface perspective (image adapted from [83]).

The ACA, MCA and PCA, in turn, subdivide, generating a network of small arteries and arterioles that run along the surface and supply the cerebral cortex, also known as pial arterioles. These penetrate into the tissue and end up becoming intraparenchymal arterioles [82]. Pial arterioles are innervated by extrinsic ends of the peripheral nervous system, while penetrating arterioles receive intrinsic innervation from the brain neurons [88, 89]. Capillary density is region dependent, being higher in grey matter than in white matter regions [90], and it can be modified by chronic conditions such as chronic hypoxia [91, 92].

2.2.1.2 Venous Drainage

The venous system that drains blood from the brain is a freely connected network of muscle free (with the exception of larger vessels) and valve free vessels [82, 93] which, contrary to the dual supply in the arterial system, exits the skull through one main vessel: the internal jugular vein [86]. The venous system can be divided into two subsystems: the superficial or cortical system, which drains both the cerebral cortex and the 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 (see Figure 2.9).

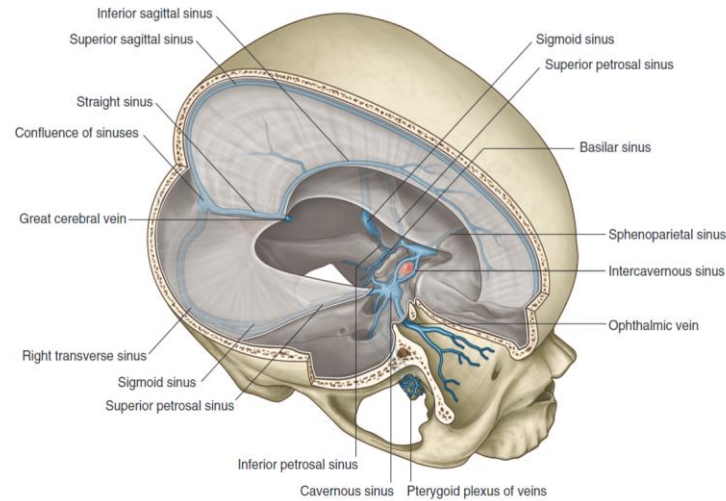


Figure 2.9. Venous drainage from the brain.
(image adapted from [84]).

2.2.2 Meeting the Brain's Oxygen Demand

2.2.2.1 The Cerebral Oxygen Supply and Demand

Maintaining an appropriate supply of nutrients and oxygen to the brain is paramount. Oxygen is delivered from the capillaries to the neuronal mitochondria by means of molecule diffusion which requires a gradient of oxygen partial pressure, and is dependent on the cerebral metabolic rate of oxygen ($CMRO_2$), as well as capillary density and distribution in the cerebral tissue [92]. Given the high proportion of whole body oxygen consumed by the brain [94], and its limited oxygen storage ability, if blood supply was stopped the $CMRO_2$ would only be sustainable for 1 second [92]. Therefore, it is crucial that oxygen delivery meets oxygen demand by means of an appropriate blood flow to the cerebral tissue.

2.2.2.2 Oxygen Intake and Release

The atmospheric air inhaled by the lungs has an approximate content of 21% of O_2 and 0.04% of carbon dioxide (CO_2), while the concentrations of oxygen and CO_2 in air exhaled are about 16% and 4.5%, respectively, due to gas exchange at the

pulmonary alveolar level [95]. The partial pressure of O_2 is higher in the lungs than in the venous blood that reaches the lung, and thus O_2 flows from the air in the lungs to the bloodstream. In the systemic capillaries, at the tissue level, the partial pressure of O_2 is lower than that of the blood, causing O_2 to diffuse into the tissues. The opposite process occurs with CO_2 .

2.2.2.3 Oxygen Transport in the Blood

O_2 is transported in the blood by haemoglobin (Hb), the most common oxygen-binding protein found in the body [96]. Haemoglobin is found in red blood cells, which facilitates binding and release of O_2 in the lungs and peripheral tissues. Hb is a tetrameric molecule and, thus, has two α monomers and two β monomers. Each of these monomers has a heme group which contains iron, where one O_2 molecule binds reversibly. Therefore, one Hb binds a total of 4 O_2 molecules. Hb bound to O_2 is known as oxygenated Hb (HbO_2), while the molecule with no oxygen is known as deoxygenated Hb (HHb). There is a rearrangement of the spatial structure and distances between iron atoms when a transition from one state to the other occurs [97], leading to higher O_2 affinity in the oxygenated configuration.

2.2.3 Cerebral Autoregulation

As detailed in the previous section, oxygen delivery to the brain is essential for brain functionality, as energy production in the neurons mostly takes place through oxidative metabolism. However, due to the delicate nature of the brain, cerebral blood flow needs to be tightly regulated to avoid tissue damage. This section focuses on one of the main mechanisms of cerebral blood flow regulation, cerebral autoregulation (CA), given that it constitutes the relationship between BP and cerebral blood flow, the two main signals studied in this thesis. For a more complete insight on the topic, we refer to the recent review by Claassen et al. [98], which provides excellent detail of the

mechanisms that regulate brain perfusion and how this knowledge has been translated clinically.

2.2.3.1 Historical Introduction to Cerebral Autoregulation

In 1939, Fog observed that pial vessels, i.e., vessels on the surface of the brain, changed their diameter in response to increasing BP [99], thus observing the phenomenon nowadays known as CA. Fog used three different strategies to cause changes in blood pressure: injections of epinephrine solutions, stimulation of the splanchnic nerves and compression of the abdominal aorta. He realised that upon an increase of blood pressure, there were two main effects occurring: most of the pial arterioles were either constricting or not changing their diameter. These responses were considered active, even in the cases where no changes occurred, as an increase in the vessels muscle tone must have occurred for them not to dilate after increasing blood pressure. In a few vessels where passive dilation was observed, it was noted that a larger increase in BP had been induced (in some cases even greater than 100%). These cases also corresponded to lower initial BP values. Therefore, he concluded that large and sudden raises in BP from an initially low BP cause a dilation of the vessels, indicating loss of tonic regulation, and causing a passive behaviour.

2.2.3.2 The Cerebral Autoregulation Mechanism

CA is the mechanism by which cerebral blood flow is maintained at an appropriate level despite changes in BP through arteriolar diameter modulation [94]. Due to the relevance of this mechanism in this thesis, a specific section has been devoted to describing this mechanism in more depth.

2.2.3.2.1 The Cerebral Autoregulation Curve

Lassen's Curve

In 1959, Lassen published a famous article on CA [100] (see Figure 2.10). In this article, he characterised the relationship between cerebral blood flow (CBF) and BP from 376 individuals, and described an autoregulatory behaviour whereby CBF is maintained across a wide range of pressures, from 60 to 170 mmHg, although below 60 mmHg CBF and BP were linearly related. However, Lassen constructed his curve from 11 different experiments performed on patients that were either medicated or suffered from hypertensive/hypotensive disorders, with a single BP and CBF measure taken from each patient, thus not considering intra-individual variability. Furthermore, these measures were taken with different measurements methods. Overall, creating a relationship using the above described methodology can lead to misleading results and conclusions [101].

In spite of all the above mentioned flaws in Lassen's review, his paper certainly was a scientific breakthrough that inspired many subsequent studies and pushed the progression of the study of CA. Relationships that resemble that of Lassen's curve have been reproduced by complex mathematical models of the physiology of blood flow regulation, such as that proposed by Ursino and Lodi [102] and Banaji et al. [103].

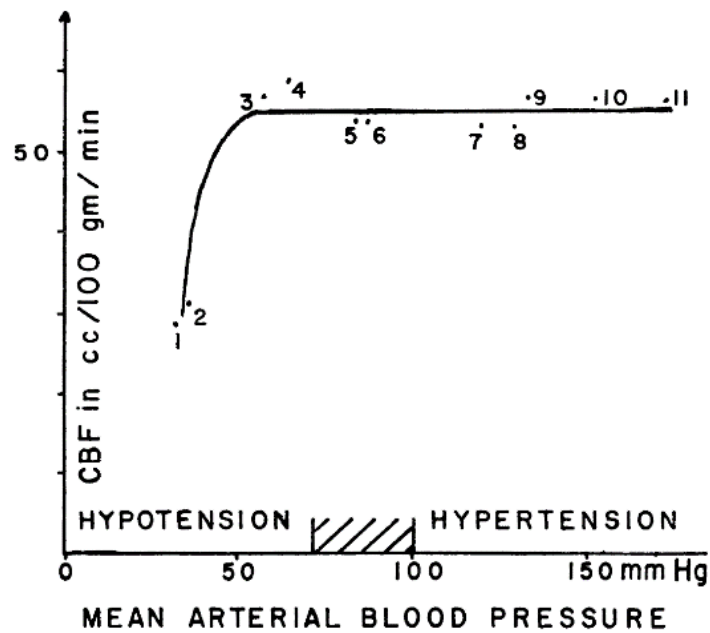


Figure 2.10. Lassen's curve.

Relationship between blood pressure and cerebral blood flow first described by Lassen (image adapted from [100]).

Beyond the Autoregulation Limits

A phenomenon of hysteresis has been described, by which the brain would be more successful at attenuating increases in BP than decreases in BP beyond the CA limits. In 2014, Numan et al. conducted a review of the literature on CA in healthy subjects [104] (see Figure 2.11). They found a significantly steeper linear relationship in the range of cerebral hypoperfusion as compared to that of cerebral hyperperfusion. Cassaglia et al. showed that, in animals, there is cerebral sympathetic activation of the cerebral vasculature during acute hypertension but not during hypotension [105]. This could mean there is a protective mechanism against quick increases in BP that is not so effective when the change is in the opposite direction.

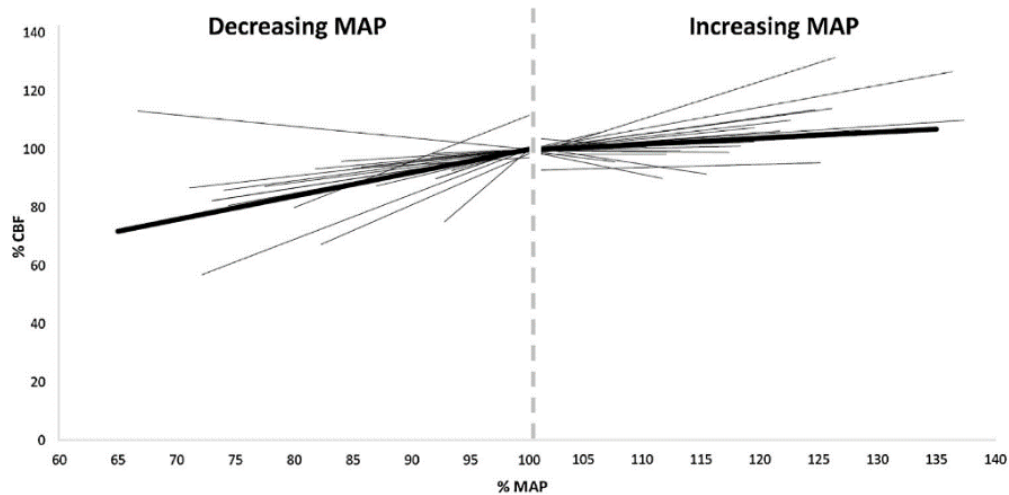


Figure 2.11. Changes in cerebral blood flow with increases and decreases in mean arterial pressure. Changes in percentage cerebral blood flow (%CBF) for percentage changes in mean arterial pressure (%MAP) studied by Numan et al. [104]. Thin lines represent the individual studies, while thick lines represent the average for those studies investigating decreases (left) and increases (right) in MAP.

Dynamic Cerebral Autoregulation

Regarding the regulatory region, Tan demonstrated that its limits might not be as wide as Lassen proposed and they might be dependent on the frequency in which BP changes [106]. Lassen's curve is intended to capture slow changes in BP (changes happening over minutes or longer periods of time), i.e., **static CA**, while Tan studied transient changes in BP, i.e., **dynamic CA** (changes happening in less than a minute) [101] (see Figure 2.12 for an intuitive graphical representation of these two concepts).

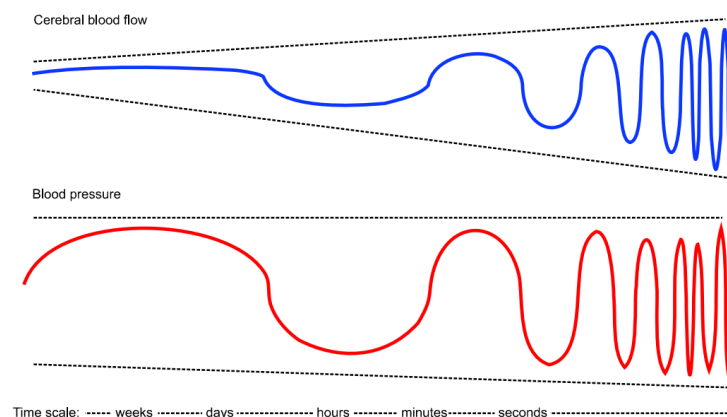


Figure 2.12. Schematic representation of cerebral autoregulation from static (left) to dynamic (right). During slow changes in blood pressure (weeks, days) cerebral blood flow amplitude is attenuated due to cerebral autoregulation. However, during fast changes in blood pressure (minutes, seconds) attenuation is less successful with increasing frequency, highlighting the high pass filter nature of this regulatory mechanism (image adapted from [98]).

Tan used oscillatory lower body negative pressure (OLBNP) and applied projection pursuit regression to the data (see Figure 2.13). When 0.03Hz oscillations were applied, he obtained a curve that resembled Lassen's autoregulatory curve, although with a smaller regulatory range. However, when the oscillations were induced at a frequency of 0.08Hz, the plateau region mostly disappeared, giving rise to an almost linear relationship between BP and CBF changes. Therefore, the shape of the autoregulatory curve is frequency dependent.

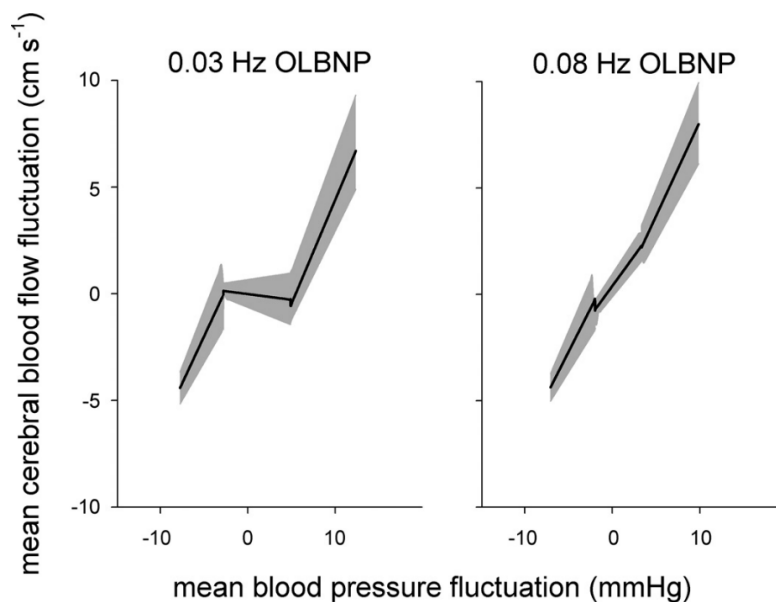


Figure 2.13. Cerebral autoregulation changes with frequency.
Relationship between cerebral blood flow and blood pressure during oscillatory lower body negative pressure (OLBNP) at two different frequencies: 0.03Hz and 0.08Hz (image adapted from [106]).

It has been determined that dynamic CA has a time delay of approximately 2 seconds with respect to changes in BP [107-109], and that it results in a transient response that lasts for 10-15s [107]. Dynamic CA is believed to have more clinical relevance than static CA [101]. It has the advantages that it is fast, does not require the use of drugs, can be studied through non-invasive methods, and allows studying other effects that affect CBF such as temperature, mental activation, and changes in CO₂.

In dynamic conditions, CA has been shown to act as a high pass filter, i.e., a filter that only allows frequencies higher than a threshold frequency of 0.07Hz to pass, attenuating to some extent frequencies below this threshold [110-112]. In higher frequencies, changes are too fast for the autoregulatory system to act and thus the predominant mechanisms that relate BP and CBF are the impedance properties of the cardiovascular system [113].

2.2.3.2.2 Mechanisms of Cerebral Autoregulation

Myogenic Control

One mechanism involved in CA is local myogenic control, i.e, control originating in the muscular cells. In vitro studies have demonstrated that increases in pressure causing increases in wall tension lead to depolarization of muscle cells, and an influx of calcium ions into the cells, resulting in muscular contraction and vasoconstriction [98]. In human isolated vessels, the myogenic response was present even after removal of endothelial cells but was not observed in the absence of extracellular calcium [114].

Literature on the effect of myogenic control in vivo is scarce and unclear. Some studies observed an attenuation in the responses of thigh cuff release when the calcium-channel blocker nicardipine was administered to the participants [115, 116]. Another study used lower body negative pressure (LBNP) to induce 120 mmHg oscillations at 0.1Hz, and observed no differences in CA when using a calcium antagonist [117]. However, a LBNP of 120 mmHg might be beyond the autoregulatory capacity of the brain vasculature. Tan et al. studied the effects of nicardipine on CA during moderate LBNP oscillations (30 mmHg) [118]. They used projection pursuit regression, which captures the intrinsic nonlinearities of CA. They observed a reduction in the width and increase in the slope of the autoregulatory range, especially at low oscillatory

frequencies (i.e., 0.03Hz) with the use of nicardipine, demonstrating a worsening in CA (see Figure 2.14).

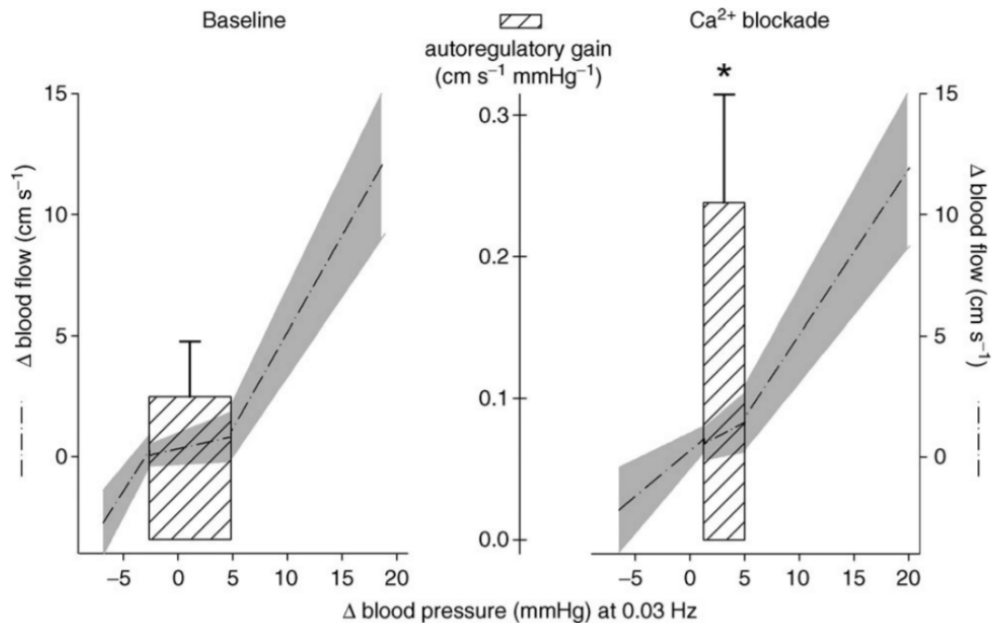


Figure 2.14. Cerebral autoregulation changes with calcium channels blockade. Cerebral autoregulation curve at baseline (left) and after calcium channels blockade (right). A smaller autoregulatory region and greater gain (highlighted by the striped bars) are indicative of less efficient cerebral autoregulation (image adapted from [118]).

Neurogenic Control

Another proposed mechanism of CA is neurogenic in nature [119]. The cerebrovasculature is innervated by both adrenergic (adrenaline/noradrenaline mediated) and cholinergic (acetylcholine mediated) neuronal terminals [120]. Neurogenic regulation occurs at the level of the neurovascular unit, composed by endothelial cells, astrocytes and neurons, and it is believed to be operated through two types of nerves, extrinsic and intrinsic [119].

Studying the role of the sympathetic nervous system in CBF regulation in humans is difficult and has only been done in a few studies. These studies either include patients that have received a ganglionectomy or involve healthy participants in which a ganglionic blocking factor has been administered [120]. The first group of studies have

demonstrated an increased CBF upon ganglion excision, revealing the constricting role of the sympathetic innervation. Results from studies using blocking agents provide conflicting evidence, and although it is believed that the sympathetic nervous system is involved in the prevention of CBF increases, its influence is regarded to be limited to static CA [98, 121].

Regarding the parasympathetic nervous system, its role in CA has been less explored, with most of the current evidence being based on animal studies [98]. In humans, Hamner et al. described that, in nine healthy volunteers undergoing OLBNP, the coherence between CBF and BP increased after administration of glycopyrrolate, a cholinergic blocking agent, indicating a potential impairment in dynamic CA [122]. The same agent was used in a different study, in which the authors found that cholinergic blockade prevented CBF from increasing during cycling and hand grip strength testing [123]. However, more research is needed, as for now the parasympathetic nervous system is not believed to play an important role in CA [98].

2.2.3.3 Other Mechanisms of Cerebral Blood Flow Regulation

CBF regulation is multifactorial, involving two more regulatory mechanisms apart from CA: cerebrovascular reactivity and neurovascular coupling.

2.2.3.3.1 Cerebrovascular CO₂ Reactivity

Cerebrovascular reactivity, also known as vasomotor reactivity, refers to the modulation of CBF through changes in arterial partial pressure of CO₂ (PaCO₂) [98]. CO₂ molecules are thought to have the highest vasoactive capacity to regulate cerebrovascular tone. This sensitivity is unique to the cerebral vasculature and is found across all levels of the vascular tree, from large cerebral arteries, to intraparenchymal vessels [120].

Increases in arterial PaCO_2 (hypercapnia) result in arterioles vasodilation, thus leading to increased perfusion, while decreases in arterial PCO_2 (hypocapnia) lead to vasoconstriction and result in a decrease in CBF. This mechanism maintains homeostasis by keeping a constant central pH. In hypercapnia, vessels dilate to enhance the removal of CO_2 excess, while during hypocapnia vasoconstriction occurs to avoid losing too much CO_2 in the cerebral tissue. Pial arteries are able to dilate up to 40% due to an increase in arterial PaCO_2 [120]. Vasodilation during hypercapnia affects smaller vessels, while vasoconstriction in hypocapnia affects all vessels equally independent of their diameter [94]. A behaviour of hysteresis has been described, with CO_2 reactivity being higher during hypercapnia (3-6% increase in CBF per mmHg increase in PaCO_2) than in hypocapnia (1-3% decrease in CBF per mmHg decrease in PaCO_2) [94, 98].

During orthostatic challenges, hypocapnia occurs due to postural hyperventilation, leading to reduced CBF and cerebral oxygenation [124, 125]. Furthermore, in presyncope induced during HUT testing, vasoconstriction attributed to hypocapnia has been reported to contribute to reductions in CBF [126].

2.2.3.3.2 Neurovascular Coupling

Neuronal activation in a certain region of the brain causes an increase in oxygen demand. CBF is regulated through a process called neurovascular coupling to meet such demand. Neurovascular coupling takes place at the level of the neurovascular unit, composed of the vasculature smooth muscle cells, the astrocytes, and the neurons [119, 127].

The mechanism behind neurovascular coupling is believed to be dual, i.e., both feed forward (triggering blood flow modulation) and feedback (adjusting blood flow to appropriate levels) [128]. By-products of metabolism due to neuronal activation

(adenosine, CO₂, hydrogen ions) cause local vasodilation and contribute to a localised increased CBF [98].

During orthostatic challenges, CBF has been demonstrated to increase with the cognitive difficulty of the protocol in healthy young adults, although it is independent of the level of orthostatic stress [129].

2.3 Methods to Assess Cerebral Circulation During the Active Stand Test

In 1880, the physiologist Angelo Mosso used a custom made plethysmograph in patients with congenital skull defects to measure brain pulsations, which he observed to intensify when patients were performing arithmetic calculations [130, 131]. This was the first demonstration of a relationship between brain activity and CBF (see Figure 2.15). To be able to study this in healthy subjects, Mosso used his ingenuity to develop a ‘human circulation scale’ that would tilt towards the head when brain blood flow increased. Using this method, he observed that in two healthy volunteers the bed tilted down on the head side when they were reading different sorts of papers (from newspapers to abstruse language writings). Interestingly, the decrease was even intensified when the piece of writing was emotionally related to the person, i.e., a letter written by the spouse of the subject or by an angry creditor [131].

Ten years later, Charles Roy and Charles S. Sherrington confirmed the relationship between metabolic demand and blood flow [127]. Furthermore, they described effects of blood pH, BP and blood gases on CBF.

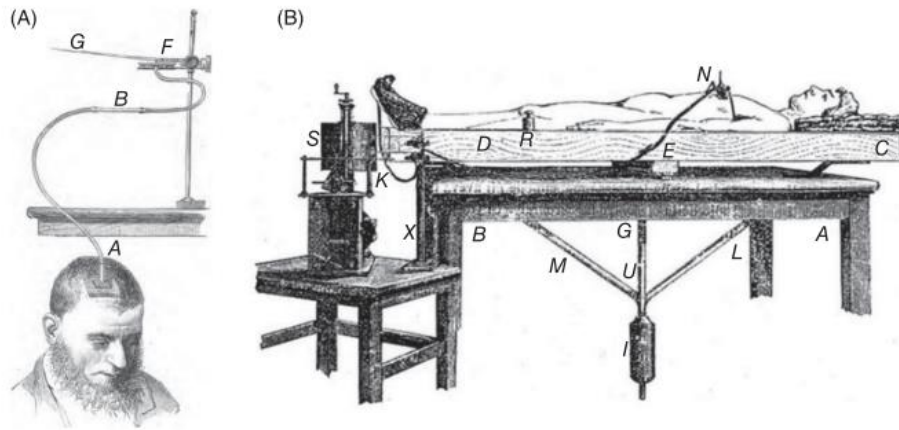


Figure 2.15. Methods developed by Mosso to study cerebral circulation.

A) Plethysmograph used in patients with congenital skull defects, B) Human circulation scale (image adapted from [127]).

It was not until the mid-1900s that the Kety-Schmidt method was developed by Seymour Kety and Carl Schmidt, a technique that uses nitrous oxide to measure volumetric CBF. Despite revolutionising the study of cerebral haemodynamics, it takes at least 10 minutes to obtain an accurate measure, and therefore, does not allow studying fast transient changes in CBF.

Other subsequently developed methods to study CBF such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), Xenon-enhanced computed tomography (XeCT), or arterial spin labelling (ASL), among others, suffer from the same limitation as the Kety-Schmit method due to their static nature. Transcranial Doppler (TCD), developed in the 80s by Rune Aaslid, has overcome this limitation by providing a measure of CBF velocity as a surrogate for CBF. Another method of relevance is NIRS. NIRS was developed by Dr. Frans Jöbsis in 1977 to study cytochrome-c-oxidase, but also allowed measurement of $\Delta[\text{HbO}_2]$ and $\Delta[\text{HHb}]$, which can be used to study changes in cerebral haemodynamics. TCD and NIRS are described in the following section. The main technical characteristics, advantages and disadvantages of these methods are compared in Table 2.1.

Table 2.1. Summary of methods commonly used to assess cerebral perfusion.

	NIRS (SRS)	TCD	PET	SPECT	XeCT	ASL
Signal measured	TSI, $\Delta[\text{HbO}_2]$, $\Delta[\text{HHb}]$	CBFV	CBF, CBFV	CBF	CBF	CBF
Spatial resolution	NA	NA	4-6 mm	4-6 mm	4 mm	2 mm
Area measured	Local (frontal lobe area under probe)	Local (one cranial artery measured)	Whole brain	Whole brain	6 cm depth	Whole brain
Temporal resolution	$\geq 50\text{Hz}$	$\geq 50\text{Hz}$	10 minutes	10 minutes	10 minutes	$\leq 0.3\text{ Hz}$
Reproducibility	4%	5%	5%	10%	12%	10%
Invasive	No	No	No	Yes	Yes	No
Allows standing manoeuvre	Yes	Yes	No	No	No	No
Advantages	No ionizing radiation exposure	No ionizing radiation exposure	Accurate	Possible to use at bedside	Accurate	No ionizing radiation exposure
	Continuous measures	Continuous measures	Quantitative measures	Low cost	Quantitative measures	High temporal and spatial resolution
	Allows dynamic manoeuvres	Allows dynamic manoeuvres				
	Easy to apply					
Disadvantages	Susceptible to motion artefacts	CBF unreliable if changes in insonated artery occur	High ionising radiation exposure	Measures relative to control	Susceptible to motion artefacts	Tendency to CBF underestimation
	Susceptible to extracranial contamination	Requires user expertise	High cost	Long acquisition time	Long acquisition time	MRI related disadvantages (claustrophobia, access difficulties)
	Signal origin poorly understood	Acoustic window not available in all individuals (worse with age)	Long acquisition time		Health risks due to inhalation of Xenon	
	Relative measures	Relative measures				

Information to create this table has been sourced from: [132-135]. NIRS: near-infrared spectroscopy, SRS: spatially resolved spectroscopy, TSI: tissue saturation index, $\Delta[\text{HbO}_2]$: changes in concentration of oxygenated haemoglobin, $\Delta[\text{HHb}]$: changes in concentration of deoxygenated haemoglobin, TCD: transcranial doppler, CBF: cerebral blood flow, CBFV: CBF velocity, PET: positron emission tomography, SPECT: single-photon emission computed tomography, XeCT: Xenon-enhanced computed tomography, ASL: arterial spin labelling, MRI: magnetic resonance imaging.

2.3.1 Transcranial Doppler Ultrasound

Aaslid et al. described for the first time the clinical application of TCD in 1982 [136]. In this version of ultrasonography, the purpose is to quantitatively measure the flow of blood in the main cerebral arteries using ultrasound penetration through relatively thin regions of the skull. In TCD, a low-frequency ultrasound probe is placed on the scalp of the patient [137], and depending on several characteristics such as the depth, the flow direction or the resistance, several arteries can be identified and monitored [138]. Frequencies of 2 MHz or lower are used, since higher frequencies are not able to penetrate through the skull [136]. Additionally, not all regions of the skull are suitable for TCD, as ultrasound transmission is only successful enough in 4 acoustic windows where foramina or thin bone are found [139, 140].

In TCD, velocity is used as a direct surrogate of flow. However, in order for this assumption to be true, the diameter of the insonated artery, the MCA, must be constant throughout the measurement (or measured concurrently). Simultaneous measurement of blood velocity and vessel diameter is currently not possible using TCD due to resolution limitations [134]. Therefore, some studies have focused on proving this assumption. Serrador et al. showed that, for a lower body negative pressure protocol, and under different levels of CO₂ concentration, the MCA diameter (as measured by magnetic resonance imaging (MRI)) remained constant despite changes in CBF (measured with TCD) [141]. Serrador's article has been cited by virtually all studies in which TCD has been used to measure dynamic changes in blood velocity. However, other MRI studies have shown that MCA diameter changes with large changes in PaCO₂ during hypocapnia (-13 mmHg) or hypercapnia (+15 mmHg) [142], and therefore it still remains unclear to what extent this could affect CBF measures. Nevertheless, some studies have validated TCD against other cerebral perfusion

methods with successful results. A study comparing values of cerebral blood velocity and flow as measured by TCD and electromagnetic flowmetry, respectively, during the thigh cuff release method [109], noted equivalence of these measures. This would imply that the diameter has been kept constant throughout the test. Some other studies have found high correlations between TCD velocity and flow measured with other methods such as the Xe133 method, SPECT, MRI and direct Fick calculations of changes in oxygen concentration across the brain [143-145]. Lastly, one main disadvantage of TCD is that in approximately 8% of the population it is not possible to obtain an adequate acoustic window, and that the prevalence of this issue increases with age [146], which poses a limitation for its clinical use with older adults.

2.3.2 Near-Infrared Spectroscopy

Given that Near-Infrared Spectroscopy (NIRS) is the method applied in this thesis to assess cerebral circulation, a detailed description is warranted. The following section describes relevant details of underlying theory, the main technical approaches available, as well as a thorough review of its advantages and disadvantages.

2.3.2.1 History of the Development of Near-Infrared Spectroscopy

Being able to visually inspect tissues within the body is highly advantageous. However, visible light is very limited for this purpose due to its high absorption in biological tissues. In 1935, motivated by the safety of aviation pilots during high altitude flights, the German Physicist Karl Matthes developed the first device to measure the oxygenation of blood from the ear lobe, using red and green light initially, and then shifting to red and infrared wavelengths instead [147]. Oxygenation monitoring was possible due to the differential light absorption patterns produced when illuminating oxygenated and deoxygenated haemoglobin.

A few decades later, in 1977, Jöbsis explored the use of near-infrared (NIR) light (wavelength $\sim 700\text{-}900\text{nm}$) to observe cerebral tissue non-invasively [148] (see Figure 2.16). His approach permitted the first observation of changes in oxygen consumption and changes in blood volume in the brain tissue. All these advances were possible due to the characterisation of the oxygenated and deoxygenated haemoglobin absorption spectrums in the visible and near infrared regions, first measured *in vitro* by Horecker et al. in 1943 [149].

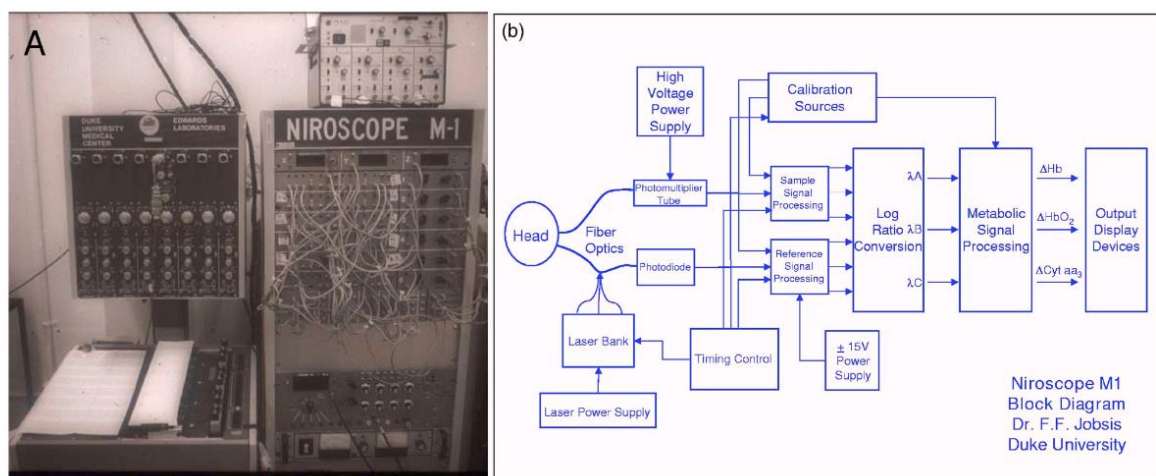


Figure 2.16. First near-infrared spectroscopy system.

A) Photograph and B) block diagram of the first near-infrared spectroscopy system developed by Jöbsis (image adapted from: [150]).

Further NIRS advancements accounted for scattering and absorption of NIR light in biological tissues. The first approach was applied in ear oximeter. By compressing the ear lobe to stop blood flow to that region, a baseline measurement of the bloodless ear was subsequently subtracted from the perfused measurement [151].

2.3.2.2 Theory of Near-Infrared Spectroscopy

NIRS has evolved from the spectrophotometers used for analysis of chemical compounds in the laboratory. The cuvette model can be used to understand the basic principles of this method (see Figure 2.17). In this model, a solution of a compound of interest (also known as chromophore) is placed inside a cuvette. A light source is placed

on one face of the cuvette, and a detector (light sensor) is placed on the opposite face. Light intensity, I_0 , illuminates the sample, with the detected light of reduced intensity, I , detected by the sensor.

Light can be understood as either a beam of photons or as a wave with a certain wavelength λ . When light shines through a solution, absorption of photons occurs.

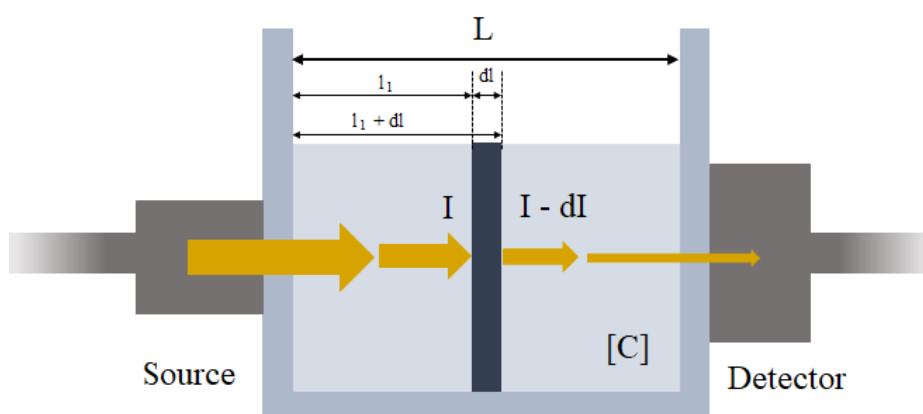


Figure 2.17. Cuvette model for near-infrared spectroscopy.

On the left side of the cuvette there is the light source, and on the right side the detector. L is the distance between the source and the detector, I is the intensity of the light, and $[C]$ is the concentration of the compound found inside the cuvette.

The concentration of chromophore $[C]$ can be derived from the Beer-Lambert law, which relates the incident intensity, I_0 , to the detected intensity I . In order to derive this law, an infinitesimal length of the cuvette, dl , is considered, with I the intensity at position l_1 , and $I - dI$ the intensity at $l_1 + dl$. Thus, the change in I , dI , can be expressed as [152]:

$$dI = -\mu a * I * dl \quad (1)$$

where μa is the absorption coefficient of the chromophore.

Integrating this equation for the whole length of the cuvette, L , results in the Beer-Lambert law:

$$I = I_0 * e^{-\mu a * L} \quad (2)$$

The attenuation coefficient μ_a can be expressed as:

$$\mu_a = \frac{[C] * \varepsilon}{\log_{10}(e)} \quad (3)$$

where ε is the molar absorption coefficient of the chromophore (sometimes also called molar extinction coefficient). The optical density (OD) can then be calculated as:

$$OD = \log_{10}\left(\frac{I_0}{I}\right) = \varepsilon[C]L \quad (4)$$

The molar extinction coefficient, ε , is dependent on the wavelength of the light source ($\varepsilon = \varepsilon(\lambda)$). Thus, for every chromophore, ε can be plotted for a range of λ values, resulting in the absorption spectra of the molecule. Figure 2.18 depicts the extinction spectrums for HbO₂ and HHb, and water (H₂O) in the NIR range.

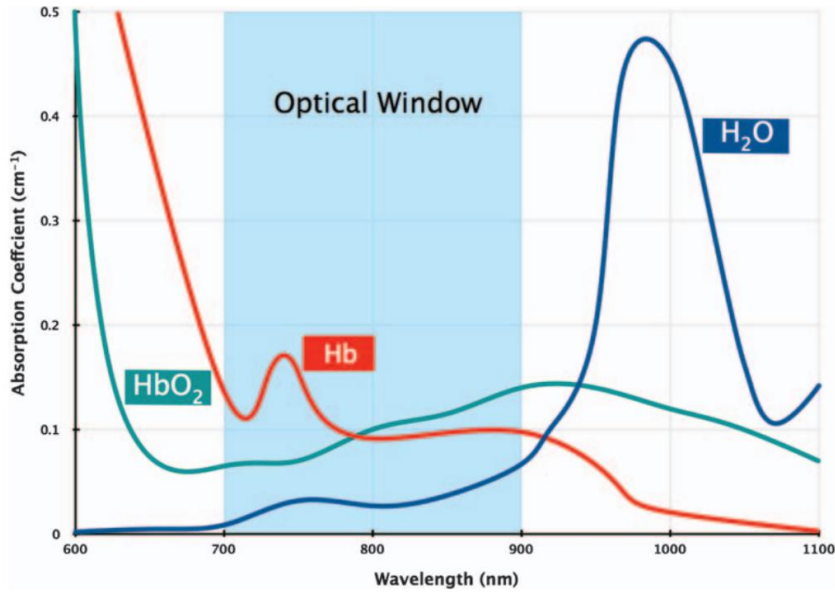


Figure 2.18. Absorption coefficient for chromophores of interest in the near-infrared spectroscopy spectrum.

Absorption coefficient in the near-infrared spectrum for oxyhaemoglobin (HbO₂), deoxyhaemoglobin (Hb), and water (H₂O) (image adapted from [153]).

Within the NIR range, the spectrums of Hb and HbO₂ cross once at a wavelength of approximately 800 nm, which is called an isosbestic point. In the rest of the NIR range, the absorption coefficients of these two chromophores are notably

different. Only one chromophore has been considered in the cuvette model. However, in the case of vascularised tissue, more than one chromophore is present (i.e., at least HbO_2 and HHb). However, this model is a simplification of reality when it comes to biological tissues. When photons pass through a tissue, some are absorbed by the molecules in the tissue, while some are also scattered, i.e., they are deviated from their path. Scattering is a complex phenomenon that has a huge effect on the light received at the detector. There are 3 possible scattering paths: the unscattered path, in which photons pass through the tissue without suffering any scattering effect; the forward scattering, in which photons get scattered but their net final direction is the same as the incidental light; and the backscattering path, in which photons undergo multiple scattering events and emerge in the opposite direction of the light beam.

When the photon is not scattered, the path length that the photon travels is equivalent to the distance between the source and the sensor. However, if scattering occurs, the path length is increased with every scattering event. The resulting travelled distance is called the mean optical path length, L_o , which can be related to the geometrical path length, L , through the differential pathlength factor (DPF): $L_o = \text{DPF} \cdot L$.

Scattering can occur in many directions. The angle with which the photon is scattered will determine its future path. When light goes into a tissue, some photons go through the tissue without any change in direction, some suffer a slight change in their direction, and some largely deviate from the incident direction and will consequently be scattered out of the field of the detector. Therefore, if only the effect of scattering was to be considered on the detected light, the attenuation due to scattering could be expressed as [152, 154]:

$$\ln\left(\frac{I_o}{I}\right) = \mu_s * L \quad (5)$$

where μ_s is the scattering coefficient, defined as the likelihood of scattering occurring per travelled centimetre by the photon. However, scattering does not occur in isolation, and neither does absorption; both interactions happen simultaneously [154].

2.3.2.3 NIRS Methods

Three main methods to monitor cerebral oxygenation using NIRS have been described: continuous wave NIRS, spatially resolved spectroscopy and time-resolved spectroscopy.

2.3.2.3.1 Continuous Wave NIRS

In continuous wave NIRS, changes in concentration are derived from changes in optical density recorded at different wavelengths (see Figure 2.20a). As previously described, the Beer-Lambert law can be expressed as: $OD = \log_{10}(I_o/I) = \epsilon[C]L$. When more than one chromophore is found, for a given wavelength, the total optical density measured by the detector, can be expressed as a linear combination of the contribution of each chromophore [154]:

$$OD(\lambda a) = \epsilon_1(\lambda a)[C1]L + \epsilon_2(\lambda a)[C2]L + \dots + \epsilon_m(\lambda a)[Cm]L \quad (6)$$

where m is the number of dominant chromophores in a sample. In order to find the concentrations for all chromophores, as many equations as unknown variables are needed. Therefore, if there are 3 chromophores of interest, a 3-equation system is required. This can be obtained by using 3 different wavelengths, which will provide a value of the molar absorption coefficient for each chromophore and for each wavelength [154]:

$$OD(\lambda a) = \epsilon_1(\lambda a)[C1]L + \epsilon_2(\lambda a)[C2]L + \dots + \epsilon_m(\lambda a)[Cm]L \quad (7)$$

$$OD(\lambda b) = \epsilon_1(\lambda b)[C1]L + \epsilon_2(\lambda b)[C2]L + \dots + \epsilon_m(\lambda b)[Cm]L \quad (8)$$

$$OD(\lambda c) = \varepsilon_1(\lambda c)[C1]L + \varepsilon_2(\lambda c)[C2]L + \dots + \varepsilon_m(\lambda c)[Cm]L \quad (9)$$

A modification of the Beer-Lambert law is required to account for scattering [155]. First, a DPF is included, which is the mean optical path length that the photons have to travel before they reach the detector, and can be defined as L_o (derivative of optical density with respect to the attenuation coefficient: $\partial OD/\partial \mu_a$) divided by L , the distance between the source and the detector: $DPF = L_o/L$ [156]. The second modification is the addition of a scattering term $OD(\mu_a = 0)$, corresponding to the changes in optical density that would occur purely due to scattering [156]:

$$OD = \log_{10}\left(\frac{I_o}{I}\right) = \varepsilon[C]L * DPF + OD(\mu_a = 0) \quad (10)$$

As it can be seen, in order to calculate an absolute value for OD , the value of the scattering term $OD(\mu_a = 0)$ needs to be known. In continuous wave NIRS, changes in optical density are measured across a certain source-detector distance L . In this method, the scattering term is assumed to be constant, with this term eliminated from the equation. Therefore, when scattering is taken into account, changes in the optical density of three chromophores can be expressed as (3 chromophores example):

$$\Delta OD(\lambda a) = \varepsilon_1(\lambda a)\Delta[C1]L + \varepsilon_2(\lambda a)\Delta[C2]L + \varepsilon_3(\lambda a)\Delta[C3]L \quad (11)$$

$$\Delta OD(\lambda b) = \varepsilon_1(\lambda b)\Delta[C1]L + \varepsilon_2(\lambda b)\Delta[C2]L + \varepsilon_3(\lambda b)\Delta[C3]L \quad (12)$$

$$\Delta OD(\lambda c) = \varepsilon_1(\lambda c)\Delta[C1]L + \varepsilon_2(\lambda c)\Delta[C2]L + \varepsilon_3(\lambda c)\Delta[C3]L \quad (13)$$

Therefore, changes in concentration of the three chromophores can be obtained. However, this method does not allow measurement of absolute values of concentration. In a first approximation, the DPF can be considered independent of the wavelength, and can be measured for a certain tissue, although its behaviour in the human head has been characterised for a range of wavelengths (more details to follow in this section) [157].

2.3.2.3.2 Time-Resolved Spectroscopy

In order to more accurately account for the optical properties of tissues, more complex approaches have been developed. Time resolved spectroscopy, divided into time-domain and frequency domain approaches, allows measurement of scattering effects and therefore absolute determination of chromophores concentrations. More advanced models of photon propagation in tissue are required for these methods. Photon propagation and scattering through tissue have been explained with two different theories: transport theory and diffusion theory [154]. From these theories, the following diffusion equation can be derived:

$$\frac{1}{c} \frac{\delta \phi(r, t)}{\delta t} - D \Delta^2 \phi(r, t) + \mu_a \phi(r, t) = S(r, t) \quad (14)$$

where D is the diffusion coefficient, which depends on the absorption coefficient μ_a and the scatter coefficient μ_s , r denotes position, t denotes time, c is the speed of light in the tissue, S represents the light source and ϕ the total energy fluence rate [152].

According to the diffusion theory, there are qualitative changes in scattering depending on the concentration of the chromophore in the medium analysed. Initially, when the concentration starts increasing from 0, no scattering occurs, and all light attenuation can be attributed to absorption. As concentration keeps increasing, photons are scattered only once and in the same direction of the incident beam, and absorption is still happening simultaneously. With higher concentrations, scattering is more prominent and occurs in different directions, which increases the mean optical path length and also causes attenuation of light due to some photons being scattered out of the field of the detector. Finally, when the chromophore concentration is very high, the mean path length is greatly increased, and backscattering starts to occur.

2.3.2.3.3 Time-Domain Spectroscopy ('Time of Flight')

Time-domain spectroscopy, also known as the 'time of flight' method, measures optical density, the DPF, scatter coefficient (μ_s) and the absorption coefficient (μ_a) [154]. In this method, a light pulse lasting a few picoseconds is delivered into the tissue [158] (see Figure 2.19 and Figure 2.20c). This signal is received at the detector as a broadened pulse due to scattering of photons in the tissue. The time of maximum detected intensity, t , considered to be the mean photon arrival time, is used to determine the mean optical path length L_o as [154]:

$$L_o = \frac{c_v}{n_t} t \quad (15)$$

where c_v is the velocity of light in vacuum and n_t the refractive index of the tissue. The ratio c_v/n_t corresponds to the phase velocity of light in the tissue. Therefore, the velocity of light in the tissue is the distance travelled within the tissue (L_o) divided by the time it takes to travel this distance (t). L_o can be used to calculate the DPF as L_o/L .

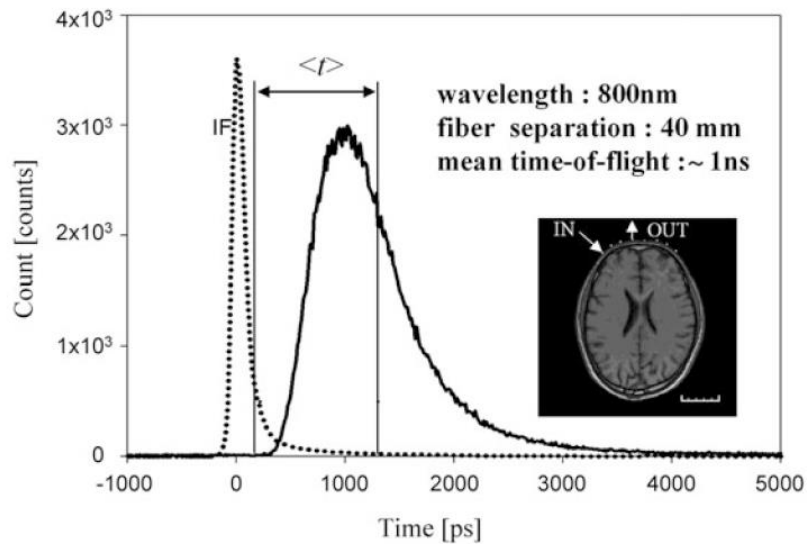


Figure 2.19. Graphical representation of time-resolved spectroscopy.
The original pulse delivered to the tissue (dotted curve on the left) is received as a broadened pulse (solid curve on the left) due to scattering (image adapted from [152]).

Then, from the diffusion equation applied to a semi-infinite homogeneous media and following a series of assumptions, it can be demonstrated that μ_a can be obtained from the slope of the asymptotic reflectance curve through nonlinear least-square fitting. And μ_a can then be used to derive μ_s [158]. Chromophore concentration can then be obtained by using the relationship [152]:

$$\mu_a = [C] * \frac{\epsilon}{\log_{10}(e)} \quad (16)$$

2.3.2.3.4 Phase Spectroscopy

Another spectroscopy approach is the use of phase-modulated measurements, also known as frequency domain spectroscopy [154] (see Figure 2.20d). An intensity modulated beam is used at the light source. The intensity detected at the sensor has a phase delay with respect to the modulated signal that is dependent on the propagation delay, and the absorption and scattering events that occur when the light travels across the tissue. Thus, the intensity detected at the sensor can be expressed as:

$$I = I_{dc} + I_{ac} * \sin(2\pi\nu t - \phi) \quad (17)$$

where ϕ is the phase shift between the modulated and the detected signals, ν is the modulated frequency, and I_{dc} and I_{ac} are the DC and AC components of the detected intensity. Similarly to how it is derived in time resolved spectroscopy, the optical path length can be calculated as [159]:

$$L_o = \frac{c_v}{n_t} 2\pi\phi \quad (18)$$

The theoretical basis of this method stems from the diffusion equation. Mathematical expressions can be derived that relate the DC and AC components of the photon density signal to the absorption and scattering coefficients as a function of the

distance between the source and the detector [154]. Then, with the received intensity at two or more different source-detector distances, the coefficients can be calculated.

2.3.2.3.5 Spatially Resolved Spectroscopy

In the case of spatially resolved spectroscopy (SRS) (see Figure 2.20b), the initial equation is also the diffusion equation (Equation 14) [39, 160]. However, in this case the fluence rate of photons is not time dependent, it is only dependent on the distance with respect to the source r , and thus, the Equation 14 can be expressed as [160]:

$$-D\Delta^2\phi(r) + \mu_a(r) = S(r, t) \quad (19)$$

Note that the first term has been dropped (derivative of the fluence rate with respect to time) due to this lack of time dependence. From this expression, the following equation can be obtained [39, 152]:

$$\mu_a\mu'_s = \ln 10 \frac{1}{3} \left(\frac{\partial OD}{\partial \rho} - \frac{2}{\rho} \right)^2 \quad (20)$$

where μ'_s is the reduced scattering coefficient and ρ is the source-detector distance [152]. The reduced scattering coefficient has a linear relationship with the light wavelength, and can be expressed as $\mu'_s(\lambda) = k \cdot (1 - h \cdot \lambda)$, where h is the normalised slope of μ'_s with respect to λ , and k is a constant [39]. Matcher et al. characterised this linear relationship in the near-infrared spectrum and provided average values for k and h for the human head [161]. Thus, it can be expressed as follows:

$$k \mu_a = \ln 10 \frac{1}{3(1 - h\lambda)} \left(\frac{\partial OD}{\partial \rho} - \frac{2}{\rho} \right)^2 \quad (21)$$

Using the data provided by Matcher et al. (k and h values), μ_a can be derived from the above expression by measuring the slope of the change in OD with ρ ($\delta OD / \delta \rho$), which can be obtained by taking at least two measurements at two different

source-detector distances. Then, absolute values of oxygenated and deoxygenated haemoglobin in the cerebral tissue can be derived using multiple wavelengths as follows [39]:

$$\begin{bmatrix} k [O_2Hb] \\ k [HHb] \end{bmatrix} = [\varepsilon_{i,j}]^{-1} \cdot \begin{bmatrix} k \mu a(\lambda_1) \\ k \mu a(\lambda_2) \\ k \mu a(\lambda_3) \end{bmatrix} \quad (22)$$

With these, a tissue saturation index (TSI), also known as tissue oxygenation index (TOI) can be calculated as [39]:

$$TSI = \frac{[O_2Hb]}{[O_2Hb] + [HHb]} \cdot 100\% \quad (23)$$

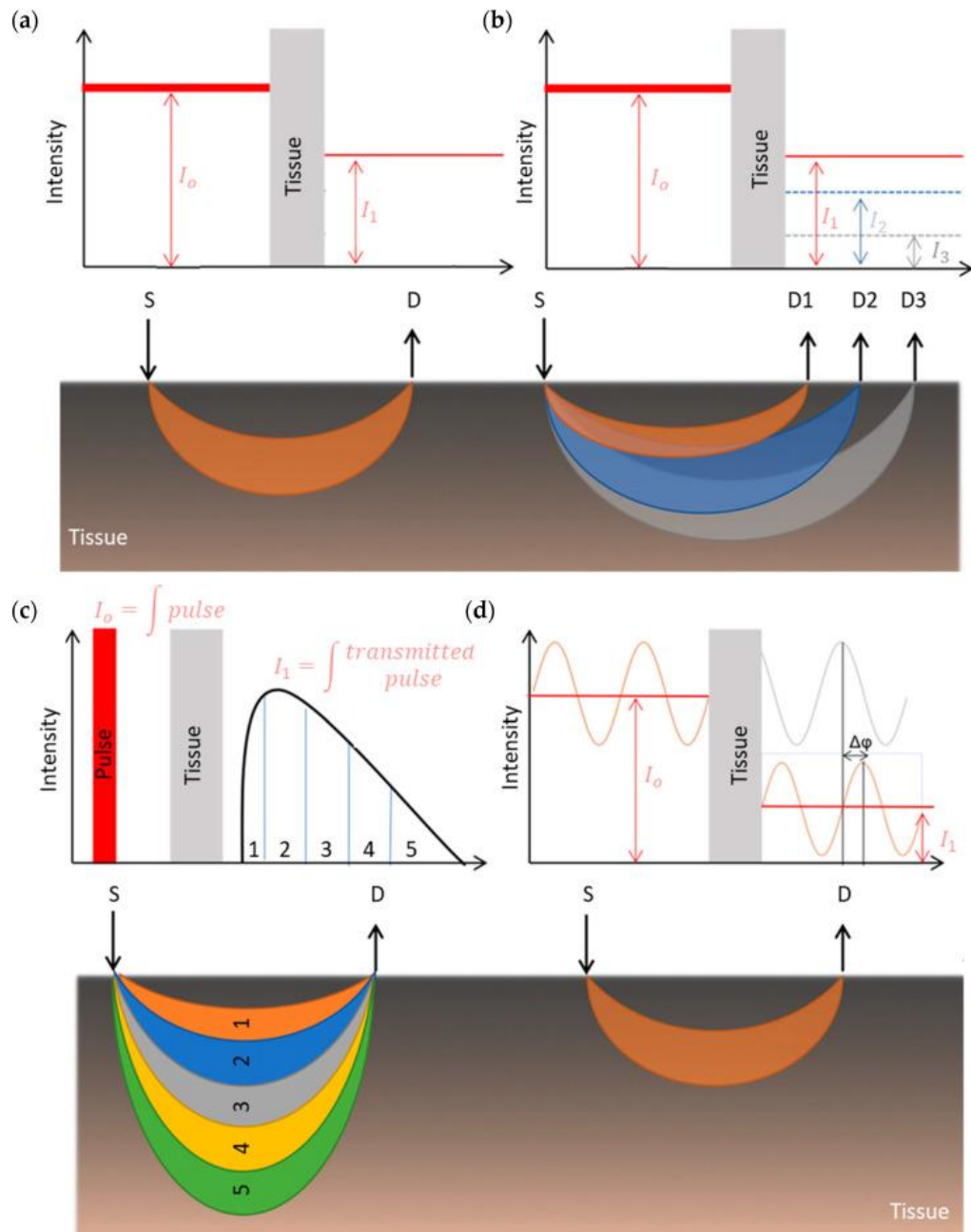


Figure 2.20. Graphical representation of the different near-infrared spectroscopy methodologies. a) continuous-wave, b) spatially-resolved, c) time-domain resolved and d) phase-resolved (image adapted from [162]).

2.3.2.4 Methodological Aspects of NIRS

2.3.2.4.1 Modified Beer-Lambert Law Parameters

The modified Beer-Lambert law requires the knowledge of 3 constants: the distance between the light source and the sensor, the molar absorption coefficient for the different chromophores measured, and the DPF.

The source-detector distance will determine the volume of tissue that is illuminated with the NIRS light, and therefore, the origin of the information contained in the received signal [163, 164]. For instance, if the distance is very short, light will only go through extracerebral tissue (i.e., skin, skull, cerebrospinal fluid), and therefore will not contain any brain tissue information. The average cranial frontal bone thickness is 7.48 mm and 6.58 mm for women and men, respectively [165], while 3 mm and 2 mm have been reported for scalp and cerebrospinal fluid thickness, respectively [166]. The average scalp to cortex distance was reported to be 14.5 ± 2.3 mm in a group of 23 young healthy adults [167]. This study also demonstrated through Monte Carlo simulations that on average 76%, 20% and 0.4% of the light was absorbed by the scalp, skull and cerebrospinal fluid, respectively, while grey and white matter only represented a 3.1% and 0.5%, respectively [167]. The use of short-distance sensors is gaining popularity as a strategy to capture extracerebral contamination and then subtract it from a longer distance sensor, so that only the brain signal remains [168]. For larger source-detector distances (2.5-6cm), Monte Carlo simulations have demonstrated that cerebral tissue can be captured by the NIRS signal, although an extracerebral component may remain [163]. In phantom and computational simulations, it has been demonstrated that for a source-detector distance of 2cm, a penetration depth of 10 mm is achieved, while for a 4cm separation the depth is of 15mm [169]. A different study using Monte Carlo simulations applied to magnetic resonance images reported an average penetration depth of 23.6 ± 0.7 mm (up to the deepest 5% of light) using an inter-optode difference of 30mm [167]. Experimentally, Al-Rawi et al. investigated intracranial and extracranial contributions to TSI by clamping the external and internal carotid arteries, respectively, during carotid endarterectomy. They observed an 87.5% sensitivity and 100% specificity in the detection of intracranial TSI changes [170].

Regarding the absorption coefficients, the absorption spectra in the NIR region of human oxygenated and deoxygenated haemoglobin were characterised in vitro by Wray et al. in 1988 [171]. They used lysed human blood with fully oxygenated and fully deoxygenated haemoglobin to characterise the absorption coefficient for a range of wavelength from 650 to 950 nm. In this frequency range, the two spectra only cross at approximately 800nm, which is known as the isosbestic point.

The DPF is probably the most troublesome parameter to obtain. While it is considered constant if the source-detector distance is above 2.5 cm [172], it is tissue dependent, wavelength dependent and it requires time resolved spectroscopy or intensity modulated spectroscopy to measure it [173]. In 1995, Duncan et al. determined that the mean DPF in a group of 100 adults was $6.26 (\pm 0.88)$ in the head [157]. In 1996 they provided 4 equations to calculate the DPF as a function of age for 4 different wavelengths derived from a population of 283 participants aged 1 to 50 years [174]. Since this was limited to only a few wavelengths and a maximum age of 50 years, in 2013 Scholkmann and Wolf derived a general equation for an age and wavelength dependent DPF [175] (see Figure 2.21). They were able to satisfactorily predict experimental data with their equation, and they recommend its use in subjects aged 0-70 years in a wavelength range of 832-950nm. Differences in DPF with age are believed to have a physiological origin. Factors that could affect DPF are increases and decreases in intracranial volume over the lifespan, changes in myelination, gray and white matter, CBF and volume, volume of cerebrospinal fluid, thickness of the cortex and bone content and density [175].

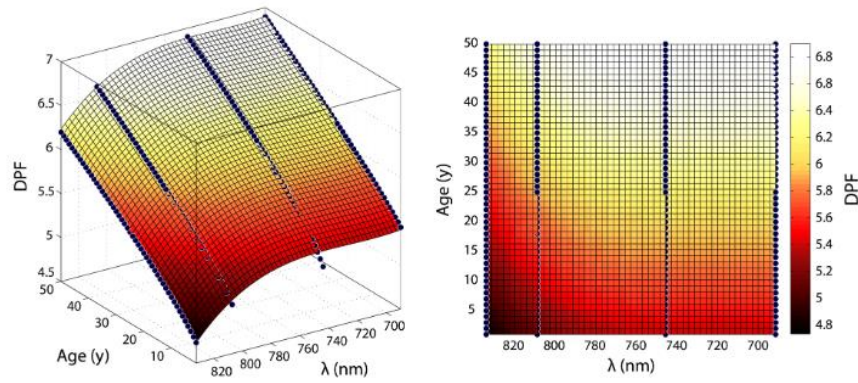


Figure 2.21. Differential pathlength factor relationship with age and wavelength.
 3D (left) and 2D (right) representation of the relationship between the differential pathlength factor (DPF), age and light wavelength (λ) derived by Scholkmann and Wolf [175].

As described in the previous section, the DPF is only used in continuous wave spectroscopy. In SRS, the accuracy of estimates of k and h used for the derivation of μ_s' are important. These parameters describe the linear relationship between μ_s' and the wavelength of the NIR light (see Figure 2.22), with k representing the intercept and $-kh$ representing the slope. These parameters cannot be calculated during the measurement and instead are taken from average values provided by Matcher et al. using time-resolved spectroscopy [161].

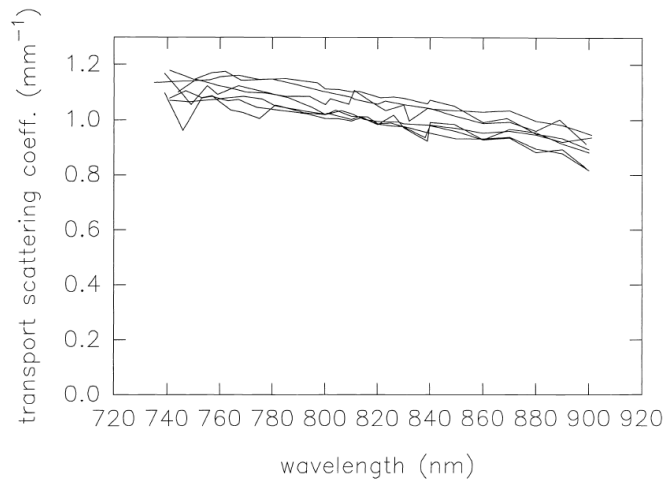


Figure 2.22. Experimental measurement of transport scattering coefficient in vivo on the adult head in the near-infrared light spectrum [161].

2.3.2.4.2 Other Chromophores

It is an oversimplification to consider that oxygenated and deoxygenated haemoglobin are the only chromophores that absorb NIR light. Water is one of the main absorbing chromophores, although its lowest absorption is found between 300-1000nm, and its contribution to the NIRS signal is considered minimal [173]. Nevertheless, water correction can be applied by establishing a constant value for its concentration and using its wavelength specific absorption coefficient. Melanin is a key light absorbing chromophore. A study that validated a NIRS device in three different skin tone groups found no differences between the groups [176]. Plasma bilirubin, however, has been found to be correlated with lower values of TSI measured with NIRS in patients with icterus, although changes in TSI could still be detected even in patients with high bilirubin [177].

2.3.2.4.3 Brain Morphology

The morphology of the brain is very varied, and therefore small changes in the NIRS sensor position can lead to changes in the values measured. Kishi et al. demonstrated that TSI significantly increased in 111 anaesthetised patients (age range 7-89 years), when moving the sensor from a more lateral position to 1cm closer to the middle forehead line [178]. In case sensor repositioning is required, it is extremely challenging to place it in the exact same position as before. Therefore, changes from baseline rather than absolute values are encouraged, and repositioning the sensor in case it detaches in the middle of a measurement is not recommended, and a new baseline needs to be established [178].

2.3.2.4.4 Extracerebral Contamination

In NIRS, despite the target tissue being the brain, both the sensor and the emitter are placed over the skin of the individual, which means that the light will pass through

non-cerebral tissues before and after brain tissue. The presence of these tissues, also known as extracerebral contamination, is one of the main sources of noise in NIRS [179]. Changes in oxygenated and deoxygenated haemoglobin recorded by NIRS are a combination of cerebral oxygenation and scalp oxygenation [180]. In comparison to continuous wave NIRS, SRS is believed to be less susceptible to extracerebral contamination [181], given that it uses changes in OD over distance, and the effect of extracerebral tissue on OD are considered relatively constant over distance [179]. Several studies have investigated the effects of extracerebral oxygenation on SRS measurements using a tourniquet around the head to induce ischemia to the skin [182-185]. These studies have demonstrated that TSI decreases after skin ischemia, with some studies reporting a small decrease (3%) [183] while others demonstrate a large change in average resting values (>20%) [184]. Despite the theoretical reasoning being that extracerebral perfusion should not affect SRS NIRS measures, experimental data proves it has a small to moderate effect. Interestingly, these changes seem to be different for different commercially available NIRS monitors [184, 185]. Germon et al. recommend that NIRS monitors should have a source-detector distance of at least 4.8cm to optimally capture cerebral tissue and minimise extracerebral contamination [186].

2.3.2.4.5 Motion Artifacts in NIRS

Head movement, skin movement due to talking or facial expressions, and optode displacement are key sources of motion artifact in NIRS [187-189]. These actions cause three main types of signal artifacts, namely baseline shifts, spikes and slow drifts [188]. A number of noise correction strategies have been developed, using different signal processing methodologies including principal component analysis, spline interpolation, wavelet analysis, Wiener filtering, Kalman filtering or polynomial

fitting [187, 188, 190, 191]. Furthermore, as discussed in previous sections, adaptive filtering with subtraction of the extracerebral signal recorded with a short source-detector distance can be used for motion artifact removal [192]. Wavelet methods have demonstrated good performance in removing spike noise, although they have to be used with care as they might introduce baseline shifts [189]. Spline interpolation strategies are generally good at removing motion artifacts, but residual spike noise might remain, although these can be successfully removed by adding further polynomial filtering or regression smoothing [188]. Finally, Kalman filters have been proposed as an attractive solution because of their good performance in real time analysis of non-stationary signals [187].

2.3.2.4.6 Validation of NIRS

NIRS has the potential to be a very powerful clinical tool due to its non-invasiveness and ease of use. However, despite the increasingly widespread use of NIRS, one of its main limitations is the challenges in its validation, with a gold standard method yet to be developed. Some validation studies have compared NIRS to other non-invasive imaging techniques or mathematical models. However, the most established method to validate NIRS, which is often accepted by European, USA and other medical devices regulatory bodies [176], is the comparison of NIRS derived measures of regional TSI, with saturation levels calculated from invasive measures of oxygenation in cerebral arterial blood supply and venous drainage vessels.

Typically, NIRS derived TSI is compared to a weighted sum of venous and arterial oxygenation using an arterial:venous (A:V) volume ratio. This volume ratio is not known and depends on the anatomy of the patient and the region observed, as well as other dynamic factors such as changes in blood gases or blood pressure [193]. Vascular volume in the human brain has been found to represent 2.43-3.02% of the

brain volume [194, 195], and 2.5% in the frontal cortex [196]. The fraction of that volume that corresponds to capillaries has been estimated to be around 48% by the Indian ink injection method [194]. Furthermore, Ito et al. used PET to estimate the arterial fraction of the cerebral circulation, which they found to be approximately 30%, while the arterial and the capillary fractions together would correspond to a 63-70% of the total circulating brain volume [196]. Commercially available NIRS devices use a fixed ratio to validate their measurements, with values typically used being 25:75 or 30:70 [197]. Pollard et al. derived the 25:75 ratio from a group of 12 healthy volunteers and validated it in 10 healthy volunteers, obtaining high correlation values for the training ($r^2 = 0.798 - 0.987$) and validation ($r^2 = 0.794 - 0.992$) groups [198]. Other approaches only compare NIRS TSI to venous oxygenation measures, which are usually collected either from the jugular bulb or the superior vena cava [193]. Cerebral blood volume is known to change due to hypercapnia and hypocapnia. Ito et al. used PET to show that, during both PaCO_2 conditions, the cerebral blood volume corresponding to veins and capillaries was kept constant while the arterial volume changed in the direction of the flow [199]. Therefore, a constant arteriovenous ratio cannot be assumed if the PaCO_2 conditions change.

La Cour et al. conducted a review of articles that validated different commercially available NIRS devices using either venous oxygenation or a combination of venous and arterial oxygenation [193]. They demonstrated a higher correlation and agreement in those methods that used a combination of arterial and venous blood. Moreover, even though the bias between the two methods was low on average (0.2%), the limits of agreement ranged from 13 to 13.4% (% refers to TSI units) [193]. This study is the best evidence that absolute values of cerebral oxygenation

have significant between individual variability and accuracy, since they vary a lot depending on the monitor and they show poor agreement during validation.

Validation of changes in oxygenation are a bigger challenge to study, and a lot of work is still needed in this field. Some studies have used phantoms to change the concentration of blood oxygenation [200], demonstrating magnitude dependent differences between monitors for the same change in oxygenation. However, these changes were very slow (hours), and thus might not be representative of how NIRS devices react to fast changes in oxygenation. Physiological studies might assist here. Mehagnoul-Schipper et al. found that $\Delta[\text{HHb}]$ induced during finger tapping correlated well with those obtained by BOLD-MRI methods, both in a group of young ($r = -0.70$) and older volunteers ($r = -0.82$) [201].

2.3.2.4.7 Repeatability of Measures

The reproducibility of NIRS derived measures of oxygenation has been studied in the context of orthostatic challenges [202, 203]. For signals derived using continuous wave NIRS, Mehagnoul-Schipper et al. demonstrated low reliability during an active stand test when repeated on different days, although the same average shape was observed for all the signals ($\Delta[\text{HbO}_2]$, $\Delta[\text{HHb}]$ and changes in concentration of total Hb ($\Delta[\text{tHB}]$) [202]. Mol et al. also evaluated these signals and TSI derived from SRS within the same hour, although in this case they derived features (mean, maximum and minimum with respect to baseline) from two periods of the signal after standing (0-30s and 30-180s) and assessed their test-retest reliability [203]. They repeated the measures after the sensors were set up by a different researcher to test inter-observer reliability, and they compared the data from two NIRS sensors placed simultaneously (left and right side of forehead) to test inter-sensor reliability [203]. This study demonstrated that $\Delta[\text{O}_2\text{Hb}]$ and $\Delta[\text{HHb}]$ had excellent test-retest reliability during the initial transient part

of the stand, while worse performance was observed for TSI, which seemed to be more reliable during the later part of the signal. Similar behaviours were observed for inter-sensor reliability, while for the inter-observer reliability good results were obtained for all signals during the second section of the active stand [203]. As it was discussed in the previous section, SRS enables estimates of absolute values of TSI. Madsen et al. studied the repeatability of SRS derived measures of cerebral oxygenation in a group of 22 subjects without cardiovascular diseases [132]. They took three measurements within 2 minutes by removing and replacing the monitor on the participants forehead, obtaining a 4% maximal variability.

In general, measures of cerebral oxygenation derived from NIRS present moderate reliability and reproducibility. This could be because of the multiple factors that contribute to this signal, including blood pressure, cerebral autoregulation and circulating blood gases, as well as other methodological causes discussed in this section.

2.3.3 Clinical Applications of NIRS

Since the development of NIRS for the assessment of cerebral oxygenation, several clinical applications have been developed for this technology [204, 205]. A brief summary of such applications is provided below:

- Cardiac surgery: cardiac surgery and, in particular, cardiopulmonary bypass, can pose a high risk of negative neurological outcomes (such as stroke and cognitive impairment) to the patients due to emboli and hypoperfusion [205]. Murkin et al. demonstrated that in the event of desaturation, strategies to quickly restore cerebral TSI are associated with a lower risk of stroke and other major organ morbidity, as well as with a shorter hospital stay and mortality [206]. Shorter

hospital stay was also observed in another similar trial, which also demonstrated that the time of hypoperfusion (TSI below 50%) was associated with the development of cognitive impairment [207]. Carotid endarterectomy is another type of surgery that can benefit from NIRS monitoring, given that cerebral ischemia can occur in the absence of appropriate collateral blood supply [205]. NIRS has been a well established monitoring technology for this application for two decades, and a 12% reduction in TSI is used as a marker to place a shunt or resaturation interventions [204]. NIRS can also be used to monitor cerebral oxygenation after declamping in carotid endarterectomy, helping in the prevention of hyperperfusion syndrome [204].

- Other types of surgery: for a review on the use of NIRS for non-cardiac surgery we refer to the systematic review by Nielsen [208]. Such applications include neurosurgery, maxillofacial surgery, thoracic surgery, orthopaedic surgery, urology surgery, gynaecological and obstetric procedures, gastro-abdominal surgery, and vascular surgery. Although the evidence is equivocal, the general belief is that desaturation during non-cardiac surgery is associated with post-operative cognitive impairment, and thus a 10% drop is recommended as a threshold for therapeutic intervention to avoid negative outcomes [208].
- Traumatic brain injury (TBI): in a healthy brain, the demand of oxygen required according to oxygen metabolic rate is met by the cerebral supply of oxygenated blood. In TBI, however, there is a mismatch between demand and supply, given that increased intracranial pressure leads to reduced cerebral perfusion in the absence of a decrease in the consumption rate [162]. A TSI lower than 60% during prolonged periods after TBI has been associated with impaired cerebral perfusion, increased mortality and higher intracranial hypertension [209]. The

main interest of using NIRS in TBI is early detection of intracranial haemorrhage, in particular in settings where computed tomography, the gold standard, is not readily available [210]. Several studies have demonstrated good sensitivity and specificity in identifying brain haemorrhage using NIRS [210], in particular when the damage is within 2.5cm of the brain surface [211]. Furthermore, NIRS has been used in the assessment of cerebral autoregulation in TBI. Cerebral autoregulation is lost during TBI, which can lead to cerebral hypo or hyper perfusion, causing secondary brain tissue damage [210]. Impaired cerebral autoregulation is associated with increased mortality, morbidity and poor functional outcomes [212]. The two main indices that have been found to be correlated with negative outcomes are the pressure reactivity index (PRx) and mean velocity index (Mx), which are moving correlations between BP/intracranial pressure and BP/cerebral blood flow, respectively [162, 212]. Similar NIRS derived indices, like the tissue oxygen reactivity index (TOx) or the total haemoglobin reactivity index (THx), which represent a moving correlation between TSI or total haemoglobin concentration and BP, respectively, have been found to be correlated to PRx and Mx, and thus have been proposed as promising alternatives for an easier and non-invasive monitoring of cerebral autoregulation in TBI [212].

- Syncope and other autonomic dysfunction disorders: although not yet established in standard clinical practice, another application of NIRS is in the monitoring of cerebral oxygenation in the assessment of syncope and autonomic dysfunction during orthostatic challenges [213]. Such clinical application is described in more detail in section 2.4 *Peripheral and Cerebral Circulatory Responses to Orthostasis in Health and Disease* of this thesis.

- Other applications: several other applications of cerebral NIRS can be highlighted. NIRS has extensively been used in the monitoring of cerebral oxygenation in neonates during cardiac surgery, in monitoring of premature newborns, in neonates with hypoxic ischemic encephalopathy or in neonates with hypotension [214]. Furthermore, NIRS has been used to study neurovascular coupling in the form of functional NIRS (fNIRS), with applications in neurocognitive function assessment, epilepsy or mild cognitive impairment [189]. fNIRS has also gained popularity in the development of brain computer interfaces [215]. A combination of feature extraction and classification algorithms can be used with NIRS to create a system to assist in neuro-rehabilitation of motor or cognitive function in patients with stroke, to aid in communication tasks in patients with motor disorders, or in the restoration of movement for individuals with mobility disabilities [215].

2.4 Peripheral and Cerebral Circulatory Responses to Orthostasis in Health and Disease

2.4.1 Ageing

In this section a distinction is made between ageing and healthy ageing, the latter referring to ageing without developing any physical or cognitive morbidities and keeping in a good physical and socially active condition [28]. Healthy ageing is known to alter both the BP and the HR response to active standing. Initial studies in the early 90s demonstrated that the initial HR and steady-state response to standing is blunted in healthy older adults [216], with older adults having an initial nadir in mean arterial pressure (MAP) equivalent in magnitude to that of a younger cohort, while also recovering to baseline by 15-20 seconds [216]. A similar investigation on a subsample of healthy agers from a populational community-dwelling study (The Irish Longitudinal Study on Ageing (TILDA)) demonstrated similar results [28]. When the whole TILDA sample was considered, 4475 community dwelling older adults (normal ageing), a progressively attenuated increase in HR after standing with increasing age was described [217]. With regards to SBP and DBP, they observed an increasingly larger drop from baseline at nadir with age in men. In women, a similar effect was only observed in SBP [217]. Furthermore, BP recovered to baseline progressively later with age in men and women. Noticeable differences can be identified between regular ageing and healthy ageing, with regular ageing being more associated with impairments in BP recovery.

Finucane et al. also reported that 15.6% of the TILDA sample had an impaired stabilisation of BP, with this prevalence increasing to 42.1% in the oldest (≥ 80 years) group [217]. Additionally, 6.9% of the subjects included presented OH in the overall

population, which increased to 18.5% in the oldest group. In other community-dwelling settings the prevalence of OH has been reported to range between 9-30% [218]. Delayed BP recovery at 40 seconds has also been reported to have a prevalence of 9.2% in older adults in their 50s as compared to 37.2% of adults over 80 years [29].

Regarding cerebral blood flow, resting values have been demonstrated to decrease with age across the lifespan using different imaging techniques, including MRI [219], PET [220], SPECT [221], ASL-MRI [222], TCD [223] and NIRS [224]. During an AS test, Sorond et al. compared young and older adults and demonstrated a comparable decrease in cerebral blood flow measured using TCD in the presence of a larger decrease in MAP in the older group [225]. On the other hand, studies using NIRS present equivocal results. Kim et al. found a significantly smaller drop in $[HbO_2]$ in older adults (median(IQR): 29(27-33) years) as compared to their younger counterparts (median(IQR): 59(52-65) years) both at nadir and steady-state [226]. On the contrary, Mehagnoul-Schipper et al. showed that 2-10 minutes after standing, a group of healthy older adults (range: 73.9 ± 3.6 years) had a significantly larger drop from baseline in $[HbO_2]$ and total Hb concentration as compared to a healthy young group (range: 27.1 ± 6.9 years) [227]. A further study by Gatto et al. did not demonstrate significant differences between two age groups of healthy participants (young 22.4 ± 5.7 years vs old 48 ± 6 years) [228]. However, participants performed a lying to sitting manoeuvre, which evokes a less pronounced haemodynamic response than a lying to standing test. Differences in the protocol or the age of the groups might have led to differences in the results obtained by these studies. Edlow et al. used a different approach and investigated the effect of age as a continuous variable in a group of 60 healthy participants (20-78 years), demonstrating a smaller drop from baseline during standing

(average of 5 minutes) with age in [HbO₂], although no age effects were found in regional blood flow measured with diffuse correlation spectroscopy [229].

Lastly, CA has often been hypothesised to be impaired with ageing, although most of the current evidence in the literature demonstrates the opposite [230]. Possible explanations proposed to explain are that there is a “built-in reserve” to protect the brain despite the impairment of other organs [231] or that age related hypocapnia might improve CA and mask potential impairments due to ageing [223].

For a detailed discussion of this topic please refer to Appendix B – which provides details of a review article published as part of this thesis, entitled “*Systemic and cerebral circulatory adjustment within the first 60 s after active standing: An integrative physiological view*” [78].

2.4.2 Sex

Blood pressure is known to be higher in men than women at all ages until the menopause, and thus men have a higher risk of cardiovascular and renal conditions associated with higher blood pressure [232]. However, after menopause, the relationship is inverted with women reaching higher blood pressures than men [232]. Finucane et al. provided normative data for the transient blood pressure response during the first 110s after standing, demonstrating that the drop at nadir in systolic and diastolic BP was larger with age in men but not in women [217]. In terms of recovery to baseline, a progressively more delayed recovery in systolic BP was observed in men with age, with even a stronger delay in women. Similar patterns were observed in diastolic BP, with a lack of recovery in the oldest groups. Finally, a higher proportion of women than men presented with impaired BP recovery at 40 seconds or OH. Orthostatic intolerance in women has been related to larger drops in cardiac output and

more vasoconstriction during an orthostatic challenge [233]. Furthermore, women have lower levels of circulating norepinephrine and lower blood volume. Men are known to have a relatively more active sympathetic nervous system while women have a stronger parasympathetic activity and lower baroreceptor sensitivity [234]. Differences in hormones such as renin, angiotensin, catecholamines and oestrogen, involved in the regulation of BP through the autonomic nervous system, are associated with differences in orthostatic peripheral responses with sex [234]. Furthermore, a lower centre of gravity in women has been associated with more pooling of blood in the legs and lower vascular resistance during orthostatic challenges [234].

Sex differences in cerebral perfusion have been widely studied using ASL [235], SPECT [236, 237], MRI [219] and TCD [223, 238] and NIRS [224] with the majority confirming the same finding: women have higher resting cerebral blood flow than men. Apart from the differences in resting cerebral blood flow, differences have also been observed in the haemodynamic response to an orthostatic challenge. In a cohort of 24 young subjects (10 male) undergoing a thigh cuff release protocol while supine and while seated, Deegan et al. demonstrated that women and men had similar cerebral blood flow responses in both positions despite women having a higher drop in BP [239]. These results are indicative of a better cerebral autoregulation mechanism, which was also demonstrated using the Autoregulatory Index [239]. Edgell et al. also reported no differences with sex in the TCD derived cerebral blood flow drops after standing between pre and post-menopausal women and age matched men [240]. In a cohort of older adults (>70 years), Deegan et al. found that women had a significantly smaller drop from baseline in cerebral blood flow and smaller change in cerebrovascular resistance (CVR) at nadir as compared to men [241]. In addition, measures of cerebral autoregulation demonstrated that women have a better cerebral autoregulatory [241].

The authors propose that this could be due to differences in hormones, in particular oestrogen. However, they argue that this option is unlikely because their participants are postmenopausal, and oestrogen levels are low in this population [241]. Furthermore, another study investigating the effect of the menstrual cycle phase on the orthostatic cerebral response in women found no differences during the cycle [242], and time to syncope in a LBNP protocol did not differ during the menstrual cycle [243]. Nevertheless, these studies have not investigated the effects of dehydroepiandrosterone sulphate, a strong male sex hormone that has been hypothesised to be involved in cerebral autoregulation sex differences through genetic pathways [244].

2.4.3 Vasovagal syncope

The European guidelines for syncope recommend the use of the active stand (AS) test in the assessment of syncope with concurrent monitoring of continuous blood pressure and heart rate [1], and further investigation using the HUT test. Studies in our group have demonstrated differences in the haemodynamic AS patterns between individuals with and without VVS [245, 246]. Kwok et al. studied a group of young patients with VVS with and without a positive HUT test and a control group, and observed that patients with a positive HUT had a hyper-reactive peripheral response to an AS test when compared to controls [245]. This response was characterised by a smaller nadir and larger overshoot after standing, as well as a higher HR and cardiac output (CO) recovery value. Similar responses were observed when comparing a cohort of older fainters with a group of controls with larger drops in stroke volume and CO combined with an increase in TPR also noted [246].

Regarding cerebral circulation during standing, Kim et al. observed that from a group of young adults performing a repeated squat-to-stand test, in those who experienced symptoms of orthostatic intolerance the initial drop rate of total

haemoglobin measured with NIRS was slower when compared to non-symptomatic individuals [247]. A different study investigated the cerebral oxygenation responses to standing in children with normal and abnormal (i.e., OH and VVS, among others) responses to an AS [248], demonstrating a lower initial nadir and steady-state reached in $\Delta[\text{O}_2\text{Hb}]$ after standing in the abnormal group.

In the HUT, the patient is attached to a bed that is tilted upright (normally 70°) with or without administration of a vasodilating agent [249]. Haemodynamic patterns evoked during an HUT are very different than in the AS, with the purpose of this test to reproduce symptoms (which in most cases includes VVS) [250]. Generally, a positive HUT response consists of three phases: an initial stabilisation phase after tilting, a progressive phase where BP slowly drops and HR increases, and the last phase, with a large drop in BP accompanied or in some cases preceded by bradycardia (if not asystole) [251]. There are two main subtypes of VVS (cardioinhibitory and vasodepressor), which may occur in isolation or most often together. During cardioinhibitory VVS sudden and profound vagal stimulation leads to bradycardia, which often results in asystole, a subsequent drop in BP, cerebral hypoperfusion, and eventually pre-syncope or syncope [252]. In the vasodepressor subtype BP is believed to decrease either due to CO drops or because of vasodilation of arterioles (decrease in TPR) due to lower sympathetic activity [252]. Despite a similar BP pattern, different combinations of underlying CO and TPR responses have been described: either a drop in CO, a drop in TPR, or a drop in both [251, 253], ultimately leading to reduced central blood volume and BP.

The ESC guidelines define syncope as a transient loss of consciousness due to cerebral hypoperfusion [1]. The recent incorporation of new technologies such as TCD and NIRS into the study of syncope has demonstrated that cerebral blood flow velocity

and oxygenation decrease during presyncope [40, 253-255] and syncope [256, 257]. When using TCD, drops of 18-26 cm/s have been found during presyncope in the middle cerebral artery velocity (MCAv) [253, 254, 258], while a drop of 5-7% in cerebral oxygenation derived from NIRS has been reported [253]. At the moment of syncope, studies report a drop from baseline of 20-35 cm/s measured by TCD [258, 259] and a drop larger than 10% in cerebral oxygenation measured with NIRS [257, 260]. Furthermore, the occurrence of syncope seems to be associated with a value of cerebral oxygenation below 60% [257], although this threshold should be taken with caution given the lower reliability and device dependence of absolute values derived from NIRS. Interestingly, cerebral blood perfusion demonstrates a similar pattern either if measured with TCD or NIRS during the development of syncope for different types of syncopal episodes (CO origin, TPR origin, or mixed origin, discussed above) [253].

Similar to BP and HR changes, the decrease in cerebral perfusion follows different phases during syncope. During HUT, Szufladowicz et al. observed a first gradual decline in cerebral oxygenation followed by a sudden drop in all subjects who experienced syncope [40]. Changes in oxygenation were noticed 3.3 minutes prior to loss of consciousness, preceded the drop in blood pressure by 2.2 minutes, and occurred 1.3 minutes before symptoms. Colier et al. also demonstrated that changes in cerebral oxygenation were present before bradycardia [255]. In a group of 54 patients with unexplained syncope, Bachus et al. demonstrated that, while no differences in BP were observed with respect to baseline one minute before fainting, a decrease in cerebral oxygenation was already present [257]. All this evidence highlights the value of monitoring cerebral perfusion, and in particular cerebral oxygenation, in the assessment of syncope. A recent review on this topic envisages two potential roles of NIRS in the assessment of syncope [261]: firstly, NIRS can help us further our understanding of the

pathophysiology of syncope and its symptoms, how peripheral circulation is related to cerebral perfusion, and what is the status of cerebral autoregulation in syncope; secondly, it may aid in further personalisation of syncope diagnosis and treatment.

The role of cerebral autoregulation in syncope has also been studied, although evidence is equivocal. As detailed above, decreases in cerebral perfusion precede changes in other peripheral cardiovascular signals. These findings have led to the hypothesis that an impairment of CA is involved in the pathophysiology of syncope. Some studies investigating CA have noted that this mechanism is not impaired during neither supine resting nor initial phases of HUT in patients with syncope as compared to healthy controls [262]. On the contrary, when more advanced signal processing methods were applied to derive CA, it was noted that CA was enhanced when drops in MAP occurred [263], suggesting a decrease in beat-to-beat cerebrovascular resistance [264]. Schondorf et al. analysed HUT responses using transfer function analysis and also concluded that CA in patients with syncope is not different to that of healthy controls [265]. CO₂ changes during syncope have also been proposed to affect CA and contribute to syncopal episodes [126]. Therefore, it remains unclear whether CA is impaired during syncope.

2.4.4 Orthostatic hypotension

Another relevant orthostatic condition is OH, which is associated with ageing (see Section 2.4.1. *Ageing* for more detail) and can also be caused by different forms of autonomic dysfunction associated with conditions such as Multiple System Atrophy (MSA), Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), Pure Autonomic Failure (PAF) or diabetic autonomic neuropathy [266].

Novak et al. studied the TCD responses during a 5-10 minute HUT in a group of patients who had neurogenic OH as a result of different autonomic dysfunction conditions [267]. In some patients, they observed no correlation between BP and CBF velocity (CBFV) signals, which was similar to the results found in a group of healthy controls and therefore indicative of intact CA. In the rest of patients a correlation was noted with CA failure identified where the slope of the regression was >0.5 [267]. This study highlights how cerebral perfusion can help identify different phenotypes of patients with OH. In a different study, Novak defined a new clinical entity, orthostatic cerebral hypoperfusion syndrome (OCHO), characterised by an abnormal drop in TCD measures of cerebral perfusion in the absence of clinical significant orthostatic hypotension during HUT testing [37]. Interestingly, all the OCHO patients experienced symptoms of orthostatic intolerance, while none of the controls did. In fact, Harms et al. demonstrated that leg crossing can improve CBFV and cerebral oxygenation in patients with autonomic failure, leading to reduction of symptoms of orthostatic intolerance [268]. Furthermore, lower cerebral oxygenation has been observed in patients suffering from PAF and MSA with symptoms of orthostatic intolerance versus those without such symptoms [269, 270]. All these studies provide evidence of the correlation between impaired cerebral perfusion and symptoms of orthostatic intolerance, which are not always well correlated with peripheral haemodynamic impairments.

2.4.5 Falls

Falls are highly prevalent in older adults over the age of 65 years, with 1 in 3 experiencing at least 1 fall every year [15]. Impaired responses in BP after an AS have been linked to an increased risk of falls in the older population [29]. Both OH and delayed recovery at 40s after standing are associated with an increased risk of all-cause falls, UF and injurious falls, independent of covariates, although there is no association

between falls and IOH in community dwelling adults [29, 271]. In a cross-sectional study, Romero-Ortuno et al. demonstrated univariately that IOH is associated with a higher prevalence of falls in patients attending a geriatrician clinic [43]. It has also been demonstrated that using OH as a falls predictor is dependent on the definition of OH [272]. A recent meta-analysis of 63 studies concluded that OH was associated with falls with an odds ratio of 1.73 (95% CI: 1.50-1.99) independent of study features such as population, OH definition, design, quality or method to monitor BP [273].

Despite some falls (and in particular UF) often being attributed to cerebral hypoperfusion [62], literature directly analysing the association between cerebral circulation and falls is limited. Sorond et al. used TCD to study autoregulation and CO₂ vasoreactivity in a cohort of 419 older adults, and they observed that those in the lowest quintile of vasoreactivity measures were 1.7 times more likely to fall than those in the highest quintile, while they found no association of falls with cerebral autoregulation [274]. The authors concluded that the dissociation between these two cerebral regulatory mechanisms might be explained by the sensitivity of cerebral autoregulation measures or by the fact that these patients might have been at an early stage in the impairment development [274]. Another study by Fitzgibbon-Collins et al. provides further evidence to support the association between balance and lower values of cerebral oxygenation [41]. The authors demonstrated that those with lower cerebral oxygenation had worse postural stability, and that a 10-second pause in a sitting position before standing improved cerebral oxygenation and reduced postural instability [41]. These results strengthen the potential role of cerebral oxygenation in the development of falls, given that postural instability is known to be associated with falls [275].

2.4.6 Other Clinical Conditions

2.4.6.1 Hypertension

Hypertension and supine hypertension are known to be associated with OH [36, 276, 277], and in particular uncontrolled hypertension is linked with a larger drop in systolic BP during standing, and is associated with an increased risk of future falls [278]. Individuals with supine hypertension have an impaired recovery in transient BP drops occurring during standing, with larger delays in the recovery with more severe levels of hypertension [279]. This picture is further complicated by the use of anti-hypertensive medication, with conflicting evidence of the interaction between OH, hypertension and anti-hypertensive use in patients at risk of falls [280, 281].

Cerebral blood flow is known to decrease with hypertension [282], and to increase after antihypertensive treatment [283], while it is unclear how hypertension impacts CA, with opposing theories suggested [98]. While some researchers have stated that CA is impaired with hypertension, others have concluded that hypertension shifts the buffer CA region to higher pressures, increasing both the lower and upper limits of autoregulation. Both theories would provide an explanation as to why a risk of hypoperfusion is often considered when lowering BP. However, a recent review on this topic has highlighted that all studies investigating cerebral autoregulation in hypertension, whether they studied dynamic or static CA, have demonstrated that this mechanism is preserved with hypertension [98]. Furthermore, studies exploring the relationship between anti-hypertensive treatment and falls, cerebrovascular damage or cognitive impairment have not demonstrated increased negative outcomes with increased anti-hypertensive treatment [284-286]. This may suggest that CA is not modified by hypertension or its treatment, or that CA resets to the prevailing status. Regarding supine hypertension, a recent study demonstrated that the transient cerebral

oxygenation response to standing is equivalent in community-dwelling adults with and without supine hypertension, but when standardised by BP, impairments were noted in the hypertensive group. The authors thus concluded that cerebral oxygenation and autoregulation were impaired in supine hypertension [279].

2.4.6.2 Cognitive Impairment and Dementia

The prevalence of cognitive decline is 15% in older adults over 60 years [287] and, in patients with dementia, the prevalence of OH is 41% [288]. McNicholas et al. demonstrated that, in community dwelling adults over the age of 50 years, there is an association between the presence of OH and a decline in cognition over a 4-year follow-up period [289]. Similar results were found in other populational studies such as the Rotterdam study [290], the Malmo Preventive Project [291], or the Three-City Study Cohort [292], which demonstrated associations between impaired orthostatic BP regulation and a risk of dementia. A recent meta- analysis reported that 56% of studies included demonstrated an association between OH and worse cognition, although when studies used more than one assessment tool, they were more likely to find an association. [293]. Despite all these studies showing evidence of this association, it still remains unclear whether the relationship between OH and worsening of cognition is causative [293].

Cognitive impairment and dementia may have vascular origin or contribution [294], but regardless of whether it is vascular or neurodegenerative in origin (such as Alzheimer's disease (AD)), it is known that cerebral blood flow is reduced and cerebrovascular resistance increased in these patients [295, 296]. Furthermore, white matter hyperintensities, a sign of small vessel disease that is associated with stroke and dementia, are associated with reduced cerebral blood flow [297]. As discussed above, cognitive decline and dementia are associated with OH, and it has been proposed that

the mechanism behind this association is an impaired cerebral autoregulation, which would lead to cerebral hypoperfusion, ultimately resulting in impairments in cognition [289, 293]. Cerebral autoregulation has not been studied in vascular dementia, but it has been studied in AD [98]. However, despite cerebrovascular abnormalities being consistently demonstrated in Alzheimer's disease, a recent review concluded that there is not enough evidence to support that cerebral autoregulation is impaired in AD [98].

2.4.6.3 Depression

There is increasing evidence that OH is associated with late-life depression [298]. Briggs et al. found that, in a population study, symptomatic OH (but not asymptomatic OH) at 30 seconds was significantly associated with an increased risk of developing depression (Odds Ratio (OR): 1.9, 95% CI: 1.15-3.15) [298]. Similar findings were those from O Regan et al., who demonstrated that symptomatic OH was cross-sectionally associated with a higher prevalence of depression in older adults [299]. Richardson et al. reported that OH was significantly more prevalent in a cohort of older adults with later-life major depression as compared to controls, and that the drop in SBP was significantly larger in the depressed group [300]. Further supporting these findings, a systematic review of late-life depression and its association to hypotension analysed 19 studies, from which 5 focused on OH and depression, all of them establishing that OH was positively associated with late-life depression [34].

A common feature of late-life depression on MRI studies are white matter hyperintensities [298, 301, 302], which are believed to be ischemic lesions [301]. It has been hypothesised that these lesions might be caused by cerebral hypoperfusion, with some studies showing an association between the presence of hyperintensities and a reduced cerebral blood flow [303] or cardiac output [304]. Furthermore, depression has also been associated with reduced cerebral blood flow [305, 306] and reduced cerebral

oxygenation during standing [307]. Briggs et al. demonstrated that lower drops in NIRS derived cerebral oxygenation responses from 30-90 seconds after standing were associated with depressive symptoms in a cohort of community-dwelling older adults [307]. They reported that this association was still present even when accounting for OH or antidepressant use, although correcting for systolic blood pressure removed this association, suggesting that the relationship noted may be explained by BP drops.

2.4.6.4 *Frailty and Multimorbidity*

Frailty is defined as an increased vulnerability to stressors resulting from the accumulation of deficits and morbidities [308]. In 2011, Romero-Ortuno et al. demonstrated that the maximal increase in HR after standing significantly decreased with frailty [44]. A subsequent study on the same cohort of patients demonstrated that patients with large SBP nadirs that did not recover to baseline had more comorbidities (marker of frailty) than those with large SBP nadirs with slow recovery [43]. Different frailty measures such as the Fried Phenotype or the Frailty Index have also been associated with OH and orthostatic intolerance [33, 42]. A study on nursing home residents demonstrated that patients classified as frail had significantly larger drops from baseline within 30s and 3 minutes of standing than those under the non-frail category [309]. Patients attending an outpatients geriatric clinic had an increasing prevalence of OH with frailty, ranging from 9% in light frail to 66% in severely frail adults [310]. The authors also observed that in patients with OH, the relative risk of mortality, disability and hospitalisation was significantly higher than in patients without OH. Thus, there is strong evidence that orthostatic peripheral haemodynamics are impaired in frailty.

While cerebral circulation has been extensively studied in geriatric syndromes associated with frailty (stroke, dementia, hypertension, etc.), relationships between

cerebral perfusion and frailty remain largely unexplored. A recent study by Maguire et al. investigated the relationship between the Frailty Index and cerebral oxygenation responses to standing in a large cohort of community-dwelling adults [311]. They observed that impaired recovery in TSI at 20-27 seconds after standing was associated with frailty. Orthostatic TSI responses were also studied in a cohort of 1270 patients undergoing a head-up tilt test, and it was observed that having multiple comorbidities was associated with lower TSI drops in this cohort, and that lower values of TSI were present in women as compared to men [312].

2.4.7 Gaps in the Literature

A number of key gaps have been identified in the literature regarding the assessment of cerebral circulation during AS testing in young and older adults.

- NIRS is a useful method to assess cerebral circulation, but a number of technical gaps still remain unexplored. Validation of NIRS devices is challenging given the lack of thorough knowledge of the signals origin as well as a lack of a gold standard method to assess cerebral oxygenation. Furthermore, variabilities in cerebral morphology are not considered. Age and sex dependencies of some parameters such as k and h (for the calculation of μ_s') in SRS remain unexplored, and represent a big technical gap in this field. Furthermore, noise identification and removal strategies that can be implemented to filter cerebral oxygenation dynamic responses to the AS test are still to be developed. Accurate absolute quantification of cerebral oxygenation remains one of the main challenges of this method.

- While the potential of NIRS in the assessment of falls and syncope has been acknowledged in the literature, few studies have used this method to characterise cerebral circulation in this clinical context.
- The effects of age and sex on the peripheral haemodynamic responses to standing have been extensively studied. However, how these two factors are associated with cerebral circulation, and in particular with cerebral oxygenation, remains controversial in the case of age and largely unexplored in the case of sex.
- While peripheral haemodynamics and cerebral oxygenation have been well characterised in patients with syncope during the HUT test, a much more limited literature exists for the AS test in both young and older patients. Understanding the cerebral haemodynamic responses during the AS test in these cohorts can help in determining whether there is a value in incorporating cerebral circulation measurement tools in this clinical context. Moreover, it can help us further our understanding of the physiology of syncope in populations of young and old adults, which are commonly seen in falls and syncope specialised units.
- This review has identified a large body of evidence demonstrating that cerebral circulation during the AS test is impaired with several age-related medical conditions that are also associated with the occurrence of falls. However, little is known about the association between cerebral circulation (and in particular cerebral oxygenation) responses to AS standing and frailty or multimorbidity. Furthermore, sex differences in this context remain largely unexplored. Understanding this association

would help in determining whether frailty or multimorbidity is a modifiable risk factor for cerebral hypoperfusion in older adults.

- There is paucity of data looking at the association of falls and syncope with cerebral circulation or oxygenation. Given that in this population falls and syncope are often attributed to cerebral hypoperfusion, it is of great interest to investigate to what extent this assumption is true and how cerebral oxygenation data can be used to predict these events.
- CA remains poorly described or uncharacterised in falls and syncope, representing an important gap for the understanding of the physiological origin of these events. Furthermore, most studies assessing CA have used TCD for monitoring CBF and thus CA assessment with NIRS needs to be further developed.

Chapter 3: Prediction of Falls and Syncope Risk Using Artificial Intelligence/Machine Learning: A Review

Falls and syncope have consequences at both an individual and societal level, often resulting in injury, emergency department visits, hospitalization, nursing home admissions or death [313-316]. With 1 in 3 older adults and 1 in 5 younger adults falling annually their economic burden is huge [10, 22]. Numerous interventions have been developed for the prevention of falls and syncope [1, 317]. However, this requires the initial identification of those individuals who are more likely to develop a fall or a syncopal event, what are the most likely underlying modifiable causes and which individuals will benefit the most from suitable interventions. This has resulted in the development of numerous risk assessment strategies to aid in the prevention of these events.

While many risk assessment strategies have focused on the development of clinical indices derived from the patient history and diagnostic tests, the use of artificial intelligence (AI) / machine learning (ML) approaches has gained popularity in recent years. AI has been defined as *“the science and engineering of making intelligent machines, especially intelligent computer programs. It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine*

itself to methods that are biologically observable” [318], and ML is a branch of AI that addresses the question of *“how to construct computer programs that automatically improve with experience”* [319]. More formally, in ML *“a computer program is said to learn from experience E with respect to some task T and some performance measure P, if its performance on T, as measured by P, improves with experience E”* [319]. AI/ML has the potential to revolutionise medicine. Advances in data collection and storage have resulted in huge amounts of data being available for interpretation [320]. ML approaches can help clinicians in analysing such large, multimodal datasets which capture the multidimensional facets of falls and syncope through mathematical models created to assist in decisions that arise at different stages of patients management: diagnosis, treatment and prognosis [321]. Given the complexity and multifactorial nature of these events, combining different aspects of patients health status (e.g. morbidities, biosignals, etc.) may help in the prediction of these conditions. A key consequence of this is that ML may lead to advances in personalised medicine [321].

This section provides an overview of the main falls and syncope risk assessment tools and the state-of-the art literature on the prediction of falls and syncope using ML. Given that the literature regarding falls and the literature on syncope are very different, this review is divided in two parts, one for each type of event. The gaps identified in the literature for both falls and syncope are then discussed at the end.

This chapter will lead to the following publication:

Pérez-Denia L, Claffey P, Byrne L, Rice C, Kenny RA, Finucane C. *Prediction of Falls and Syncope Risk Using Artificial Intelligence/Machine Learning: A Review*

3.1 Prediction of falls

3.1.1 Introduction

3.1.1.1 *Standard Falls Risk Assessment*

International guidelines such as the NICE Assessment and Prevention of Falls in Older People [322], the Guideline for the Prevention of Falls in Older Persons by the American Geriatrics Society, British Geriatrics Society and American Academy of Orthopaedic Surgeons Panel on Falls Prevention [323], or the Preventing Falls in Older Persons guidelines by the American Academy of Family Physicians [324] identify a history of falls in the last year as the first screening step that will most successfully identify patients at a risk of future falls, and recommend that this be done routinely in primary care settings. In case a previous fall is reported, the guidelines recommend the use of gait and balance assessment, which will lead to no further intervention if they are completed successfully or to a multifactorial risk assessment in case a gait or balance abnormality is identified [323, 324]. Such multifactorial assessment might include further assessment of gait, balance or muscle strength, visual examination, cognitive impairment assessment, reviewing of medications, or postural dizziness and hypotension assessment, among others [322-324]. If deemed necessary after this comprehensive examination, falls prevention interventions will be designed by the clinicians to target the main deficits of the patient, which can include patient education, medication modifications, physical therapy, vision improvement, or modifications in the footwear or the home environment [322-324]. Only the guidelines from the American Academy of Family Physicians suggest specific tests for gait and balance assessment, with the timed up and go (TUG) being the main recommendation and the Berg Balance Scale (BBS) being suggested as an optional complementary test [324].

Several systematic reviews and meta-analyses have been conducted to evaluate the usefulness of these two instruments and other falls risk assessment tools [314, 325].

Some examples of such falls assessments include the TUG [326] and BBS [327], as mentioned above, and others like the Morse Fall Scale (MFS) [328], the Falls Risk Assessment Tool (FRAT) [329], the Tinetti scale (also known as the Performance-Oriented Mobility Assessment (POMA)) [330], the Hendrich II fall risk assessment [331] or the St Thomas Risk Assessment Tool in Falling Elderly Inpatients (STRATIFY) [332]. These instruments generally include a battery of questions regarding the health status of the individuals (including morbidities, medication, activities of daily living (ADLs), etc.) and/or a series of physical tests that assess the balance and gait capabilities of the person. Then, a score is derived, and a threshold is established (usually using receiver operating curve (ROC) and area under the curve (AUC) analysis evaluating falls during a certain follow-up period) beyond which an individual will be at a high risk of experiencing a future fall. A recent meta-analysis demonstrated that the Berg Balance Scale had a pooled sensitivity, specificity and AUC of 73%, 90% and 0.92 for falls prediction, while these values were 76%, 60% and 0.75 for the Hendrich II scale; 89%, 67% and 0.81 for STRATIFY; 76%, 49% and 0.80 for TUG; and 63%, 60% and 0.76 for the Tinetti Balance Scale [325]. The study suggests that a combination of two assessment tools should be used instead of only one in order to achieve a higher diagnostic accuracy, while it recommends that the TUG and BBS could be complementary for community-dwelling adults [325]. Compared to other functional tests, the TUG is the one that encompasses more features that are relevant attributes of gait and balance for predicting falls [333], since it is a very easy and short test that can assess static and dynamic stability as well as gait, turning, sitting, and standing motions. However, despite its widespread use and popularity, two reviews and

meta-analyses have questioned its usefulness in predicting falls, given the overall poor-to-moderate predicting performance and the lack of a clearly established cut-offs [334, 335]. Greene et al. used body-worn sensors during TUG in a cohort of community-dwelling adults and compared the performance of sensors derived metrics to the standard TUG and BBS tests [336]. This quantitative TUG approach was proven superior in predicting falls, achieving a sensitivity and specificity of 77.3% and 75.9%, respectively, while these values were 58% and 64% for the normal TUG and 57.8% and 64.2% for the BBS in the same cohort. The use of wearable sensors during functional testing for the assessment of falls risk is gaining interest and popularity, and a few recent studies have reviewed the literature in this field [337-339]. A large variability still exists regarding the methodologies used in this field (e.g. test, sensors, features derived, etc.), making it difficult to compare studies, and leading to a wide range of performance results, with accuracy ranging from 47.9-100%, sensitivity from 16.7-100%, and specificity 40-100% [337].

3.1.1.2 Research Question

In recent years, machine learning approaches have been developed for the prediction of falls, given that they allow integration of multidimensional data developing models using large amounts of patient data. In this section a systematic literature search reviewing the use of ML methods in the prediction of falls is conducted.

3.1.2 Methods

3.1.2.1 Search strategy

Three different databases were used: PubMed, Embase and IEEE Xplore. A two-stage search strategy was conducted. First, a broad search was performed using the terms “fall* AND predict*” in these databases. Screening these articles was used as a

strategy to learn about this field and identify the main instruments used for the prediction of falls. Then, from the results obtained, those using the following methods were identified: “machine learning”, “deep learning”, “support vector machine”, “decision tree”, “random forest”, “boost”. The second stage of the search consisted of extending the results obtained by using “fall* AND classif*” or “fall* AND risk assessment” and the methods terms listed above. Further detail of these searches and the results obtained is detailed in Table 1.

Citations containing the title and abstract of the studies were imported into Covidence, an online systematic review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Duplicates were automatically detected by the software, and the remaining articles were screened to identify studies that fulfilled the following inclusion/exclusion criteria:

- Inclusion criteria:
 - Prediction/identification/classification of falls into two or more categories
 - Outcome variable is:
 - Either prospective or retrospective falls, defined according to the definition provided by Tinetti et al. in 1988: “a subject unintentionally coming to rest on the ground or at some other lower level” [18].
 - Risk of falls
 - Adult cohorts
 - Use of ML algorithms
- Exclusion criteria:

- Detection or prediction of real-time falls
- Conference abstracts
- Non-English articles

Relevant information was extracted from articles that met the criteria, and other articles that were found to be relevant during the process were added to the list of selected articles.

Table 3.1. Number of articles identified according to the search steps and terms used in the literature search.

Search strategy	Number of articles found
<i>Initial search: Fall*AND predict* (Title)</i>	
Embase	1587
PubMed	1161
IEEE Xplore	80
<i>Extended search 1: Fall* AND classif*(Title) AND (machine learning OR deep learning OR support vector machine OR decision tree OR random forest OR boost) (Title/Abstract)</i>	
Embase	25
PubMed	28
IEEE Xplore	57
<i>Extended search 2: Fall* AND risk assessment(Title) AND (machine learning OR deep learning OR support vector machine OR decision tree OR random forest OR boost) (Title/Abstract)</i>	
Embase	12
PubMed	7
IEEE Xplore	6

3.1.3 Results and Discussion

A total of 2963 studies were found, which resulted in 51 selected studies after duplicates removal, exclusion/inclusion filtering, and adding extra references (see Figure 3.1). Surprisingly, while ML methods have been used for decades for many different applications, the majority of studies employing ML algorithms identified were only published during the last two years (2020-2021) (see Figure 3.2). Table 3.2 summarises the studies selected for this review.

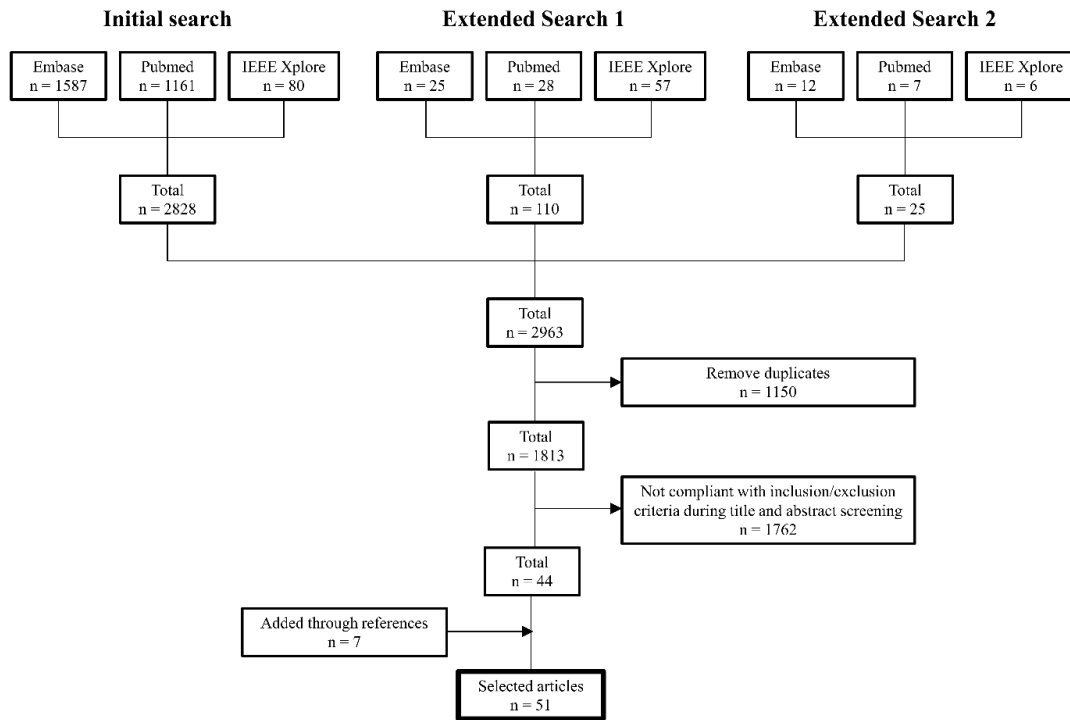


Figure 3.1. Block diagram with the results of the literature search on machine learning for falls prediction.

Details of initial search, extended search 1 and extended search 2 are provided in Table 3.1.

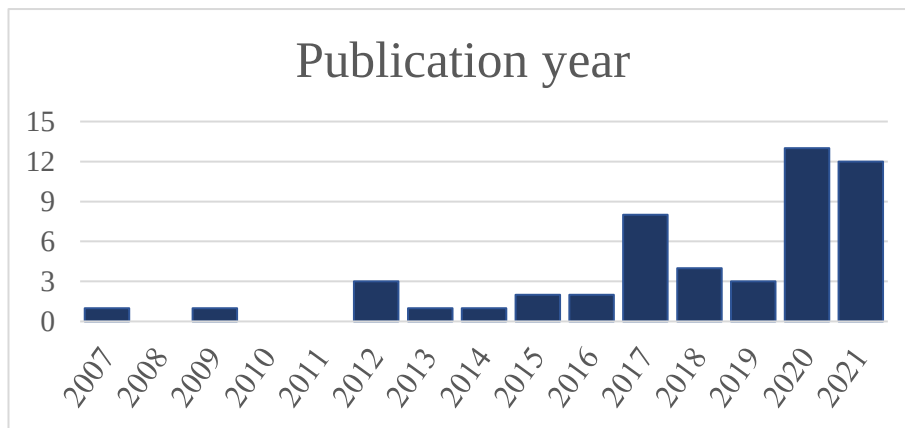


Figure 3.2. Histogram summarising the number of articles by publication year resulting from the literature search on machine learning for falls prediction.

ML methods for predicting falls have been used in different contexts, including the prediction of falls in community-dwelling adults [46, 47, 340], in hospitalised patients [341-343], or in patients with different conditions associated with a higher risk

of falls such as Parkinson's disease [344], multiple sclerosis [345], stroke [346], hypertension [347] or dementia [348, 349]. A wide range of sample sizes have been used in these studies, with 24 (47%) of them having 101-1000 participants and 11 (22%) having over a thousand participants. Surprisingly, 31% of the studies had a sample size of 100 or less participants, with most having less than 20 "fallers" [47, 346, 348-351]. This represents a significant limitation for ML approaches, especially when Deep Learning algorithms are employed. It was observed that in most of the studies the groups were unbalanced [46, 347, 352, 353]. While this is more representative of real-world scenarios (given that falls occur in about 30% of older adults), having an unbalanced dataset for classification purposes requires more attention when it comes to interpreting the results. In such cases, these studies might report a misleadingly high value of accuracy resulting from the high proportion of non-fallers. If 70% of the participants are non-fallers, an a priori chance level accuracy of 70% would be expected, and could be misleading in interpreting the performance of the model as high. Thus, other measures such as sensitivity, specificity or the AUC need to be evaluated to obtain a better picture of the model performance.

In terms of outcome variables, two main categories were identified: actual falls ($n = 40$, 75%) and risk of falls ($n = 10$, 19.6%). The former includes studies that used retrospective ($n = 11$) or prospective ($n = 32$) falls as the outcome variable, with the study by Kabeshova et al. investigating both retrospective and prospective falls [354]. In the case of studies designed to identify risk of falls rather than fall events, the risk is evaluated and derived from gait, balance, or medical information, from which a score is obtained and a threshold determines what the risk category of the participants is. While this approach has the advantage of being retrospective and thus not needing a follow-up period, it is possible that the performance on predicting actual falls would be lower if

that outcome was evaluated, since the measures used to assess falls risk are highly correlated with falls but do not achieve perfect prediction. Thus, these models have the issue that they are predicting a predictor, although it could be argued that, in this case, having a high risk of having a fall might be as clinically relevant as the fall itself, and might be equally useful in informing management and treatment of these patients. While most of the studies aim at predicting the occurrence of all-cause falls (or do not specify otherwise), some have focused on specific types of falls that might be considered as more complex, such as injurious falls [46, 345], recurrent falls [354, 355], serious falls (requiring a medical visit) [356] or accidental falls [357].

Protocols and predictors could also be classified into two main categories, namely, clinical data ($n = 18$), functional tests ($n = 26$), or both ($n = 4$). One study used data from a cognitive test as predictors [341], and the study by Silva et al. was unique in their use of ECG derived heart rate variability measures to predict future falls [358]. In those studies using clinical data, known falls predictors or risk factors are usually extracted from studies or surveys derived databases [46, 47, 354] or electronic patients records [343, 359, 360]. The latter strategy is of special of interest given that it allows the use of routinely collected data during clinical visits or hospitalisation periods. Of note, while most papers extracted specific conditions that are risk factors for falls, some papers captured a measure of overall frailty by considering multimorbidity as a predictor in their models [333, 356]. Functional testing often involves gait or balance tests such as walking [340, 352, 361], the timed-up-and-go (TUG) test [333, 350], or postural sway analysis [357, 362, 363], with the simultaneous recording of kinematic or pressure sensors such as inertial mass units (IMUs) (which contain accelerometers and gyroscopes) [333, 340, 350] or force plates [363, 364]. As compared to clinical databases, this approach has the drawback that different gait or postural tests have to be

performed by the patients, involving extra patient testing, time and resources, although in some clinical settings this type of testing is performed routinely as part of a geriatrics assessment [363]. These tests assess measures of gait and balance which characterise the mobility status of the patient and can be the direct cause of the fall, and therefore are meaningful predictors of falls.

A wide range of models have also been explored in this application of ML, with the most popular ones being support vector machines (SVM) [333, 341, 346, 350, 352, 353, 365-368] (n = 22), random forests (RF) [46, 353, 357, 359, 361, 363] (n = 19) and neural networks (NN) (n = 19) [333, 341, 352, 353, 364, 368]. A number of studies also used logistic regression in their analyses [47, 340, 344, 346, 354] (n = 16), often as a reference model.

Overall, ML algorithms have proven useful in the prediction of falls or falls risk. A few studies stand out for their excellent performance, achieving values of around 90% or more for accuracy, sensitivity and specificity simultaneously. One of these, by Giansanti et al. [362], classified participants into high risk and low risk of falling (defined by a threshold on the Tinetti score) using features derived from IMU sensors during standing sway testing. The authors explored different algorithms including Naïve Bayes, Bayesian Network, SVM and different types of NN, and reported values of accuracy, sensitivity and specificity > 91% for all models except SVM and the Naïve Bayes, which demonstrated much lower values in the 60-75% range. This study was performed in a relatively large sample (n = 260, 130 high risk) and performance was assessed in an unseen test set. Although the Tinetti score and the postural sway features could be expected to be highly correlated, the fact that not all the models achieved an excellent performance emphasises the added value of exploring more complex models such as neural networks. Another study with a large sample size is the one by Bates et

al. [369], who developed a SVM algorithm that could predict a history of falls from an electronic radiology report with a 94.5% accuracy and 0.97 AUC. These results are less surprising, given that the predictions were based on words derived from a text analysis system, and some of the words extracted were “fell”, “fall” or “falling”. Similar studies by Tremblay et al. [370] and McCart et al. [371] used data from the Veterans Health Administration to identify patient records corresponding to injurious falls with a LR model and falls with a SVM, respectively, demonstrating values of sensitivity and specificity in the range of 88-94%. Tunca et al. used a long-short term memory (LSTM) neural network to identify neurological patients with a history of falls using gait parameters [361]. Despite high performance, with accuracy, sensitivity and specificity >91%, and an AUC of 0.987, these results must be interpreted with care, since their test set included only 16 patients (7 fallers and 9 non-fallers), and therefore results can be biased by the small sample. Rehman et al. also used gait parameters to predict a history of falls in neurological patients using different ML algorithms [372]. In this case, LR, LDA, SVM and RF algorithms demonstrated performance values over 90%, with RF being the best model with a 98.67% accuracy, 99% sensitivity and 98% specificity. Despite this high performance, the lack of a test set impedes a complete interpretation of the results, since the models could be overfitting the training data. Similarly, Chen et al. reported high performance metrics (94% accuracy, 95% sensitivity and 94% specificity) with a neural network algorithm using gait features derived from a TUG assessment with accelerometer recordings [373]. Like in Rehman et al. [372], no test set was used and only 44 participants were included in the study, which makes the interpretation of the results difficult. In addition, the outcome variable of this study was a risk of falls based on the TUG time (threshold 12.47 seconds), and the gait parameters were derived from the same test. This could have increased the performance, given than

the outcome variable and the predictors were derived from the same information. Another study investigating data derived from accelerometers is the one by Yang et al. [374], although in this case data was recorded during normal living for 7 days. This data was combined with clinical data from the participants and yielded an accuracy of 89.2%, 90% sensitivity and 0.89 AUC using a RF algorithm when classifying participants into 1 or less falls vs recurrent falls. Similar results were obtained when differentiating between no falls and 1 or more falls.

Another group of studies which report high performance values, also demonstrate a trade-off between sensitivity and specificity [46, 47, 345, 364, 375, 376]. In most cases, these differences could be a consequence of the unbalanced class groups, with most studies having a lot less participants in the “fallers” or “high risk of falls” category, thus usually resulting in high specificity and low sensitivity.

While some studies used sex as a predictor in their models [47, 344, 354, 356], only two of the studies by Greene and colleagues adopted the approach of sex stratification [45, 377]. These two studies investigated a cohort of community-dwelling adults, although one was designed to predict a history of falls from pressure sensor data collected during postural sway testing[45], while the other predicted future falls from IMU derived features during TUG [377]. In the former study, a SVM algorithm was used and values of 71.52%, 65.38%, 68.36% were observed for accuracy, sensitivity and specificity, respectively, for all participants, while after sex stratification these values were 72.8%, 64.19%, 63.46% for men, and 73.33%, 74.71%, 64.14% for women [45]. In the second study, the female cohort was further divided into <75 years and ≥ 75 years, and accuracy, sensitivity and specificity values of 72.97%, 73.41%, 72.69% and 83.02%, 90%, 79.12% were obtained, respectively. In the case of men, such age separation could not be achieved due to a smaller sample size, and the overall results

were 83.06%, 56.00%, 95.95% for accuracy, sensitivity and specificity [377]. Therefore, based on these two studies, falls are easier to predict in women than in men, independent of whether they are retrospective or prospective and what type of testing is performed. Another interesting aspect of these two studies is that the results were compared to predictions obtained from standard fall risk assessment tools such as the TUG and the Berg Balance Scale, in all cases yielding a much lower performance, in particular in the case of older women [45, 377].

Table 3.2. Summary of studies using machine learning to predict or classify falls or risk of falls.

Study reference	n participants	Age (years)	Population type	Outcome variable	Protocol	Predictors	Algorithms	Best results
Giansanti et al. 2007 [362]	260 (130 high risk)	Range 65-84)	-	Tinetti score 1 vs Tinetti score 3 (low/high risk)	Standing sway testing with IMU sensors	Kinematic parameters from IMU sensors	NB, Bayes Net, MLP, SVM, NN	For all algorithms: 99.8% accuracy, 99.8% sensitivity, 99.8% specificity, 0.99 AUC
Tremblay et al. 2009 [370]	2157 (693 injurious fallers)	-	Veterans	History of injurious falls	Clinical data	Structured text-based information	LOG	91% accuracy, 89% sensitivity, 93% specificity
Marshollek et al. 2012 [378]	5176 (493 fallers)	Average 77.5	Geriatric hospitalised patients	Falls during hospitalisation	Hospital reports	Demographics and clinical data	DT (C4.5), LOG	DT: 66% accuracy, 55.4% sensitivity, 67.1% specificity
Greene et al. 2012 [45]	120 (65 with history of falls and 55 without)	73.7 ± 5.8	Community-dwelling adults	History of falls	Three 40 s trials with eyes open and three 30 s trials with eyes closed	Pressure sensor data, inertial sensor data (either separate or in combination)	SVM	All participants: 71.52% accuracy, 65.38% sensitivity, 68.36% specificity. Male: 72.8% accuracy, 64.19% sensitivity, 63.46% specificity. Female: 73.33% accuracy, 74.71% sensitivity, 64.14% specificity
Greene et al. 2012 [377]	226(3 groups: 1) 60 men (20 fallers), 2) 111 women < 75 (44 fallers), 3) 53 women ≥75 (19 fallers)	71.5 ± 6.7	Community-dwelling adults	Falls after 2 year follow up period in 3 cohorts	TUG with two body worn inertial sensors (triaxial accelerometer and triaxial gyroscope)	Features (inertial sensor-derived and demographic parameters)	Discriminant classifier models	Mean validation accuracy 79.69%, 0.78 AUC.
McCart et al. 2013 [371]	2241 (26010 documents in total, of which 5034 falls reports)	-	Veterans	History of falls	Clinical reports within 48h of a visit	Structured text-based information	LOG, SVM, SVM-cost	SVM-cost: 0.95-0.98 AUC, 89-94% 89-93% sensitivity, 88-94% specificity
Gietzelt et al. 2014 [349]	28 (13 fallers)	76.0 ± 8.3	Patients with dementia in a nursing home	Prospective falls (during duration of study – 6 clinical visits)	Accelerometer worn during normal daily activities	Accelerometer-derived gait parameters	DT (C4.5)	74.8% accuracy, 78.2% sensitivity, 71.2% specificity, 0.8 AUC
Deschamps et al. 2015 [379]	426 (82 fallers)	69.5 ± 2.6	Community-dwelling adults	Prospective falls (1 year)	Clinical examination	Clinical data and balance measures	DT	89% accuracy with 82% sensitivity 61% specificity, 0.72 AUC

Kabeshova et al. 2015 [354]	<i>Dataset 1:</i> n=1760 (678 $\geq$ 1 falls, 346 $\geq$ 2 falls), (retrospective) <i>Dataset 2:</i> n=1765 (567 $\geq$ 1 fall, 224 $\geq$ 12 falls) (prospective)	≥ 65	Community-dwelling adults	Non-fallers, fallers (≥ 1 falls), recurrent fallers (≥ 2 falls)	Demographic and clinical data	Demographic and clinical data	LOG, LDA, Bayes Network, DT, RF, boosted trees, MLP, genetic algorithm, NEAT, ANFIS	<i>Dataset 1:</i> NEAT: 92.9% sensitivity, 57.5% specificity, 78.7% accuracy and 0.8 AUC. <i>Both datasets:</i> NEAT: 24.6% sensitivity, 97.4% specificity, 88.2% accuracy, 0.7 AUC. ANFIS: 27.2% sensitivity, 95.9% specificity, 87.2% accuracy, 0.7 AUC.
Bates et al. 2016 [369]	8288 (541 fallers)	-	Veterans	History of falls	Radiology reports	Data from electronic radiology reports	SVM	0.97 AUC, 94.5% sensitivity
Howcroft et al. 2016 [364]	100 (76 non-fallers, 24 fallers)	75.5 ± 6.7	Community-dwelling adults	6 months retrospective fall occurrence	Walked 7.62 m while wearing F-Scan insoles and tri-axial accelerometers at the left and right shanks, pelvis, and head	Sensor derived features	MLP, NB, and SVM	MLP: 84% accuracy, 0.60 F1 score, 0.521 MCC score, 50% sensitivity, 94.7% specificity
Howcroft et al. 2017 [352]	75 (28 fallers)	75.2 ± 6.6	Community-dwelling adults	Prospective falls (6 months)	Walked 7.62 m while wearing F-Scan insoles and tri-axial accelerometers at the left and right shanks, pelvis, and head	Sensor derived features	NN, NB, SVM	NN: 57% accuracy, 43% sensitivity, and 65% specificity
Howcroft et al. 2017 [368]	75 older adults without prior falls, 47 nonfallers and 28 fallers during next 6 months	75.2 ± 6.6	Community-dwelling adults	Prospective falls (6 months)	Walked 7.62 m while wearing F-Scan insoles and tri-axial accelerometers at the left and right shanks, pelvis, and head	Sensor derived features	NB, MLP-NN, SVM	SVM: 65% accuracy, 59% sensitivity, 69% specificity
Castaldo et al. 2017 [347]	170 (34 fallers)	72 ± 8	Hypertensive patients	Prospective falls (3 months)	Electrocardiogram recording during clinical visit	Time and frequency domain HRV features	NB, MNB, SVM, MLP, IKB	NB: 72% sensitivity, 61% specificity, and 68% accuracy
Beauchet et al. 2017 [380]	848 (73 fallers)	83.0 ± 7.2	Hospitalised patients in acute care	No falls or $\geq$ falls during hospital stay	Clinical data	Clinical data	MLP, averaged NN, NEAT	NEAT: 29.63% sensitivity, 94.3% specificity, 83.83% accuracy
Yokota et al. 2017 [381]	1.2 million patient-days	62.4 ± 16.6	Hospitalised patients	Fall tomorrow	Demographic and clinical data	Demographic and clinical data	SVM	64.9% sensitivity, 69.6% specificity
Melillo et al. 2017 [351]	141 (13 fallers)	73.2 ± 11.4	Eye clinic patients	Falls after 12 months	Demographic and clinical data	Demographic and clinical data	C4.5, AB, RF, LOG, NB	AdaBoost: 69.2% sensitivity, 76.6% specificity

Howcroft et al. 2017 [375]	101 (76 non-fallers, 24 fallers)	75.5 ± 6.7	Community-dwelling adults	Fall during the last 6 months	Walk 7.62 m while wearing pressure-sensing insoles and tri-axial accelerometers	Features derived from pressure sensors and accelerometers	MLP, NB, SVM	SVM: 78% accuracy, 26% sensitivity, 95% specificity, 0.36 F1 score, and 0.31 MCC
Drover et al. 2017 [382]	71 (43 nonfallers, 28 fallers)	74.15 ± 7.0	Community-dwelling adults	Fall during the last 6 months	6-minute walk test (6MWT) with accelerometers	Accelerometer derived features	k-NN, SVM, RF	RF: 77.3% accuracy, 66.1% sensitivity, 84.7% specificity
Mateen et al. 2018 [341]	337 in-patients receiving neurosurgical, neurological, or neurorehabilitation-based care. (54 had a fall during hospitalization)	-	Hospitalized patients	History of falls during hospitalization	Cognitive testing	Trail walking test data	RF, NN, SVM	RF: 68% (± 7.7) sensitivity, and 90% (± 2.3) specificity.
Aicha et al. 2018 [383]	296 (34.1% experienced a fall)	75.3 ± 6.8	Community dwelling older adults	falls during 6 months follow up	Activity from a triaxial accelerometer recorded on lower back during 1 week	Biomechanical features	DNN, LSTM and ConvLSTM	0.75 AUC
Razmara et al. 2018 [384]	200 (number of fallers not specified)	> 60	Pension centre members	Falls risk (not clear definition)	Questionnaire including physiological and public factors	Questionnaire items	NN	Psychological factors: 90% accuracy Public factors: 87.5% accuracy Combining all factors: 91% accuracy
Gao et al. 2018 [344]	2 datasets: Michigan (225 participants, 48 fallers), Tel-Aviv (105 participants, 41 fallers), combined (330 participants (89 fallers))	-	Michigan dataset: Parkinson's Disease (PD) patients and healthy participants. Tel-Aviv dataset: PD patients	History of falls	Clinical data and neuroimaging study	Demographic, clinical, gait, balance and imaging data	LOG, RF, AB, SVM, NN, SuperLearner	<i>Tel-Aviv:</i> RF: 77% accuracy, 81% sensitivity, 74% specificity. <i>Michigan:</i> Super learner: 78% accuracy, 47% sensitivity, 92% specificity. <i>Both datasets:</i> AdaBoost: 72% accuracy, 56% sensitivity, 80% specificity
Sun et al. 2019 [363]	153 (Group 1: 50 controls Group 2: 34 low risk Group 3: 27 moderate-risk Group 4: 42)	Group 1: 64.94 ± 4.91, Group 2: 54.00 ± 13.12, Group 3: 58.26 ± 8.28,	Multiple Sclerosis patients	Controls, low risk of falls, moderate risk of falls or high risk of falls (based on physiological	30s stand in force plate, physiological profile assessment, Berga Balance Scale, balance confidence questionnaires	Postural sway measures and clinical balance measures	RF	71.2% accuracy, 71.4% sensitivity, 73.5% specificity

	high-risk)	Group 4: 56.76 ± 9.71		profile assessment)				
Lo et al. 2019 [359]	59028 patients (3034 fallers)	≥65	Home care patients	History of falls	Standard data elements for home health care patients (OASIS)	Selected OASIS items relevant to falls predicition	RF	62% accuracy, 0.67 AUC, 10% PPV
Yang et al. 2019 [374]	40 (16 no previous falls, 8 1 fall, 16 more than 1 fall)	75.2 ± 7.5	Community -dwelling adults	Previous falls categories	Wear smart wristband for 7 days while carrying out day-to- day activities	Data from wearable and Resident Assessment Instrument-Home Care (RAI-HC) sensors	LOG, DT, RF	Comparing 0 or 1 fall vs recurrent falls: RF using RAI-HC and wearable combined: 89.2% accuracy, 90.8% sensitivity, 0.894 AUC. Comparing 0 falls vs ≥1 falls, similar results.
Hsu et al. 2020 [343]	50 patients (16 high risk patients)	57.4 ± 14.13 (range: 18– 87)	Stroke survivors that had never fallen	High/low risk of falling based on Berg Balance Scale score	TUG, Berga Balance Scale	Accelerometer derived gait and turning measures	LOG, EN, LASSO, SVM	EN: 85% accuracy, 64% sensitivity, 94% spec, 0.88 AUC
Nakatani et al. 2020 [360]	743 (335 fallers)	67.0 ± 17.1	Acute care hospital	Falls during hospitalisation	Text in electronic patient record	Hospital clinical data	Natural Language Processing and Concept Encoder	0.83 AUC, 77% sensitivity, 78% specificity
Womack et al. 2020 [356]	275940	59±5 (range 45-65)	Veterans	Serious falls	Clinical data	Clinical data	LOG	0.76 AUC
Hsu et al. 2020 [346]	639 (297 fall patients 342 controls) + (132 participants for prospective testing (42 fallers, 991 nonfallers)	Derivation cohort: 69.30 ± 13.75, Validation cohort: 69.32 ± 15.18	Hospitalize d patients	History of falls during hospitalization	Clinical data	Clinical data, Morse Fall Scale (MFS)	XGB	75% specificity, 65% sensitivity
Lindberg et al. 2020 [342]	272 fallers, 542 nonfallers	57.8 ± 16.3	Hospitalize d patients	History of falls during hospitalization	Clinical data	Clinical data	CT, bagging, RF, AB	Sensitivities were 73-79%, specificity 78-86%, and AUC 0.85-0.90
Suzuki et al. 2020 [348]	42 (8 fell within 150 days), 11 fell after 300 days, 31 didn't fall	85.7 ± 5.6	Alzheimers	Time of falling	Clinical assessment	Clinical and functional testing data	CNN	49–65% accuracy
Silva et al. 2020 [358]	281 (74 fallers)	75.1 ± 6.9	Community -dwelling adults	Prospective falls (1 year)	Demographic, clinical and functional testing data	Clinical data, inertial sensor features, pressure	LOG, DT	DT: 77.8% sensitivity, 21.2% specificity, 35.8% accuracy, 0.50 AUC

						platform features		
Tunca et al.2020 [361]	76 (37 fallers, 39 nonfallers) (60 used for training/validation and 16 used for testing)	76.8 ± 10.3	Patients with neurological disorders	History of falls	Walk back and forth along line of 8 m, ≥ 3 times, with accelerometer and gyroscope on their feet	Spatio-temporal gait parameters	SVM, RF, MLP, MNB, LSTM	LSTM: 92.1% accuracy, 91.5% sensitivity, 92.7% specificity, 0.99 AUC
Greene et al. 2020 [355]	277 (100 fallers)	74.7 ± 6.6	Community-dwelling adults	Non-faller, 1 fall in past 12 months, recurrent faller	Stand for 30 seconds holding their phone	Questionnaire and inertial sensor data	FRE combined (combines two LOG)	FRE combined: 61.8% accuracy, class sensitivity of 86.9%, 25.0% and 9.0% for the non-faller, 1 fall in the past 12 months and recurrent faller, respectively.
Zhou et al. 2020 [385]	384 (156 fallers)	Range 49-80	Neurology ward	History of falls in the last 2 years	Walk 20 m (single task: ST) and while dual task with motor component (DT1) and dual task with cognitive component (DT2)	Twenty-seven spatial-temporal gait variables	PLS-DA	0.7, 0.6 and 0.7 AUC for three gait tasks (ST, DT1, and DT2), respectively
Rehman et al. 2020 [372]	384 neurological patients (190 nonfallers, 159 fallers)	Non-Fallers: 61.6 ± 12.2, Fallers: 65.0 ± 12.2	Neurological patients	History of falls in the 2 years before recruitment	Walk 20 m, IMU in the shoes	Features derived from sensors	LDA, LOG, NB, SVM, KNN, RF	RF: 98.67% accuracy, 99% sensitivity, 98% specificity.
Martinez et al. 2020 [386]	657 participants collected, 422 labelled as low risk and 235 as high risk	76.9 ± 7.1	Older adults (no further specification)	High or low risk of falls	Gait data for 30 s while individual walked down, turned and walked back down to starting location	Smartphone gait data from inertial sensors	LOG, RF and SVM. DNN with transfer learning	DNN: 0.93 AUC, 86.4% accuracy, 85.1% sensitivity and 87.1% specificity
Kiprijanovska et al. 2020 [387]	18 participants who performed normal walking and abnormal walking with impairment glasses	Range 19-54	Healthy young (19-54 years)	High or low risk of falling	Repeat 15-m walk ten times, with five “regular gait” sessions and five simulated “abnormal gait” sessions	IMU sensors signals	SVM, RF, CNN-LSTM	CNN-LSTM: accuracy of 88.9% accuracy, 90.6% sensitivity, 86.2% specificity
Dubois et al. 2021 [353]	30 rehabilitation patients (21 high risk)	83.28 ± 8.45 (range: 61-93)	Transitional care unit patients	High/low risk of falls as assessed by the Tinetti	Person living in their rooms with a depth sensors	Features derived from depth images	DT, AB, NN, NB, k-NN, RBF,	All models: 94.4% accuracy using only one variable and 100% using two variables

				test and TUG			RF, QDA, SVM	
Speiser et al. 2021 [46]	1635 (159 injurious fallers)	Range: 70–89 (78.8 ± 5.3 in training set, 79.0 ± 5.2 in test set)	Community -dwelling adults	Prospective injurious falls (2 years)	Lifestyle Interventions and Independence for Elders (LIFE) study database	Selected LIFE items relevant to falls prediction	DT, RF	DT: AUC 0.54, 85% accuracy, 8% sensitivity, 94% specificity. RF: 0.66 AUC, 73% accuracy, 40% sensitivity, 77% specificity
Piryonesi et al. 2021 [345]	606 (115 fallers, 50 injurious)	-	Multiple Sclerosis patients	History of falls and injurious falls	Clinical historical data	Multiple Sclerosis related historical data	DT, GBT	<i>Predicting falls:</i> GBT: 87.45% accuracy, 69.5% sensitivity, and 91.6% specificity. <i>Predicting injurious falls:</i> GBT: 92.08% accuracy, 56% sensitivity, 95.32% specificity
Yang et al. 2021 [47]	214777	70.27 ± 6.76	Community -dwelling adults	History of falls (last year)	Health related risk behaviours survey	Demographic and clinical data	RF, LOG	RF: 33% sensitivity, 79.9% specificity. LR: 24% sensitivity, 93.3% specificity
Roshdibenam et al. 2021 [333]	98 (53 high risk, 25 fallers)	Average 75.41 (range 65–96)	Geriatrics patients	High/low risk of falls and actual falls	TUG with IMU sensors	IMU derived features and clinician assessment	SVM, CNN, training and test groups	CNN: 66.2% accuracy, 86.5% sensitivity, 41.27% specificity, 0.75 AUC in predicting risk of falls. For prediction of actual falls results were too poor, with almost 0% sensitivity.
Noh et al. 2021 [340]	746(290 high risk)	73.0 ± 5.2	Community -dwelling adults	High/low risk of falls	20 min walking at three speeds with IMU sensors	Gait features and demographic data	XGB, LOG, CT, RT, RF	XGB: 68%, 70%, and 67% accuracy, 43%, 53%, and 51% sensitivity, 84%, 81%, and 77% specificity, and 0.709, 0.706 and 0.722 AUC for slower-walking, preferred-walking and faster-walking speed, respectively
Polus et al. 2021 [350]	72 (15 high risk)	71.87 ± 6.45 (high risk), 63.47 ± 8.74 (low risk)	Hip arthroplasty patients	High/low risk of falls derived from 6-weeks postoperative TUG	TUG with IMU sensors and iPod touch	Sensor derived features during preoperative TUG and 2 week postoperative TUG	SVM, LDA	LDA: 90% accuracy, 93% sensitivity, 59% specificity, 0.88 AUC
Tawaki et al. 2021 [357]	212 (53 fallers)	<i>Dataset 1 (average):</i>	Community -dwelling	Past accidental falls	Subjects performed three quiet stances in	Mass-spring-damper model	RF	77% accuracy, 18% sensitivity, 96% specificity

		Young 28, Older 71 <i>Dataset 2</i> (<i>average</i>): Young 28, Older 68	adults		each condition, for a total of 12 tests per person,	parameters derived from the tests		
Meyer et al. 2021 [388]	37 patients (18 fallers, 19 non- fallers)	51 ± 12	Multiple sclerosis	History of falls in last 6 months	Accelerometers, 1 minute straight walk at self-pace	Accelerometers data (features extracted for traditional ML algorithms and raw data for LSTM)	LSTM, BiLSTM, SVM, LOG	BiLSTM: 0.88 AUC, 86% accuracy, 83% specificity, 88% sensitivity
Liu et al. 2021 [389]	108940 (256 cases of falls, matched number of non- fallers extracted from big sample)	60.2 ± 17.3	Hospitalise d patients	Inpatients who had falls during hospitalisation	Clinical data	Clinical data	DT, BN, SVM, RF with AB and Bagging (ensemble strategies)	Bagging+RF: AUC = 0.74, 65% acc, 72% sens, 65% spec)
Daines et al. 2021 [376]	89 (32 fallers, 57 nonfallers)	62.3 ± 12.5	Participants with lower limb amputations	Fall during the last 6 months	6MWT with accelerometer and gyroscope data from smartphone	Accelerometer and gyroscope derived features	RF	81.3% accuracy, 57.2% sensitivity, and 94.9% specificity
Chen et al. 2021 [373]	44 (22 high risk, 22 low risk)	78.18 ± 7.97	Community -dwelling adults	Risk of falls based on TUG time higher than 12.47s	TUG	Accelerometer derived features or TFA of signals	LDA, DNN	DNN: 94% accuracy, 95% sensitivity and 94% specificity

Abbreviations in order of appearance: IMU = inertial mass unit, NB = naïve Bayes, MLP = multilayer perceptron, SVM = support vector machine, LOG = logistic regression, DT = decision tree, TUG = timed up and go, LDA = linear discriminant analysis, BN = Bayes network, RF = random forest, ANFIS = adaptive neuro fuzzy inference system, NEAT = neuroevolution of augmenting topologies, AB = AdaBoost, NN = neural network, MNB = multinomial naïve bayes, IKB = neighbour search, k-NN = k nearest neighbour, DNN = deep neural network, LSTM = long short-term memory, LASSO = least absolute shrinkage and selection operator, XGB = extreme gradient boost, CT = classification tree, CNN = convolutional neural network, FRE = falls risk estimate, PLS-DA = partial least square discriminant analysis, RBF = radial basis function, QDA = quadratic discriminant analysis, GBT = gradient boosted tree,

3.2 Prediction of Syncope

3.2.1 Introduction

3.2.1.1 *Standard Syncope Risk Assessment*

While the previous section mostly refers to all-cause falls, it is recommended that unexplained falls (UF) are managed in the same way as syncope [1], as they are believed to be overlapping conditions [62]. In the assessment of these events, clinical history is taken first in order to determine whether there was a transient loss of consciousness (TLOC) [1]. Then, whether the event was a syncope or a different form of TLOC (e.g. epilepsy, psychogenic Pseudosyncope (PPS)) is established. In the case of syncope, where a clear diagnosis is not possible, then history and physical examination, electrocardiogram (ECG) testing, and supine and orthostatic blood pressure (BP) evaluation are performed (including active stand (AS) and head-up tilt (HUT) testing as appropriate). This allows determining the level of risk of the patients and what the subsequent medical interventions should be. Interventions can range from patient education to admission into hospital in the most severe cases.

Clinical implementation of risk assessment in the context of syncope has focused on assessing the risk of future health outcomes in patients with syncope, rather than assessing the risk of future syncope. Negative health outcomes include pacemaker implantation, stroke, surgery or death, amongst others [390]. Several scales have been developed for this purpose, such as the San Francisco Rule, the Risk Stratification of Syncope in the emergency department rule (ROSE) or the Canadian Syncope Risk Score [391]. Although still at the research stage, several studies have developed indices for the prediction of syncope. Aydin et al. demonstrated that recurrence of syncope could be predicted with a 0.83 AUC from medical history and demographic data [392]. Furthermore, age alone has proven useful in the prediction of recurrent syncope in older

adults [393]. Features derived from BP and heart rate (HR) during HUT have also been used to predict the occurrence of syncope during HUT with high sensitivity (97.6%) and specificity (88.2%) [394].

3.2.1.2 *Research Question*

Machine learning methods are becoming a promising approach that could integrate data from different sources (clinical data, haemodynamic data, etc.) to assist clinicians in the assessment of syncope. In this section a systematic literature search reviewing the use of ML methods in the prediction of syncope was conducted.

3.2.2 **Methods**

The same search was conducted in three different databases: PubMed, Embase and IEEE Xplore. The terms used were “syncope OR faint*” and “predict* OR classif*” (see Figure 3.2). Citation files containing the title and abstract of the searches results were exported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Duplicates were automatically removed, and then articles were screened according to the following inclusion and exclusion criteria:

- Inclusion criteria:
 - Prediction/classification of syncope into two or more categories
 - Outcome variable is syncope (since the outcome of a HUT and lower body negative pressure (LBNP) tests is also syncope (or pre-syncope), studies focusing on the outcome of these tests were also included)
 - Adult cohorts
 - Use of ML algorithms
- Exclusion criteria:

- Conference abstracts
- Non-English articles

Once articles that met the criteria were selected, relevant information was extracted from them, and if new relevant articles were identified in the process, they were included in this study.

Table 3.3 Number of articles identified according to the search strategy used in the literature search.

	Number of articles found
Search strategy: (syncope OR faint*) AND (predict* OR classif*) (Title)	
Embase	382
PubMed	227
IEEE Xplore	18

3.2.3 Results and Discussion

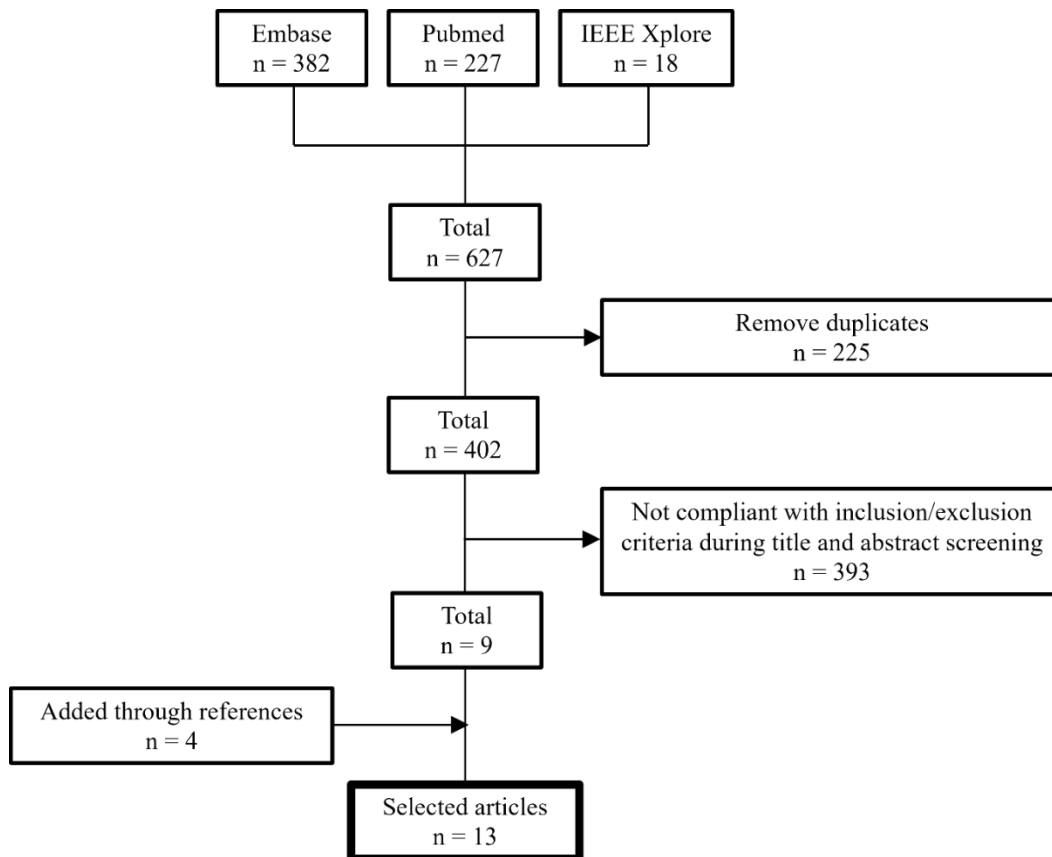


Figure 3.3. Block diagram with the results of the literature search on machine learning for syncope prediction.

Details of the search on machine learning for syncope prediction are provided in Table 3.3.

A total of 627 articles were found, which resulted in 13 selected articles after duplicates removal, inclusion/exclusion filtering and addition of other references (see Figure 3.3). All of the articles were published in 2006 or later (see Figure 3.4). A summary of relevant information extracted from all studies is presented in Table 3.4.

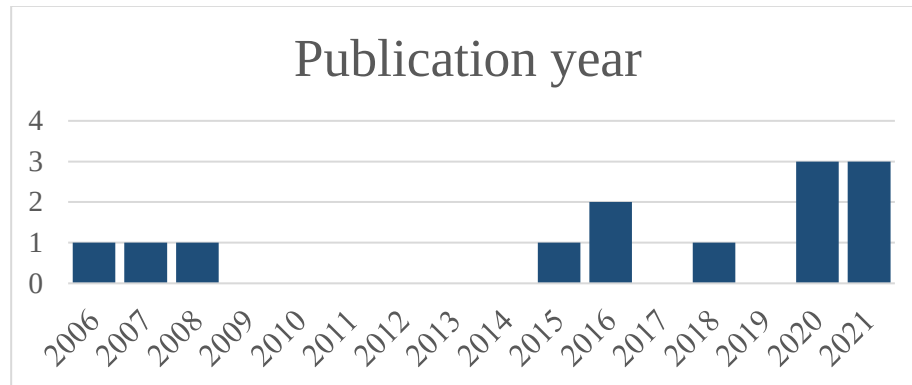


Figure 3.4. Histogram summarising the number of articles by publication year resulting from the literature search.

Most studies ($n = 9$) included patients recruited in specialised syncope clinics during their visit for investigation of syncope or related symptoms. Four studies used data from healthy adults, either as control participants [245, 246] or as the main population [395], and one more study included data from patients attending a specialised epilepsy clinic [396]. All studies had relatively small sample sizes, with the largest study having 687 participants (although only 95 of them were in the positive outcome group) [397]. Generally, studies were well balanced in numbers of participants per outcome group, with the most extreme cases of imbalance found in the studies by Hussain et al. [397, 398]. The authors, however, used an oversampling method (Synthetic Minority Oversampling Technique) to create synthetic data to overcome this issue. Interestingly, despite the knowledge that syncope is common in older adults, studies tended to use either young populations [246, 399] or a broad range of ages [397, 400, 401], but only the one by Kwok et al. focused on a population of older adults [245]. In the majority of cases ($n = 9$), the outcome variable was the result of a HUT

test, with the reproduction of syncope being the positive outcome. From the other 4 studies, in 3 the outcome included the diagnosis of VVS [245, 396, 402], and the last study aimed at distinguishing between different parts of LBNP pre-syncope provocation [395]. Regarding machine learning algorithms, the most commonly used were support vector machines ($n = 6$), logistic regression ($n = 4$), k-NN ($n = 3$), NN ($n = 2$) and linear discriminant analysis ($n = 2$).

Studies using HUT provocation used different phases of the HUT to predict the outcome. The studies by Hussain et al. [397, 398] and the one by Klemenc et al.[401] used data from the entire duration of the HUT. While the first studies achieved high performance (accuracies $>97\%$), the latter study only achieved an accuracy comparable to the frequency of the majority class. These differences might be due to differences in sample size or the choice of predictors, given that Klemenc et al. only used baroreflex sensitivity (BRS) and heart rate variability (HRV) measures, while Hussain et al. used a much broader variety of features derived from peripheral haemodynamic signals. Couceiro et al. used a combination of ECG and BP data from the 2nd minute of HUT and the last 1.5 min of the test to predict HUT outcome, achieving 100% sensitivity and 92.3% specificity [403]. Lastly, Khodor et al. demonstrated an 87.5% sensitivity and 93.8% specificity using HR and BP data from the 15 first minutes of HUT testing [399]. It comes as no surprise that studies using data from minutes well into the progression of syncope development during HUT achieve high classification performance, given the distinctive morphology of peripheral haemodynamic signals between positive and negative HUT tests. A study by van der Ster et al. also demonstrated good performance in classifying the different stages of pre-syncope provocation by LBNP combining peripheral and cerebral haemodynamic data [395].

Another group of studies, motivated by the prospect of dispensing with the HUT test in assessing syncope to save patients from the uncomfortable experience, used different strategies that mostly avoid this test. The two studies by Schang et al. [404, 405], used features derived from transthoracic impedance signals measured during the supine resting period before the start of the HUT to predict whether the test would be positive or not. High performance was reported for both studies when using a NN (86% sensitivity, 64% specificity) [404] and a SVM (94% sensitivity, 79% specificity) [405]. A study combining BP and HRV data from baseline and the first 5 minutes of the HUT test also demonstrated high performance with 89.7% accuracy, 82.4% sensitivity and 91.8% specificity [400]. These studies demonstrate that resting haemodynamics are valuable predictors of syncope occurrence on that day. The studies from our group by Kwok et al. and Carmody et al. also demonstrated that peripheral haemodynamic signals during an AS test (performed on the same day as HUT and VVS diagnosis), can successfully be used to predict HUT outcomes and diagnosis of VVS both in young and older adults with good sensitivity and specificity (72-84%) [245, 246]. Lastly, two studies have used syncope related symptoms and morbidities reported by the patients to distinguish between causes of transient loss of consciousness: cardiac syncope vs VVS or PPS [402], and syncope vs epilepsy vs psychogenic non-epileptic seizure (PNES) [396].

Table 3.4. Summary of studies using machine learning to predict or classify syncope.

Study reference	n participants	Age (years)	Population type	Outcome variable	Protocol	Predictors	Algorithms	Best results
<i>Schang et al. 2006 [404]</i>	70 retrospective patients (37 positive HUT) and 59 prospective patients (26 positive HUT)	Retrospective: 42±15, prospective: 43±14	Patients with unexplained syncope or presyncope	Positive HUT	HUT test with transthoracic impedance measurement	Age, sex and features derived from transthoracic impedance signal and its derivative 10 minutes supine resting before HUT	NN, PCA	NN: 86% sensitivity, 64% specificity
<i>Schang et al. 2007[405]</i>	128 participants (65 positive HUT), 64 training/validation, 64 test set	Positive HUT: 40±15, Negative HUT: 49±15	Unexplained recurrent syncope	Positive HUT	HUT test with transthoracic impedance measurement	Features derived from transthoracic impedance signal and its derivative during 10 minutes supine resting before HUT	SVM	94% sensitivity, 79% specificity
<i>Graf et al. 2008 [402]</i>	317 participants for training, 65 for validation	53±20	Syncope clinic patients	Two outcomes: cardiac syncope vs other types, VVS or PPS syncope vs other types	Medical history and symptoms, physical examination, ECG, HUT, upright and supine CSM	Cardiac syncope model: age, number of prodromal symptoms. VVS/PPS syncope model: age, number of prodromal symptoms and ECG P wave duration	Two multivariate LOG leading to a rule based classifier	Cardiac syncope: 59% Sensitivity, 71% Specificity, 42% PPV, 83% NPV. VVS/PPS syncope: 84% sensitivity, 50% specificity, 51% PPV and 83% NPV
<i>Klemenc et al. 2015 [401]</i>	92 participants (42 positive HUT)	44.5 ± 16.7 (range: 16-82)	Patients with recurrent syncope	Positive HUT	HUT test	Measures of baroreflex sensitivity and heart rate variability during the first 15 and 30 minutes of HUT testing	LOG	56.2 % and 75% accuracy for prediction of syncope before 15 and 30 minutes, respectively

<i>Couceiro et al. 2016 [403]</i>	53 patients (21 positive HUT)	-	Patients with unexplained syncope	Positive HUT	HUT test	ECG and BP features during 2nd minute and last 1.5 minutes of HUT: Pulse arrival time, stiffness index, heart rate, reflection index	Interior point algorithm with Minkowski distance	100% sensitivity, 92.3% specificity, 85.7% PPV
<i>Khodor et al. 2016 [399]</i>	57 subjects undergoing HUT (28 positive HUT)	Range: 18-35	Healthy male individuals (29 positive HUT)	Positive HUT	HUT test	Time-frequency features of BP and HR during supine resting and 15 first minutes of the HUT	k-NN, SVM	SVM: 87.5% sensitivity, 93.8% specificity
<i>van der Ster et al. 2018 [395]</i>	42 participants	24 ± 4	Healthy subjects	Three classes: normovolemia (C0), initial central blood volume reduction (C1), advanced central blood volume reduction (C2)	LBNP until presyncope	SV, CO, BP, NIRS cerebral oxygenation, ETCO ₂ , thoracic bio-impedance, TCD blood flow velocity	SVM	Class 1: 73% sensitivity, 98% specificity, Class 2: 56% sensitivity, 96% specificity
<i>Kwok et al. 2020 [245]</i>	132 (46 VVS, 86 controls)	VVS: 66.9±10.3, Controls: 65.3±9.5	Patients diagnosed with VVS and controls	VVS vs control	AS test	Features from signals during AS: systolic BP, HR, HRV, BPV, CO, TPR, SV	LDA, QDA, SVM, ensemble majority vote classifier	Ensemble majority vote classifier: 82.6% sensitivity, 76.8% specificity, 78.9% accuracy
<i>Carmody et al. 2020 [246]</i>	101 (37 controls, 64 VVS patients (34 with positive HUT, 30 with negative HUT))	25± 9	Patients diagnosed with VVS and controls	Positive HUT vs controls	AS test	Features from signals during AS: systolic BP, HR, SV, CO	LDA	84% sensitivity, 72.9% specificity, 84.4% PPV, 72.9% NPV, 80.2% accuracy, 0.832 AUC

Wardrope et al. 2020 [396]	249 participants (84 epilepsy, 79 syncope, 84 PNES)	≥ 16	Syncope and epilepsy clinics patients	Syncope, epilepsy or patients with PNES	Questionnaire (demographic data, morbidities, symptoms, witness)	Two options: patient only data, patient and witness data	RF	Patient data only: 78.3% overall accuracy (83.8% syncope, 81.5% epilepsy, 67.9% PNES). Patient and witness data: 86% overall accuracy (100% syncope, 85.7% epilepsy, 75% PNES)
Myrovali et al. 2021 [400]	26 participants (11 positive HUT)	Positive HUT: 37.7 $\pm$ 19.7, Negative HUT: 50.92 $\pm$ 21.69	History of VVS	Positive HUT	HUT test	HRV (time domain and wavelet bispectrum measures) and systolic BP during supine rest and 5 first minutes of HUT	NN	89.7% accuracy, 82.4% sensitivity, 91.8% specificity, 92.3% PPV, 92.6% NPV
Hussain et al. 2021[398]	687 participants (96 with positive HUT)	Range: 0-95	Syncope clinic patients	Positive HUT	HUT test	Peripheral haemodynamic data recorded during HUT baseline and upright phases	DT, GNB, k-NN, MNB, SVM, LOG	LR: 0.892 AUC, 97% accuracy (no test set). SVM and GNB similar results
Hussain et al. 2021[397]	687 participants (96 with positive HUT)	Range: 0-95	Syncope clinic patients	Positive HUT	HUT test	Peripheral haemodynamic data recorded during HUT baseline and upright phases	SVM, k-NN, SGD	SVM: 0.987 AUC, 98% accuracy, 98% PPV, 99% sensitivity

Abbreviations in order of appearance: HUT = head-up tilt, NN = neural network, PCA = principal component analysis, SVM = support vector machine, VVS = vasovagal syncope, PPS = psychogenic pseudosyncope, ECG = electrocardiogram, CSM = carotid sinus massage, LOG = logistic regression, PPV = positive predictive value, HR = heart rate, k-NN = k nearest neighbour, LBNP = lower body negative pressure, ETCO₂ = end tidal CO₂, TCD = transcranial doppler, AS = active stand, BP = blood pressure, HRV = heart rate variability, BPV = blood pressure variability, CO = cardiac output, TPR = total peripheral resistance, SV = stroke volume, LDA = linear discriminant analysis, QDA = quadratic discriminant analysis, PNES = psychogenic non-epileptic seizures, DT = decision tree, GNB = gaussian naïve bayes, MNB = multinomial naïve bayes.

3.3 Gaps in the Literature

This review helps in highlighting the key gaps in the literature regarding the prediction and classification of syncope and falls using machine learning.

Prediction of falls

Firstly, although some studies reported excellent performance, these results are often obtained from a very small dataset and lack validation in an unseen test set. Therefore, further conclusions cannot be extracted from these. One study that stands out for its rigorous methodology is the one by Giansati et al., who achieved values of accuracy, sensitivity and specificity >91% using neural networks [362]. However, future research will be needed to determine whether their proposed method can be implemented as a useful risk assessment tool in clinical practice. Although some other studies have reported good performance, this does not seem to be exceedingly superior to that of already well established clinical tools such as the ones described in the first section of this review [325]. Thus, future research should be benchmarked against existing clinical tool to justify its clinical applications.

It is also possible that the multifactorial nature of falls poses an intrinsic limitation for this problem, and perhaps higher accuracies cannot be achieved at a wider level. Based on this hypothesis, separating falls into different categories depending on their characteristics or severity might segregate their aetiology and reduce the number of contributing factors, which could improve the predicting performance. This constitutes another gap in the current literature, with only 6 of the studies investigating specific types of falls (injurious, recurrent, serious or accidental) [46, 345, 354-357].

Most of the studies focus on using either gait and/or balance measures or clinical data. While these assessments might be useful to predict accidental falls with an

underlying mechanical/gait cause, a very clinically relevant type of falls may be missed: UF. UF are clinically assessed and managed as syncope [1], and are thus believed to be neurocardiovascular in origin and a consequence of cerebral hypoperfusion. They are associated with impaired peripheral circulation during standing, a marker that is more strongly associated with this type of falls than with all-cause falls [29]. To the best of the author's knowledge, no studies have investigated the use of ML approaches to predict or classify UF. Another related gap is the fact that no studies have investigated neither peripheral nor cerebral circulation signals (e.g. blood pressure, cerebral perfusion, etc.) in individuals with falls, with only the study by Castaldo et al. using heart rate variability features [347]. This is a surprising gap given the well known associations of falls with impairments in orthostatic haemodynamics [273].

Prediction of syncope

Studies designed to predict or classify syncope using machine learning approaches identified in this review have generally reported high performance. However, unlike the studies on falls, syncope studies mostly focused either on the prediction of provoked syncopal events or on the classification of causes of past TLOC events. None of them attempted at differentiating between individuals at risk of spontaneous syncope (unprovoked, during normal living) from those not at risk, neither retrospectively nor prospectively. Therefore, studies predicting falls and those predicting syncope cannot be compared, as their methodologies are too different.

Most of syncope studies were aimed at predicting the occurrence of syncope from peripheral haemodynamic features. However, these features were extracted on the same day the syncopal event occurred. This might explain why the overall prediction in these studies is higher than in falls studies. It is still impressive how well some models

performed at predicting syncope from data that was not recorded during the upright HUT test, such as those predicting it from baseline data, AS tests data [245, 246] or medical and symptoms history [396, 402]. Nevertheless, none of these studies has combined haemodynamics data with medical data in their models.

Another important gap identified is in the age demographics of the participants involved in the studies, with only one study focusing on syncope only in older adults [245]. While VVS is the most common cause of syncope in young individuals, cardiac causes of syncope are known to be relevant to the aetiology of syncope in older adults [69, 70], and therefore it is more than likely that the pathophysiology of syncope in the young and the old are very different.

Lastly, only one study used cerebral circulation measures as predictors [395], although the aim of this study was to predict pre-syncope during LBPV, and therefore it might not be translatable to the prediction of spontaneous syncope during everyday life.

3.4 Conclusion

In the last decade, machine learning algorithms have been widely explored for the prediction of falls and syncope, with good performance being often reported, demonstrating the potential of these methods in this clinical application. However, despite the relationship between falls and syncope and both cerebral and peripheral circulation, few studies have incorporated such high resolution biosignals. Furthermore, no studies have combined the two types of events as an outcome, despite their overlap. Future research should focus on exploring the use of haemodynamic signals in the prediction of falls and syncope, to investigate their potential to support clinicians in the assessment and management of these patients.

Chapter 4: Research Questions

In this project a cohort of patients recruited from a Falls and Syncope Unit was investigated. Initially, the entire population of patients was investigated, which led to the identification of two main subgroups of patients: young patients with vasovagal syncope (VVS), and older patients with falls and syncope. Given the gaps identified in the literature and highlighted in sections 2.4.7 and 3.3 of this thesis, the studies presented in this work have been designed to answer the research questions (RQ) detailed below. The answers to these questions will provide novel information towards the development of clinical decision support tools for Falls and Syncope assessment.

- All patients attending a Falls and Syncope Unit:
 - RQ 1: Are age and sex associated with cerebral oxygenation responses to standing measuring with NIRS in a cohort of patients with falls and syncope?
 - RQ 2: Do associations remain when only considering a subset of older adults?
 - RQ 3: Are there differences in the distribution of falls and syncope with age and sex?
 - RQ 4: Do the findings obtained justify the separation of falls and syncope patients into subcohorts according to age and sex?
- Young patients with syncope (specifically VVS):
 - RQ 5: Do young patients with VVS have an altered cerebral oxygenation response to an active stand (AS) test as compared to healthy controls?

- RQ 6: Do young patients with VVS have an altered peripheral circulation response to an AS test as compared to healthy controls?
- Older adults with falls and syncope:
 - RQ 7: Is multimorbidity associated with impaired peripheral hemodynamics during an AS test?
 - RQ 8: Is multimorbidity associated with impaired cerebral oxygenation responses during an AS test independent of peripheral hemodynamics?
 - RQ 9: Does sex modulate the relationships between peripheral and cerebral oxygenation responses to an AS test?
 - RQ 10: Can machine learning approaches applied to measures of cerebral and peripheral circulation be used to identify individuals with a history of unexplained and/or syncope in older adults?
 - RQ 11: Is the performance of these methods improved if both blood pressure and cerebral measures are used?
 - RQ 12: Can the classification performance be improved by adding medical history in the form of a morbidity count as a predictor?

Chapter 5: General Materials and Methods

This chapter provides an overview of the materials and methods developed to implement the goals of the thesis. Figure 5.1 provides a comprehensive overview of the methodologies developed and details the research outputs generated throughout the thesis.

This thesis primarily uses data from the Falls and Syncope Unit (FASU) at St. James's Hospital, Dublin (Chapters 6-9), and from The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin (Chapter 9).

The overarching study was designed as a collaboration between two PhD projects: one led by a Geriatrician (Dr. Paul Claffey) and the other led by a Biomedical Engineer (the author of this thesis) with both researchers closely collaborating. The researchers also collaborated with a broader multidisciplinary team consisting of geriatricians, nurses and biomedical engineers who are world-leading experts in the study of falls and syncope.

Given the datacentric nature of the thesis, particular focus is given to the development and harmonisation of relevant datasets and analytical software tools (signal processing, machine learning and biostatistical), created to facilitate the processing of this data.

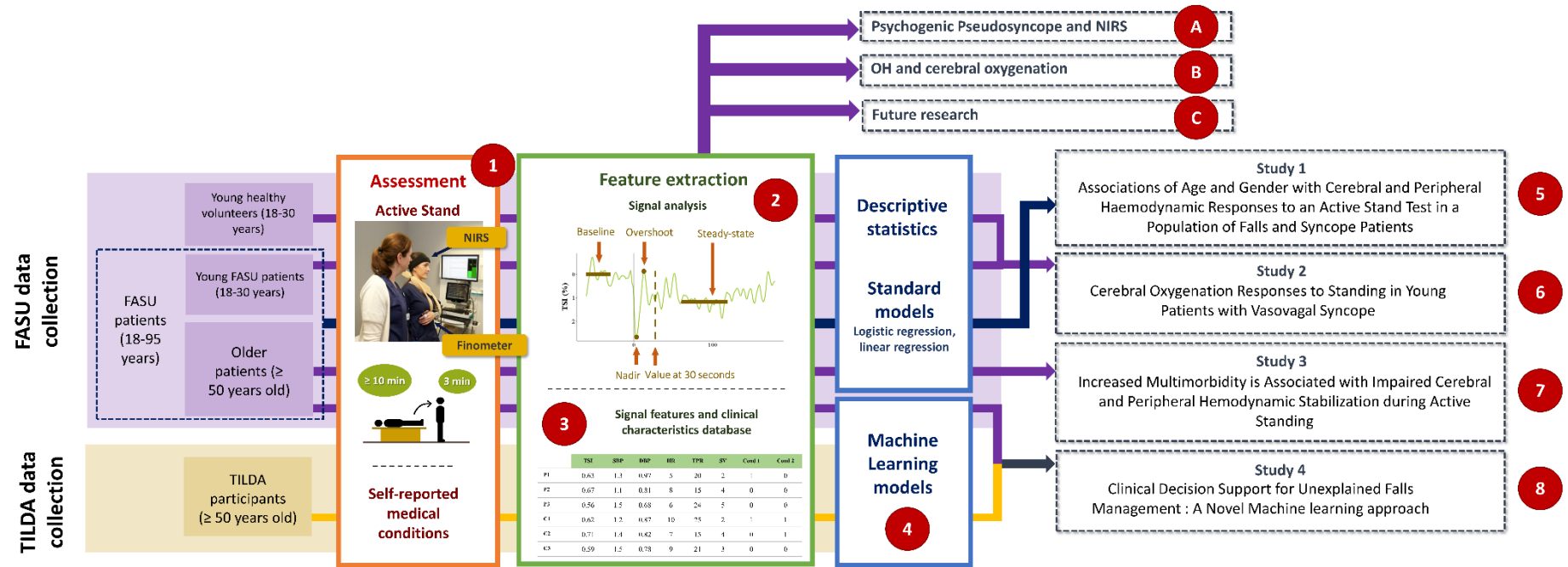


Figure 5.1 Diagram of the overall materials and methods used in this thesis.

Data was acquired from two different settings, FASU and TILDA. All participants underwent an Active Stand (AS) test with concurrent monitoring of cerebral oxygenation and peripheral haemodynamics by near-infrared spectroscopy (NIRS) and the Finometer, respectively. Self-reported medical conditions were also recorded. Signal processing was performed on the NIRS and Finometer signals, obtaining a dataset of features. This dataset was combined with the clinical characteristics of the participants. Different subsets of data were analysed using standard models and machine learning models, resulting in studies 1, 2, 3 and 4. Outputs of this thesis are highlighted in red (description in the text in section 5.10. Methodological Research Outputs). A, B and C represent additional outputs contributing to collaborative work.

The methods detailed in this section were applied in the studies of this thesis, which were designed to answer the research questions presented in

Chapter 4: Research Questions as follows:

- **Study 1:**
 - **Chapter 6:** Associations of Age and Sex with Cerebral and Peripheral Haemodynamic Responses to an Active Stand Test in a Population of Falls and Syncope Patients
 - **Research questions addressed:** 1-4
 - **Data source:** all FASU patients
- **Study 2:**
 - **Chapter 7:** Oxygenation Responses to Standing in Young Patients with Vasovagal Syncope
 - **Research questions addressed:** 5-6
 - **Data sources:** young patients from FASU and young healthy controls
- **Study 3:**
 - **Chapter 8:** Multimorbidity is Associated with Impaired Cerebral and Peripheral Haemodynamic Stabilisation during Active Standing
 - **Research questions addressed:** 7-9
 - **Data used:** older patients from FASU
- **Study 4:**

- **Chapter 9:** Clinical Decision Support for Unexplained Falls and Syncope Management: A Novel Explainable Machine Learning Approach
- **Research questions addressed:** 10-12
- **Data sources:** older patients from FASU and older community-dwelling adults from TILDA

5.1 Ethical Approval

All studies had ethical approval from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08, CA,16) and the Faculty of Health Science Research Ethics Committee at Trinity College Dublin, Ireland (Main Wave 3 TILDA Study. Approved 9th June 2014).

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 (GDPR) 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 E) were approved by the St. James's Hospital ethics committee and Research and Innovation office.

5.2 Participants

Participants included in this project are either patients recruited from FASU at St. James's Hospital (Chapters 6-9) or participants from TILDA (Chapter 9).

During their visits to FASU, patients were informed about the study and invited to participate. The 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. They then underwent a standardised clinical testing protocol as described below. The author of this thesis had the privilege to join the FASU as a research biomedical engineer, performing data collection in collaboration with the clinical staff members on a daily basis over a 12-month period.

A convenience sample of healthy controls was also recruited from community-dwelling adults and underwent the same data collection procedures as patients from FASU (Chapter 7).

Data from TILDA participants were collected by TILDA researchers independently of the author of this thesis. A collaboration was initiated with TILDA to enable access to this data set, with access granted following standard TILDA procedures (as detailed below in Section 5.3). Then, a subset of TILDA participants was identified after matching for the age and sex characteristics of a subgroup of patients from FASU (as detailed below in Section 5.4), with access to both clinical data and biomedical signals obtained for this cohort.

5.3 Data Management

All clinical data remained on the hospital's network during the development of the three first studies (Chapters 6-8). For the last study (Chapter 9), access to TILDA data was obtained after submitting an access application form, which was reviewed and approved by the TILDA management team. To process data from both sources, storage of the two datasets on the same computer was required, which posed a significant challenge in terms of data protection. A data sharing agreement was arranged between St. James's Hospital and Trinity College Dublin to facilitate this process. Approval was

obtained from the St. James's Hospital and Trinity College Data Protection Officer to combine both datasets on a password protected and encrypted PC residing in St. James's Hospital, which had TCD network access. A merged dataset with TILDA and FASU data was created temporarily in the code during data processing, but this dataset was never exported nor saved to avoid multiples copies of data and/or moving data from their respective drives.

5.4 Inclusion and Exclusion Criteria

Specific inclusion and exclusion criteria have been described in the methods section of each of the chapters (Chapters 6-9) according to their specific research questions. General inclusion/exclusion criteria for FASU patients were as follows:

- Patients aged 18 years or older
- With no cognitive impairment that would affect their ability to understand the study and provide informed consent
- Without contraindications to perform an Active Stand test such as mobility issues or pain
- Pregnant women were excluded from the study

5.5 Active Stand Testing

5.5.1 Equipment

During the AS test, cerebral oxygenation and peripheral circulation were concurrently measured [71] (see Figure 5.2). Peripheral circulation signals were monitored using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). This device employs finger plethysmography to provide noninvasive beat-to-beat estimates of brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR). Furthermore, values

of stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) can be derived using the ModelflowTM algorithm from the blood pressure waveforms collected with the Finometer. As per manufacturer specifications, a finger cuff was placed on the middle or proximal phalanx of a finger. The finger cuff size was selected according to the finger circumference. A brachial arm cuff was also placed on the contralateral arm to perform oscillometric blood pressure (BP) measurements to enable device calibration. Together with PhysiocalTM, 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 the level of the heart, at the 5th intercostal space in the mid-axillary line) to correct for hydrostatic differences [71]. If considered appropriate by the nurse who was performing the test with the patient, the Finometer arm was supported by a sling [71].

Cerebral oxygenation was monitored using a PortaLite near-infrared spectroscopy (NIRS) probe (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands). The monitor was placed over the left side of the participant's forehead, approximately centred 3cm laterally and 3.5cm above the nasion [406]. This technology employs the Beer-Lambert Law to derive changes in concentration in oxyhaemoglobin ($\Delta[\text{O}_2\text{Hb}]$) and deoxyhaemoglobin ($\Delta[\text{HHb}]$) in the cerebral tissue. Furthermore, when using the Spatially Resolved Spectroscopy mode, values of tissue saturation index (TSI) (units of %) are derived, calculated as changes in concentration of oxygenated haemoglobin divided by changes in total concentration of haemoglobin ($\Delta[\text{tHB}]$) (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 artifacts.

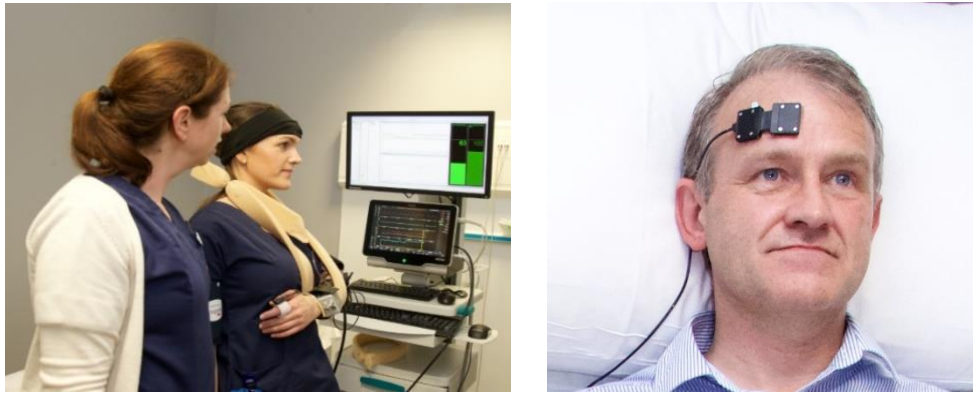


Figure 5.2. Near-infrared spectroscopy setup in the Falls and Syncope Unit.

Left: Active Stand in the Falls and Syncope Unit. The participant, who has the Finometer attached to her arm and the PortaLite NIRS monitor to her forehead, is assisted by a nurse during the standing period of the test. Right: Closer look at the PortaLite NIRS device.

5.5.2 Protocol

All participants included in this thesis, whether FASU patients, volunteers or TILDA participants, underwent an active stand (AS) test following the same protocol designed as per international guidelines [1, 71]. Once the Finometer and NIRS monitors were applied, a marker was pressed twice simultaneously in each system, which allowed for future synchronisation of the two files as described below in Section 5.6.3. Then, the Finometer was calibrated using the oscillometric BP measurements (Physiocal calibration was automatically on from the beginning of the recording). Then, instructions were given to the patient as follows:

“Now we are going to do a standing test. We will do a countdown, 5, 4, 3, 2, 1, Stand, and when we say “Stand” you will have to swing the legs out of the bed and stand up as quickly as you can. Do not worry if this is difficult for you, we will help you and we will not let you fall. It is very important that you do not move your left arm, in particular the hand. Keep it still as if it was dead and just bring it with you, but do not use it to push yourself out of the bed and do not squeeze the fingers, as doing so will interfere with the readings. Once you are standing, look straight ahead to the wall in front of you, try not to move your head as it will interfere with the head sensor

measurements. We will not be able to talk during the duration of the test, but do let us know if you feel too uncomfortable or unwell. Try to pay attention to any symptoms you may experience so that you can report them at the end of the test. The test will last for 3 minutes”

Five to ten minutes of supine resting were allowed before starting the standing manoeuvre. Just before standing, Physiocal calibration was turned off. Then a countdown was done (5, 4, 3, 2, 1, Stand) and on Stand a mark was pressed on the Finometer keyboard. The Physiocal was turned back on after 30 seconds of standing. Patients were helped to stand and were provided support during the rest of the test if they had mobility difficulties or were feeling unstable. The patient remained standing for 180 seconds. The test was terminated early if the participant experienced intolerable symptoms of orthostatic intolerance. For more detailed information on the protocol, refer to Appendix F: Active Stand Protocol.

5.6 Data Analysis

5.6.1 Software Framework for FASU Data

Custom code was developed in MATLAB (The Math Works, Inc., MATLAB, Version 2020a, Natick, MA) to process the multimodal physiological data collected during the course of this work. Details of the software tools and the code files developed for the extraction of FASU patients data are provided in the appendices (see Appendix G: Software Framework).

Several steps were required from the original Finometer and NIRS files to obtain the results of the studies (see Figure 5.3). Firstly, only patients who had Finometer (file extension .nsc) and Portalite (file extension .oxy3) data for the AS test were selected, and those in which a problem had occurred and one or two of the files

were missing were filtered out. Then, the .nsc and .oxy3 files were converted from their native binary format into .mat files for easier data processing, with two .mat files resulting for each patient. In this step, pseudonymisation of the data was also achieved by removing identifiable information from the files and assigning a study ID to each participant. Mat files were filtered out when they did not have the right amount of synchronisation (two marks) and AS (one mark) marks (due to errors in conducting the protocol). Then, quality of the signals was assessed as described in Section 5.6.2. Finometer and NIRS signals were then synchronised using the synchronisation marks from both files. The start of the stand was identified from the height correction unit as described in Section 5.6.3. Feature extraction was then performed as described in Section 5.6.3 for FASU patients and TILDA participants, resulting in a database of synchronised NIRS and BP features. This was then combined with demographic and clinical information of participants. Lastly, statistical and machine learning tools were developed to analyse the data and obtain the results for the different studies.

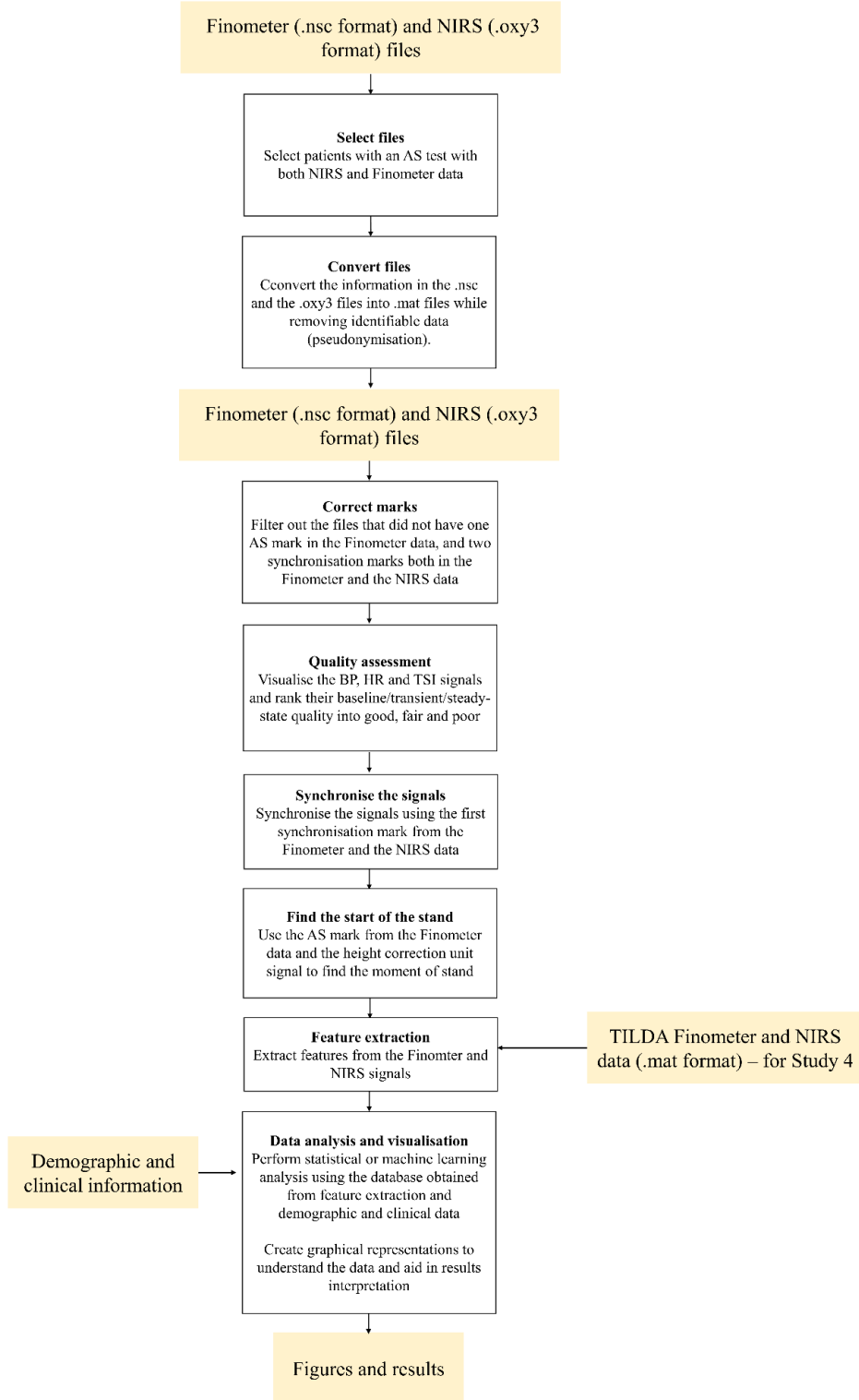


Figure 5.3. Main steps of the analysis pipeline developed for this thesis for FASU patients.

5.6.2 Signal Quality Evaluation

The quality of each AS signal was evaluated by dividing the signal into three sections (baseline (-60 to -30 seconds), transient (0 to 30 seconds) and steady-state (60

to 120 seconds)). A set of signal quality assessment criteria were agreed by the author and primary supervisor of this thesis before the start of quality assessment, and remained unchanged throughout. Each section was labelled as good, moderate, or poor quality according to these criteria. An overview of the signal evaluation criteria is detailed below, with full detail provided in the appendices (Appendix H: Criteria for Signal Quality Evaluation) (note that criteria are expressed as inclusion rather than exclusion):

- BP and HR signals:
 - Signal used: beat-to-beat BP waveform
 - Threshold: signals within 40-220mmHg (for BP) and 30-200 bpm (for HR)
 - Without multiple Physiological interruptions
 - Clean beats with physiological morphology (with or without dicrotic notch)
- Tissue saturation index signal:
 - Signal used: tissue saturation index signal
 - Threshold: signals within 40-80%
 - Beats can be easily distinguished (dicrotic notch not expected).
- For all signals:
 - Smooth signal without abrupt changes or discontinuities. An exception for this is the first few seconds of the transient region, where motion artifact often occurs, although smoothness is expected in the rest of the transient period.
 - Respiratory (0.3 Hz) or Mayer (0.1 Hz) waves, as well as slower oscillations, may be present

- Without drifting (in particular during baseline and steady-state)

Based on these criteria, those signal sections that were labelled as poor were not used for further analysis.

5.6.3 Feature Extraction for FASU Data

The two .mat files obtained from the above described process were synchronised using the synchronisation markers pressed during the test (described above). To do so, the time of the marker was subtracted from all the time values, so that both signals were zeroed in time at the time of the marker.

The start and the end of the standing motion were derived from the height correction unit (HCU) signal following an improved method inspired by a recently developed algorithm [407]. Firstly, the HCU signal was interpolated at 1Hz. Then a region of interest was identified in the range [-30,60] seconds around the time of the AS mark, and this data was differentiated. A cutoff of -2 mmHg/s was then used to identify points of the original HCU signal where large fast changes were occurring, as suggested by O'Connor et al. [407]. From all the points identified, those transitions in which the differential signal was decreasing (i.e., going from above threshold to below threshold) and that did not have another transition 5 seconds earlier were selected. For each of the transition times identified, the mean HCU value was calculated for the 10 seconds before and 10 seconds after the transition, and the difference was computed. If there were negative differences (i.e., the HCU changed to a lower value), then the largest negative value was selected. In case there were no negative differences (e.g. the HCU signal changed to a higher value), the largest positive difference was selected. Then the time of such transition was determined as the start of the standing motion. Note that if the Finometer arm is free, standing usually results in a large drop in the HCU signal,

while when the arm is supported by a sling such drops might not be large enough and/or can result in a change to a higher HCU value instead. In order to identify the end of the standing motion, from the points previously identified to cross the -2 mmHg threshold, those occurring after the start of the motion were selected. Then, the ones in which the differential signal was increasing (i.e., going from below the threshold to above the threshold) were identified. The first point without another cutoff crossing point in the next 5 seconds was identified as the end of the standing motion. The speed of standing was calculated as the difference in time between the start and the end of the standing motion.

All signals were zeroed in time to the start of the standing motion. NIRS signals in the FASU cohort were recorded with a 10Hz sampling frequency, while in the TILDA study they were recorded at 50Hz. Thus, the TILDA NIRS signals were downsampled to 10Hz. Finometer signals were originally beat-to-beat, and thus were resampled at 10Hz to match the NIRS signals. Baseline values were then calculated as the average value from -60 to -30 seconds prior to standing, while steady-state values were derived as the average from 60 to 120 seconds after standing. For the extraction of nadir and overshoot values, signals were then filtered using a 2nd order 0.2Hz Butterworth zero phase forward-reverse low pass filter to minimise the heart rate and respiration components [408]. Then, the time of nadir was identified as the time of the lowest trough occurring within 30 seconds of standing, while the overshoot time was identified as the first peak occurring after nadir within 60 seconds of standing. Finally, the raw signal was filtered to extract a ± 1 second moving average value at the time corresponding to the nadir and overshoot. This process was used for the SBP, DBP, MAP, TPR and $\Delta[\text{O}_2\text{Hb}]$ signals (see Figure 5.4). In the case of HR, $\Delta[\text{HHb}]$ and SV, given their somewhat opposite morphologies, instead of nadir and overshoot, the

maximum and minimum were obtained as the first peak and the subsequent trough. A local maximum speed of recovery between nadir and overshoot (or maximum and minimum in case of HR, $\Delta[\text{HHb}]$ and SV) was derived as the maximum of the differential signal between the two points (i.e., the fastest slope of recovery). An average recovery was also computed as the difference in magnitude divided by the difference in time. Additionally, a ± 2.5 second moving average filter was applied to the raw signal to obtain average values at 5, 10, 20, 30, 60, 90 and 120 seconds for all signals. Different combinations of these features were used for the three studies presented in this thesis as detailed in their respective materials and methods sections.

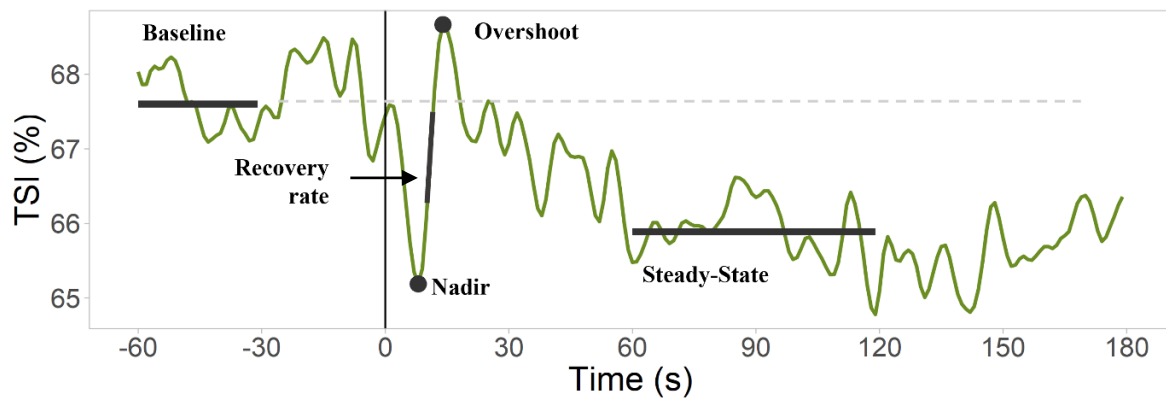


Figure 5.4. Features extracted from signal processing.

5.6.4 Feature Extraction for TILDA Data

Data provided from TILDA consisted of files in .mat format that contained the signals. The signals were already zeroed in time to the standing moment, which was found using the method described by O'Connor et al. [407]. The same processing steps as described for the FASU data were applied for the TILDA data for feature extraction.

5.7 Dataset Harmonisation and Other Covariates

During their clinical visit to FASU, study participants provided self-reported history of different medical conditions (see Table 5.1). As part of their participation in

the study, TILDA participants also self-reported history of several medical conditions. However, not all of the conditions recorded in FASU matched those in the TILDA dataset. A harmonised set of variables was therefore required. Harmonised conditions have been highlighted in Table 5.1. A multimorbidity count derived as an index of frailty used in Chapter 8 and Chapter 9 was also derived.

Table 5.1. Medical conditions that were self-reported by participants from FASU and TILDA.

Conditions reported in FASU	Corresponding TILDA variable
Falls in the last year	Fallen in the last year or since their last interview
Unexplained falls in the last year	The fall or falls reported were non-accidental
Syncope in the last year	Fainted in the last year or since their last interview
Transient ischemic attack	Self-reported diagnosis of transient ischemic attack
Stroke	Self-reported diagnosis of stroke
Carotid stenosis	-
Hypertension	Self-reported diagnosis of hypertension
Ischemic heart disease	-
Angina	Self-reported diagnosis of angina
Myocardial infarction	Self-reported diagnosis of heart attack - including myocardial infarction or coronary thrombosis
Atrial fibrillation	Self-reported diagnosis of atrial fibrillation
Other rhythm abnormalities	Self-reported diagnosis of other rhythm abnormalities
Heart failure	Self-reported diagnosis of congestive heart failure
Diabetes	Self-reported diagnosis of diabetes
High cholesterol	Self-reported diagnosis of high cholesterol
Other cardiovascular diseases	Self-reported diagnosis of other cardiovascular diseases
Mild cognitive impairment	Montreal Cognitive Assessment Score <18
Parkinson's disease	Self-reported diagnosis of Parkinson's disease
Other neurodegenerative diseases	-
Migraine	-
Epilepsy	-
Depression or anxiety	Self-reported diagnosis of depression or anxiety
Other psychological diseases	Self-reported diagnosis of hallucinations, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder, other
Benign paroxysmal positional vertigo or other vestibular disorders	-
Obstructive sleep apnoea	-
Chronic obstructive airway disease	Self-reported diagnosis of Chronic lung disease such as chronic bronchitis or emphysema
Endocrine diseases	Self-reported diagnosis of thyroid problems

5.8 Statistical Analysis

In this thesis, different statistical analyses were used. Statistical analysis was conducted in RStudio (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). When comparing proportions between groups, Chi-squared tests were used. In case of continuous variables, to compare between two groups a T-test or a Mann Whitney U test was used, depending on whether the data was normally or non-normally distributed, respectively. Univariate and multivariate linear/non-linear regression were used to study the association between continuous features derived from cerebral and peripheral haemodynamic signals and patients characteristics.

5.9 Machine Learning Classification Algorithms

A number of ML algorithms, described in this section, were explored in Chapter 9 of this thesis. These algorithms were implemented in RStudio (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA), using the *Caret* package.

5.9.1 Logistic Regression

In logistic regression, a linear combination of variables is constructed in a similar manner to linear regression. However, in this case, the objective is not to predict a continuous value. Instead, when there are two possible classes to classify into, the purpose of logistic regression is to classify a new instance into one class or the other. If p is the probability of the positive class occurring, then the odds of that class are $p/(1-p)$. In logistic regression, the log odds of that class can be modelled as a linear function:

$$\text{Log} \left(\frac{p}{1-p} \right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_m x_m \quad (5.1)$$

Where m is the number of predictors. This expression can be rearranged to find the relationship of p with the predictors:

$$p = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \dots + \beta_m x_m)}} \quad (5.2)$$

This expression is nonlinear and models the probability of the positive class as a function of the linear combination of predictors using a sigmoidal relationship. The parameters β then are estimated by maximising the likelihood for our data (i.e., maximising the probability of having our data given a certain value for the parameters). Due to the sigmoidal behaviour of logistic regression, when new instances are predicted using the estimated β parameters the predicted probability p will be constrained between 0 and 1. Typically, for $p < 0.5$ the negative class is assigned, while for $p \geq 0.5$ the new instance is classified as positive.

5.9.2 Linear Discriminant Analysis

Linear discriminant analysis (LDA) theory stems from the Bayes' Rule [409]:

$$\Pr[Y = C_l | X] = \frac{\Pr[Y = C_l] \Pr[X | Y = C_l]}{\Pr[X]} \quad (5.3)$$

The probability of predictors X belonging to class C_l ($\Pr[Y = C_l | X]$) can be expressed as the a priory probability of belonging to class C_l ($\Pr[Y = C_l]$) (normally determined from the proportions of each class), multiplied by the condition probability of observing predictors X given that the data belongs to class C_l , and divided by the probability of the predictors X . In the method proposed by Welch [409], the objective is to minimise the probability of misclassification, which will occur if an instance with predictors X is classified into the positive class (1) instead of the negative class (0) if $\Pr[Y = C_1 | X] > \Pr[Y = C_0 | X]$, and vice versa. Then, using Equation 5.3, this can be expressed as:

$$\Pr[Y = C_1] \Pr[X|Y = C_1] > \Pr[Y = C_2] \Pr[X|Y = C_2] \quad (5.4)$$

If the distribution of the predictions is assumed to be multivariate normal, such distributions can be described by a mean vector (μ_i) and a covariance matrix (Σ_i). Furthermore, if it is assumed that the means are unique for the different classes but the covariances are identical across the groups, then Equation 5.4 can be solved, resulting in a linear discriminant function for class C_l of the form:

$$L_l = X' \Sigma^{-1} \mu'_l - 0.5 \mu'_l \Sigma^{-1} \mu_l + \log(\Pr[Y = C_l]) \quad (5.5)$$

L_l defines the separating class boundary, and it is linear in X , which gives rise to the name LDA. Equation 5.5 is then applied to vectors of predictors of different classes.

LDA was also approached in a non-probabilistic way by Fisher [410], providing a more intuitive perspective of the method. In summary, the objective is to find the linear combination of predictors that maximises the separation between the mean of the data for the two groups while minimising the variation within each group.

5.9.3 Quadratic Discriminant Analysis

In quadratic discriminant analysis (QDA), unlike in LDA, the covariance is not assumed to be the same for all the classes. Therefore, Equation x2 can be expressed as [411]:

$$Q_l = (X' - \mu'_l) \Sigma_l^{-1} (X' - \mu'_l)^T + \log|\Sigma_l| - 2 \log(\Pr[Y = C_l]) \quad (5.6)$$

Which is a quadratic function of X , and hence the name QDA. This results in quadratically curvilinear decision boundaries [412].

5.9.4 Linear Support Vector Machine

In support vector machines (SVM), the objective is to find a classification boundary that maximises the distance between the boundary and the closest points to

the boundary, which are called support vectors. In Figure 5.5, where blue and orange represent different classes, the decision boundary is represented by the solid line, and the support vectors are the points over the dashed lines.

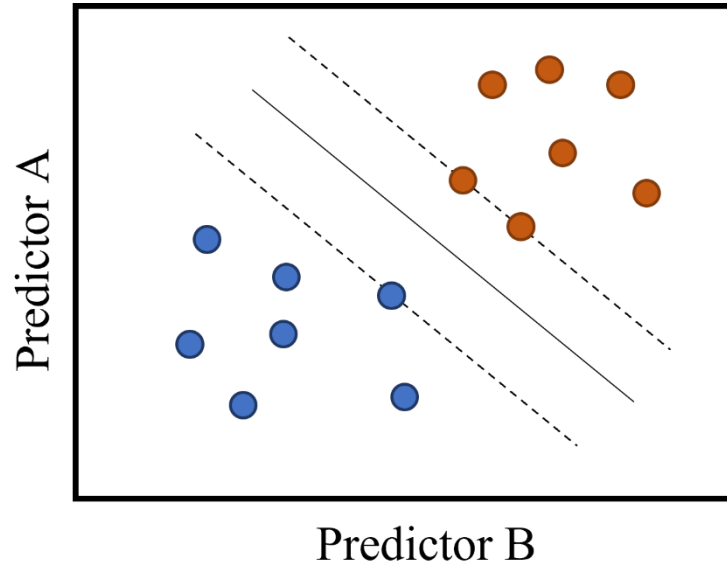


Figure 5.5. Schematic representation of a support vector machine.
Separation of two classes (blue and orange) with a decision boundary (solid line) based on predictor A and predictor B. The data points represented over the dashed lines are the support vectors.

A decision equation can be written as a linear combination of slopes and intercept [412]:

$$D(u) = \beta_0 + \beta' u = \beta_0 + \sum_{j=1}^P \beta_j u_j \quad (5.7)$$

Where u is a vector of predictor values for an unknown sample. If $D(u) > 0$, a new instance is classified as positive, and otherwise as negative. This equation can be rewritten so that it is expressed in terms of a datapoint of the sample [412]:

$$D(u) = \beta_0 + \sum_{j=1}^P \beta_j u_j = \beta_0 + \sum_{i=1}^n y_i \alpha_i x_i' u \quad (5.8)$$

Where x_i are the vectors containing the training data, y_i are the classes of the training data points (coded as 1 or -1), and α_i are the unknown parameters to be estimated, which are >0 for support vectors and 0 for all other points. This expression leads to a linear boundary that separates the groups.

5.9.5 Radial Support Vector Machine

The complexity of SVM can be increased if the boundary is not linear. To do so, the kernel trick is used, whereby the dot product $x_i \cdot u$ is substituted by a kernel function of the two vectors. A commonly used kernel function is the Radial Basis Function, which can be expressed as:

$$\text{Radial basis function} = e^{-\sigma \|x-u\|^2} \quad (5.9)$$

Therefore, the decision boundary for a SVM with a radial kernel can be written as:

$$D(u) = \beta_0 + \sum_{i=1}^n y_i \alpha_i e^{-\sigma \|x-u\|^2} \quad (5.10)$$

5.10 Methodological Research Outputs

Several key methodological research outputs were developed as a result of this thesis and are summarised as follows (see Figure 5.1). The contribution of the author of this thesis to each of these outputs has been stated:

- **Research Output 1: Translation of NIRS from Research into Clinical Activity.** Full integration of NIRS measurements into FASU clinical setting with a clinical protocol developed was achieved. These processes are now enabling the translation of NIRS research into clinical use thereby impacting patient care and enabling future research. The author was part of the team

that led the integration of NIRS and developed the following activities: contributed to the installation and technical maintenance of the devices, performed device testing, organised and delivered multiple training sessions to the clinical team, collected NIRS data from all the patients recruited in FASU and included in this thesis. Furthermore, the author assisted in the collection of peripheral haemodynamic data (which was predominantly performed by the nursing team) and provided technical support for the clinical team for both NIRS and Finometer devices.

- **Research Output 2: Analysis Software.** Analysis software was developed to fully automatise the processing of all data collected during the studies combining clinical and biosignal information into a reusable database, together with automating feature extraction and machine learning processes. The author of the thesis was the only developer of the analysis software, with input from the two supervisors and Dr. Paul Claffey, who advised and assisted in the conceptualisation and design of the variables and the analytical approaches used.
- **Research Output 3: Databases.** The databases were formed by a combination of features derived with the analysis software described in Research Output 2 and clinical history data recorded during patients visit (or during study participation in the case of TILDA participants). In the case of the TILDA database, the TILDA team provided files containing biosignals from NIRS and Finometer devices, which were processed by the author with the same analysis software. Clinical history data collection and cleaning was performed by Dr. Paul Claffey and research assistant Ms. Maria Delgado-

Ortet. The author of this thesis organised and managed the two databases (FASU and TILDA).

- **Clinical Database.** the features extracted by the above process led to the development of a novel reusable database of peripheral and cerebral haemodynamic data from FASU patients – which will be available for future studies.
 - **Harmonised database.** A harmonised and reusable database including the same features extracted for TILDA participants was also created – which will be available for future studies.
- **Research Output 4:** Data from patients and TILDA participants was analysed using descriptive statistics, standard models and machine learning models. These models represent a novel output of this thesis, and will inform the development of future methods to predict the future risk of falls and syncope in specialised units and a wider community. The author developed these models with the advice and input of the project supervisors and Dr. Paul Claffey.
- **Research Output 5:** Data from all FASU patients (18-95 years) was analysed using the above methodologies as part of **Study 1** (Chapter 6: Associations of Age and Sex with Cerebral and Peripheral Haemodynamic Responses to an Active Stand Test in a Population of Falls and Syncope Patients). The author fully developed this study, with the advice and input of the project supervisors and Dr. Paul Claffey.
- **Research Output 6:** Data from young FASU patients and young healthy volunteers was analysed, resulting in **Study 2** (Chapter 7: Cerebral Oxygenation Responses to Standing in Young Patients with Vasovagal

Syncope). The author fully developed this study, with the advice and input of the project supervisors and Dr. Paul Claffey.

- **Research Output 7:** Data from older FASU patients was analysed, resulting in **Study 3** (Chapter 8: Increased Multimorbidity is Associated with Impaired Cerebral and Peripheral Haemodynamic Stabilisation during Active Standing). The author fully developed this study, with the advice and input of the project supervisors and Dr. Paul Claffey.
- **Research Output 8:** Data from older FASU patients and TILDA participants was analysed, resulting in **Study 4** (Chapter 9: Clinical Decision Support for Unexplained Falls and Syncope Management: A Novel Explainable Machine Learning Approach). The author fully developed this study, with the advice and input of the project supervisors and Dr. Paul Claffey.

The methods used for this thesis also contribute to the collaborative studies with Dr. Paul Claffey for his PhD. In particular, the database used for those studies stems from the FASU database created by the methods developed in this thesis (Output 3) and was co-created with Dr. Claffey. This has resulted in the following collaborative research outputs:

- **Research output A:** A peer reviewed publication on the use of NIRS for the assessment of patients with Psychogenic Pseudosyncope (author's contribution is described in Appendix A)

*Claffey P, **Pérez-Denia L**, Rivasi G, Finucane C, Kenny RA. Near-infrared spectroscopy in evaluating psychogenic pseudosyncope - a novel diagnostic approach. QJM : monthly journal of the Association of*

Physicians. 2020 Apr 1;113(4):239-244. doi: 10.1093/qjmed/hcz257.

PMID: 31596496.

- **Research output B:** an article in preparation on cerebral oxygenation responses to standing in patients with orthostatic hypotension (article in preparation, author's contribution is described in Appendix C)

*Claffey P, **Pérez-Denia L**, Dyer A, McNicholas T, Briggs R, Finucane C, Kenny RA. Is Orthostatic Hypotension Associated with Altered Cerebral Perfusion During Active Standing?*

- **Research output C:** future articles will be developed using this database for completion of Dr. Claffey's PhD thesis and other related studies

Chapter 6: Associations of Age and Sex with Cerebral and Peripheral Haemodynamic Responses to an Active Stand Test in a Population of Falls and Syncope Patients

Age and sex are known to influence the peripheral haemodynamic responses to active standing. Nevertheless, how these factors affect the cerebral oxygenation responses during this orthostatic manoeuvre remains largely unexplored, in particular in the context of patients with symptoms of falls and syncope. This Chapter explores the associations of age and sex with near-infrared spectroscopy (NIRS) derived measures of cerebral oxygenation responses during an active stand (AS) test in a large cohort of patients with falls and syncope. The dependency of these responses with blood pressure (BP) is also assessed. Furthermore, a subset of older adults (≥ 50 years) is investigated, to understand the influence of these two factors in this population of interest. Differences in relevant clinical outcomes (i.e., syncope, falls and unexplained falls (UF)) with age and sex are also investigated.

This chapter will lead to the following publication:

Pérez-Denia L, Claffey P, Byrne L, Rice C, Kenny RA, Finucane C.
Associations of Age and Sex with Cerebral and Peripheral Haemodynamic Responses to an Active Stand Test in a Population of Falls and Syncope Patients

6.1 Introduction

Syncope affects a large proportion of the population across ages [2]. Although in young populations the most common form of syncope is vasovagal syncope, in older populations syncope coexists and often presents in the form of a fall [62]. Dedicated falls and syncope units are specialised in managing cardiovascular causes of falls and faints. International guidelines recommended an AS test for the management of falls, whereby patients are asked to stand up as fast as they can and then stay standing for 3 minutes after being supine for 5-10 minutes [1]. BP and heart rate (HR) responses to an AS are known to be affected by age [28], and features derived from these responses are known predictors of falls and increased mortality in older adults [29, 35]. Given the increasingly recognised overlap between UF and syncope [62], the AS is recommended for both type of events [1].

Syncope and falls of unexplained origin have been attributed to cerebral hypoperfusion [1]. Thus, there is an interest in understanding how cerebral perfusion is regulated during orthostatic challenges and identifying new biomarkers that can aid in the risk assessment of falls and syncope patients. NIRS is an emerging technology that allows monitoring cerebral oxygenation as a surrogate for perfusion during dynamic manoeuvres such as the AS test [227]. Previous studies have investigated the effect of age on cerebral oxygenation signals during standing manoeuvres, showing contradicting results regarding the direction of change with age in oxygenated, deoxygenated and total haemoglobin [226-229]. As for sex, evidence is scarce, with only one article by Mehagnou-Schipper et al. reporting a trend towards a lower oxygenated haemoglobin in women during a 10 minute stand [227].

The main aim of this study is to answer the following research questions: 1) Are age and sex associated with cerebral oxygenation responses to standing measured with NIRS in a cohort of patients with falls and syncope? 2) Do associations remain when only considering a subset of older adults? 3) Are there differences in the distribution of falls and syncope with age and sex? 4) Do the findings observed justify the separation of falls and syncope patients into subcohorts according to age and sex?

6.2 Materials and Methods

Study population

Patients were recruited consecutively during their visit to the Falls and Syncope Unit at St. James's Hospital, Dublin. They were referred to this unit due to suspected syncope, falls or dizziness. A GDPR compliant ethics application was approved by the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08,CA,16). Approval was also granted from the Research & Innovation office at St. James's Hospital.

Inclusion and exclusion criteria

Patients over the age of 18 years were recruited. Patients were excluded if they had any contraindications to perform the Active Stand protocol, such as pain, mobility difficulties or severe symptoms of orthostatic intolerance. Pregnant women were not included in the study.

Active standing testing

Protocol

Participants performed an AS test as per international recommendations [1, 71]. Subjects rested in a supine position for 10-15 minutes. Then, they were instructed to

stand up as fast as possible and remain standing quiet and still for another 3 minutes. The test was terminated earlier if the participant experienced severe symptoms of orthostatic intolerance or was unable to be standing for the entire duration. Assistance was provided during the stand if required by the patient due to mobility issues. The initiation of the standing manoeuvre was marked simultaneously by pressing a key in both the Finometer NOVA and the PortaLite computer keyboard. These marks were used to synchronise both signals in subsequent signal analysis steps.

Equipment

Cerebral oxygenation was monitored using NIRS with a PortaLite (Portalite, Artinis Medical Systems B.V., Elst, The Netherlands). The PortaLite system uses spatially resolved spectroscopy to derive a Tissue Saturation Index (TSI, expressed in units of %), i.e., a measure of cerebral blood oxygen saturation. TSI is calculated as the ratio between the concentration of oxygenated haemoglobin and total concentration of haemoglobin. The PortaLite sensor was placed on the left side of the forehead, centred at 3 cm lateral and 3.5 cm over the nasion [406]. An opaque bandage was placed around the head to provide ambient light protection and minimise motion artefact.

Continuous beat-to-beat BP and was measured using a Finometer NOVA (Finometer NOVA, Finapres Medical Systems, Amsterdam, The Netherlands), which implements the volume clamp method. As per manufacturer instructions, a finger cuff was placed on the left arm, and an arm cuff was attached to the contralateral arm to perform calibration measurements. A high correction unit system was placed over the finger cuff and at the level of the heart to correct for vertical height differences. Calibration was periodically performed using Physiocal™.

Covariates

During the clinical visit, information was collected from patients regarding their demographics and anthropometrics (age, sex, weight, height, body mass index (BMI)) and self-reported morbidities, including cardiovascular diseases, neurological diseases, psychological disorders, vestibular disorders and other relevant medical conditions. Clinical outcomes of interest were also collected, including a history of falls (all-cause), unexplained (non-accidental) falls, and syncope. Smoking status (non-smoker, current smoker or ex-smoker) and excessive alcohol intake (>14 units/weeks for women, > 21 units/weeks for men) were also recorded. Medication records were also taken during the visit.

Data analysis

Custom code was developed in MATLAB 2019a to process the data. Signals analysed were systolic BP (SBP), diastolic BP (DBP), and TSI. Finometer signals were resampled at 10 Hz (TSI was already captured at 10Hz). Baseline values were obtained as the average value from -60 to -30 seconds prior to standing. A ± 2.5 second moving average filter was implemented to derive values at 30 seconds after standing. Raw data was filtered using a 2nd order 0.2 Hz Butterworth zero phase forward-reverse filter to minimise the contribution of heart rate [408]. The nadir time was obtained as the lowest trough within the first 30s of standing (15s in the case of TSI), and the overshoot was the subsequent peak. A ± 2.5 second average filter was applied to the raw data on the identified timepoints to extract magnitude values. The recovery rate between nadir and overshoot was calculated as the difference in magnitude by the difference in time. Differences from baseline were then extracted. See Table 6.1 and Figure 6.1 for a description of the features.

The standing speed was calculated from the Finometer height correction unit signal using a method based on that published by O'Connor et al. [407], and the duration of supine rest was estimated as the duration of the recording before standing.

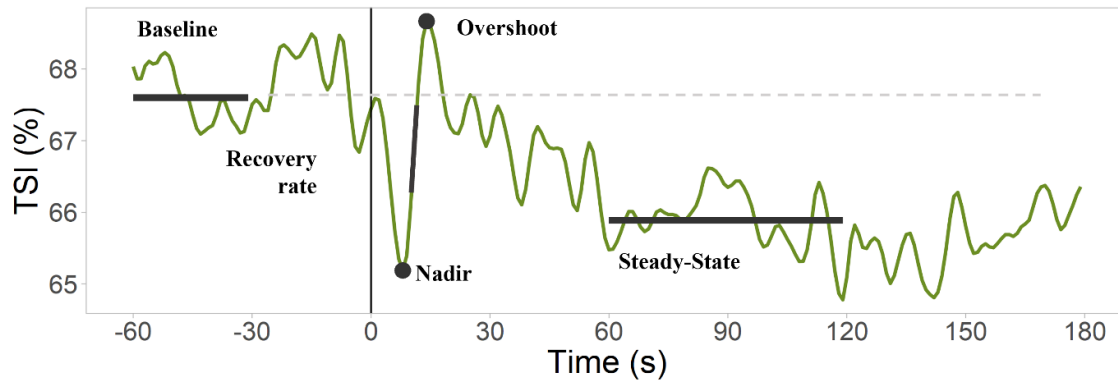


Figure 6.1. Features extracted in a representative real sample.

Table 6.1. Description of features used in the analysis

Feature	Description
Baseline	Average value of signal between -60 to -30 seconds before standing.
Absolute nadir	Value of largest local minimum found within the following time range: 2-30 seconds for BP signals 2-15 seconds for TSI
Nadir time	Time at which TSI nadir has been identified
Nadir	Absolute nadir – Baseline
Absolute Overshoot	Value of first local maxima found after nadir in the first minutes of the recording
Overshoot time	Difference between nadir and next local maximum found after the nadir
Overshoot	Absolute overshoot – Baseline
Nadir to overshoot time	Overshoot time – Nadir time
Nadir to overshoot difference	Overshoot – Nadir
Recovery rate	$(\text{Overshoot} - \text{Nadir}) / (\text{Overshoot time} - \text{Nadir time})$
Drop at 30 seconds	Value at 30 seconds obtained applying a ± 2.5 second average filter – Baseline
Steady-state	Average value between 60 and 120 seconds after standing – Baseline

Statistical analysis

Data were analysed using Rstudio (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). Data was screened for normality using histograms, QQplots and the Shapiro-Wilk test. T-tests and Mann Whitney U tests were used to compare continuous variables between sex groups that were normally and non-normally distributed, respectively. Normal variables are expressed as mean and standard deviation (SD), while non-normal variables are reported as median and interquartile range (IQR). Chi-squared tests were used for binary variables.

Robust linear regression was used to investigate the association between age, sex and features of cerebral oxygenation. Univariate analyses investigated the association between age (model 1) and sex (model 2) and cerebral oxygenation features. Age and sex were simultaneously analysed in model 3, and a more complete multivariate model (model 4) was also considered taking into account the two variables plus a set of covariates: weight, height, number of morbidities, number of medications, baseline SBP and baseline HR.

Sensitivity analysis was performed by further accounting for the following covariates: standing speed, lying duration, alcohol excess, smoking status and the concurrent SBP feature (e.g. when the TSI nadir was analysed, the SBP nadir was used in the model). Sensitivity analysis was further run only in patients over 50 years to further investigate the effect of age.

To investigate the association between clinical outcomes and age and sex, logistic regression was used. The same models as described above were employed (see Table 6.2). Histograms were plotted to further understand the distribution of outcomes in the population.

To correct for multiple testing, false discovery rate (FDR) was used. A significance level of 0.05 was considered.

Table 6.2. Models explored

Model number	Model terms
1	Age
2	Sex
3	Age + Sex
4	Age + Sex + BMI + Morbidity count + Antidepressants + Antihypertensives + Baseline SBP + Baseline HR

Outcome variables were tissue saturation index features (in linear regression models) and clinical outcomes, i.e., syncope, falls and unexplained falls (in logistic regression models).

6.3 Results

Patients' characteristics

A total of 411 patients were included in the study, 58% women (see Table 6.3 for table of participants characteristics). Women had significantly lower weight (69(20) vs 83(18) Kg, $p < 0.001$) and height (162(10) vs 175(10) cm, $p < 0.001$) than men. Both sex groups had similar multimorbidity accumulation and equivalent antihypertensive intake, although a higher proportion of women were taking antidepressants (28% vs 18%, $p = 0.020$). Women and men were well matched in history of relevant events (i.e., syncope, all cause falls and UF) and baseline haemodynamics, with only a slightly lower resting HR in women (71(17) vs 73(16) bpm, $p = 0.027$). Regarding TSI features, women had a smaller drop at nadir (-1.76(1.63)% vs -2.27(1.95)%, $p = 0.006$) and a smaller overshoot-to-nadir magnitude difference (2.21 (2.12)% vs 2.51 (2.53)%, $p = 0.017$).

Table 6.3. Participants' characteristics

	All participants (n = 411)	Women (n = 248)	Men (n = 163)	p-value
Demographic data				
Age (years), median (IQR)	65 (25)	64 (30)	67 (20)	0.071
Female, % (n)	58 (288)	-	-	-
Weight (Kg), median (IQR)	74 (22)	69 (20)	83 (18)	<0.001***
Height (cm), median (IQR)	166 (14)	162 (10)	175 (10)	<0.001***
BMI (Kg/m ²), median (IQR)	26 (7)	26 (8)	27 (5)	0.048*
Morbidities and medications				
Number of morbidities, median (IQR)	3 (2)	3 (2)	3 (3)	0.098
Taking antihypertensives, % (n)	41 (167)	39 (96)	44 (71)	0.327
Taking antidepressants, % (n)	24 (98)	28 (69)	18 (29)	0.020*
History of events				
History of syncope, % (n)	54 (222)	54 (133)	55 (89)	0.847
History of all cause falls, % (n)	27 (109)	29 (73)	22 (36)	0.099
History of unexplained falls, % (n)	21 (87)	24 (59)	17 (28)	0.108
Baseline haemodynamics				
Baseline SBP (mmHg), median (IQR)	140 (26)	139 (27)	142 (25)	0.089
Baseline DBP (mmHg), mean (sd)	82 (13)	82 (13)	83 (11)	0.183 ⁺
Baseline HR (bpm), median (IQR)	73 (16)	71 (17)	73 (16)	0.027*

⁺ indicates a t-test was performed, otherwise a Mann Whitney U test was used for continuous variables, p-value correspond to the comparison between women and men. *p-value <0.05, ** p-value < 0.01, *** p-value < 0.001

Table 6.4. Cerebral oxygenation features values and sex comparison

	All participants (n = 411)	Women (n = 248)	Men (n = 163)	p-value
TSI features				
Nadir	-1.94 (1.88)	-1.76 (1.63)	-2.27 (1.95)	0.006**
Overshoot	0.34 (1.88)	0.34 (1.55)	0.32 (2.21)	0.587
Overshoot-nadir	2.30 (2.33)	2.21 (2.12)	2.51 (2.53)	0.017*
Recovery rate	0.24 (0.23)	0.23 (0.25)	0.26 (0.21)	0.135
Drop at 30s	-0.66 (1.51)	-0.63 (1.50)	-0.69 (1.67)	0.324
Steady-state	-1.05 (1.96)	-1.08 (1.79)	-0.97 (2.05)	0.076

Mann Whitney U tests were performed, p-value correspond to the comparison between women and men. *p-value <0.05, ** p-value < 0.01.

Age and sex associations with cerebral oxygenation

Univariate analysis

Age was univariately associated with a smaller overshoot (β (CI): -0.018 (-0.025 -0.010), $p < 0.001$), a smaller overshoot to nadir difference (β (CI): -0.018 (-0.026 -0.010), $p < 0.001$), a slower recovery rate (β (CI): -0.003 (-0.004 -0.003), $p < 0.001$) and

a larger drop at 30s (β (CI): -0.008 (-0.014 -0.001), $p = 0.024$) and during steady-state (β (CI): -0.008 (-0.016 -0.001), $p = 0.036$) (see Figure 6.2 and Table 6.5). Women had a significantly smaller drop at nadir (β (CI): 0.403 (0.135 0.672), $p = 0.003$), a smaller overshoot-to-nadir difference (β (CI): -0.432 (-0.752 -0.113), $p = 0.008$) (see Table 6.5 and Figure 6.3).

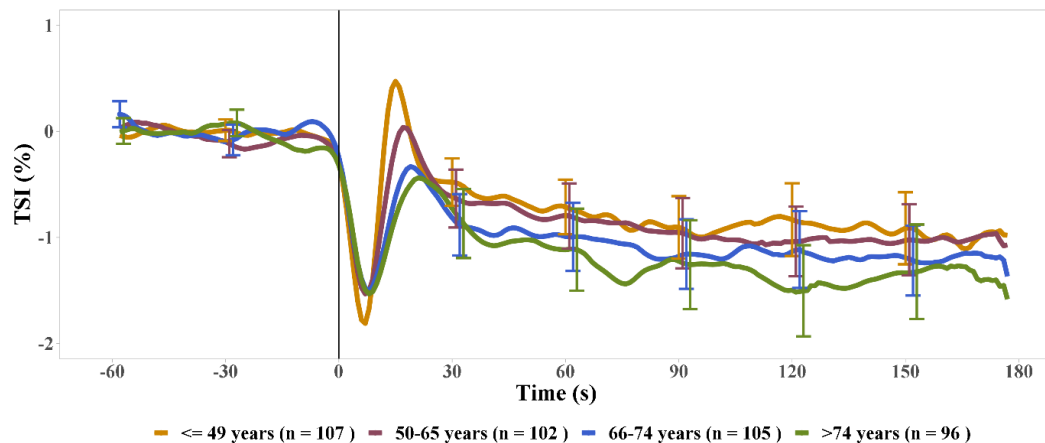


Figure 6.2. Cerebral oxygenation responses in overall population.
(Note that the cohort has been divided into groups (age quartiles) for visualization, age was analysed as a continuous variable).

Multivariate analysis

In model 3, when age and sex were included together in the same model, results were equivalent to those observed univariately, with the recovery rate also being associated with sex (β (CI): -0.038 (-0.070 -0.007), $p = 0.018$) (see Table 6.5). When all covariates were included in the complete model (model 4), except for the drop at 30s and steady-state, all the associations found with age remained. All associations with sex remained significant after covariate adjustment. Other significantly associated covariates were BMI, which was associated with a smaller overshoot-to-nadir difference (β (CI): -0.039 (-0.069 -0.009), $p = 0.012$) and slower recovery rate (β (CI): -0.004 (-0.007 -0.001), $p = 0.005$), and baseline SBP, which was associated with a

smaller drop at nadir (β (CI): 0.013 (0.007 0.020), $p < 0.001$), and at 30 seconds (β (CI): 0.007 (0.000 0.013), $p = 0.043$).

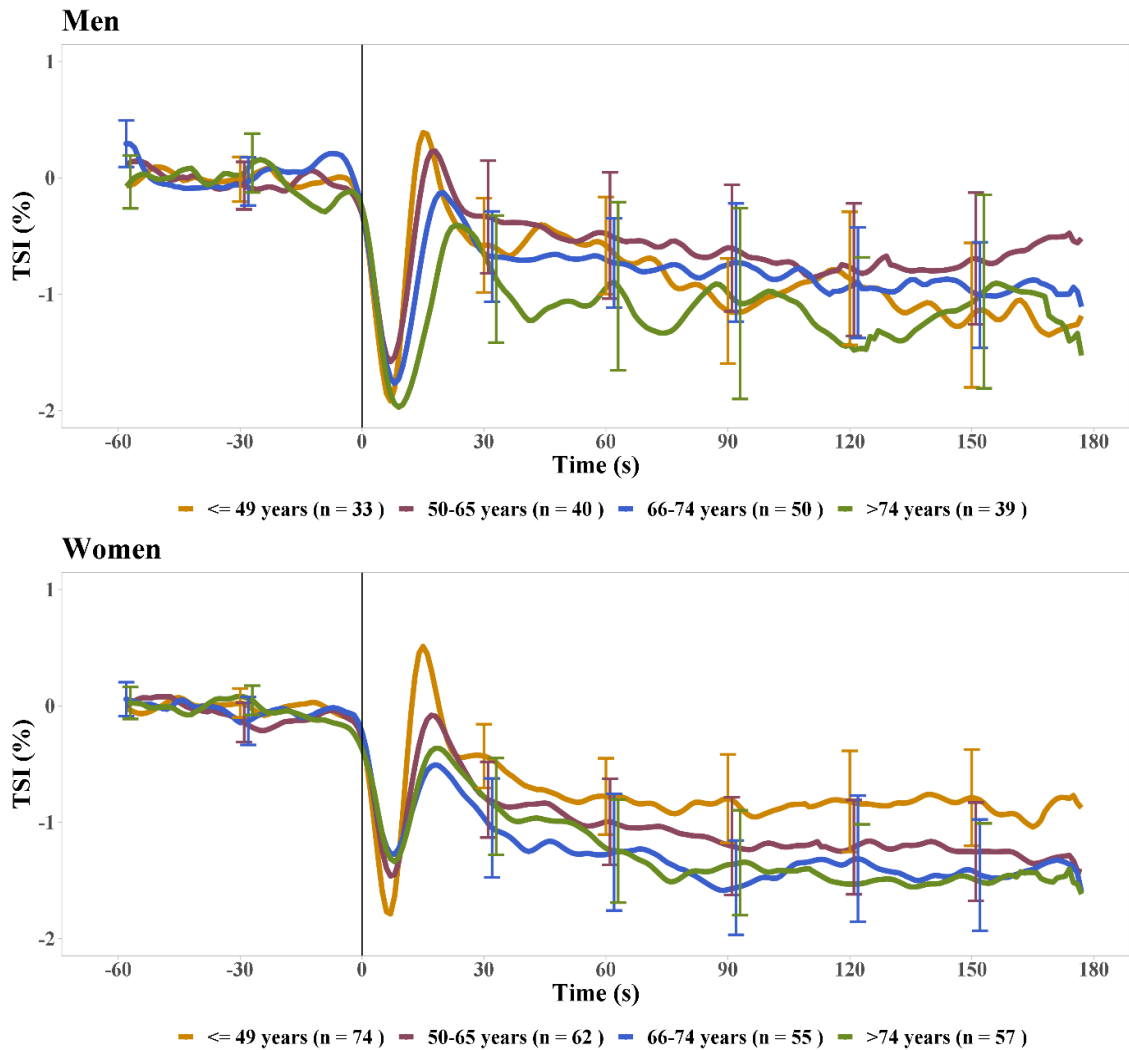


Figure 6.3. Cerebral oxygenation responses in men and women subgroups.
(Note that the cohort has been divided into groups for visualization, age was analysed as a continuous variable).

Linear Regression Sensitivity Analysis

Sensitivity analysis including the extra set of covariates (standing speed, lying duration, alcohol excess, smoking status and the concurrent SBP feature) demonstrated similar results, with associations only slightly weakened.

In sensitivity analysis only including patients over the age of 50 years age was no longer significantly associated with cerebral oxygenation features, while sex effects remained.

Age and sex associations with clinical outcomes

Falls were almost no existent in patients aged under 50 years, with most patients having symptoms of syncope (see Figure 6.4). Univariately, age was positively associated with a history of falls (β (CI): 0.051 (0.036 0.069), $p < 0.001$) and UF (β (CI): 0.045 (0.029 0.063), $p < 0.001$), and negatively associated with a history of syncope (β (CI): -0.031 (-0.043 -0.020), $p < 0.001$), while sex was not associated with either outcome (see Table 6.6). In multivariate analyses, the associations with age remained significant, while new associations were observed with sex in falls (β (CI): 0.785 (0.262 1.328), $p = 0.004$) and UF (β (CI): 0.850 (0.279 1.453), $p = 0.004$). Multimorbidity was also associated with all clinical outcomes in model 4 (see Table 6.6).

Table 6.5. Results of the models studying the association of NIRS variables with patients characteristics.

		Nadir (%)	Overshoot (%)	Overshoot-Nadir (%)	Recovery rate (%)	Drop at 30s (%)	Steady-state (%)
Model 1							
Age	β	0.003 (-0.004 0.010)	-0.018 (-0.025 -0.010)	-0.018 (-0.026 -0.010)	-0.003 (-0.004 -0.003)	-0.008 (-0.014 -0.001)	-0.008 (-0.016 -0.001)
	p-value	0.402	<0.001*** ⁽⁺⁾	<0.001*** ⁽⁺⁾	<0.001*** ⁽⁺⁾	0.024* ⁽⁺⁾	0.036* ⁽⁺⁾
Model 2							
Sex	β	0.403 (0.135 0.672)	-0.140 (-0.429 0.148)	-0.432 (-0.752 -0.113)	-0.024 (-0.058 0.010)	-0.164 (-0.423 0.095)	-0.281 (-0.584 0.022)
	p-value	0.003** ⁽⁺⁾	0.339	0.008** ⁽⁺⁾	0.162	0.213	0.069
Model 3							
Age	β	0.004 (-0.003 0.011)	-0.018 (-0.026 -0.011)	-0.020 (-0.028 -0.011)	-0.004 (-0.004 -0.003)	-0.008 (-0.015 -0.001)	-0.009 (-0.017 -0.001)
	p-value	0.279	<0.001*** ⁽⁺⁾	<0.001*** ⁽⁺⁾	<0.001*** ⁽⁺⁾	0.019* ⁽⁺⁾	0.028* ⁽⁺⁾
Sex	β	0.415 (0.145 0.684)	-0.208 (-0.490 0.073)	-0.526 (-0.844 -0.209)	-0.038 (-0.070 -0.007)	-0.188 (-0.446 0.071)	-0.297 (-0.600 0.005)
	p-value	0.003** ⁽⁺⁾	0.146	0.003** ⁽⁺⁾	0.018* ⁽⁺⁾	0.154	0.054
Model 4							
Age	β	0.000 (-0.008 0.009)	-0.017 (-0.026 -0.008)	-0.017 (-0.027 -0.007)	-0.003 (-0.004 -0.002)	-0.005 (-0.014 0.003)	-0.009 (-0.019 0.001)
	p-value	0.909	<0.001*** ⁽⁺⁾	0.001** ⁽⁺⁾	<0.001*** ⁽⁺⁾	0.204	0.080
Sex	β	0.486 (0.217 0.755)	-0.214 (-0.503 0.075)	-0.552 (-0.875 -0.229)	-0.041 (-0.073 -0.008)	-0.177 (-0.438 0.085)	-0.258 (-0.567 0.051)
	p-value	<0.001*** ⁽⁺⁾	0.146	0.001** ⁽⁺⁾	0.014* ⁽⁺⁾	0.185	0.102
BMI	β	0.007 (-0.023 0.038)	-0.021 (-0.048 0.006)	-0.039 (-0.069 -0.009)	-0.004 (-0.007 -0.001)	-0.008 (-0.032 0.016)	0.007 (-0.022 0.035)
	p-value	0.163	0.136	0.012* ⁽⁺⁾	0.005** ⁽⁺⁾	0.530	0.650
Morbidity count	β	-0.057 (-0.145 0.031)	-0.068 (-0.162 0.026)	0.020 (-0.085 0.124)	0.000 (-0.011 0.010)	-0.110 (-0.194 -0.025)	-0.069 (-0.170 0.031)
	p-value	0.206	0.157	0.708	0.943	0.011*	0.175
Antihypertensives	β	0.126 (-0.182 0.433)	0.027 (-0.304 0.357)	-0.167 (-0.535 0.201)	-0.029 (-0.066 0.008)	-0.065 (-0.365 0.235)	0.133 (-0.222 0.489)
	p-value	0.423	0.873	0.374	0.123	0.672	0.461
Antidepressants	β	-0.388 (-0.710 -0.067)	-0.222 (-0.569 0.124)	0.171 (-0.214 0.556)	-0.018 (-0.056 0.021)	-0.168 (-0.482 0.146)	-0.429 (-0.800 -0.058)
	p-value	0.018	0.208	0.383	0.369	0.293	0.024
Baseline SBP	β	0.013 (0.007 0.020)	0.004 (-0.003 0.012)	-0.006 (-0.014 0.002)	0.000 (-0.001 0.001)	0.007 (0.000 0.013)	0.004 (-0.004 0.012)
	p-value	<0.001*** ⁽⁺⁾	0.229	0.117	0.987	0.043*	0.308
Baseline HR	β	0.010 (-0.001 0.021)	0.002 (-0.010 0.014)	-0.005 (-0.018 0.009)	0.000 (-0.001 0.002)	-0.001 (-0.012 0.010)	0.004 (-0.009 0.017)
	p-value	0.078	0.691	0.494	0.597	0.813	0.520

⁽⁺⁾indicates that the association was significant even after false discovery rate correction. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

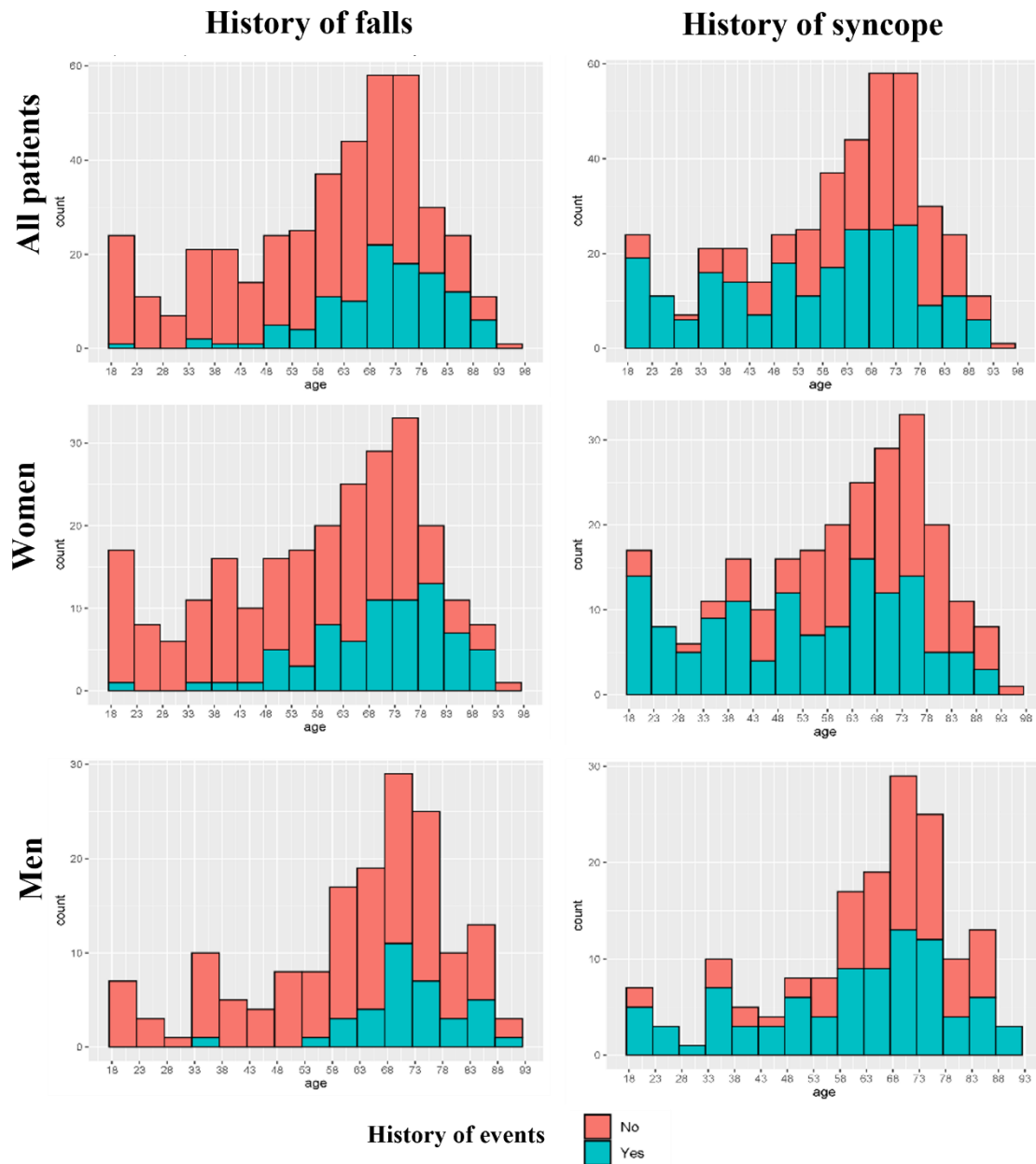


Figure 6.4. Falls and syncope distribution in the cohort studied.

Distribution of falls (left column) and syncope (right column) for all participants (top row), women (middle row) and men (bottom row). Unexplained falls followed a very similar distribution to that of falls.

Table 6.6. Associations between history of falls, unexplained falls and syncope with age, sex and other covariates

		History of falls	History of unexplained falls	History of syncope
Model 1				
Age	β	0.051 (0.036 0.069)	0.045 (0.029 0.063)	-0.031 (-0.043 -0.020)
	p-value	<0.001*** (+)	<0.001*** (+)	<0.001*** (+)
Model 2				
Sex	β	0.386 (-0.068 0.853)	0.401 (-0.084 0.921)	-0.039 (-0.437 0.357)
	p-value	0.100	0.110	0.847
Model 3				
Age	β	0.053 (0.037 0.071)	0.046 (0.030 0.064)	-0.031 (-0.043 -0.020)
	p-value	<0.001*** (+)	<0.001*** (+)	0.028* (+)
Sex	β	0.587 (0.104 1.085)	0.571 (0.057 1.052)	-0.162 (-0.579 0.250)
	p-value	0.019* (+)	0.032* (+)	0.440
Model 4				
Age	β	0.043 (0.024 0.063)	0.033 (0.013 0.054)	-0.040 (-0.056 -0.026)
	p-value	<0.001*** (+)	0.002** (+)	<0.001*** (+)
Sex	β	0.785 (0.262 1.328)	0.850 (0.279 1.453)	-0.034 (-0.466 0.397)
	p-value	0.004* (+)	0.004* (+)	0.876
BMI	β	0.001 (-0.045 0.047)	-0.008 (-0.057 0.041)	-0.019 (-0.060 0.021)
	p-value	0.962	0.763	0.343
Morbidity count	β	0.314 (0.161 0.474)	0.401 (0.236 0.574)	0.228 (0.090 0.372)
	p-value	<0.001*** (+)	<0.001*** (+)	0.001** (+)
Antihypertensives	β	-0.286 (-0.842 0.260)	-0.092 (-0.685 0.494)	-0.455 (-0.944 0.028)
	p-value	0.309	0.759	0.066
Antidepressants	β	0.046 (-0.544 0.621)	0.195 (-0.424 0.796)	-0.347 (-0.866 0.167)
	p-value	0.876	0.530	0.186
Baseline SBP	β	0.002 (-0.010 0.013)	-0.006 (-0.020 0.007)	0.004 (-0.006 0.015)
	p-value	0.758	0.357	0.444
Baseline HR	β	0.006 (-0.015 0.026)	-0.002 (-0.024 0.021)	-0.009 (-0.027 0.009)
	p-value	0.603	0.866	0.317

(+) indicates that the association was significant even after false discovery rate correction. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

6.4 Discussion

The main findings of this study are that TSI responses to standing are associated with age and sex in a cohort of patients with falls and syncope. When only older adults were considered (≥ 50 years), the sex effects remained, although age was no longer associated with cerebral oxygenation features. Furthermore, age was positively associated with falls (either all-cause or unexplained) and negatively associated with syncope, while sex effects were only observed when adjusting for covariates.

Age

The results observed demonstrate that age had no effect on the initial nadir in cerebral oxygenation for any model. However, significant differences were found in recovery and steady-state features. The β coefficient for overshoot-to-nadir difference was -0.018, which implies that for a 10-year difference, subjects would have an overshoot-to-nadir difference 0.18% smaller than subject 10 years younger, ~1% smaller if a 50-year difference is considered. Considering that a change from baseline of approximately 10% is believed to be required to cause syncope [255], these differences might be of clinical relevance.

Regarding the initial transient response in cerebral oxygenation upon standing, Kim et al. found that there was a significant effect of age in the drop in oxygenated haemoglobin, which they found to be larger in younger participants [226]. Kawaguchi et al. observed a significant decrease in oxygenated (HbO₂) and total haemoglobin (tHb) occurring within 10 seconds of standing in younger participants (23.5 (21-32) years) and within 15 seconds in older volunteers (68.2 (64-79) years) [413]. They also reported that the younger group had recovered by approximately 20 seconds while the older had not reached baseline by 20-25 seconds. Regarding steady-state responses,

conflicting evidence exists in the literature. Mehagnoul-Schipper et al. showed that 2-10 minutes after standing, a group of healthy older adults (70-83 years) had a significantly larger drop from baseline in HbO₂ as compared to a healthy young group (22-54 years) [227]. On the contrary, Kim et al. demonstrated significantly larger drops in HbO₂ and larger increase in deoxyhaemoglobin (HHb) in a group of young healthy participants (29(27-33) years) as compared to an older group (59(52-65) years) [226]. Gatto et al. did not demonstrate significant differences between two age groups of healthy participants (young (22.4±5.7 years) vs old (48±6years) [228]. However, participants performed a lying to sitting manoeuvre, which evokes a less pronounced haemodynamic response than a lying to standing test. Additionally, differences in age of the groups investigated make comparisons between studies challenging. Lastly, Eldow et al. investigated the effect of age as a continuous variable in a group of 60 patients (20-78 years), and reported that age was associated with a smaller drop in oxygenated haemoglobin [229].

The results presented demonstrate delayed and poorer recovery of TSI with age, given the lower values of recovery rate and larger drops at 30s and steady-state with age, although statistically significant effects of age at nadir were not observed. However, this might be due to the different signals used for analysis (HbO₂, HHb, tHb vs TSI), which present different dynamic and steady-state responses [203]. The associations at 30s and steady-state did not remain significant when adjusting for covariates, which the above studies did not do, which might explain the differences with previous literature.

Adjusting for the effects of SBP did not remove the significant associations found in cerebral oxygenation, and thus the TSI results are independent of SBP. This would support the current evidence that cerebral autoregulation remains preserved with

age [230], although appropriate cerebral autoregulation measures should be derived in order to study it in this cohort.

An important finding of this study is that, when only considering older adults (≥ 50 years old), age was no longer associated with cerebral oxygenation responses to standing, which implies that the age effects found were mostly driven by the youngest group. This result could be anticipated by looking at Figure 6.2, where the youngest group (< 50 years) demonstrates a more pronounced response in TSI as compared to the other three groups. The results of the logistic regression and histogram analysis also demonstrated that age is associated with the clinical outcomes of interest (i.e., all-cause falls, UF and syncope), with adults under 50 years mostly having syncope while a mix of syncope and falls was found in older adults.

Sex

A significant sex effect on the TSI nadir and recovery (magnitude and rate) was observed, resulting in women having a more attenuated response as compared to men. Mehagnoul-Schipper et al. reported a trend towards a lower HbO₂ during a 10 minute standing period in women as compared to men in a healthy population [227]. Edlow et al. used three different posture changes (head-of-bed 30° to supine, supine to stand, and stand to supine again) and investigated the effect of sex and posture change in cerebral oxygenation [229], finding no significant differences for sex groups. Studies using transcranial doppler have demonstrated that cerebral blood flow velocity, is higher in women than in men during supine rest [223, 414]. Deegan et al. reported that, upon standing, the nadir drop from baseline in cerebral blood flow velocity was smaller in women than in men in a population of adults older than 70 years, a response similar to

that observed in the current study, with indices of cerebral autoregulation indicating a more effective mechanism in women as compared to men [241].

Regarding clinical outcomes, equivalent proportions of falls and syncope patients were found for both sex group, although correcting for age and other covariates revealed significant associations of sex with outcomes. This is probably due to the fact that in younger participants the most common outcome was syncope both in women and men. Therefore, since proportions of outcomes in younger patients would be similar, adjusting for this in the model may have revealed associations corresponding to differences in outcomes between sex groups in the older groups.

Limitations

One of the main limitations of this study is heterogeneity of patient presentation. All patients recruited for the project were included in this analysis (18-95 years), in order to obtain an overall characterisation of the current cohort. Nevertheless, some patients presented to the clinic with a history of dizziness, syncope or falls, and some others presented with combinations of them. This study demonstrated that young patients mostly had a history of syncope, while in older adults there was a mixed presentation of falls and syncope. These results and the differences in age associations found in sensitivity analyses encourage an age separation of the population in future studies to better isolate groups. Another relevant limitation is the lack of CO₂ partial pressure (PaCO₂) measures. CO₂ is a strong vasodilator that might have confounded the associations observed [415]. Regarding NIRS, it is very susceptible to motion artifacts as well as extracerebral contamination [185, 189, 416], although features calculated relative to baseline were used here, which should reduce these effects. Other limitations of NIRS are that it only captures regional oxygenation in a small proportion of the

frontal lobe, and that its interpretation can be challenging given that it is the result of arterial and venous oxygenation [417].

Strengths

One of the main strengths of this study is the broad range of ages included (18-95 years). Furthermore, the database of cerebral oxygenation responses to standing in patients with falls and syncope used in this study constitutes one of the largest in the world. Simple biomarkers were derived in this study that describe the transient nature of cerebral oxygenation responses to standing. While nadir and steady-state features have been reported in the literature, the features describing the recovery rate after nadir presented here are novel. Furthermore, not only all-cause falls were considered, but also UF, which represent a relevant and complex clinical entity that overlaps with syncope and is therefore often considered to be cardiovascular in origin [62]. Lastly, sensitivity analyses were performed to study the confounding effects of multiple patients characteristics (alcohol excess, smoking status), methodological factors (lying duration, standing speed) and the concurrent SBP waveform.

Conclusion

TSI responses to standing are affected by age and sex in a population of patients attending a Falls and Syncope Unit. Age is associated with a worse recovery in cerebral oxygenation to standing. These associations are driven by the youngest cohort (< 50 years), where mostly symptoms of syncope are present. The differences in outcomes and cerebral oxygenation responses between this youngest cohort and older adults (≥ 50 years) encourages the investigation of these groups separately in future studies. Furthermore, women had smaller nadir drops and slower recovery patterns, which

remained significant in all analyses, also suggesting that men and women are distinct enough to be studied separately.

Chapter 7: Cerebral Oxygenation Responses to Standing in Young Patients with Vasovagal Syncope

Vasovagal syncope (VVS) is common in young adults and is attributed to cerebral hypoperfusion. However, during AS testing, only peripheral and not cerebral haemodynamic responses are measured. This Chapter seeks to determine whether near-infrared spectroscopy (NIRS) derived cerebral oxygenation and peripheral haemodynamic responses to an active stand (AS) test are altered in young VVS patients when compared to young healthy controls. These responses can provide new insight and understanding of the pathophysiology of VVS in young adults, as well as evidence of the value of using NIRS in this clinical context.

This chapter will lead to the following publication:

Pérez-Denia L, Claffey P, Byrne L, Rice C, Kenny RA, Finucane C. *Cerebral Oxygenation Responses to Standing in Young Patients with Vasovagal Syncope*

7.1 Introduction

Syncope is defined as a transient loss of consciousness due to cerebral hypoperfusion that resolves in a rapid and spontaneous manner [1]. VVS is common in teenagers and young adults, with its prevalence peaking in those aged 15 years [418]. Syncope is associated with increased rates of injury, hospital admission and reduced quality of life [419]. Although the pathophysiology of vasovagal syncope is poorly understood, exaggerated systemic cardiovascular responses during orthostasis have been recently observed in patients with syncope as compared to healthy controls, a behaviour that has been attributed to a hyper-reactive autonomic nervous system [420, 421]. It has been hypothesized that such hyper-reactivity could increase an individual's susceptibility to reflex syncope during episodes of hypotension.

The European Society of Cardiology recommends that patients investigated for syncope undergo the AS test as part of standard evaluation [1]. Standard practice requires concurrent measurement of continuous beat-to-beat blood pressure (BP), heart rate (HR) and self-reported symptoms. Thus, cerebral perfusion status is only inferred, with no objective measures applied clinically. Having such direct surrogates of cerebral perfusion may obviate the need for clinicians to rely solely on peripheral haemodynamics, which often represent a poor surrogate for brain blood flow and would enhance personalised management of these patients.

NIRS, an objective, portable and readily applicable yet non-invasive surrogate for cerebral perfusion, has emerged as a potential tool for the clinical evaluation of syncope [40, 262, 417]. NIRS uses absorbed near-infrared light to determine changes in concentration of cerebral tissue oxyhaemoglobin ($\Delta[\text{O}_2\text{Hb}]$), deoxyhaemoglobin ($\Delta[\text{HHb}]$) and tissue saturation index (TSI), a percentage ratio between $[\text{O}_2\text{Hb}]$ and total

haemoglobin ($[O_2Hb] + [HHb]$) concentrations [38, 39]. NIRS is applied in monitoring of neonates, critically ill patients or patients undergoing cardiac surgery [422], and is an emerging tool in syncope assessment. Cerebral oxygenation responses elicited during an AS have been described in healthy young individuals [203, 226, 423], with deficits in oxygenation patterns observed in patients with autonomic failure [269], and orthostatic intolerance [247, 424]. Furthermore, deterioration in cerebral circulation has been detected in children [248, 425] and adolescents [426] with impaired peripheral haemodynamic responses to AS. Methodological studies have demonstrated good repeatability of transient NIRS responses during an AS test [203], as well as reproducible directions of change during later steady-state periods [202].

However, despite the crucial role of the AS test and the increasing interest in the use of NIRS to evaluate syncope, to our knowledge, there have been no studies investigating cerebral oxygenation responses measured during an AS in young patients with a clinical diagnosis of VVS.

The aim of this study is to investigate the following research questions: Are there differences in cerebral oxygenation and peripheral haemodynamics measured during an AS test, between young patients with VVS and healthy controls?

7.2 Materials and Methods

Setting and Participants

Consecutive patients were recruited prospectively from a National Falls and Syncope Unit based at St James's Hospital, Dublin, Ireland. Patients were referred for investigation of suspected syncope or presyncope and had a history of presyncope and/or syncope.

A convenience sample of young healthy community dwelling controls were also prospectively recruited. The study had ethical approval from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08,CA,16).

Inclusion and exclusion criteria

Patients and controls were aged between 18 and 30 years. Patients had a clinical diagnosis of vasovagal syncope. Controls with a history of syncope, cardiovascular disease or other comorbidities were excluded. All controls were physically fit and were not taking any cardioactive medication. Patients and controls were excluded if they were not able to stand up from a lying position and stay standing for at least 2 minutes. Pregnant women were also excluded.

Active stand testing

Protocol

Participants underwent an AS test as per international guidelines [1, 71]. Participants lay supine for 5-10 minutes as per standard practice until haemodynamic stabilisation occurred, and were then instructed to stand up as quickly as possible and remain standing quietly for 3 minutes. Assistance was provided during the stand if necessary. The test was stopped early if participants were unable to stand for the entire test duration due to severe symptoms of orthostatic intolerance.

Equipment

During AS testing, cerebral oxygenation was monitored using NIRS (Portalite, Artinis Medical Systems B.V., Elst, The Netherlands) to derive values of TSI (reported in units of percentage (%)) and $\Delta[\text{O}_2\text{Hb}]$ and $\Delta[\text{HHb}]$ (measured in $\mu\text{mol/L}$). The sensor was placed on the left side of the forehead to measure frontal lobe cerebral

oxygenation, centred at 3 cm lateral and 3.5 cm above the nasion [406]. An opaque head bandage was applied to provide ambient light protection and minimise sensor motion artefact.

Continuous beat-to-beat systolic BP (SBP), diastolic BP (DBP) and HR were also measured in parallel using a Finometer NOVA (Finometer NOVA, Finapres Medical Systems, Amsterdam, The Netherlands), which uses the volume-clamp method to obtain non-invasive values of peripheral haemodynamics. A finger cuff was attached to the middle or proximal phalanx of a finger of the left hand (as per manufacturer instructions), and a height correction unit was applied to correct hydrostatic effects. The Finometer signal was further calibrated using Physiocal™ and brachial calibration based on the average of two oscillometric BP measurements recorded during the resting period.

Covariates

A comprehensive medical history was recorded and included the following covariates: anthropometrics (age (years), sex, weight (kg), height (m), body mass index (BMI, kg/m²)), cardiovascular diseases, neurological diseases, vestibular disorders, and other relevant medical conditions. 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 also taken at the time of testing.

Data analysis

Signal Processing

Custom code was developed in MATLAB R2020a (The Math Works, Inc., MATLAB, Version 2020a, Natick, MA) to process the multimodal physiological data

collected as previously described [407, 427]. The following signals were analysed: SBP, DBP, HR and TSI, $\Delta[\text{O}_2\text{Hb}]$ and $\Delta[\text{HHb}]$, with a standardised process applied to all signals [427]. A description of the features extracted is detailed Table 7.1 and depicted in Figure 7.1. All baseline values were obtained as the average from 60 to 30 seconds prior to standing. Finometer signals were resampled at 10Hz, and a 2nd order 0.2 Hz Butterworth zero phase forward-reverse filter was used to minimise the contribution of heart rate [408]. The time of the initial nadir was identified as the time of the lowest trough occurring within 30 seconds of standing [217, 226]. The raw signal was then filtered to extract a ± 1 sec moving average value at the time corresponding to the nadir [427]. In the case of $\Delta[\text{HHb}]$, the time of the largest peak was determined. This process was then repeated to determine the overshoot as the first peak (or trough in case of $\Delta[\text{HHb}]$) occurring after the nadir (or after the $\Delta[\text{HHb}]$ peak) (see Table 7.1 and Appendix I: Supplementary Table for an expanded version of features definition). The maximum recovery rate was determined as the maximum of the differentiated signal occurring between the nadir and the overshoot. In NIRS derived signals ($\text{TSI}/\Delta[\text{O}_2\text{Hb}]/\Delta[\text{HHb}]$), a recovery rate normalised by SBP changes was also derived. Finally, a ‘steady-state’ feature was calculated as the average value between 60 and 120 seconds after standing.

Duration of supine rest was estimated from the duration of the Finometer recording prior to standing. Speed of standing was obtained by processing the height correction signal to identify the start and stop of the standing manoeuvre [407].

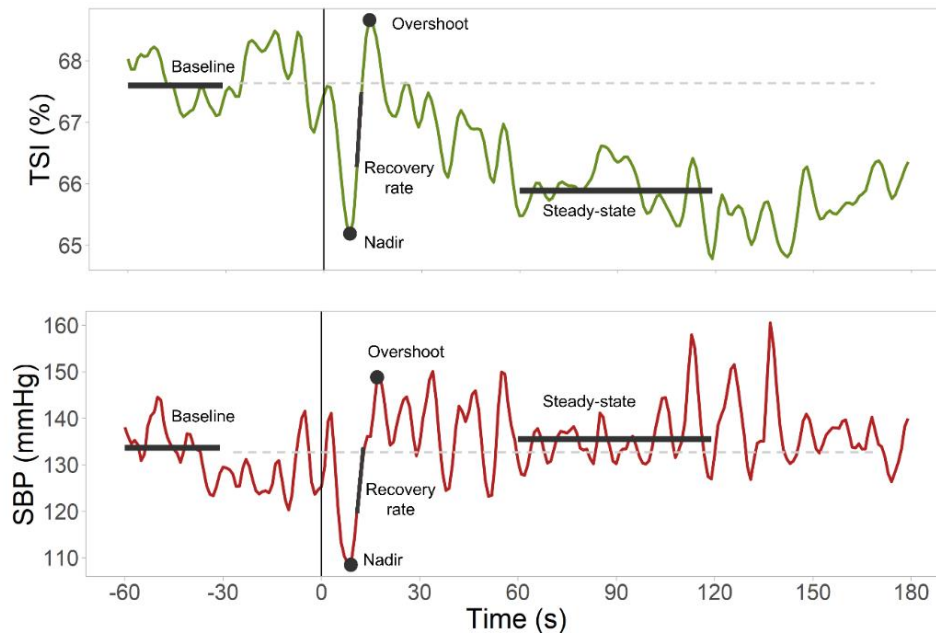


Figure 7.1. Features extracted from TSI and SBP responses to an active stand test in a selected participant.

Features extracted from the signals (i.e., baseline, nadir, recovery rate, overshoot and steady-state) are indicated in both graphs. The standing moment is indicated by a black vertical line at $t = 0$. The baseline value is indicated by a grey dashed line across the graph. SBP = systolic blood pressure, TSI = tissue saturation index.

Table 7.1. Definitions, units, description of variables used in the analyses

Signal (units)	Variable	Description
SBP (mmHg), HR (bpm), TSI (%)	Baseline	Mean value 30-60 s before standing
SBP (mmHg), TSI (%)	Nadir	Largest trough after standing (in first 30s)
SBP (mmHg)	Overshoot	First peak found between SBP nadir time +5s and 60 s after standing
TSI (%)	Overshoot	First peak found between TSI nadir time +2s and 60 s after standing
SBP (mmHg), TSI (%)	Steady-state	Mean value 60-120 s after standing
SBP (mmHg), TSI (%)	Delta	Nadir – Baseline
SBP (mmHg), TSI (%)	Nadir to overshoot	Overshoot – Nadir
SBP (mmHg), TSI (%)	Steady-state change	Steady-state – Baseline
SBP (mmHg/s), TSI (%/s)	Maximum recovery rate	Largest difference between consecutive points divided by the time between points (within the time interval between the nadir and overshoot)
TSI / SBP (%/mmHg)	Normalised TSI recovery rate	Maximum TSI recovery rate / maximum SBP recovery rate

HR: heart rate (units: beats per minute (bpm)), SBP: systolic blood pressure (units: mmHg); TSI: tissue saturation index (units: %).

Statistical analysis

Statistical analysis was performed using Rstudio (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). All data was

assessed for normality using histograms, Q-Q plots, and the Shapiro-Wilk test. Differences in baseline characteristics between healthy participants and patients were assessed using a Mann Whitney U test to account for the relatively small number of subjects in the study and deviations from normality. A Chi-squared test was used for binary variables. Therefore, values are reported as median and interquartile range (IQR). Linear regression was employed to evaluate unadjusted differences in SBP and cerebral oxygenation (Model 1) features between the two groups. Multivariate linear regression was used to adjust for a number of covariates as part of 3 adjusted models: model 2 corrected for sex; model 3 also included corrections for BMI and HR baseline; and model 4 (only applicable to NIRS signals) added the concurrently recorded SBP feature, e.g. SBP nadir was used when TSI nadir was being analysed (see Table 7.2). Outliers were identified and removed if present when their standardised residual was greater than 3 [428]. A false discovery rate (FDR) procedure was used to correct for multiple testing comparisons [429]. Differences were considered to be statistically significant for $p\text{-value} < 0.05$.

Post-hoc sensitivity analyses were performed to assess the robustness of the above results to the following factors: 1) adjustment for the effects of standing speed and duration of lying; 2) definition of recovery rate and normalised recovery rate as averaged rates between nadir and overshoot rather than local maxima rates, 3) age and sex matching of a subset of patients to the group of controls.

Table 7.2. Correction for covariates in SBP, TSI, $\Delta[O_2Hb]$, and $\Delta[HHb]$ regression analyses.

	Covariates
Model 1	None
Model 2	Age + Sex
Model 3	Age + Sex + BMI + HR baseline
Model 4	Age + Sex + BMI + HR baseline + SBP concurrent feature*

**Model 4 only applicable for NIRS variables (TSI, $\Delta[O_2Hb]$, and $\Delta[HHb]$): e.g., when the dependent variable was 'TSI nadir', then 'SBP nadir' was used as a covariate in the model. BMI: body mass index,*

SBP: systolic blood pressure, TSI: tissue saturation index, $\Delta[O_2Hb]$: concentration of oxygenated haemoglobin, $\Delta[HHb]$: concentration of deoxygenated haemoglobin.

7.3 Results

Patients' characteristics

A total of 40 participants were recruited: 27 patients and 13 controls. A summary of the participants characteristics is presented in Table 7.3. Participants were well matched in demographic and baseline haemodynamic characteristics, except for the baseline HR, which was significantly higher in VVS patients (76 (14) vs 66 (16), $p = 0.039$). There was a higher proportion of women in the patient vs the control group (78% vs 54%, $p = 0.122$). Syncope patients presented with different comorbidities (cardiovascular diseases, cholesterol, chronic obstructive airway disease, migraine, depression/anxiety) with 8 taking medications. Controls did not have any comorbidities. All patients had either a history of syncope or presyncope in the last year.

Table 7.3. Participants Characteristics

	Controls (n = 13)	Patients (n = 27)	p-value
Age (years)	22 (1)	21 (6)	0.220
Female, % (n)	54 (7)	78 (21)	0.122
Weight (Kg)	75 (15)	69 (17)	0.496
Height (cm)	174 (11)	168 (13)	0.310
BMI (Kg/m ²)	23 (3)	23 (5)	0.806
SBP baseline (mmHg)	132 (22)	130 (27)	0.479
DBP baseline (mmHg)	81 (5)	77 (18)	0.875
MAP baseline (mmHg)	101 (11)	102 (23)	0.977
HR baseline (bpm)	66 (16)	76 (14)	0.039*
Cardiovascular diseases, % (n)	0	4 (1)	-
Cholesterol, % (n)	0	4 (1)	-
Chronic obstructive airway disease, % (n)	0	15 (4)	-
Migraine, % (n)	0	15 (4)	-
Depression/anxiety, % (n)	0	30 (8)	-
Current smokers, % (n)	23 (3)	15 (4)	0.519
Previous smokers, % (n)	0	0	-
History of syncope, % (n)	0	85 (23)	-
History of presyncope, % (n)	0	52 (14)	-
Medications, % (n)	8 (1)	31 (8)	0.107

Values expressed as median (interquartile range). * $p < 0.05$. BMI: body mass index, DBP: diastolic blood pressure, HR: heart rate, MAP: mean arterial pressure, SBP: systolic blood pressure.

Univariate analyses

Ensemble average responses are depicted in Figure 7.2 for both patients and controls. TSI analysis revealed a significantly smaller TSI nadir (β : 0.93, CI: [0.12 1.74], $p = 0.026$) that did not remain significant after FDR correction (Table 7.4, Figure 7.3). There was a larger $\Delta[\text{O}_2\text{Hb}]$ drop at nadir (β : 3.62, CI: [0.05 7.19], $p = 0.047$), which was not significant after FDR correction (see Appendix I: Supplementary Table A.I.2). The $\Delta[\text{HHb}]$ drop at nadir (β : -1.09, CI: [-2.07 -0.12], $p = 0.029$), nadir to overshoot difference (β : 0.93, CI: [0.16 1.71], $p = 0.019$), recovery rate (β : 0.29, CI: [0.09 0.48], $p = 0.005$) and normalised recovery rate (β : 0.05, CI: [0.02 0.08], $p = 0.002$) were attenuated in patients (see Appendix I: Supplementary Table A.I.3). Patients recovered to a higher SBP steady-state value above baseline when compared to controls (β : 10.80, CI: [3.42 – 18.17], $p = 0.005$), which remained significant after correcting for multiple testing (see Appendix I: Supplementary Table A.I.4).

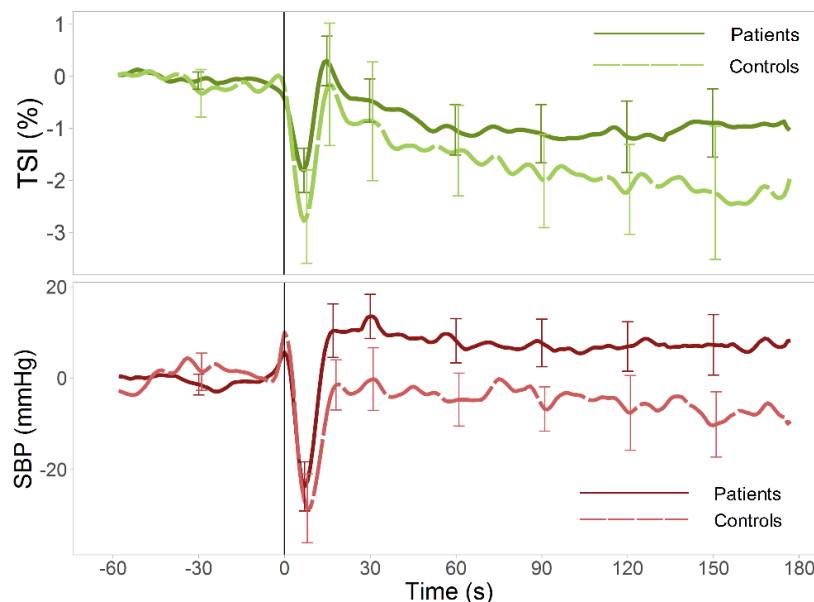


Figure 7.2. Average TSI and SBP responses for VVS patients and controls.

Average (5% trimmed mean and interquartile range) traces for SBP (mmHg) and TSI (%) relative to baseline for VVS patients (dark colour, solid line) and controls (light colour, dashed line). Stand occurred at $t = 0$, indicated by a black vertical line. VVS patients presented a higher SBP value during steady-state (average value during 60-120s) and smaller initial drop after standing than controls. SBP = systolic blood pressure, TSI = tissue saturation index, VVS = vasovagal syncope.

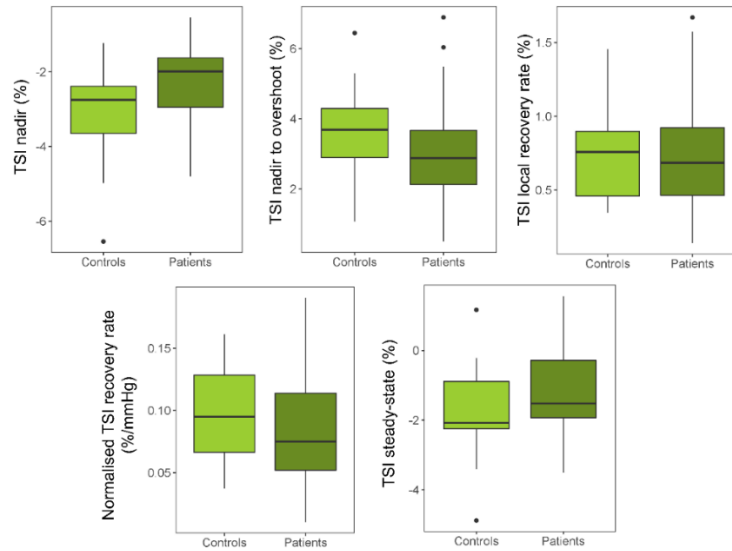


Figure 7.3 Differences in TSI between patients and controls for the TSI features analysed. TSI nadir, TSI nadir to overshoot, maximum TSI recovery rate, normalised TSI recovery rate and TSI nadir steady state. None of the differences were significant after correction for multiple testing (see Table 7.4). TSI = tissue saturation index.

Multivariate Analyses

A smaller drop was observed in TSI nadir when correcting for sex, BMI and baseline HR (Model 3: β : 0.84, CI: [-0.13 1.80], $p = 0.080$), which disappeared after FDR correction (Table 7.4). No associations were observed when further adjusting for the concurrent SBP variable in Model 4. A slower $\Delta[\text{O}_2\text{Hb}]$ recovery rate was also observed in patients (β : -0.37, CI: [-0.72 -0.01], $p = 0.046$), which did not hold significant after FDR adjustment (see Appendix I: Supplementary Table A.I.2). In the case of $\Delta[\text{HHb}]$, multivariate analysis yielded similar results to the univariate analysis, except for the drop at nadir, which was no longer significant (see Appendix I: Supplementary Table A.I.3).

Regarding SBP, a significantly higher steady-state value was present in patients after correcting for sex, BMI and HR baseline (β : 8.37, CI: [0.44 16.30], $p = 0.039$), which was not significant after FDR adjustment (see Appendix I: Supplementary Table A.I.4).

Sensitivity analyses

Correction for the duration of lying and speed of standing slightly strengthened the TSI association at nadir (see Appendix I: Supplementary Table A.I.5). Defining the recovery and normalised recovery rates as averaged rates did not impact the associations detected (see Appendix I: Supplementary Table A.I.6). Furthermore, when repeating the analysis with a subset of patients matched with the controls in age and sex, the differences in cerebral oxygenation and SBP were in a similar direction but somewhat reduced (Appendix I: Supplementary Table A.I.7- Appendix I: Supplementary Table A.I.7).

Table 7.4. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls (reference)) on TSI responses to active stand testing

	β coefficient (CI)	p-value	FDR corrected p-value
Model 1			
TSI nadir (%)	0.93 (0.12 1.74)	0.026*	0.130
TSI nadir to overshoot difference (%)	-0.53 (-1.55 0.49)	0.300	0.500
Maximum TSI recovery rate (%/sec)	-0.04 (-0.30 0.23)	0.790	0.790
Normalised TSI recovery rate (%/mmHg)	-0.01 (-0.04 0.02)	0.426	0.532
TSI baseline to steady-state change (%)	0.72 (-0.27 1.71)	0.148	0.370
Model 2			
TSI nadir (%)	0.84 (0.00 1.68)	0.050	0.250
TSI nadir to overshoot difference (%)	-0.62 (-1.68 0.44)	0.242	0.318
Maximum TSI recovery rate (%/sec)	-0.06 (-0.33 0.22)	0.688	0.688
Normalised TSI recovery rate (%/mmHg)	-0.02 (-0.05 0.01)	0.254	0.318
TSI baseline to steady-state change (%)	0.66 (-0.37 1.69)	0.202	0.318
Model 3			
TSI nadir (%)	0.84 (-0.13 1.80)	0.088	0.401
TSI nadir to overshoot difference (%)	-0.77 (-1.98 0.45)	0.208	0.401
Maximum TSI recovery rate (%/sec)	-0.15 (-0.46 0.16)	0.324	0.401
Normalised TSI recovery rate (%/mmHg)	-0.02 (-0.05 0.02)	0.401	0.401
TSI baseline to steady-state change (%)	-0.15 (-0.46 0.16)	0.324	0.401
Model 4			
TSI nadir (%)	0.73 (-0.27 1.72)	0.147	0.314
TSI nadir to overshoot difference (%)	-0.86 (-2.06 0.35)	0.157	0.314
Maximum TSI recovery rate (%/sec)	-0.17 (-0.47 0.14)	0.282	0.376
Normalised TSI recovery rate (%/mmHg)	-	-	-
TSI baseline to steady-state change (%)	0.45 (-0.84 1.73)	0.484	0.484

Model 1: univariate, **Model 2:** model 1 + sex, **Model 3:** model 2 + sex + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. HR: heart rate, SBP: systolic blood pressure, TSI: tissue saturation index. $p^* < 0.05$.

7.4 Discussion

This study has led to the following novel observations: 1) the initial cerebral tissue oxygenation response evoked by an active stand test in patients diagnosed with VVS is similar to that of healthy controls, 2) standing steady-state SBP is higher in VVS patients.

Patients with VVS included in this study presented with an attenuated initial $\Delta[\text{HHb}]$ response when compared to healthy individuals. These effects were reduced when the data from an age and sex matched subset was analysed. Furthermore, no significant associations were observed in TSI or $\Delta[\text{O}_2\text{Hb}]$ signals. Cerebral oxygenation has been previously studied in patients with syncope before and during the occurrence of an episode of transient loss of consciousness, either using the head-up tilt test in young adults [40, 261] or using an AS test in children [248, 255, 425], demonstrating significant drops in oxygenation during these episodes. However, to our knowledge, this is the first study that investigates differences in cerebral oxygenation during an AS test in young adults with VVS syncope as compared to controls. Kim et al. derived similar features in a group of 20 healthy young adults during a repeated squat-to-stand test [247]. They observed a slower and more delayed maximum drop rate in total haemoglobin upon standing in participants who reported symptoms of orthostatic intolerance as compared to asymptomatic individuals [247]. Kim et al. also studied children with normal and abnormal (i.e., orthostatic syndromes including orthostatic hypotension and VVS, among others) peripheral haemodynamic responses to an AS [248], showing a lower initial drop and steady-state reached in $\Delta[\text{O}_2\text{Hb}]$ after standing in the abnormal group. The first study is the closest to ours regarding population, given that they investigated young adults [247]. However, the repeated squat-to-stand test causes stronger oscillatory haemodynamic waves, which might explain the differences

with the current study. In the second study, even though the AS was used, a heterogeneous population of children with different orthostatic conditions was investigated, which poses a challenge when comparing to this study.

The shape of the cerebral perfusion signal depends on a number of factors, including the passive effect of the underlying blood pressure waveform and the active modulation of cerebral autoregulation (CA) (amongst other factors). Differences in the initial $\Delta[\text{HHb}]$ response were observed, which might be indicative of differences in brain activation between the two cohorts [430], with the attenuated response in patients potentially indicating a less pronounced activation in this group. However, these $\Delta[\text{HHb}]$ differences did not seem to be strong enough to be reflected in TSI, with only the drop at nadir demonstrating a smaller value in patients univariately. However, despite the association found in the TSI nadir drop was not independent of covariates, it is important to note that the magnitude of the association was relatively large ($\beta \sim 1\%$), considering that a 5-10% drop can cause a syncopal episode. Moreover, this magnitude remained relatively stable even after covariates adjustment and in the age and sex matched comparison ($\beta \geq 0.8\%$ TSI). Therefore, the current study might motivate future research with larger sample sizes to investigate this potential difference. Nevertheless, the current results do not provide enough evidence to support that the overall cerebral tissue oxygenation (TSI) is affected in patients with VVS with respect to healthy controls.

Interestingly, differences in the SBP responses were observed between the two groups, with a higher SBP during steady-state in patients. Our group previously reported an exaggerated peripheral haemodynamic response to standing in patients with VVS vs controls both in young [245] and older adults [246]. This led to the novel hypothesis that patients with VVS may have a hyper-reactive autonomic nervous

system [245, 246], characterised by a smaller BP and total peripheral resistance at nadir, lower steady-state stroke volume and cardiac output, and overall higher HR. Similarly, recent evidence from Brignole et al. demonstrated that VVS patients presented increased resting HR and DBP [431]. In their study, VVS patients demonstrated signs of decreased venous return and stroke volume, which the authors proposed may have led to chronic compensatory increased sympathetic outflow. Likewise, higher resting HR and exaggerated BP responses were observed in the VVS patient group vs controls. These responses may seem protective during an AS. However, these potentially enhanced compensatory mechanisms may bring the neurocardiovascular system closer to its physiological limit, requiring a smaller orthostatic challenge to activate the vasovagal reflex (i.e., hyper-reactivity), increasing susceptibility to syncope. The lack of correspondence between cerebral oxygenation and SBP might indicate that cerebral autoregulation is preserved in patients with VVS, although further research is required to better understand whether CA and other regulators of cerebral oxygenation such as CO₂ partial pressure (PaCO₂) could be altered in VVS patients, leading to the responses observed [417].

Limitations

Firstly, challenges exist in NIRS interpretation, as it is unclear what proportion of the NIRS signal corresponds to arterial, venous or capillaries blood, although it is believed that the main contribution comes from the venous circulation [417]. Furthermore, NIRS only measures a small region of the prefrontal cortex, therefore other regions of the cerebral circulation are not captured. Methodological limitations of NIRS must also be considered, such as extracerebral contamination, the differences in tissue morphology captured, the thickness of extracerebral layers, and its susceptibility to motion artifacts [185, 189, 416]. Finally, the lack of CO₂ measures must be noted.

CO₂ is one of the strongest vasoactive molecules that affect the cerebrovasculature and CA [415, 417], with an increase in PaCO₂ resulting in an increase in cerebral blood flow. Thus, it remains unclear whether the results found could be attributed to changes in PaCO₂ that could occur in case of postural hyperventilation [124, 125].

Strengths

This study also has a number of strengths. Firstly, an AS was used instead of the commonly utilised head-up tilt test to study a population with syncope. The AS test provides a simpler and faster way of assessing the cerebrovascular regulation of brain perfusion upon an orthostatic challenge [432]. Furthermore, the application of NIRS in this context is novel and provides a wider picture of an individual's physiology. Correction for BP has also been applied, which allows investigating the extent of its driving effect. Relative changes from baseline were investigated, a more accurate and reliable measure when compared to absolute values of NIRS derived signals. Furthermore, the influence of duration of lying and speed of standing were examined, which have been previously demonstrated to influence the responses to an AS [407], but did not alter the results obtained.

Conclusion

Young VVS patients demonstrate an equivalent cerebral oxygenation response during an AS in overall cerebral tissue oxygenation when compared to healthy controls, although differences in the initial $\Delta[\text{HHb}]$ responses were noted. These were accompanied by an exaggerated BP recovery, which may be due to a hyper-reactive autonomic nervous system, supporting previous evidence of this theory. This study furthers our understanding of cerebral oxygenation in VVS and motivates future

research to unveil the role of cerebral perfusion regulation in maintaining cerebral oxygenation during standing in VVS.

Chapter 8: Increased Multimorbidity is Associated with Impaired Cerebral and Peripheral Haemodynamic Stabilisation during Active Standing

In this Chapter a cohort of older patients (≥ 50 years) attending a national Falls and Syncope Unit was investigated. A morbidity count was derived from self-reported clinical history of patients to study the association of multimorbidity with cerebral oxygenation responses to an active stand (AS) in these patients. The value of NIRS in the assessment of the neurocardiovascular system in falls and syncope patients is consequently investigated in this Chapter. Furthermore, the dependency of the cerebral oxygenation responses with BP was studied. Understanding whether multimorbidity (as an index of frailty) is linked to impairments in cerebral oxygenation during standing can be helpful in identifying vulnerable patients at risk of repeated episodes of hypoperfusion, potentially aiding in the prevention of related negative outcomes.

The study presented in this chapter has led to the following peer-reviewed publication [433]:

Pérez-Denia L, Claffey P, Byrne L, Rice C, Kenny RA, Finucane C. *Increased multimorbidity is associated with impaired cerebral and peripheral hemodynamic stabilization during active standing. Journal of the American Geriatrics Society. 2022 May 10. doi: 10.1111/jgs.17810. Epub ahead of print. PMID: 35535653.*

8.1 Introduction

Age-related conditions commonly experienced by older populations including falls [29], hypertension [434], cognitive impairment [435] and depression [298], are associated with impaired orthostatic peripheral hemodynamics such as delayed blood pressure (BP), impaired heart rate (HR) recovery, and orthostatic hypotension (OH). Frailty, often defined as a count of morbidities, has been consistently associated with neurocardiovascular dysregulation, characterized by blunted compensatory HR and BP responses after active standing [33, 42]. Current hypotheses suggest that hypoperfusion related deficits in cerebral oxygenation play a pivotal role in the aetiology of age-related conditions. However, to date, little is known about transient cerebrovascular haemodynamics during standing, particularly in frailer older patients with multimorbidity.

Near-infrared spectroscopy (NIRS) measures of cerebral oxygenation have recently emerged as objective surrogates of cerebral perfusion, suitable for clinical testing of dynamic cerebrovascular haemodynamics during standing [40, 417]. While impairments in cerebral oxygenation recovery have been associated with OH [261], syncope [257], depression [307] and postural instability [41] in older adults, the relationship between cerebral oxygenation responses and multimorbidity remains largely unexplored [311], especially in clinical cohorts.

During dynamic BP transient stressors such as standing, cerebral oxygenation is expected to decrease and then recover due to contributions of peripheral BP and stroke volume (SV) recovery, and the active regulation of cerebral autoregulation (CA), amongst other factors [98]. Despite the strong influence of BP, whether impairments in cerebral oxygenation reported in age related conditions are independent of BP, SV and total peripheral resistance (TPR) remains largely unknown. Furthermore while

peripheral hemodynamic impairments [217], multimorbidity [436], frailty [437] and orthostatic intolerance [438] are known to be increased in older women, no studies have examined the interaction between multimorbidity, sex and cerebrovascular responses in clinical cohorts.

Given the recognized associations between age-related conditions and impairments in both peripheral and cerebral responses to standing, we hypothesize that multimorbidity is accompanied by impairments in both of these responses during orthostatic challenges. Therefore, this study addresses the following research questions in a clinical cohort of older patients presenting with syncope and falls: 1) is multimorbidity associated with impaired peripheral haemodynamics during an AS test? 2) is multimorbidity associated with impaired cerebral oxygenation responses during an AS test independent of peripheral haemodynamics? and 3) does sex modulate these relationships?

8.2 Methods

Setting and patients

Consecutive patients were recruited prospectively from a national Falls and Syncope Unit (FASU) based at St. James's Hospital in Dublin, Ireland, with patients referred to the clinic from the emergency department and general practitioner services for investigation of episodes of dizziness, falls or syncope. The study had ethical approval from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08,CA,16).

Inclusion and exclusion criteria

Patients aged 50 years and over attending the FASU were included in this study. Patients were excluded if they were unable to provide informed consent, had a previous

diagnosis of cognitive impairment, or had any contraindication to perform an AS (e.g., mobility issues, severe pain).

Multimorbidity

Multimorbidity was measured as a count of self-reported morbidities within a 26-item scale collected from a comprehensive medical history, which included the presence or absence of the following: cardiovascular 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 apnea, chronic obstructive airway disease, and endocrine diseases). A recent (in last year) history of all-cause falls and syncope was also included.

Active stand testing

Protocol

All patients underwent an AS test as per standard international protocol [71]. Following a 5–10-minute signal calibration and stabilization period, patients were instructed to stand up quickly and remain standing quietly for 3 minutes. Assistance was provided during the test as required, and the test was terminated early if patients developed symptoms of severe orthostatic intolerance.

Equipment

Cerebral oxygenation was measured using a PortaLite NIRS monitor, (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands), which provides continuous values of tissue saturation index (TSI) (units of percentage, %) [39]. The

probe was placed on the left side of the forehead, i.e., centered at 3cm lateral and 3.5cm above the nasion [406], and secured with an opaque bandage. A Finometer NOVA (Finapres Medical Systems, Amsterdam, The Netherlands) was used concurrently to measure continuous beat-to-beat systolic BP (SBP), diastolic BP (DBP), and HR, and ModelflowTM derived TPR and SV. A finger cuff was placed on the middle or proximal phalanx of a finger (as per manufacturer instructions) on the left hand. Calibration was performed using brachial artery BP measurements and PhysiocalTM, while hydrostatic pressures differences were corrected for using the system's height correction unit.

Covariates

A comprehensive medical history was recorded which included age (years), sex, weight (kg), height (m), and body mass index (BMI, kg/m²). Behavioural health including smoking status (non-smoker, current smoker or ex-smoker) and history of excessive alcohol intake (>14 units/week for females, >21 units/week for males) was also captured. A detailed medication record was also taken (using the ATC classification system) at the time of testing, including key cardioactive medications: antihypertensives (C0, C0C-CC, C07), and antidepressants (N06A). Finally, medical conditions encompassing the multimorbidity count (see above) were also recorded.

Data analysis

Data quality

Patients with incomplete clinical information were excluded from analyses. BP, HR and TSI signals were visually inspected and screened for signal quality following a pre-established set of criteria, with poor signals not included in further analyses.

Signal Processing

SBP, DBP, HR, TPR, SV and TSI signals were analyzed with custom software developed in MATLAB R2019a (The Math Works, Inc., MATLAB, Version 2019a,

Natick, MA) applying a standardized analytical process [71, 427]. The Finometer height correction signal was used to derive the time of stand, standing speed [407], and the supine rest duration was estimated as the duration of the recording before the stand.

Features extracted from the AS stand responses are detailed in Figure 8.1 (see Appendix J: Supplementary Text A.J.1 and Supplementary Table A.J.1 for more specific details). A resting baseline (average [-60,-30] seconds before standing), value at 30 seconds and steady-state (average from [60,120] seconds) values were obtained [71]. For TSI, BP and TPR signals, nadir and overshoot values were defined, while for HR and SV the maximum and subsequent minimum were extracted [427]. The average recovery rate from nadir to overshoot (or maximum and minimum for HR/SV) was also derived for all signals. Values at nadir (maximum for HR/SV), overshoot (minimum for HR/SV), 30s, and steady-state are reported as absolute changes from baseline, unless otherwise indicated. Absolute values for TPR, SV and TSI are considered less accurate and therefore are not reported here [193, 439]. Additional features were derived and are reported in the Supplementary Material in Appendix J.

Statistical analysis

RStudio was used to perform all statistical analyses (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). Histograms, Q-Q plots and Shapiro-Wilk tests were implemented to assess normality of the data. Differences in patients characteristics were tested using t-tests for normally distributed variables (mean, standard deviation (SD)) and Mann-Whitney U tests for non-normal distributions (median, interquartile range (IQR)). A Chi-squared test was used for binary and categorical variables.

Multimorbidity was analysed as a continuous variable (please note groups with ≤ 2 and ≥ 5 morbidities were used for the purposes of displaying the data only). Robust

linear regression was employed to evaluate unadjusted and fully adjusted effects of multimorbidity on SBP, DBP, HR, TPR, SV and TSI as independent variables. Models were adjusted for age, sex, BMI, baseline SBP, baseline HR, standing speed, supine rest duration, smoking status (non-smoker, previous smoker, non-smoker), alcohol excess, and antihypertensives and antidepressants use. TSI models were further corrected by simultaneously measured peripheral hemodynamic features (e.g. when analyzing the TSI nadir, the model included the SBP/DBP/mean arterial pressure (MAP)/TPR/SV nadir feature as a covariate). Sensitivity analyses were performed in separate models to examine the effect of controlling for OH (drop from baseline >20 mmHg in SBP and/or >10 mmHg in DBP) at 30 seconds and sustained OH. Analyses repeated after sex stratification. A false discovery rate (FDR) procedure was used to correct for multiple testing effects. A p-value <0.05 was considered significant.

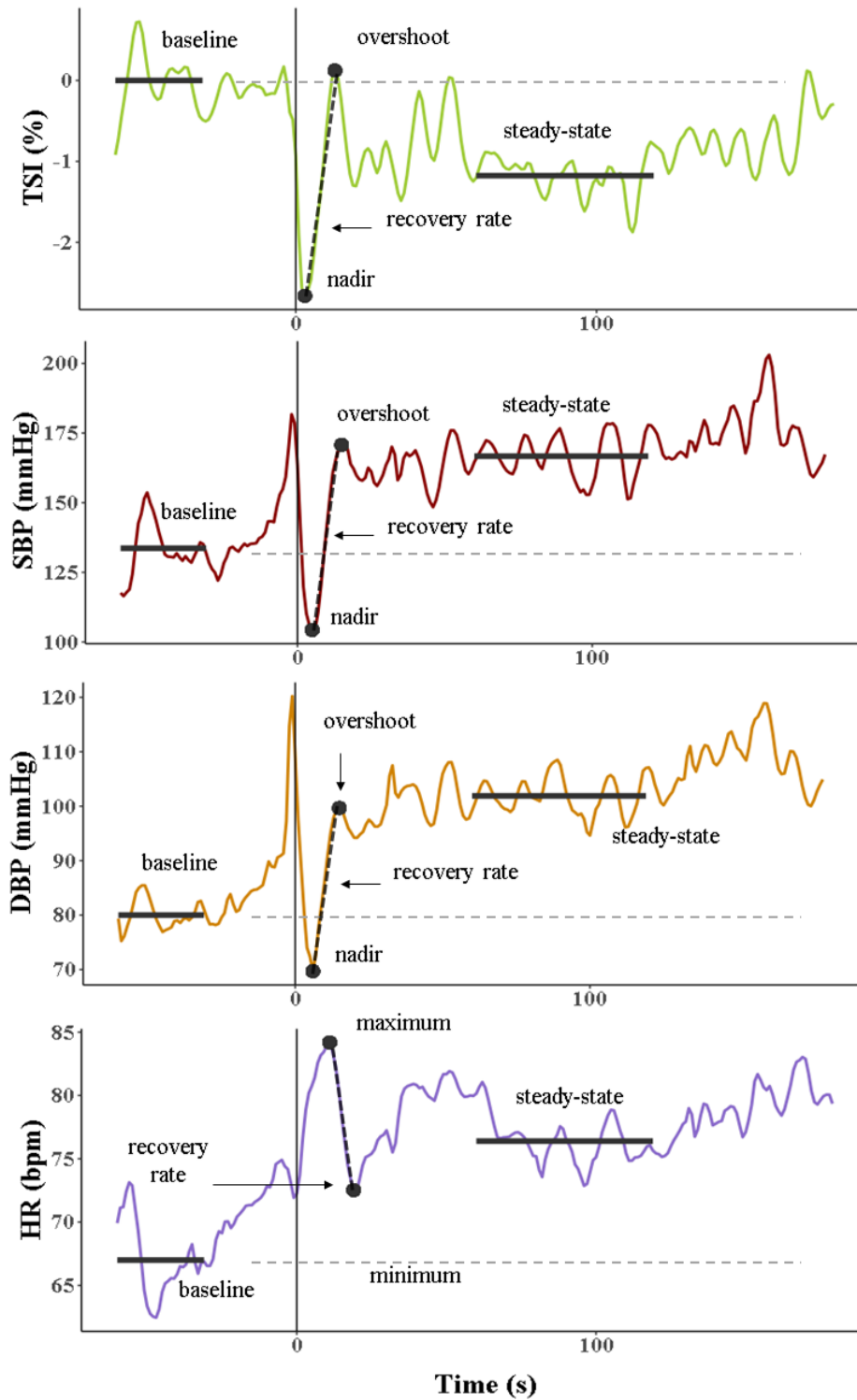


Figure 8.1. Features extracted from cerebral (TSI) and peripheral (SBP, DBP, HR) responses to an active standing test in a selected patient.

Features extracted from the signals have been indicated. DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure, TSI = tissue saturation index. Note that time is in seconds, and both TSI/SBP/DBP nadir and HR maximum occur within 15 seconds of standing ($t = 0$).

8.3 Results

Patients' characteristics

A total of 351 patients were recruited. After screening for signal quality, 303 patients remained, aged 71(15) years (57% females), with a BMI of 27(6) kg/m² (Table 8.1). Cardiovascular diseases, neurological and psychological disorders were present in 76%, 17%, and 25% of patients, respectively. Almost half of the patients had experienced syncope in the last year, with 34% reporting a fall. Polypharmacy was common, with patients prescribed 5(4) medications; 52% of patients were taking antihypertensives, and 24% antidepressants.

After sex stratification, a higher proportion of females reported a recent fall (f:40% vs m:27%, $p = 0.020$) (Table 8.1). More males were either current (f:21% vs m:43%, $p < 0.001$) or past smokers (f:8% vs m:17%, $p = 0.027$), with males also reporting higher rates of alcohol excess (f:3% vs m:29%, $p < 0.001$).

Figure 8.2 shows the group averages for TSI, SBP, DBP, and HR across 2 levels of accumulated morbidities (groups with ≤ 2 morbidities (lowest tertile) and ≥ 5 morbidities (highest tertile), were used only for the purpose of displaying the data, multimorbidity was analysed as a continuous variable). Females had a significantly smaller TSI drop at nadir (f:-1.71(1.67) vs m:-2.41(2.07), $p = 0.015$) and a slower recovery rate (f:0.19(0.16) vs m:0.23(0.19), $p = 0.005$) (Figure 8.2, Table 8.2, Appendix J: Supplementary Table A.J.2). Females recovered more quickly to higher SBP and DBP values (Figure 8.2, Table 8.2, Appendix J: Supplementary Table A.J.2). No significant sex differences were observed in HR responses. Furthermore, females recovered to higher TPR values while they had lower SV recovery values (Appendix J: Supplementary Figure A.J.1, Table 8.2, Appendix J: Supplementary Table A.J.2). Regarding absolute values, only a higher SBP steady-state value in females was

identified to be different between both sexes (Appendix J: Supplementary Figure A.J.2 and Table S3).

Table 8.1. Patients' characteristics.

Characteristic	All (n = 303)	Females (n= 173)	Males (n = 130)	p-value [^]
Age, years (median, IQR)	71 (15)	71 (15)	71 (12)	0.830
Weight, kg (median, IQR)	74 (23)	67 (20)	84 (19)	<0.001***
Height, m (mean, SD)	166 (10)	160 (7)	174 (7)	<0.001***
Body Mass Index, kg/m ² (median, IQR)	27 (6)	26 (8)	27 (5)	0.135
Cardiovascular diseases, % (n)	76 (231)	75(129)	79 (102)	0.430
Neurological disorders % (n)	17 (51)	16 (28)	18 (23)	0.729
Psychological disorders, % (n)	25 (75)	27 (47)	22 (28)	0.261
Vestibular disorders, % (n)	8 (23)	9 (16)	5 (7)	0.209
Other conditions, % (n)	30 (92)	34 (59)	25 (33)	0.102
Syncope, % (n)	47 (142)	45 (77)	50 (65)	0.343
Falls, % (n)	34 (104)	40 (69)	27 (35)	0.019*
Multimorbidity (count of morbidities), n (median (IQR)	3 (3)	3(2)	3(3)	0.139
Smoking status (n = 11 missing)				
Non-smoker, % (n)	57 (168)	70 (118)	40 (50)	<0.001***
Current smoker, % (n)	31 (90)	21 (36)	43 (54)	<0.001***
Ex-smoker, % (n)	12 (35)	8 (14)	17 (21)	0.027*
Excess of alcohol intake, %(n) (n = 1 missing)	14 (42)	3 (5)	29 (37)	<0.001***
Medication				
Antihypertensives, % (n)	52 (157)	51 (89)	52 (68)	0.882
Antidepressants, % (n)	24 (72)	29 (50)	17 (22)	0.015*
Total number of medications, median (IQR)	5(4)	5 (5)	5(5)	0.817
Baseline features				
Baseline SBP, mmHg (median, IQR)	144 (27)	145 (29)	144 (27)	0.714
Baseline DBP, mmHg (median, IQR)	82 (13)	81 (14)	83 (11)	0.222
Baseline HR, bpm (median, IQR)	71 (16)	72 (15)	70 (17)	0.045*

[^]P-values represent differences between males and females. **p***<0.05, **p****<0.01, **p*****<.001. IQR = interquartile range, SD = standard deviation, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

All patients

Multimorbidity was associated with impaired cerebral oxygenation recovery at 30 seconds (β :-0.15, CI:(-0.25,-0.06), $p = 0.009$) (Figure 8.3, Appendix J: Supplementary Table A.J.4) even after peripheral haemodynamics adjustment (Appendix J: Supplementary Table A.J.5 – A.J.9).

Multimorbidity was also associated with delayed DBP recovery at 30 seconds (β : -1.34, CI:(-2.29, -0.40), $p = 0.032$) and a lower steady-state DBP (β : -1.18, CI:(-2.04, -0.32), $p = 0.032$) (Figure 8.3, Appendix J: Supplementary Table A.J.4). While a similar pattern was observed in SBP, none of these effects remained after correcting for covariates.

Multimorbidity was associated, after adjustment, with attenuated HR responses, characterized by a lower maximum HR (β :-0.70, CI:(-1.25,-0.15), $p = 0.029$), lower HR minimum (β :-0.75, CI:(-1.28,-0.22), $p = 0.027$) and a lower HR at 30 seconds (β : -0.63, CI:(-1.10 -0.16), $p = 0.027$) after standing (Figure 8.3, Appendix J: Supplementary Table A.J.4). Multimorbidity was also associated with a smaller TPR overshoot-to-nadir difference (β :-0.041, CI:(-0.070,-0.013), $p = 0.045$) and a higher value in SV at 30 seconds (β :1.30, CI:(0.45,2.15), $p = 0.027$) (Figure 8.3, Appendix J: Supplementary Figure A.J.2 and Appendix Supplementary Table A.J.4).

Finally, when examining absolute values, multimorbidity was associated with deficits in DBP only (Appendix J: Supplementary Figure A.J.2 and Supplementary Table A.J.12).

Table 8.2. Average values for TSI, SBP, DBP and HR features analysed for all patients, females and males, comparing differences between sex. Nadir, maximum, overshoot, minimum, value at 30s and steady-state values represent changes from baseline.

	All patients (n = 303)	Females (n = 173)	Males (n = 130)	FDR p- value [^]
TSI (%)				
TSI nadir, med (IQR)	-1.91 (1.67)	-1.71 (1.67)	-2.41 (2.07)	0.015*
TSI overshoot, med (IQR)	0.12 (1.3)	0.09 (1.3)	0.14 (2.22)	0.379
TSI recovery rate, med (IQR) ⁺	0.21 (0.16)	0.19 (0.16)	0.23 (0.19)	0.005**
TSI at 30 at seconds, med (IQR)	-0.76 (1.52)	-0.82 (1.52)	-0.72 (1.55)	0.357
TSI steady-state, med (IQR)	-1.09 (1.79)	-1.19 (1.79)	-1.0 (2.12)	0.104
SBP (mmHg)				
SBP nadir, med (IQR)	-31.94 (21.64)	-31.94 (21.64)	-31.96 (24.63)	0.839
SBP overshoot, m (SD)	1.38 (25.81)	1.42 (25.81)	1.24 (34.1)	0.839
SBP recovery rate, med (IQR) ⁺	2.91 (2.00)	2.9 (2.00)	2.94 (2.19)	0.839
SBP at 30 seconds, m (SD)	-2.02 (27.35)	-0.96 (27.35)	-4.08 (26.92)	0.130
SBP steady-state, m (SD)	4.81 (21.78)	6.54 (21.78)	1.46 (17.83)	0.027*
DBP (mmHg)				
DBP nadir, med (IQR)	-17.38 (16.15)	-15.27 (16.15)	-21.23 (17.12)	0.007**
DBP overshoot, m (SD)	2.51 (17.95)	4.50 (17.95)	0.60 (18.08)	0.009**
DBP recovery rate, med (IQR) ⁺	1.77 (1.19)	1.80 (1.19)	1.74 (1.12)	0.371
DBP at 30 seconds, m (SD)	1.62 (16.87)	3.72 (16.87)	-2.11 (15.14)	<0.001***
DBP steady-state, m (SD)	6.07 (15.03)	8.72 (15.03)	2.11 (13.32)	<0.001***
HR (bpm)				
HR maximum, med (IQR)	14.65 (9.1)	15.24 (9.1)	13.18 (10.52)	0.272
HR minimum, med (IQR)	5.8 (7.9)	6.29 (7.9)	5.19 (9.64)	0.479
HR recovery rate, med (IQR) ⁺	-1.11 (1.55)	-1.21 (1.55)	-0.99 (2.52)	0.643
HR at 30 seconds, m (SD)	6.35 (7.45)	6.24 (7.45)	6.46 (8.68)	0.389
HR steady-state, med (IQR)	7.05 (7.41)	6.9 (7.41)	7.36 (8.16)	0.920
TPR (mmHg·min/L)				
TPR nadir, med (IQR)	-0.52 (0.52)	-0.53 (0.52)	-0.5 (0.37)	0.562
TPR overshoot, med (IQR)	0.13 (0.54)	0.24 (0.54)	0.01 (0.41)	<0.001***
TPR recovery rate, med (IQR) ⁺	0.05 (0.04)	0.05 (0.04)	0.04 (0.03)	<0.001***
TPR at 30 seconds, med (IQR)	0.11 (0.49)	0.20 (0.49)	-0.06 (0.38)	<0.001***
TPR steady-state, med (IQR)	0.15 (0.49)	0.23 (0.49)	0.06 (0.34)	<0.001***
Stroke volume (ml)				
SV maximum, med (IQR)	7.80 (20.63)	4.44 (20.63)	13.63 (26.20)	<0.001***
SV minimum, med (IQR)	-7.90 (11.73)	-8.62 (11.73)	-5.25 (20.11)	0.033*
SV recovery rate, med (IQR) ⁺	-2.03 (1.67)	-1.86 (1.67)	-2.46 (2.29)	<0.001***
SV at 30 seconds, med (IQR)	-8.80 (11.01)	-9.28 (11.01)	-7.34 (16.23)	0.070
SV steady-state, med (IQR)	-9.62 (12.14)	-10.27 (12.14)	-7.70 (17.29)	0.046*

[^]P-values resulting from t-test or Mann Whitney U test (for normal and non-normal distributions, respectively) comparing females vs males populations. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ⁺recovery rates are expressed in units of the signal/seconds. False discovery rate (FDR) corrected p-values are also reported. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume, m (SD) = mean (standard deviation), med (IQR) = median (interquartile range).

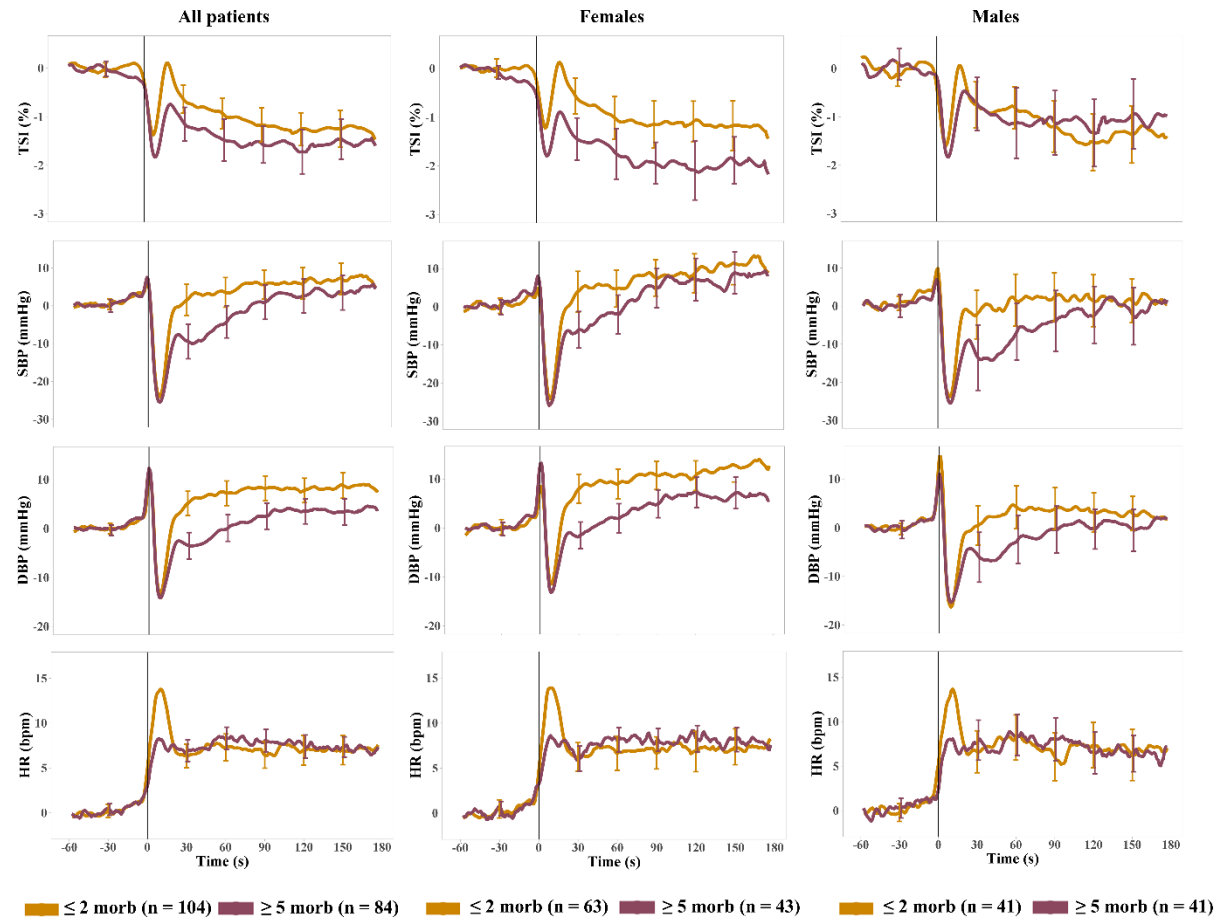


Figure 8.2. Cerebral and peripheral haemodynamic responses to the active stand test.

Absolute drops from baseline for cerebrovascular (TSI) and cardiovascular (SBP, DBP, HR) haemodynamics for all patients (left), females (middle) and males (right) during the active standing test for patients accumulating 2 or less morbidities (orange) and 5 or more morbidities (purple) (note that these categories were used only for the purpose of displaying the data, multimorbidity was analysed as a continuous variable). Multimorbidity was associated with impaired TSI and DBP recovery, and an attenuated HR response in all patients and in the females cohort, while no associations were observed in males (after covariates adjustment). The start of the test has been indicated with a vertical line at $t = 0$. Error bars represent the confidence intervals of the mean at $t = -30, 30, 60, 90, 120$ and 150 seconds after standing. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, morb = morbidities.

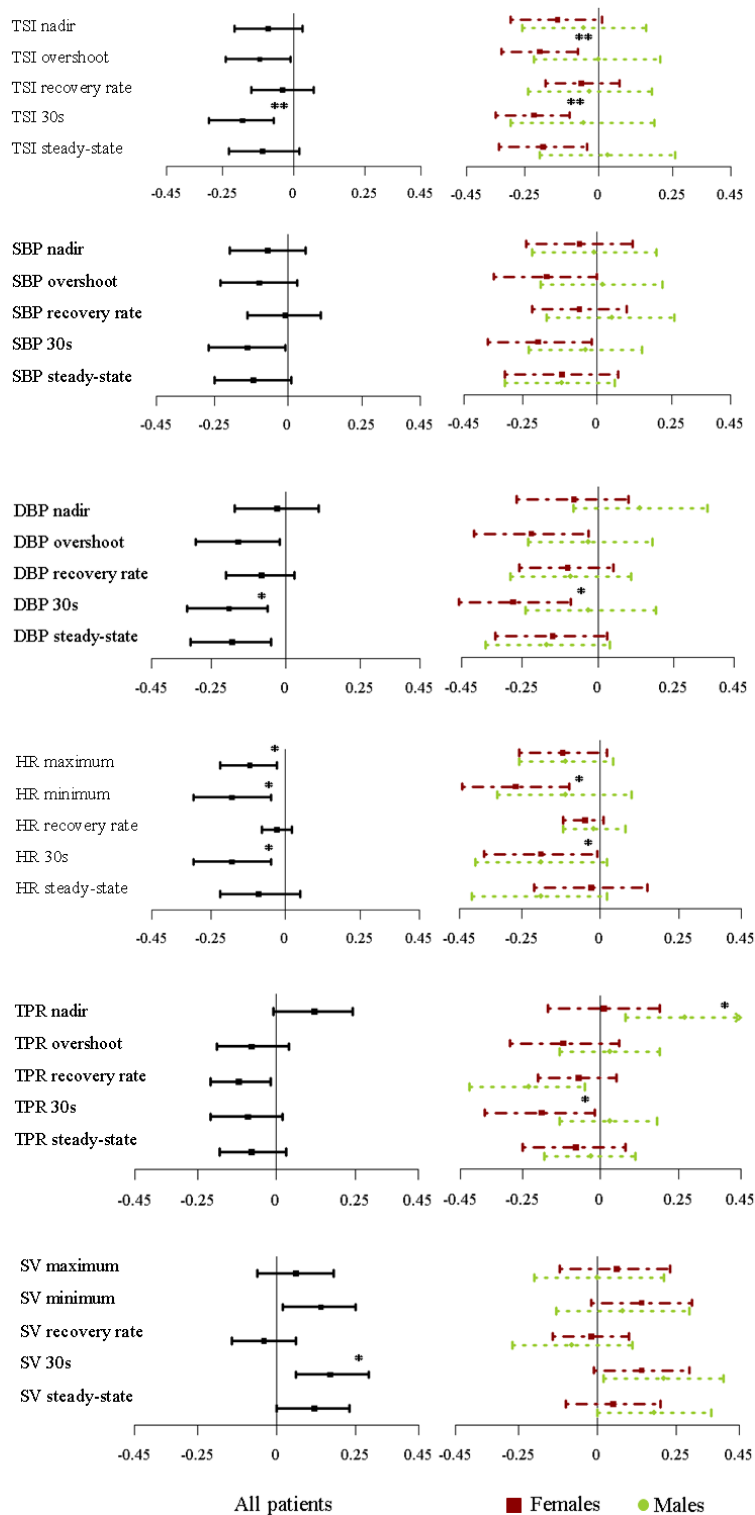


Figure 8.3. Graphical representation of the results obtained from multivariate linear regression analyses.

Forest plot representing standardized β coefficients and confidence intervals for the association of multimorbidity and the different features derived from TSI, SBP, DBP, HR, TPR and SV for all patients (left), females (right, red squares) and males (right, green circles) in the multivariate model adjusting for: age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate. * indicates p -value < 0.05 and ** p -value < 0.01 after multiple comparison correction.

Sex Differences

Females

In females, multimorbidity was associated with lower TSI at overshoot (β : -0.19, CI: (-0.32,-0.07), $p = 0.009$), 30 seconds (β :-0.22 (-0.35,-0.10), $p = 0.005$) and during steady-state (β : -0.20, CI:(-0.35 -0.04), $p = 0.023$) (Figure 8.3, Appendix J: Supplementary Table A.J.10), independent of SBP, DBP, MAP, TPR and SV (Appendix J: Supplementary Table A.J.5 – A.J.9). Multimorbidity was also associated with impaired DBP recovery at 30 seconds (β : -2.04, CI:(-3.41, -0.68), $p = 0.027$) after standing after adjustment, with similar effects noted in SBP recovery patterns at a univariate level only (Figure 8.3, Appendix J: Supplementary Table A.J.10).

HR features were also significantly impaired in multimorbidity, with females demonstrating lower HR minima with higher multimorbidity (β : -1.14, CI:(-1.86,-0.42), $p = 0.018$) (Figure 8.3, Appendix J: Supplementary Table A.J.10). Lastly, while univariate associations were observed between multimorbidity and TPR and SV, they did not remain significant after adjusting for covariates (Figure 8.3, S Appendix J: Supplementary Figure A.J.1 and Supplementary Table A.J.10).

In females, multimorbidity was not associated with differences in absolute values for any of the signals analysed (Appendix J: Supplementary Figure A.J.2 and Supplementary Table A.J.13).

Males

Cerebral oxygenation indices were not significantly associated with multimorbidity in males. Multimorbidity was associated with delayed DBP recovery at a univariate level only while it was not associated with any SBP features in males (Figure 8.3, Appendix J: Supplementary Table A.J.11). While a blunted HR response was also noted in males with higher multimorbidity (lower HR maximum), none of

these effects remained after correction. However, with increasing multimorbidity, men demonstrated a smaller TPR drop at nadir (β :0.046, CI:(0.014,0.078), $p = 0.034$), as well as a smaller overshoot-to-nadir difference (β :-0.040, CI:(-0.072,-0.008), $p = 0.034$) (Figure 8.3, Appendix J: Supplementary Figure A.J.1 and Supplementary Table A.J.11).

Multimorbidity was associated with lower absolute DBP steady-state values (Appendix J: Supplementary Figure A.J.2, and Supplementary Table A.J.14).

8.4 Discussion

This study presents a number of novel and clinically relevant findings: multimorbidity is associated with impairments in the initial recovery of TSI and peripheral hemodynamic responses to active standing in older patients, with effects most evident in females.

Our main result supports the hypothesis that impairments in cerebral perfusion accompany multimorbidity. Here we noted that cerebral oxygenation recovery at 30 seconds after standing was impaired in adults with more morbidities (β :-0.15%/morbidity), translating into a TSI change of 1.1% in adults accumulating 7 morbidities (~25% of the total count). This change is clinically relevant, given that a 5-10% TSI drop is associated with presyncope or loss of consciousness [440]. Maguire et al. similarly reported impaired cerebral oxygenation recovery with increasing levels of frailty (measured as an index of morbidities and deficits in activities of daily living) at 20-27 seconds after standing in a population sample of community-dwelling adults (mean(SD): 64.4(7.7) years) [311]. In a large study of patients undergoing head-up tilting (median(IQR): 40(35) years), Jedrzejczyk-Spaho et al. also demonstrated that having multiple comorbidities was associated with larger TSI drops [312].

On initial inspection, impaired cerebral oxygenation may suggest that CA is impaired in multimorbidity. However, with a CA impairment one would expect TSI to

follow BP drops, while intact CA would counteract BP drops. If multimorbidity resulted in impaired CA, we would expect that correcting for the effects of BP would attenuate or even eliminate the associations found between TSI and multimorbidity. This was not the case here, with TSI impairments remaining unattenuated after BP adjustment (Appendix J: Supplementary Table A.J.5, A.J.6 and A.J.7). Thus, our results indicate that the deficits in TSI recovery may not be attributed to impaired CA. CA is a complex, nonlinear and multifactorial mechanism and thus more advanced models are likely necessary to better understand the relationship between multimorbidity and CA. Other mechanisms of cerebral oxygenation regulation must therefore be considered, e.g. decreases in CO₂ partial pressure (PaCO₂), which could be induced due to postural hyperventilation and lead to a reduced cerebral perfusion and oxygenation [124, 125]. We also tested the hypothesis that SV might be driving the cerebral oxygenation impairments observed [441], but adjusting for SV did not alter the results.

In this study, we identified for the first time, to our knowledge, significant impairments in TPR and SV mostly univariately (especially in males), which may underlie the impairments observed in BP. Moloney et al. demonstrated a univariate association between different BP recovery groups and the prevalence of multimorbidity in a population of community-dwellers (mean(SD) age: 61.0(8.8) years) [442]. Conversely, Lagro et al. reported an equivalent level of multimorbidity between three SBP recovery groups in 238 falls patients (mean(SD) age: 78.4(7.8) years)[443], although their multimorbidity scale was more exhaustive than ours. Capturing a broader range of morbidities may have masked underlying differences in cardiovascular multimorbidity, which may ultimately be the driver of the observed BP differences. Lastly, our finding of impaired BP and HR recovery with multimorbidity agrees with previous studies investigating frailty indices [33, 43, 44, 309, 311], suggesting that our

multimorbidity scale captures key frailty factors contributing towards peripheral circulation impairment, and is likely an appropriate surrogate for frailty in the context of falls and syncope patients. Furthermore, we have found the strongest associations during the recovery period (30 seconds), which encourages the use of newly developed definitions such as delayed BP recovery [29] over more classic definitions such as initial OH or classical OH.

After sex stratification, an association between increased multimorbidity and lower TSI independent of peripheral haemodynamics was identified in females at 30 seconds after standing, suggesting that cerebral oxygenation is not passively following BP. In males, similar but weaker trends may support a similar hypothesis, but the alternative hypothesis may also apply. Maguire et al. identified differences in TSI between males and females during the first 30 seconds after standing [311], and Jedrzejczyk-Spaho et al. found lower values of TSI during a HUT in females than in males in their cohort of patients with suspected syncope [312]. Interestingly, resting cerebral perfusion is known to be higher in healthy females [444], with CA often preserved in this cohort [241]. However, studies investigating these differences have not considered the modulating effect of multimorbidity. The reasons why cerebrovascular responses to orthostasis are more affected by multimorbidity in females than in males remain unclear. However, these sex differences are in line with a well described lower tolerance to orthostatic challenges in females [234]. It is also noteworthy to highlight the higher proportion of patients with a history of falls in females (42% in females vs 29% in males, $p = 0.016$). These results might suggest that frailer females are more prone to the effects of cerebral hypoperfusion and consequently syncope and falls, although further research is needed to confirm the causality of this relationship.

A number of hypotheses may explain our results. The impairments identified here in cerebral circulation may result from the cumulative effect of sub-components of multimorbidity such as atrial fibrillation [445], heart failure [446], stroke [447], small vessel disease [448], hypertension [283], depression[307], and falls [41], which are all associated with impaired cerebral perfusion. Conversely, transient deficits in perfusion may lead to brain and end organ damage, contributing to the development of new morbidities. Previous work has shown that cerebral hypoperfusion is associated with hypoxia induced cerebral tissue damage [449], which may accelerate progression of depression, cognitive impairment, or dementia through hypoperfusion related neurodegenerative changes. Regarding peripheral haemodynamics, baroreflex impairment [217], increased arterial stiffness [450] or reduced muscle pump [124] resulting from the cumulative effect of coexisting morbidities may mechanistically underlie the observed TPR, SV and HR impairments. This may ultimately reduce BP and cerebral oxygenation and contribute to orthostatic intolerance symptoms and postural instability [41], increasing the likelihood of negative outcomes such as falls and syncope. In our study, adjusting the cerebral oxygenation features by concurrent peripheral signals did not eliminate TSI differences, suggesting that the impairments in cerebral oxygenation observed are partially independent of peripheral circulation. Correction was performed using separate analyses considering either the concurrent BP values or the presence of delayed BP recovery and OH (not reported). Similar results were obtained in both analyses.

Limitations

A number of limitations need to be considered. Firstly, we studied a population of patients attending a FASU. Secondly, the accumulation of morbidities in our population was skewed, with only 31 participants (10%) accumulating more than 25%

of the morbidities recorded, but this is comparable to community-dwelling populations[451]. The moderate levels of multimorbidity observed here were sufficient to highlight cerebral oxygenation impairments, although increasing the number of patients with high levels of multimorbidity may increase the study power to detect changes in SPB, TPR and SV. Additionally, our multimorbidity scale included 26 deficits. Covering more morbidities could enhance our ability to capture the multi-system aspects of multimorbidity, especially given that our scale has a cardiovascular bias (~60%). The lack of PaCO₂ measurements is also an important limitation, given its strong vasoactive action on the cerebrovasculature [415], therefore limiting our ability to fully understand the pathophysiology underlying our results. Finally, the interpretation of NIRS derived signals is challenging, with the venous and arterial contribution to the signal remaining unclear [417]. A number of factors influence the interpretation of absolute TSI values, including extracerebral tissue contamination, motion artifacts, underlying tissue heterogeneity and skull and cerebrospinal fluid thickness [185, 189, 416]. Here we only interpreted relative changes in TSI given the challenges of interpreting absolute values of NIRS. Furthermore, NIRS only captures a small region of the prefrontal cortex circulation, thus not accounting for differences in blood flow redistribution throughout the cerebral tissue.

Strengths

To our knowledge, this is the first clinical study to investigate the role of multimorbidity on the cerebral oxygenation responses to standing as measured by NIRS in a population of older patients with a wide range of ages (50-95 years). We have identified novel biomarkers of multimorbidity during the initial transient part of the cerebral oxygenation response to standing. In addition, we have separated our population by sex, which has allowed us to identify major differences in their

cardiovascular and cerebrovascular responses to standing and how they are associated with multimorbidity. A further novel contribution is the adjustment for BP and other peripheral signals, which demonstrated that the deficits in cerebral oxygenation found are independent of such signals.

Conclusion

NIRS derived cerebral oxygenation recovery during standing is impaired with multimorbidity (frailty) (particularly females), independent of BP, TPR and SV. TSI responses may represent new biomarkers for identifying multimorbidity in clinical populations. Clinical interventions targeting improvements in both peripheral and cerebral haemodynamics, and the use of readily applicable systems like NIRS may prove valuable in the future management of older adults with multimorbidity, potentially reducing poor health outcomes like faints and falls, and improving their quality of life. Similarly, interventions to reverse or prevent multimorbidity may prevent the development of cerebral hypoperfusion and its associated negative health outcomes.

Chapter 9: Clinical Decision Support for Unexplained Falls and Syncope Management: A Novel Explainable Machine Learning Approach

This study presented in this Chapter addresses the research questions 10-12 outlined in Chapter 4 of this thesis. There is a gap in the literature regarding the use of artificial intelligence/machine learning methods applied to the classification of patients with falls and syncope using blood pressure and cerebral haemodynamic signals. Furthermore, given that the previous Chapter (Chapter 8) demonstrated the importance of considering multimorbidity when investigating orthostatic cerebral oxygenation responses in older patients, multimorbidity is further incorporated as a predictor in the models. This Chapter represents the first steps towards developing a clinical decision support tool for an easy identification and management of individuals with unexplained falls (UF) and syncope.

This chapter will lead to the following publication:

Pérez-Denia L, Claffey P, Byrne L, Rice C, Kenny RA, Finucane C. *Clinical Decision Support for Unexplained Falls and Syncope Management: A Novel Explainable Machine learning approach.*

9.1 Introduction

One in three adults over the age of 65 years fall at least once annually [15]. Falls, and in particular UF, tend to overlap with syncope in older adults [62] with often common underlying cardiovascular causes [13]. UF and syncope are often attributed to a period of cerebral hypoperfusion associated with a concurrent transient hypotensive episode [1], and are associated with patterns of delayed blood pressure recovery at 40 seconds after standing [29] and orthostatic hypotension (OH) [273] during active stand (AS) testing. Moreover, a recent study demonstrated a trend towards an increased risk of falls in those with a pattern of impaired cerebral oxygenation after standing [41]. Importantly, falls are associated with frailty, with frailty associated with impaired peripheral [42] and cerebral [311] circulation.

Falls risk assessment and prediction have been extensively studied in the literature for decades [314], but it is only in recent years that artificial intelligence (AI)/machine learning (ML) algorithms have been employed for this purpose. Most of these studies have investigated all-cause falls [347, 368] but, to our knowledge, no studies have investigated subtypes of falls including UF. Previous studies have primarily used either gait, balance [45, 361] or medical history data [47, 359] as predictor variables. However, despite the predictive potential of blood pressure (BP) and brain perfusion patterns during AS [41, 42], no studies have used them in the design of classifiers to differentiate between fallers and non-fallers.

To address these challenges, a unique harmonised translational dataset was created from the combination of data collected from The Irish Longitudinal Study on Ageing (TILDA) and prospective clinical data obtained from patients attending a specialised national falls and syncope unit who underwent harmonised testing

protocols. Using this rich and unique dataset, AI/ML algorithms were explored for the first time in combination with near-infrared spectroscopy (NIRS) derived measures of cerebral oxygenation and continuous BP features recorded during an AS test to identify an individual's risk of UF, syncope, or UF or syncope (UFS). Specifically, the following research questions are addressed: 1) Can approaches applied to measures of cerebral and peripheral circulation be used to identify individuals with a history of UF and/or syncope? 2) Is the performance of these methods improved if both BP and cerebral measures are used? 3) Can classification performance be improved by adding medical history in the form of a morbidity count as a predictor?

9.2 Methods

Participants

Two unique datasets were harmonised. Firstly, a cohort of patients referred for falls, syncope and/or dizziness assessment were consecutively recruited from a national Falls and Syncope Unit (FASU). They were age and sex matched to a group of controls from wave 3 of The Irish Longitudinal Study on Ageing (TILDA), a national population study of community-dwelling adults who underwent a harmonised health assessment protocol. The study had ethical approval from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC:2018-08,CA,16) and the Faculty of Health Science Research Ethics Committee at Trinity College Dublin, Ireland (Main Wave 3 TILDA Study. Approved 9th June 2014).

Inclusion/Exclusion Criteria

Individuals aged 50 years and over were included in the study. FASU patients who had a history of an unexplained fall or syncope were selected from an initial sample. Patients were excluded if they were unable to provide informed consent, had a

previous diagnosis of cognitive impairment or Parkinson's disease, or had any contraindication to perform an AS test (e.g. mobility difficulties or severe pain). TILDA participants with cognitive impairment (defined as MOCA score ≤ 18) or a diagnosis of Parkinson's disease were excluded. From the remaining participants, a subset of 289 TILDA participants were age and sex matched with the patient group.

Outcome variables

Three different outcome variables were used: a history of UF, defined as a fall that has no apparent mechanical or accidental cause; a history of syncope, defined as a transient loss of consciousness; and a history of either UF or syncope (UFS). For each of the three outcome variables a subset of data was created that included these patient cases and their matched controls (see Figure 9.1).

Predictor Variables

Combinations of features extracted from the AS were used: only cerebral tissue saturation index (TSI) features, only systolic BP (SBP) features, and a combination of TSI and SBP features (TSI+SBP). Model training was run only considering haemodynamic features first, and then a morbidity count (described below) was included as a predictor and models were trained and re-evaluated.

Active Stand Protocol

All participants underwent the same AS protocol, consisting of a 5-10 minute supine rest period followed by a 3 minutes active standing as per international recommendations [3, 71]. Participants were asked to stand up as quick as possible and were provided assistance as needed. The test was terminated early if participants developed symptoms of severe orthostatic intolerance.

Tissue saturation index (TSI, units of %) as a measure of cerebral oxygenation was measured using a non-invasive near-infrared spectroscopy (NIRS) monitor (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands), placed on the left side of the forehead, approximately centred at 3 cm lateral and 3.5 cm over the nasion [406]. A Finometer NOVA (Finometer NOVA, Finapres Medical Systems, Amsterdam, The Netherlands) was used to continuously monitor beat-to-beat blood pressure.

Active Stand Feature extraction

Details on the feature extraction process, which follows a standardised analysis ([71, 427]), is described elsewhere (see

Chapter 5: General Materials and Methods). In summary, signals were initially visually screened for data quality. Mean and standard deviation values were obtained for baseline (-60 to -30 seconds before standing) and steady-state (60 to 120 seconds after standing) periods for TSI and SBP signals, with moving average values at 5, 10, 20, 30, 60, 90 and 120 seconds also obtained. All values are reported relative to the signal baseline. Furthermore, the initial nadir and subsequent overshoot values were derived, also reported relative to baseline, and a recovery rate was calculated as the largest value of the derivative between nadir and overshoot. Whether the overshoot was higher than the baseline was also used as a binary variable. Table 9.1 provides details of all the features derived. Custom software was developed in MATLAB R2021a (The Math Works, Inc., MATLAB, Version 2021a, Natick, MA) to implement this process.

Other covariates

Sex, age and BMI were recorded. The following harmonised self-reported medical conditions were recorded: transient ischemic attack, stroke, hypertension, angina, myocardial infarction, atrial fibrillation, other heart rhythm abnormalities, heart

failure, diabetes, cholesterol, other cardiac conditions, depression or anxiety, other psychological disorders, chronic obstructive airway disease and endocrine diseases (see Section 5.7. *Dataset Harmonisation and Other Covariates* for details on the harmonisation process). A morbidity count was derived from this list of morbidities. Cardioactive and psychogenic medications were also recorded.

Table 9.1. Features descriptions and abbreviations

Variable	Description	TSI Abbreviation	SBP Abbreviation
Baseline*	Mean value 30-60 s before standing	-	-
TSI Baseline SD	Standard deviation during the baseline period	TSI _{SD,B}	SBP _{SD,B}
Nadir	(Largest trough after standing (within 30 s)) - Baseline	Δ TSI _N	Δ SBP _N
Overshoot	(First peak found between 5 s after nadir and 60 s after standing) - Baseline	Δ TSI _O	Δ SBP _O
Overshoot – Nadir magnitude difference	Overshoot – Nadir	TSI _{N-O}	SBP _{N-O}
Overshoot – Nadir time difference	Overshoot time – Nadir time	TSI _{N-O,t}	SBP _{N-O,t}
Overshoot₀₁	Overshoot went over baseline (binary, 0 or 1)	TSI _{N-O,01}	SBP _{N-O,01}
Slope of recovery rate	Largest value of derivative of signal between nadir and overshoot	TSI _{SRR}	SBP _{SRR}
TSI/SBP slope of recovery rate⁺	TSI recovery rate / SBP recovery rate	TSI/SBP _{SRR}	
Drop at 5, 10, 20, 30, 60, 90, 120 s	Average values timepoints using a $\pm$ 2.5s moving average filter subtracted from baseline	Δ TSI ₅ , Δ TSI ₁₀ , Δ TSI ₂₀ , Δ TSI ₃₀ , Δ TSI ₆₀ , Δ TSI ₉₀ , Δ TSI ₁₂₀ ,	Δ SBP ₅ , Δ SBP ₁₀ , Δ SBP ₂₀ , Δ SBP ₃₀ , Δ SBP ₆₀ , Δ SBP ₉₀ , Δ SBP ₁₂₀ ,
Steady-state	(Mean SBP 60-120 s after standing) – Baseline	Δ TSI _{SS}	Δ SBP _{SS}
Steady-state SD	Standard deviation during the steady-state period	TSI _{SD,SS}	SBP _{SD,SS}

Tissue saturation index (TSI, units of %), systolic blood pressure (SBP, units of mmHg). ⁺ Units of %/mmHg. *Baseline values were not used as predictors in the models, but rather used to derive other features by deriving differences from baseline.

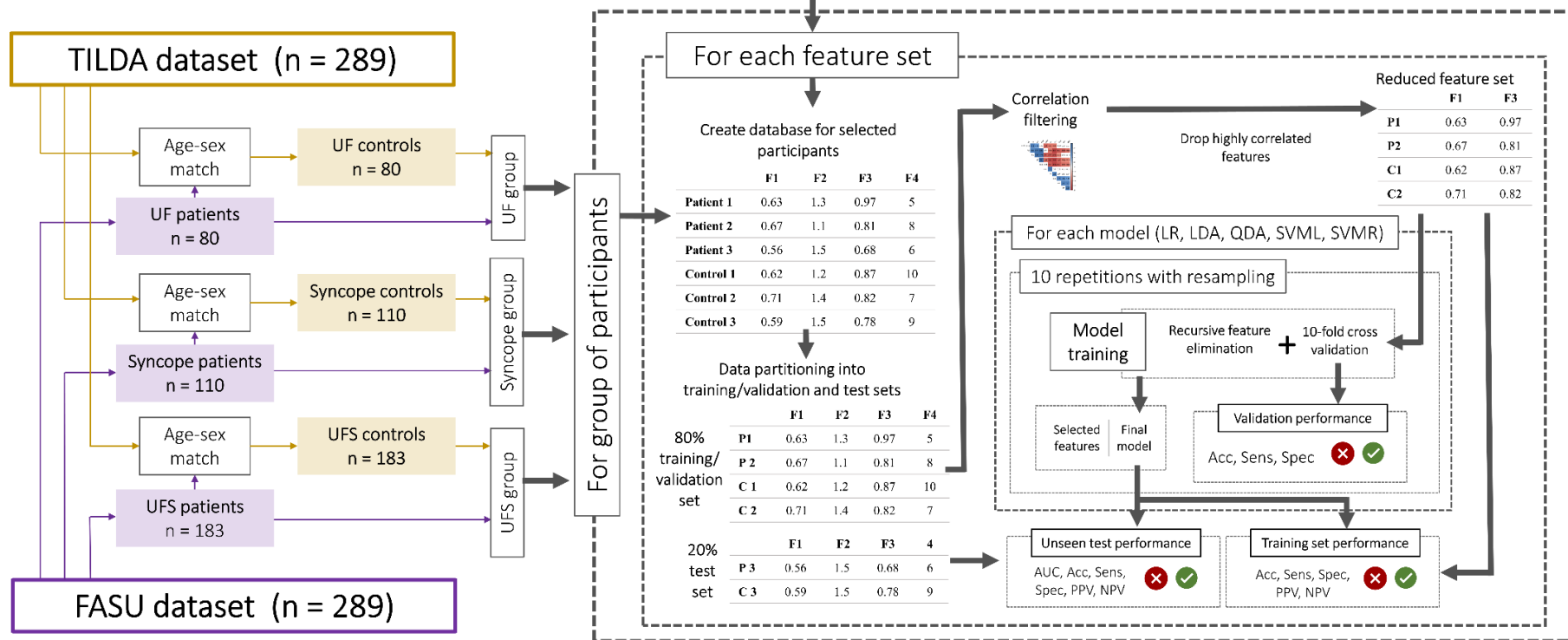
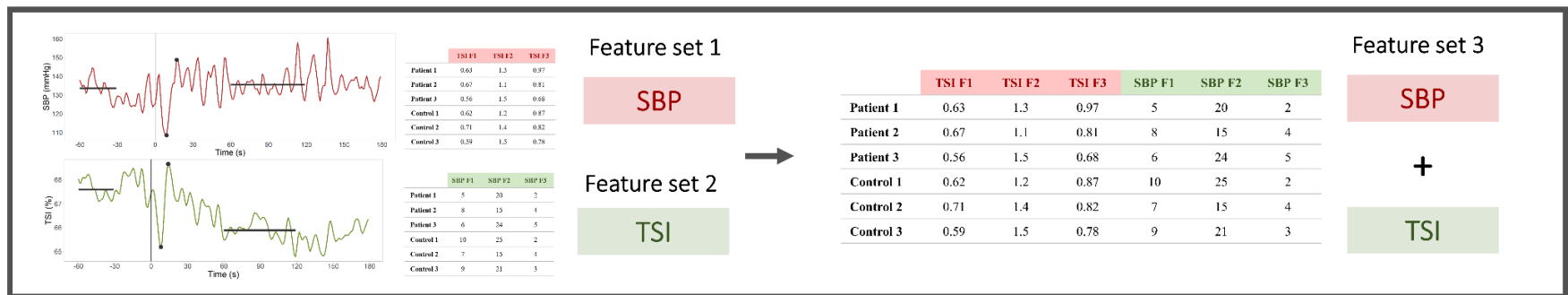


Figure 9.1. Block diagram representing the methodology used in the current study.

Three groups of patients are selected from the FASU cohort: patients with unexplained falls (UF), with syncope, or with either UF or syncope (UFS).

The three groups are then matched in age and sex to the same number of participants from the TILDA dataset. Tissue saturation index (TSI) and systolic blood pressure (SBP) features are extracted from the AS signals, resulting in three feature sets: only SBP (feature set 1), only TSI (feature set 2), and TSI and SBP features (feature set 3). A subset of data is created for each set of participants (UF, syncope and UFS) and for each of the three feature sets. Each subset is then divided into a training/validation set (80% of the participants) and a test set (20% of the participants) while maintaining 1:1 balance between patients and controls. Then, the training/validation set undergoes correlation filtering, with the most highly correlated features being eliminated, resulting in a reduced feature set. Five different models are developed on this set: logistic regression (LOG), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), linear support vector machine (SVML), and radial support vector machine (SVMR). For each model, 10 repetitions of 10-fold cross-validation with recursive feature elimination are used for model training, resulting in a final set of selected features and a final model. Summary performance metrics are extracted from the model training (validation performance), and the performance of the final model was assessed on the training/validation (training performance) and on the test set (test performance).

Machine Learning Models

A ML analysis pipeline was developed in RStudio (RStudio Team, 2016, RStudio: Integrated Development for R. RStudio, Inc., Boston, MA) and used to model the relationship between outcome variables and predictor features. This pipeline was composed of the following stages: correlation filtering, training and test set creation, classifier models, model training and cross validation, recursive feature elimination, and performance evaluation.

Missing values

When a participant had more than half of the predictors missing, they were eliminated from the dataset. Otherwise, if any predictors were missing they were imputed using 5-k nearest neighbours.

Feature Set Correlation Filtering

Before model building, features that were strongly correlated were filtered out using a threshold correlation of 0.8. Features were scaled and centred by subtracting the mean value and dividing by the standard deviation.

Training and Test Set Creation

Data was initially divided into two groups with a 20/80 ratio keeping a 1:1 ratio of patients and controls. 80% of the data was used for the iterative process of model training and cross-validation (training/validation set), while the remaining 20% of the data was unseen and used for the final model testing (test set). Evaluating the model performance in an unseen test set provides a less biased assessment of the model developed and allows generalisability of the results.

Classifier Models

Five different classifier models were used to model the relationship between the predictor feature sets and the outcome variables: logistic regression (LOG), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), linear support vector machine (SVML) and support vector machine with a radial kernel (SVMR) (see section 5.9. *Machine Learning Classification Algorithms* for detailed explanation).

Model training and Cross Fold Validation

Each classifier model was trained using the training/validation set using 10-fold cross validation. During model training, the training/validation dataset was randomly divided into 10 equally sized subsets, with one subset used for model validation while the rest were used for model training. This was repeated for each of the 10 subsets. Then, this 10-fold cross validation method was repeated 10 times, with the final validation results derived from the distribution of results generated from these iterations.

Feature Selection with Recursive feature elimination

Feature selection through recursive feature elimination (RFE) was implemented during model training. First, a list of model sizes was defined (Sizes = $S_1, S_2, \dots, S_i, \dots, S_m$, i = position in list, m = list length). A model containing all the available variables was then evaluated and variables were ranked from highest to lowest variable importance (logistic regression: model coefficients, other models: area under the curve (AUC) for each predictor). Subsequently, for each model size included in Sizes, a new model was built with the top S_i ranked variables. To improve the estimate of the average performance, this process was embedded in an

outer layer of resampling, i.e., for each resampling iteration within the cross validation process this process was applied. The best model size with its corresponding variables was chosen based on the best accuracy value.

Performance evaluation

The derived models were used to classify the individuals from the different datasets into cases (positive (P)), and controls (negative (N)) with the number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) derived. These values were then used to calculate the following classifier performance indices: accuracy $\frac{TP+TN}{P+N}$, sensitivity $\frac{TP}{P}$, specificity $\frac{TN}{N}$, positive predictive value (PPV) $\frac{TP}{TP+FP}$, and negative predictive value (NPV) $\frac{TN}{TN+FN}$. Accuracy, sensitivity and specificity were obtained for training/validation and test sets. Furthermore, the receiver operating characteristic (ROC) curve and its AUC were derived, with higher AUC values corresponding to better performance. The best model was chosen based on the AUC value. When the same AUC was found for more than one model, other performance metrics and the number of variables were considered.

Statistical analysis

Patient characteristics (UF, syncope and UFS groups) were compared to those of their matched controls using chi-squared tests for binary variables, while continuous variables were compared using a t-test or Mann-Whitney U test, depending on whether the variable was normally distributed or not, respectively.

9.3 Results

Participants characteristics

A total of 366 participants were included in the study, 183 controls (TILDA) and 183 patients (FASU) with a history of UF and/or syncope. From the patients, 80 had a history of UF and 110 a history of syncope, with 7 of them having a history of both (overlap between the two groups). The UF, Syncope and UFS patient groups had 80, 110 and 183 patients, respectively, with the same number of matched controls for each group. All groups were generally well matched in age, sex and BMI (See Table 2). The burden of most co-morbidities was higher in the 3 patient groups versus their controls. Regarding baseline haemodynamics, syncope and UFS patients had higher resting BP values when compared to their control groups (see Table 9.2). Figure 9.2 represents the mean TSI and SBP traces, respectively, for the three groups studied. When characterising univariate differences, UF and UFS patients had lower TSI values at overshoot and from 30 to 120 seconds after standing, while in syncope patients variables were comparable to their controls (see Table 9.3). Regarding SBP, the main differences were found in the initial transient part of the signal in syncope patients, while UF and UFS patients had larger variability (SD) during steady state and baseline (see Table 9.3).

Table 9.2. Participants characteristics.

	Controls (n = 80)	UF patients (n = 80)	p-value	Controls (n = 110)	Syncope patients (n = 110)	p-value	Controls (n = 183)	UF or syncope patients (n = 183)	p-value
Sex, %female (n)	55(44)	66.2(53)	0.145	53.6(59)	53.6(59)	1	54.6(100)	59.6(109)	0.342
Age, years (med, IQR)	71(12)	72(14)	0.519	69(16)	69(16)	0.743	70(13)	70(14)	0.563
BMI, kg/m ² (med, IQR)	27(5)	27(6)	0.673	27(5)	26(6)	0.315	27(5)	27(6)	0.823
Medical conditions									
TIA, %(n)	1.2(1)	8.8(7)	0.03*	0.9(1)	3.6(4)	0.175	1.1(2)	5.5(10)	0.019*
Stroke, %(n)	0(0)	8.8(7)	0.007**	0(0)	3.6(4)	0.044*	0(0)	6(11)	0.001**
Hypertension, %(n)	37.5(30)	51.2(41)	0.080	34.5(38)	54.5(60)	0.003**	36.1(66)	53.6(98)	0.001**
Angina, %(n)	3.8(3)	6.2(5)	0.468	6.4(7)	4.5(5)	0.553	5.5(10)	5.5(10)	1.000
MI, %(n)	1.2(1)	5(4)	0.173	0(0)	1.8(2)	0.155	0.5(1)	3.3(6)	0.056
AFib, %(n)	2.5(2)	20(16)	<0.001***	2.7(3)	9.1(10)	0.045*	2.7(5)	13.1(24)	<0.001***
Other Rhythm, %(n)	13.8(11)	11.2(9)	0.633	4.5(5)	5.5(6)	0.757	8.2(15)	7.7(14)	0.847
Heart Failure, %(n)	0(0)	5(4)	0.043*	0(0)	1.8(2)	0.155	0(0)	3.3(6)	0.014*
Diabetes, %(n)	6.2(5)	20(16)	0.010*	6.4(7)	10.9(12)	0.230	5.5(10)	14.8(27)	0.003**
Cholesterol, %(n)	33.8(27)	57.5(46)	0.003**	37.3(41)	45.5(50)	0.218	35(64)	50.8(93)	0.002**
Other Cardiac, %(n)	10(8)	0(0)	0.004**	7.3(8)	0(0)	0.004**	8.2(15)	0(0)	<0.001***
Dep/Anxiety, %(n)	0(0)	30(24)	<0.001***	1.8(2)	20.9(23)	<0.001***	1.1(2)	23.5(43)	<0.001***
Other Psych, %(n)	0(0)	5(4)	0.043*	2.7(3)	2.7(3)	1	1.6(3)	3.8(7)	0.200
COAD, %(n)	2.5(2)	21.2(17)	<0.001***	2.7(3)	20.9(23)	<0.001***	2.7(5)	21.3(39)	<0.001***
Endocrine, %(n)	5(4)	16.2(13)	0.021*	7.3(8)	8.2(9)	0.801	6(11)	11.5(21)	0.064
Count of morbidities, med (IQR)	1(2)	3(2)	<0.001***	1(2)	2(2)	<0.001***	1(2)	2(2)	<0.001***
More than 2 morbidities	11.2(9)	51.2(41)	<0.001***	10(11)	32.7(36)	<0.001***	10.4(19)	40.4(74)	<0.001***
Medication									
Antidepressants	2.5(2)	32.5(26)	<0.001***	2.7(3)	20.9(23)	<0.001***	2.7(5)	25.7(47)	<0.001***
Antihypertensives	50(40)	57.5(46)	0.341	42.7(47)	48.2(53)	0.417	45.9(84)	52.5(96)	0.210
Baseline haemodynamics									
Baseline SBP, mmHg (med, IQR)	143(25)	145(23)	1.000 ⁽⁺⁾	143(23)	149(21)	<0.001*** (+)	142(31)	144(29)	0.066
Baseline DBP, mmHg (med, IQR)	75(14)	79(18)	0.043*	74(11)	82(17)	<0.001***	74(13)	81(18)	<0.001***
Baseline MAP, mmHg (med, IQR)	98(21)	101(18)	0.135	99(19)	105(19)	<0.001***	99(19)	104(19)	<0.001***

P-values represent the comparison between each patient group with their respective controls. Normally distributed variables are reported as mean (SD) (these cases are indicated with a ⁽⁺⁾ in the p-value), and non-normally distributed variables are reported as median (interquartile range): med(IQR).

Table 9.3. Univariate comparison of TSI and SBP features between UF, Syncope, and UF or syncope (UFS) patients and their controls.

	Controls (n = 80)	UF (n = 80)	p-value	Controls (n = 110)	Syncope (n = 110)	p-value	Controls (n = 183)	UFS (n = 183)	p-value
TSI overshoot01	68.8(55)	53.8(43)	0.051	55.5(61)	51.8(57)	0.589	60.7(111)	53(97)	0.140
SBP overshoot01	53.8(43)	51.2(41)	0.752	60.9(67)	52.7(58)	0.221	57.4(105)	53.6(98)	0.462
ΔTSI5	-0.69(1.71)	-1.04(1.5)	0.102	-0.84(1.38)	-1.21(1.58)	0.065	-0.77(1.53)	-1.12(1.58)	0.021*
ΔTSI10	-1.56(2.4)	-1.07(2.14)	0.742	-1.43(1.94)	-1.03(1.98)	0.084	-1.48(2.01)	-1.06(2.04)	0.106
ΔTSI20	0.08(1.82)	-0.2(1.92)	0.133	-0.19(1.59)	-0.28(1.51)	0.318	-0.09(1.77)	-0.2(1.57)	0.072
ΔTSI30	-0.06(1.63)	-0.67(1.75)	0.019*	-0.41(1.66)	-0.8(1.31)	0.029*	-0.21(1.66)	-0.78(1.53)	<0.001***
ΔTSI60	-0.31(1.76)	-1.04(1.71)	0.006**	-0.52(2.14)	-0.78(1.69)	0.527	-0.46(1.95)	-0.98(1.61)	0.017*
ΔTSI90	-0.36(1.89)	-1.34(2.23)	0.004**	-0.7(2.11)	-1.02(1.76)	0.329	-0.54(2.07)	-1.13(1.88)	0.007**
ΔTSI120	-0.26(1.87)	-1.4(2.24)	<0.001***	-0.96(2.27)	-1.12(1.83)	0.088	-0.52(2.06)	-1.14(2.04)	<0.001***
TSI nadir	-1.84(2.14)	-1.85(2.33)	0.731	-1.84(2.29)	-2.04(2.2)	0.737	-1.83(2.23)	-1.93(2.3)	0.704
SD TSI baseline	0.35(0.32)	0.42(0.42)	0.127	0.34(0.29)	0.38(0.35)	0.222	0.34(0.29)	0.40(0.39)	0.059
SD TSI steady-state	0.41(0.3)	0.41(0.3)	0.698	0.40(0.28)	0.42(0.28)	0.944	0.39(0.28)	0.41(0.28)	0.525
TSI steady-state	-0.47(1.64)	-1.25(2.19)	0.005**	-0.7(1.99)	-1(1.52)	0.22	-0.6(2.12)	-1.08(1.84)	0.004**
TSI overshoot	0.6(1.13)	0.16(1.64)	0.042*	0.34(1.73)	0.08(1.62)	0.325	0.47(1.59)	0.12(1.61)	0.041*
TSI overshoot-to-nadir	2.39(2.2)	1.98(2.16)	0.172	2.06(2.66)	1.96(2.18)	0.843	2.29(2.57)	1.98(2.19)	0.227
TSI overshoot-nadir time	9.6(4.6)	9.4(5)	0.760	9.6(5.55)	9.1(4)	0.275	9.75(4.98)	9.15(4.28)	0.227
TSI slope of recovery	0.4(0.35)	0.36(0.29)	0.260	0.38(0.42)	0.38(0.32)	0.963	0.4(0.4)	0.38(0.32)	0.474
ΔSBP5	-14.97(21.07)	-17.59(21.43)	0.078	-17.23(17.6)	-20.44(22.01)	0.082	-16.21(20.18)	-18.44(23.1)	0.036*
ΔSBP10	-26.24(15.01)	-22.38(17.58)	<0.001***	-24.88(19.58)	-26.89(18.88)	<0.001***	-25.81(17.87)	-24.74(18.45)	1.000
ΔSBP20	-1.45(24.68)	-4.46(26.46)	0.647	-1.68(19.53)	-4.71(22.42)	<0.001***	-3.05(19.37)	-4.56(21.65)	<0.001***
ΔSBP30	-2.94(17.06)	-2.58(20.35)	1.000	-1.38(16.57)	-4.13(20.2)	<0.001***	-2.06(16.93)	-2.94(20.01)	1.000
ΔSBP60	-3.47(17.38)	0.27(17.9)	<0.001***	-0.04(16.67)	2.2(21.72)	0.163	-0.66(19.09)	2.25(21.38)	0.061
ΔSBP90	2.8(22.75)	7.53(22.35)	0.156	2.74(20.01)	4.16(21.1)	0.309	2.68(22.08)	5.65(22.58)	0.060
ΔSBP120	4.53(19.58)	6.13(25.43)	0.203	4.42(16.94)	3.14(18.64)	1.000	4.97(20.75)	5.32(24.01)	0.507
SBP nadir	-34.46(15.73)	-33.92(17.14)	1.000	-33.38(23.76)	-32.99(22.83)	0.499	-34.83(20.59)	-31.9(23.79)	0.967
SD SBP baseline	5.52(4.3)	6.72(5.53)	0.025*	5.56(3.41)	5.93(3.63)	0.306	5.52(3.67)	6.32(4.45)	0.015*
SD SBP steady-state	5.35(3.2)	7.06(2.91)	0.002**	5.44(2.87)	5.91(3.55)	0.309	5.35(3.04)	6.63(3.45)	0.002**
SBP steady-state	2.74(18.39)	4.97(22.57)	0.085	1.38(17.23)	4(20.21)	0.368	1.89(18.06)	4.97(22.13)	0.055
SBP overshoot	5.24(24.05)	1.2(21.49)	0.350	5.21(19.17)	-0.18(22.03)	<0.001***	3.15(19.4)	0.18(21.35)	<0.001***
SBP overshoot-to-nadir	35.06(20.27)	31.89(20.28)	0.299	39.3(17.48)	36.58(18.86)	<0.001***	36(18.31)	35.13(20.74)	0.204
SBP overshoot-nadir time	10.65(4.25)	10.65(5.2)	0.828	10.15(3.25)	11.05(4.5)	0.439	10.4(3.55)	10.9(4.9)	0.635
SBP slope of recovery	6.47(3.85)	5.82(4.22)	0.403	7.14(3.78)	6.5(3.56)	0.069	6.79(3.86)	6.24(3.74)	0.117
TSI/SBP slope of recovery	0.07(0.07)	0.06(0.07)	0.658	0.06(0.07)	0.06(0.06)	0.320	0.06(0.07)	0.06(0.06)	0.901

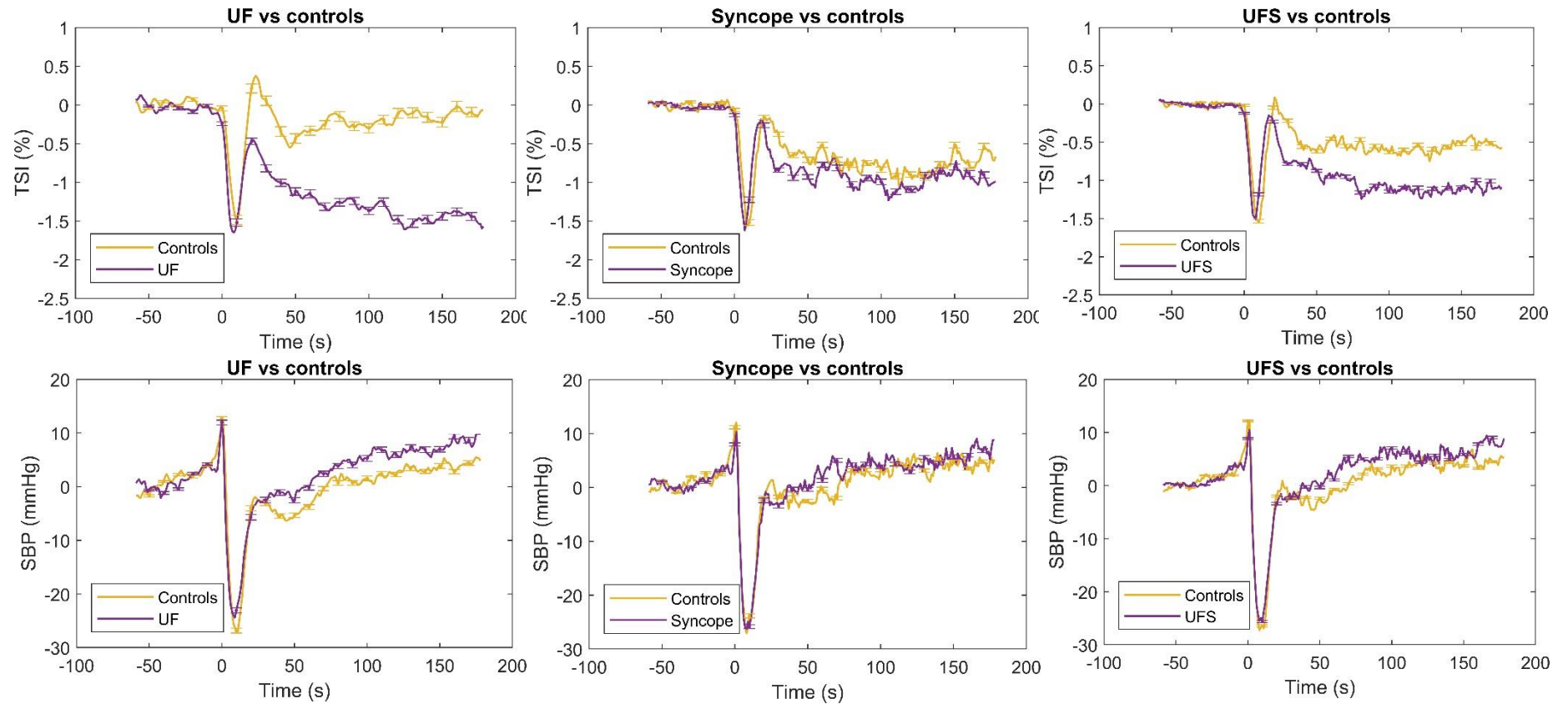


Figure 9.2. Average TSI and SBP responses to standing for patients with unexplained falls and syncope, and their control groups.
Mean (CI) TSI (top row) and SBP (bottom row) traces for controls and patients with UF (Figures A and D), syncope (Figures B and E), and UFS (Figures C and F). All cohorts have a similar time course during the initial drop, although patient groups have poorer recovery in their cerebral oxygenation after nadir. Standing occurred at $t = 0$. UF = unexplained falls, UFS = unexplained falls or syncope.

Feature correlation analysis

For SBP and TSI+SBP feature sets, while specific time points selected varied from model-to-model, values representative of the nadir, the initial stabilisation period, its recovery rate, the steady-state period and their variability remained after initial correlation filtering in each model (See Figure 9.3 for example). This was not the case for the UF TSI features set, in which features corresponding to the later part of the standing (30-120 s) were mostly eliminated during correlation filtering. Features describing the morphology of the waveform (i.e., nadir, overshoot, steady-state etc.) were generally eliminated more often than timepoint features (i.e., ΔTSI_5 , ΔTSI_{10} , ΔTSI_{20} , etc.) (see Appendix K: Supplementary Figures A.K.1 – A.K.8 for full details).

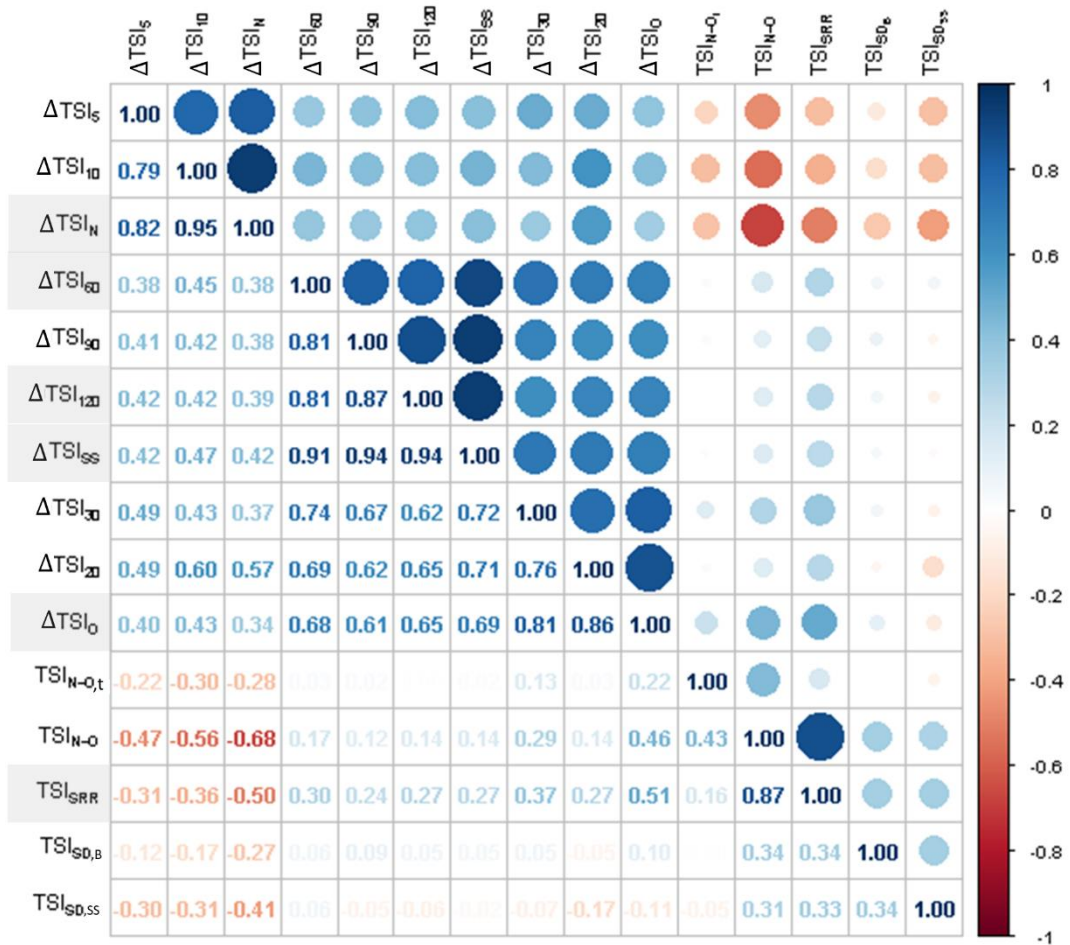


Figure 9.3. Correlation matrix for TSI features used in the classification of syncope.
Features marked in grey on the left side of the matrix were eliminated by correlation filtering.

Model performance

TSI based Classifier models

The TSI LDA model was able to classify UF with an AUC of 0.700 (see Table 9.4, Figure 9.4, for further information regarding all models tested see Appendix K: Supplementary Table A.K.1). Models classifying syncope had a poorer performance in the test set, with QDA being the best model with a 0.437 AUC. For UFS a test AUC of 0.690. The most important predictor variables in each model, while varying from model to model, all follow a common trend, i.e., they are features which capture overall TSI variability (at baseline or steady-state) and transient TSI stabilisation patterns, while TSI steady-state features were only relevant in models to classify UFS (see Figure 9.6).

SBP based Classifier Models

SBP models classified UF with test set AUC 0.779 (see Table 9.5, Figure 9.4, for further information regarding all models tested see Appendix K: Supplementary Table A.K.2). Again, models to classify syncope had poorer performance, with test set AUC of 0.584 for SVMR. When classifying UFS, LOG and LDA based models had equivalent performance values, with a test AUC of 0.667. The most important SBP features included in the models captured SBP variability, SBP nadir and stabilisation, and steady-state values (see Figure 9.7).

Combined TSI + SBP based classifier models

The combined TSI+SBP classifier models for UF achieved a high test AUC of 0.812 AUC (see Table 9.6, Figure 9.4, for further information regarding all models tested see Appendix K: Supplementary Table A.K.3). In the classification of syncope, test AUC for the best performing model, LDA, was 0.418. The SVML model for classifying UFS had a test AUC of 0.715. Similar to the results for TSI and SBP, the

most important features chosen for the TSI+SBP models represent variability (all models except for LOG use most of the TSI and SBP variability measures), initial transient period, and steady-state region, with a balance between TSI and SBP features (see Appendix K: Supplementary Figures A.K.9-Supplementary Figure).

Morbidity count Classifiers

Models which also included the participants morbidity count as a predictor were slightly better than those without it. UF, syncope and UFS could be predicted using only TSI features with a 0.858 AUC, 0.613 AUC and 0.717 AUC, respectively (see Table 9.4, Figure 9.5, for further information regarding all models tested see Appendix K: Supplementary Table A.K.14). Similar results were obtained for SBP models, with test AUC of 0.875, 0.553, 0.717 for UF, syncope and UFS, respectively (see Table 9.5, Figure 9.5, for further information regarding all models tested see Appendix K: Supplementary Table A.K.15). Lastly, models that combined TSI and SBP features achieved AUC values of 0.875, 0.5524, 0.774 for UF, syncope and UFS, respectively (see Table 9.6, Figure 9.5, for further information regarding all models tested see Appendix K: Supplementary Table A.K.16). Generally, these models presented higher specificity than sensitivity, with the exception of SBP and TSI+SBP models to classify UFS, which were better at correctly determining which patients had had a UFS than those who had not. Most models had the morbidity count as their most important variable, and they all also included TSI and/or SBP features representing the entire AS test waveform as a result of the feature selection process (see Appendix K: Supplementary Figures A.K.14 – A.K.20).

Table 9.4. Summary of results for the best performing TSI models (without and with morbidity count) derived for three outcomes (unexplained falls (UF), syncope and unexplained falls or syncope (UFS)).

	Models WITHOUT morbidity count			Models WITH morbidity count		
Outcome variable	History of UF	History of Syncope	History of UFS	History of UF	History of Syncope	History of UFS
Algorithm name	LDA	QDA	LDA	LDA	SVMR	QDA
AUC	0.700	0.437	0.690	0.858	0.613	0.717
Number of variables	7	5	8	7	1	9
Performance metrics (%)						
Validation Accuracy	59.7	62.0	59.0	69.9	64.0	63.4
Validation Sensitivity	58.3	61.6	59.5	71.5	67.8	72.6
Validation Specificity	60.9	62.6	58.5	68.3	60.3	54.5
Training Accuracy	65.4	72.6	62.2	74.0	64.6	70.1
Training Sensitivity	70.3	77.3	61.2	71.9	60.2	60.5
Training Specificity	60.3	67.8	63.2	76.2	69.0	79.9
Test Accuracy	64.5	46.5	62.0	74.2	65.1	69.0
Test Sensitivity	56.2	45.5	61.1	62.5	50.0	63.9
Test Specificity	73.3	47.6	62.9	86.7	81.0	74.3

Values > 70% have been highlighted in bold.

Table 9.5. Summary of results for the best performing SBP models (without and with morbidity count) derived for three outcomes (unexplained falls (UF), syncope and unexplained falls or syncope (UFS)).

	Models WITHOUT morbidity count			Models WITH morbidity count		
Outcome variable	History of UF	History of Syncope	History of UFS	History of UF	History of Syncope	History of UFS
Algorithm name	QDA	SVMR	LOG	SVML	SVML	LDA
AUC	0.779	0.584	0.667	0.842	0.604	0.746
Number of variables	11	11	7	9	5	7
Performance metrics (%)						
Validation Accuracy	64.8	55.4	63.3	75.7	66.5	69.8
Validation Sensitivity	67.8	54.0	61.9	77.9	70.7	73.8
Validation Specificity	61.9	56.9	64.6	73.5	62.5	65.9
Training Accuracy	75.6	76.0	67.7	81.9	70.9	70.8
Training Sensitivity	68.8	76.1	70.1	79.7	64.8	66.7
Training Specificity	82.5	75.9	65.3	84.1	77.0	75.0
Test Accuracy	71.0	62.8	67.3	74.2	58.1	69.0
Test Sensitivity	68.8	68.2	68.1	68.8	50.0	77.8
Test Specificity	73.3	57.1	64.8	80.0	66.7	60.0

Values > 70% have been highlighted in bold.

Table 9.6. Summary of results for the best performing TSI+SBP models (without and with morbidity count) derived for three outcomes (unexplained falls (UF), syncope and unexplained falls or syncope (UFS)).

	Models WITHOUT morbidity count			Models WITH morbidity count		
Outcome variable	History of UF	History of Syncope	History of UFS	History of UF	History of Syncope	History of UFS
Algorithm name	QDA	LDA	SVML	SVMR	LOG	SVMR
AUC	0.812	0.418	0.715	0.875	0.552	0.774
Number of variables	15	17	17	17	3	17
Performance metrics (%)						
Validation Accuracy	60.8	66.6	61.2	66.7	70.2	67.8
Validation Sensitivity	60.8	68.2	58.8	62.0	71.3	66.2
Validation Specificity	61.1	65.1	63.7	71.4	69.2	69.4
Training Accuracy	81.1	74.3	68.4	78.7	72.6	79.7
Training Sensitivity	82.8	72.7	66.0	76.6	70.5	78.9
Training Specificity	79.4	75.9	70.8	81.0	74.7	80.6
Test Accuracy	74.2	44.2	60.6	74.2	55.8	69.0
Test Sensitivity	62.5	36.4	58.3	62.5	40.9	83.3
Test Specificity	86.7	52.4	62.9	86.7	71.4	54.3

Values > 70% have been highlighted in bold.

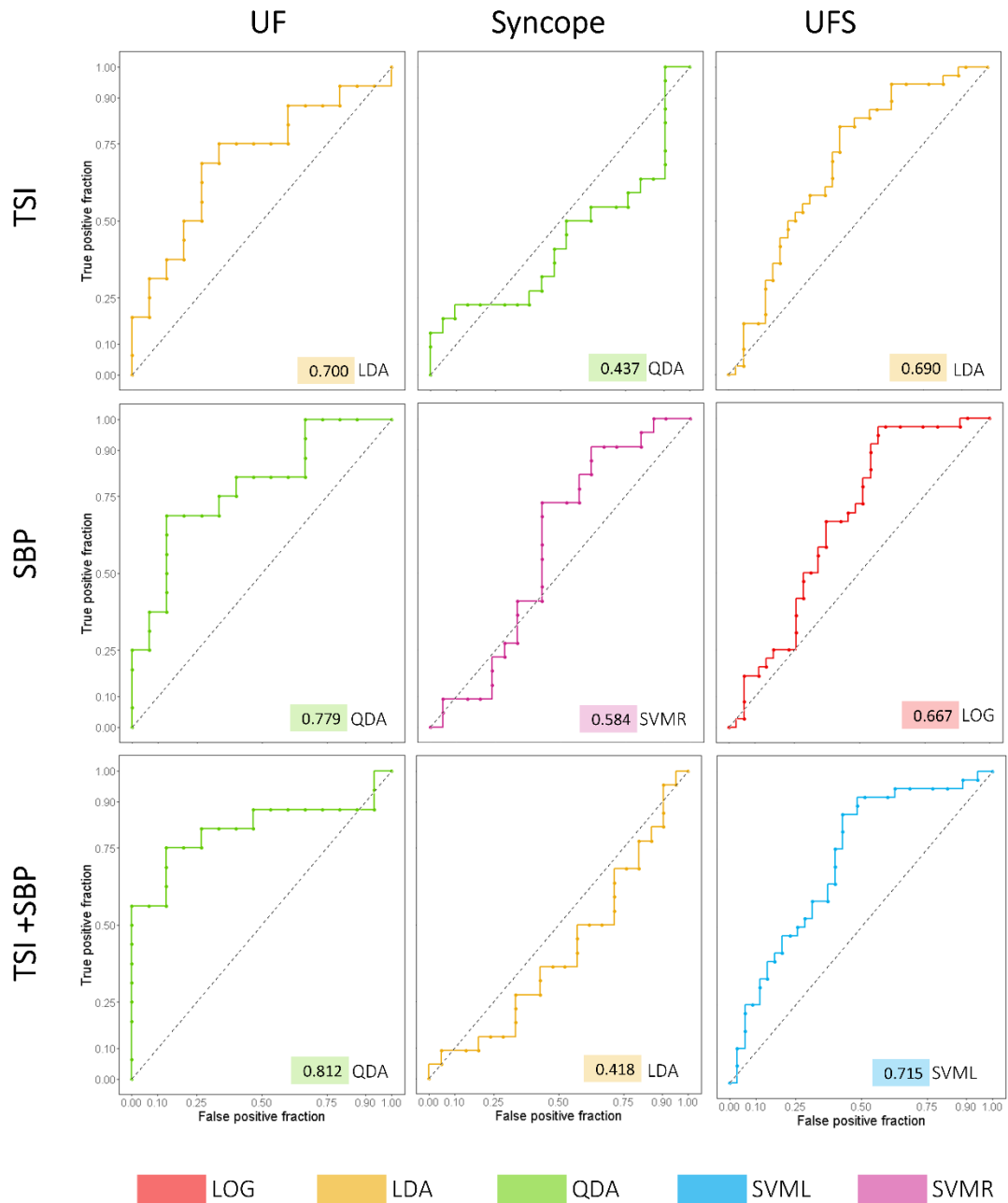


Figure 9.4. Receiver operating curves (ROC) evaluating the performance of the models developed. ROC curves representing the performance of the best classifier model to identify three different outcomes (UF, syncope, and UF or syncope) using only TSI features, only SBP features or a combination of TSI and SBP features. AUC values for each model have been indicated within each graph.

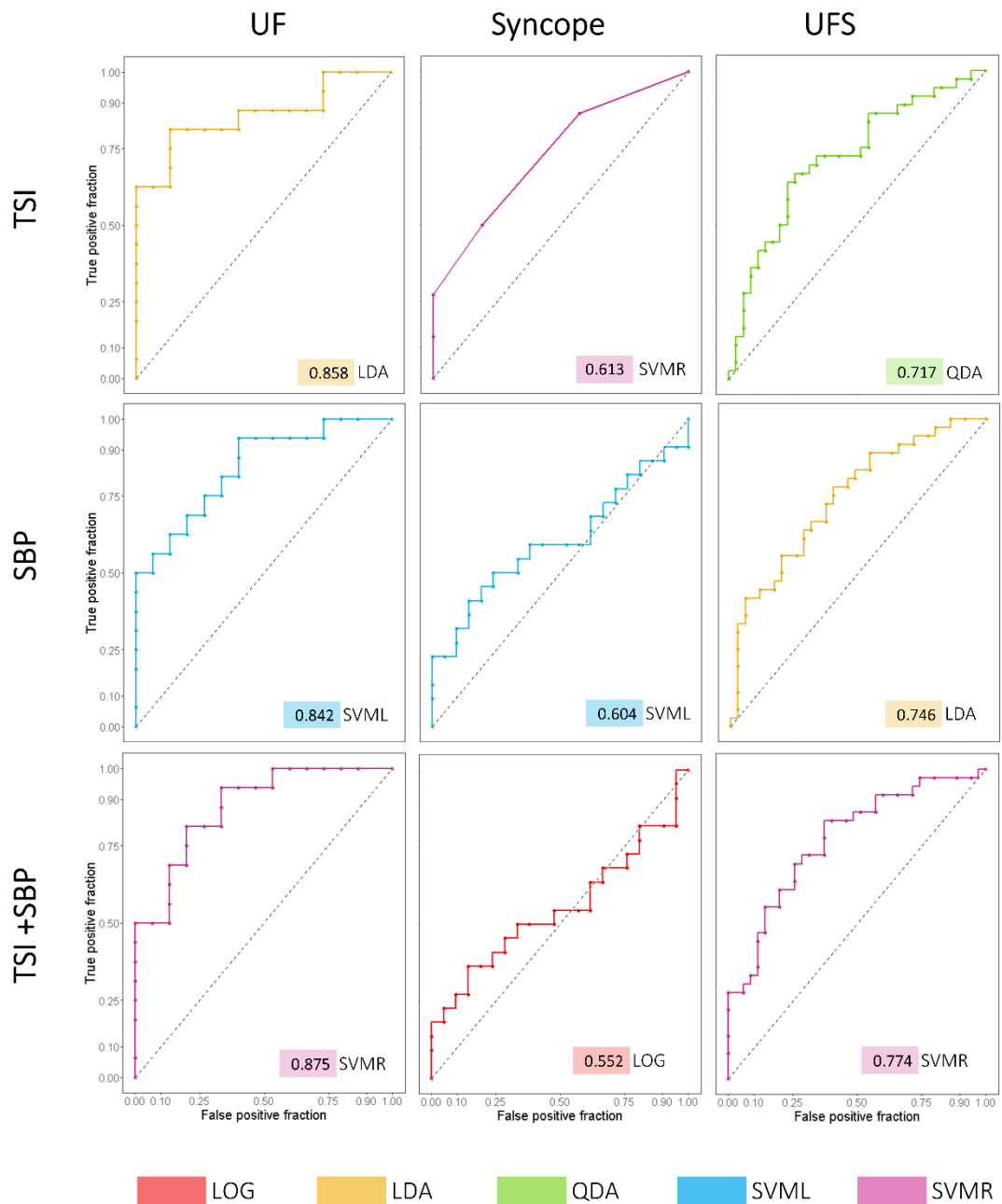


Figure 9.5. Receiver operating curves (ROC) evaluating the performance of the models developed that included multimorbidity count as a predictor.

ROC curves representing the performance of the best classifier model (**including morbidity count**) to identify three different outcomes (UF, syncope, and UF or syncope) using only TSI features, only SBP features or a combination of TSI and SBP features. AUC values for each model have been indicated within each graph.

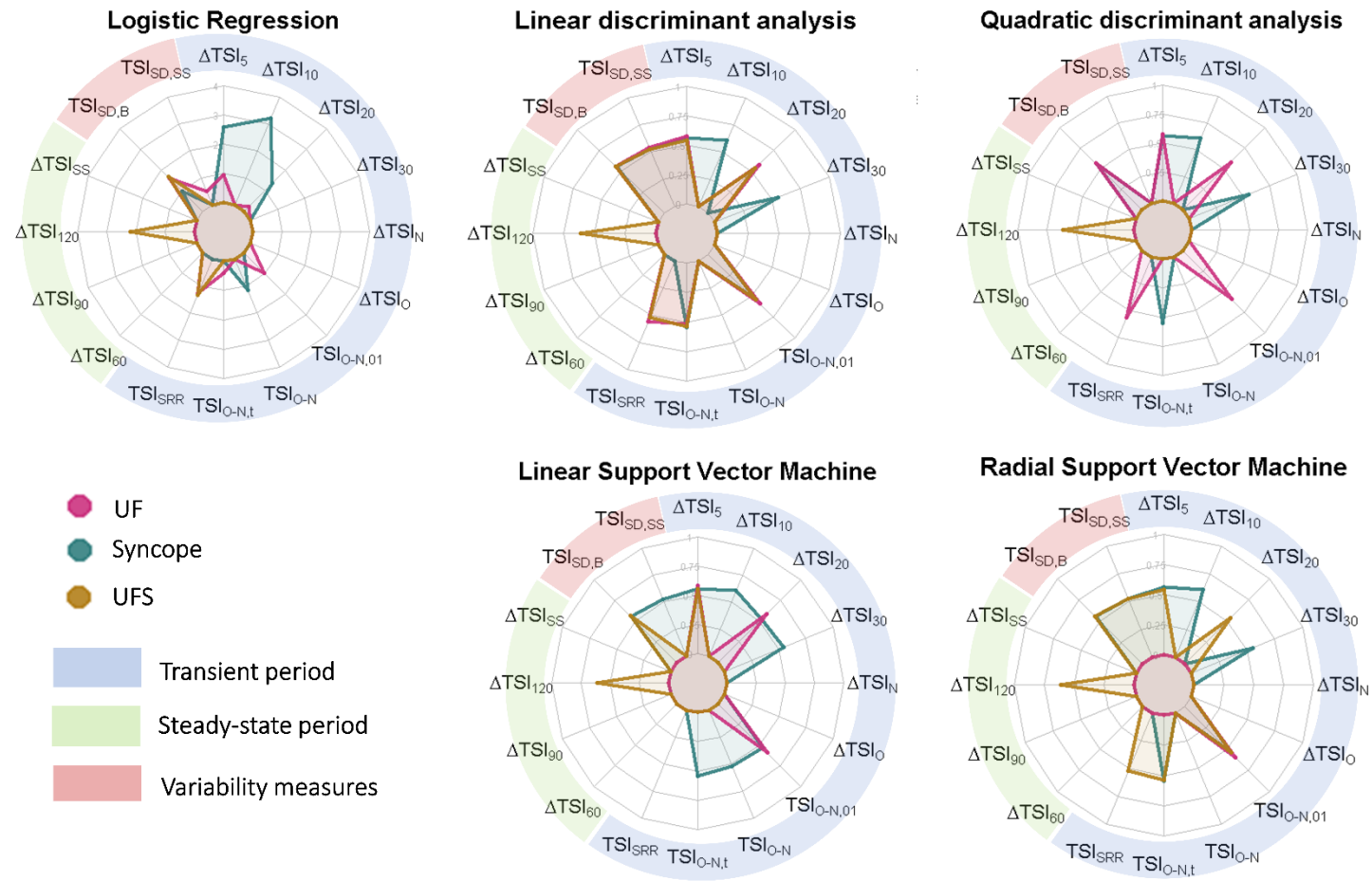


Figure 9.6. Feature importance for the TSI models developed.
 Feature importance for the variables selected for each of the algorithms and the three outcome variables in tissue saturation index (TSI) models: unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

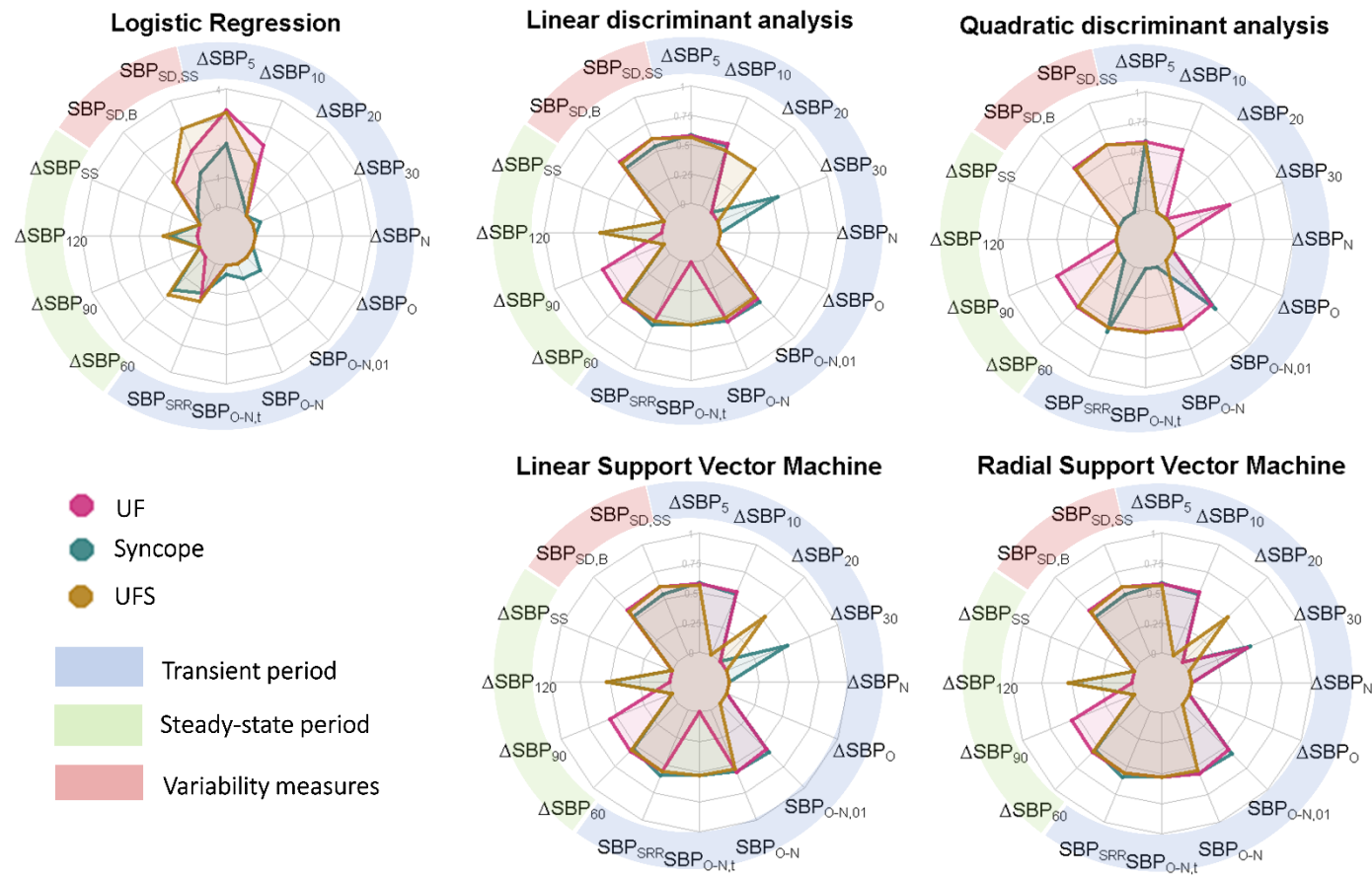


Figure 9.7. Feature importance for the SBP models developed.

Feature importance for the variables selected for each of the algorithms and the three outcome variables in systolic blood pressure (SBP) models: unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

9.4 Discussion

This study demonstrates, for the first time, that a history of UF and/or syncope can be identified from cerebral and peripheral circulation features during an AS test using AI/ML algorithms, and that including medical history (morbidity count) improves model performance further. While history of syncope was the most challenging to classify, good performance in classifying patients with a history of UF or UFS was achieved when combining information on TSI, BP and multimorbidity features, an intuitively satisfying result.

Models demonstrated a high performance when classifying UF and UFS, with the best haemodynamics models for UF (QDA, AUC 0.812, 74.2% accuracy) and UFS (SVML, AUC 0.715, 60.6% accuracy) based on a combination of TSI and SBP features. In Figure 9.2 it can be seen how UF and UFS patients recover to an overall lower TSI value with respect to their controls. Interestingly, only the UFS model used steady-state variables (Figure 5), while they were not used for UF classification, given that they were eliminated during correlation filtering. In the case of syncope, classification performance was poor, suggesting potential differences in underlying factors contributing to syncope and UF. Variability features during baseline and steady-state, not commonly investigated in AS studies, were important in most models. Increased beat-to-beat BP variability indicates poorer autonomic regulatory ability [452], and has been associated with increased arterial stiffness [453, 454] and worse health outcomes [455, 456]. In the current study, patients generally demonstrated higher BP variability than controls, which might indicate poorer autonomic modulation contributing to their falls and syncope events. Furthermore, increased cerebral perfusion variability has been reported to be associated with impaired CA during orthostasis and with hypertension [457]. All models also included variables representing the transient

period (approx. first 30s after standing), which is also associated with autonomic regulation [78]. These results demonstrate that the entire AS test, from baseline until the end of the test, provides valuable information in the classification of patients vs controls, and emphasises the value of beat-to-beat measures in the assessment of falls and syncope patients.

Clinical history plays a pivotal role in the evaluation of patients with syncope and falls [1]. Previous work from this thesis [433] (see *Chapter 8: Increased Multimorbidity is Associated with Impaired Cerebral and Peripheral Haemodynamic Stabilisation during Active Standing*) demonstrated that cerebral oxygenation recovery to standing is impaired with increasing multimorbidity. Thus, morbidity count was included in the models as a predictor to capture previous clinical history and multimorbidity effects. This improved model performance for all the outcomes, with the best models obtained in this study including morbidity count, TSI and SBP features for UF (SVMR, 0.875 AUC, 74.2% accuracy) and UFS (SVMR, 0.774 AUC, 69.0% accuracy). The improvement with the addition of morbidity count constitutes an important finding, and may inform the future development of clinical decision support tools to aid clinicians in identifying patients at a higher risk of falls and syncope.

The fact that the combination of TSI, SBP and clinical information yields the best performance, emphasises the added value of combining detailed and novel objective measures such as NIRS with more traditional clinical history (SBP and multimorbidity) to provide a better and more personalised assessment of patients. However, it must be noted that the performance of models that did not include TSI (i.e. models that only used SBP or a combination of SBP and multimorbidity) was only marginally lagging behind those that did include TSI features. This indicates that traditional methods already in use in standard practice have the potential to be readily

incorporated in clinical decision support tools to predict the risk of syncope and UF, and that these tools could be further enhanced with the future incorporation of novel technologies such as NIRS in this clinical scenario.

UF and syncope are often considered to be the same clinical entity [1]. Given that amnesia for loss of consciousness often occurs in UF, these are believed to be syncopal episodes that result in the person losing balance and falling without an apparent cause [62]. Based on this, the initial hypothesis was that combining UF and syncope into UFS would result in a similar or better classifier performance. However, the performance of UFS models is lower as compared to that of UF, likely a consequence of how challenging it is to classify syncope alone. From a clinical point of view, it can be hypothesised that the pathophysiology of UF and syncope might be different, even if currently treated similarly in clinical practice [1]. A study from our group observed that UF but not syncope were associated with impaired blood pressure recovery after standing [29], which also suggests that different pathological pathways might be responsible for these events, especially in older adults. In the models that did not include the morbidity count, syncope was better classified when only using SBP features, while for UF a combination of TSI and SBP features performs better. This may suggest that the cause of UF might be attributed to both dysregulation of blood pressure and cerebral perfusion, while syncope may be mainly peripheral in origin with potentially healthier brains than UF patients.

It is known that falls are associated with impaired recovery of peripheral haemodynamics after AS. Delayed blood pressure recovery at 40 seconds after standing is associated with an increased risk of UF at 2-year follow-up with a risk ratio (RR) of 1.52 in community-dwellers [29]. Similarly, sustained drops, i.e., OH are associated with all-cause falls, UF and injurious falls with a 1.40, 1.81 and 1.58 RR, respectively

[29]. A meta-analysis by Mol et al. including 63 studies demonstrated that falls are associated with OH with an odds ratio of 1.72 [273]. A study from our group (see Appendix D) recently demonstrated for the first time that larger drops in TSI and BP are associated with an increased risk of future falls, including all-cause and UF.

Regarding the prediction of syncope using AI/ML, previous literature has focused on predicting syncope reproduction during head-up tilt (HUT) testing, generally using data collected during the test [246, 397-400, 403-405]. These studies generally achieved excellent performances, with accuracy ranging from 56-98%, sensitivity from 82-100% and specificity from 64-94%. In this study poorer performance was obtained, which might be explained by the differences in the outcome variable (history of syncope vs reproduction of syncope during HUT testing), the protocol (AS vs HUT) or the age of participants (older adults vs young populations). A previous study from our group used peripheral haemodynamics AS data to predict a diagnosis of vasovagal syncope (VVS) in older adults [245], reporting an accuracy of 76.8%. Instead of a diagnosis of VVS, the aim of the current study was to identify a self-reported history of syncope, which might not have always been vasovagal in origin (e.g. cardioinhibitory). Therefore, this work uses a more heterogeneous sample, which might explain the differences in performance between the studies.

To our knowledge, the current study is the first to use AS haemodynamic signals in combination with AI/ML approaches to classify (unexplained) fallers and fainters. Most studies identifying history of falls with ML have used data collected from pressure or acceleration sensors worn during walking or balance tests [45, 355, 364, 375, 376, 382, 385], or from demographic and clinical databases [344, 354, 359]. These studies achieved accuracies ranging from 62-93% although, in cases in which accuracy values were larger than 80%, a low sensitivity (~ 50%) and high specificity (~90%) was

usually reported [354, 364, 376]. This study adds to this literature by focusing on falls outcomes (i.e., UF) that are complex and more costly to manage clinically, utilising a novel set of haemodynamic predictors with accuracy (AUC) values of up to 74% (0.875) achieved, with a good balance between sensitivity and specificity.

Strengths

To our knowledge, this is the first study to use NIRS derived measures of cerebral oxygenation to classify a history of UF, syncope or UFS. Furthermore, multimorbidity was considered as an important factor, which resulted in higher model performance. In addition, features that capture the morphology of the initial response to standing were used, which provides higher resolution data than other studies only considering OH definitions for falls risk assessment. A large group of older adults (age range 50-92 years) that had undergone an AS with concurrent measurement of BP and TSI was investigated, which constitutes a unique translational dataset combining community-dwelling and clinical data. Moreover, UF and syncope were investigated, which are believed to be of cardiovascular origin and are therefore more likely to be associated with BP and TSI signals than all-cause falls. The models used in this work were developed using explainable AI algorithms, i.e., the model is a function of predefined features used as inputs for the models. This allows studying the influence of each of those features on the results, which may aid clinicians in understanding the decisions produced by these models and help understanding the pathophysiology of these patients to provide a more personalised management. This work also demonstrates the value of using AI/ML to combine data from different sources and nature into advanced nonlinear models to identify clinical conditions.

Limitations

Combining the FASU and TILDA database required data harmonisation, with some clinical questions and variables not exactly matching. The cross-sectional design of the study also constitutes a limitation, and while the current study sets the ground for future research, such studies should focus on the prediction of future falls, which are of most clinical importance. Furthermore, sex is associated with different responses in SBP and TSI during the AS. Therefore, sex stratification might result in better sex-specific models for the identification of fallers and fainters. NIRS can only capture a small region of the brain, and is therefore not representative of other parts of the cerebral tissue, where more significant differences might be found. NIRS is also affected by extracerebral circulation contamination, tissue heterogeneity and the thickness of extracerebral layers (e.g. skull or cerebrospinal fluid), and is susceptible to movement artifacts [185, 189, 416]. Lastly, feature selection algorithms are intended to improve model performance by choosing an optimal combination of features, but this is not always guaranteed. Correlation filtering removes variables that are highly correlated with each other, but does not take into account the association of that variable with the outcome variable or what the impact of its removal is. In turn, RFE is designed to avoid type I errors, which therefore results in a large number of combination of features remaining unexplored, which could yield a better performance than the one found by the algorithm.

Conclusion

In this work, it has been demonstrated that TSI and SBP features derived from an AS test can be combined with clinical history data using explainable AI/ML algorithms to classify patients with a history of syncope and/or UF, opening up a new approach to identify these complex cases. Information from the entire AS test is used by these models, including the initial transient part, which highlights the value of

incorporating high resolution NIRS and beat-to-beat blood pressure measurements in the evaluation of syncope and falls. These results set the ground for future studies to investigate how cerebral oxygenation and blood pressure measures can be used in combination with clinical data to predict the future occurrence of falls and syncope. Thus, this work contributes to the development of clinical decision support tools to assist in the identification of individuals at risk of falling and fainting, aiding in its prevention, assessment and management.

Chapter 10: Discussion and Conclusion

10.1 Thesis Summary

Early identification of patients at risk of falls and syncope could help prevent these events through appropriately targeted and personalised interventions. While a number of haemodynamic biomarkers have been defined and used in clinical practice for assessing this risk, they are usually normative threshold values applied to capture phenotypical patterns (e.g. orthostatic hypotension (OH)) that primarily focus on peripheral circulatory responses during orthostatic challenges. However, falls and syncope are believed to be often attributed to cerebral hypoperfusion. Near-infrared spectroscopy (NIRS) is emerging as a suitable technology to assess cerebral circulation during falls and syncope assessment, given its ease of use and its ability to capture transient changes in cerebral oxygenation during dynamic changes in posture.

In this thesis it was hypothesised that biomarkers of altered cerebral oxygenation in falls and syncope patient cohorts could be identified from NIRS and used in combination with peripheral haemodynamics (blood pressure (BP), heart rate (HR), total peripheral resistance (TPR), cardiac output (CO), etc) to establish a framework for the development of clinical decision support tools, which could ultimately assist clinicians in the assessment and management of these patients. This work has demonstrated that NIRS is a feasible and suitable method for this purpose and that it can be successfully integrated within the workflow of real-life clinical settings. An important outcome of this thesis is a reusable database of clinical and haemodynamic data resulting from the harmonisation of two comprehensive and unique

dataset from a community-dwelling and clinical databases. An analytical framework using artificial intelligence (AI)/ machine learning (ML) algorithms was also developed for the identification of patients with unexplained falls (UF) and syncope, which represents the first step towards a clinical decision support tool to assist clinicians in the risk assessment of these patients. Furthermore, this work has provided more in-depth scientific understanding of the cerebral oxygenation responses evoked by standing in patients at risk of falls and syncope, which will inform future directions of research into understanding how these episodes originate and can be prevented.

10.2 Main Findings

Figure 10.1 provides an overview of the thesis and summarises the main results of the four key studies. In these studies, it has been demonstrated that older adults with falls and syncope, have different cerebral oxygenation responses to standing than controls, representing new biomarkers to identify at risk patients. Two main cohorts were identified based on age and clinical outcomes: young individuals with vasovagal syncope, and older adults with UF and syncope. Moreover, both sex and multimorbidity/frailty strongly modified orthostatic cerebral oxygenation and peripheral haemodynamic responses, suggesting that these factors should be accounted for when assessing cerebral and systemic haemodynamic patterns in older adults. In young patients with syncope, some differences were observed in the changes in concentration of deoxyhaemoglobin ($\Delta[\text{HHb}]$) response to standing when compared to controls, while no differences were found in the overall tissue saturation index (TSI) response. In peripheral haemodynamics, clear differences were observed when compared to controls, especially in the blood pressure response to standing. Furthermore, for the first time, AI/ML algorithms have been successfully employed using cerebral and peripheral haemodynamic predictors, together with a comprehensive clinical history

(multimorbidity/frailty index), to accurately classify individuals with complex clinical falls and faints. All these results represent significant steps towards the translation of NIRS into clinical use and the development of future clinical decision support tools for falls and syncope assessment and management. Below, the clinical importance of the findings of this thesis is discussed according to the research questions presented in *Chapter 4: Research Questions*.

10.2.1 Age and Sex are Important Factors in Studying Cerebral Oxygenation Responses to Standing in Patients with Falls and Syncope

Age and sex are often essential factors to consider in medicine. Physiological and clinical differences are well established between men and women, and ignoring this sex dimension may mask them, negatively impacting the ability of clinicians to tailor treatments to specific patients. Similarly, ageing involves a series of physiological changes and development of clinical conditions that must be acknowledged. Chapter 6 investigated how age and sex influenced the cerebral oxygenation responses to standing in the initial cohort of patients recruited from a Falls and Syncope Unit (FASU). Additionally, age and sex differences in clinical outcomes of interest (falls, UF and syncope) were investigated.

Age was associated with impairments in the cerebral oxygenation response to standing independent of systolic blood pressure (SBP) during the recovery phase between nadir and overshoot when considering the entire cohort. However, if only older adults ($50 \geq$ years) were analysed, the age effects were no longer statistically significant, which suggests that the age associations observed were attributed to differences between the youngest and older groups. Furthermore, strong associations of clinical outcomes of interest (falls, UF and syncope) with age were noted. These observations contributed to the decision to separate the patient cohort into a young

group (with vasovagal syncope (VVS)) and an older group with a more heterogeneous clinical profile, including UF and syncope.

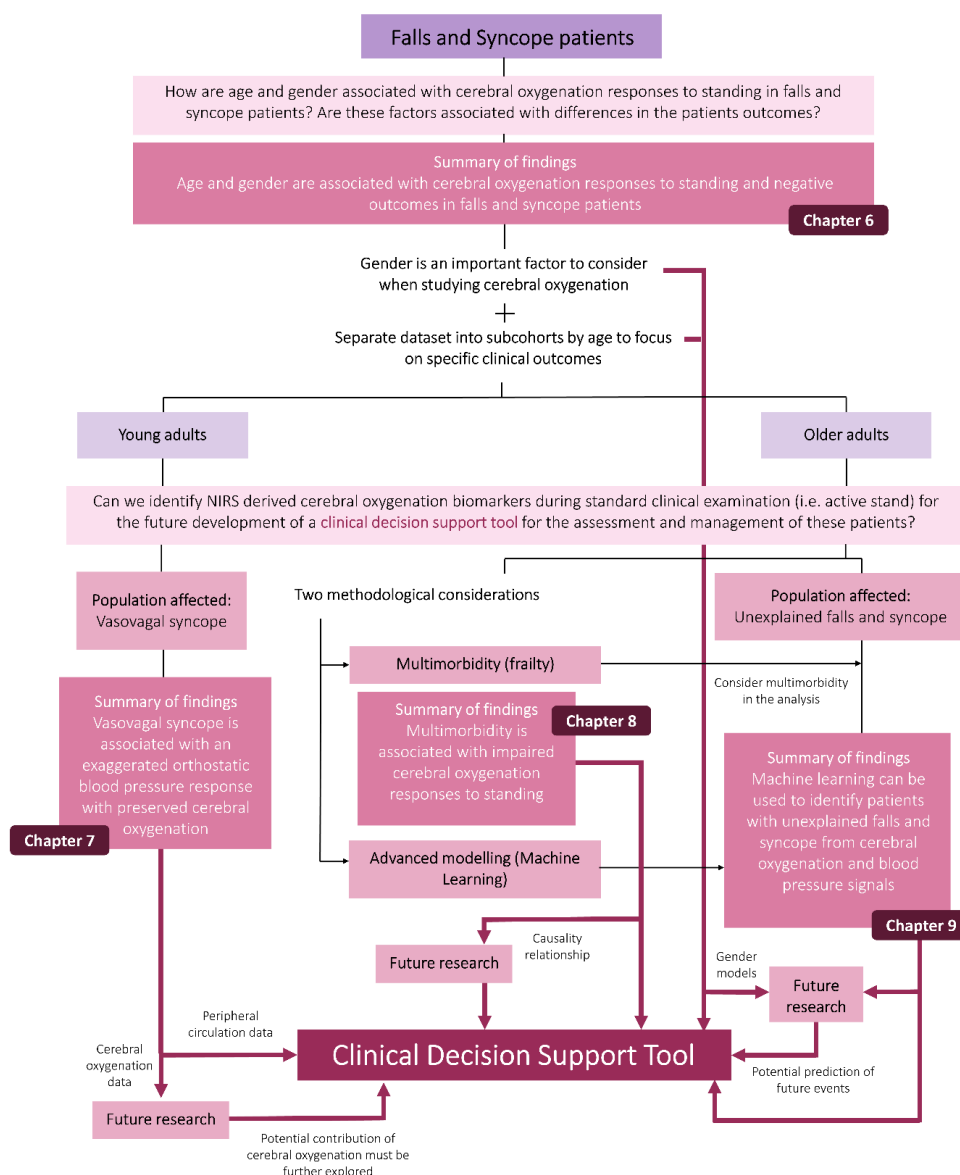


Figure 10.1. Summary diagram of the studies presented in this thesis.

Diagram depicting an overview of the thesis studies and how they contribute to the future development of a clinical decision support tool to assist clinicians in the assessment and management of patients with falls and syncope. The results from Chapter 6 suggested the separation of the clinical cohort studied into two subcohorts, young adults with vasovagal syncope and older adults with unexplained falls and syncope. Results from Chapter 7 demonstrated that blood pressure responses to standing in young patients with vasovagal syncope are altered, and suggested that future studies should continue to focus on differences in cerebral oxygenation responses to fully understand the role of NIRS in the evaluation of these patients as part of a software decision support tool. In older adults, Chapter 8 demonstrated that multimorbidity is associated with impairments in the cerebral oxygenation responses to active standing. This finding directly contributes to the development of the decision support tool, as well as to Chapter 9, in which multimorbidity was used as part of artificial intelligence/machine learning algorithms in combination with cerebral and peripheral haemodynamic signals for the classification of patients with unexplained falls and syncope. Future research in this area should consider sex-specific models. Furthermore, the results from Chapter 9 represent the first step towards the prediction of future falls and syncopal events using artificial intelligence, multimorbidity and haemodynamics data.

These impairments observed with age in Chapter 6 during the initial recovery were in line with other studies [226, 413]. During steady-state weaker effects were observed as compared to those observed in the initial response, with age being associated with lower TSI values only univariately. While some studies have performed similar investigations during steady-state, further research is needed to establish whether ageing and in particular healthy ageing are modifiers of orthostatic cerebral oxygenation responses, given that the literature to date provides equivocal evidence [226-228].

Regarding sex, strong differences were observed in the cerebral oxygenation responses to standing, with women having a more attenuated initial response in cerebral oxygenation (i.e., smaller nadir and initial recovery (first 30 seconds)). These results are in line with previous investigations, and may potentially be suggestive of a better CA mechanism in women [241]. Additionally, sex was found to be associated with clinical outcomes in multivariate analyses. These findings highlight the value of considering sex in studies involving measures of orthostatic cerebral oxygenation for the assessment of falls and syncope. Sex was therefore used as a covariate in Chapter 7, while in Chapter 8 a larger sample size allowed the study of women and men separately. Chapter 9 used for the first time cerebral oxygenation measures as predictors of falls and syncope events using AI/ML models. Given the exploratory and technical nature of this study, the focus was on investigating different technical approaches (e.g. predictors, algorithms), while sex specific models remain a logical next step.

10.2.2 Peripheral and Cerebral Oxygenation Responses to Standing in Young Patients with Vasovagal Syncope

While this thesis focuses on UF and syncope, UF in young adults are an unusual presentation in FASU settings. For that reason, the focus was on syncope in this

population. In particular, the most common type of syncope in this cohort is VVS. Thus, given the participants age (18-30 years) and to avoid heterogeneity resulting from including different clinical entities, VVS and not other types of syncope was the focus in this cohort. To our knowledge, this is the first time that cerebral oxygenation patterns have been studied in a group of young adults with VVS during the active stand (AS) test.

In this study, limited if any differences in cerebral oxygenation were observed, only noting a blunted initial deoxygenated haemoglobin response to standing in patients with VVS as compared to controls, which might be due to a less pronounced brain activation [430] or more efficient cerebral autoregulation (CA) [432] in VVS patients. Furthermore, potential differences in resting (CO_2 partial pressure) PaCO_2 and orthostatic induced hypocapnia might have contributed to the results, given that CO_2 can influence cerebral perfusion via changes in CA [107]. It was not possible to test this hypothesis given that the lack of CO_2 measurement was a limitation of this project. The deoxygenated haemoglobin differences identified were not strong enough to be reflected in the overall cerebral oxygenation, given that TSI responses were comparable to that of controls. Therefore, the results presented do not provide enough evidence to support the hypothesis that cerebral oxygenation supply after standing is altered in syncope. This suggests that syncope may not be associated with dysfunction of cerebral regulatory mechanisms and that, as detailed in the next paragraph, syncope might be cardiovascular in origin instead. However, the sample size used is relatively small, and therefore the differences detected in deoxygenated haemoglobin patterns motivate further investigations of cerebral oxygenation in larger groups of VVS patients.

From the peripheral circulation perspective, the results observed contribute to an emerging theory regarding the origin of syncope. Researchers from our group

previously suggested that patients with vasovagal syncope demonstrate peripheral haemodynamic patterns during standing that correspond to a hyper-sensitive autonomic nervous system [420, 421]. This hypothesis is supported by recent work by Brignole et al., who demonstrated increased resting haemodynamics in patients with VVS [431]. The results presented on peripheral circulation, which demonstrate that syncope patients recover to a higher systolic blood pressure (SBP) value, are in line with these observations, and support a hyper-sensitive autonomic function theory. According to this theory, the autonomic nervous system would have chronically higher activity, which would result in its activation level being closer to its physiological limit. In a test like the AS, which represents a moderate challenge for the neurocardiovascular system, an over-reaction in the haemodynamic response would therefore be observed. Nevertheless, in the event of a stronger disturbance, such as a spontaneous or head up tilt (HUT) provoked syncope, and given that the autonomic system is closer to its physiological limit, a smaller disturbance is required to reach it, and this results in an increased susceptibility to triggering the syncope reflex.

10.2.3 Multimorbidity is Associated with Impairments in the Cerebral Oxygenation Response to Standing in Older Adults with Falls and Syncope

The third study presented in this thesis (Chapter 8) demonstrated a novel and clinically important result i.e., cerebral oxygenation recovery after standing is impaired with increasing multimorbidity (as an index of frailty) in a clinical cohort of older adults. While cerebral blood flow and oxygenation impairments have been previously reported in age-related morbidities [41, 307, 446, 447, 449], to our knowledge, no clinical studies have investigated how the accumulation of morbidities or frailty is related to cerebral oxygenation. This is therefore a very young and novel field. Maguire et al. recently demonstrated a delayed recovery in cerebral oxygenation responses to

standing in community-dwelling adults with frailty [311]. Arguably stronger results have been observed in the cohort of patients used in Chapter 8. This provides strong evidence that multimorbidity/frailty in older adults is associated with poorer cerebral perfusion, and that this may generalise to different populations, i.e., community and clinical populations. Whether these associations are causal remains to be investigated in longitudinal studies. However, the proposed hypothesis is that it is most likely a positive feedback process, with frailty related morbidities resulting in impairments in cerebral oxygenation (directly or through peripheral impairments), which further feeds into future cerebral dysfunction (neuronal, cerebrovascular, inflammation), likely resulting in further cerebral hypoperfusion, which then contributes to the development of further morbidities (Figure 10.2). Whether the origin is the development of morbidities, cerebral dysfunction, peripheral impairments, or cerebral hypoperfusion remains unknown, and is likely multifactorial and patient dependent.

Besides furthering the current understanding of cerebral oxygenation in multimorbidity, this study has the potential to have significant clinical impact. Firstly, it provides evidence that multimorbidity/frailty is associated with poorer recovery in brain haemodynamics during standing, a manoeuvre that occurs repeatedly on a daily basis. Therefore, this emphasises the clinical role of multimorbidity/frailty as an indicator of patient vulnerability. Furthermore, given that the multimorbidity index used has a strong cardiovascular focus (when compared to other indices [37]) it is possible that it captures the key elements of frailty that are relevant to cerebral oxygenation in falls and syncope assessment. In addition, this work demonstrated the added value of including NIRS in this clinical context, given that the cerebral oxygenation impairments observed were independent of BP measures, which currently constitute the gold standard assessment for falls and syncope [1]. Therefore, these results suggest that NIRS should

be incorporated in the evaluation of falls and syncope especially in older frailer adults to provide a more personalised and complete clinical management.

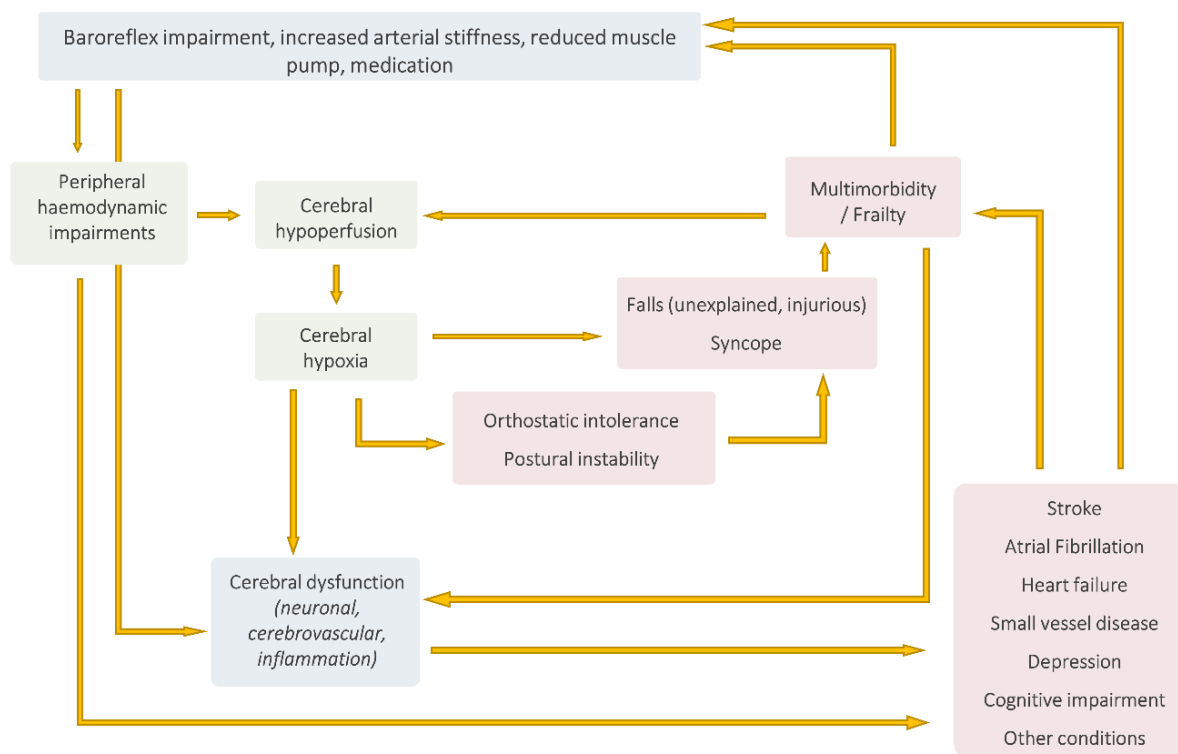


Figure 10.2. Theoretical mechanism by which peripheral and cerebral haemodynamics are hypothesised to be related to multimorbidity/frailty in older adults.

Blue boxes represent the pathophysiological mechanisms, green boxes their haemodynamic consequences, and red boxes are the resulting negative clinical outcomes. Mechanisms such as baroreflex impairment, increased arterial stiffness, reduced muscle pump or medications are proposed to cause peripheral haemodynamic impairments and directly contribute to cerebral dysfunction. Impairments in cerebral circulation might result in cerebral hypoperfusion, leading to cerebral hypoxia, which is proposed as another contributor for cerebral dysfunction development. This dysfunction may result in several medical conditions such as stroke, atrial fibrillation, heart failure, small vessel disease, depression or cognitive impairment. Cerebral hypoxia can also lead to falls and syncope either directly or after causing symptoms of orthostatic intolerance and postural instability. Falls and syncope, together with the other aforementioned medical conditions, contribute to increased multimorbidity and frailty. Multimorbidity and frailty can then further aggravate or initiate the development cerebral dysfunction either directly or through baroreflex impairment, increase arterial stiffness and reduced muscle pump, as well as result in the addition of more medications.

Despite being beyond the scope of this study, the time relationship between BP and TSI deserves some attention. The overall average time to nadir in SBP was 8.9s, while for TSI it was 7.9s (data not provided in the study). Although the signal synchronisation method used had some limitations (two marks pressed in two different keyboards and collected by two different software tools), unreported experimental

testing revealed that the maximum time error introduced by this system would be of about 1 second. This implies TSI recovers at the same time as SBP, if not earlier. This behaviour has been previously described in studies investigating dynamic CA [458], and two hypotheses have been proposed. Some authors have suggested that this cerebral circulation phase lead may be indicative of sympathetic neural regulation of the cerebrovasculature [459, 460]. On the other hand, there is a clearer consensus on the second hypothesis, which supports that this phase difference is a consequence of the underlying increase in cerebrovascular resistance through the mechanism of CA, which would help cerebral circulation recover faster than it would if it depended solely on BP recovery. In the case of the patient population presented in this study, the results observed would be suggestive of a preserved cerebral autoregulatory mechanism, which is more noticeable in patients with less morbidities (see Figure 8.2). However, a more robust synchronisation system and appropriate CA measures would be required in the future to fully understand how multimorbidity affects CA.

10.2.4 Artificial Intelligence/Machine Learning based Clinical Decision Support Tools for Identifying those at risk of unexplained falls and syncope

The last study of this thesis (Chapter 9) demonstrated for the first time that cerebral oxygenation and peripheral hemodynamic signals and AI/ML models can be used to accurately identify patients with UF, syncope and unexplained falls and/or syncope (UFS). Furthermore, combining cerebral oxygenation measures with blood pressure (BP) measures yields better performance, with accuracies (AUC) obtained being 74.2% (0.812), 62.8% (0.584) and 67.3% (0.667) for UF, syncope and UFS, respectively. From section 10.2.3 above (and Chapter 8), multimorbidity was considered a relevant methodological factor that should be accounted for when investigating cerebral oxygenation patterns in older adults. Therefore, clinical history

(i.e., morbidity count) was included as a predictive factor in the models design. This resulted in better performance than only using BP and TSI for the classification of UF and UFS, with accuracies (AUC) of 74.2% (0.875) and 67.3% (0.667), respectively. This study was retrospective and therefore did not include the prediction of future risk of falls and syncope. However, the results observed serve as a very strong base for future prospective studies. The three elements of information included in these investigations (clinical data (morbidity), BP and TSI) were found to be most useful in combination, as part of a clinical decision support tool to help clinicians identify patients at a higher risk of future falls and syncope. The harmonisation of a community-dwelling and clinical datasets also yielded a unique database of blood pressure, cerebral oxygenation and clinical information, the largest of its kind in the world, which represents a valuable research output of this thesis. Additionally, from a physiological point of view, the results from Chapter 9 suggest that alterations in both peripheral and cerebral regulatory mechanisms might be involved in UF, while syncope might be more attributable to impairments in peripheral haemodynamics regulation despite a healthier brain.

In the models that did not include the morbidity count, syncope was better classified when only using SBP features, while for UF a combination of TSI and SBP features performs better. This may suggest that the cause of UF might be attributed to both dysregulation of blood pressure and cerebral perfusion, while syncope may be mainly peripheral in origin with potentially healthier brains than UF patients.

The AI/ML framework developed in this work has the potential to be implemented in a software tool that could be used in clinical settings. Two main scenarios can be envisaged. The first one, with a huge and broad potential, is the early identification of future fallers and fainters in community settings such as GP clinics or

nursing homes. Patients could be routinely screened by performing an AS test with BP and TSI measured. This data, together with clinical data from an electronic patient record, would then be integrated into the software, which would extract and derive the relevant features and use them as inputs for ML models. The clinician would then receive a score on the user interface of the software with a probability risk of the patient falling or fainting in the future, together with a highlight of key modifiable predictors. This information, together with values of relevant features highlighted by the program, could be used by clinicians to design a personalised strategy to help prevent the occurrence of such falls and faints in that specific patient (i.e., physiotherapy, medication modifications, social support, etc.). The second scenario is in more falls/syncope-focused clinical environments, such as the emergency department or specialised falls and syncope clinics. The data would be collected in a similar manner, but in this case it would be from complex patients who had an event of unclear origin (e.g. the patient is confused and is not able to tell whether they had a fall or lost consciousness). The software would then provide a score related to the probability of the event being a fall or a faint, which would assist the clinicians in determining what future interventions are required. Future research is needed to develop models that allow distinguishing between these two types of events.

10.3 Strengths

A key ingredient for the success of this thesis work is its collaborative nature, given the close collaborative ties established between the biomedical engineering and medical gerontology departments in St. James's Hospital Dublin. Two PhD projects were designed to develop complementary investigations from a clinical (Dr. Claffey's project) and biomedical engineering perspective (the current project) to understand the role of NIRS in the assessment of falls and syncope. On the one hand, clinical insights

from this collaboration have been incorporated at all stages of this thesis, including study design, data collection, software planning, signal and data analysis design, feature definition and statistical analysis design. Assistance in the clinical interpretation of the results was also paramount for a thorough and multilevel discussion of the findings observed in each study. On the other hand, the software framework developed for this project was designed to allow data analysis and feature extraction for Dr. Claffey's clinical investigations. Furthermore, scientific and biomedical engineering input was provided throughout study design, data collection, statistical analysis and results interpretation and discussion (see Appendices A and C for reference to the studies resulting from this collaboration other than the ones presented in this thesis).

One of the main strengths of this thesis relies on the data used and how it was collected. The author had the valuable and unique opportunity of working as a biomedical engineer for 2 years on a daily basis in the Falls and Syncope Unit at St. James's Hospital Dublin. This enabled prospective collection of NIRS data and assisting in the collection of BP and clinical data, which was already part of standard patient assessment in this clinical setting. This resulted in a large database of patient data, which represents a unique cohort of FASU patients with clinical, cerebral oxygenation and peripheral circulation data.

Furthermore, for the last study, control participants without falls and syncope were needed in order to create appropriate classifier models. Given that this would require recruitment of a large number of community-dwelling volunteers, which was not possible within the time constraints of this project, this data was sourced through collaboration with The Irish Longitudinal Study on Ageing (TILDA). TILDA participants selected were community-dwelling adults without falls or faints who underwent the same AS protocol (with NIRS and BP measurements) as patients in

FASU. Despite some considerable logistical challenges, the two datasets were successfully harmonised and feature extraction was performed using the same software on both cohorts.

The test used in the studies presented in this thesis, the AS, is a simple manoeuvre that can be performed easily by most people, and is more comfortable/natural than other orthostatic challenges such as the head-up-tilt or squat-to-stand tests. Furthermore, NIRS can be easily integrated in the protocol, with an easy 2-3 minute setup that is barely noticeable for the patient.

The morbidity count developed was a simple index of multimorbidity or frailty derived from clinical conditions relevant to falls and syncope. While most studies investigating orthostatic changes in peripheral or cerebral circulation in older adults use chronological age as a covariate, they do not include a marker of biological age. This morbidity count represents an indicator of biological age that has proven to be useful when considered as a methodological factor in the study of cerebral oxygenation in older adults.

This thesis also explored for the first time the use of AI/ML approaches to classify participants into unexplained fallers or fainters from their peripheral and cerebral haemodynamic signals. ML algorithms have the ability to combine large number of features in complex non-linear relationships, while automatically selecting optimal combinations of features that can result in better classification performance. Furthermore, UF rather than all-cause falls were investigated, given that they are the ones that are most likely to be related to the neurocardiovascular system and thus be predicted from haemodynamic signals.

10.4 Limitations

The studies presented in this thesis have different limitations that must be highlighted. Firstly, the study on young patients with syncope presented in Chapter 6 has a small sample size and therefore is exploratory. This may explain why no differences were found in TSI responses between patients and controls. However, some differences were noted in deoxygenated haemoglobin, which might motivate future studies to investigate this further.

Regarding multimorbidity, while the morbidity count used is useful in identifying associations between cerebral oxygenation and frailty, it is a relatively simple index of frailty. While it contains 26 variables, it does not strictly meet the minimum number of variables (30-40) recommended for developing a frailty index from clinical data [461]. Furthermore, in the last study, the combination of the FASU and TILDA datasets required harmonisation of common variables. This resulted in a smaller list of morbidities that constituted the morbidity count for the ML analyses, given that not all the morbidities collected in the FASU cohort were also collected in the TILDA study, and viceversa. The harmonisation of the common variables also poses a limitation, as some of the clinical variables were similar but did not have the exact same definition in the two cohorts (e.g., while in FASU a history of self-reported chronic obstructive airway disease was recorded, the TILDA equivalent variable was a history of self-reported chronic lung disease such as chronic bronchitis or emphysema). Another relevant limitation of this study was the lack of inclusion of a cohort of fallers and fainters from TILDA. This would allow determining whether the models developed are useful not only for differentiating between falls and syncope patients and community-dwelling controls, but also between fallers/fainter and non-fallers/non-fainters within a community-dwelling population. This would strengthen the promising

application of the developed models in identifying individuals at risk of falls and syncope, extending its potential use to broader community settings such as GP services.

The aim of this thesis was to use the available technology for the assessment of falls and syncope with the addition of NIRS to find biomarkers that would help identify more vulnerable patients. Therefore, the studies presented were not designed to thoroughly study the pathophysiology of the medical conditions investigated, although that did not impede the derivation of potential physiological explanations for the results obtained. A big limitation on this regard is the lack of CO₂ monitoring in the protocol used. Therefore, the possibility that respiratory variables such as CO₂ partial pressure (PaCO₂) contribute to the presented findings remains. These limitations are often difficult to overcome in a busy clinical setting like the one of this thesis, given the challenges in feasibly integrating the technology in the clinic workflow, nursing and medical team training, and comfortability for the patients. However, these answers could be derived by studying a relatively smaller subset of patients with properly designed respiratory protocols and equipment.

A number of limitations of NIRS have been extensively discussed in section 2.3.2.4. Methodological Aspects of NIRS and might have affected the results obtained in these studies. All the data used in this thesis was obtained using SRS NIRS, and therefore DPF adjustments were not required. SRS is theoretically not susceptible to extracerebral tissue, although some evidence suggests this should be accounted for [182, 185]. An attempt was made to minimise this effect by only analysing changes from baseline, although to what extent extracerebral contamination is influencing these variables remains unknown. Motion artifact is another relevant source of noise in NIRS. While patients were instructed not to talk or move during the AS test, in some occasions this was not possible due to mobility or stability issues, or even because patients were

nervous and they needed to interact with the nurses during the test. Therefore, motion artefacts were often inevitable given the real-world nature of the clinical setting used, and might have confounded the results observed. Nevertheless, these type of real-world signals are valuable even if with noise, given that they are more representative of what clinicians would encounter in medical units than those from well controlled experimental settings. Furthermore, noise was minimised by a number of steps including visual signal quality inspection following a thorough set of criteria (described in section 5.6.2 Signal Quality Evaluation) and signal filtering strategies implemented in the software framework developed for this project.

Future Work

Future work concerning this thesis can be discussed in the context of the specific studies and with regards to the broader scientific field.

As previously highlighted, future work regarding the investigation in young syncope patients should focus on studying larger cohorts, given that the associations observed in the TSI data were only present in the univariate analysis and before applying correction for multiple testing. Sex stratification would also be necessary to determine whether there are differences in cerebral oxygenation responses in syncope between men and women.

With regards to the multimorbidity study in older adults, other clinical populations should be investigated to understand the generalisability of the observed findings. Furthermore, other frailty indices that capture different components of frailty could be explored. For instance, the Fried phenotype incorporates physical objective measures of strength and walking speed [462], which might help capture episodes of falls and faints related to postural stability and balance issues. The relationship between

cerebral oxygenation, multimorbidity and falls should also be explored, preferably with a longitudinal study design in order to understand the causality of these interactions.

The AI/ML investigations presented could also be further developed by using deep learning approaches such as neural networks, which represent more complex models that do not require the user to extract features from the signals, but are rather selected by the algorithm. Furthermore, adding community-dwelling fallers and fainters during training and evaluation of the model would reveal whether the developed models are generalisable to the community, or if otherwise they are only useful in classifying between community-dwelling adults and the most complex cases of UF and syncope (i.e., those that are seen in falls and syncope units). Sex has been identified in this thesis as a crucial factor to consider when studying cerebral oxygenation in falls and syncope. Thus, sex specific models would represent a step forward in the personalisation provided by the models developed. Lastly, as previously discussed, the presented models could be used as the basis for developing models to predict the risk of future falls and syncope events.

Besides the above mentioned future directions for the specific studies, overall future directions can also be highlighted. Firstly, deriving measures of CA would improve our understanding of this mechanism in the context of falls and syncope, and might be useful variables to include in the models for predicting and classifying these events. Monitoring CO₂ in a FASU clinical setting as standard practice would be relatively easy, with incorporating CO₂ in smaller subsets of participants beneficial for understanding how this vasoactive gas influences the cerebral oxygenation responses observed. From a signal processing perspective, future studies should explore the use of noise identification and reduction strategies to improve the signal to noise ratio of clinical cerebral oxygenation data.

Future work on the field of falls and syncope should be developed at different methodological levels. The study on ML presented here represents only the first steps towards the development of a software tool to assist clinicians in community and specialised clinical contexts. However, software needs to be complemented with appropriate hardware. At the moment, beat-to-beat blood pressure monitors such as the one used in this work remain inaccessible for non-specialised settings, given their cost and the expertise required for their use. Nevertheless, with emerging novel technologies for this purpose [463, 464], it seems realistic to predict that continuous measures of BP will be soon possible in this type of community clinics. The combination of these two factors (software and hardware) will allow the full development of a tool that will assist clinicians in identifying the most vulnerable individuals at risk of falls and faints.

A number of gaps still remain also regarding NIRS. More research is needed in the validation of this technology, as well as for a more in depth understanding of the origin of the signals captured. Furthermore, how some factors such as sex and age influence specific parameters involved in the derivation of cerebral oxygenation (i.e., k or h in the derivation of TSI, see Section 2.3.2.4 Methodological Aspects of NIRS) still remains unexplored, and could confound some of the associations observed in this thesis.

In this project, the PortaLite monitor from Artinis Medical Systems was used. This is a non-medical grade device, which limits the direct translation of this monitor into standard clinical practice. When considering the future incorporation of NIRS into a FASU unit, two possibilities can be considered. The first one constitutes the approval of the PortaLite by regulatory bodies such as the US FDA or the European Union Medical Device Directive [176]. This would require validation of the device during controlled levels of end tidal CO_2 using measures of co-oximetry taken from the brain

arterial supply and venous drainage, typically obtained from the carotid artery and jugular bulb, respectively. These two saturation measures are then weighted (usually 0.25 or 0.30 for arterial contribution and 0.75 or 0.70 for venous contribution), and a global measure of cerebral oxygenation is derived. Alternatively, instead of using the PortaLite, a commercially available medical grade NIRS device could be implemented in clinical practice. Examples of such monitors include the INVOS (Medtronic, Minneapolis, Minnesota), FORESIGHT (CAS Medical Systems, Branford, Connecticut) or TRS-20 (Hamamatsu Photonics, Hamamatsu city, Japan) [193]. This would entail validation of the results obtained in this thesis with the new monitor. However, results are not expected to be hugely impacted by the change in device, given that values relative to baseline were used, which are encouraged over absolute values due to a higher reliability.

Lastly, more research is needed to understand the pathophysiology of syncope (in the young and the old) and falls, in particular UF, which represent a complex type of events with a huge impact in the quality of life of these patients and a potentially avoidable economic burden to society. This research should focus on determining the direction of causality between cerebral oxygenation/perfusion, multimorbidity and falls and syncope events.

10.5 Impact of Current Work

The current work has several relevant and significant impacts. Firstly, it has impacted clinical practice in different ways. The studies presented demonstrated that investigating cerebral oxygenation with NIRS provides information that adds value to that already collected in standard practice (i.e., BP and clinical data) for the assessment of falls and syncope in older adults. Therefore, these studies study might motivate

future investigations using NIRS during an AS test and in the long run the incorporation of NIRS as part of standard medical practice in falls and syncope units, which might enhance assessment and management of these patients by providing more personalised insight on their conditions and disease progression. Another clinical impact of this thesis is the use of multimorbidity as an index of frailty in the assessment of patients with falls and syncope. Frailty is standardly assessed in geriatrics clinical settings, but the findings from this work highlight that a simple morbidity count can identify what patients might be at a higher risk of impaired cerebral oxygenation recovery after standing.

This work also has valuable methodological impacts. Firstly, it was repeatedly observed that variables derived from the initial transient period (30 first seconds) after standing played an important role in the studies findings. This highlights the value of using finger plethysmography to capture beat-to-beat fast transient changes that cannot be studied with other methods such as the oscillometric approach, which is normally used in community clinical settings for the medical evaluation of falls and syncope. New features of the haemodynamic response of BP and NIRS after an AS that are not usually studied were also investigated, such as the overshoot or the recovery pattern from the nadir to the overshoot, which are encouraged in future similar studies to fully characterise the morphology of the responses. Lastly, novel AI/ML models were developed which could be validated in other clinical and community-dwelling populations and could set the grounds for developing new models for predicting future falls.

In summary, the findings from this thesis contribute to the future development of clinical decision support tools that could assist clinical teams in identifying patients at an increased risk of cerebral oxygenation impairments, falls and faints. These support

tools would be of use in non-specialised settings with less expertise on the assessment and management of falls and syncope. The author of this thesis envisages a future in which clinical history collected by medical personnel would be combined with transient BP and cerebral oxygenation measures from an AS using software based on the analytical framework developed in this thesis. AI/ML algorithms would then process and integrate the data and provide a value of the predicted risk of future falls or syncope events. Given the explainability nature of the models developed in this work, clinicians would be able to identify predictors of interest, which may assist them in tailoring personalised interventions for those patients by targeting modifications on those specific predictors.

10.6 Conclusion

The work presented in this thesis demonstrates that incorporating NIRS in the assessment of patients with falls and syncope can help identify cerebral oxygenation impairments in older adults with multimorbidity, and can be used in combination with already collected clinical and peripheral circulation data to classify patients with UF and syncope. This thesis established a framework for the future development of clinical decision support tools that could assist clinicians in providing a more personalised and enhanced assessment and management of patients with falls and syncope.

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Appendices

This section contains the appendices of this thesis as outlined below:

- **Appendix A:** contribution to collaborative research article by Dr. Paul Claffey on the use of near-infrared spectroscopy for the management of patients with Psychogenic Pseudosyncope
- **Appendix B:** contribution to collaborative review on systemic and cerebral circulatory initial responses to standing
- **Appendix C:** contribution to research article by Dr. Paul Claffey on the use of near-infrared spectroscopy for the management of patients with Orthostatic Hypotension.
- **Appendix D:** contribution to research article by Dr. Susie O’Callaghan on the use of near-infrared spectroscopy for falls risk assessment in community-dwelling adults
- **Appendix E:** informed consent documents
- **Appendix F:** standard operating procedure for the active stand protocol
- **Appendix G:** details on the software framework developed
- **Appendix H:** criteria for signal quality evaluation
- **Appendix I:** supplementary material for Chapter 7
- **Appendix J:** supplementary material for Chapter 8
- **Appendix K:** supplementary material for Chapter 9

Appendix A: NIRS in Psychogenic Pseudosyncope

Claffey P, **Pérez-Denia L**, Rivasi G, Finucane C, Kenny RA. Near-Infrared Spectroscopy in Evaluating Psychogenic Pseudosyncope - A Novel Diagnostic Approach.

QJM: monthly journal of the Association of Physicians.. 2020 Apr 1;113(4):239-244.
doi: 10.1093/qjmed/hcz257. PMID: 31596496.

Author's contribution

The author of this thesis contributed to the following aspects of the above cited research article:

- Study co-design
- Collection of near-infrared and peripheral haemodynamics data
- Signal processing and feature extraction
- Creation of article figures
- Statistical analysis
- Results interpretation and discussion
- Review and approval of the final manuscript

Abstract

Psychogenic pseudosyncope (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). Electroencephalogram (EEG), a time consuming and resource intensive technology, is used during HUT to demonstrate absence of cerebral hypoperfusion during transient loss of consciousness (TLOC). Near-infrared spectroscopy (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 HUT.

Eight consecutive patients with suspected PPS referred to a syncope unit underwent evaluation. During HUT, continuous beat-to-beat blood pressure (BP), heart rate (HR) and NIRS-derived tissue saturation index (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.

Eight predominantly female patients (6/8,75%) 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. 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).

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

Appendix B: Systemic and Cerebral Initial Response to Standing Review

Harms MPM, Finucane C, **Pérez-Denia L**, Juraschek SP, van Wijnen VK, Lipsitz LA, van Lieshout JJ, Wieling W. Systemic and cerebral circulatory adjustment within the first 60 s after active standing: An integrative physiological view. *Autonomic Neuroscience: Basic & Clinical*. 2021 Mar;231:102756. doi: 10.1016/j.autneu.2020.102756. Epub 2020 Dec 10. PMID: 33385733; PMCID: PMC8103784.

Author's contribution

The author of this thesis contributed to the following aspects of the above cited literature review article:

- Active communication and discussion with the primary authors on the contents and focus of the review
- Thorough review of multiple versions of the article during an iterative review process
- Assistance with image editing
- Review and approval of the final manuscript

Abstract

Transient cardiovascular and cerebrovascular responses within the first minute of active standing provide the means to assess autonomic, cardiovascular and cerebrovascular regulation using a real-world everyday stimulus. Traditionally, these responses have been used to detect autonomic dysfunction, and to identify the hemodynamic correlates of patient symptoms and attributable causes of (pre)syncope and falls.

This review addresses the physiology of systemic and cerebrovascular adjustment within the first 60 s after active standing. Mechanical factors induced by standing up cause a temporal mismatch between cardiac output and vascular conductance which leads to an initial blood pressure drops with a nadir around 10 s. The arterial baroreflex counteracts these initial blood pressure drops, but needs 2–3 s to be initiated with a maximal effect occurring at 10 s after standing while, in parallel, cerebral autoregulation buffers these changes within 10 s to maintain adequate cerebral perfusion. Interestingly, both the magnitude of the initial drop and these compensatory mechanisms are thought to be quite well-preserved in healthy aging.

It is hoped that the present review serves as a reference for future pathophysiological investigations and epidemiological studies. Further experimental research is needed to unravel the causal mechanisms underlying the emergence of symptoms and relationship with aging and adverse outcomes in variants of orthostatic hypotension.

Appendix C: NIRS in Orthostatic Hypotension

Claffey P, **Pérez-Denia L**, Dyer A, McNicholas T, Briggs R, Finucane C, Kenny RA.

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

(Article in preparation)

Author's contribution

The author of this thesis contributed to the following aspects of the above cited research article:

- Study co-design
- Collection of near-infrared and peripheral haemodynamics data
- Signal processing and feature extraction
- Results interpretation and discussion
- Review and approval of the final manuscript

Abstract

Orthostatic Hypotension (OH) is associated with poor health outcomes in later life including depression, cognitive impairment and falls. Whilst it is hypothesised that OH compromises cerebral autoregulation leading to hypoperfusion, this has not been robustly demonstrated to date. This study investigated the association between OH and cerebral perfusion during orthostasis using a non-invasive surrogate of cerebral perfusion, Near Infrared Spectroscopy (NIRS).

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 blood pressure (BP) by finometry and real-time frontal lobe perfusion (% TSI: Tissue Saturation Index) by NIRS during the active stand manoeuvre. We examined the association between OH and change in cerebral perfusion (delta TSI) using mixed-effects linear regression, with adjustment for important clinical covariates.

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, -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 perfusion levels differed for those with OH compared to those without.

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

Appendix D: NIRS in Falls in Community-Dwelling adults

O’Callaghan S, Finucane C, **Pérez-Denia L**, Claffey P, Newman L, Reilly R, Kenny RA. Orthostatic Pressure-Perfusion Product: A New Approach for Assessing Personalised Falls Risk in Older Adults combining Continuous Real-time Near Infrared Spectroscopy and beat-to-beat Blood Pressure Measurement.

(Article in review)

The author of this thesis contributed to the following aspects of the above cited research article:

- Thorough review of article during an iterative review process
- Review and approval of the final manuscript

Abstract

Growing evidence suggests that cardiovascular disorders underlie many age-related falls, in particular unexplained (UF) and injurious falls (IF). While current hypotheses suggest cerebral hypoperfusion and impaired peripheral blood pressure (BP) regulation plays a key role in these events, there exists a paucity of evidence to support this assertion. We test the hypothesis that cerebral hemodynamics and orthostatic BP responses are independent risk factors for future all cause falls, UF, IF and recurrent falls (RF).

Analysis was performed on data obtained from wave 3 and wave 4 of The Irish Longitudinal Study on Ageing (TILDA). At wave 3 each participant underwent a comprehensive health assessment which included real-time measurements of NIRS based frontal lobe oxygenation and continuous beat-to-beat BP during an active standing test (5-10 minutes lying + 3 minutes standing) and other covariate assessment. Features obtained from BP and NIRS derived tissue saturation index (TSI) included: nadir, recovery value at 30s, steady-state. OPP was calculated as the normalised product of the BP deficit from supine baseline at 40 seconds after standing and the maximum drop in TSI within 25 seconds of standing. A follow up interview took place approximately 2 years later which captured detailed falls history outcome data. Poisson regression was used to assess the association between drops in TSI, BP and OPP and risk of future falls (all-cause, UF, IF, and RF), while correcting for covariates. A p-value <0.05 was considered statistically significant.

Participants (n=2478) had a mean age of 64(7.7) years (55.6 % female). The degree of initial TSI drop was associated with all-cause falls (IF (RR:1.09 95% CI(1.01-1.18); p=0.012) independent of BP drops while OH was associated with an increased

risk of all-cause falls (RR: 1.44 95% CI (1.02-2.02); $p = 0.039$), IF (RR: 1.70 95% CI (1.00-2.89); $p = 0.050$), UF (RR: 1.67 95% CI (1.15-2.44); $p = 0.007$) and RF (RR: 1.45 95% CI (1.03-2.04); $p = 0.035$). Those with higher values of OPP i.e. those with coexisting hypotension and hypoperfusion were at an increased risk of all-cause falls (RR: 1.07 95% CI (0.99-1.15); $p = 0.073$), IF (RR: 1.15 95% CI (1.04-1.27); $p = 0.008$), UF (RR: 1.09 95% CI (1.01-1.19); $p = 0.033$) and RF (RR: 1.07 95% CI (0.99-1.15); $p = 0.090$). After stratification by sex these associations remained consistent in women primarily.

NIRS based cerebral hemodynamic measurements provide objective and clinically suitable assessment of brain perfusion status in older adults at risk of falls. We provide evidence to support the hypothesis that reductions in cerebral oxygenation and cerebral autoregulation are associated with an increased risk of UF and IF. NIRS may add significant value to current clinical practice when combined with peripheral BP measurements and further aid targeted clinical intervention and hypertension management. The Orthostatic Pressure-Perfusion product provides a simple means to combine continuous NIRS and continuous BP data in a manner suitable for rapid and intuitive clinical interpretation.

Appendix E: Informed Consent Documents

This appendix contains the Patient Information Leaflet and Informed Consent Form given to the patients from the Falls and Syncope Unit at St. James's Hospital when invited to participate in the study presented in this thesis.



MERCER'S INSTITUTE FOR SUCCESSFUL AGEING

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 PARTICIPATE?

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 BENEFITS 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 won't affect your current or future medical care. You don't 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?

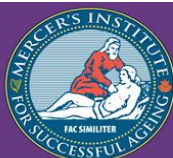
Yes, this study was approved by the Joint Research Ethics Committee of St. James's and Tallaght University Hospitals.

CONTACT DETAILS

Name: Professor Rose Anne Kenny

Address: Director, Falls & Syncope Unit
Mercer's Institute for Successful Ageing,
St. James's Hospital,
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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

Sticker of the patient here

FASU Staff (name in print):

Staff Grade:

FASU Staff Signature:

Date:

Appendix F: Active Stand Protocol

This Appendix describes a detailed Standard Operating Procedure (SOP) for the Active Stand (AS) test, including the Finometer setup, the near-infrared spectroscopy (NIRS) monitor setup and the protocol for the AS test.

Finometer setup

See Figure A.F.1 for visual guidance on the Finometer setup. Steps are as follows:

1. Input the patient's weight, height, and age into the Finometer software
2. Attach the wrist worn front end unit to the left wrist of the patient. Use the straps to secure the front end cable to the arm of the patient: one at the level of the heart and the other one around the forearm.
3. Apply the finger cuff on the middle, ring or index finger. The thumb can also be used if it is difficult to obtain a signal from the other fingers.
4. Connect the finger cuff to the front end.
5. Attach the height correction sensors: one to the strap that was placed at the level of the heart (approximately at the 5th intercostal space in the mid-axillary line) and the other one over the finger cuff.
6. If needed for patient arm stability, apply a sling to the monitored arm.
7. Start the measurement by pressing the bottom left button on the Finometer screen.
8. Press F11 twice on the Finometer keyboard at the same time that you press S twice on the NIRS keyboard. These marks will be used for signal synchronisation during signal processing.

9. Press the Bracal button on the Finometer screen to perform two BP oscillometric measurements that will be used to calibrate the BP signal. If the arm is on the contralateral arm (which is normally the case), select the option “Calibration cuff is on contralateral arm”.
10. Another calibration mechanism, the Physiocal, will be constantly running to further calibrate the signal. Make sure Physiocal is at a level of 30 or higher (ideally the highest value, 70) before starting the AS test.
11. Allow the patient to rest in the lying position for at least 5 minutes before starting the AS test.
12. Instruct the patient on how to perform the AS (described below in the Active Stand Protocol section)
13. Turn Physiocal off. This will stop the signal from being interrupted from by this calibration mechanism during the transient period of the AS, which normally occurs within 30 seconds of standing.
14. Do the countdown: “5, 4, 3, 2, 1, Stand”. When you say stand, press F1 on the Finometer keyboard. Help the patient stand if they need it.
15. Allow the patient to stand for 3 minutes (180 seconds), and press F4 to mark the end of the test.
16. Stop the recording by pressing again the bottom left button on the Finometer screen.

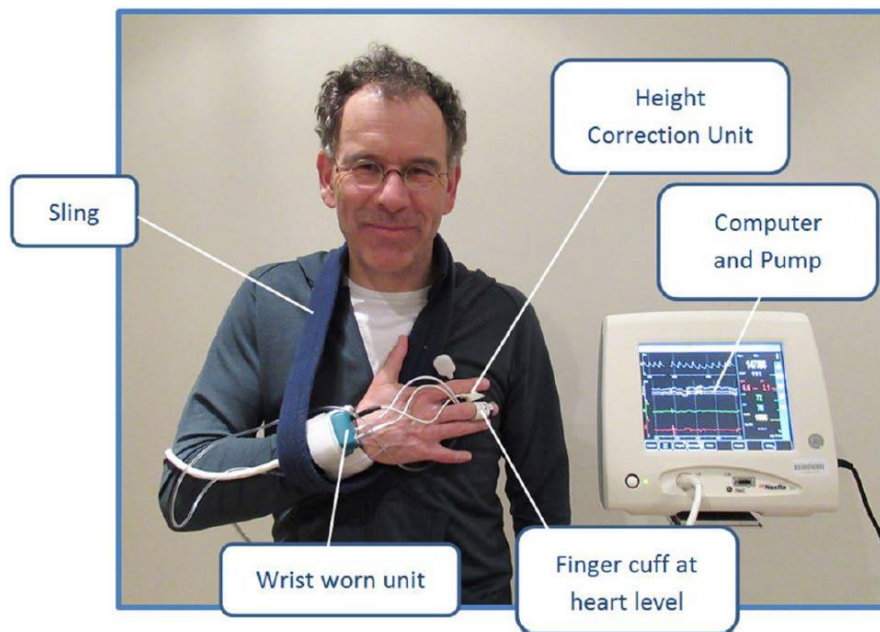


Figure A.F.1 Finometer setup for an Active Stand test (image adapted from [71]).

NIRS setup

1. Prepare 3 pieces of adhesive tape (2 long and 1 short).
2. Cut a long piece of bandage (approximately 1 m long) to create a disposable bandana.
3. Stick two EEG stickers on the surface of the probe that will be in contact with the skin. Do not cover the emitter or the receivers. Apply a bit of pressure to make sure the sticker is well attached to the probe.
4. Let the patient know you will place the sensor over their forehead.
5. Place the sensor over the left eyebrow, over the left side of the participant's forehead, approximately centred 3cm laterally and 3.5cm above the nasion. Take the cable attached to the sensor and place it after the ear of the patient (only if possible, avoid this if they are wearing hearing aids).
6. Use the shorter adhesive tape piece you prepared to stick the cable to the shirt of the patient. Allow a bit of extra cable to avoid pulling if the patient's head position changes.

7. Attach the PortaLite battery case to the Finometer front end cable using a strap.
8. Place the bandage around the patient's head. Start by placing one of the ends of the bandage over the sensor, and then wrap it around the head until it covers the sensor again. Take the two long pieces of adhesive tape and place them in an X shape to close the bandage.
9. Open OxySoft in the computer.
10. Double click the open button () and load the *FASU_template.oxyproj* file from the NIRS 201X folder. Double click on the *Save Project File As* button, right next to the open button and provide a name for the project. Name the project file using the following structure:

Surname Name MRN TEST day_month_year

Use only 2 digits for each of the numbers in the date. An example of a name would be:

Perez Laura 123456 AS 03_10_18

11. Double click the green button to the right of the *Save Project File As* button to start a new measurement. Use the same name as for the project.
12. Press *Quick start* and select the ID of the NIRS sensor you are using.
13. Once the Finometer is also reading, you will have to synchronise the two software recordings. To do so, first make sure the active window of the computer is the Oxysoft window. Just to be sure, click on the TSI window or any other point inside the window. Then, press at the same time the F11 key from the Finometer keyboard and the S key from the computer keyboard. After you press any key when using oxysoft, a new window opens. You do not need to modify anything here, just press ENTER to continue with the

reading. Repeat this marking process again to obtain two consecutive sync marks within a couple of seconds.

14. Press the red button when the AS test is over to stop the recording

15. Press the save button to save the recording.

Active Stand Protocol

1. Once both the Finometer and the NIRS monitor are recording, press the markers as described in Sections 0 and 0 for future synchronisation of the files.
2. Perform the oscillometric Finometer calibration
3. Wait for at least 5 minutes and until the Physiocal is 30 or higher.
4. Explain the protocol to the patient: “Now we are going to do a standing test. We will do a countdown, 5, 4, 3, 2, 1, Stand, and when we say “Stand” you will have to swing the legs out of the bed and stand up as quickly as you can. Do not worry if this is difficult for you, we will help you and we will not let you fall. It is very important that you do not move your left arm, in particular the hand. Keep it still as if it was dead and just bring it with you, but do not use it to push yourself out of the bed and do not squeeze the fingers, as doing so will interfere with the readings. Once you are standing, look straight ahead to the wall in front of you, try not to move your head as it will interfere with the head sensor measurements. We will not be able to talk during the duration of the test, but do let us know if you feel too uncomfortable or unwell. Try to pay attention to any symptoms you may experience so that you can report them at the end of the test. The test will last for 3 minutes”.
5. Do the countdown: 5, 4, 3, 2, 1, stand. When starting the countdown, press the Physiocal button on the Finometer to turn it off. When the word ‘stand’ is said,

quickly press F1 (AS) on the Finometer keyboard (optionally, also press 'M' on the computer keyboard).

6. After 30 seconds of stand, press the Physiocal button again to turn it on.
7. After 3 minutes, press F4 (END) on the Finometer keyboard (and optionally M on the NIRS keyboard)
8. Stop the Finometer and the NIRS readings.

Appendix G: Software Framework

The diagram in Figure A.G.1 represents the framework pipeline developed for this thesis for the extraction of data from FASU patients. Note that the [C#] refers to the column in the file “AS traces code.xlsx” where the information is stored.

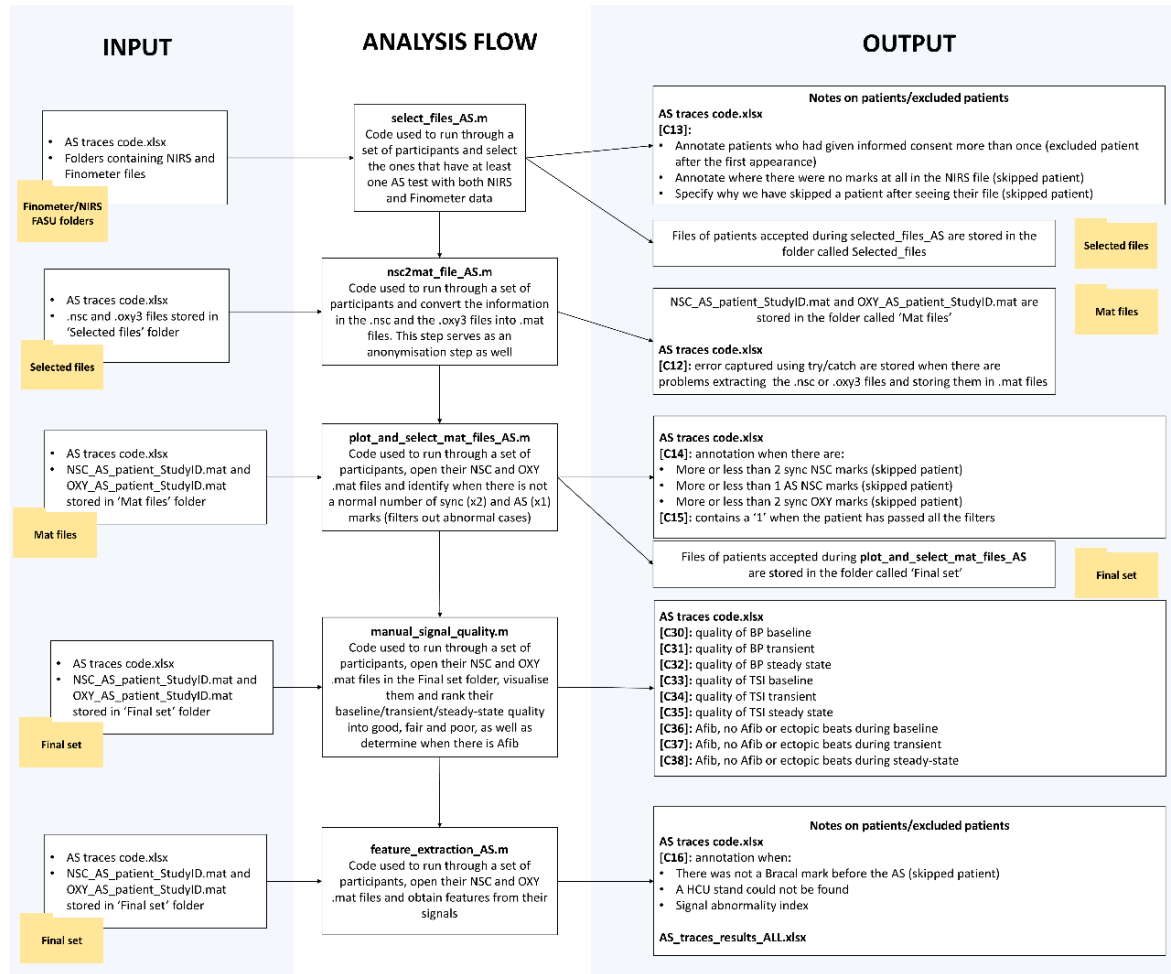


Figure A.G.1. Diagram of the analysis pipeline followed for FASU data, from the selection of files to be included in the study to extraction of features to create the final dataset.

Figures A.G.2 to A.G.6 provide detail of the 5 steps implemented:

1. Select files for each patient included in the study in their original format
2. Convert files from their original format to .mat files
3. Filter out files that do not have the right amount of markers needed
4. Code to facilitate manual inspection and labelling of signal quality
5. Feature extraction

select_files_AS.m

IMPORTANT NOTE: before starting with this step of the process, make sure that NIRS and Finometer folders for surnames starting with M and Mc are blended into just one folder called M.

- Iterate through a range of indices that correspond to pseudonymised patient ID codes
- Identify first letter of patients surname
- Check if patient had given informed consent more than once [C13]: if so, analyse the first entry found in database (the rest will remain empty)
- Find date of consent, with this we can determine the date of the visit and therefore look for files either in the 2018 or 2019 NIRS and NSC folders
- Open NIRS and Finometer folders starting with that letter
- Find all .nsc and .oxy3 files containing the corresponding patient MRN number
- Copy those files into analysis folder
- Find files that were recorded within 1 week (7 days) of obtaining consent – this step is particularly relevant when studying frailty [C27, C28]
- Find what files correspond to an AS test
- If there were not at least 1 AS .nsc file and 1 AS .oxy3 files the code iterates to the following patient
- If there are at least 1 AS .nsc file and 1 AS .oxy3 files:
 - If there are only 1 of each:
 - Check if both the .nsc and the .oxy3 files were recorded on the same day
 - If so, save the .nsc and .oxy3 files in a **'Selected_files' folder**
 - If there are 2 or more .nsc or .oxy3 files:
 - A popup window opens up that allows selecting a .nsc and .oxy3 file
 - Another window opens asking if we want to plot the two files we have selected
 - If we don't want to plot them they are automatically **saved into 'Selected_files'** if the .nsc and .oxy3 dates coincide
 - If we want to plot them:
 - If there are no marks we move on to the following patient [C13]
 - If there are marks program plots the SBP, DBP and TSI signals so that we can visually decide whether they belong to the same test
 - Then we are asked if we are happy with those 2 files
 - If we are happy, the files are **saved into 'Selected_files'** if the .nsc and .oxy3 dates coincide
 - If we are not happy we can try a different combination of files or skip to the next patient
 - If we want to skip to the next patient we are allowed to fill a free text field to specify why we have decided to do this [C13]
 - If we want to try a new combination the loop starts again
 - At the end of the code all the .nsc and .oxy3 files are deleted from the analysis folder, since the important files have been stored in 'Selected_files'

Inputs:

 - AS traces code.xlsx
 - Folders containing NIRS and Finometer files

Outputs:

 - **AS traces code.xlsx:**
 - [C6]: number of AS .nsc files found under the patients MRN
 - [C7]: name of the .nsc file saved
 - [C8]: number of AS .oxy3 files found under the patients MRN
 - [C9]: number of AS
 - [C10]: number of .nsc files found under the patients MRN
 - [C11]: number of .oxy3 files found under the patients MRN
 - [C13]:
 - Annotate patients who had given informed consent more than once
 - Annotate where there were no marks at all in the NIRS file
 - Specify why we have skipped a patient after seeing their file
 - [C27]: there were .nsc files found within a week of consent
 - [C28]: there were .oxy3 files found within a week of consent

Figure A.G.2. Details of code to select files for each patient included in the study in their original format

nsc2mat_file_AS.m

- Load 'AS traces code.xlsx' into AS_traces_code variable
- Iterate through a range of indices that correspond to pseudonymised patient ID codes
- If the field in AS_traces_code where the name of the .nsc file is not empty (which means that both an .nsc and .oxy3 files were found):
 - Try:
 - Open .nsc file
 - Save the following variables into a struct variable, which will then be stored into a .mat file:
 - Output (fiAP, reBAP, IBI, MAP Arm, SYS Arm, reSYS, reMAP, Hgt, reDIA, HR AP, CO, TPR), markers, gender, age, weight, height
 - Open .oxy3 file
 - Save the following variables into a struct variable, which will then be stored into a .mat file
 - OD, xmlInfo, nirs_t, O2Hb1, reO2Hb, reHHb, ua, absO2Hb, absHHb, TSI, TSI_FF
 - All files are saved using the Study ID instead of MRN of the patients, thus anonymising the data at this point
 - Save files into 'Mat_files' folder
 - Catch:
 - If there is an error during the .nsc or .oxy3 extraction, it will be caught and the message will be stored in AS_traces_codes
 - AS_traces_codes is then saved into AS traces code.xlsx
- **Inputs:**
 - AS traces code.xlsx
 - .nsc and .oxy3 files
- **Outputs:**
 - **AS traces codes.xlsx:**
 - [C12]: 1 if both the .nsc and the .oxy3 were saved into .mat files and 0 if not
 - [C29]: save the error returned by matlab when the code fails to extract .nsc or .oxy file
 - NSC_AS_patient_StudyID.mat
 - OXY_AS_patient_StudyID.mat

Figure A.G.3. Details of code to convert files from their original format to .mat files

plot_and_select_mat_files_AS.m

- **NOTE:** the name of this file might be a bit confusing. Initially, it was coded to plot and select files, but the plotting section was commented to speed up the process, so the final version only goes through the selecting process described below
- Load 'AS traces code.xlsx' into AS_traces_code variable
- Iterate through a range of indices that correspond to pseudonymised patient ID codes
- If the field in AS_traces_code where the name of the .nsc file is not empty [C7] (which means that both an .nsc and .oxy3 files were found) or in all cases where [C12] is 1 in the case of frailty study:
 - Load NSC_AS_patient_StudyID.mat and OXY_AS_patient_StudyID.mat files
 - Count how many sync and AS marks there are in the NSC file
 - If there are less or more than 2 sync marks, we will annotate [C14]
 - If there are two sync marks:
 - If there are no AS marks in the nsc file, annotate in [C14]
 - If there are more than 1 AS marks in the nsc file, annotate in [C14]
 - If there is only 1 AS mark in the nsc file:
 - If there are less than 2 sync marks in the oxy file, annotate in [C14]
 - If there are more than 2 sync marks in the oxy file, annotate in [C14]
 - If there are 2 sync marks in the oxy file:
 - Save a '1' in the 'final set selection' column in AS_traces_code.xlsx [C15]
 - Save the NSC_AS_patient_StudyID.mat and OXY_AS_patient_StudyID.mat in the 'Final set' folder
- **Inputs:**
 - AS_traces_code.xlsx
 - NSC_AS_patient_StudyID.mat
 - OXY_AS_patient_StudyID.mat
- **Outputs:**
 - [C14]: annotation when there are:
 - More or less than 2 sync NSC marks
 - More or less than 1 AS NSC marks
 - More or less than 2 sync OXY marks
 - [C15]: contains a '1' when the patient has passed all the filters

Figure A.G.4. Details of code to filter out files that do not have the right amount of markers needed

manual_signal_quality.m

- Load 'AS traces code.xlsx' into AS_traces_code variable
- Iterate through a range of indices that correspond to pseudonymised patient ID codes
- If the final set column [C15] in AS_traces_code contains a '1':
 - Load NSC_AS_patient_StudyID.mat and OXY_AS_patient_StudyID.mat files
 - Plot the reBAP signal from -120 to 200 seconds around the AS mark
 - A pop-up window appears to select the quality of the BP signal during baseline, transient and steady-state [C30,C31,C32]
 - A pop-up window appears to select whether there was Afib or not, or if there were ectopic beats during baseline, transient and steady-state [C36,C37,C38]
 - Plot TSI signal from -120 to 200 seconds around the AS mark
 - A pop-up window appears to select the quality of the BP signal during baseline, transient and steady-state [C33,C34,C35]
- **Inputs:**
 - AS_traces_code.xlsx
 - NSC_AS_patient_StudyID.mat
 - OXY_AS_patient_StudyID.mat
- **Outputs:**
 - [C30]: quality of BP baseline
 - [C31]: quality of BP transient
 - [C32]: quality of BP steady state
 - [C33]: quality of TSI baseline
 - [C34]: quality of TSI transient
 - [C35]: quality of TSI steady state
 - [C36]: Afib, no Afib or ectopic beats during baseline
 - [C37]: Afib, no Afib or ectopic beats during transient
 - [C38]: Afib, no Afib or ectopic beats during steady-state

Figure A.G.5. Details of code to facilitate manual inspection and labelling of signal quality


```

feature_extraction_AS.m

• Load 'AS_traces_code.xlsx' into AS_traces_code variable
• Iterate through a range of indices that correspond to pseudonymised patient ID codes
• If the field in AS_traces_code where the name of the .nsc file is not empty (which means that both an .nsc and .oxy3 files were found):
• Load NSC_AS_patient_StudyID.mat and OXY_AS_patient_StudyID.mat from patients who have a '1' in the 'final set selection' column [C15] in
  AS_traces_code
• Find first sync mark both in the NSC and the OXY file and synchronise the signals to those times
• Locate the AS mark in the NSC file
• Find the standing moment using the HCU signal and when not found annotate in [C16]
• Obtain demographic data (age, gender, weight, height, bmi) and store in demographic_data variable
• If NSC file does not have a Brachial Calibration (Bracal) marker before the AS marker, we will skip this patient and continue with the next one, annotating
  this in [C16]
• Perform quality analysis of the signal (BP and TSI signal abnormality indices) and store into new_as_traces_code and new_as_traces_code_tsi_sai
• Load all signals to be used in the analysis: SBP, DBP, MAP, HR, HCU, PP (created signal), CO, TPR, SV (created signal, not from .nsc file), TSI, relO2Hb, relHHb
  and corresponding time variables.
• For each signal, obtain the following features (these are just headlines, there are several features for each of them):
  • Baseline
  • 5 second interval averaged values
  • Nadir
  • Recovery time
  • Steady state
  • Overshoot
• Save in as_traces_results_all
• Save as_traces_results_all into AS_traces_results_ALL.xlsx
• Save new_as_traces_code and new_as_traces_code_tsi_sai into AS_traces_code.xlsx

• Inputs:
  • AS_traces_code.xlsx
  • NSC_AS_patient_StudyID.mat
  • OXY_AS_patient_StudyID.mat

• Outputs:
  • [C16]: annotation when:
    • There was not a Bracal mark before the AS
    • A HCU stand could not be found
  • AS_traces_results_ALL.xlsx
  • AS_traces_code.xlsx: data on signal abnormality index

```

Figure A.G.6. Details of code to extract features

Appendix H: Criteria for Signal Quality Evaluation

A set of criteria was developed and agreed by the author of this thesis and the primary supervisor before starting the screening process and remained unchanged throughout. The set of rules described below comprise criteria for inclusion (rather than exclusion) of signals. Signals were divided into baseline, transient and steady-state and quality of each of these sections was assessed. Based on the criteria described below, signals were labelled as having good, moderate or poor quality.

Blood pressure/heart rate signal

Most of the criteria established for this signal can be observed from the reBAP signal. However, the heart rate signal was also plotted for visually aiding in the identification of noisy periods.

General thresholds of inclusion:

- Blood pressure signal: signal values are within the range 40-220 mmHg
- Heart rate signal: signal values are within the range 30-200 bpm

The vertical limits of the blood pressure and heart rate plots were defined to meet these ranges, so that it would be easy to identify when the thresholds were overcome.

Baseline criteria for inclusion:

- Beats can be easily distinguished and have a physiological morphology.
Clean beats may have a dicrotic notch, but not always.
- The signal is smooth, i.e., it does not contain abrupt changes or discontinuities

- The presence of Mayer waves (0.1Hz) may be identified, as well as other faster (e.g. 0.3Hz respiration waves) or slower oscillations.
- The signal is not interrupted multiple times by Physiological checks. Physiological checks look like a staircase with two stairs. Physiological periods with more than two stairs may be considered too noisy if the duration is significant. A single physiological within this 30 second range would be optimal
- A significant drift in the signal is not expected in this region
- Overall, 90% of the signal presents good quality according to the above described characteristics

Transient period criteria for inclusion:

- Given that this period corresponds to the moments right after the stand, more motion artifacts are expected, especially during the first few seconds of the signal (before the nadir).
- Beats can be easily distinguished and have a physiological morphology. Clean beats may have a dicrotic notch, but not always. Changes in the morphology are expected during this transient part of the signal
- Despite fast changes are expected in this region, smoothness of the signal, i.e., lack of abrupt changes or discontinuities, is still required.
- The general expected morphology of this transient region is as follows: there is an initial dip (lowest part is referred to as the nadir) with a subsequent increase that sometimes creates a local maximum (overshoot) and then the signal trends towards a more steady value. The overshoot

might not always be present, and other morphologies can be accepted as long as the smoothness and beats of the signal look physiological.

- The signal is not interrupted by Physiological checks. In case it is, the signal can be accepted if Physiological would not affect the derivation of features during this period (nadir, overshoot and values at 10, 20 and 30 seconds).
- Overall, 80-85% of the signal presents good quality according to the above described characteristics

Steady-state period criteria for inclusion:

- Beats can be easily distinguished and have a physiological morphology. Clean beats may have a dicrotic notch, but not always.
- The signal is smooth, i.e., it does not contain abrupt changes or discontinuities
- The presence of Mayer waves (0.1Hz) may be identified, as well as other faster (e.g. 0.3Hz respiration waves) or slower oscillations
- The signal is not interrupted multiple times by Physiological checks. Physiological checks look like a staircase with two stairs. Physiological periods with more than two stairs may be considered too noisy if the duration is significant. A single physiological within this 30 second range would be optimal
- A significant drift in the signal is not expected
- Overall, 90% of the signal presents good quality according to the above described characteristics

Tissue saturation index signal

The criteria established for this signal applies to the TSI signal. An average fit factor value was also derived for the three regions of interest, which can be applied as a further filter to identify signals in which the model fit for the TSI derivation may be too low. The set of criteria defined below comprise the requirements of inclusion, not exclusion, of signals.

General thresholds of inclusion:

- Signal values are within the range 40-80 %

In this case, the vertical limits for displaying the graphs were defined to be $\pm 7\%$ around the average value of the entire signal. It was not optimal to use 40-80 %, since the amplitude of TSI signals is very small compared to such a range. The $\pm 7\%$ range allows viewing all signals within an equivalent range in the vertical axis but still accommodating for different trace averages. However, horizontal lines are plotted at 40 and 80% when those values are within the display range of the graph in order to identify signal that go outside the thresholds for inclusion.

Baseline criteria for inclusion:

- Beats can be easily distinguished. A dicrotic notch is not expected in these beats. Their shape might resemble that of the beats in the reBAP signal or might just be a small local maximum, depending on the amplitude of the signal
- The signal is smooth, i.e., it does not contain abrupt changes or discontinuities

- The signal range of values is around 1-2%, values of 3-4% are considered too high to be physiological
- The presence of Mayer waves (0.1Hz) may be identified, as well as other faster (e.g. 0.3Hz respiration waves) or slower oscillations
- A significant drift in the signal is not expected in this region
- Overall, 90% of the signal presents good quality according to the above described characteristics
- When there is a non-physiological abrupt drop from baseline on standing, this should be indicated with a poor quality of the baseline even if the overall quality in terms of smoothness and beats is good, since this baseline value is not reliable to be used to calculate changes from baseline

Transient period criteria for inclusion:

- Given that this period corresponds to the moments right after the stand, more motion artifacts are expected, especially during the first few seconds of the signal (before the nadir).
- Large non-physiological high frequency shifts in the signal just after standing should not be considered to evaluate this region, but should be taken into account for the baseline region instead.
- Beats can be easily distinguished. Changes in the beats amplitude can occur during this transient part of the signal, although this is normally not very noticeable.
- Despite fast changes are expected in this region, smoothness of the signal, i.e., lack of abrupt changes or discontinuities, is still required.

- The general expected morphology of this transient region is as follows: there is an initial dip (lowest part is referred to as the nadir) with a subsequent increase that most of the time creates a local maximum (overshoot) and then the signal trends towards a more steady value. The overshoot might not always be present, and other morphologies can be accepted as long as the smoothness and beats of the signal look physiological.
- Overall, 80-85% of the signal presents good quality according to the above described characteristics

Steady-state period criteria for inclusion:

- Beats can be easily distinguished. A dicrotic notch is not expected in these beats. Their shape might resemble that of the beats in the reBAP signal or might just be a small local maximum, depending on the amplitude of the signal
- The signal is smooth, i.e., it does not contain abrupt changes or discontinuities
- When the signal is stable, the range of values is around 1-2%, values of 3-4% are considered too high to be physiological
- The presence of Mayer waves (0.1Hz) may be identified, as well as other faster (e.g. 0.3Hz respiration waves) or slower oscillations
- A pronounced drift in the signal may be physiological and therefore can be accepted in this period
- Overall, 90% of the signal presents good quality according to the above described characteristics

Further filter applied a posteriori: TSI fit factor must be $> 98\%$ to ensure sufficient performance of the fitted model in the derivation of TSI values.

Recording the information

In order to facilitate the author's work during reviewing the signals, the code was programmed with a set of predefined noise sources to select from, so that the reason chosen when poor quality was identified would be recorded if needed for future inspection (Table A.H.1).

Table A.H.1 Predefined sources of noise that the user is provided with when running the code and classifying a region of the signal as poor.

	BP			TSI		
	Baseline	Transient	Steady-state	Baseline	Transient	Steady-state
Beats undistinguishable	x	x	x	x	x	x
Not smooth	x	x	x	x	x	x
Multiple Physiocal interruptions	x	x	x			
Physiocal signal shift	x	x	x			
Significant drift	x	x	x	x	x	
BP outside 40-220 range	x	x	x			
HR outside 30-200 range	x	x	x			
TSI outside 40-80 range				x	x	x
Significant shift on stand				x		
Other	x	x	x	x	x	x

Appendix I: Chapter 7 Supplementary Material

Supplementary Table A.I.1. Features from Table 7.1 expanded with all features extracted and calculation method detailed.

Variable	Units	Description	Calculation method
SBP baseline	mmHg	Mean SBP 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} SBP_t$
DBP baseline	mmHg	Mean DBP 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} DBP_t$
HR baseline	bpm	Mean HR 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} HR_t$
TSI baseline	%	Mean TSI 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} TSI_t$
$\Delta[O_2Hb]$ baseline	$\mu\text{mol/L}$	Mean $\Delta[O_2Hb]$ 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} \Delta[O_2Hb]_t$
$\Delta[HHb]$ baseline	$\mu\text{mol/L}$	Mean $\Delta[HHb]$ 30-60 s before standing	$\frac{1}{n} \sum_{t=-60}^{-30} \Delta[HHb]_t$
SBP nadir	mmHg	Largest trough in SBP after standing (within 30 s)	$\min(\text{local minima}(SBP_t)), t = 0, \dots, 30$
TSI nadir	%	Largest trough in TSI after standing (within 30 s)	$\min(\text{local minima}(TSI_t)), t = 0, \dots, 30$
$\Delta[O_2Hb]$ nadir	$\mu\text{mol/L}$	Largest trough in $\Delta[O_2Hb]$ after standing (within 30 s)	$\min(\text{local minima}(\Delta[O_2Hb]_t)), t = 0, \dots, 30$
$\Delta[HHb]$ peak	$\mu\text{mol/L}$	Largest peak in $\Delta[HHb]$ after standing (within 30 s)	$\max(\text{local maxima}(\Delta[HHb]_t)), t = 0, \dots, 30$
SBP overshoot	mmHg	First peak found between 5 s after SBP nadir and 60 s after standing	$\text{first}(\text{local maxima}(SBP_t)), t = \text{nadir} + 5, \dots, 60$
TSI overshoot	%	First peak found between 2 s after TSI nadir and 60 s after standing	$\text{first}(\text{local maxima}(TSI_t)), t = \text{nadir} + 2, \dots, 60$
$\Delta[O_2Hb]$ overshoot	$\mu\text{mol/L}$	First peak found between 2 s after $\Delta[O_2Hb]$ nadir and 60 s after standing	$\text{first}(\text{local maxima}(\Delta[O_2Hb]_t)), t = \text{nadir} + 2, \dots, 60$
$\Delta[HHb]$ trough	$\mu\text{mol/L}$	First trough found between 2 s after $\Delta[HHb]$ peak and 60 s after standing	$\text{first}(\text{local minima}(\Delta[HHb]_t)) = \text{nadir} + 2, \dots, 60$
SBP steady-state	mmHg	Mean SBP 60-120 s after standing	$\frac{1}{n} \sum_{t=60}^{120} SBP_t$
TSI steady-state	mmHg	Mean TSI 60-120 s after standing	$\frac{1}{n} \sum_{t=60}^{120} TSI_t$
$\Delta[O_2Hb]$ steady-state	$\mu\text{mol/L}$	Mean $\Delta[O_2Hb]$ 60-120 s after standing	$\frac{1}{n} \sum_{t=60}^{120} \Delta[O_2Hb]_t$
$\Delta[HHb]$ steady-state	$\mu\text{mol/L}$	Mean $\Delta[HHb]$ 60-120 s after standing	$\frac{1}{n} \sum_{t=60}^{120} \Delta[HHb]_t$

Delta SBP	mmHg	SBP baseline - SBP nadir	$SBP_B - SBP_N$
Delta TSI	%	TSI baseline - TSI nadir	$TSI_B - TSI_N$
Delta $\Delta[O_2Hb]$	$\mu\text{mol/L}$	$\Delta[O_2Hb]$ baseline - $\Delta[O_2Hb]$ nadir	$\Delta[O_2Hb]_B - \Delta[O_2Hb]_N$
Delta $\Delta[HHb]$	$\mu\text{mol/L}$	$\Delta[HHb]$ baseline – $\Delta[HHb]$ peak	$\Delta[HHb]_B - \Delta[HHb]_P$
SBP nadir to overshoot difference	mmHg	SBP overshoot – SBP nadir	$SBP_O - SBP_N$
TSI nadir to overshoot difference	%	TSI overshoot – TSI nadir	$TSI_O - TSI_N$
$\Delta[O_2Hb]$ nadir to overshoot difference	$\mu\text{mol/L}$	$\Delta[O_2Hb]$ overshoot – $\Delta[O_2Hb]$ nadir	$\Delta[O_2Hb]_O - \Delta[O_2Hb]_N$
$\Delta[HHb]$ peak to through difference	$\mu\text{mol/L}$	$\Delta[HHb]$ trough – $\Delta[HHb]$ peak	$\Delta[HHb]_T - \Delta[HHb]_P$
SBP steady-state change	mmHg	SBP baseline - SBP steady-state	$SBP_B - SBP_{SS}$
TSI steady-state change	%	TSI baseline - TSI steady-state	$TSI_B - TSI_{SS}$
$\Delta[O_2Hb]$ steady-state change	$\mu\text{mol/L}$	$\Delta[O_2Hb]$ baseline – $\Delta[O_2Hb]$ steady-state	$\Delta[O_2Hb]_B - \Delta[O_2Hb]_{SS}$
$\Delta[HHb]$ steady-state change	$\mu\text{mol/L}$	$\Delta[HHb]$ baseline – $\Delta[HHb]$ steady-state	$\Delta[HHb]_B - \Delta[HHb]_{SS}$
Maximum recovery rate	SBP mmHg/s	In the range between SPB nadir and SBP overshoot: largest difference between consecutive points / time between points	$\text{Max}((SBP_{i+1} - SBP_i)/(1/fs)), i = \text{nadir index}, \dots, \text{overshoot index}$
Maximum recovery rate	TSI %/s	In the range between TSI nadir and TSI overshoot: largest difference between consecutive points / time between points	$\text{Max}((TSI_{i+1} - TSI_i)/(1/fs)), i = \text{nadir index}, \dots, \text{overshoot index}$
$\Delta[O_2Hb]$ maximum recovery rate	$\mu\text{mol/L/s}$	In the range between $\Delta[O_2Hb]$ nadir and $\Delta[O_2Hb]$ overshoot: largest difference between consecutive points / time between points	$\text{Max}((\Delta[O_2Hb]_{i+1} - \Delta[O_2Hb]_i)/(1/fs)), i = \text{nadir index}, \dots, \text{overshoot index}$
$\Delta[HHb]$ maximum recovery rate	$\mu\text{mol/L/s}$	In the range between $\Delta[HHb]$ nadir and $\Delta[HHb]$ overshoot: largest difference between consecutive points / time between points	$\text{Max}((\Delta[HHb]_{i+1} - \Delta[HHb]_i)/(1/fs)), i = \text{nadir index}, \dots, \text{overshoot index}$
Normalised recovery rate	TSI %/mmHg	Maximum TSI recovery rate / maximum SBP recovery rate	TSI_{RR} / SBP_{RR}
Normalised $\Delta[O_2Hb]$ recovery rate	$\mu\text{mol/L/mmHg}$	$\Delta[O_2Hb]$ maximum recovery rate / maximum SBP recovery rate	$\Delta[O_2Hb]_{RR} / SBP_{RR}$
Normalised $\Delta[HHb]$ recovery rate	$\mu\text{mol/L/mmHg}$	$\Delta[HHb]$ maximum recovery rate / maximum SBP recovery rate	$\Delta[HHb]_{RR} / SBP_{RR}$

DBP = diastolic blood pressure, $\Delta[HHb]$ = concentration of deoxygenated haemoglobin, HR = heart rate, $\Delta[O_2Hb]$ = concentration of oxygenated haemoglobin, SBP = systolic blood pressure, TSI = tissue saturation index.

Supplementary Table A.I.2. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls (reference)) on $\Delta[\text{O}_2\text{Hb}]$ responses to active stand testing.

	β coefficient (CI)	p-value	FDR p-value
Model 1			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	3.62 (0.05 7.19)	0.047*	0.235
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	0.07 (-1.33 1.47)	0.919	0.919
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.10 (-0.47 0.26)	0.572	0.715
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-0.02 (-0.06 0.02)	0.292	0.487
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	2.38 (-2.05 6.82)	0.284	0.487
Model 2			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	2.87 (-0.60 6.35)	0.102	0.432
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.17 (-1.56 1.23)	0.810	0.810
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.14 (-0.52 0.23)	0.441	0.684
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-0.03 (-0.06 0.01)	0.173	0.432
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.33 (-3.09 5.74)	0.547	0.684
Model 3			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	3.24 (-0.67 7.15)	0.101	0.168
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.68 (-2.13 0.77)	0.346	0.432
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.37 (-0.72 -0.01)	0.046*	0.168
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-0.04 (-0.08 0.00)	0.070	0.168
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.77 (-3.27 6.81)	0.481	0.481
Model 4			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	2.53 (-1.38 6.45)	0.197	0.263
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.88 (-2.22 0.46)	0.191	0.263
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.38 (-0.74 -0.02)	0.042*	0.168
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-	-	-
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.54 (-4.02 7.10)	0.577	0.577

Model 1: univariate, **Model 2:** model 1 + sex **Model 3:** model 2 + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. $p^* < 0.05$. HR = heart rate, $\Delta[\text{O}_2\text{Hb}]$ = concentration of oxygenated haemoglobin, SBP = systolic blood pressure.

Supplementary Table A.I.3. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls (reference)) on Δ [HHb] responses to active stand testing.

	β coefficient (CI)	p-value	FDR p-value
Model 1			
Delta Δ [HHb] ($\mu\text{mol/L}$)	-1.09 (-2.07 -0.12)	0.029*	0.036*
Δ [HHb] peak to trough difference ($\mu\text{mol/L}$)	0.93 (0.16 1.71)	0.019*	0.032*
Maximum Δ [HHb] recovery rate ($\mu\text{mol/L/sec}$)	0.29 (0.09 0.48)	0.005**	0.013*
Normalised Δ [HHb] recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	0.05 (0.02 0.08)	0.002*	0.010*
Δ [HHb] baseline to steady-state change ($\mu\text{mol/L}$)	0.34 (-1.85 2.52)	0.756	0.756
Model 2			
Delta Δ [HHb] ($\mu\text{mol/L}$)	-1.20 (-2.19 -0.21)	0.019*	0.024*
Δ [HHb] peak to trough difference ($\mu\text{mol/L}$)	1.02 (0.23 1.805)	0.013*	0.022*
Maximum Δ [HHb] recovery rate ($\mu\text{mol/L/sec}$)	0.30 (0.10 0.495)	0.004**	0.010*
Normalised Δ [HHb] recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	0.05 (0.03 0.083)	0.001**	0.005**
Δ [HHb] baseline to steady-state change ($\mu\text{mol/L}$)	-0.26 (-2.40 1.876)	0.807	0.807
Model 3			
Delta Δ [HHb] ($\mu\text{mol/L}$)	-0.85 (-1.94 0.24)	0.123	0.154
Δ [HHb] peak to trough difference ($\mu\text{mol/L}$)	1.24 (0.36 2.12)	0.007**	0.012*
Maximum Δ [HHb] recovery rate ($\mu\text{mol/L/sec}$)	0.38 (0.18 0.60)	0.001**	0.002**
Normalised Δ [HHb] recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	0.06 (0.03 0.09)	0.001**	0.002**
Δ [HHb] baseline to steady-state change ($\mu\text{mol/L}$)	-0.17 (-2.6 2.27)	0.891	0.891
Model 4			
Delta Δ [HHb] ($\mu\text{mol/L}$)	-0.93 (-2.06 0.21)	0.106	0.141
Δ [HHb] peak to trough difference ($\mu\text{mol/L}$)	1.21 (0.32 2.11)	0.009**	0.018*
Maximum Δ [HHb] recovery rate ($\mu\text{mol/L/sec}$)	0.39 (0.17 0.60)	0.001**	0.004**
Normalised Δ [HHb] recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-	-	-
Δ [HHb] baseline to steady-state change ($\mu\text{mol/L}$)	0.09 (-2.59 2.76)	0.949	0.949

Model 1: univariate, **Model 2:** model 1 + sex **Model 3:** model 2 + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. $p^* < 0.05$, $p^{**} < 0.01$. HR = heart rate, Δ [HHb] = concentration of deoxygenated haemoglobin, SBP = systolic blood pressure.

Supplementary Table A.I.4. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls (reference)) on SBP responses to active stand testing

	β coefficient (CI)	p-value	FDR corrected p-value
Model 1			
Delta SBP nadir (mmHg)	5.67 (-4.13 15.47)	0.249	0.249
Delta SBP nadir to overshoot (mmHg)	5.51 (-3.19 14.20)	0.207	0.249
Maximum SBP recovery rate (mmHg/sec)	1.22 (-0.70 3.14)	0.205	0.249
Delta SBP steady-state (mmHg)	10.80 (3.42 18.17)	0.005*	0.020*
Model 2			
Delta SBP nadir (mmHg)	3.36 (-6.40 13.12)	0.490	0.490
Delta SBP nadir to overshoot (mmHg)	7.63 (-1.00 16.25)	0.081	0.127
Maximum SBP recovery rate (mmHg/sec)	1.63 (-0.30 3.56)	0.095	0.127
Delta SBP steady-state (mmHg)	9.34 (1.88 16.80)	0.016	0.064
Model 3			
Delta SBP nadir (mmHg)	4.99 (-5.52 15.49)	0.342	0.438
Delta SBP nadir to overshoot (mmHg)	4.15 (-4.30 12.61)	0.326	0.438
Maximum SBP recovery rate (mmHg/sec)	0.60 (-0.95 2.15)	0.438	0.438
Delta SBP steady-state (mmHg)	8.37 (0.44 16.30)	0.039*	0.156

Model 1: univariate; **Model 2:** model 1 + sex; **Model 3:** model 2 + body mass index + HR baseline. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. HR = heart rate, SBP = systolic blood pressure.

Supplementary Table A.I.5. Sensitivity analysis to lying duration and speed of standing

	β coefficient (CI)	p-value	FDR corrected p-value
Delta TSI nadir (%)	1.00 (0.05 1.94)	0.039*	0.195
Delta TSI nadir to overshoot (%)	-0.95 (-2.17 0.27)	0.121	0.258
Maximum TSI recovery rate (%/sec)	-0.20 (-0.50 0.11)	0.203	0.258
Normalised TSI recovery rate (%/mmHg)	-0.02 (-0.06 0.02)	0.283	0.283
Delta TSI baseline to steady-state (%)	0.76 (-0.44 1.95)	0.206	0.258

Model: patients vs healthy + sex + body mass index + HR baseline + lying duration + speed of standing + SBP corresponding feature (for all features except for the normalised TSI recovery rate). HR = heart rate, SBP = systolic blood pressure, TSI = tissue saturation index. $p^* < 0.05$.

Supplementary Table A.I.6. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls (reference)) on TSI responses to active stand testing using averaged rates for TSI recovery rate and normalised TSI recovery rate.

	β coefficient (CI)	p-value	FDR corrected p-value
Model 1			
TSI nadir (%)	0.93 (0.12 1.74)	0.026*	0.130
TSI nadir to overshoot difference (%)	-0.53 (-1.55 0.49)	0.300	0.375
Average TSI recovery rate (%/sec)	-0.04 (-0.19 0.11)	0.587	0.587
Normalised TSI recovery rate (%/mmHg)	-0.02 (-0.06 0.02)	0.285	0.375
TSI baseline to steady-state change (%)	0.72 (-0.27 1.71)	0.148	0.370
Model 2			
TSI nadir (%)	0.84 (0.00 1.68)	0.050	0.250
TSI nadir to overshoot difference (%)	-0.62 (-1.68 0.44)	0.242	0.302
Average TSI recovery rate (%/sec)	-0.05 (-0.21 0.10)	0.483	0.483
Normalised TSI recovery rate (%/mmHg)	-0.03 (-0.07 0.01)	0.116	0.290
TSI baseline to steady-state change (%)	0.66 (-0.37 1.69)	0.202	0.302
Model 3			
TSI nadir (%)	0.84 (-0.13 1.80)	0.088	0.240
TSI nadir to overshoot difference (%)	-0.77 (-1.98 0.45)	0.208	0.260
Average TSI recovery rate (%/sec)	-0.12 (-0.284 0.05)	0.167	0.260
Normalised TSI recovery rate (%/mmHg)	-0.04 (-0.08 0.01)	0.096	0.240
TSI baseline to steady-state change (%)	-0.15 (-0.46 0.16)	0.324	0.324
Model 4			
TSI nadir (%)	0.73 (-0.27 1.72)	0.147	0.209
TSI nadir to overshoot difference (%)	-0.86 (-2.06 0.35)	0.157	0.209
Average TSI recovery rate (%/sec)	-0.13 (-0.30 0.04)	0.132	0.209
Normalised TSI recovery rate (%/mmHg)	-	-	-
TSI baseline to steady-state change (%)	0.45 (-0.84 1.73)	0.484	0.484

Model 1: univariate, **Model 2:** model 1 + sex, **Model 3:** model 2 + sex + body mass index + SBP baseline, **Model 4:** model 3 + corresponding SBP variable. **TSI recovery rate is calculated as:** $(TSI \text{ overshoot} - TSI \text{ nadir}) / (TSI \text{ overshoot time} - TSI \text{ nadir time})$. **Normalised TSI recovery rate is calculated as:** $((TSI \text{ overshoot} - TSI \text{ nadir}) / (TSI \text{ overshoot time} - TSI \text{ nadir time})) / ((SBP \text{ overshoot} - SBP \text{ nadir}) / (SBP \text{ overshoot time} - SBP \text{ nadir time}))$. HR = heart rate, SBP = systolic blood pressure, TSI = tissue saturation index.

Supplementary Table A.I.7. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls(reference)) on TSI responses to active stand testing using a subcohort of patients matched by sex to the controls.

	β coefficient (CI)	p-value	FDR corrected p-value
Model 1			
Delta TSI (%)	0.81 (-0.22 1.846)	0.117	0.454
TSI nadir-overshoot difference (%)	-0.61 (-1.95 0.742)	0.363	0.454
TSI recovery rate (%/sec)	-0.00 (-0.36 0.350)	0.981	0.981
Normalised TSI recovery rate (%/mmHg)	-0.02 (-0.06 0.020)	0.343	0.454
TSI baseline to steady-state change (%)	0.54 (-0.58 1.655)	0.333	0.454
Model 3			
Delta TSI (%)	0.73 (-0.52 1.98)	0.238	0.697
TSI nadir-overshoot difference (%)	-0.66 (-2.29 0.97)	0.411	0.697
TSI recovery rate (%/sec)	-0.08 (-0.50 0.34)	0.697	0.697
Normalised TSI recovery rate (%/mmHg)	-0.01 (-0.05 0.03)	0.647	0.697
TSI baseline to steady-state change (%)	0.51 (-0.86 1.88)	0.445	0.697
Model 4			
Delta TSI (%)	0.68 (-0.62 1.98)	0.287	0.614
TSI nadir-overshoot difference (%)	-0.84 (-2.50 0.83)	0.307	0.614
TSI recovery rate (%/sec)	-0.14 (-0.57 0.29)	0.498	0.663
Normalised TSI recovery rate (%/mmHg)	-	-	-
TSI baseline to steady-state change (%)	0.32 (-1.19 1.83)	0.663	0.663

Model 1: univariate, **Model 3:** model 1 + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. SBP = systolic blood pressure, TSI = tissue saturation index

Supplementary Table A.I.8. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls(reference)) on $\Delta[\text{O}_2\text{Hb}]$ responses to active stand testing using a subcohort of patients matched by sex to the controls

	β coefficient (CI)	P-value	FDR corrected p-value
Model 1			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	2.99 (-2.16 8.14)	0.242	0.605
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.03 (-1.89 1.83)	0.976	0.976
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.09 (-0.59 0.42)	0.722	0.902
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-0.03 (-0.08 0.01)	0.157	0.605
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.21 (-5.12 7.54)	0.697	0.902
Model 3			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	3.50 (-2.29 9.28)	0.222	0.370
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.44 (-2.37 1.50)	0.643	0.643
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.32 (-0.81 0.18)	0.200	0.370
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-0.04 (-0.10 0.01)	0.092	0.370
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.84 (-5.53 9.20)	0.610	0.643
Model 4			
Delta $\Delta[\text{O}_2\text{Hb}]$ ($\mu\text{mol/L}$)	2.81 (-2.89 8.50)	0.315	0.420
$\Delta[\text{O}_2\text{Hb}]$ nadir-overshoot difference ($\mu\text{mol/L}$)	-0.89 (-2.63 0.86)	0.302	0.420
Maximum $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L/sec}$)	-0.36 (-0.89 0.16)	0.164	0.420
Normalised $\Delta[\text{O}_2\text{Hb}]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)	-	-	-
$\Delta[\text{O}_2\text{Hb}]$ baseline to steady-state change ($\mu\text{mol/L}$)	1.71 (-6.50 9.92)	0.668	0.668

Model 1: univariate, **Model 3:** model 1 + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. $p^* < 0.05$, $p^{**} < 0.01$. SBP = systolic blood pressure, $\Delta[\text{O}_2\text{Hb}]$ = changes in concentration of oxygenated haemoglobin.

Supplementary Table A.I.9. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls(reference)) on $\Delta[HHb]$ responses to active stand testing using a subcohort of patients matched by sex to the controls.

	β coefficient (CI)	P-value	FDR corrected p-value
Model 1			
<i>Delta $\Delta[HHb]$ ($\mu\text{mol/L}$)</i>	-1.07 (-2.41 0.27)	0.112	0.140
<i>$\Delta[HHb]$ peak to trough difference ($\mu\text{mol/L}$)</i>	0.89 (-0.200 1.99)	0.104	0.140
<i>Maximum $\Delta[HHb]$ recovery rate ($\mu\text{mol/L /sec}$)</i>	0.23 (-0.035 0.49)	0.086	0.140
<i>Normalised $\Delta[HHb]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)</i>	0.05 (0.01 0.09)	0.028*	0.140
<i>$\Delta[HHb]$ baseline to steady-state change ($\mu\text{mol/L}$)</i>	-0.11 (-3.263 3.05)	0.946	0.946
Model 3			
<i>Delta $\Delta[HHb]$ ($\mu\text{mol/L}$)</i>	-0.56 (-2.05 0.94)	0.445	0.556
<i>$\Delta[HHb]$ peak to trough difference ($\mu\text{mol/L}$)</i>	1.11 (-0.16 2.38)	0.082	0.137
<i>Maximum $\Delta[HHb]$ recovery rate ($\mu\text{mol/L /sec}$)</i>	0.32 (0.03 0.61)	0.034*	0.117
<i>Normalised $\Delta[HHb]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)</i>	0.05 (0.00 0.10)	0.047*	0.117
<i>$\Delta[HHb]$ baseline to steady-state change ($\mu\text{mol/L}$)</i>	0.10 (-3.47 3.68)	0.952	0.952
Model 4			
<i>Delta $\Delta[HHb]$ ($\mu\text{mol/L}$)</i>	-0.68 (-2.21 0.85)	0.365	0.487
<i>$\Delta[HHb]$ peak to trough difference ($\mu\text{mol/L}$)</i>	1.02 (-0.29 2.32)	0.121	0.242
<i>Maximum $\Delta[HHb]$ recovery rate ($\mu\text{mol/L /sec}$)</i>	0.29 (-0.01 0.60)	0.060	0.240
<i>Normalised $\Delta[HHb]$ recovery rate ($\mu\text{mol/L}\cdot\text{mmHg}$)</i>	-	-	-
<i>$\Delta[HHb]$ baseline to steady-state change ($\mu\text{mol/L}$)</i>	0.53 (-3.42 4.48)	0.783	0.783

Model 1: univariate, **Model 3:** model 1 + body mass index + HR baseline, **Model 4:** model 3 + corresponding SBP variable. $p^* < 0.05$. SBP = systolic blood pressure, $\Delta[HHb]$ = changes in concentration of deoxygenated haemoglobin.

Supplementary Table A.I.10. Univariate (model 1) and multivariate analyses of the effects of group (patients vs controls(reference)) on SBP responses to active stand testing using a subcohort of patients matched by sex to the controls.

	β coefficient (CI)	p-value	FDR corrected p-value
Model 1			
Delta SBP (%)	1.25 (-11.92 14.41)	0.847	0.847
SBP nadir-overshoot difference (%)	10.31 (-0.73 21.35)	0.066	0.088
SBP recovery rate (%/sec)	2.53 (0.14 4.92)	0.039*	0.088
SBP baseline to steady-state change (%)	9.05 (-0.48 18.58)	0.062	0.088
Model 3			
Delta SBP (%)	2.87 (-11.56 17.30)	0.684	0.684
SBP nadir-overshoot difference (%)	6.65 (-4.44 17.75)	0.227	0.303
SBP recovery rate (%/sec)	1.36 (-0.64 3.36)	0.173	0.303
SBP baseline to steady-state change (%)	7.83 (-2.56 18.21)	0.132	0.303

Model 1: univariate, **Model 3:** model 1 + body mass index + HR baseline. $p^* < 0.05$.
SBP = systolic blood pressure, TSI = tissue saturation index

Appendix J: Chapter 8 Supplementary Material

Supplementary Text A.J.1: Feature derivation

The full set of features derived in this study is detailed in Supplementary Table 1. Baseline and steady-state values were obtained as the average between [-60, -30] seconds before and [60, 120] seconds after standing, respectively. Average values at 10, 20 and 30 seconds after standing were calculated using a ± 2.5 sec moving average filter, with changes from baseline also calculated [71].

The nadir was defined as the lowest local minima within 30 seconds of standing, and the overshoot as the first peak following the nadir [217] for BP, TSI and TPR signals. For HR and SV, the maximum value within the first 30 seconds and the first minimum occurring after the maximum were extracted. A drop rate (or increase rate in the case of HR and SV) was derived as the average rate between baseline and nadir (or baseline and maximum HR and SV). The average recovery rate between BP, TSI or TPR nadir and overshoot (or HR/SV maximum and recovery) were also derived. Values at specific time points (i.e., nadir, overshoot, 10s, 20s, 30s, and steady state) are reported as changes from baseline, unless otherwise indicated.

Supplementary Table A.J.1. Definitions, units, description of variables used in the analyses.

Signal (units)	Variable	Units	Description
SBP (mmHg), DBP (mmHg), TSI (%), TPR (mmHg·min/L)	Baseline	Signal units	Mean value 30-60 s before standing
	Nadir	Signal units	Largest trough after standing (within 30 s)
	Overshoot	Signal units	First peak found between 5 s after nadir and 60 s after standing
	Steady-state	Signal units	Mean SBP 60-120 s after standing
	Nadir-to-baseline	Signal units	Nadir - Baseline
	Overshoot-to-nadir	Signal units	Overshoot – Nadir
	Steady-state-to-baseline	Signal units	Steady-state - Baseline
	Recovery rate	Signal units/s	Overshoot-to-nadir / (Overshoot time – Nadir time)
HR (bpm), SV (ml)	Value at 10s, 20s, 30s	Signal units	Average values timepoints using a $\pm 2.5s$ moving average filter
	Baseline	Signal units	Mean value 30-60 s before standing
	Maximum	Signal units	Largest peak after standing (within 5-20 s)
	Minimum	Signal units	First trough found between 5 s after maximum and 60 s after standing
	Minimum-to-baseline	Signal units	Minimum – Baseline
	Minimum-to-maximum	Signal units	Minimum– Maximum
	Steady-state-to-baseline	Signal units	Steady-state – Baseline
	Recovery rate	Signal units/s	(Minimum-to-Maximum) / (Minimum time - Maximum time)
	Value at 10s, 20s, 30s	Signal units	Average values timepoints using a $\pm 2.5s$ moving average filter
	TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume.		

Supplementary Table A.J.2. Average and variability values for the TSI, SBP, DBP, HR, TPR and SV features analysed for all patients, females and males, comparing differences between sex groups. False discovery rate (FDR) corrected p-values are also reported.

	All patients	Females	Males	p-value	FDR p-value
Tissue Saturation Index (%)					
TSI nadir, median (IQR)	-1.91 (1.67)	-1.71 (1.67)	-2.41 (2.07)	0.005**	0.015*
TSI drop rate, median (IQR) ⁺	-0.26 (0.23)	-0.24 (0.23)	-0.29 (0.31)	0.030*	0.068
TSI overshoot-to-nadir, median (IQR)	1.98 (1.83)	1.69 (1.83)	2.34 (2.41)	0.001**	0.005**
TSI overshoot, median (IQR)	0.12 (1.3)	0.09 (1.3)	0.14 (2.22)	0.337	0.379
TSI recovery rate, median (IQR) ⁺	0.21 (0.16)	0.19 (0.16)	0.23 (0.19)	0.001**	0.005**
TSI at 10 seconds, median (IQR)	-1.19 (1.68)	-0.97 (1.68)	-1.48 (2.25)	0.038*	0.068
TSI at 20 seconds, median (IQR)	-0.21 (1.31)	-0.2 (1.31)	-0.34 (2.04)	0.527	0.527
TSI at 30 seconds, median (IQR)	-0.76 (1.52)	-0.82 (1.52)	-0.72 (1.55)	0.278	0.357
TSI steady-state, median (IQR)	-1.09 (1.79)	-1.19 (1.79)	-1.01 (2.12)	0.069	0.104
Systolic Blood pressure (SBP)					
SBP nadir, median (IQR)	-31.94 (21.64)	-31.94 (21.64)	-31.96 (24.63)	0.662	0.839
SBP drop rate, median (IQR) ⁺	-3.68 (3.87)	-3.8 (3.87)	-3.55 (3.17)	0.321	0.722
SBP overshoot-to-nadir, median (IQR)	33.86 (22.6)	32.45 (22.6)	35.53 (22.25)	0.927	0.927
SBP overshoot, mean (SD)	1.38 (25.81)	1.42 (25.81)	1.24 (34.1)	0.604	0.839
SBP recovery rate, median (IQR) ⁺	2.91 (2.00)	2.9 (2.00)	2.94 (2.19)	0.746	0.839
SBP at 10 seconds, mean (SD)	-24.1 (23.54)	-24.1 (23.54)	-24.23 (24.03)	0.308	0.722
SBP at 20 seconds, mean (SD)	-4.37 (28.76)	-4.17 (28.76)	-5 (28.44)	0.537	0.839
SBP at 30 seconds, mean (SD)	-2.02 (27.35)	-0.96 (27.35)	-4.08 (26.92)	0.029*	0.130
SBP steady-state, mean (SD)	4.81 (21.78)	6.54 (21.78)	1.46 (17.83)	0.003**	0.027*
Diastolic Blood Pressure (DBP)					
DBP nadir, median (IQR)	-17.38 (16.15)	-15.27 (16.15)	-21.23 (17.12)	0.003**	0.007**
DBP drop rate, median (IQR) ⁺	-2.11 (2.00)	-1.96 (2.00)	-2.30 (2.19)	0.201	0.258
DBP overshoot-to-nadir, mean (SD)	20.59 (13.92)	20.64 (13.92)	20.29 (12.85)	0.371	0.371
DBP overshoot, mean (SD)	2.51 (17.95)	4.50 (17.95)	0.60 (18.08)	0.006**	0.009**
DBP recovery rate, median (IQR) ⁺	1.77 (1.19)	1.80 (1.19)	1.74 (1.12)	0.341	0.371
DBP at 10 seconds, mean (SD)	-12.37 (13.91)	-11.19 (13.91)	-14.51 (14.09)	0.001**	0.003**
DBP at 20 seconds, mean (SD)	-0.28 (16.31)	0.9 (16.31)	-2.03 (16.92)	0.004**	0.007**
DBP at 30 seconds, mean (SD)	1.62 (16.87)	3.72 (16.87)	-2.11 (15.14)	<0.001***	<0.001***
DBP steady-state, mean (SD)	6.07 (15.03)	8.72 (15.03)	2.11 (13.32)	<0.001***	<0.001***
Heart Rate (bpm)					
HR maximum, median (IQR)	14.65 (9.1)	15.24 (9.1)	13.18 (10.52)	0.107	0.272
HR increase rate, median (IQR) ⁺	1.37 (1.17)	1.49 (1.17)	1.19 (1.19)	0.082	0.272

HR min-to-max, median (IQR)	-7.04 (12.7)	-7.86 (12.7)	-5.34 (12.18)	0.121	0.272
HR minimum, median (IQR)	5.8 (7.9)	6.29 (7.9)	5.19 (9.64)	0.319	0.479
HR recovery rate, median (IQR) ⁺	-1.11 (1.55)	-1.21 (1.55)	-0.99 (2.52)	0.500	0.643
HR at 10 seconds, median (IQR)	10.91 (8.69)	11.67 (8.69)	10.02 (9.01)	0.088	0.272
HR at 20 seconds, median (IQR)	7.01 (9.06)	7.03 (9.06)	6.91 (8.19)	0.871	0.920
HR at 30 seconds, mean (SD)	6.35 (7.45)	6.24 (7.45)	6.46 (8.68)	0.216	0.389
HR steady-state, median (IQR)	7.05 (7.41)	6.9 (7.41)	7.36 (8.16)	0.920	0.920
Total peripheral resistance (mmHg·min/L)					
TPR nadir, median (IQR)	-0.52 (0.52)	-0.53 (0.52)	-0.5 (0.37)	0.752	0.752
TPR drop rate, median (IQR) ⁺	-0.07 (0.06)	-0.07 (0.06)	-0.06 (0.05)	0.465	0.562
TPR overshoot-to-nadir, median (IQR)	0.63 (0.64)	0.76 (0.64)	0.49 (0.41)	<0.001***	<0.001***
TPR overshoot, median (IQR)	0.13 (0.54)	0.24 (0.54)	0.01 (0.41)	<0.001***	<0.001***
TPR recovery rate, median (IQR) ⁺	0.05 (0.04)	0.05 (0.04)	0.04 (0.03)	<0.001***	<0.001***
TPR at 10 seconds, median (IQR)	-0.42 (0.57)	-0.42 (0.57)	-0.42 (0.39)	0.500	0.562
TPR at 20 seconds, median (IQR)	0.01 (0.45)	0.09 (0.45)	-0.12 (0.45)	<0.001***	<0.001***
TPR at 30 seconds, median (IQR)	0.11 (0.49)	0.20 (0.49)	-0.06 (0.38)	<0.001***	<0.001***
TPR steady-state, median (IQR)	0.15 (0.49)	0.23 (0.49)	0.06 (0.34)	<0.001***	<0.001***
Stroke volume (ml)					
SV maximum, median (IQR)	7.80 (20.63)	4.44 (20.63)	13.63 (26.20)	<0.001***	<0.001***
SV increase rate, median (IQR) ⁺	1.07 (2.43)	0.62 (2.43)	1.67 (2.90)	<0.001***	<0.001***
SV min-to-max, median (IQR)	-15.87 (17.82)	-13.79 (17.82)	-18.28 (17.41)	0.005**	0.009**
SV minimum, median (IQR)	-7.90 (11.73)	-8.62 (11.73)	-5.25 (20.11)	0.026*	0.033*
SV recovery rate, median (IQR) ⁺	-2.03 (1.67)	-1.86 (1.67)	-2.46 (2.29)	<0.001***	<0.001***
SV at 10 seconds, median (IQR)	3.59 (14.93)	-0.15 (14.93)	7.5 (18.26)	<0.001***	<0.001***
SV at 20 seconds, median (IQR)	-6.84 (10.49)	-7.29 (10.49)	-5.68 (17.88)	0.016*	0.024*
SV at 30 seconds, median (IQR)	-8.80 (11.01)	-9.28 (11.01)	-7.34 (16.23)	0.070	0.070
SV steady-state, median (IQR)	-9.62 (12.14)	-10.27 (12.14)	-7.70 (17.29)	0.041*	0.046*

⁺ rates are expressed in units of the signal/seconds. False discovery rate (FDR) corrected p-values are also reported. *p < 0.05, **p < 0.01, ***p < 0.001. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume, SD = standard deviation, IQR = interquartile range.

Supplementary Table A.J.3. Average and variability absolute values for the SBP, DBP and HR features analysed for all patients, females and males, comparing differences between sex. False discovery rate (FDR) corrected p-values are also reported.

	All patients	Females	Males	p-value	FDR p-value
Systolic Blood Pressure (mmHg)					
SBP baseline, mean (SD)	144.02 (28.67)	144.89 (28.67)	143.77 (26.63)	0.714	0.818
SBP absolute nadir, mean (SD)	111.79 (34.95)	111.42 (34.95)	112.64 (27.54)	0.793	0.818
SBP absolute overshoot, mean (SD)	145.79 (40.66)	145.02 (40.66)	148.34 (32.76)	0.590	0.818
Absolute SBP at 10 seconds, mean (SD)	120.21 (35.41)	119.82 (35.41)	121.43 (33.3)	0.818	0.818
Absolute SBP at 20 seconds, mean (SD)	140.43 (38.82)	140.85 (38.82)	139.46 (33.6)	0.730	0.818
Absolute SBP at 30 seconds, mean (SD)	143.69 (41.39)	146.00 (41.39)	141.31 (35.3)	0.413	0.818
SBP absolute steady-state, mean (SD)	149.28 (34.81)	151.45 (34.81)	148.48 (33.3)	0.180	0.818
Diastolic Blood Pressure (mmHg)					
DBP baseline, mean (SD)	81.08 (16.94)	79.64 (16.94)	83.11 (16.78)	0.207	0.207
DBP absolute nadir, mean (SD)	63.34 (21.37)	64.87 (21.37)	62.16 (19.33)	0.182	0.207
DBP absolute overshoot, mean (SD)	84.27 (24.48)	85.77 (24.48)	83.81 (19.37)	0.167	0.207
Absolute DBP at 10 seconds, mean (SD)	68.08 (23.11)	68.91 (23.11)	67.22 (20.17)	0.181	0.207
Absolute DBP at 20 seconds, mean (SD)	81.05 (22.67)	82.72 (22.67)	80.08 (25.95)	0.160	0.207
Absolute DBP at 30 seconds, mean (SD)	83.16 (23.37)	85.11 (23.37)	80.64 (21.93)	0.025*	0.088
SBP absolute steady-state, mean (SD)	88.08 (22.39)	91.12 (22.39)	85.71 (18.55)	0.007**	0.049*
Heart Rate (bpm)					
HR baseline, median (IQR)	70.78 (14.91)	71.88 (14.91)	69.55 (17.28)	0.045*	0.079
HR absolute nadir, median (IQR)	85.21 (18.63)	87.23 (18.63)	82.96 (22.78)	0.028*	0.065
HR absolute overshoot, median (IQR)	76.7 (16.32)	78.15 (16.32)	74.5 (14.67)	0.019*	0.065
Absolute HR at 10 seconds, median (IQR)	81.93 (18.19)	83.97 (18.19)	78.54 (19.75)	0.023*	0.065
Absolute HR at 20 seconds, median (IQR)	78.64 (17.78)	79.76 (17.78)	75.96 (19.19)	0.088	0.123
Absolute HR at 30 seconds, median (IQR)	77.39 (17.25)	77.63 (17.25)	76.66 (19.24)	0.306	0.306
HR absolute steady-state, median (IQR)	78.74 (16.32)	79.56 (16.32)	77.65 (18.84)	0.113	0.132

$p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SD = standard deviation, IQR = interquartile range.

Supplementary Table A.J.4. Effects of multimorbidity on the full set of cardiovascular (SBP, DBP, HR, SV, TPR) and cerebrovascular (TSI) features in **all patients**. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants. False discovery rate (FDR) corrected p-values are also reported.

	Univariate model			Adjusted model		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI (%)						
TSI nadir	-0.07 (-0.16 0.02)	0.143	0.198	-0.08 (-0.19 0.02)	0.125	0.188
TSI drop rate ⁺	0.00 (-0.02 0.01)	0.580	0.652	-0.01 (-0.02 0.01)	0.271	0.348
TSI overshoot-to-nadir	0.02 (-0.08 0.11)	0.745	0.745	0.02 (-0.09 0.13)	0.676	0.676
TSI overshoot	-0.07 (-0.15 0.01)	0.085	0.191	-0.11 (-0.20 -0.01)	0.033*	0.074
TSI recovery rate ⁺	-0.01 (-0.01 0.00)	0.137	0.198	0.00 (-0.01 0.01)	0.435	0.489
TSI at 10 seconds	-0.11 (-0.20 -0.02)	0.014*	0.048*	-0.15 (-0.25 -0.04)	0.005**	0.015*
TSI at 20 seconds	-0.13 (-0.21 -0.05)	0.002**	0.018*	-0.17 (-0.27 -0.08)	0.001**	0.009**
TSI at 30 seconds	-0.10 (-0.17 -0.02)	0.016*	0.048*	-0.15 (-0.25 -0.06)	0.002**	0.009**
TSI steady-state	-0.07 (-0.16 0.03)	0.154	0.198	-0.10 (-0.21 0.02)	0.094	0.169
SBP (mmHg)						
SBP nadir	-0.87 (-1.95 0.22)	0.116	0.149	-0.70 (-1.97 0.57)	0.280	0.504
SBP drop rate ⁺	0.03 (-0.13 0.18)	0.731	0.731	-0.01 (-0.20 0.19)	0.959	0.959
SBP overshoot-to-nadir	-1.37 (-2.43 -0.31)	0.012*	0.036*	-0.52 (-1.75 0.71)	0.405	0.608
SBP overshoot	-1.87 (-3.22 -0.52)	0.007**	0.032*	-1.18 (-2.72 0.37)	0.136	0.408
SBP recovery rate ⁺	-0.11 (-0.21 -0.01)	0.024*	0.036*	-0.01 (-0.12 0.10)	0.834	0.938
SBP at 10 seconds	-0.27 (-1.42 0.89)	0.651	0.731	-0.19 (-1.54 1.16)	0.781	0.938
SBP at 20 seconds	-1.59 (-2.93 -0.25)	0.020*	0.036*	-0.91 (-2.46 0.65)	0.253	0.504
SBP at 30 seconds	-2.23 (-3.47 -0.98)	0.001**	0.009**	-1.58 (-3.05 -0.11)	0.035*	0.297
SBP steady-state	-1.23 (-2.26 -0.19)	0.020*	0.036*	-1.19 (-2.46 0.08)	0.066	0.297
DBP (mmHg)						
DBP nadir	-0.31 (-1.00 0.38)	0.379	0.42	-0.16 (-1.00 0.68)	0.713	0.889
DBP drop rate ⁺	0.05 (-0.05 0.14)	0.349	0.42	0.01 (-0.10 0.13)	0.809	0.889
DBP overshoot-to-nadir	-1.32 (-1.92 -0.72)	<0.001***	<0.001***	-0.82 (-1.54 -0.10)	0.025*	0.056
DBP overshoot	-1.30 (-2.08 -0.52)	0.001**	0.002**	-1.08 (-2.01 -0.14)	0.024*	0.056
DBP recovery rate ⁺	-0.09 (-0.14 -0.04)	<0.001***	<0.001***	-0.04 (-0.10 0.02)	0.163	0.244
DBP at 10 seconds	-0.30 (-1.03 0.43)	0.420	0.42	-0.06 (-0.94 0.81)	0.889	0.889
DBP at 20 seconds	-1.17 (-1.98 -0.37)	0.004**	0.006**	-0.80 (-1.75 0.16)	0.102	0.184
DBP at 30 seconds	-1.72 (-2.50 -0.93)	<0.001***	<0.001***	-1.34 (-2.29 -0.40)	0.005**	0.032*

DBP steady-state	-1.26 (-1.95 -0.57)	<0.001***	<0.001***	-1.18 (-2.04 -0.32)	0.007**	0.032*
HR (bpm)						
HR maximum	-1.10 (-1.55 -0.65)	<0.001***	<0.001***	-0.70 (-1.25 -0.15)	0.013*	0.029*
HR increase rate ⁺	-0.12 (-0.17 -0.07)	<0.001***	<0.001***	-0.08 (-0.15 -0.01)	0.018*	0.032*
HR min-to-max	0.39 (-0.07 0.85)	0.093	0.167	-0.07 (-0.62 0.49)	0.817	0.817
HR min-to-baseline	-0.60 (-1.01 -0.18)	0.005**	0.011*	-0.75 (-1.28 -0.22)	0.006**	0.027*
HR recovery rate ⁺	0.02 (-0.04 0.09)	0.461	0.519	-0.05 (-0.13 0.03)	0.248	0.279
HR at 10 seconds	-1.26 (-1.65 -0.87)	<0.001***	<0.001***	-0.80 (-1.28 -0.32)	0.001**	0.009**
HR at 20 seconds	-0.26 (-0.65 0.12)	0.176	0.264	-0.44 (-0.91 0.04)	0.070	0.105
HR at 30 seconds	-0.15 (-0.53 0.22)	0.423	0.519	-0.63 (-1.10 -0.16)	0.009**	0.027*
HR steady-state	-0.03 (-0.40 0.33)	0.867	0.878	-0.30 (-0.76 0.16)	0.196	0.252
TPR (mmHg·min/L)						
TPR nadir	0.027 (0.006 0.048)	0.011*	0.016*	0.023 (-0.002 0.048)	0.072	0.166
TPR drop rate ⁺	0.004 (0.002 0.007)	0.001**	0.002**	0.003 (-0.001 0.006)	0.126	0.189
TPR overshoot-to-nadir	-0.055 (-0.078 -0.032)	<.001***	<.001***	-0.041 (-0.070 -0.013)	0.005**	0.045*
TPR overshoot	-0.028 (-0.051 -0.005)	0.016*	0.021*	-0.019 (-0.046 0.009)	0.187	0.210
TPR recovery rate ⁺	-0.003 (-0.005 -0.002)	<.001***	<.001***	-0.002 (-0.004 -0.001)	0.014*	0.063
TPR at 10 seconds	0.023 (0.002 0.044)	0.030*	0.034*	0.023 (-0.002 0.049)	0.074	0.166
TPR at 20 seconds	-0.018 (-0.039 0.004)	0.102	0.102	-0.007 (-0.032 0.019)	0.607	0.607
TPR at 30 seconds	-0.037 (-0.060 -0.014)	0.002**	0.004**	-0.023 (-0.050 0.004)	0.098	0.176
TPR steady-state	-0.036 (-0.056 -0.016)	0.001**	0.002**	-0.018 (-0.043 0.007)	0.153	0.197
SV (ml)						
SV maximum	0.43 (-0.54 1.40)	0.386	0.434	0.58 (-0.60 1.76)	0.331	0.426
SV increase rate ⁺	-0.01 (-0.13 0.10)	0.809	0.809	0.00 (-0.14 0.14)	0.956	0.956
SV min-to-max	0.54 (-0.20 1.28)	0.151	0.194	0.80 (-0.15 1.75)	0.099	0.178
SV min-to-baseline	0.94 (0.22 1.67)	0.011*	0.025*	1.06 (0.16 1.97)	0.022*	0.066
SV recovery rate ⁺	-0.07 (-0.15 0.02)	0.120	0.180	-0.04 (-0.15 0.06)	0.385	0.433
SV at 10 seconds	0.81 (-0.02 1.64)	0.054	0.097	0.75 (-0.26 1.77)	0.145	0.217
SV at 20 seconds	0.93 (0.25 1.61)	0.007**	0.021*	1.14 (0.32 1.97)	0.007**	0.032*
SV at 30 seconds	1.32 (0.63 2.02)	<.001***	<.001***	1.30 (0.45 2.15)	0.003**	0.027*
SV steady-state	1.08 (0.44 1.72)	0.001**	0.005*	0.84 (0.03 1.66)	0.042*	0.094

⁺ rates are expressed in units of the signal/seconds. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume.

Supplementary Table A.J.5. Effects of multimorbidity on TSI when correcting for covariates and concurrent **SBP** features. Model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants + concurrent SBP feature. False discovery rate (FDR) corrected p-values are also reported.

TSI (%) ⁺	All patients			Females			Males		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI nadir	-0.07 (-0.17 0.04)	0.193	0.347	-0.12 (-0.25 0.02)	0.086	0.129	-0.05 (-0.23 0.13)	0.609	0.737
TSI drop rate ⁺	-0.01 (-0.02 0.01)	0.271	0.348	-0.01 (-0.03 0.01)	0.178	0.229	-0.01 (-0.04 0.02)	0.513	0.737
TSI overshoot-to-nadir	0.03 (-0.08 0.14)	0.620	0.620	-0.05 (-0.20 0.10)	0.496	0.496	0.08 (-0.09 0.26)	0.339	0.737
TSI overshoot	-0.10 (-0.20 0.00)	0.045*	0.101	-0.18 (-0.30 -0.06)	0.005**	0.015*	0.00 (-0.18 0.17)	0.959	0.959
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.415	0.467	-0.01 (-0.02 0.01)	0.466	0.496	0.00 (-0.02 0.01)	0.530	0.737
TSI at 10s	-0.14 (-0.23 -0.04)	0.005**	0.015*	-0.17 (-0.29 -0.05)	0.007**	0.016*	-0.10 (-0.26 0.07)	0.264	0.737
TSI at 20s	-0.15 (-0.25 -0.06)	0.001*	0.009**	-0.19 (-0.31 -0.08)	0.002**	0.014*	-0.09 (-0.26 0.09)	0.322	0.737
TSI at 30s	-0.14 (-0.24 -0.04)	0.005*	0.015*	-0.18 (-0.30 -0.06)	0.003**	0.014*	-0.04 (-0.21 0.13)	0.655	0.737
TSI steady-state	-0.07 (-0.18 0.05)	0.256	0.348	-0.16 (-0.31 -0.01)	0.041*	0.074	0.05 (-0.15 0.24)	0.638	0.737

⁺TSI drop rate and recovery rate are expressed in %/seconds. TSI = tissue saturation index, SBP = systolic blood pressure, *p < 0.05, **p < 0.01, ***p < .001.

Supplementary Table A.J.6. Effects of multimorbidity on tissue saturation index when correcting for covariates and concurrent **DBP** features. Model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants + concurrent DBP feature. False discovery rate (FDR) corrected p-values are also reported.

TSI (%) ⁺	All			Females			Males		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI nadir	-0.08 (-0.18 0.03)	0.151	0.226	-0.12 (-0.26 0.01)	0.080	0.120	-0.05 (-0.24 0.13)	0.583	0.911
TSI drop rate ⁺	-0.01 (-0.03 0.01)	0.252	0.324	-0.01 (-0.03 0.01)	0.201	0.258	-0.01 (-0.04 0.02)	0.584	0.911
TSI overshoot-to-nadir	0.05 (-0.07 0.16)	0.419	0.471	-0.04 (-0.18 0.11)	0.621	0.621	0.13 (-0.05 0.31)	0.152	0.911
TSI overshoot	-0.10 (-0.20 0.00)	0.051*	0.115	-0.18 (-0.31 -0.05)	0.005**	0.015*	-0.01 (-0.18 0.16)	0.911	0.911
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.522	0.522	0.00 (-0.02 0.01)	0.470	0.529	0.00 (-0.02 0.01)	0.813	0.911
TSI at 10s	-0.13 (-0.23 -0.04)	0.007**	0.021*	-0.17 (-0.30 -0.04)	0.009**	0.020*	-0.10 (-0.26 0.07)	0.266	0.911
TSI at 20s	-0.15 (-0.25 -0.05)	0.003**	0.021*	-0.19 (-0.31 -0.06)	0.004**	0.015*	-0.08 (-0.26 0.09)	0.350	0.911
TSI at 30s	-0.14 (-0.24 -0.04)	0.006**	0.021*	-0.19 (-0.32 -0.06)	0.004**	0.015*	-0.04 (-0.21 0.13)	0.628	0.911
TSI steady-state	-0.09 (-0.20 0.03)	0.150	0.226	-0.18 (-0.33 -0.02)	0.027*	0.049*	0.02 (-0.18 0.22)	0.844	0.911

⁺TSI drop rate and recovery rate are expressed in %/seconds. TSI = tissue saturation index, DBP = diastolic blood pressure, *p < 0.05, **p < 0.01.

Supplementary Table A.J.7. Effects of multimorbidity on tissue saturation index when correcting for covariates and concurrent **MAP** features. Model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants + concurrent MAP feature. False discovery rate (FDR) corrected p-values are also reported.

TSI (%) ⁺	All			Females			Males		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI nadir	-0.07 (-0.18 0.03)	0.172	0.310	-0.12 (-0.26 0.01)	0.079	0.118	-0.05 (-0.23 0.14)	0.609	0.780
TSI drop rate ⁺	-0.01 (-0.02 0.01)	0.324	0.417	-0.01 (-0.03 0.01)	0.208	0.267	-0.01 (-0.04 0.02)	0.579	0.780
TSI overshoot-to-nadir	0.03 (-0.08 0.14)	0.554	0.554	-0.04 (-0.18 0.11)	0.607	0.607	0.10 (-0.07 0.28)	0.238	0.780
TSI overshoot	-0.10 (-0.20 0.00)	0.052	0.117	-0.18 (-0.30 -0.06)	0.005**	0.015*	-0.01 (-0.18 0.17)	0.937	0.937
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.518	0.554	0.00 (-0.02 0.01)	0.603	0.607	0.00 (-0.02 0.01)	0.652	0.780
TSI at 10s	-0.14 (-0.23 -0.04)	0.006**	0.021*	-0.17 (-0.29 -0.05)	0.008**	0.018*	-0.10 (-0.27 0.07)	0.257	0.780
TSI at 20s	-0.15 (-0.25 -0.06)	0.002**	0.018*	-0.19 (-0.31 -0.07)	0.003**	0.015*	-0.08 (-0.26 0.09)	0.333	0.780
TSI at 30s	-0.13 (-0.23 -0.04)	0.007**	0.021*	-0.18 (-0.30 -0.05)	0.005**	0.015*	-0.04 (-0.21 0.13)	0.653	0.780
TSI steady-state	-0.07 (-0.19 0.04)	0.221	0.332	-0.16 (-0.32 -0.01)	0.037*	0.067	0.04 (-0.16 0.24)	0.693	0.780

⁺TSI drop rate and recovery rate are expressed in %/seconds. TSI = tissue saturation index, MAP = mean arterial pressure, *p < 0.05, **p < 0.01.

Supplementary Table A.J.8. Effects of multimorbidity on tissue saturation index when correcting for covariates and concurrent **TPR** features. Model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants + concurrent TPR feature. False discovery rate (FDR) corrected p-values are also reported.

TSI (%) ⁺	All			Females			Males		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI nadir	-0.08 (-0.19 0.02)	0.119	0.178	-0.13 (-0.27 0.01)	0.066	0.099	-0.05 (-0.23 0.14)	0.614	0.801
TSI drop rate ⁺	-0.01 (-0.03 0.00)	0.181	0.233	-0.01 (-0.03 0.01)	0.167	0.215	-0.01 (-0.04 0.02)	0.409	0.801
TSI overshoot-to-nadir	0.05 (-0.06 0.16)	0.397	0.447	-0.03 (-0.18 0.12)	0.679	0.679	0.11 (-0.07 0.30)	0.228	0.801
TSI overshoot	-0.12 (-0.22 -0.02)	0.022*	0.049**	-0.20 (-0.32 -0.07)	0.003**	0.009**	-0.03 (-0.21 0.14)	0.723	0.813
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.581	0.581	-0.01 (-0.02 0.01)	0.415	0.467	0.00 (-0.02 0.02)	0.956	0.956
TSI at 10s	-0.16 (-0.26 -0.05)	0.003**	0.009**	-0.18 (-0.31 -0.05)	0.008**	0.018*	-0.10 (-0.28 0.07)	0.245	0.801
TSI at 20s	-0.17 (-0.27 -0.07)	0.001**	0.005**	-0.21 (-0.34 -0.08)	0.002**	0.009**	-0.09 (-0.27 0.08)	0.295	0.801
TSI at 30s	-0.17 (-0.26 -0.07)	0.001**	0.005**	-0.24 (-0.37 -0.11)	<.001***	<.001***	-0.06 (-0.23 0.11)	0.485	0.801
TSI steady-state	-0.11 (-0.23 0.01)	0.064	0.115	-0.19 (-0.35 -0.04)	0.015*	0.027*	-0.05 (-0.24 0.14)	0.623	0.801

⁺TSI drop rate and recovery rate are expressed in %/seconds. TSI = tissue saturation index, TPR = total peripheral resistance, *p < 0.05, **p < 0.01, ***p < .001.

Supplementary Table A.J.9. Effects of multimorbidity on tissue saturation index when correcting for covariates and concurrent **SV** features. Model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + supine rest duration + alcohol excess + smoking status + antihypertensives + antidepressants + concurrent SV feature. False discovery rate (FDR) corrected p-values are also reported.

TSI (%) ⁺	All			Females			Males		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI nadir	-0.08 (-0.19 0.02)	0.133	0.200	-0.13 (-0.27 0.01)	0.071	0.106	-0.03 (-0.21 0.15)	0.712	0.883
TSI drop rate ⁺	-0.01 (-0.02 0.01)	0.275	0.354	-0.01 (-0.03 0.01)	0.178	0.229	-0.01 (-0.04 0.02)	0.630	0.883
TSI overshoot-to-nadir	0.02 (-0.09 0.13)	0.703	0.703	-0.06 (-0.20 0.09)	0.440	0.440	0.10 (-0.08 0.28)	0.283	0.882
TSI overshoot	-0.10 (-0.20 0.00)	0.055	0.099	-0.21 (-0.34 -0.08)	0.002**	0.006**	0.01 (-0.16 0.19)	0.883	0.883
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.366	0.412	-0.01 (-0.02 0.01)	0.240	0.270	0.00 (-0.02 0.01)	0.798	0.883
TSI at 10s	-0.16 (-0.26 -0.05)	0.003**	0.009**	-0.17 (-0.31 -0.04)	0.011*	0.020*	-0.09 (-0.25 0.08)	0.294	0.882
TSI at 20s	-0.19 (-0.29 -0.09)	<.001***	<.001***	-0.24 (-0.37 -0.11)	<.001***	<.001***	-0.10 (-0.28 0.07)	0.251	0.882
TSI at 30s	-0.17 (-0.26 -0.07)	0.001**	0.005**	-0.24 (-0.37 -0.12)	<.001***	<.001***	-0.03 (-0.21 0.14)	0.696	0.883
TSI steady-state	-0.13 (-0.24 -0.01)	0.027*	0.061	-0.21 (-0.37 -0.06)	0.008**	0.018*	-0.03 (-0.23 0.16)	0.729	0.883

⁺TSI drop rate and recovery rate are expressed in %/seconds. TSI = tissue saturation index, SV = stroke volume, *p < 0.05, **p < 0.01, ***p < .001.

Supplementary Table A.J.10. Effects of multimorbidity on **the full set** of cardiovascular (SBP, DBP, HR) and cerebrovascular (TSI) features investigated **in females**. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants.

	Univariate model			Adjusted model		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
TSI (%)						
TSI nadir	-0.08 (-0.20 0.03)	0.168	0.189	-0.13 (-0.27 0.01)	0.065	0.098
TSI drop rate ⁺	-0.01 (-0.02 0.01)	0.477	0.477	-0.01 (-0.03 0.01)	0.163	0.21
TSI overshoot-to-nadir	-0.11 (-0.23 0.01)	0.076	0.098	-0.05 (-0.20 0.09)	0.484	0.484
TSI overshoot	-0.19 (-0.30 -0.09)	<.001***	<.001***	-0.19 (-0.32 -0.07)	0.003**	0.009**
TSI recovery rate ⁺	-0.01 (-0.03 0.00)	0.009**	0.020*	-0.01 (-0.02 0.01)	0.363	0.408
TSI at 10 seconds	-0.12 (-0.24 0.00)	0.045*	0.068	-0.17 (-0.30 -0.04)	0.012*	0.023*
TSI at 20 seconds	-0.18 (-0.29 -0.08)	0.001**	0.003**	-0.22 (-0.34 -0.09)	0.001**	0.005**
TSI at 30 seconds	-0.18 (-0.28 -0.08)	0.001**	0.003**	-0.22 (-0.35 -0.10)	0.001**	0.005**
TSI steady-state	-0.15 (-0.27 -0.02)	0.022*	0.040*	-0.20 (-0.35 -0.04)	0.013*	0.023*
SBP (mmHg)						
SBP nadir	-0.79 (-2.39 0.82)	0.334	0.429	-0.65 (-2.60 1.29)	0.509	0.654
SBP drop rate ⁺	0.05 (-0.21 0.31)	0.684	0.730	0.04 (-0.26 0.35)	0.772	0.772
SBP overshoot-to-nadir	-1.68 (-3.18 -0.18)	0.028*	0.084	-1.08 (-2.84 0.69)	0.231	0.416
SBP overshoot	-2.31 (-4.19 -0.42)	0.017	0.077	-2.24 (-4.50 0.02)	0.053	0.238
SBP recovery rate ⁺	-0.12 (-0.25 0.01)	0.061	0.137	-0.06 (-0.21 0.09)	0.446	0.654
SBP at 10 seconds	-0.31 (-2.10 1.48)	0.730	0.730	-0.44 (-2.56 1.68)	0.684	0.770
SBP at 20 seconds	-1.51 (-3.49 0.47)	0.134	0.241	-1.78 (-4.14 0.58)	0.138	0.414
SBP at 30 seconds	-2.47 (-4.26 -0.67)	0.007**	0.063	-2.47 (-4.69 -0.26)	0.029*	0.238
SBP steady-state	-1.10 (-2.71 0.51)	0.179	0.268	-1.29 (-3.33 0.76)	0.216	0.416
DBP (mmHg)						
DBP nadir	-0.45 (-1.45 0.55)	0.375	0.482	-0.58 (-1.84 0.68)	0.366	0.471
DBP drop rate ⁺	0.02 (-0.13 0.17)	0.781	0.781	-0.05 (-0.23 0.13)	0.598	0.642
DBP overshoot-to-nadir	-1.33 (-2.24 -0.42)	0.004**	0.012*	-0.76 (-1.84 0.32)	0.166	0.288
DBP overshoot	-1.65 (-2.77 -0.53)	0.004**	0.012*	-1.62 (-2.99 -0.25)	0.021*	0.094
DBP recovery rate ⁺	-0.09 (-0.17 -0.02)	0.017*	0.038*	-0.06 (-0.15 0.03)	0.192	0.288
DBP at 10 seconds	-0.39 (-1.50 0.72)	0.489	0.550	-0.32 (-1.69 1.04)	0.642	0.642
DBP at 20 seconds	-1.26 (-2.40 -0.12)	0.030*	0.045	-1.39 (-2.78 0.00)	0.050	0.15
DBP at 30 seconds	-2.12 (-3.22 -1.02)	<0.001***	<0.001***	-2.04 (-3.41 -0.68)	0.003**	0.027*
DBP steady-state	-1.16 (-2.16 -0.16)	0.023*	0.041*	-1.04 (-2.29 0.22)	0.104	0.234
HR (bpm)						
HR maximum	-1.10 (-1.74 -0.46)	0.001**	0.005*	-0.67 (-1.49 0.14)	0.103	0.162
HR increase rate ⁺	-0.11 (-0.19 -0.03)	0.006**	0.018*	-0.09 (-0.19 0.01)	0.075	0.162

HR min-to-max	0.23 (-0.44 0.90)	0.497	0.746	-0.34 (-1.16 0.49)	0.422	0.543
HR minimum-to-baseline	-0.78 (-1.36 -0.20)	0.009**	0.020*	-1.14 (-1.86 -0.42)	0.002**	0.018*
HR recovery rate ⁺	-0.01 (-0.10 0.08)	0.862	0.862	-0.09 (-0.20 0.02)	0.108	0.162
HR at 10 seconds	-1.36 (-1.94 -0.77)	<0.001***	<0.001***	-0.99 (-1.74 -0.24)	0.010*	0.045*
HR at 20 seconds	-0.15 (-0.73 0.43)	0.606	0.775	-0.12 (-0.82 0.58)	0.744	0.745
HR at 30 seconds	-0.42 (-0.96 0.12)	0.126	0.227	-0.72 (-1.39 -0.06)	0.034*	0.102
HR steady-state	0.11 (-0.42 0.63)	0.689	0.775	-0.11 (-0.77 0.55)	0.745	0.745
TPR (mmHg·min/L)						
TPR nadir	0.014 (-0.021 0.048)	0.431	0.432	0.002 (-0.037 0.042)	0.904	0.904
TPR drop rate ⁺	0.004 (-0.001 0.008)	0.108	0.139	0.001 (-0.004 0.007)	0.707	0.795
TPR overshoot-to-nadir	-0.055 (-0.095 -0.015)	0.007**	0.032*	-0.028 (-0.078 0.021)	0.264	0.475
TPR overshoot	-0.039 (-0.077 0.000)	0.048*	0.086	-0.033 (-0.081 0.015)	0.180	0.475
TPR recovery rate ⁺	-0.003 (-0.006 0.000)	0.036*	0.081	-0.002 (-0.005 0.001)	0.246	0.475
TPR at 10 seconds	0.014 (-0.021 0.049)	0.432	0.432	0.013 (-0.028 0.054)	0.544	0.699
TPR at 20 seconds	-0.032 (-0.066 0.003)	0.072	0.108	-0.032 (-0.075 0.010)	0.132	0.475
TPR at 30 seconds	-0.061 (-0.099 -0.023)	0.002**	0.018*	-0.052 (-0.100 -0.005)	0.031*	0.279
TPR steady-state	-0.042 (-0.077 -0.008)	0.016*	0.048*	-0.022 (-0.067 0.022)	0.320	0.480
SV (ml)						
SV maximum	0.78 (-0.47 2.03)	0.217	0.326	0.48 (-1.02 1.98)	0.526	0.676
SV increase rate ⁺	0.06 (-0.09 0.21)	0.425	0.496	0.04 (-0.14 0.22)	0.655	0.737
SV min-to-max	0.35 (-0.74 1.44)	0.525	0.525	0.66 (-0.75 2.07)	0.357	0.643
SV min-to-baseline	1.07 (0.19 1.96)	0.018*	0.081	0.96 (-0.14 2.06)	0.087	0.261
SV recovery rate ⁺	-0.04 (-0.15 0.06)	0.441	0.496	-0.02 (-0.15 0.11)	0.740	0.740
SV at 10 seconds	1.12 (0.02 2.23)	0.046*	0.104	0.79 (-0.51 2.08)	0.231	0.520
SV at 20 seconds	0.93 (0.08 1.78)	0.032*	0.096	0.99 (-0.02 2.00)	0.054	0.261
SV at 30 seconds	1.19 (0.35 2.04)	0.006**	0.054	0.95 (-0.09 1.99)	0.074	0.261
SV steady-state	0.72 (-0.12 1.55)	0.092	0.166	0.36 (-0.69 1.42)	0.499	0.676

⁺ rates are expressed in units of the signal/seconds. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume.

Supplementary Table A.J.11. Effects of multimorbidity on the full set of cardiovascular (SBP, DBP, HR) and cerebrovascular (TSI) features investigated in males. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants. False discovery rate (FDR) corrected p-values are also reported.

	Univariate model			Adjusted model			
	β (CI)	p-value	FDR value	p-value	β (CI)	p-value	FDR value
TSI (%)							
TSI nadir	-0.02 (-0.16 0.12)	0.759	0.854		-0.04 (-0.23 0.14)	0.631	0.889
TSI drop rate ⁺	0.00 (-0.02 0.03)	0.723	0.854		-0.01 (-0.04 0.02)	0.575	0.889
TSI overshoot-to-nadir	0.09 (-0.04 0.23)	0.184	0.854		0.09 (-0.09 0.27)	0.309	0.889
TSI overshoot	0.03 (-0.10 0.16)	0.664	0.854		0.00 (-0.18 0.17)	0.969	0.969
TSI recovery rate ⁺	0.00 (-0.01 0.01)	0.614	0.854		0.00 (-0.02 0.01)	0.778	0.889
TSI at 10 seconds	-0.07 (-0.21 0.07)	0.293	0.854		-0.09 (-0.26 0.08)	0.276	0.889
TSI at 20 seconds	-0.07 (-0.20 0.06)	0.306	0.854		-0.09 (-0.26 0.09)	0.312	0.889
TSI at 30 seconds	-0.02 (-0.14 0.10)	0.719	0.854		-0.04 (-0.21 0.13)	0.653	0.889
TSI steady-state	-0.01 (-0.16 0.14)	0.887	0.887		0.03 (-0.17 0.22)	0.790	0.889
SBP (mmHg)							
SBP nadir	-0.88 (-2.41 0.65)	0.255	0.328		-0.10 (-1.90 1.70)	0.912	0.912
SBP drop rate ⁺	-0.02 (-0.21 0.17)	0.848	0.950		0.06 (-0.20 0.31)	0.666	0.912
SBP overshoot-to-nadir	-1.03 (-2.60 0.54)	0.196	0.328		-0.24 (-2.16 1.68)	0.803	0.912
SBP overshoot	-1.39 (-3.37 0.58)	0.164	0.328		0.17 (-2.02 2.37)	0.876	0.912
SBP recovery rate ⁺	-0.09 (-0.24 0.06)	0.231	0.328		0.04 (-0.14 0.21)	0.670	0.912
SBP at 10 seconds	-0.05 (-1.58 1.48)	0.950	0.950		0.59 (-1.18 2.36)	0.509	0.912
SBP at 20 seconds	-1.58 (-3.48 0.31)	0.101	0.303		0.54 (-1.55 2.64)	0.608	0.912
SBP at 30 seconds	-1.81 (-3.59 -0.02)	0.047*	0.303		-0.37 (-2.33 1.59)	0.710	0.912
SBP steady-state	-1.12 (-2.45 0.22)	0.101	0.303		-1.13 (-2.81 0.55)	0.185	0.912
DBP (mmHg)							
DBP nadir	-0.01 (-0.95 0.94)	0.988	0.988		0.73 (-0.40 1.85)	0.204	0.376
DBP drop rate ⁺	0.09 (-0.04 0.21)	0.185	0.238		0.12 (-0.05 0.28)	0.157	0.376
DBP overshoot-to-nadir	-1.27 (-2.08 -0.45)	0.003**	0.027*		-1.22 (-2.22 -0.22)	0.018	0.162
DBP overshoot	-0.79 (-1.89 0.32)	0.161	0.238		-0.18 (-1.45 1.09)	0.783	0.808
DBP recovery rate ⁺	-0.09 (-0.16 -0.01)	0.018*	0.081		-0.04 (-0.13 0.05)	0.375	0.562
DBP at 10 seconds	0.04 (-0.90 0.99)	0.929	0.988		0.72 (-0.41 1.86)	0.209	0.376
DBP at 20 seconds	-0.89 (-2.05 0.26)	0.129	0.232		0.45 (-0.82 1.72)	0.483	0.621
DBP at 30 seconds	-1.06 (-2.19 0.07)	0.065	0.146		-0.17 (-1.54 1.20)	0.808	0.808
DBP steady-state	-1.08 (-2.03 -0.12)	0.028*	0.084		-0.98 (-2.18 0.23)	0.111	0.376
HR (bpm)							

HR maximum	-1.10 (-1.78 -0.41)	0.002**	0.009**	-0.63 (-1.49 0.24)	0.152	0.228
HR increase rate ⁺	-0.12 (-0.19 -0.04)	0.003**	0.009**	-0.07 (-0.17 0.02)	0.139	0.228
HR min-to-max	0.49 (-0.19 1.17)	0.157	0.29	0.12 (-0.83 1.08)	0.801	0.801
HR minimum-to-baseline	-0.45 (-1.08 0.18)	0.161	0.29	-0.47 (-1.35 0.40)	0.287	0.369
HR recovery rate ⁺	0.04 (-0.06 0.14)	0.460	0.591	-0.03 (-0.18 0.12)	0.677	0.762
HR at 10 seconds	-1.14 (-1.68 -0.59)	<0.001***	<0.001***	-0.75 (-1.41 -0.09)	0.027*	0.153
HR at 20 seconds	-0.35 (-0.89 0.18)	0.197	0.296	-0.73 (-1.40 -0.06)	0.034*	0.153
HR at 30 seconds	-0.03 (-0.59 0.52)	0.906	0.906	-0.64 (-1.35 0.07)	0.078	0.182
HR steady-state	-0.14 (-0.67 0.40)	0.610	0.686	-0.63 (-1.33 0.08)	0.081	0.182
TPR (mmHg·min/L)						
TPR nadir	0.034 (0.009 0.058)	0.007**	0.016*	0.046 (0.014 0.078)	0.006**	0.034*
TPR drop rate ⁺	0.005 (0.002 0.008)	0.004**	0.016*	0.004 (0.000 0.008)	0.070	0.126
TPR overshoot-to-nadir	-0.034 (-0.058 -0.010)	0.006**	0.016*	-0.040 (-0.072 -0.008)	0.014*	0.034*
TPR overshoot	-0.004 (-0.030 0.022)	0.756	0.851	0.006 (-0.027 0.038)	0.723	0.747
TPR recovery rate ⁺	-0.003 (-0.004 -0.001)	0.005**	0.016*	-0.003 (-0.005 -0.001)	0.015*	0.034*
TPR at 10 seconds	0.031 (0.006 0.055)	0.015*	0.027*	0.042 (0.010 0.075)	0.011*	0.034*
TPR at 20 seconds	0.000 (-0.026 0.026)	0.975	0.975	0.023 (-0.006 0.053)	0.118	0.177
TPR at 30 seconds	-0.006 (-0.031 0.020)	0.647	0.832	0.005 (-0.027 0.037)	0.747	0.747
TPR steady-state	-0.017 (-0.039 0.005)	0.137	0.206	-0.006 (-0.034 0.021)	0.647	0.747
SV (ml)						
SV maximum	-0.244 (-1.821 1.334)	0.760	0.760	0.038 (-2.053 2.130)	0.971	0.971
SV increase rate ⁺	-0.122 (-0.299 0.055)	0.174	0.313	-0.097 (-0.341 0.148)	0.436	0.567
SV min-to-max	0.933 (-0.148 2.015)	0.090	0.27	0.965 (-0.530 2.460)	0.204	0.459
SV min-to-baseline	0.797 (-0.545 2.139)	0.242	0.363	0.704 (-1.099 2.506)	0.441	0.567
SV recovery rate ⁺	-0.064 (-0.198 0.069)	0.342	0.44	-0.073 (-0.249 0.103)	0.415	0.567
SV at 10 seconds	0.269 (-1.010 1.549)	0.678	0.760	0.311 (-1.449 2.071)	0.727	0.818
SV at 20 seconds	0.821 (-0.363 2.006)	0.172	0.313	1.203 (-0.338 2.744)	0.125	0.375
SV at 30 seconds	1.341 (0.144 2.539)	0.028*	0.126	1.651 (0.151 3.151)	0.031*	0.238
SV steady-state	1.320 (0.268 2.372)	0.014*	0.126	1.325 (-0.015 2.664)	0.053	0.238

⁺ rates are expressed in units of the signal/seconds. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. TSI = tissue saturation index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, TPR = total peripheral resistance, SV = stroke volume.

Supplementary Table A.J.12. Effects of multimorbidity on **absolute values** of cardiovascular (SBP, DBP, HR) and cerebrovascular (TSI) features in **all patients**. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants. False discovery rate (FDR) corrected p-values are also reported.

			Univariate model			Adjusted model		
			β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
Systolic Blood Pressure (mmHg)								
SBP baseline ⁺			0.56 (-0.68 1.80)	0.377	0.829	-0.63 (-2.17 0.91)	0.424	0.424
SBP absolute nadir			-0.14 (-1.58 1.30)	0.847	0.847	-1.14 (-2.86 0.58)	0.192	0.336
SBP absolute overshoot			-0.62 (-2.32 1.08)	0.474	0.829	-1.48 (-3.57 0.62)	0.166	0.336
Absolute SBP at 10 seconds			0.63 (-0.97 2.22)	0.440	0.829	-0.88 (-2.75 1.00)	0.358	0.418
Absolute SBP at 20 seconds			-0.46 (-2.24 1.32)	0.612	0.847	-1.22 (-3.39 0.95)	0.269	0.377
Absolute SBP at 30 seconds			-1.05 (-2.79 0.69)	0.235	0.829	-1.80 (-3.97 0.37)	0.104	0.336
SBP absolute steady-state			-0.26 (-1.82 1.31)	0.749	0.847	-1.47 (-3.35 0.41)	0.126	0.336
Diastolic Blood Pressure (mmHg)								
DBP baseline ⁺			-0.40 (-1.17 0.36)	0.301	0.301	-0.68 (-1.58 0.23)	0.144	0.202
DBP absolute nadir			-0.55 (-1.46 0.35)	0.227	0.265	-0.58 (-1.64 0.49)	0.286	0.286
DBP absolute overshoot			-1.90 (-2.91 -0.89)	<0.001***	<0.001***	-1.52 (-2.71 -0.33)	0.012*	0.028*
Absolute DBP at 10 seconds			-0.63 (-1.60 0.35)	0.207	0.265	-0.67 (-1.84 0.49)	0.256	0.286
Absolute DBP at 20 seconds			-1.69 (-2.73 -0.66)	0.001**	0.002**	-1.24 (-2.45 -0.02)	0.046*	0.080
Absolute DBP at 30 seconds			-2.30 (-3.29 -1.31)	<0.001***	<0.001***	-1.88 (-3.07 -0.69)	0.002**	0.007**
DBP absolute steady-state			-1.79 (-2.74 -0.84)	<0.001***	<0.001***	-1.72 (-2.82 -0.62)	0.002**	0.007**
Heart Rate (bpm)								
HR baseline ⁺			0.67 (-0.01 1.35)	0.053	0.296	0.73 (-0.12 1.57)	0.091	0.637
HR absolute nadir			-0.71 (-1.61 0.19)	0.122	0.296	0.08 (-1.02 1.19)	0.882	0.882
HR absolute overshoot			-0.14 (-0.91 0.64)	0.729	0.734	-0.18 (-1.15 0.79)	0.712	0.882
Absolute HR at 10 seconds			-0.65 (-1.46 0.16)	0.116	0.296	-0.10 (-1.10 0.89)	0.837	0.882
Absolute HR at 20 seconds			0.47 (-0.36 1.30)	0.263	0.302	0.36 (-0.68 1.41)	0.495	0.882
Absolute HR at 30 seconds			0.48 (-0.34 1.30)	0.250	0.302	0.13 (-0.91 1.17)	0.806	0.882
HR absolute steady-state			0.53 (-0.27 1.33)	0.193	0.302	0.40 (-0.60 1.41)	0.430	0.882

⁺ SBP baseline was not used as a covariate in the SBP baseline and DBP baseline models, and HR baseline was not used as a covariate in the HR baseline model. p* < 0.05, p** < 0.01, p*** < 0.001. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

Supplementary Table A.J.13. Effects of multimorbidity on **absolute values** of cardiovascular (SBP, DBP, HR) and cerebrovascular (TSI) features investigated **in females**. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants. False discovery rate (FDR) corrected p-values are also reported.

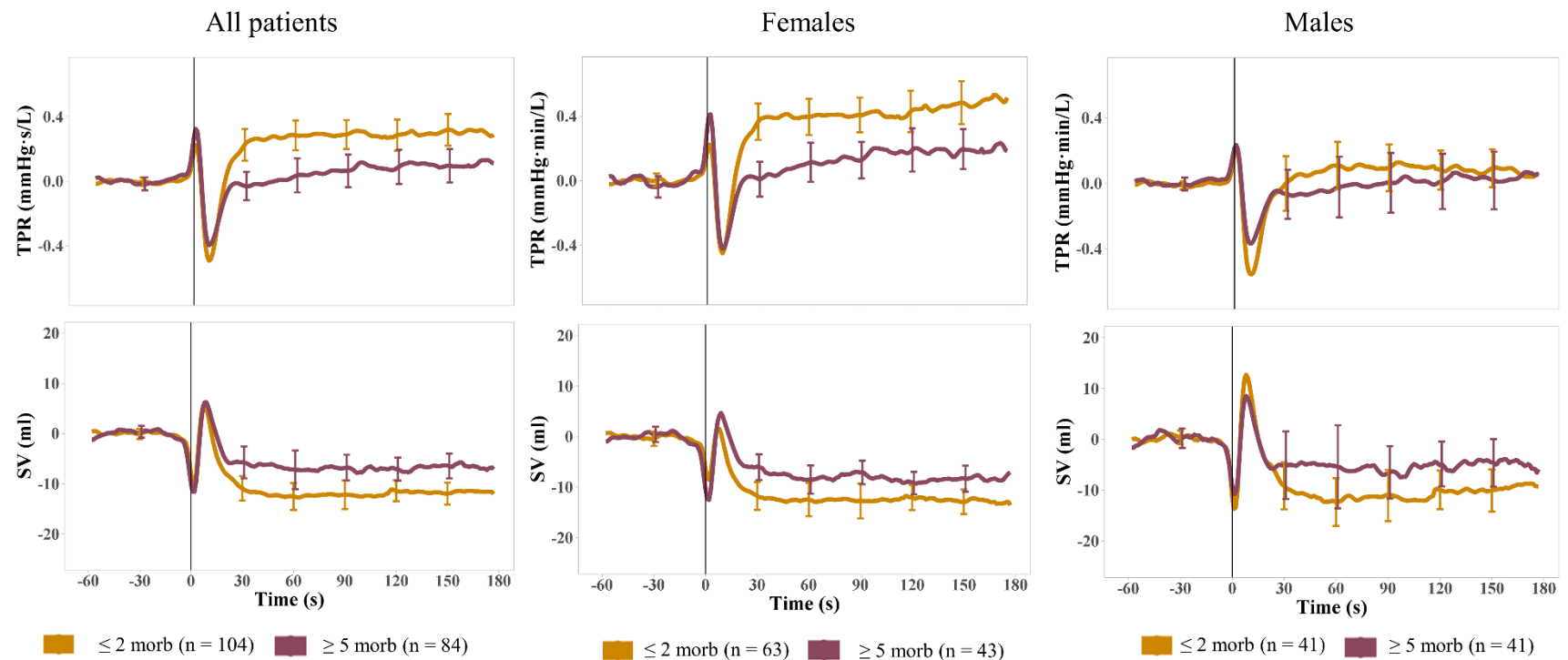
	Univariate model			Adjusted model		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
Systolic Blood Pressure (mmHg)						
SBP baseline ⁺	1.23 (-0.68 3.14)	0.206	0.781	-0.31 (-2.66 2.04)	0.794	0.794
SBP absolute nadir	0.79 (-1.47 3.04)	0.492	0.781	-1.00 (-3.61 1.60)	0.449	0.629
SBP absolute overshoot	-0.56 (-3.17 2.05)	0.671	0.783	-2.45 (-5.66 0.77)	0.135	0.473
Absolute SBP at 10 seconds	1.49 (-0.93 3.91)	0.227	0.781	-0.58 (-3.31 2.14)	0.673	0.785
Absolute SBP at 20 seconds	0.15 (-2.59 2.88)	0.917	0.917	-1.90 (-5.24 1.44)	0.263	0.612
Absolute SBP at 30 seconds	-0.79 (-3.47 1.88)	0.558	0.781	-2.71 (-6.06 0.63)	0.111	0.473
SBP absolute steady-state	0.80 (-1.67 3.27)	0.523	0.781	-1.40 (-4.33 1.54)	0.350	0.612
Diastolic Blood Pressure (mmHg)						
DBP baseline ⁺	-0.17 (-1.44 1.10)	0.787	0.892	-0.28 (-1.76 1.19)	0.706	0.706
DBP absolute nadir	-0.10 (-1.57 1.37)	0.892	0.892	-0.62 (-2.32 1.07)	0.468	0.655
DBP absolute overshoot	-1.56 (-3.14 0.01)	0.052	0.182	-1.48 (-3.35 0.39)	0.119	0.310
Absolute DBP at 10 seconds	-0.28 (-1.91 1.34)	0.731	0.892	-0.52 (-2.39 1.35)	0.586	0.684
Absolute DBP at 20 seconds	-1.21 (-2.80 0.38)	0.134	0.235	-1.29 (-3.16 0.59)	0.177	0.310
Absolute DBP at 30 seconds	-2.15 (-3.67 -0.64)	0.006**	0.042*	-2.29 (-4.13 -0.45)	0.015	0.105
DBP absolute steady-state	-1.14 (-2.63 0.36)	0.134	0.235	-1.24 (-2.97 0.49)	0.158	0.310
Heart Rate (bpm)						
HR baseline ⁺	0.55 (-0.44 1.53)	0.277	0.646	0.68 (-0.54 1.89)	0.275	0.801
HR absolute nadir	-0.71 (-2.00 0.57)	0.276	0.646	-0.16 (-1.72 1.40)	0.839	0.968
HR absolute overshoot	-0.38 (-1.56 0.80)	0.523	0.687	-0.61 (-2.05 0.83)	0.405	0.801
Absolute HR at 10 seconds	-0.94 (-2.17 0.28)	0.131	0.646	-0.44 (-1.95 1.06)	0.560	0.801
Absolute HR at 20 seconds	0.33 (-0.87 1.53)	0.589	0.687	0.43 (-1.08 1.94)	0.572	0.801
Absolute HR at 30 seconds	0.19 (-0.97 1.35)	0.742	0.742	-0.03 (-1.48 1.42)	0.968	0.968
HR absolute steady-state	0.46 (-0.67 1.59)	0.421	0.687	0.42 (-0.99 1.83)	0.558	0.801

⁺ SBP baseline was not used as a covariate in the SBP baseline and DBP baseline models, and HR baseline was not used as a covariate in the HR baseline model. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

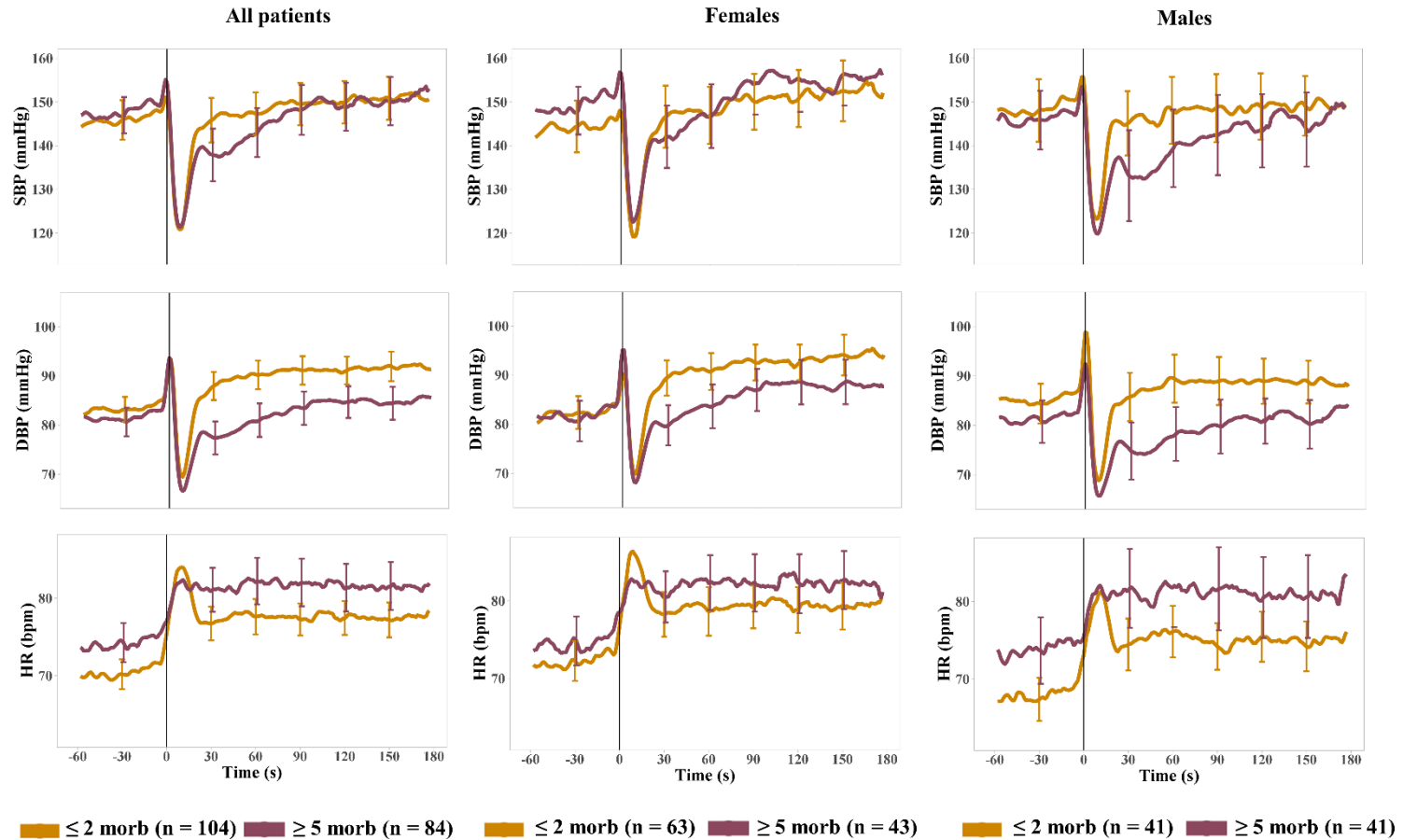
Supplementary Table A.J.14. Effects of multimorbidity on **absolute values** of cardiovascular (SBP, DBP, HR) and cerebrovascular (TSI) features investigated **in males**. Univariate model: multimorbidity. Multivariate adjusted model: multimorbidity + age + sex + BMI + baseline SBP + baseline HR + speed of standing + duration of lying down + alcohol excess + smoking status + antihypertensives + antidepressants. False discovery rate (FDR) corrected p-values are also reported.

	Univariate model			Adjusted model		
	β (CI)	p-value	FDR p-value	β (CI)	p-value	FDR p-value
Systolic Blood Pressure (mmHg)						
SBP baseline ⁺	-0.02 (-1.70 1.66)	0.982	0.982	-0.82 (-2.98 1.35)	0.456	0.897
SBP absolute nadir	-0.91 (-2.77 0.96)	0.337	0.707	-0.74 (-3.10 1.61)	0.532	0.897
SBP absolute overshoot	-0.76 (-3.03 1.50)	0.505	0.707	-0.42 (-3.23 2.40)	0.769	0.897
Absolute SBP at 10 seconds	-0.03 (-2.20 2.14)	0.976	0.982	-0.43 (-3.23 2.37)	0.760	0.897
Absolute SBP at 20 seconds	-1.04 (-3.42 1.35)	0.391	0.707	-0.16 (-2.96 2.64)	0.912	0.912
Absolute SBP at 30 seconds	-1.16 (-3.52 1.19)	0.330	0.707	-0.98 (-3.93 1.97)	0.510	0.897
SBP absolute steady-state	-0.84 (-2.88 1.20)	0.417	0.707	-1.34 (-3.88 1.20)	0.298	0.897
Diastolic Blood Pressure (mmHg)						
DBP baseline ⁺	-0.77 (-1.72 0.17)	0.109	0.153	-1.20 (-2.30 -0.11)	0.031	0.084
DBP absolute nadir	-0.77 (-1.90 0.36)	0.181	0.211	-0.51 (-1.88 0.85)	0.458	0.458
DBP absolute overshoot	-2.08 (-3.39 -0.77)	0.002**	0.005**	-1.63 (-3.14 -0.11)	0.036*	0.084
Absolute DBP at 10 seconds	-0.66 (-1.85 0.54)	0.278	0.278	-0.58 (-2.04 0.88)	0.432	0.458
Absolute DBP at 20 seconds	-1.96 (-3.36 -0.56)	0.006**	0.011*	-1.13 (-2.69 0.44)	0.157	0.220
Absolute DBP at 30 seconds	-2.23 (-3.57 -0.89)	0.001**	0.004**	-1.50 (-3.09 0.09)	0.064	0.112
DBP absolute steady-state	-2.13 (-3.34 -0.92)	0.001**	0.004**	-2.06 (-3.54 -0.58)	0.007**	0.049*
Heart Rate (bpm)						
HR baseline ⁺	0.92 (-0.05 1.88)	0.064	0.415	0.73 (-0.53 1.98)	0.256	0.958
HR absolute nadir	-0.53 (-1.85 0.79)	0.428	0.599	0.30 (-1.29 1.90)	0.707	0.958
HR absolute overshoot	0.24 (-0.83 1.30)	0.662	0.662	0.18 (-1.19 1.55)	0.796	0.958
Absolute HR at 10 seconds	-0.26 (-1.36 0.85)	0.648	0.662	-0.01 (-1.38 1.36)	0.989	0.989
Absolute HR at 20 seconds	0.77 (-0.43 1.96)	0.206	0.415	0.19 (-1.31 1.69)	0.803	0.958
Absolute HR at 30 seconds	0.88 (-0.34 2.11)	0.155	0.415	0.18 (-1.40 1.76)	0.821	0.958
HR absolute steady-state	0.71 (-0.47 1.90)	0.237	0.415	0.20 (-1.33 1.73)	0.792	0.958

⁺ SBP baseline was not used as a covariate in the SBP baseline and DBP baseline models, and HR baseline was not used as a covariate in the HR baseline model. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.



Supplementary Figure A.J.1. Absolute drops from baseline for total peripheral resistance (TPR) and stroke volume (SV) responses for all patients (left), females (middle) and males (right) during the active standing test for patients accumulating 2 or less morbidities (orange) and 5 or more morbidities (purple) (note that these categories were used only for the purpose of displaying the data, multimorbidity was analysed as a continuous variable). The start of the test has been indicated with a vertical line at $t = 0$. Error bars represent the confidence intervals of the mean at $t = -30, 30, 60, 90, 120$ and 150 seconds after standing.

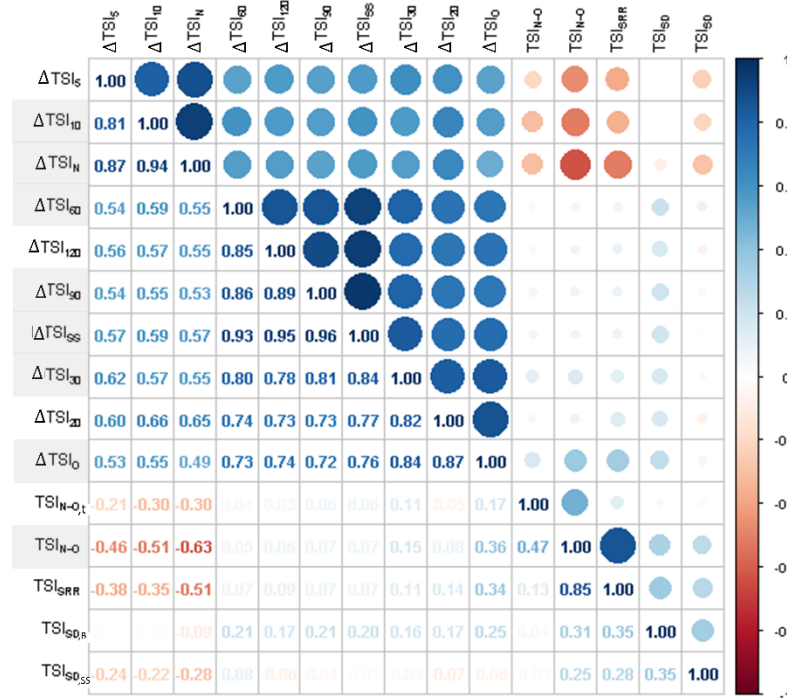


Supplementary Figure A.J.2. Absolute cardiovascular (SBP, DBP, HR) haemodynamic responses for all patients (left), females (middle) and males (right) during the active standing test for patients accumulating 2 or less morbidities (orange) and 5 or more morbidities (purple)(note that these categories were used only for the purpose of displaying the data, multimorbidity was analysed as a continuous variable). The start of the test has been indicated with a vertical line at $t = 0$. Error bars represent the confidence intervals of the mean at -30, 30, 60, 90, 120 and 150 seconds after standing. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, morb = morbidities.

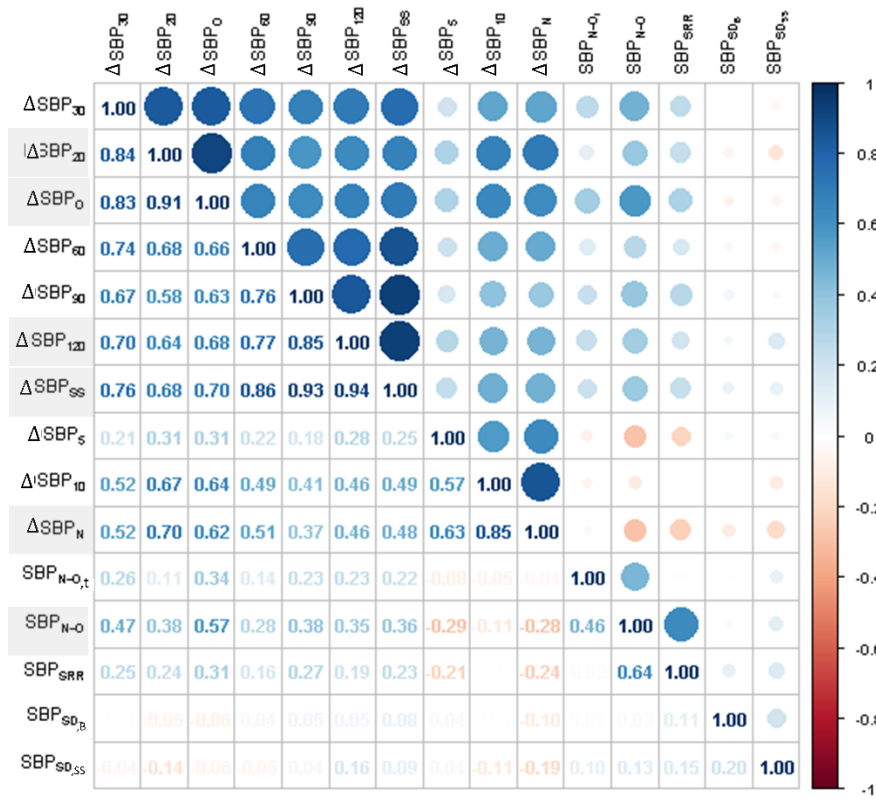
Appendix K: Chapter 9 Supplementary Material



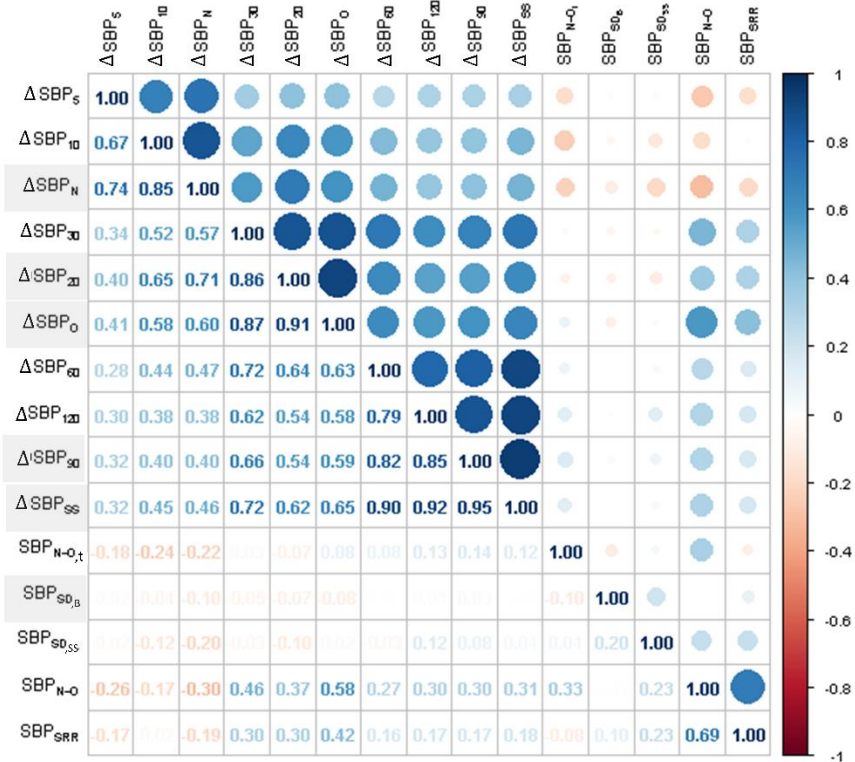
Supplementary Figure A.K.1. Correlation matrix for TSI features used in the classification of unexplained falls (UF). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



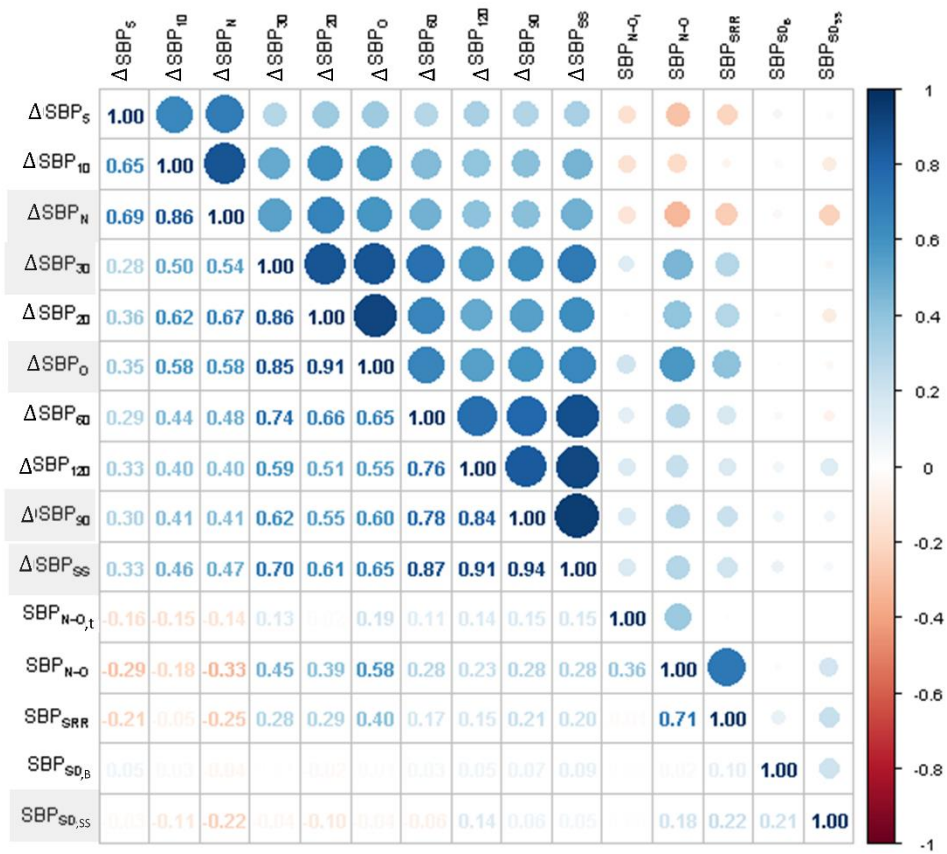
Supplementary Figure A.K.2. Correlation matrix for TSI features used in the classification of unexplained falls or syncope (UFS). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



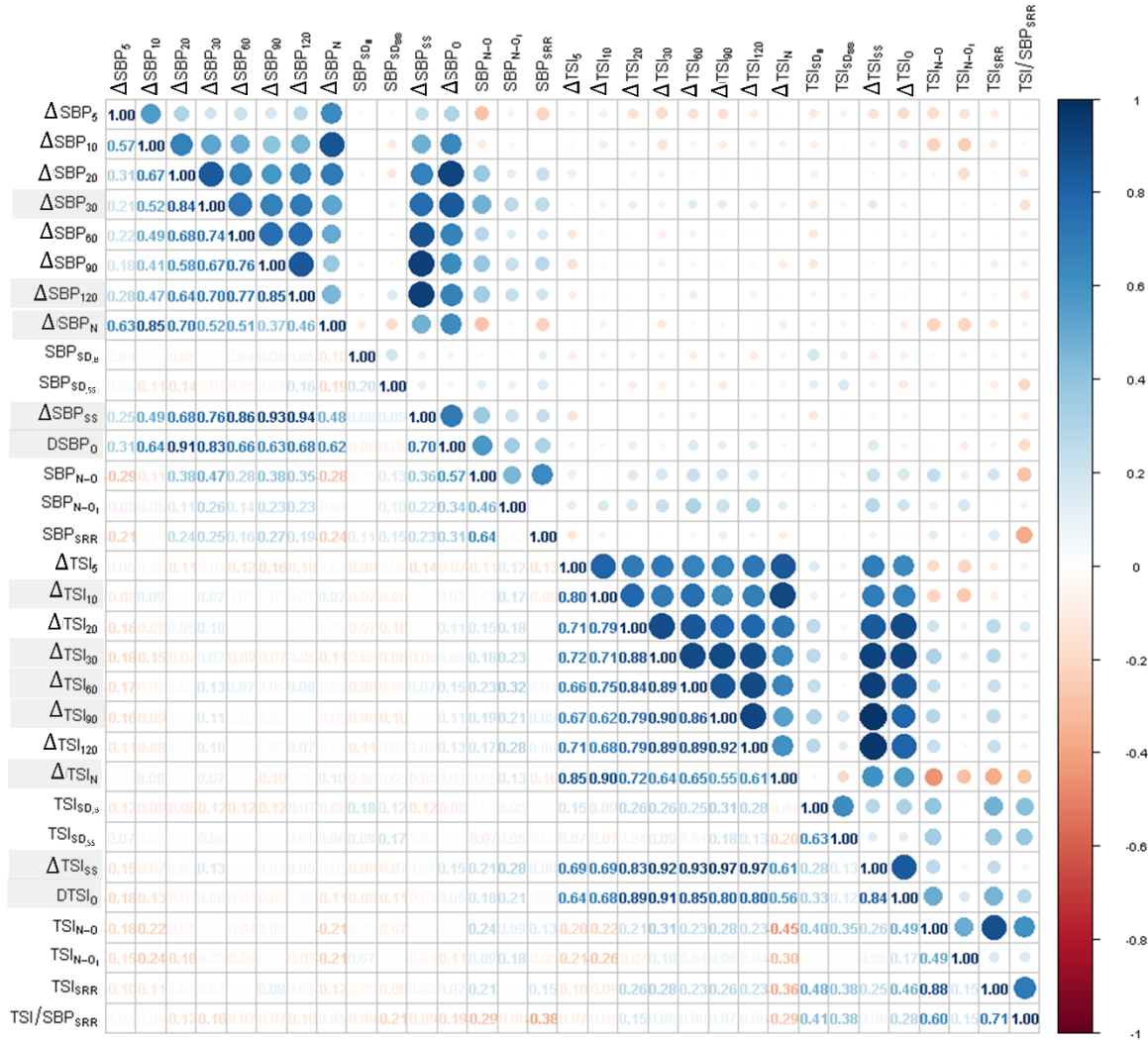
Supplementary Figure A.K.3. Correlation matrix for SBP features used in the classification of unexplained falls (UF). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



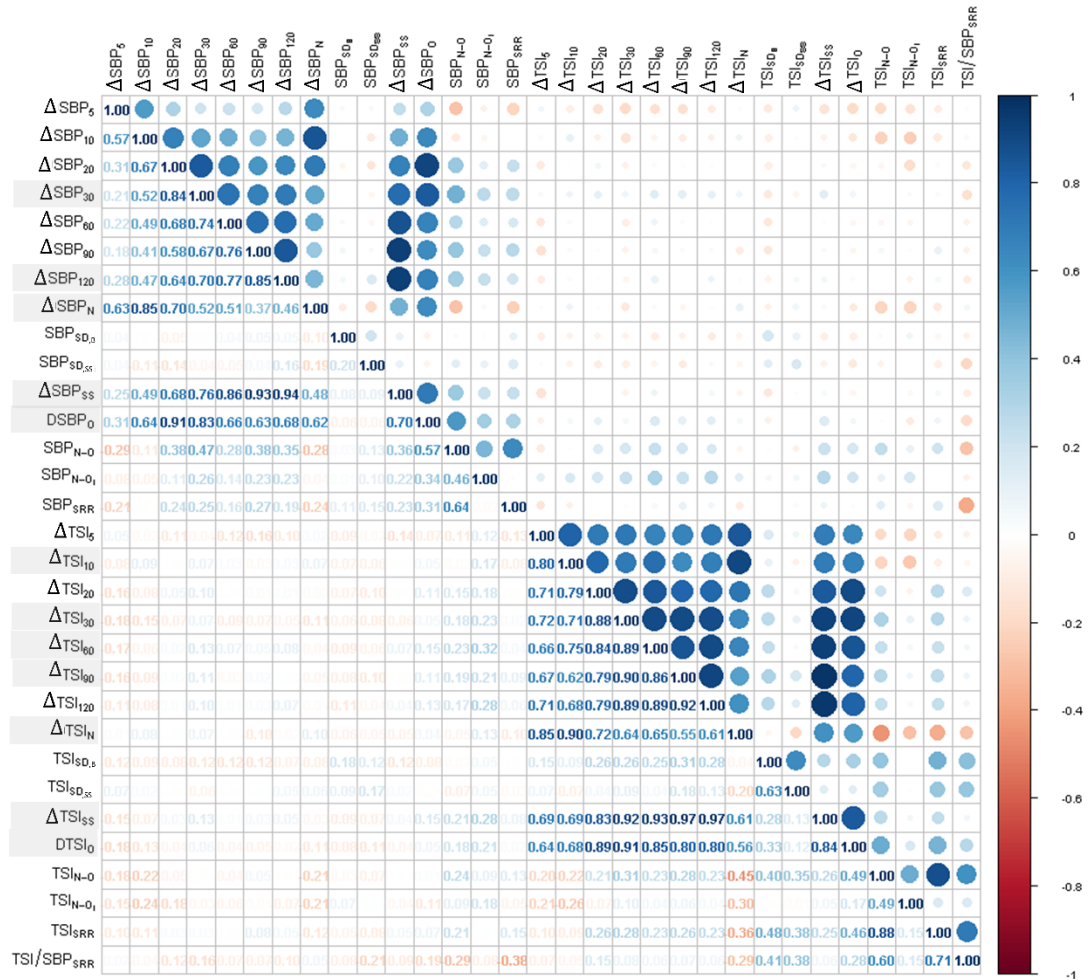
Supplementary Figure A.K.4. Correlation matrix for SBP features used in the classification of syncope. Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



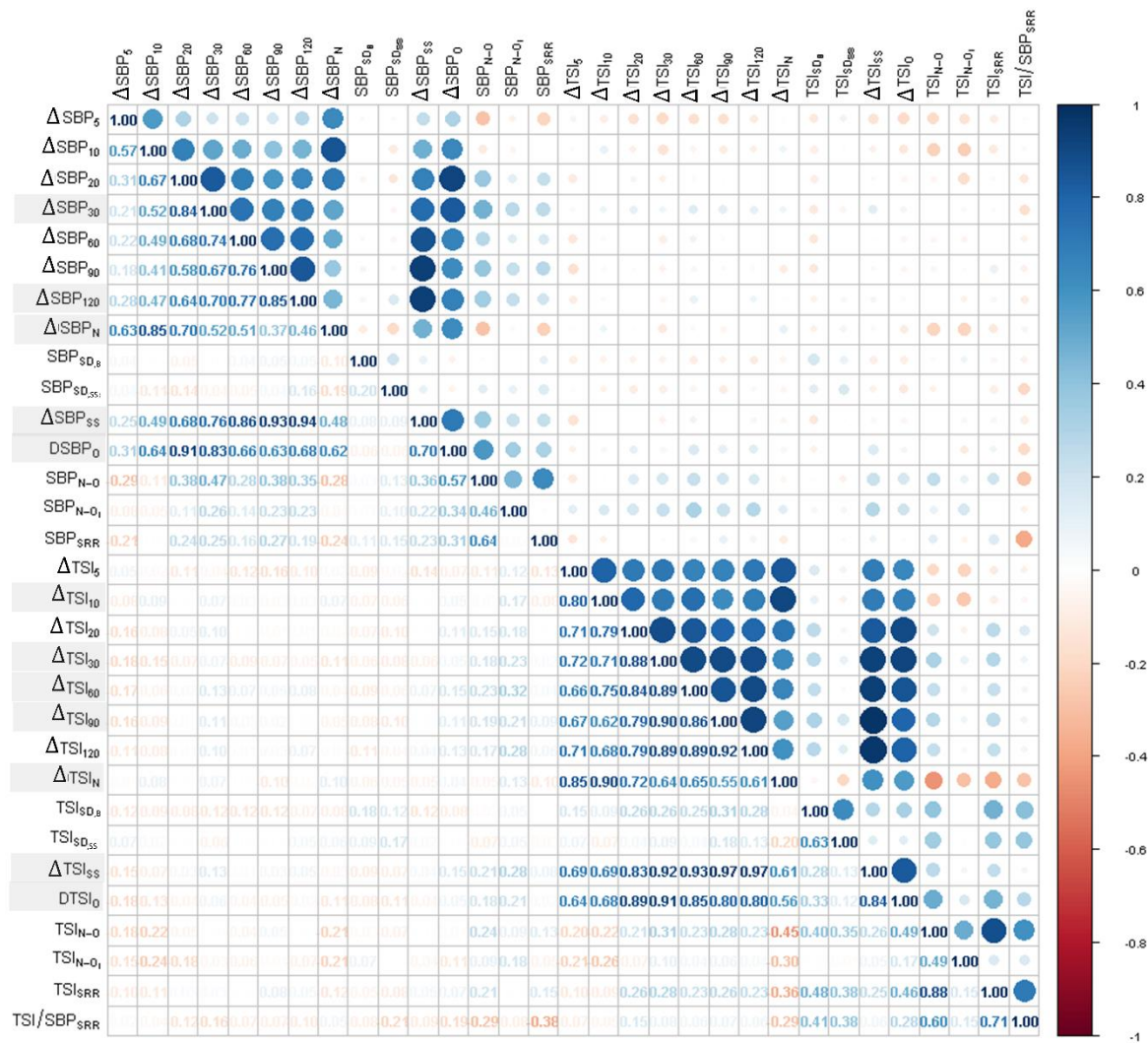
Supplementary Figure A.K.5. Correlation matrix for SBP features used in the classification of unexplained falls or syncope (UFS). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



Supplementary Figure A.K.6. Correlation matrix for TSI+SBP features used in the classification of unexplained falls (UF). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



Supplementary Figure A.K.7. Correlation matrix for TSI+SBP features used in the classification of syncope. Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1



Supplementary Figure A.K.8. Correlation matrix for TSI+SBP features used in the classification of unexplained falls or syncope (UFS). Features marked in grey on the left side of the matrix were eliminated by correlation filtering. Abbreviations are described in Table 9.1

Supplementary Table A.K.1. Training and evaluation results for TSI models **without** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

	History of UF					History of Syncope					History of UFS				
Algorithm name	LOG	LDA	QDA	SVM L	SVM R	LOG	LDA	QDA	SVM L	SVM R	LOG	LDA	QDA	SVM L	SVM R
AUC	0.696	0.700	0.650	0.575	0.554	0.422	0.424	0.437	0.407	0.426	0.689	0.690	0.623	0.673	0.606
Number of variables	7	7	5	3	1	5	7	5	9	7	3	8	1	3	8
Performance metrics (%)															
Validation Accuracy	58.7	59.7	51.0	56.6	51.8	65.3	66.5	62.0	64.1	59.0	59.5	59.0	56.1	57.4	59.1
Validation Sensitivity	58.1	58.3	27.8	64.0	57.1	68.7	70.6	61.6	70.5	61.3	60.8	59.5	51.2	61.2	58.7
Validation Specificity	59.1	60.9	73.9	49.4	46.5	62.0	62.6	62.6	57.9	56.9	58.3	58.5	60.9	53.7	59.6
Training Accuracy	64.6	65.4	59.8	59.1	59.1	70.3	72.6	72.6	70.3	77.1	61.2	62.2	55.7	61.2	70.1
Training Sensitivity	68.8	70.3	89.1	48.4	48.4	65.9	68.2	77.3	63.6	79.5	59.9	61.2	61.2	55.8	64.6
Training Specificity	60.3	60.3	30.2	69.8	69.8	74.7	77.0	67.8	77.0	74.7	62.5	63.2	50.0	66.7	75.7
Training PPV	63.8	64.3	56.4	62.0	62.0	72.5	75.0	70.8	73.7	76.1	62.0	62.9	55.6	63.1	73.1
Training NPV	65.5	66.7	73.1	57.1	57.1	68.4	70.5	74.7	67.7	78.3	60.4	61.5	55.8	59.6	67.7
Test Accuracy	64.5	64.5	58.1	54.8	54.8	44.2	44.2	46.5	41.9	41.9	66.2	62.0	63.4	63.4	59.2
Test Sensitivity	56.2	56.2	75.0	37.5	37.5	31.8	36.4	45.5	31.8	45.5	66.7	61.1	66.7	61.1	58.3
Test Specificity	73.3	73.3	40.0	73.3	73.3	57.1	52.4	47.6	52.4	38.1	65.7	62.9	60.0	65.7	60.0
Test PPV	69.2	69.2	57.1	60.0	60.0	43.8	44.4	47.6	41.2	43.5	66.7	62.9	63.2	64.7	60.0
Test NPV	61.1	61.1	60.0	52.4	52.4	44.4	44.0	45.5	42.3	40.0	65.7	61.1	63.6	62.2	58.3

Supplementary Table A.K.2. Training and evaluation results for SBP models **without** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

	History of UF					History of Syncope					History of UFS				
Algorithm name	LOG	LDA	QDA	SVML	SVMR	LOG	LDA	QDA	SVML	SVMR	LOG	LDA	QDA	SVML	SVMR
AUC	0.721	0.738	0.779	0.733	0.729	0.541	0.537	0.344	0.539	0.584	0.667	0.667	0.607	0.645	0.573
Number of variables	5	9	11	9	11	11	11	3	11	11	7	11	7	9	9
Performance metrics (%)															
Validation Accuracy	68.5	67.7	64.8	67.5	64.2	58.0	57.7	57.9	57.5	55.4	63.3	62.7	59.4	63.6	62.1
Validation Sensitivity	69.9	68.7	67.8	67.2	62.9	57.5	57.9	57.8	55.4	54.0	61.9	62.1	71.4	62.3	62.1
Validation Specificity	67.2	66.9	61.9	68.0	65.7	58.5	57.5	58.0	59.8	56.9	64.6	63.3	47.7	64.8	62.0
Training Accuracy	74.8	73.2	75.6	74.8	74.0	62.9	64.0	62.9	62.9	76.0	67.7	67.4	64.6	63.6	70.1
Training Sensitivity	71.9	73.4	68.8	79.7	76.6	62.5	63.6	60.2	65.9	76.1	70.1	70.1	51.7	63.3	67.3
Training Specificity	77.8	73.0	82.5	69.8	71.4	63.2	64.4	65.5	59.8	75.9	65.3	64.6	77.8	63.9	72.9
Training PPV	76.7	73.4	80.0	72.9	73.1	63.2	64.4	63.9	62.4	76.1	67.3	66.9	70.4	64.1	71.7
Training NPV	73.1	73.0	72.2	77.2	75.0	62.5	63.6	62.0	63.4	75.9	68.1	67.9	61.2	63.0	68.6
Test Accuracy	64.5	67.7	71.0	67.7	64.5	55.8	60.5	44.2	55.8	62.8	64.8	64.8	53.5	56.3	56.3
Test Sensitivity	75.0	75.0	68.8	75.0	56.2	63.6	63.6	40.9	68.2	68.2	66.7	66.7	41.7	52.8	58.3
Test Specificity	53.3	60.0	73.3	60.0	73.3	47.6	57.1	47.6	42.9	57.1	62.9	62.9	65.7	60.0	54.3
Test PPV	63.2	66.7	73.3	66.7	69.2	56.0	60.9	45.0	55.6	62.5	64.9	64.9	55.6	57.6	56.8
Test NPV	66.7	69.2	68.8	69.2	61.1	55.6	60.0	43.5	56.2	63.2	64.7	64.7	52.3	55.3	55.9

Supplementary Table A.K.3. Training and evaluation results for TSI+SBP models **without** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

	History of UF					History of Syncope					History of UFS				
Algorithm name	LOG	LDA	QDA	SVML	SVMR	LOG	LDA	QDA	SVML	SVMR	LOG	LDA	QDA	SVML	SVMR
AUC	0.758	0.779	0.812	0.771	0.767	0.413	0.418	0.357	0.390	0.366	0.681	0.696	0.622	0.715	0.661
Number of variables	5	17	15	17	20	11	17	19	21	21	9	20	13	17	15
Performance metrics (%)															
Validation Accuracy	69.9	70.1	60.8	70.2	60.8	66.6	66.6	61.3	69.2	62.1	63.7	62.0	57.2	61.2	61.5
Validation Sensitivity	71.4	71.2	60.8	70.1	54.5	68.8	68.2	61.8	69.7	62.9	63.3	60.6	65.2	58.8	59.1
Validation Specificity	68.4	69.0	61.1	70.4	67.2	64.5	65.1	60.8	68.9	61.4	64.2	63.4	49.3	63.7	63.9
Training Accuracy	74.0	75.6	81.1	78.7	76.4	73.1	74.3	87.4	77.1	82.9	68.7	68.0	70.4	68.4	76.6
Training Sensitivity	73.4	78.1	82.8	78.1	76.6	70.5	72.7	83.0	76.1	77.3	69.4	70.1	62.6	66.0	76.2
Training Specificity	74.6	73.0	79.4	79.4	76.2	75.9	75.9	92.0	78.2	88.5	68.1	66.0	78.5	70.8	77.1
Training PPV	74.6	74.6	80.3	79.4	76.6	74.7	75.3	91.3	77.9	87.2	68.9	67.8	74.8	69.8	77.2
Training NPV	73.4	76.7	82.0	78.1	76.2	71.7	73.3	84.2	76.4	79.4	68.5	68.3	67.3	67.1	76.0
Test Accuracy	64.5	74.2	74.2	71.0	61.3	46.5	44.2	37.2	39.5	39.5	62.0	66.2	57.7	60.6	60.6
Test Sensitivity	62.5	68.8	62.5	68.8	50.0	36.4	36.4	27.3	36.4	31.8	58.3	72.2	58.3	58.3	69.4
Test Specificity	66.7	80.0	86.7	73.3	73.3	57.1	52.4	47.6	42.9	47.6	65.7	60.0	57.1	62.9	51.4
Test PPV	66.7	78.6	83.3	73.3	66.7	47.1	44.4	35.3	40.0	38.9	63.6	65.0	58.3	61.8	59.5
Test NPV	62.5	70.6	68.4	68.8	57.9	46.2	44.0	38.5	39.1	40.0	60.5	67.7	57.1	59.5	62.1

Supplementary Table A.K.4. Training and evaluation results for TSI models **with** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

	History of UF					History of Syncope					History of UFS				
Algorithm name	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>
AUC	0.808	0.858	0.783	0.854	0.775	0.552	0.55	0.532	0.587	0.613	0.64	0.763	0.717	0.764	0.65
Number of variables	5	7	1	7	1	3	7	7	7	1	1	3	9	3	1
Performance metrics (%)															
Validation Accuracy	70.0	69.9	68.4	71.5	65.4	70.5	68.6	64.5	69.2	64.0	67.3	67.3	63.4	67.7	67.3
Validation Sensitivity	71.0	71.5	85.7	75.9	62.5	71.8	72.4	68.8	72.6	67.8	72.2	74.5	72.6	74.1	72.2
Validation Specificity	69.1	68.3	51.4	67.2	68.1	69.2	65.0	60.5	66.0	60.3	62.5	60.4	54.5	61.5	62.5
Training Accuracy	73.2	74.0	68.5	71.7	68.5	72.6	71.4	73.7	74.3	64.6	67.4	68.0	70.1	68.4	67.4
Training Sensitivity	71.9	71.9	51.6	65.6	51.6	70.5	70.5	73.9	75.0	60.2	62.6	61.9	60.5	61.9	62.6
Training Specificity	74.6	76.2	85.7	77.8	85.7	74.7	72.4	73.6	73.6	69.0	72.2	74.3	79.9	75.0	72.2
Training PPV	74.2	75.4	78.6	75.0	78.6	73.8	72.1	73.9	74.2	66.3	69.7	71.1	75.4	71.7	69.7
Training NPV	72.3	72.7	63.5	69.0	63.5	71.4	70.8	73.6	74.4	63.2	65.4	65.6	66.5	65.9	65.4
Test Accuracy	77.4	74.2	74.2	77.4	74.2	55.8	55.8	51.2	58.1	65.1	66.2	63.4	69.0	64.8	66.2
Test Sensitivity	68.8	62.5	50.0	68.8	50.0	40.9	40.9	50.0	45.5	50.0	75.0	66.7	63.9	72.2	75.0
Test Specificity	86.7	86.7	100.0	86.7	100.0	71.4	71.4	52.4	71.4	81.0	57.1	60.0	74.3	57.1	57.1
Test PPV	84.6	83.3	100.0	84.6	100.0	60.0	60.0	52.4	62.5	73.3	64.3	63.2	71.9	63.4	64.3
Test NPV	72.2	68.4	65.2	72.2	65.2	53.6	53.6	50.0	55.6	60.7	69.0	63.6	66.7	66.7	69.0

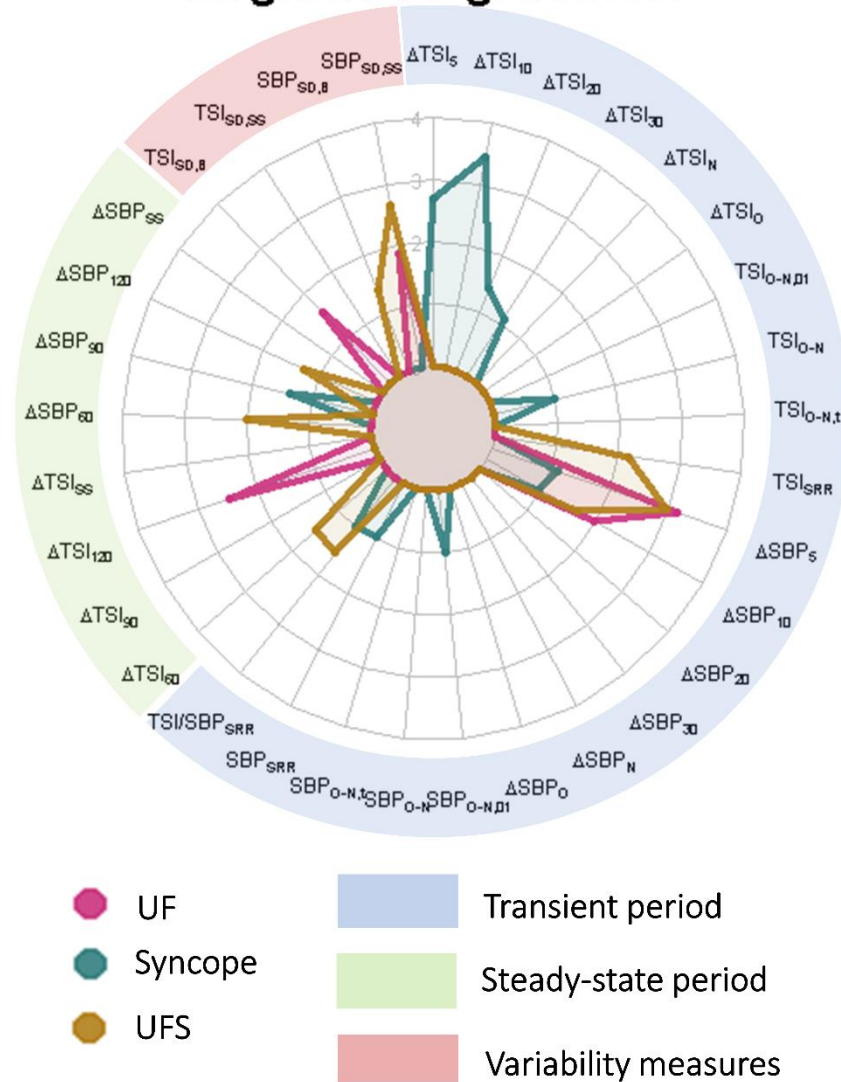
Supplementary Table A.K.5. Training and evaluation results for SBP models **with** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

	History of UF					History of Syncope					History of UFS				
Algorithm name	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>
AUC	0.838	0.821	0.783	0.842	0.825	0.584	0.58	0.509	0.604	0.558	0.719	0.746	0.688	0.745	0.721
Number of variables	9	9	1	9	11	5	5	1	5	5	3	7	7	7	7
Performance metrics (%)															
Validation Accuracy	75.0	76.6	68.4	75.7	68.1	63.9	64.9	64.0	66.5	64.8	69.5	69.8	65.1	69.3	68.1
Validation Sensitivity	74.3	81.4	85.7	77.9	69.2	66.0	67.9	67.8	70.7	66.8	71.7	73.8	76.1	73.2	67.4
Validation Specificity	75.6	71.7	51.4	73.5	66.9	61.9	61.9	60.3	62.5	62.9	67.4	65.9	54.4	65.4	68.8
Training Accuracy	82.7	81.1	68.5	81.9	77.2	67.4	67.4	64.0	70.9	73.1	70.1	70.8	69.8	71.8	74.9
Training Sensitivity	79.7	76.6	51.6	79.7	73.4	65.9	64.8	60.2	64.8	71.6	68.7	66.7	59.2	66.0	74.1
Training Specificity	85.7	85.7	85.7	84.1	81.0	69.0	70.1	67.8	77.0	74.7	71.5	75.0	80.6	77.8	75.7
Training PPV	85.0	84.5	78.6	83.6	79.7	68.2	68.7	65.4	74.0	74.1	71.1	73.1	75.7	75.2	75.7
Training NPV	80.6	78.3	63.5	80.3	75.0	66.7	66.3	62.8	68.4	72.2	69.1	68.8	65.9	69.1	74.1
Test Accuracy	74.2	71.0	74.2	74.2	74.2	60.5	55.8	65.1	58.1	53.5	69.0	69.0	64.8	66.2	64.8
Test Sensitivity	68.8	68.8	50.0	68.8	62.5	54.5	45.5	50.0	50.0	45.5	75.0	77.8	58.3	72.2	75.0
Test Specificity	80.0	73.3	100.0	80.0	86.7	66.7	66.7	81.0	66.7	61.9	62.9	60.0	71.4	60.0	54.3
Test PPV	78.6	73.3	100.0	78.6	83.3	63.2	58.8	73.3	61.1	55.6	67.5	66.7	67.7	65.0	62.8
Test NPV	70.6	68.8	65.2	70.6	68.4	58.3	53.8	60.7	56.0	52.0	71.0	72.4	62.5	67.7	67.9

Supplementary Table A.K.6. Training and evaluation results for TSI+SBP models **with** morbidity count for unexplained falls (UF), syncope and UF or syncope (UFS).

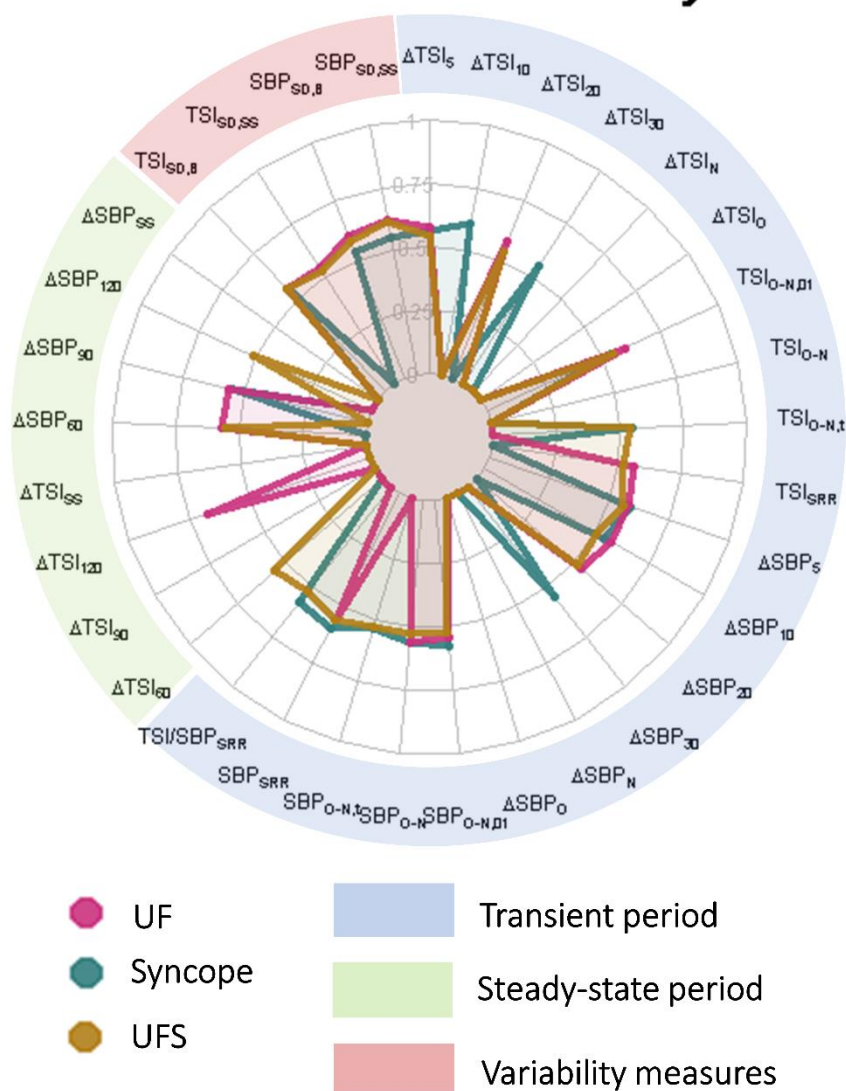
	History of UF					History of Syncope					History of UFS				
Algorithm name	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>	<i>LOG</i>	<i>LDA</i>	<i>QDA</i>	<i>SVML</i>	<i>SVMR</i>
AUC	0.829	0.850	0.783	0.838	0.875	0.552	0.506	0.435	0.5	0.455	0.740	0.750	0.668	0.765	0.774
Number of variables	5	17	1	17	17	3	15	9	15	22	5	21	11	13	17
Performance metrics (%)															
Validation Accuracy	73.9	76.1	68.4	76.6	66.7	70.2	71.9	65.2	72.4	70.7	70.4	67.9	63.3	68.4	67.8
Validation Sensitivity	72.5	80.2	85.7	81.2	62.0	71.3	72.8	68.9	73.5	71.5	75.1	71.7	70.3	71.4	66.2
Validation Specificity	75.2	72.0	51.4	72.1	71.4	69.2	71.2	61.7	71.3	70.0	65.8	64.1	56.5	65.6	69.4
Training Accuracy	77.2	81.9	68.5	85.8	78.7	72.6	77.7	77.1	77.7	90.3	72.2	72.9	72.5	71.5	79.7
Training Sensitivity	79.7	78.1	51.6	82.8	76.6	70.5	77.3	72.7	76.1	88.6	68.0	67.3	64.6	66.0	78.9
Training Specificity	74.6	85.7	85.7	88.9	81.0	74.7	78.2	81.6	79.3	92.0	76.4	78.5	80.6	77.1	80.6
Training PPV	76.1	84.7	78.6	88.3	80.3	73.8	78.2	80.0	78.8	91.8	74.6	76.2	77.2	74.6	80.6
Training NPV	78.3	79.4	63.5	83.6	77.3	71.4	77.3	74.7	76.7	88.9	70.1	70.2	69.0	68.9	78.9
Test Accuracy	71.0	77.4	74.2	77.4	74.2	55.8	48.8	46.5	51.2	48.8	67.6	69.0	63.4	67.6	69.0
Test Sensitivity	62.5	68.8	50.0	75.0	62.5	40.9	40.9	36.4	45.5	50.0	66.7	72.2	69.4	69.4	83.3
Test Specificity	80.0	86.7	100.0	80.0	86.7	71.4	57.1	57.1	57.1	47.6	68.6	65.7	57.1	65.7	54.3
Test PPV	76.9	84.6	100.0	80.0	83.3	60.0	50.0	47.1	52.6	50.0	68.6	68.4	62.5	67.6	65.2
Test NPV	66.7	72.2	65.2	75.0	68.4	53.6	48.0	46.2	50.0	47.6	66.7	69.7	64.5	67.6	76.0

Logistic Regression



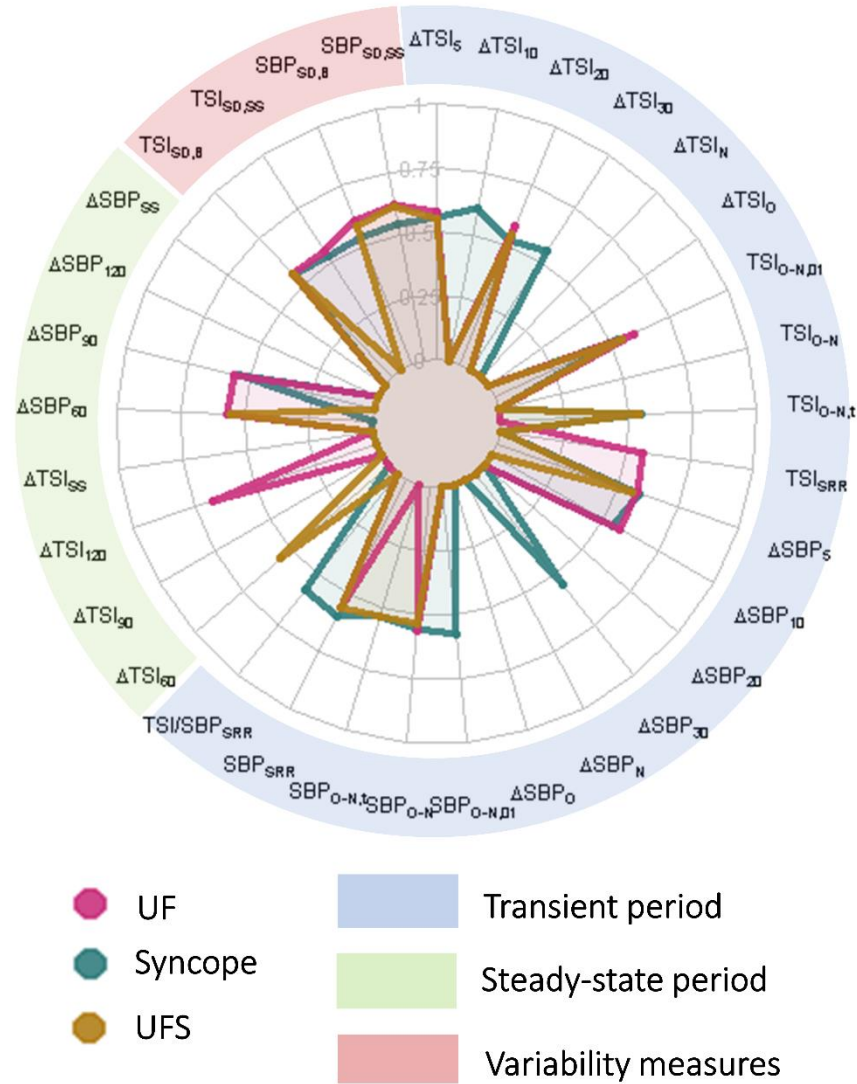
Supplementary Figure A.K.9. Feature importance for TSI + SBP LOG model (without morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

Linear discriminant analysis



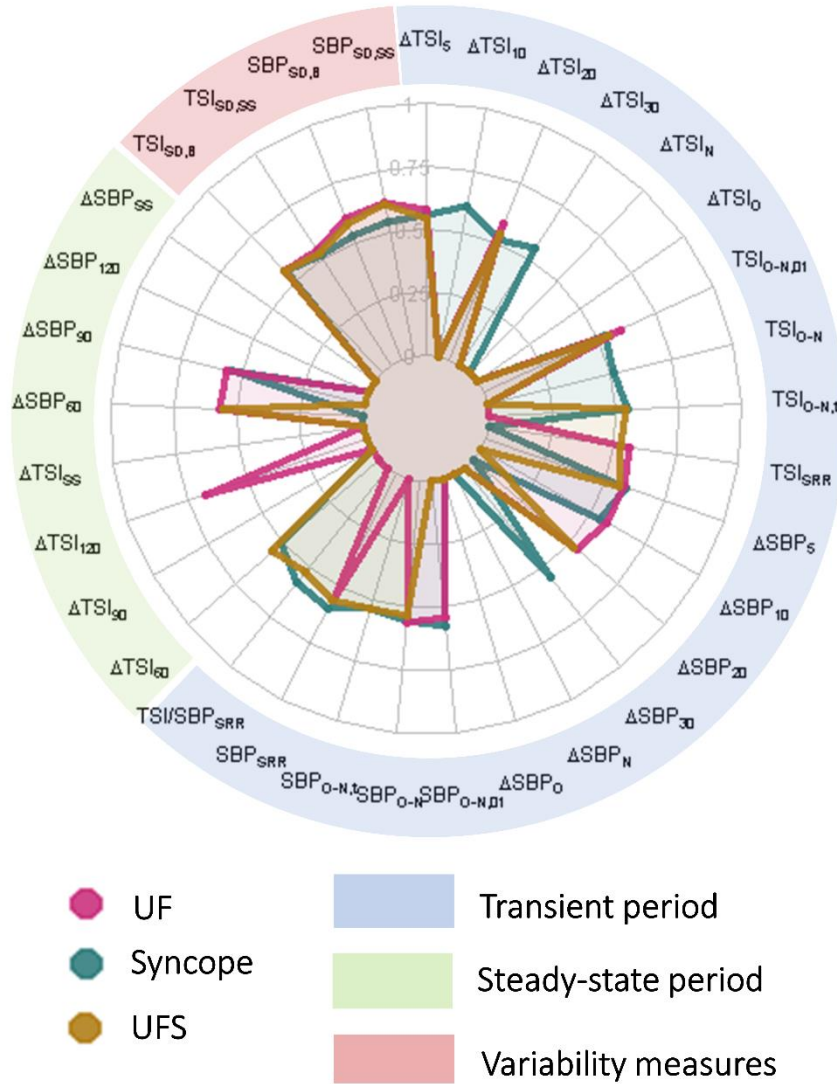
Supplementary Figure A.K.10. Feature importance for TSI + SBP LDA model (without morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

Quadratic discriminant analysis



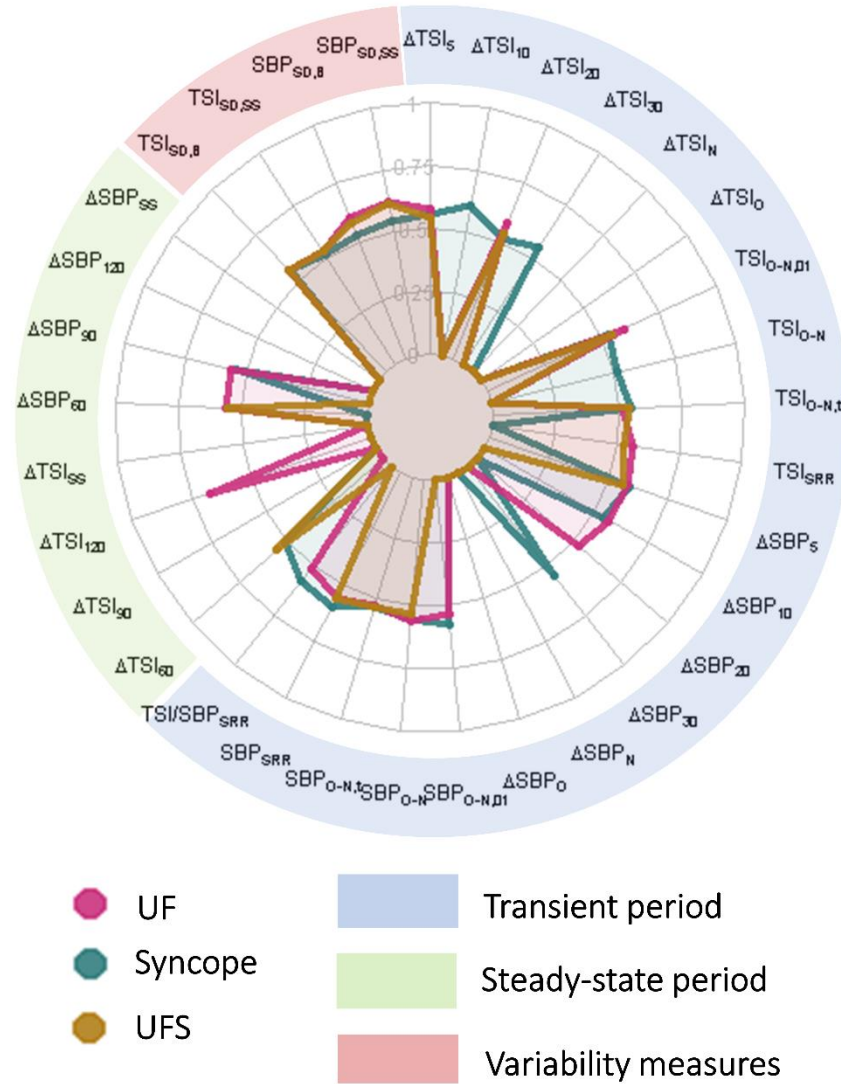
Supplementary Figure A.K.11. Feature importance for TSI + SBP LDA model (without morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

Linear Support Vector Machine

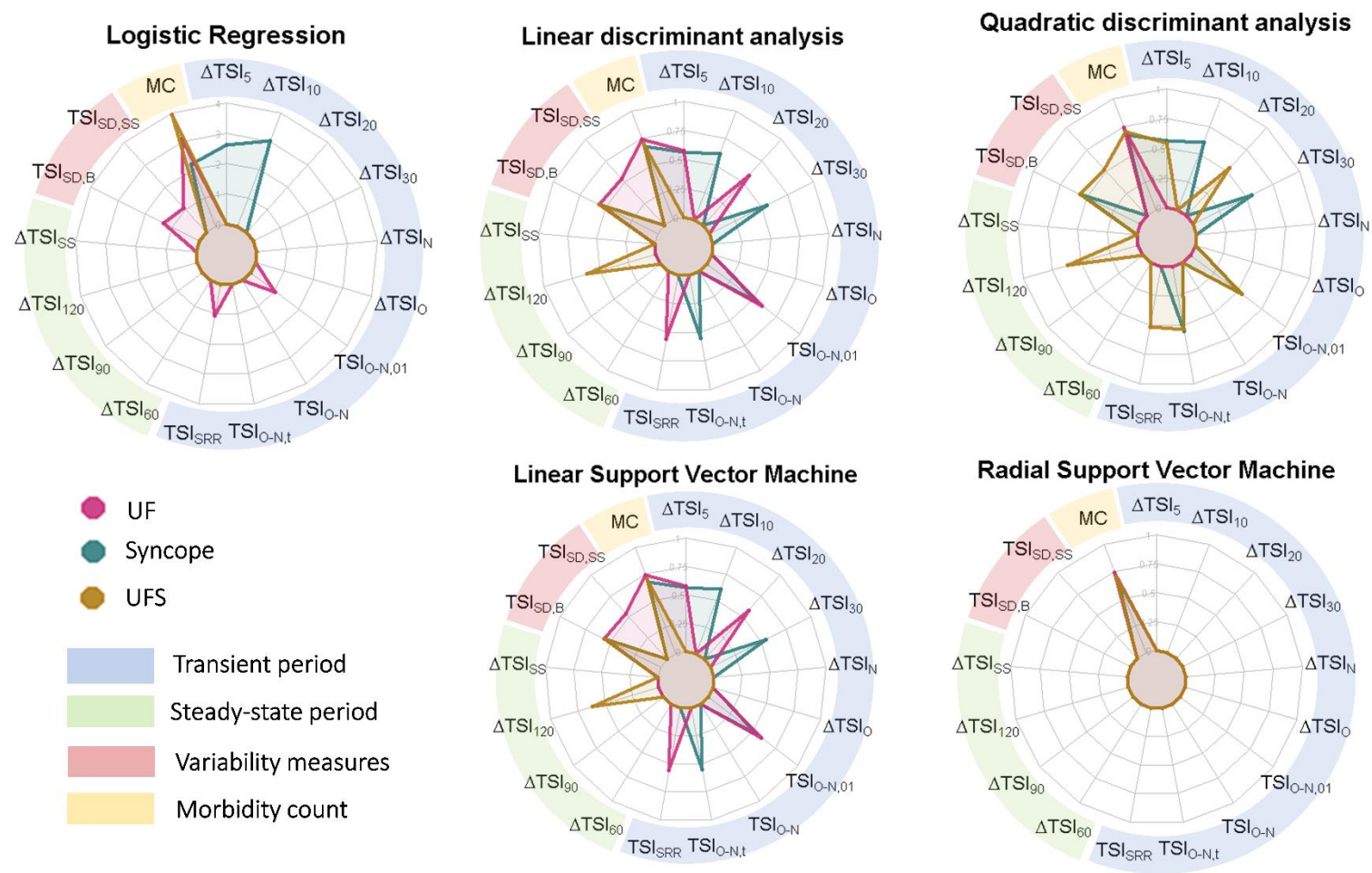


Supplementary Figure A.K.12. Feature importance for TSI + SBP SVM model (without morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

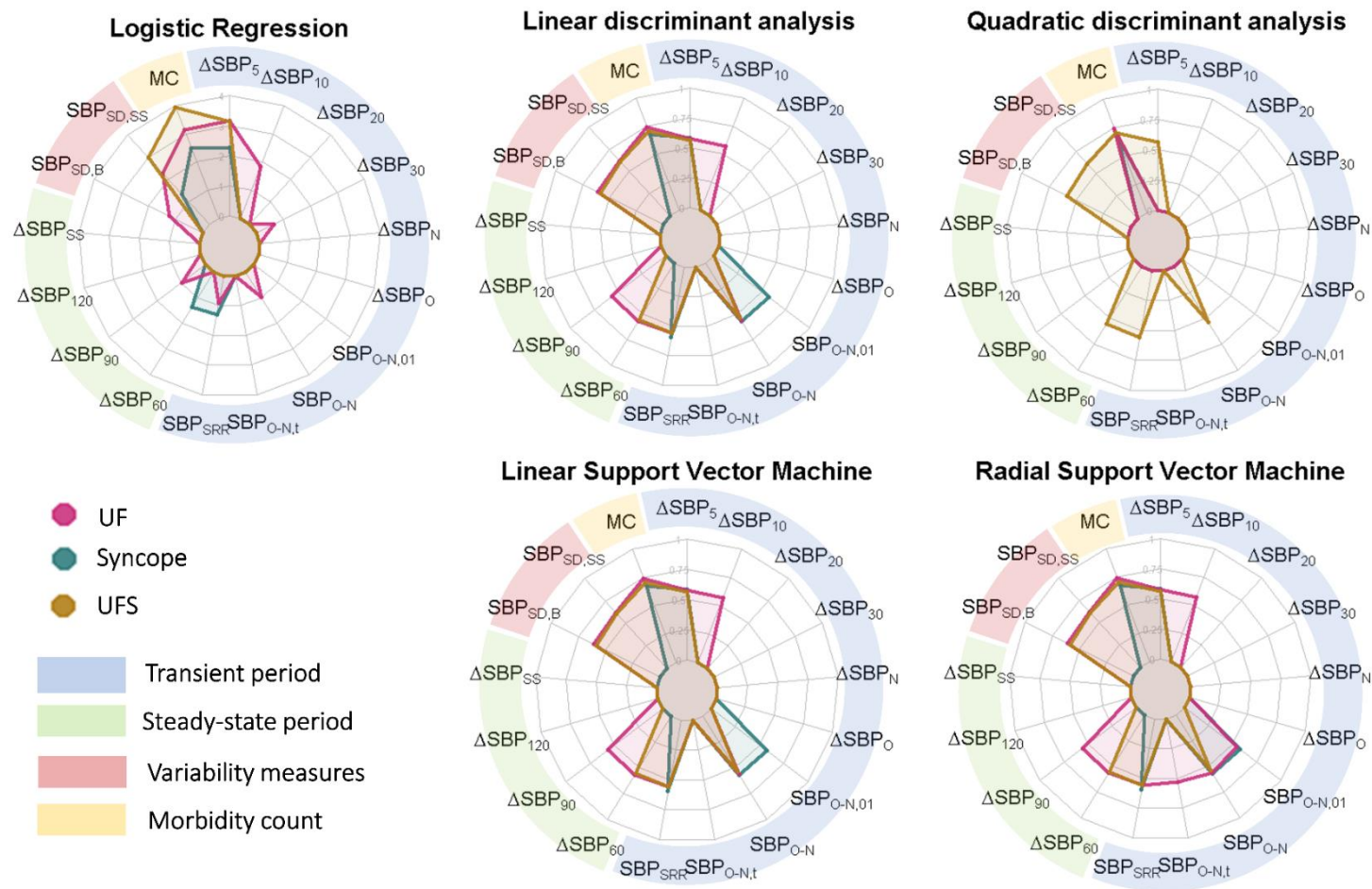
Radial Support Vector Machine



Supplementary Figure A.K.13. Feature importance for TSI + SBP SVMR model (without morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1

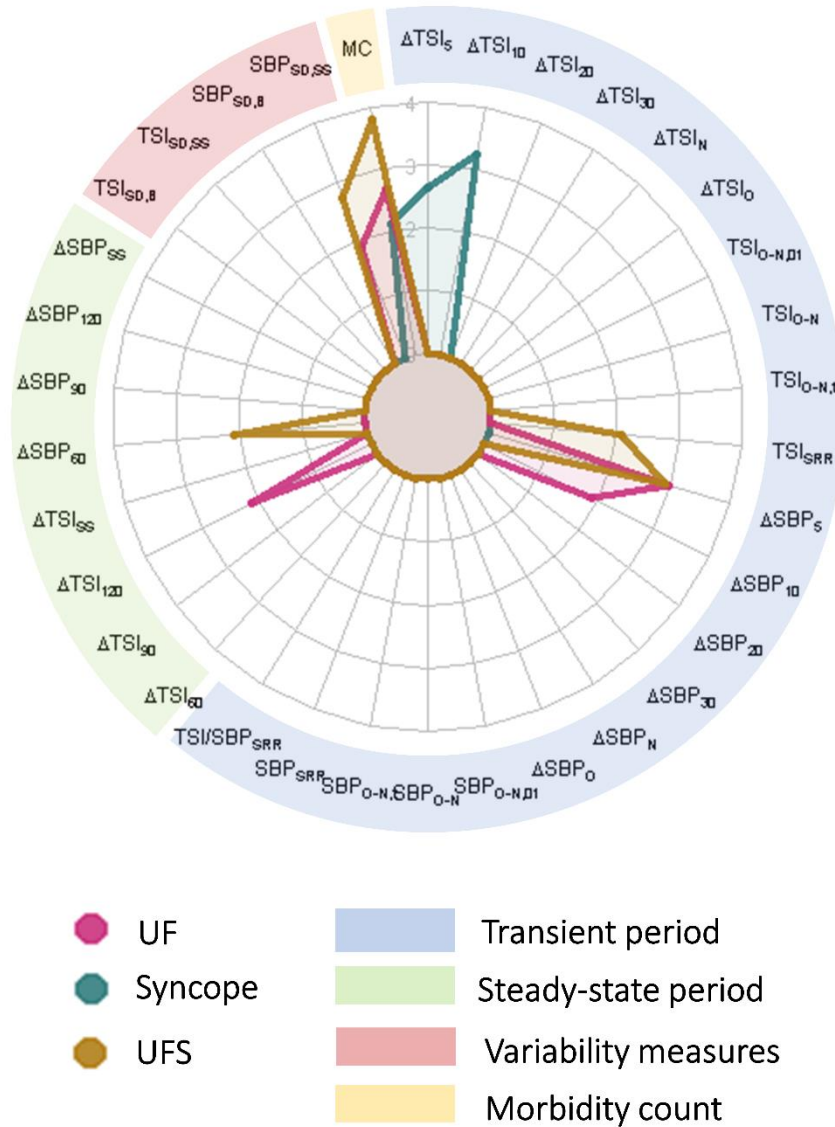


Supplementary Figure A.K.14. Feature importance for the variables selected for each of the algorithms and the three outcome variables in TSI models including morbidity count (MC): unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.



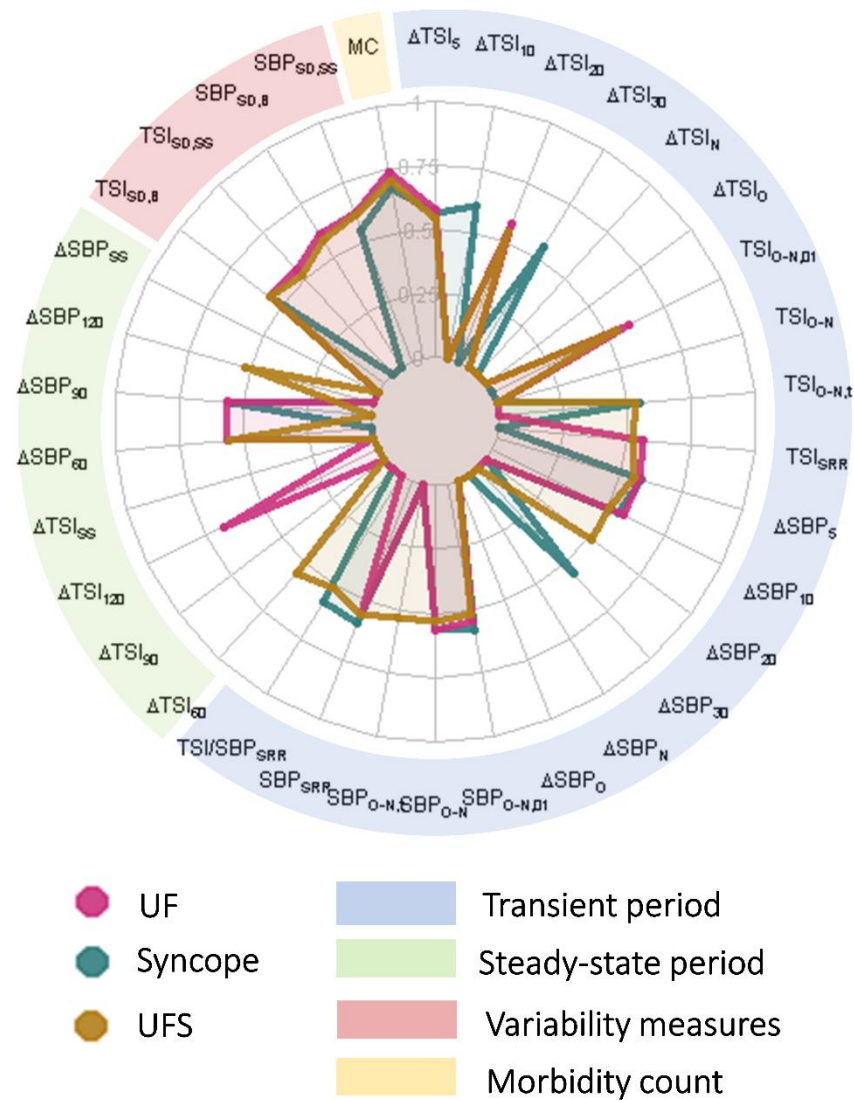
Supplementary Figure A.K.15. Feature importance for the variables selected for each of the algorithms and the three outcome variables in SBP models including morbidity count (MC): unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

Logistic Regression



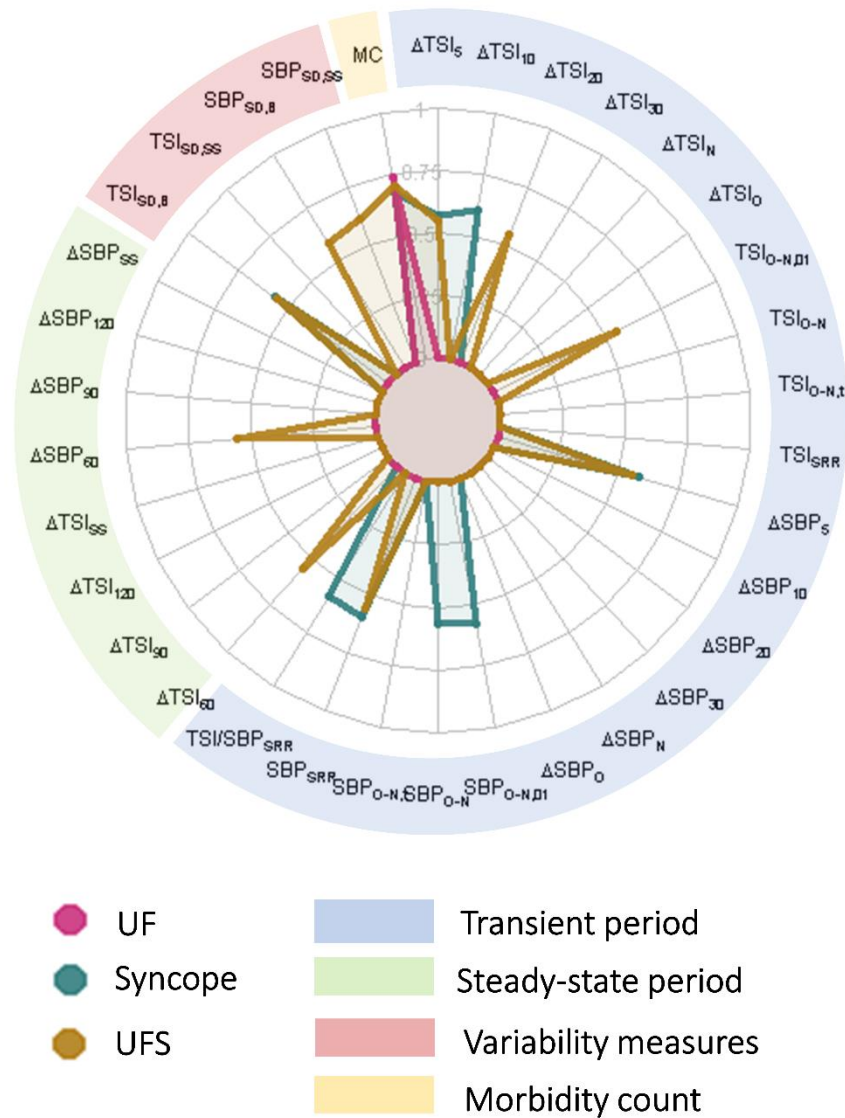
Supplementary Figure A.K.16. Feature importance for TSI + SBP LOG model (**with** morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

Linear discriminant analysis



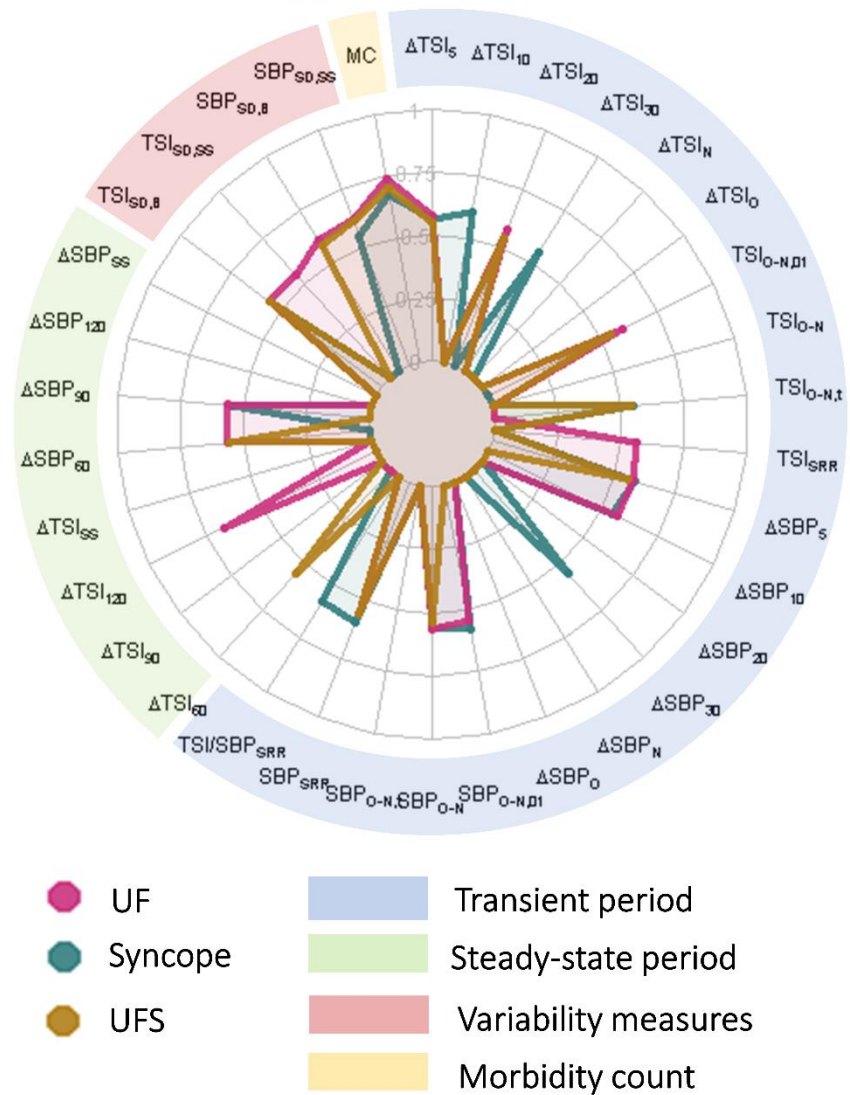
Supplementary Figure A.K.17. Feature importance for TSI + SBP LDA model (**with** morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

Quadratic discriminant analysis



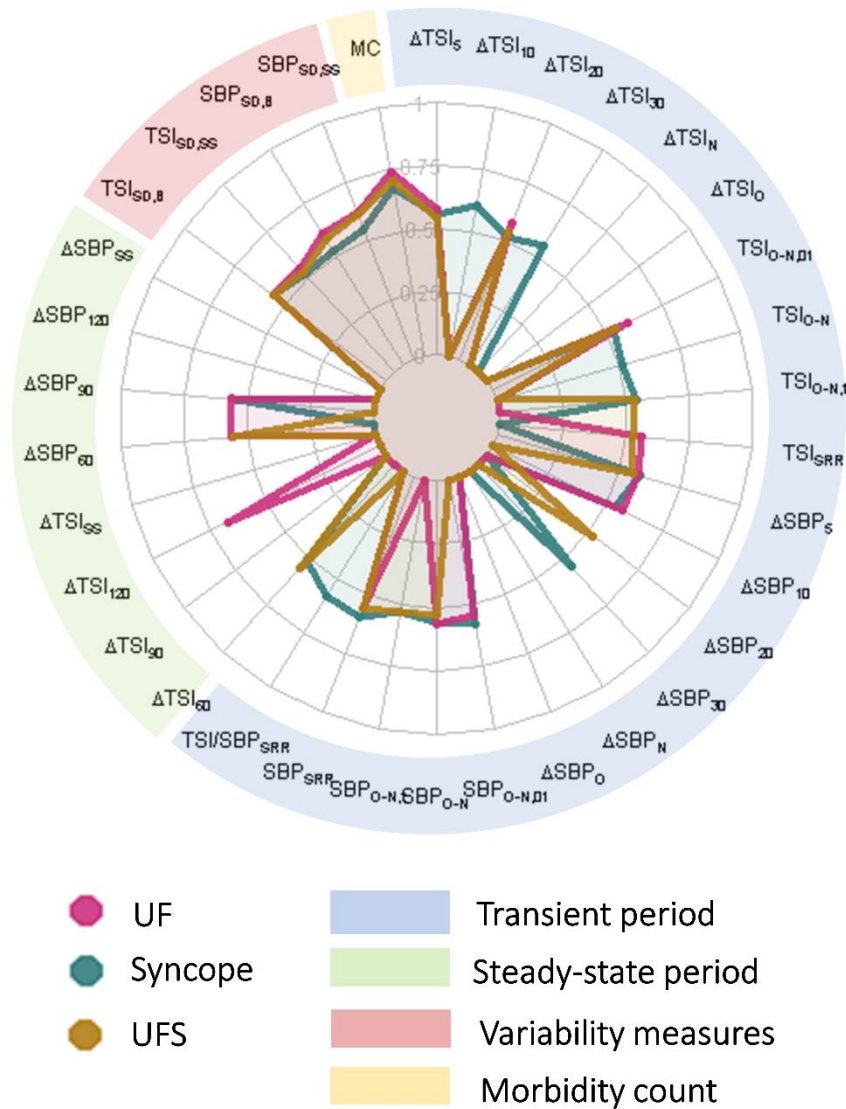
Supplementary Figure A.K.18. Feature importance for TSI + SBP QDA model (**with** morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

Linear Support Vector Machine



Supplementary Figure A.K.19. Feature importance for TSI + SBP SVM model (**with** morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.

Radial Support Vector Machine



Supplementary Figure A.K.20. Feature importance for TSI + SBP SVMR model (**with** morbidity count) when classifying unexplained falls (UF), syncope and UF or syncope (UFS). Abbreviations are described in Table 9.1.