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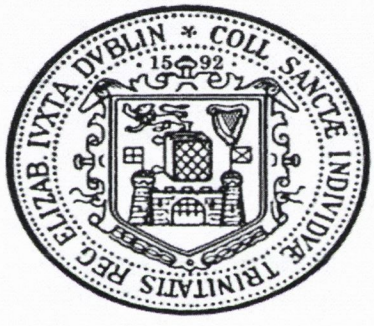
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Vasovagal Syncope in the Older Adult

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Trinity College Dublin

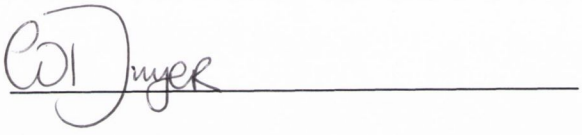
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Acknowledgements

I would like to acknowledge my principal supervisor Professor Rose Anne Kenny, for her support and advice throughout the process of completing this thesis. I would like to thank her in particular for the invaluable experience I have attained under her guidance in relation to the multidisciplinary work-up of individuals with falls, syncope and associated conditions. I wish to equally acknowledge my co-supervisor Dr Chie Wei Fan for imparting her knowledge and guidance, in particular in relation to data analysis during this study. I would like to acknowledge the assistance of Dr Kathleen Bennett with statistical analysis.

None of this research would have been possible without the assistance and support of the hard working staff of the Falls and Blackout Unit in St. James's Hospital, where all patients were recruited for this study. In particular I would like to mention Dr. Conal Cunningham Consultant Geriatrician working within the unit for his ongoing support and advice, along with Dymphna Hade, Lisa Byrne, Ciara Rice and Nicola O'Doherty for the time and effort which they applied in making this project possible. I would also like to acknowledge the help of all the medical staff rotating through the unit for their assistance and support with patient recruitment and assessments.

For her patience in the education of EEG interpretation I would like to acknowledge Dr Yvonne Langan Consultant Neurologist St. James's Hospital and also the support of Dr. Sean Connolly Consultant Neurophysiologist St. James's Hospital. I would also like to take this opportunity to thank Martina Healion and Aine Sweeney in the Department of Neurophysiology, St. James's Hospital for their assistance with EEG assessments. For their expert guidance and assistance with quantitative EEG analysis, I would like to

acknowledge Professor Richard Reilly and Hugh Nolan in the Department of Bioengineering, Trinity College Dublin.

I would particularly like to thank the patients attending the Falls and Blackout Unit who agreed to participate in this research study. Finally my family deserve credit for their never ending support and encouragement, not just in the completion of this thesis but in all aspects of my training and career to date.

Summary

Introduction

Vasovagal Syncope (VVS) is a common form of neurally mediated syncope which affects at least one third of the population at least once in their lifetime. Commonly referred to as a "simple faint" and often described as benign in nature, little is known surrounding VVS in older adults. Through the use of clinical assessments, this thesis aims to clarify if age-related differences exist with VVS.

Methods

Detailed questionnaires relating to real time syncopal episodes were completed by subjects with a diagnosis of VVS. Their diagnosis was confirmed with symptom reproduction during a Head-up tilt (HUT) test. Haemodynamic parameters during HUT induced VVS or presyncope were recorded. The presence or absence of amnesia for loss of consciousness (A-LOC) following VVS on HUT was documented. A subgroup of subjects underwent combined HUT and electroencephalograph (EEG) assessments in order to further analyse changes in cerebral activity prior to VVS.

Results

Older subjects ($\geq$ 60 years) with VVS reported significantly less prodrome with real time syncopal episodes when compared to younger subjects (< 60 years). Older subjects developed symptom reproduction and syncope later than younger subjects during HUT induced VVS. There was a higher prevalence of A-LOC in older subjects when compared to younger subjects, but age was not found to be an independent risk factor for A-LOC. A significant difference in delta band increase from baseline values with quantitative EEG

was demonstrated in older subjects when compared to younger subjects in the thirty seconds preceding first symptom onset, and this difference was seen to demonstrate a left lateralisation in effect.

Conclusion

Lack of recall for prodromal symptoms along with A-LOC are prevalent in VVS and significantly so in older subjects. Age-related haemodynamic differences prior to first reproductive symptom onset do occur in VVS. Age-related cerebral differences demonstrated with EEG remains difficult to explain but the left lateralisation effect may represent cerebral autoregulation differences which occur between younger and older subjects. VVS is not as benign a condition as first thought and the use of HUT to investigate unexplained syncope in older adults is important for the diagnosis of VVS.

Abbreviations

ANS	autonomic nervous system
A-LOC	amnesia for loss of consciousness
BP	blood pressure
Bpm	beats per minute
CI	confidence Interval
CO	cardiac output
CSM	carotid sinus massage
CSS	carotid sinus syndrome
DBP	diastolic blood pressure
ECG	electrocardiograph
Echo	echocardiogram
ED	emergency department
EEG	electroencephalograph
EP	electrophysiology
ESC	European Society of Cardiology
FDR	false discovery rate
FLHUT	Front-Loaded head-up tilt
GTN	Glyceryl trinitrate
HR	heart rate
HUT	head-up tilt
Hz	hertz
IPHUT	Italian Protocol head-up tilt
Mcg	microgram
Mins	minutes
ml	millilitre

mmHg	millimetres of mercury
MMSE	mini mental state examination
MRI	magnetic resonance imaging
MWU	mann whitney U
OH	orthostatic hypotension
OR	odds ratio
PVR	peripheral vascular resistance
RTF	return to flow
Secs	Seconds
SBP	systolic blood pressure
SD	standard deviation
SV	stroke volume
TCD	transcranial doppler
TGA	transient global amnesia
TIA	transient ischaemic attack
TLOC	transient loss of consciousness
VASIS	Vasovagal Syncope International Study
VVS	vasovagal syncope
Yrs	years

CONTENTS

1 INTRODUCTION

1.1 SYNCOPE **14**
1.11 Definition of Syncope 14
1.12 Classification of Syncope 14
1.2 VASOVAGAL SYNCOPE **15**
1.21 Background 15
1.22 Epidemiology 16
1.3 VASOVAGAL SYNCOPE AND THE OLDER ADULT **19**
1.31 Epidemiology 19
1.32 Morbidity and Vasovagal Syncope 20
1.33 Neurally mediated syncope, unexplained falls and amnesia for loss of consciousness 22
1.34 Mortality and Vasovagal Syncope 24
1.4 ECONOMIC COST AND VASOVAGAL SYNCOPE **25**
1.5 PATHOPHYSIOLOGY **26**
1.51 The autonomic nervous system 26
1.52 Normal response to upright posture 30
1.53 Pathophysiology of Vasovagal Syncope 31
1.54 Classification of Vasovagal Syncope 37
1.55 Pathophysiology of amnesia for loss of consciousness 40
1.56 Cortical changes with Vasovagal Syncope 44
a) Transcranial Doppler and Vasovagal Syncope
b) The Electroencephalograph and Vasovagal Syncope
1.6 DIAGNOSIS OF VASOVAGAL SYNCOPE **51**
1.61 The head-up-tilt table test 51
1.62 Conditions and indications for Head-up-tilt 54
1.63 Complications and contraindications for Head-up-tilt 57

2 LITERATURE REVIEW

2.1 AIMS OF LITERATURE REVIEW **60**
2.2 SEARCH STRATEGY **60**
2.3 DATA EXTRACTION **60**
2.4 REPORTED PRODROME IN VASOVAGAL SYNCOPE **61**
2.5 HAEMODYNAMIC CHANGES IN VASOVAGAL SYNCOPE **65**
2.6 VASOVAGAL SYNCOPE AND AMNESIA FOR LOSS OF CONSCIOUSNESS **69**
2.7 ELECTROENCEPHALOGRAPH ANALYSIS OF PRODROME ONSET IN VASOVAGAL SYNCOPE **70**
2.8 RESEARCH QUESTIONS AND HYPOTHESES **71**

3 METHODS

3.1 SUBJECT RECRUITMENT **74**
3.11 Research setting 74
3.12 Questionnaire 75
3.13 Subject assessments in the clinic 77
3.14 Pathway of investigation 78
3.15 Inclusion and exclusion criteria for further participation in the study 82

3.2 BASELINE CHARACTERISTICS OF SUBJECTS **84**
3.21 Analysis of questionnaires 84
3.22 Statistics 84
3.3 HAEMODYNAMIC MEASUREMENTS DURING VASOVAGAL SYNCOPE **84**
3.31 Equipment 85
3.32 Head-up-tilt protocol 86
a) Italian protocol Head-up-tilt
b) Front Loaded Head-up-tilt
3.33 Data analysis of haemodynamic parameters 90
3.34 Exclusion criteria for Head-up-tilt files 92
3.35 Statistics 93
3.4 ASSESSMENT OF AMNESIA FOR LOSS OF CONSCIOUSNESS **93**
3.41 Protocol 93
3.42 Analysis 94
3.43 Statistics 94
3.5 COMBINED ELECTROENCEPHALOGRAPH AND HEAD-UP TILT ASSESSMENTS – SUBGROUP ANALYSIS **95**
3.51 Head-up-tilt equipment 95
3.52 Electroencephalograph equipment 96
3.53 Protocol of combined Head-up-tilt and Electroencephalograph 98
3.54 Qualitative Electroencephaograph analysis 99
3.55 Quantitative Electroencephalograph analysis 101
3.56 Statistics Head-up-tilt 101
3.57 Statistics Electroencephalograph 102

4 REPORTED CHARACTERISTICS WITH VASOVAGAL SYNCOPE – AGE RELATED DIFFERENCES

4.1 PATHWAY OF PARTICIPANT SELECTION **104**
4.2 AGE DISTRIBUTION **105**
4.3 BASELINE CHARACTERISTICS **106**
4.4 PRESENTING SYMPTOMS **112**
4.5 PRECIPITATING FACTORS **113**
4.6 CONSEQUENCES **115**
4.7 SUMMARY OF RESULTS **117**

5 HAEMODYNAMIC PARAMETERS IN VASOVAGAL SYNCOPE – AGE RELATED DIFFERENCES

5.1 PATHWAY TO SUBJECTS UNDERGOING HEAD-UP-TILT **120**
5.2 RESULTS: REPRODUCTIVE SYMPTOMS DURING HEAD-UP-TILT **122**
5.21 Pre analysis Italian Protocol Head-up-tilt versus Front Loaded Head-up-tilt 122
5.22 Italian Protocol head-up-tilt analysis 123
5.23 Front loaded Head-up-tilt analysis 125
5.3 RESULTS: SYNCOPE DURING HEAD-UP-TILT **126**
5.31 Pre analysis Italian Protocol Head-up-tilt versus Front loaded Head-up-tilt 126
5.32 Head-up-tilt analysis 126
5.4 SUMMARY OF RESULTS **128**

6 AMNESIA FOR LOSS OF CONSCIOUSNESS IN VASOVAGAL SYNCOPE

6.1 BACKGROUND 130
6.2 PATHWAY TO SUBJECT SELECTION 131
6.3 PREVALENCE OF AMNESIA FOR LOSS OF CONSCIOUSNESS 132
6.4 BASELINE CHARACTERISTICS OF THOSE WITHOUT AND THOSE WITH AMNESIA FOR LOSS OF CONSCIOUSNESS 133
6.5 HAEMODYNAMIC PARAMETERS IN THOSE WITHOUT AND THOSE WITH AMNESIA FOR LOSS OF CONSCIOUSNESS 137
6.51 Pre analysis Italian protocol Head-up-tilt versus Front Loaded Head-up-tilt 137
6.52 Head-up-tilt analysis 137
6.6 PREDICTORS FOR AMNESIA FOR LOSS OF CONSCIOUSNESS IN VASOVAGAL SYNCOPE 140
6.7 SUMMARY OF RESULTS 141

7 QUALITATIVE AND QUANTITATIVE ELECTROENCEPHALOGRAPHY DURING HEAD-UP-TILT INDUCED VASOVAGAL SYNCOPE

7.1 DEMOGRAPHICS 144
7.2 QUALITATIVE ANALYSIS ELECTROENCEPHALOGRAPHY 146
7.3 QUANTITATIVE ANALYSIS ELECTROENCEPHALOGRAPHY 149
7.4 AGE-GROUP COMPARISONS IN ELECTROENCEPHALOGRAPH WAVEFORM CHANGE 150
7.5 AGE-GROUP COMPARISONS δ WAVE AND HAEMODYNAMIC CHANGE 152
7.51 Five minute analysis pre symptom onset 153
7.52 One minute analysis pre symptom onset 154
7.53 Thirty seconds analysis pre symptom onset 155
7.54 Thirty seconds analysis post symptom onset 156
7.6 ELECTROENCEPHALOGRAPHY IN THOSE WITHOUT AND THOSE WITH AMNESIA FOR LOSS OF CONSCIOUSNESS 157
7.61 Qualitative analysis 157
7.62 Quantitative analysis 157
7.7 SUMMARY OF RESULTS 158

8 DISCUSSION

8.1 REPORTED CHARACTERISTICS WITH VASOVAGAL SYNCOPE – AGE RELATED DIFFERENCES 160
8.11 Discussion of results 160
8.12 Current literature 161
8.13 Study limitations 162
8.14 Conclusion 162
8.2 HAEMODYNAMIC PARAMETERS IN VASOVAGAL SYNCOPE – AGE RELATED DIFFERENCES 163
8.21 Discussion of results 163
8.22 Current literature 164
8.23 Study limitations 165
8.23 Conclusion 166

8.3 AMNESIA FOR LOSS OF CONSCIOUSNESS IN VASOVAGAL SYNCOPE **167**
8.31 Discussion of results 167
8.32 Current literature 168
8.33 Study limitations 169
8.34 Conclusion 169
8.4 QUALITATIVE AND QUANTITATIVE ELECTROENCEPHALOGRAPHY DURING HEAD-UP-TILT INDUCED VASOVAGAL SYNCOPE **171**
8.41 Discussion of results 171
8.42 Current literature 172
8.43 Study limitations 173
8.44 Conclusion 174

9 BIBLIOGRAPHY **175**

10 DISSEMINATION OF THESIS **188**

11 APPENDIX **190**

Chapter 1

Introduction

1.1 Syncope

1.11 Definition of Syncope

Syncope is defined as a transient loss of consciousness (TLOC) due to transient global hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery.[1]

1.12 Classification of Syncope

The primary causes of syncope are cardiac (either structural heart disease or arrhythmia), orthostatic hypotension (primary autonomic failure or secondary causes) or what is termed neurally-mediated or reflex syncope. Neurally-mediated syncope is by far the most common cause of syncope and incorporates carotid sinus syndrome (CSS) and vasovagal syncope (VVS). Carotid sinus syndrome is a syndrome found in adults forty years of age or older. [2]

Vasovagal syncope is often referred to as a "common faint" and occurs in all age-groups. [3]

Cardiac Syncope	*Syncope due to Orthostatic Hypotension (OH)*	*Reflex (Neurally-mediated) Syncope*
Arrhythmia Bradycardia: Sinus node dysfunction Atrioventricular conduction disease Tachycardia: Supraventricular Ventricular Drug induced Bradycardia or tachycardia ***Structural Heart Disease*** Valvular Disease: Aortic Stenosis Hypertrophic Cardiomyopathy Cardiac tumour Congenital Prosthetic valve malfunction ***Other*** Pulmonary Embolus Aortic dissection Pulmonary Hypertension	***Primary autonomic failure*** Pure autonomic failure Multiple systems atrophy Parkinson's disease Lewy body dementia ***Secondary autonomic failure*** Diabetes Amyloidosis Uraemia Spinal cord injury ***Drug induced orthostatic hypotension*** ***Volume depletion***	***Vasovagal*** (mediated by orthostatic or emotional stress) ***Situational*** Cough Sneeze Pain Defecation, Swallow Micturition Post-prandial Post-exercise Laughter ***Carotid Sinus Syndrome***

Table 1.1: Causes of Syncope

1.2 Vasovagal syncope

1.21 Background

Sir William Gowers first described vasovagal attacks in 1907 [4] with Sir Thomas Lewis and his colleague Cotton first describing in detail the condition known as vasovagal syncope. [5] They described it in soldiers who worked in active service in the army. They noted that when trying to salute in an upright position while on guard duty that VVS occurred not only in unwell de-conditioned subjects but also in subjects with 'robust health'. Lewis described these 'fainting attacks' in 1932 as preceded by a 'warning

consisting of a feeling of instability or uncertainty, a dimming of vision, and a feeling of giddiness'. [6] 'Nervous agitation', 'emotional stress', 'blood flow into a syringe', 'period of fasting', 'over heated, overcrowded room' were described as potential precipitants. Lewis makes the point even at this early stage, that heart rate could slow to below 30 beats per minute (secondary to vagal slowing) but that loss of consciousness was frequently present with decrease in blood pressure alone, suggesting that syncope aetiology was 'vasomotor' but was worsened in the presence of a bradycardia. The noted combination of both these features during a syncopal attack coined the expression "vasovagal".

1.22 Epidemiology

Incidence and prevalence

Epidemiological studies comment on reflex syncope as the most common cause of syncope in any setting. Not all individuals who experience VVS will attend a doctor or an accident and emergency department, so exact information on incidence and prevalence in the community is difficult to ascertain for different populations. Depending on the setting studied, different figures exist.

Community studies

The Framingham offspring study (n=7814) demonstrated a 6.2 per 1000 person-years incidence rate of first report of syncope with a 10-year cumulative incidence of syncope of 6% in a community setting. Reflex syncope (mostly VVS) accounted for 21% of all episodes in this population. [7] The majority of those surveyed in the Framingham cohort were 30 years of age or older (mean age 51 ± 14 years), and were prospectively followed over 17 years. Adolescents were excluded. Median age of first syncope onset reported in

this group was 15 years of age with a female predominance. The numbers who had a diagnosis of VVS confirmed with a Head-up tilt (HUT) table test in this study is unknown.

In a cross-sectional American community study, Chen et al established a 19% prevalence rate of syncope in those 45 years of age or older (n=1925). [8] Median age in this cohort was 62 years with a median age of syncope onset at 25 years, and females had a higher prevalence than males (22% vs 15%). No significant difference in prevalence of syncope across different age-groups ie. 45-54 yrs, 55-64 yrs, 65-74 yrs and 75 yrs were shown in this study. Knowledge of reflex versus other causes of syncope was however unknown.

As part of a ten year follow-up longitudinal study of 10,000 Irish adults, the Irish Longitudinal Study on Ageing (TILDA) launched in 2006, has collected cross sectional data on the lifetime prevalence of fainting reported in 8500 individuals who are 50 years of age or older. Overall prevalence of lifetime fainting was 16.95%, with a female prevalence of 18.68% and a male prevalence of 15%. Prevalence of fainting within the preceding 12 month period was 4.45% with equal male and female preponderance. However females reported a 5.14% prevalence of fainting in their youth in comparison to 1.84% of males.

Emergency departments (ED) and specialised syncope units

In a group of subjects who attended ED's with syncope, mean age of 62 (age range of 13-95 years) the prevalence rates of reflex syncope ranged from 35-48%. [9-11] A further dutch study reporting prevalence of syncope in the ED reported median age of subjects at 46 years. [12] Dedicated syncope units have reported higher prevalence rates of reflex syncope which range between 56 – 73% reflecting selection bias. These higher rates no

doubt reflect the advantage of advanced testing and a reduction of individuals with a diagnosis of unexplained syncope and cohort selection. Age ranges in these studies vary with mean ages of 50 ± 21 years up to 66 ± 21 years. [13, 14] [15] [16, 17]

Recent research from Holland has shed more light on the prevalence of reflex syncope in younger populations. [18] Ganzeboom et al report a 39% incidence rate of reflex syncope in medical students with a median age of 21 years (n=394). Syncope was seldom reported before the age of 10 years with a steady increase between ages 10-20 years. Lifetime cumulative incidence of syncope in women was twice that of men, 47% vs 24%. [19] A further community based study of 35-60 year adults reported a 35% lifetime cumulative incidence of syncope with a female to male ratio of 41% vs 28% and a median age of first onset of syncope at 18 years. [20]

Air personnel

Vasovagal syncope in pilot studies has also been reported. [21] Lamb et al reported a lifetime incidence of syncope of 7% in Air force personnel interviewed (n=3000). [22] Later studies documented a 20% lifetime prevalence of syncope in 1056 Air personnel aged between 17-46 years. [23] One must be cautious however in interpreting these figures due to possible underreporting of syncope within this group.

Military personnel

32% of (n=389) military soldiers (mean age 20+/-2 years) reported at least one lifetime episode of loss of consciousness. [24]

Age and gender

Vasovagal syncope during blood donation is common. Young age, low estimated blood volume and first time donors were more likely to experience VVS. [25] In terms of age and gender, younger females experience increased frequency of syncope than males.[26] In one Dutch study (n=503), 60% of those presenting with transient loss of consciousness had reflex syncope which was twice as common in patients younger than 40 years of age than in patients aged 60 years or older. [27] Whatever the age of presentation of VVS at assessment many will have had their first fainting episode in adolescence, with peak age of first faint at thirteen years of age. [3] Thirty seven per cent of first degree relatives of fainters have experienced a faint by 60 years of age. [28]

1.3 Vasovagal syncope and the older adult

1.31 Epidemiology

Little is reported on the incidence and prevalence of VVS in those 60 years of age or older. Overall syncope rates increase sharply with age, 16.9-19.5 per 1000 person years in those 80 years of age or older. [7] Lipsitz et al reported a 23% syncope rate over a 10 year period in 711 nursing home residents with a mean age in this group of 87±6 years. Following a two year prospective follow up, 48% of syncopal episodes were attributed to non cardiac causes while 31% remained unknown. [29] Sutton et al reported a 16% incidence of VVS in a group with unexplained recurrent syncope (n=322). [30]

In a recent 2 year longitudinal study assessing mortality and syncope recurrences in those 65 years of age or older, neurally-mediated syncope was reported at a rate of 65.6% in those referred to a geriatric department for syncope workup (n=242, mean age 78.7 ± 6.8

years). [31] VVS is diagnosed more frequently in older age-groups today with the use of HUT table testing and it is likely to be more common than previously suspected.

Although VVS is often referred to as a benign condition, many of the studies relating to VVS have been performed on those 60 years of age or younger. Diagnosing VVS in the older adult is shrouded in complexity due to various confounding factors.

Firstly, history may be unreliable in the older adult. The older adult may be less likely to recall prior fainting episodes at a younger age due to the length of recall period involved. The older adult with VVS may report less prodrome and warning prior to syncope and therefore VVS episodes may initially be suspected as being cardiac events. Cognitive impairment, common with advancing age, may affect the accuracy of the recall of syncope. Furthermore no witness account is available in 60% of syncopal events. [32]

1.32 Morbidity and VVS

Co-morbidities contributing to a vasovagal episode are more prevalent amongst older adults. [33] These include conditions such as anaemia and underlying ischaemic heart disease or congestive heart failure. The distinction between an isolated vasovagal 'syncope' and that of vasovagal 'disease' is an important one. [34] Classical VVS is described as that which initiates at a young age, has a specific trigger, is easily diagnosed with history alone and often never recurs. In other words classical VVS can occur in perfectly healthy individuals as a response to a precipitant stressor or due to volume depletion. Baseline blood pressure is often normal in these individuals. Vasovagal disease is representative of that which occurs in older age in conjunction with co-morbid conditions and may explain the bimodal peak in VVS incidence seen in some studies.[35] Vasovagal syncope in the older adult may therefore occur in conjunction with underlying

autonomic dysfunction (primary or secondary), orthostatic hypotension, postprandial hypotension or carotid sinus hypersensitivity. Orthostatic hypotension is very common in the elderly with some reports as high as 33% in community studies. [36] Overlap between orthostatic hypotension and carotid sinus hypersensitivity in the older adult with VVS has been described. [37] These individuals often have baseline hypertension.

Use of medications which contribute to hypotension and syncope are more frequently prescribed in the elderly. [38]

Whilst falls in the older person are mainly attributed to balance and gait abnormalities, amnesia for loss of consciousness may present as a fall. [39] We know that orthostatic hypotension and carotid sinus syndrome contribute significantly to falls. [40] Amnesia for loss of consciousness has been described in carotid sinus syndrome [32] and its contribution to significant injury has also been described. [41] The overlap between falls and VVS is less well researched in older adults but has been described. [42-44]

Falls associated with loss of consciousness in the elderly have a higher risk of injury or fracture in comparison to non-syncopal causes. [45] A higher prevalence of Carotid sinus hypersensitivity has been reported in those admitted with fractured neck of femur than in those admitted for elective hip replacement surgery. [41] In one study, 25% of those with Carotid sinus syndrome had sustained fractures due to syncope. [32]

In a group of patients diagnosed with VVS, there was a significant injury rate of 53% with 13% sustaining fractures (n=62). Mean age was 50$\pm$21 years suggesting an older population and Carotid sinus hypersensitivity had been ruled out prior to testing. [46] A further study examining characteristics in those > 65 years of age with syncope (73% having neurally-mediated syncope as a cause (n=232)) had a fracture rate of 11.2%. [47]

We know little regarding injury rates secondary to VVS in a younger age. One study reporting syncope rates post immunisation in the US, recorded 74% of cases of syncope occurring in those less than 20 years of age (n=697) of whom six subjects less than 28 years of age sustained a skull fracture or cerebral contusion/bleed requiring hospitalisation with 2 having longstanding residual injury. [48] A recent study assessing the use of non-pharmacological methods of preventing VVS recurrence had 42% of individuals reporting previous injury with an episode of VVS. [49]

1.33 Neurally mediated syncope, unexplained falls and amnesia for loss of consciousness

An unexplained fall is a fall for which no underlying cause is apparent. [42] Distinguishing a syncopal event from a non syncopal event may be difficult. [50] If an individual does not recall syncope and the event was not witnessed, an inappropriate pathway of investigation of falls rather than syncope may ensue and modifiable underlying causes may be overlooked. Further falls may increase the risk of injury and fracture. [51] Aetiology of falls in an older adult is diverse ranging from accidental, a gait or balance disorder, vertigo, a drop attack or syncope. However in those without an obvious cause and where a witness account is unavailable it can be difficult to determine a definite cause and increasing evidence has emerged in recent years that syncope and drop attacks may play a significant causal role. [52-54] Witness account may only be available in up to 40% of older adults with syncope or unexplained falls. [32, 55] Cognitive impairment or dementia may have a role in amnesia for syncopal events. However, previous research has demonstrated that up to 32% of cognitively normal adults 60 years of age or older were unable to recall a documented fall within three months of its occurrence. [39]

Diagnosis of CSS, a form of neurally-mediated syncope is confirmed with carotid sinus massage (CSM). In recent years emerging evidence has demonstrated the existence of a strong overlap between CSS and unexplained falls. CSS is one of the attributible causes of syncope and unexplained falls in patients referred to syncope clinics. [32, 56] A 27% incidence of amnesia for loss of consciousness (A-LOC) in the setting of CSS was first demonstrated in a group of patients (n=33) who presented for workup for unexplained syncope and falls. [2] Follow up studies demonstrated similar percentages. [32, 42, 57-59] The relationship between CSS and injurious falls and morbidity has been documented. [41] Parry et al assessed characteristics of patients with normal baseline cognition presenting with unexplained falls versus those presenting with unexplained syncope (n=68) . While 27% of those with unexplained syncope were found to have a positive CSM with associated A-LOC, 95% of those with unexplained falls had A-LOC with CSM. [60] Less than one quarter of the subjects in the same study had sustained fractures at the time of assessment in clinic. Therefore strong evidence exists for a relationship between carotid sinus syndrome, amnesia for loss of consciousness and falls.

An association between VVS, unexplained falls and amnesia for loss of consciousness has also been suggested. A retrospective study by Eltafi et al reported that the prevalence of VVS in those with unexplained syncope or falls (mean age 59 years) was 8.7%. [61] Prevalence of A-LOC in VVS is unknown. Case reports have alluded to its existence. Parry et al reported the case of a 78 year old lady who presented with a history of unexplained injurious falls and who had sudden loss of consciousness with a pure vasodepressor response during HUT accompanied by complete A-LOC. [43] Some cases of A-LOC with VVS have also been documented in the literature in younger age-groups.

[62-64] Existence of A-LOC in VVS may have further implications particularly for older adults in the setting of unexplained falls and syncope.

1.34 Mortality and VVS

The Framingham heart study remains the best informed study regarding survival with syncope over a 25 year period. Reassuringly those diagnosed with VVS in this study had similar survival rates to those with no history of syncope again suggesting VVS as a benign phenomenon in comparison to other causes of syncope. [7]

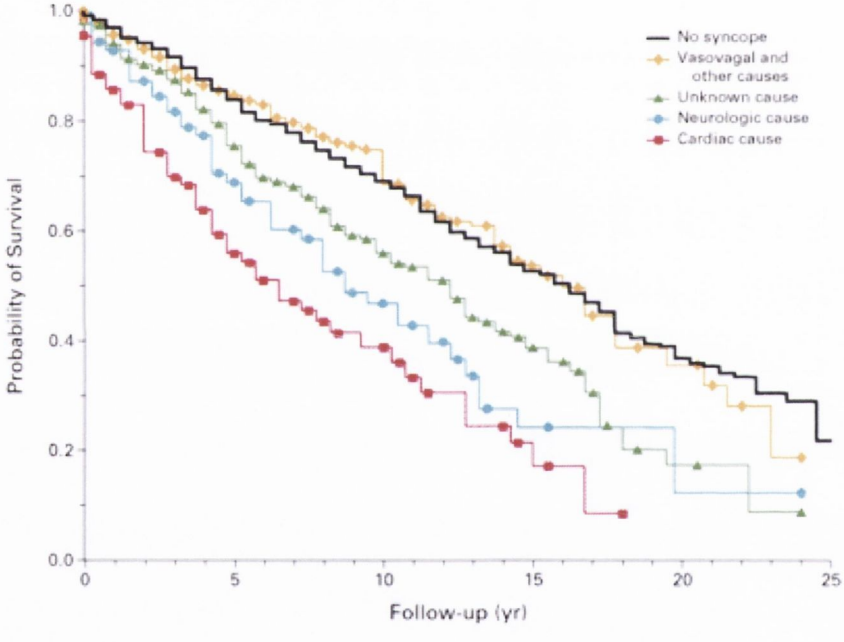


Figure 1.1: Kaplan Meier curve showing the overall survival of participants with and without syncope, according to cause. [7]

Recent research following survival and syncope recurrence rate in those 65 years of age and older in a two year longitudinal study again confirmed that mortality rate overall was 17.2% and was highest in those with cardiac syncope compared to those without (21.7 vs 12.3% $p = 0.03$) while there was no difference in mortality rates for neurally-mediated

syncope (62.1 vs 66.2% p = 0.357) or unexplained syncope (10.8 vs 11.8% p = 0.397). [31]

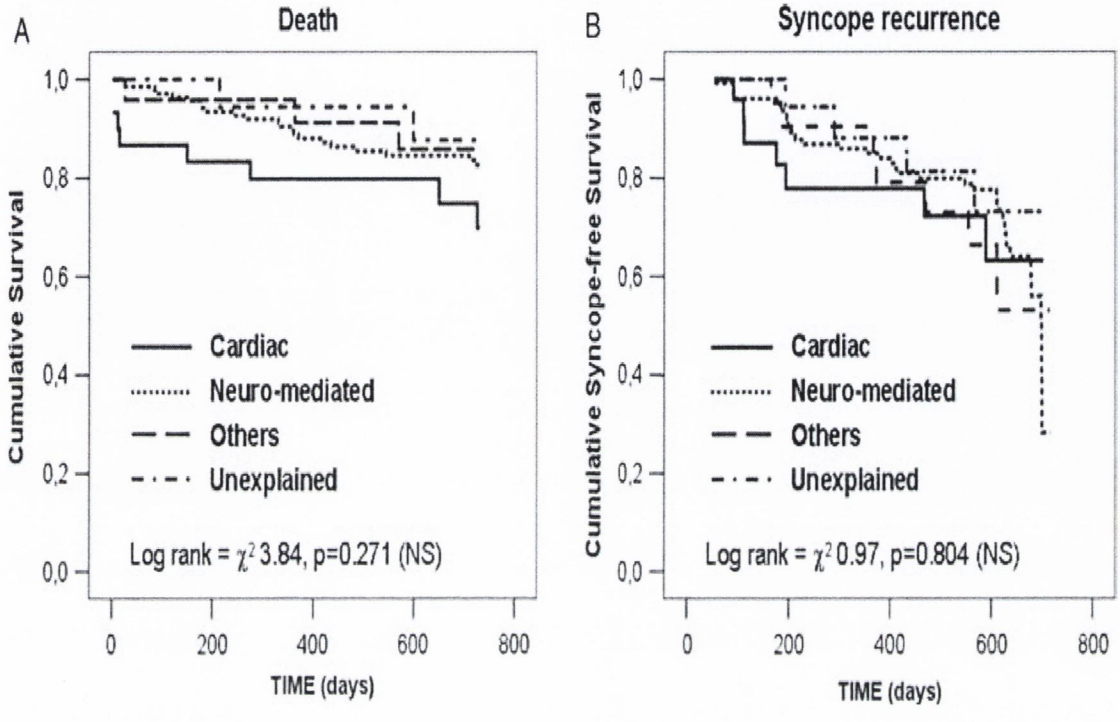


Figure 1.2: 2 year mortality and syncope recurrence rates (n=242) **[31]**

1.4 Economic cost and VVS

The overall economic cost of both investigations and consequences of syncope are difficult to estimate. The main reason for this as illustrated previously, is that much research into the underlying aetiology of syncope has been carried out in different settings, ie.both community and hospital settings. Data on cost mainly exists for emergency department investigations and hospital admissions. $2.4 billion per annum has been quoted for syncope based hospitalisations in the USA [65] with one state recently suggesting a cost per patient of $2517 for the investigation of one "faint" episode. [66] UK cost per patient previously has been estimated at £611, with the

majority of this cost based on inpatient hospital stay. [67] Much of the cost incurred with syncope is proven to be related to unnecessary investigation and unnecessary admissions. [68] Dedicated syncope units and syncope pathways within the emergency department which can lead to investigation of subjects in an outpatient dedicated facility improves such figures substantially. [15, 69, 70]While a low threshold for admission exists where a high suspicion of cardiac syncope exists, investigation costs of syncope are more likely due to unnecessary admissions, and investigations such as brain imaging in those with VVS. [71-73]

Quality of life

In terms of impact on quality of life, VVS has as great an impact as has epilepsy. [74] Up to 60% of those with recurrent VVS demonstrate increased levels of psychological distress with follow-up. [75] This study did not include subjects 60 years of age or older. One study found reduced quality of life reported in older adults with VVS at one year follow up, particularly those with co-morbidities. [76]

1.5 Pathophysiology of VVS

1.51 Autonomic Nervous System

Circulatory change in the human body is under the control of the autonomic nervous system (ANS). The ANS provides a fine discrete control over the the functions of many organs and tissues, including heart muscle, smooth muscle and the exocrine glands. It is a complex system comprising of afferent, connector and efferent neurons. Afferent neurons originate in visceral receptors and travel via afferent pathways to the central nervous system, where they integrate with connector neurons at various levels and then leave via

efferent pathways to visceral effector organs. The ANS is distributed throughout the central and peripheral nervous systems, and is divided into two parts, the sympathetic and the parasympathetic systems. (Figure 1.3) Both divisions produce opposite effects in most organs and although considered physiologic antagonists operate in conjuction with each other and complement each other in maintaining a stable internal environment. Both divisions have pre-ganglionic neurons located in the brainstem or spinal cord and an autonomic ganglion neuron that innervates the target organ.

The sympathetic system is the larger of the two parts of the ANS. Its function is to prepare the body for emergency. Heart rate is increased, arterioles of the skin and intestine are constricted, arterioles of skeletal muscle are dilated and blood pressure is raised. Its pre-ganglion neurons are located in the spinal thoracolumbar cord at T1 to L3 and pass via myelinated communicantes to the paravertebral ganglia of the sympathethic trunk. These utilise the neurotransmitter acetylcholine to synapse with an excitor neuron in the ganglion. Postganglionic unmyelinated axons are distributed to smooth muscle in blood vessel walls, sweat glands, and muscles of hair and skin. The primary neurotransmitter of the sympathetic ganglion neurons is noradrenaline which acts via three families of adrenergic receptors ($\alpha 1$, $\alpha 2$ and β receptors). The $\alpha 1$ receptors mediate sympathetic stimulation of vascular and visceral smooth muscle. The $\alpha 2$ receptors mediate presynaptic inhibition of noradrenaline and other neurotransmitters.The $\beta 1$ receptors mediate the stimulating effects on heart rate, excitability and contraction while the $\beta 2$ receptors mediate smooth muscle relaxation.

The activities of the parasympathetic part of the ANS are directed toward conserving and restoring energy. Heart rate is slowed, pupils constricted, peristalsis and glandular activity increased, sphincters are opened and the bladder wall is contracted. Connector nerve cells

are located in the brainstem involving the oculomotor (III), facial (VII), glossopharyngeal (IX), Vagus (X) nerves and the sacral segments of the spinal cord (S2,3,4). The most important cranial parasympathetic output is carried by the vagus nerve (X) and the primary parasympathetic neurotransmitter is acetylcholine. It exerts a beat to beat control of the heart rate and facilitates motility of, secretion in the gastrointestinal tract. Acetylcholine acts via muscarinic receptors. The M1 like receptors mediate excitatory effects of acetylcholine in the ANS while M2 receptors mediate inhibitory effects of acetylcholine.

Both postganglionic fibres from the thoracic portions of the sympathetic trunk and postganglionic parasympathetic fibres originating from the dorsal nucleus of the vagus nerve synapse with postganglionic neurons in the cardiac plexuses. These fibres terminate in the sinoatrial and atrioventricular nodes, on cardiac muscle fibres and coronary arteries. Activation of the postganglionic sympathetic fibres will lead to cardio acceleration while activation of the postganglionic parasympathetic fibres result in reduction in rate and force of myocardial contraction.

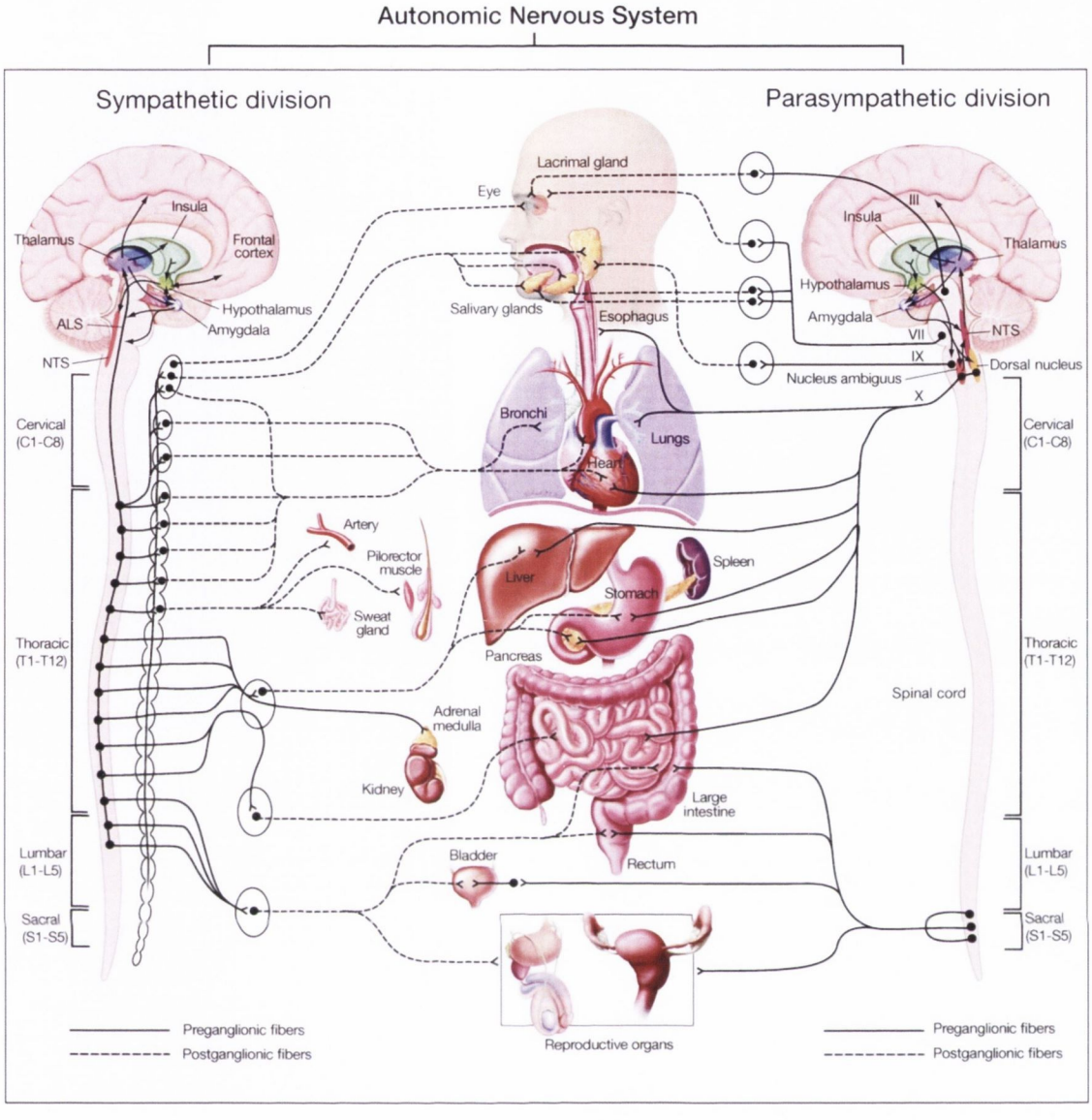


Figure 1.3 Diagrammatic representation of the sympathetic and parasympathetic nervous system (Autonomic nervous system) and target organs

The hypothalamus is regarded as having a higher control of the autonomic nervous system. Stimulation of the anterior region of the hypothalamus can influence parasympathetic responses, whereas stimulation of the posterior region of the hypothalamus gives rise to sympathetic responses. Lower brainstem centres such as vasodepressor, vasodilator, cardioaccelerator, cardiodecelerator, and respiratory centres have been located in the reticular formation. The neurons of the thoracolumbar outflow of

the sympathetic part and the neurons of the craniosacral outflow of the parasympathetic part of the ANS receive their control through the descending tracts of the reticular formation.

The carotid sinus located at the bifurcation of the common carotid artery and the aortic arch serve as baroreceptors. When blood pressure increases nerve endings situated in the walls of these vessels are stimulated. Afferent fibres from the carotid sinus ascend in the glossopharygeal (IX) nerve and from the aortic arch in the vagus (X) nerve and terminate in the nucleus solitarius. Connector neurons in the medulla oblongata activate the dorsal nucleus of the vagus which slows heart rate. Preganglionic sympathetic outflow to the heart and arterioles are inhibited by descending reticulospinal fibres. These two combined effects reduce peripheral resistance in blood vessels and blood pressure falls. Therefore baroreceptors play a role in modifying blood pressure control.

1.52 Normal response to upright posture

The human adult weighing 70kg has a blood volume of approximately 5 litres. The thorax contains approximately one quarter of our circulating blood volume. When an individual stands upright from a supine position, the shift in gravity causes displacement of between 300 – 800 mililitres (mls) of blood or 6-10 ml/kg of blood to the lower abdomen or lower extremities. [77] Up to 25% drop in volume can occur on standing and 50% of this may occur within seconds. There is peripheral pooling of blood in veins below the cardiac level and plasma moves into the interstitial fluid. This leads to a decrease in venous return to the heart with a corresponding decrease in stroke volume (SV), decrease in cardiac output (CO) and in turn a decrease in blood pressure (BP). Cardiac mechanoreceptors are present in cardiac ventricles; baroreceptors are located in the carotid sinus and the aortic arch. The cardiac mechanoreceptors (vagal c-fibres) transmit

afferent impulse information to the dorsal vagal nucleus of the medulla. The decrease in ventricular filling and in SV is thought to reduce stretch on these cardiac mechanoreceptors (c-fibres) which in turn reduces afferent output to the medulla in the brainstem. The effect of this is to cause a reflex increase in sympathetic output with vagal withdrawal, thereby precipitating an increase in heart rate and peripheral vascular resistance (PVR). The decrease in blood pressure also activates carotid and aortic baroreceptors giving rise to a reflex tachycardia and venoconstriction. Baseline blood pressure levels are then restored. [78] The initial and early steady state circulatory adjustment is, in essence , governed by the neural system. Arterial (especially carotid) baroreceptor reflex control of peripheral resistance is the most important component to maintaining postural normotension in humans.

1.53 Pathophysiology of VVS

The exact pathophysiology responsible for VVS is not completely understood but research has suggested some possible mechanisms. Blood flow in the human brain remains relatively constant. Cerebral blood flow is approximately 50-60ml/min/100g of brain tissue. Total cerebral blood flow at baseline is about 800ml/min which represents approximately 20% of cardiac output. Arterial perfusion pressure is the main determinant for cerebral blood flow and is proportional to systolic blood pressure and inversely proportional to cerebral vascular resistance. Cerebral blood flow is autoregulated and is not affected by arterial pressure provided it remains within the autoregulatory range. [79] If blood pressure falls, dilatation of the arteriolar bed occurs and cerebral perfusion is maintained. Conversely if blood pressure rises vasoconstriction protects the vascular bed of the brain. (figure 1.4) Transient loss of consciousness is thought to be secondary to cerebral hypoperfusion. If cerebral blood flow is reduced by 50-60%, prodromal

symptoms occur and should flow fall to below 16 ml/min/100g, electrical activity ceases ie. once mean arterial pressure reaches 60mmHg autoregulation of cerebral blood flow is no longer maintained and syncope occurs. [80] This may have implications for the older hypertensive subject presenting with VVS. With hypertension a shift to the right occurs in the autoregulation curve in order to protect the brain from side effects of hypertension. Therefore a hypertensive subject who experiences prodrome or syncope may be more likely to do so at a higher mean arterial pressure. (figure 1.5)

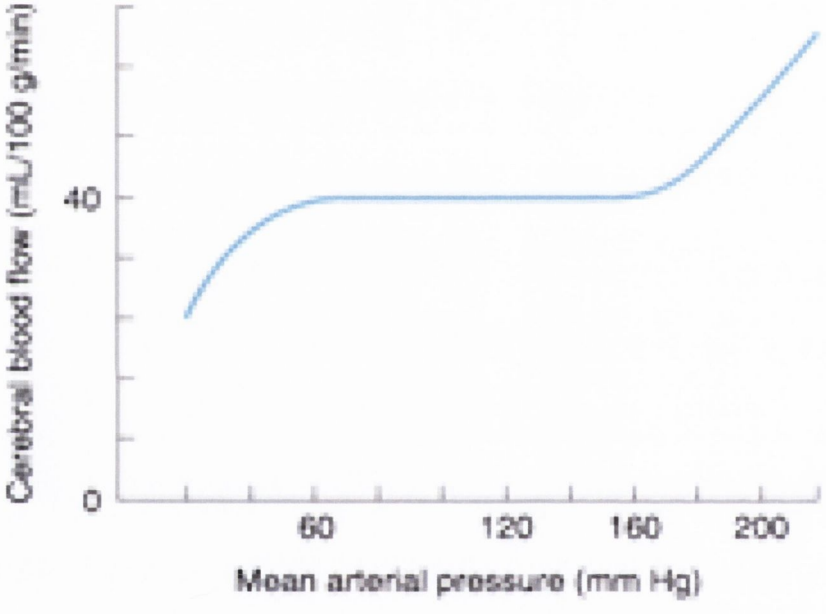


Figure 1.4 Flow pressure curve of the cerebral circulation.

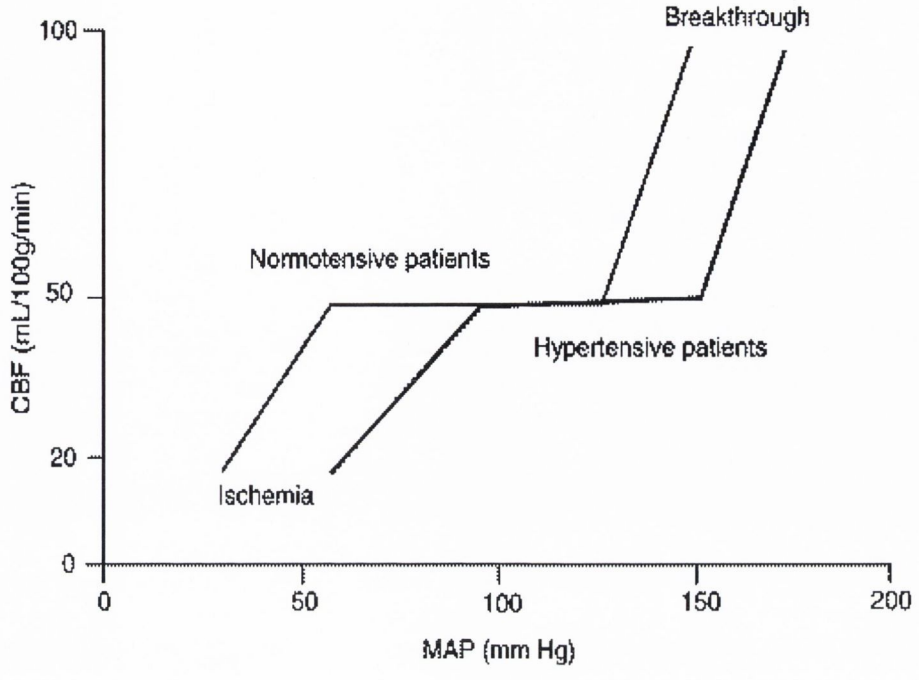


Figure 1.5 Flow pressure curve with an increase in both upper and lower limit for autoregulation demonstrated in the Hypertensive subject

One mechanism commonly suggested surrounding VVS physiology is that VVS occurs due to exagerated autonomic reponses to upright posture. The effect of gravity alone causes cerebral perfusion pressure to be lower than that in the brachial artery. [81] Normal autonomic responses to upright gravity are sufficient to prevent significant cerebral hypoperfusion and syncope from occurring. In predisposed individuals it is thought that excessive venous pooling in upright posture leads to an exagerated drop in venous return. The sudden reduction in ventricular volume activates a larger number of mechanoreceptors including those that normally respond to stretch in the left ventricle. Increased afferent neural traffic to the brainstem increases efferent sympathetic activity which enhances total peripheral resistance. Sympathetic stimulation of a hypovolaemic ventricle activates ventricular afferents in the left ventricle which trigger an inhibitory

response causing hypotension and bradycardia. This is termed the "Bezold-Jarisch reflex" named after the German physiologist Albert Von Bezold and the Austrian dermatologist Adolf Jarisch junior who both described the triad of responses apnoea, bradycardia and hypotension. (figure 1.6)

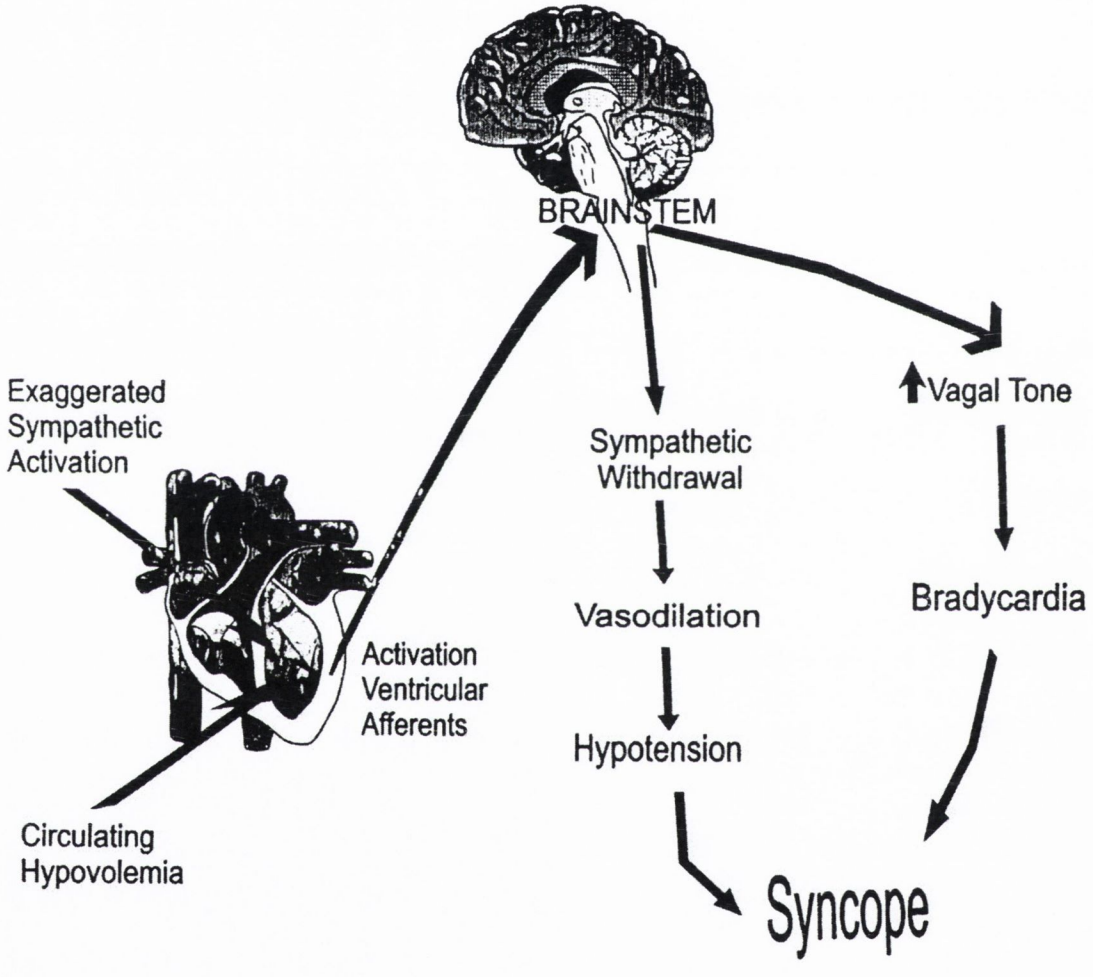


Figure 1.6 Abnormal responses to upright posture [78]

There are however controversies surrounding this theory. Animal studies by Oberg and Thoren demonstrated that only a minority (circa 20%) of ventricular efferents excited after a vena cava occlusion also responded with excitation during a hemorrhagic event. [82] Fitzpatrick et al demonstrated vasovagal responses on head-up tilt testing in seven individuals who had had a cardiac transplant. Given that surgical denervation of ventricular receptors occurs with transplant and re innervation takes up to six months to begin, one might expect the vasovagal reflex to be impaired in these individuals. [83, 84]

Echocardiograph studies suggest no significant decrease in ventricular volume in patients with reproduction of presyncope or syncope during HUT test [85] [86] Measurement of plasma norepinephrine levels preceding syncope on head-up tilt has had contradictory findings also with some showing decreased as opposed to expected increased levels. However this may be explained by the variability in time of blood sampling or lack of correlation to haemodynamic changes at time of blood extraction. [87, 88]

Serotonin surges have also been implicated as a potential cause for VVS. An abrupt alteration in serotonin levels may initiate sympathetic withdrawal . [89] Response to treatment with serotonin reuptake inhibitors has been recommended [90] but recent studies have contradicted such benefit. [91]

Furthermore VVS also occurs in the setting of an emotionally stressful or traumatic event, for example; the sight of blood or witnessing a medical procedure. Syncope in this setting does not necessarily have a postural element for precipitation and can occur with little or no warning raising suspicion of a central or cerebral trigger rather than a haemodynamic trigger. This is further supported by simultaneous transcranial doppler (TCD) studies and HUT testing assessing cerebral vasoconstriction at the time of syncope. There is some evidence to suggest that cerebral vasoconstriction occurs prior to

symptoms or peripheral haemodynamic change in VVS. [92, 93] Initially attributed to hypocapnia due to hyperventilation, further studies have also demonstrated evidence of cerebral vasoconstriction in the absence of hypocapnia. [94]

There is wide variation in symptoms and precipitants of VVS as well as hormonal and cerebrovascular change at the time of syncope. It is more likely that a common pathway exists, perhaps originating in the brainstem which promotes the inhibitory response of hypotension with or without bradycardia therefore inducing syncope.

Studies which have assessed the pathophysiology of VVS have for the most part been performed in younger adults and so it remains unclear if the same theories regarding pathophysiology can be applied to older adults. Older adults with VVS are also more likely to have overlapping conditions such as OH or CSS [95], supine hypertension, or be on antihypertensive medication. They are more likely to have multiple co-morbidities as well. Differences in plasma epinephrine and norepinephrine levels have been demonstrated between younger and older adults with VVS during HUT testing. A reduced surge in epinephrine has been reported in those older than 65 years of age whereas norepinephrine levels remain similar when compared to those younger than 65 years. [96] Reduced heart rate variability, a sign of blunting of autonomic response has also been demonstrated with increasing age during HUT. [97-100] Research suggests that older adults may have a greater arterial pressure reserve for blood pressure fall than younger adults while remaining conscious during HUT ie. syncope occurs at the same systolic blood pressure even though older adults may have a higher baseline systolic blood pressure secondary to hypertension. [101]

1.54 Classification of VVS

Based on what is known about its pathophysiology, VVS has been classified according to the haemodynamic response, during HUT testing. The main types of response are vasodepressor (hypotensive), cardioinhibitory (bradycardic) or a combination of both responses; mixed (hypotension and bradycardia). A classification based on the HUT table test response was proposed for the first time by the Vasovagal Syncope International Study (VASIS) in 1992 [102] and has since been revised to the current classification. [103] (Table 1.2) This classification is based on syncope during HUT at a 60 degree angle.

Classification Type	*Blood pressure and heart rate response*
Type 1 Mixed	Heart rate does not fall < 40 beats/min (bpm) or falls < 40bpm for less than 10 seconds with or without asystole for < 3 seconds. Blood pressure falls prior to fall in heart rate
Type 2A Cardioinhibition without asystole	Heart rate falls to < 40 bpm for more than 10 seconds but asystole > 3 seconds does not occur. Blood pressure falls prior to fall in heart rate.
Type 2B Cardioinhibition with asystole	Asystole > 3 seconds occurs. Heart rate fall coincides with or precedes blood pressure fall.
Type 3 Vasodepressor	Heart rate does not fall > 10% from its peak at the time of syncope.

Table 1.2 VASIS classification of VVS [103]

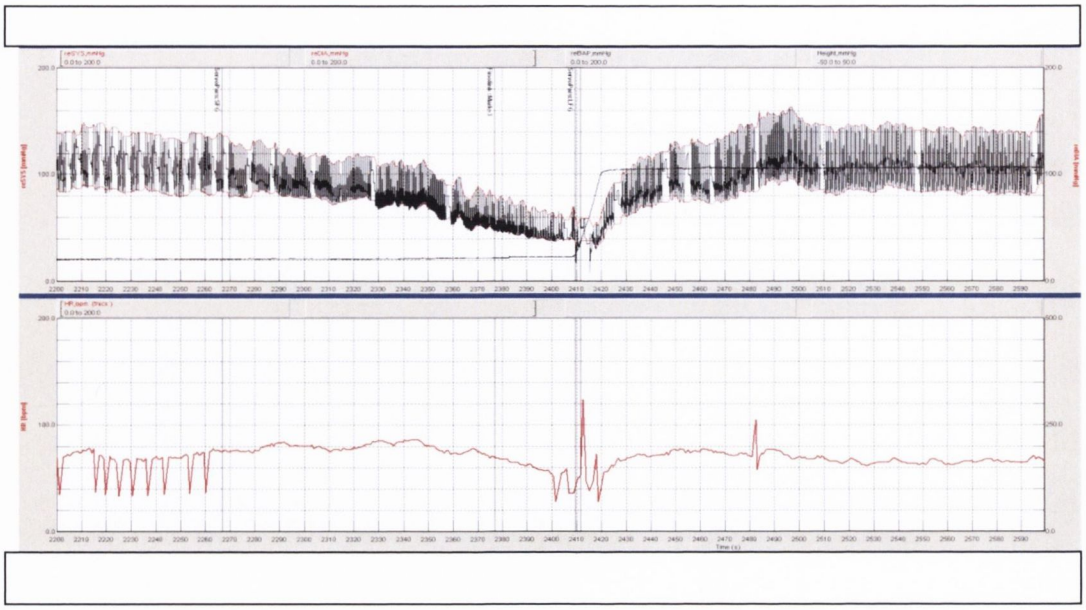


Figure 1.7 Beatscope data demonstrating Type 1 VVS. The two red lines in the top segment represent systolic and diastolic blood pressure. The red line in the bottom segment represents heart rate.

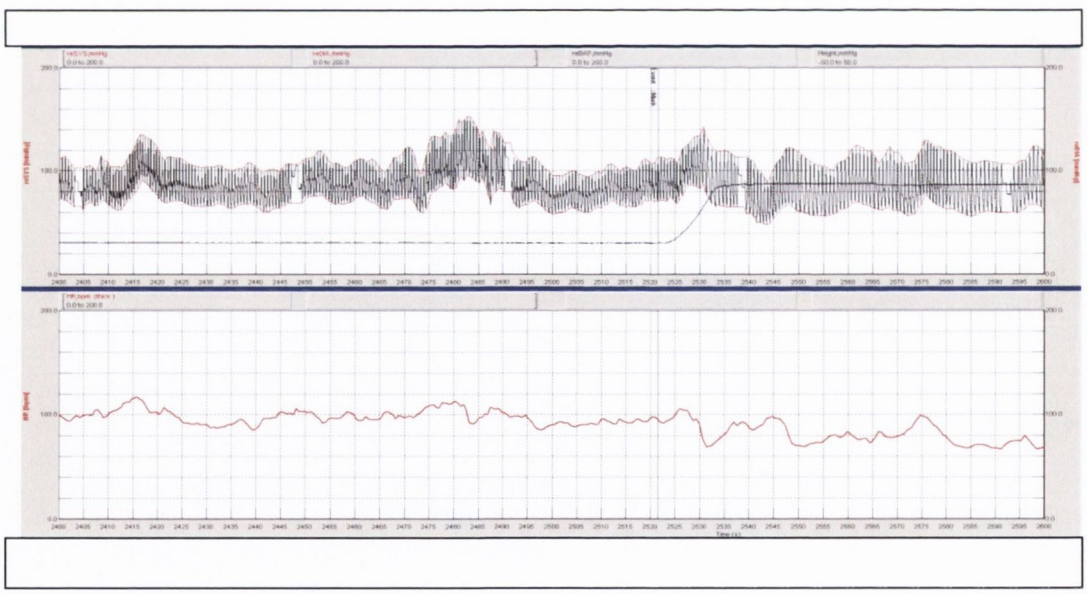


Figure 1.8 Beatscope data demonstrating Type 2A VVS. The two red lines in the top segment represent systolic and diastolic blood pressure. The red line in the bottom segment represents heart rate.

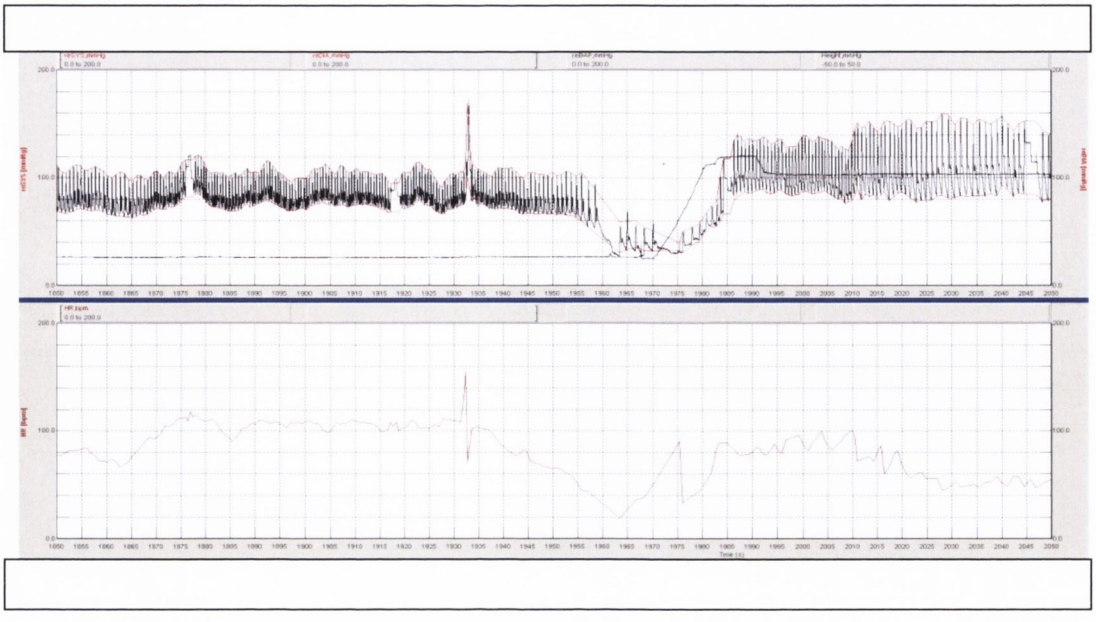


Figure 1.9 Beatscope data demonstrating Type 2B VVS. The two red lines in the top segment represent systolic and diastolic blood pressure. The red line in the bottom segment represents heart rate.

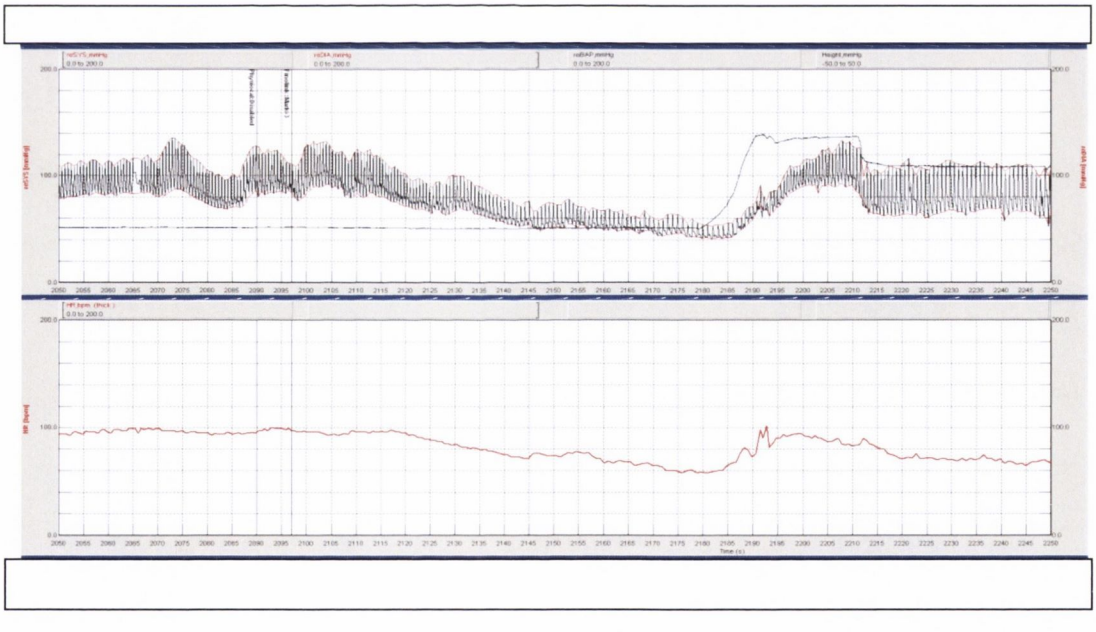


Figure 1.10 Beatscope data demonstrating Type 3 VVS. The two red lines in the top segment represent systolic and diastolic blood pressure. The red line in the bottom segment represents heart rate.

Based on the VASIS classification older subjects are more likely to demonstrate a vasodepressor response on HUT than younger subjects who have a greater tendency to demonstrate a cardioinhibitory response. [104, 105]

Postural orthostatic tachycardia syndrome (POTs) is often described [106] as a variant of VVS. It is defined as an increase of at least 30 bpm or a maximum heart rate of > 120bpm within the first 10 minutes of tilting. Profound hypotension does not occur. Although its mechanism is not fully understood, it is thought to overlap with chronic fatigue syndrome. [107]

1.55 Amnesia for loss of consciousness – Pathophysiology

The pathophysiology underlying amnesia in the setting of loss of consciousness remains unexplained. Retrograde A-LOC has been described in traumatic brain injury, concussion, epilepsy, transient global amnesia and syncope but brain imaging has been unhelpful in determining the aetiology of A-LOC. [108] Conflicting electroencephalographic (EEG) findings have been reported with concussion and have not been helpful in deciphering the underlying aetiology for amnesia. Some EEG studies with boxers in the acute phase of concussion, detected little or no alteration in EEG activity, some demonstrated diffuse slowing of cerebral rhythms, while others suggested an epileptic like discharge which then subsided in the acute phase. [109] Transient global amnesia (TGA) is defined as a sudden onset of an anterograde and retrograde amnesia that lasts up to 24 hours followed by recovery. [110] Temporal lobe structures involvement including the hippocampus have been suggested in TGA. Probable mechanisms for TGA include posterior circulation ischaemia, seizure or migraine aetiology. [111] High resolution imaging with Magnetic Resonance Imaging (MRI) implicate the involvement of memory circuits in the mesiotemporal region, MRI

abnormalities were detected in the hippocampal area in some studies in TGA and furthermore in a location of the hippocampus corresponding to the CA1 sector known to be involved with memory. [112] Overlap of TGA with vascular transient ischaemic attack (TIA) has not been proven but case reports demonstrated the presence of cerebral emboli in the setting of cerebral angiography. [113] Transient epileptic amnesia can also occur with inter ictal memory disturbances particularly in middle-aged and older aged adults. [114] Prevalence of amnesia for seizure episodes is unknown in epilepsy.

A theory for the aetiology of A-LOC with syncope is that selective hypoperfusion in certain areas of the brain involved in memory formation occurs with hypotension. It is possible that the interaction of the autonomic nervous system with the cerebral cortex, subcortical areas and brainstem, in particular the amygdala and hypothalamus which are associated with memory formation, plays some role. Jennings et al reported an association between poor memory task performance with reduced regional blood flow in the amygdale-hippocampal complex. There was a simultaneous reduction in parasympathetic activity. [115]

Another possible explanation for A-LOC is a neuro-endocrine response during syncope. Previous animal studies showed that cortisol levels increase during memory tasks. Studies have shown that increasing cortisol levels in healthy aging humans correlate with impaired hippocampal dependent memory and reduced hippocampal volume. [116, 117] One study assessing 139 adults 65 years of age and older showed that cortisol levels inversely related to simple memory tasks and were independent of subjective ratings on stress and perceived performance . [118] The introduction of a cortisol synthesis inhibitor was associated with improvement in spatial memory performance during repeat testing. Investigators reported the crucial role of the central nucleus of the amygdala and

hypothalamus in evoking cardiovascular responses of bradycardia and hypotension in relation to a freezing or "playing dead" response to fearful situations in animal studies. [119] Stimulation of the central amygdala in both anaesthetised and conscious animals has evoked cardiovascular responses similar to responses to fear. [120] The amygdala is located below the hippocampus in the medial temporal lobes and has an association with both emotional learning and memory. It is therefore involved in the process of transferring information often secondary to emotional events from currently working memory into long term memory. [121] The strong association and overlap of the hippocampus and amgydala with the autonomic nervous system response could certainly underlie an amnesic response with neurally-mediated syncope. Deciphering the reason why some have amnesia and others don't is more difficult.

The papez circuit is the process by which long term memory is laid down with the involvement of the hippocampal and limbic system. Most research focuses on the memory process and deficits in the laying down of long term memory. (figure 1.11) The papez circuit was first described in 1937 by James Papez and later with additional research the amygdala and prefrontal cortex were added to make a larger circuit.

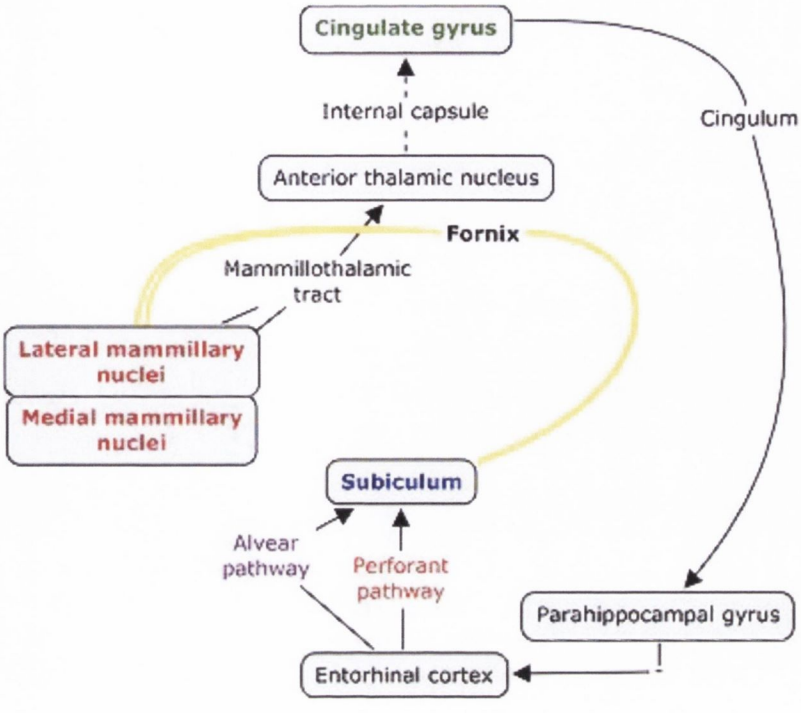


Figure 1.11 The papez circuit

Damage to the hippocampus and structures within the papez circuit have been associated with amnesic syndromes.

Recent attempts at fractionating amnesia into a number of subtypes based on the type of memory loss have met with little success. Since the 1990s it has been suggested by researchers that a distinction is required between long term memory and working memory deficits. [122] Conscious recollection of events or episodic memory is thought to depend specifically on the hippocampus while working memory or short term memory may be more dependent on the temporo-parietal and frontal lobes. Subjects with damage to the temporo-parietal cortex rather than the diencephalon or hippocampus have been reported to have impaired short-term memory but preserved longterm memory. [123] However there is ongoing debate as to whether recall and recognition involves different retrieval mechanisms of the same memory system or whether different memory processes may be involved. The exact pathophysiology of A-LOC following hypoperfusion and syncope

may have mixed aetiology involving all the above processes and therefore remains unexplained.

1.56 Cortical changes with VVS

Transcranial Doppler (TCD) and the EEG are some of the main tools for evaluating cerebral blood flow and cortical activity during real time VVS with HUT. [124]

TCD has demonstrated evidence of cerebral vasoconstriction prior to haemodynamic change during HUT. In 1998 Grubb et al reported an increase in cerebrovascular resistance prior to systemic hypotension in five subjects with VVS during HUT. [125] This was further supported by Sung et al who found a significantly reduced diastolic cerebral blood flow velocity in subjects regardless of whether there was associated hypotension or heart rate increase prior to presyncope during HUT. [126] Although cerebral vasoconstriction occurs during presyncope, two studies in 2001 suggested that in habitual fainters cerebral vasoconstriction prior to peripheral hypotension may be explained by the physiological consequence of hyperventilation-induced hypocapnia. [127, 128] Hoag et al reported cerebral flow velocity increases occurring an average 67 seconds prior to first mean arterial pressure fall in 8 presyncope subjects, again suggesting a cerebral trigger for VVS. Moreover Silvani et al suggested that an increase in cerebrovascular resistance was more pronounced at the start of prodromal symptoms in those displaying a cardioinhibitory rather than mixed or vasodepressor response during VVS. [129, 130] Further work in 2011 again reiterates a consistent demonstration of increased cerebrovascular resistance or reduced middle cerebral artery flow velocity prior to peripheral haemodynamic change in those who developed VVS during HUT. [131]

The EEG has been used in combination with HUT for monitoring electrical activity during syncope for many years. EEG was first discovered by the German psychiatrist Hans Berger in 1929 who described measuring electrical brain activity by electrodes placed on the scalp. Data measured by the scalp EEG has been used for both clinical and research purposes. In a clinical setting it is used mainly for the diagnosis of seizures and epilepsy and for the localisation of seizure origin within the brain. In recent times EEG has been a helpful tool in clarifying the diagnosis of epilepsy or syncope in cases where history alone has been unhelpful. [132-139] Difficulty can arise in part due to the onset of tonic spasms and myoclonus which can occur with syncopal loss of consciousness which in turn can lead to a misdiagnosis of epilepsy. [140, 141] EEG changes depend greatly on the type of seizure and region of localisation. Interictal features on EEG can often be normal while ictal EEG features can include spike or polyspike activity and slow wave discharge at 3-5 hertz (Hz).

Seizures can rarely provoke asystolic or arrhythmogenic responses and documented EEG changes in combination with Electrocardiograph (ECG) changes are beneficial in this scenario. [142-148] Experimental evidence suggests that the insular cortex may exert a lateralised influence on cardiovascular autonomic control. Oppenheimer provoked bradycardia and vasodepressor responses intraoperatively when the left caudal anterior insula was stimulated, whereas stimulation of the right insula elicited a tachycardic response and hypertension. This suggests a lateralisation of parasympathetic activity to the left insula and sympathetic activity to the right. [149, 150] This may suggest a reason why epileptic seizures may also instigate asystole during or following an attack depending on the focal region involved.

In the setting of neurally-mediated syncope, which incorporates carotid sinus syncope and vasovagal syncope, EEG has improved knowledge surrounding cortical activity during cerebral hypoperfusion and syncope. The characteristic changes on EEG during syncope have been well described. [151]

In 1944 Engel et al combined two channell EEG and ECG together to evaluate changes which occurred during syncope. [152] Blood pressure was also monitored during this study. Vasodepressor syncope was evoked by the authors in nine patients using a variety of precipitating manoeuvres including venepuncture. They noted that slow waves appeared on EEG once the individual was allowed to progress to full loss of consciousness. The first definitive EEG study with syncope was carried out by Gastaut and Fisher-Williams in 1957. [153] One hundred subjects who presented with a history of syncope were evaluated with simultaneous EEG and ECG recordings. Ocular pressure was used to induce syncope in the majority of subjects. In 71 subjects, cardiac asystole occurred. In those with less than 6 seconds asystole no clinical or electrical abnormalities were documented. In those with a cardiac asystole of between 7-13 seconds, bilateral and synchronous slow waves were seen on EEG. This may or may not have been accompanied by full loss of consciousness. If asystole was 14 seconds or greater, clonic jerking could occur with a normal EEG, followed by generalised tonic contraction and accompanied by complete flattening of the EEG. Therefore an initial generalised waveform slowing was followed by high voltage delta wave activity and in the setting of persistent cerebral hypoperfusion, EEG flattening was also demonstrated. Complete recovery of normal EEG pattern with resumption of consciousness in reverse sequence occurred. This was the first definitive study to describe "convulsive syncope" ie to explain the generalised convulsion which could be seen with prolonged asystole. The

authors suggested that the tonic fits often seen in convulsive syncope were as a result of release of control of brainstem structures from corticoreticular inhibitory fibres. Further studies using combined EEG and ECG further enhanced our understanding of "infantile syncope" or anoxic seizures occurring in children. [154]

In 1964 a study evaluating EEG during micturition syncope noted no seizure activity on EEG but similar EEG changes such as those described by Gastaut were seen. [155] Seventeen patients between the ages of 29-63 years of age with cough syncope were evaluated using combined EEG and ECG. [156] Diffuse theta and delta slowing were seen during episodes with EEG. Eight patients had clonic-like movements but an increase in heart rate rather than bradycardia was reported.

In 1961 Karp et al observed circulatory, electroencephalographic and neurological changes in syncope in young healthy volunteers during HUT. [64] Ten normal males with no known history of syncope, between the ages of 17 and 24 years volunteered. They underwent a HUT for a maximum of 30 minutes at a 60 degree angle. Subjects received sodium nitrite orally prior to testing. Intra-arterial pressures were used for blood pressure monitoring along with simultaneous ECG and EEG monitoring. When mean arterial pressures fell during presyncope to between 18 and 43 mmHg the appearance of high voltage synchronous slow waves in the EEG recordings occurred which coincided with the onset of unconsciousness. No EEG abnormalities were documented before the onset of presyncope in this study. During hypotension normal alpha and beta activity was replaced by low voltage theta waves. Within 10 seconds this was followed by bilateral synchronous high-voltage delta wave activity. These delta waves arose *"symmetrically and simultaneously from both hemispheres and were often prominent over the anterior and frontal regions .... duration of high-voltage slow activity varied from 9 to 29*

seconds." One patient developed myoclonic jerking with asystole. Reversal of EEG pattern seen prior to syncope was seen on recovery.

In 1990, 279 patients with a history of transient loss of consciousness underwent evaluation with HUT and EEG. EEG findings were correlated in 28 patients (21 convulsive and 7 non convulsive) who experienced syncope during testing. [157] Patients who had syncope were between the ages of 10 and 63 years with a mean age of 33 years. Blood pressure was monitored every minute during testing by an automatic dynamap monitor. This study confirmed a pattern during convulsive syncope as one of *"middle or high amplitude, often synchronous, delta waves followed by transient EEG flattening"*. The non convulsive syncope pattern on EEG was characterised by *"slowing of background activity and by bilateral and synchronous delta waves"*. The authors did comment on poor correlation between duration of EEG flattening and duration of asystole during syncope.

The changes seen during cerebral hypo-perfusion were further reiterated in a smaller study in 1991 evaluating HUT and EEG response in individuals with witnessed generalised seizures who had a normal neurological and cardiology work-up and who were found to be resistant to antiepileptic medication. [158] During HUT a standard sphygmomanometer was used for measuring blood pressure with continuous EEG and ECG monitoring. The provocative agent used during testing was Isoproterenol. Baseline EEG was normal in all patients but during convulsive syncope the EEG exhibited a pattern of *"3 to 5 cycles per second slowing during prodromal symptoms, which decreased to 1 to 3 cycles per second with loss of consciousness"*. No spike or spike wave activity was recorded.

In 1994 Lempert et al induced vasovagal syncope and videoed 56 healthy volunteers through a sequence of hyperventilation, orthostasis and valsalva manoeuvres. [63]

Nine of the volunteers who had vasovagal syncope induced in this manner agreed to repeat the procedure with a four lead EEG attachment, (C3, C4, P3 and P4). Six recordings were suitable for analysis. Muscle activity was visible during straining and hyperventilation. At the time of loss of consciousness, high-amplitude theta and delta waves occurred followed by a flatline EEG in 3 cases. These waves returned to normal alpha activity with resumption of normal consciousness. The flatline EEG coincided with myoclonic jerking of the subject.

EEG changes have been observed at time of presyncope as well as at time of syncope in young subjects (mean age 30 ± 19) undergoing HUT using isoproterenol as a provocative agent and sphygmomamometer for blood pressure monitoring. [159] While theta wave slowing and delta wave slowing were demonstrated at the onset of pre-syncope, no EEG abnormalities were documented prior to the first onset of symptoms. Furthermore in terms of temporal evolution, EEG abnormalities and progressive slowing was generalised over most leads ie.no evidence of lateralisation was documented. Similar EEG changes were seen at onset of presyncope and syncope but changes were more abrupt in transition from one to the other. The authors make the point that all patients in this study were young and healthy and that no studies have focussed on age related EEG changes during VVS.

EEG dysfunction in the form of increased bilateral alpha wave activity has also been documented preceding heart rate changes in one case report with lateralization of alpha activity prominence in the left hemisphere suggesting a potential cerebral change occurring prior to haemodynamic change. [160] Ammirati et al in 1998 performed a

larger study observing the correlation of EEG changes and VVS. [161, 162] Sphygmomanometry was used for blood pressure monitoring. 27 patients (mean age 41 ± 11 yrs) had VVS reproduced during HUT of a total of 63 participants and 10 controls studied. No EEG abnormalities were noted at baseline or in those with a negative study. EEG was normal during prodromal symptoms. Patients experiencing vasodepressor syncope had a generalised high-amplitude, 4 to 5 Hz (theta range) slowing of EEG activity at onset of syncope, followed by reduction of frequency 1.5 to 3 Hz (delta range). Cardioinhibitory syncope showed similar responses at the start of syncope followed by a disappearance of cerebral activity or flat-line EEG.

These results were reiterated by Silvani et al in 2000 who found that EEG changes at the time of syncope differed in those with a type 2A (cardioinhibitory) versus type 1 (vasodepressor) response(n=6) and suggested a different involvement of the central nervous system in the various forms. [163] This was the first combined EEG and HUT study to use a finapres system for continuous non-invasive blood pressure monitoring.

In 2002 Mercader et al added new insight into the involvement of the central nervous system in neurally-mediated syncope. [164] Six subjects undergoing combined HUT and EEG assessments experienced a positive HUT. The six subjects' EEG's showed evidence of slow wave activity prior to syncope or presyncope. The slow wave activity in 5 of 6 patients lateralised to the left cerebral cortex (temporal lobe region) on visual inspection. Spectral analysis was then performed using digitalised EEG. The increase and peak in delta wave activity was four times higher in the left hemisphere compared to the right hemisphere and these changes occurred prior to symptom onset. Mercader argues that as these changes were not found in 2 subjects who developed orthostatic hypotension during HUT without syncope it raises the question of VVS or neurally-mediated syncope having

a cerebral rather than cardiac aetiology. However blood pressure was recorded at three minute intervals only, up to time of symptoms and therefore the association between cerebral activity and hypotension was not accurate.

While studies have concentrated on the observation of EEG patterns, few have analysed quantitative changes in EEG. Mecarelli et al in 2004 compared baseline EEGs of those with a known diagnosis of VVS (n=43; mean age 26.3±7.1 years) and healthy controls (n=32; mean age 25.7±5.4 years) at rest and during hyperventilation. [165] As well as visible differences in EEG between VVS subjects and controls, the absolute and relative power of frequency bands in random tracings were compared. In those with a diagnosis of VVS at baseline, a larger amount of delta and theta activity was present when compared to controls. The baseline physiological alpha rhythm was slower in subjects with VVS when compared to controls indicating possible baseline cortical differences in those who are prone to vasovagal syncope.

Therefore electrical activity changes of the brain at time of syncope have been well described but a lack of knowledge remains surrounding both qualitative and quantitative EEG analysis at time of first symptom onset during HUT induced VVS particularly in older subjects.

1.6 Diagnosis of vasovagal syncope

1.61 The head-up-tilt (HUT) table test

Careful history taking remains key in proceeding to the correct path of investigation for an individual presenting with syncope, and together with a normal cardiovascular examination and a normal electrocardiogram can be sufficient to make a diagnosis of

VVS. In someone with a history of known ischaemic heart disease, cardiac investigations should be performed to outrule a cardiac cause for symptoms.

There is no gold standard test for the diagnosis of VVS but the HUT table test remains the best method of reproducing symptoms experienced during spontaneous attacks. Initially the tilt table was employed to study the normal human response to positional and gravitational change, and for assessment of OH and autonomic dysfunction. Before the introduction of the HUT, diagnosis of VVS was always made from history taking alone and by methods of exclusion of other forms of syncope such as cardiac syncope. In 1986 HUT was first described as a method of provoking syncope in those with unexplained syncope. [166] Following an overnight fast, patients in this initial study were tilted to a 40 degree angle for 60 minutes and returned to a supine position with the onset of symptoms or syncope. Blood pressure was monitored intraarterially or by an automatic blood pressure monitor. This protocol was refined further to a HUT table test at 60 degree for 45 minutes (Westminster Protocol). [167] This time interval was chosen after analysis suggested a mean time to syncope of 25 minutes. HUT increases orthostatic stress which causes blood to pool in the lower extremities triggering VVS in those who are susceptible. Initially drug free passive HUT testing was used but various protocols have since evolved involving pharmacological provocation. The majority of protocols involve an initial drug-free state followed by drug administration. One of the first provocative agents, Isoproterenol, was administered as an intravenous infusion during HUT to provoke hypotension and bradycardia over a shorter duration of time. [168, 169] Isoproterenol stimulates β1 and β2 receptors increasing heart rate and contractility and causing vasodilatation of the peripheral vasculature.This protocol is still in use today but there are risks with isoproterenol use, particularly in those with a prior history of

ischaemic heart disease and side effects during testing are commonly reported. Nitroglycerin infusion was first demonstrated as a provocating agent for VVS in 1994. [170] Sublingual nitroglycerin was as effective as intravenous nitroglycerin making the HUT test more efficient and simpler to perform. [171] It is postulated that the vasodilatory effects of nitroglycerin increases venous pooling which has been enhanced already by upright posture. Both Isoproterenol and nitroglycerin use with HUT have similar sensitivity and specificity but the side effect profile is considerably lower with nitroglycerin. [172, 173] Therefore nitroglycerin is less invasive, less expensive, and safer to use. Following review of all nitroglycerin induced HUT studies 'The Italian Protocol' was established as a standard method of tilt testing in 2000. [174] This protocol involves a passive HUT phase followed by nitroglycerin provocation and remains the most common protocol in use today. More recently a shorter version of this test, the "Front-loaded" HUT (FLHUT) has been validated by Parry et al. [175] The FLHUT test gives higher diagnostic rates than passive tilting albeit with higher false positivity rates. Both Isoproterenol and nitroglycerin protocols have similar rates of positive responses (61-69%), with a high specificity (92-94%). [1] The main HUT protocols are summarised in Table 1.3.

HUT Protocol	*Methods*
Original Westminster	Overnight Fast 30 minutes supine rest Passive HUT to 60 degree for 60 minutes
Modified Westminster	Overnight Fast 30 minutes supine rest Passive HUT to 60 degree for 45 minutes
Isoproterenol	Overnight Fast 5 minutes rest supine or @ least 20 minutes post intravenous cannulation Passive HUT to 70 degree for 20-45 minutes If negative infusion commenced @ 1mcg/min and increased at 10 minute stages to a maximum of 4mcg/min
Italian	Overnight fast Supine position 5-10 minutes Passive HUT to 60 degree for 20 minutes Nitroglycerin 400mcg sublingual spray followed by 15 minutes HUT
Front-loaded	Overnight fast Supine position 10 minutes HUT to 70 degree with administration of 800mcg nitroglycerin at start of test: Duration 20 minutes

Table 1.3 Recognised and validated HUT protocols

1.62 Conditions and indications for HUT

Regardless of whether pharmacological provocation is used there is general consensus on the methodology for HUT. [1, 176] A supine pre-tilt phase of at least 5 minutes in a quiet dimly lit room at room temperature is recommended. This supine period should be extended to 20 minutes if venous cannulation is required. Fasting of at least four hours

before testing is recommended and in some cases overnight fast. Continual three lead ECG recording is recommended, ideally 12 lead ECG recording throughout HUT testing. Continuous beat-to-beat non-invasive blood pressure measurement is preferable. A tilt table using a foot-board support with the ability of rapid smooth transition to the supine position should be used. Tilt angle of 60 – 80 degree has the best sensitivity and specificity; 70 degree is the more common angle employed at present. A passive phase of at least 20 minutes is recommended with a maximum tilt duration of 45 minutes. Isoproterenol and nitroglycerin are acceptable as provocative agents but caution is required with isoproterenol particularly in the setting of ischaemic heart disease. All HUT testing should be supervised by a nurse or laboratory technician experienced in carrying out the test, and with a physician in close proximity or attendance. Not all patients with vasovagal syncope require a HUT. The consensus for HUT indications is summarised in Table 1.4.

Indications for HUT test
Widespread consensus that HUT test is required: Recurrent unexplained syncope in the absence of cardiac disease or in the presence of cardiac disease where a cardiac cause has been excluded Single episode of syncope in a high risk setting: Physical injury acquired; driving or road traffic accident; occupational implications such as driving/pilot or working with heights; related to a sporting activity.
General consensus HUT test required but some difference of opinion exists: Discrimination of convulsive VVS with jerking movements from epilepsy Evaluation of patients with unexplained falls Assessment of unexplained dizziness or presyncope Discrimination between VVS and OH syncope Diagnosis of psychogenic pseudosyncope Hypotensive induced transient ischaemic attack assessment in the setting of normal cardiac and carotid doppler work-up To reassure patients of the diagnosis even if diagnosis of VVS is obvious for history
Widespread consensus HUT test not required: Single syncopal episode without injury and not in a high risk setting Alternative specific cause of syncope has been established To assess response to treatment for VVS

Table 1.4 Indications for HUT

1.63 Complications and contraindications for HUT

The potential complications and contraindications are listed in Table 1.5.

Complications of HUT
Life-threatening ventricular arrhythmias with isoproterenol with a history of Sick Sinus Syndrome or ischaemic heart disease.
Self limiting atrial fibrillation may occur.
Side effects experienced may be headache post nitroglycerin and palpitations post Isoproterenol.
Contraindications and caution with HUT
Uncontrolled Hypertension
Known cardiac arrhythmias
Left ventricular outflow obstruction (hypertrophic cardiomyopathy)
Significant Aortic/mitral stenosis
Significant Carotid stenosis
Pregnancy

Table 1.5 Complications and contraindications to HUT

Chapter 2

Literature Review

2.1 Aims of literature review

A systematic review of the literature was performed to establish evidence surrounding age and its' relationship to warning symptoms in VVS, haemodynamic responses in VVS both at time of symptoms and syncope, evidence of unexplained falls or amnesia with VVS and evidence regarding cerebral activity during VVS. Methodology was reviewed in relevant studies to best advise towards methodology for this study.

2.2 Search Strategy

A standardised search strategy was used to search computerised bibliographic databases (Medline 1955 – 2011, EMBASE 1980 -2011). Headings combined during the initial search were syncope; syncope vasovagal; syncope neurocardiogenic; along with adult; young adult; aged; middle aged; aged 80 and over. Further searches using a combination of the above terms were then combined with signs and symptoms; tilt table test; haemodynamics; amnesia; falls accidental; falls unexplained; Drop attacks; electroencephalography and sonography transcranial. Searches were limited to human studies of all ages, and only abstracts or articles in the English language were considered.

2.3 Data Extraction

On review of studies, information such as design, setting, number of participants, age and diagnostic methods were documented. The main findings of relevant studies are summarised.

2.4 Reported prodrome in VVS

The typical presentation of VVS is characterised by a preceding prodrome which has been well described. [177] Symptoms typically described are those of dizziness/lightheadedness, feeling of warmth, sweating, blurred or dark vision, abdominal discomfort sometimes associated with nausea, along with hearing disturbance or paraesthesia. Studies which have looked specifically at the prevalence of reported symptoms recalled by individuals prior to having a diagnosis of VVS confirmed with HUT are summarized in table 2.1

Further studies assessing reported symptoms prior to investigations for individuals with unexplained syncope have found differences in prodrome prevalence between those with a positive HUT table test and those who had a negative HUT table test. These studies are summarized in table 2.2. [178, 179]

Other studies have focussed on differences in reported prodrome in those who have a diagnosis of VVS in comparison to those with an alternative diagnosis for syncope such as cardiac syncope. Those with cardiac syncope report significantly less prodrome than those with VVS. [13, 180] These studies are summarised in table 2.3. Lack of prodrome in an older adult raises suspicion of cardiac syncope.

Very few studies have examined age related differences with reported prodrome prior to VVS. Del Rossa et al as part of a larger study comparing prodromal VVS symptoms to cardiac symptoms also found that in those with VVS, those 65 years of age or older reported less prodrome than those younger than 65 years. Not all subjects in this study had a diagnosis of VVS confirmed with HUT. [181] Similarly as part of the 'FAST' Dutch study, younger individuals with reflex syncope reported prodrome more often than

their older counterparts. It is not clear from this study if a diagnosis of VVS was confirmed in all cases with a HUT. [27] A large retrospective study has been performed by the Newcastle group which reports reduced prodrome in older adults with VVS. [182] A recent Italian prospective study found that those 35 years of age or younger were more likely to report prodromal symptoms than older adult groups. Interestingly however older adults report prodrome during HUT to the same degree as younger adults, suggesting a lack of recall of original prodrome with history taking. [183]Prodrome is essential in order to give warning and allow time to abort a syncopal episode and prevent injury. Details of these studies are summarized in table 2.4.

Reference	*Study design*	*Population: Number HUT positive*	*Mean Age (yrs)*	*Prior prodromal symptoms*
2009 [184] Guida et al	Prospective N=239	N=149	32 ± 16	79% reported prior prodrome vs 96% reported prodrome during HUT
2008 [185] Fazelifar et al	Prospective N=85	N=79	45 ± 19	68.4% reported prior prodrome Palpitations 29.1% Nausea 43% Diaphoresis 72% Blurred vision 54.4% Asymptomatic 26.6%
2006 [186] Emkanjoo et al	Prospective N=90	N=64	43.2 ± 17	60% reported prior prodrome 27% reported prior physical injury
2001 [187] Ammirati et al	Prospective N=346	U/A	U/A	27.2% reported prior trauma 8.6% reported prior admission Less prodrome reported in those with trauma vs no trauma P< 0.01
2001 [46] Graham et al	Prospective N=62	N=62	50 ± 21	61% reported prior prodrome [Lightheadness 92% Fatigue 68% Blurred vision 68% Sweating 66% Nausea 60% Palpitations 37% 37% Short of breath 29% headache 25% chest pain]

Table 2.1 Reported prodrome with VVS prior to diagnosis with HUT

Reference	*Study design*	*Population*	*Age (yrs)*	*Prior prodromal symptoms*
2002 [178] Graham et al	Prospective Questionnaire N=87	N=31 passive HUT +ve N=31 provoked HUT +ve N=25 HUT -ve	47 ± 22 53 ± 19 52 ± 18	77% passive HUT +ve 57% provoked HUT +ve 24% HUT -ve
2007 [179] Vallejo et al	Prospective Questionnaire N=101	N=67 HUT +ve N=26 HUT -ve	28 26	Visual 69% vs 31% p= 0.001 Dyaesthesia 58% vs 23% p= 0.004 Dyspnoea 66% vs 31% p=0.003 Tremor 40% vs 15% p= 0.028 Diaphoresis 66% vs 42% p= 0.043
2005 [188] Kulakowski et al	Prospective Questionnaire N=202	N=67 HUT +ve N=135 HUT-ve	43 ± 20	Cold 50% vs 32% p= 0.039 Crowded 73% vs 41% p= 0.001 Standing 73% vs 45% p= 0.0001 Nausea 24% vs 10% p= 0.01 Diaphoresis62%vs39%p=0.002 Prodrome 19% vs 8% p= 0.04
2002 [189] Asensio et al	Prospective N=117	N=89 HUT +ve N=28 HUT -ve	39 ± 19 46 ± 18	Dizzy 78% vs 43% p= 0.001 Weak 58% vs 36% p= 0.037 Nausea 60% vs 25% p= 0.001 Diaphoresis 56% vs 32% p= 0.027

Table 2.2 Prior reported prodrome in those who proceed to have a diagnosis of VVS with symptom reproduction during HUT versus those with a negative HUT and consequent unexplained syncope

Reference	*Study*	*Population number and end diagnosis*	*Age (years)*	*Prodromal symptoms*
2008 [190] Patel et al	Retrospective N=358	N = 126 VVS (15 HUT +ve) N = 64 Unknown N = 50 Cardiac N = 26 OH N = 3 Psyche	25 v 34 v 54 v 34 v 0% Were > 65 years of age	Dizzy 69 v 62 v 46 v 48 v 100 % Visual disturbance 26 v 14 v 8 v 20 v 33 % Nausea 21 v 18 v 20 v 33 v 33 % Palpitations 18 v 18 v 20 v 33 v 33 % Sweating 21 v 17 v 12 v 24 v 33 % Chest pain 9 v 9 v 8 v 12 v 0 % Short of breath 10 v 8 28 v 4 v 0 %
2005 [191] Hamer et al	Prospective VVS vs control	N=472 VVS n=86 controls	mean 52 VVS range(12-92) mean 74 control range(61-94)	Nausea 54 v 37 % Sweating 61 v 44 % Visual 51 v 26 % Palpitations 34 v 17 % Seizure activity 9 v 1 % Pallor 68 v 54 % Fatigue 67 vs 41 % Combined>2 88 v 62 % VVS vs control p<0.05
2006 [180] Sheldon et al	Prospective Questionnaire	N=235 HUT +ve VVS N=88 cardiac	42 ± 18 63 ± 16	Nausea 36% p= 0.0001 Sweating 51.7% p <0.0001 Visual 47.4%p =0.0004 Auditory 29.7% p= 0.0002 Abdominal sensation 12.7% p =0.0004 Numbness22.6% p= 0.0007
2004 [95] Alboni et al	Prospective Questionnaire	N = 39 VVS- N = 34 situational syncope N = 142 VVS N = 34 CSS	35 ± 18 53 ± 19 57 ± 21 70 ± 11	95% reported prodrome 61% reported prodrome 76% reported prodrome 62% reported prodrome
2009 [192] Colman et al	Prospective Questionnaire (FAST)	N=69 VVS N=32 LQTS	27 (median) 42 (median)	Nausea 60% vs 29% p= 0.005 Pallor 83% vs 67% p= 0.08 Standing 87% vs 33% p <0.001 Venipuncture 17.6% vs 3.3% p= 0.04
2001 [13] Alboni et al	Prospective Questionnaire	N=199 VVS N=78 cardiac	59±21 72±13	Diaphoresis 28 vs 17% p= 0.05 Abdo sensation. 8% vs 1% p= 0.05 Cold 12% vs 1% p= 0.01 Pallor 80% vs 55% p= 0.002

Table 2.3 Prior reported prodrome in VVS versus cardiac syncope/other causes of syncope

Reference	*Study design*	*Age-groups and numbers*	*Age (years)*	*Prodromal symptoms*
2010 [183] Guida et al	Prospective N = 743 (460 HUT +ve)	N = 312 (≤ 35) N = 329 (36 - 64) N = 102 (≥ 65)	23 ± 7 50 ± 8 71 ± 5 (mean)	≤ 35 vs ≥ 65 p < 0.001 36-64 vs ≥ 65 p= 0.11 ≤ 35 vs 36 – 64 p < 0.001
2010 [182] Duncan et al	Retrospective N = 1060 HUT +ve	N = 453 (< 60) N = 607 (≥ 60)	42 median 73 median	Dizziness 22 v 19 % p= 0.345 Palpitations 10 vs 5 % p < 0.001 Unexplained falls 3 vs 7 % p= 0.006 Fractures 3 v 5 % p= 0.097
2008 [27] Romme et al	Prospective N = 503 TLOC N = 303 VVS (FAST) HUT +ve (Unknown)	N = 116 VVS N = 110 VVS N = 77 VVS	< 40 40 – 59 ≥ 60	Nausea p= 0.02 Dizziness p < 0.01 Visual p < 0.01 Palpitations p < 0.01 Need to lie down p < 0.01
2005 [181] Del Rossa et al	Prospective VVS vs cardiac N = 296 VVS (N = 142 HUT +ve) (N=189 cardiac)	N = 154 VVS N = 142 VVS	< 65 >65	Prodrome 84 v 59% p= 0.001 Presyncope 51 v 37% p= 0.001 Blurred vision 15 v6 % p= 0.005 Lightheadedness 29 v 18% p= 0.005 Diaphoresis 43 v 20 % p= 0.0001 Nausea 23 v 9 % p= 0.0005 Weakness 38 v 14 % p= 0.0005 Cold 19 v 4 % p= 0.001

Table 2.4 Age related differences in reporting of prodrome-evidence to date

2.5 Haemodynamic changes in VVS

Age related differences in haemodynamic characteristics have been demonstrated in VVS with the use of HUT. Positive response to HUT declines with age. [193] Following the introduction of the VASIS classification as a method of describing blood pressure and heart rate reponses during HUT, many studies characterised VASIS responses to syncope in younger and older age groups. [103] There is a distinct pattern in those 60 years of age and older who lose consciousness during HUT, in comparison to younger individuals; those 60 years of age and older demonstrate a higher baseline systolic or arterial blood pressure as well as a a higher incidence of pure vasodepressor response during syncope in

comparison to their younger counterparts. [104, 105, 194] Younger individuals develop a tachycardic response initially in response to hypotension during HUT in comparison to a dysautonomic response in older adults ie. less of an increase in heart rate in response to postural change. [100, 195] Heart rate variability is reduced in older adults with VVS. [104, 196] In the preceding few minutes prior to syncope younger adults have higher incidence of a cardioinhibitory response in comparison to older adults. [100, 105, 197] The findings of previous studies analysing responses of older and younger adults during HUT are summarized in table 2.5 and suggest less responsive sympathetic activity by older adults preceding syncope onset. Younger individuals experience increased cardiac and autonomic responses to stress , whereas older individuals experience a more generalised autonomic response. The plasma renin-angiotensin system has previously been shown to be less active at regulating orthostatism in ageing. [198] Reduced baroreflex sensitivity has also been demonstrated in ageing.[199] In a recent study by Folino et al use of antihypertensive medication in the elderly did not induce any significant alterations to these cardiovascular parameters. [100]

While haemodynamic responses in different age groups have been analysed in those with positive tilt tests who develop presyncope and syncope, little information is available regarding SBP and HR response at the time of onset of first symptoms or indeed regarding awareness of symptom reproduction during HUT in younger and older adults. A recent prospective study by Guida et al analysed SBP and HR in different age groups at time of first prodrome (symptom) onset and furthermore the time from first prodrome (symptom) to syncope. [183] Authors reported no significant difference in time of onset of syncope from time of prodrome onset during HUT, and found no significant difference in SBP and HR at time of prodrome onset across all age groups. While

prodrome onset was reported less frequently in the history given by older adults prior to HUT it was reported in equal frequency across all age groups during HUT indicating a possible lack of recall of prodrome with real time episodes in older adults. Time to prodrome (symptom) onset as well as other haemodynamic variables to prodrome (symptom) onset were not analysed in this study. Information regarding same may be more beneficial in guiding us to understanding the trigger for prodromal onset and this in turn may assist in understanding better methods to abort syncope occurrence.

Reference	Study design	Population numbers	Mean Age (years)	Haemodynamic Differences documented
2010 [100] Folino et al	Prospective N=115 (65 HUT+)	Gp 1.N=13 (10-30yrs) Gp 2.N=28 (31-50yrs) Gp 3.N=24 (>51 yrs)	20.4 ± 5.7 41.1 ± 6.4 67.6 ± 8.8	Gp 2 and 3 v Gp 1 ↓HR 1st 20 min P<0.001 Gp 2 and 3 v Gp 1 ↓ SBP in 1st 20 min Gp 3 showed progressive ↓ SBP in last 90 secs p<0.01 GP 1 had initial ↑ HR followed by steep decline p<0.005 *Symptom onset not addressed*
2010 [183] Guida et al	Prospective N=743 (460 HUT+)	≤ 35 yrs 36- 64 yrs ≥65 yrs	23 ± 7 50 ± 8 71 ± 5	Equal time prodrome to syncope each age-group NsΔ in SBP & HR @ *time of symptom onset*
2007 [197] Verheyden et al	Retrospective N=29	Mean age 41±18 (16-71yrs)	Age 31 v Age 69	Rapid ↓SBP in younger versus older p=0.005 ↓HR pre tilt back in Younger v Older P=0.041
2006 [200] Kazemi et al	Retrospective N=640 (344 HUT+)		39 ± 19 49 ± 20	↑Age OR 1.54 CI 1.04-2.47 p = 0.016 VD response
2006 [194] Martinez et al	Prospective N=338 (HUT +231)	Gp A N = 168 Gp B N = 63	40 (23-57) 66 (57-73) (median)	VD response 33% VD response 49% p=0.01
2004 [104] Galetta et al	Prospective N=380	N = 188 (HUT + 162) N = 192 (HUT + 163)	25 ± 9 67.2 ± 6.8	↓ HRV elderly P<0.001 Y oung v Old (P < 0.001) Mixed VASIS 61.2 v 13 % VASIS 2A 22.3 v 7 % VASIS 2B 2.1 v 0 % VASIS-3 2.1 v 65 %
2004 [96] Benditt et al	Prospective N=40	N=17 (HUT+) < 35 yrs N = 7 (HUT+) > 65 yrs	26 ± 7 74 ± 8	Mean % ↑Adrenaline +1014% v +356% (P<0.05) Noradrenaline +84% v 117%
2004 [101] Benditt et al	Prospective N=42 HUT+	Gp 1 N=17 Gp 2 N=18 Gp 3 N=7	< 25 yrs 25 – 59 yrs ≥60yrs	Time to syncope (mins) 10 ± 2 **v** 15 ± 3 **v** 26 ± 7 (P = 0.003 Gp 1 v 3) SBP(mmHg) @ syncope 54 ± 4 **v** 58 ± 6 **v** 61 ± 6 (NS) HR response (NS) Higher BP reserve Gp 3, Gp 2 v 3 p = 0.0085
2004 [196] Hartikainen et al	Prospective N=63 Healthy subjects	Gp 1 N = 20 Gp 2 N = 18 Gp 3 N = 25	29.5 ± 1 51.2 ± 1 68.3 ± 1	↑TPR Gp 3 v Gp 1 p < 0.001 ↓CO Gp 3 v Gp 1 p < 0.001 ↓HRV Gp 3 V Gp 1 p < 0.001 ↓BRS Gp 3 v Gp 1 p < 0.001
2004 [201] Kochiadakis et al	Prospective N = 80	N = 24 Young N = 31 Older N = 25 Control	28 ± 8 56 ± 5 48 ± 12	↑test duration older p < 0.01 ↓SBP in older syncopeP < 0.01

2003 [105] Kurbaan et al	Prospective (HUT+) N=505 N=472	Gp 1 N = 165 Gp 2 N = 169 Gp 3 N = 171	≤35 yrs 36-64 yrs ≥65 yrs	↑ HR Gp 1 v Gp 3 p<0.00005 ↑VASIS2B Gp 1vGp p<0.0005 ↓VASIS3 Gp1vGp 3 p<0.0005
2000 [97] Ruiz et al	Prospective N=77	Gp 1 N = 41 Gp 2 N = 36	15-35 yrs >60 yrs	↓HRV values in Gp 2
1999 [195] Beck et al	Prospective N=46	Gp 1 N = 25 Gp 2 N = 21	≤ 65 yrs > 65 yrs	NS Time to syncope (mins) Gp 1 (19 ± 9) v Gp 2 (22 ± 2) Dysautonomic response Gp2 R=0.54 p<0.001
1996 [202] Marangoni et al	N=175	Gp 1 N = 59 Gp 2 N = 57 Gp 3 N = 59	< 40 yrs 40 – 60 yrs ≥ 60 yrs	↓ SBP and less ↑ HR in older patients
1994 [203] Sheldon et al	Prospective N=85	N=13 N=28 N=26 N=18	12 -20 yrs 21-35 yrs 36-60 yrs 61-88 yrs	HUT + less with age p=0.033 Time to presyncope correlated weakly with advancing age r=0.30,p=0.003,n=52 Age had no sig effect in peak or trough SBP p=0.38,p=0.70 Decrease in HR from peak to trough was inversely related to age p< 0.001
1991 [204] Shannon et al	Prospective N=16 healthy volunteers	Gp 1 N = 7 Gp 2 N = 9	27 ± 3 74 ± 2	↓SV Gp 2 v Gp 1P < 0.05 ↑CO Gp 1 v Gp 2 p < 0.01 ↑PVR Gp 2 v Gp 1 p < 0.05
2002 [205] Alboni et al	Prospective N=63 VVS	N=23 HUT +	43 ± 20	Presycope @ 15±12 min Syncope @ 16±13 min ↓BP to prodrome onset p<0.01 ↑HR prodrome p<0.001 ↓ HR to syncope p<0.001 Time from presyncope to syncope 48±36 secs

Table 2.5 Age related haemodynamic studies in VVS

2.6 Vasovagal Syncope (VVS) and amnesia for loss off consciousness (A-LOC)

The following table details studies where A-LOC has been specifically documented in the presence of VVS. These are eitheir case reports or cases within studies assessing VVS.

Reference	*Study design*	*Population*	*Age (years)*	*Results*
2002 [43] Parry et al	Case study	N=1	78 years	A-LOC post HUT in the setting of unexplained falls and injury
1994 [63] Lempert et al	Observational Healthy	N=56	Student population (17-24 years)	A-LOC following induced VVS in one student
1968 [64] Karp et al	Observational Healthy	N=9		A-LOC in one individual post HUT

Table 2.6 A-LOC and VVS

2.7 VVS and EEG – Analysis of prodrome onset

Previous work and studies analysing EEG at the time of syncope during HUT are discussed in section 1.54. One study by Sheldon et al has qualitatively examined EEG prior to the onset of presyncope (ie. feeling of generalised weakness felt prior to impending syncope) and found no differences from baseline resting EEG on visual inspection. [159] No other studies, to the best of my knowledge have analysed EEG change at time of first symptom onset with VVS. Likewise although Mercader et al analysed EEG using quantitative methods the changes prior to syncope were the main focus of study. [164] Studies to date were done with young healthy volunteers or younger adults with VVS.

2.8 Research questions and hypotheses

This section has summarised relevant literature and concludes that haemodynamic differences and presentations of VVS may differ with age. Haemodynamic differences during VVS at time of first symptom/prodrome onset in relation to age have not been clarified succinctly. This thesis focuses on clarifying if age-related differences of clinical characteristics occur in those with VVS? This question is subdivided into four main research questions.

1. Do younger and older adults with VVS recall and report similar frequency and characteristics of prodrome prior to real time syncopal episodes?

   It has been demonstrated that older adults experience less warning for cardiac syncope. [206] We hypothesise that younger adults report prodrome more frequently than older adults do with real time episodes of VVS and that amnesia of symptom occurence in older adults contributes to this difference.

2. Do younger and older adults with VVS display similar haemodynamic characteristics during HUT at the time of first symptom or prodrome onset?

   Onset of symptoms acts as a trigger to abort a syncopal attack. Lack of awareness of hypotension or lack of a sympathetic response secondary to autonomic dysfunction are well established in older adults. We hypothesise that younger adults have a higher prevalence of prodromal symptoms in VVS and this is secondary to haemodynamic differences which occur at the time of first symptom onset.

3. Does amnesia for loss of consciousness (A-LOC) occur in VVS and is this solely an age-related phenomenon?

   We hypothesise that A-LOC does occur in VVS and is more prevalent in older adults than younger adults and contributes to a lack of prodrome recall and to unexplained falls. This research question is further subdivided into four questions;

   (a) What is the prevalence of A-LOC in VVS?

   (b) Do baseline characteristics differ between those without and those with A-LOC?

   (c) Do haemodynamic changes contribute to the absence or presence of A-LOC?

   (d) What are the predictors for occurrence of A-LOC with VVS?

4. Do changes in cortical activity occur prior to or at time of first symptom onset and if so does the degree of change differ, between younger and older adults?

   We hypothesise that cortical activity change occurs independent to haemodynamic change and may contribute also to the absence or presence of prodrome and A-LOC in younger and older adults with VVS.

Chapter 3

Methods

3.1 Subject Recruitment

3.11 Research Setting

Recruitment of patients to this study occurred in the *Falls and Blackout Unit* in St. James's Hospital Dublin between August 2008 and December 2010. This is a dedicated unit which was established in 2005 at St. James's Hospital, Dublin and is located beside the accident and emergency department. The model is that of a rapid access, one site one stop day-case facility. [67] The unit accepts referrals nationwide assessing up to 600 new patients and 1200 review patients per annum. An integrated care pathway has been established for referrals from accident and emergency and for inpatient referrals. [71]

Main source of referrals include:

- Accident and Emergency St. James's Hospital
- Inpatients St. James's Hospital
- Consultant Physicians and Surgeons Nationwide
- Cardiology Nationwide
- Neurology Nationwide
- General Practitioner's local and National

The unit is staffed and supervised by two consultant geriatricians, one lecturer, senior specialist registrars gaining experience rotating through the clinics during training, three specialist nurses in the area of falls and one member of administrative staff. Four weekly clinics (9am – 1pm) provided the main source for recruitment for this study.

Patients accepted for assessment to the *Falls and Blackout Unit* may have any of the following presenting complaints:

- Dizziness/Lightheadedness
- Syncope/Blackouts
- Falls

3.12 Questionnaire

Ethics approval

This research was carried out in compliance with the 1964 World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects [207] last amended in 2008. [208] Local research ethics committee approval was obtained via St. James's Hospital and the Adelaide and Meath Hospital incl. The National Children's Hospital (SJH/AMNCH) research ethics committee. All persons gave written informed consent prior to inclusion into the study. **(Appendix 1)**

Questionnaire

All consecutive new subjects aged $\geq$ 16 years of age, attending the *Falls and Blackout unit* between August 2008 and December 2010, were invited to complete a questionnaire prior to their medical assessment within the unit. Written informed consent for use of this information was given at the time of questionnaire completion. The questionnaire contained 32-stemmed questions all of which were relevant to a history of syncope or unexplained falls/drop attacks. **(Appendix 2)** Particular emphasis was placed on recall of prodrome prior to syncope or fall and the various symptoms described as part of such a prodrome should it arise. Further information surrounding trigger factors for syncope and

the characteristics recalled on recovery were obtained. Further information of any injuries in particular fractures obtained as a result of such an event were enquired after.

The questionnaire was initially completed by the subject alone without a medical doctor being present. A family member or a witness to a previous event, who accompanied the subject were encouraged to assist with any relevant information when filling in the questionnaire where appropriate. This was for the most part a tick-box questionnaire and was based on previous questionnaires which have been used in syncope and falls research [180, 192, 209-211]

Information collected included:

- History of blackouts and falls
- Age of first blackout
- Number of blackouts
- Whether witness account available
- Number of presyncopal episodes per month
- Prodrome experienced
- Recovery period
- Precipitating factors
- History of falls
- History of fractures
- History of ischaemic heart disease and stroke

- Family history of syncope and sudden death

3.13 Subject assessments in the clinic

All subject assessments were carried out in keeping with the European Society of Cardiology (ESC) guidelines on syncope. [1] All subjects had a detailed history taken by the doctor in the clinic following which cross comparison was carried out with the previously answered questionnaire and any discrepancies noticed were clarified with the subject prior to discharge from the clinic. A full physical examination was then performed. Particular attention during cardiovascular examination focussed on exclusion of evidence of structural heart disease such as cardiac murmurs and abnormalities in heart rhythm. Neurological examination focussed on exclusion of balance and gait abnormalities and disorders such as Parkinson's related syndromes or vascular disorders which may contribute to falls or syncope aetiology.

Mini Mental State Examination (MMSE)

Cognitive testing using the MMSE [212] was completed in all subjects undergoing investigation in the clinic, 60 years of age or older. **(Appendix 6)** The MMSE was developed in 1975 by Fonstein et al. It is one of the most widely used tools for dementia screening in clinical practice and has been validated and found to be reliable in tracking cognitive changes over time. This 30 – point questionnaire assesses orientation, immediate recall, short term verbal memory, attention, calculation, language and praxis. A test score of 24 or less suggests significant cognitive impairment. The sensitivity is high (80-100%) and scores are affected by age and education. [213]

3.14 Pathway of investigation

All subjects had a twelve lead electrocardiogram (ECG) which was reviewed by the doctor prior to further investigations in the clinic. Measurement of supine blood pressure and standing blood pressure were performed (Active stand test) using Finometer® pro equipment with continuous finger blood pressure measurement.(figure 3.3) This is a non-invasive beat-to-beat blood pressure device using digital photoplethsmography *(Finapres Pro; Philips Medical).* A brachial cuff was placed on the right upper arm and a finger cuff of adequate size was placed on the right index finger. A height correction system on the finometer was used during testing. Subjects rested quietly for ten minutes prior to standing with the aid of one person if required. SBP was recorded for a further 180 seconds.

Routine blood tests to outrule anaemia or electrolyte imbalance were performed in those 60 years of age or older as per ESC guideline recommendations.

A diagnosis was then made based on the history, examination and above tests. If a diagnosis was still unavailable a further suitable pathway of investigation ensued based on ESC guidelines. (Figure 3.1)

If a diagnosis could be made at this point treatment or advice was given.

If a cardiac cause such as structural heart disease or arrhythmia was suspected echocardiogram and ECG/event monitoring were performed and where appropriate, if underlying ischaemic heart disease was suspected then an exercise stress test was arranged +/- referral to a cardiologist.

If a neurological cause such as seizure or epilepsy was suspected a brain scan and Electroencephalograph (EEG) was arranged +/- referral to a neurologist.

A psychogenic cause of falls or syncope was dealt with in liaison with psychology and psychiatry services.

Where the diagnosis of falls or syncope remained unexplained in the setting of a normal cardiovascular exam and a normal ECG or where further investigations proved normal a neurally-mediated cause was sought. In those 50 years of age or older, without contraindication and in whom the diagnosis remained unexplained, carotid sinus massage was performed. This was performed in both the supine and upright position. Continuous longitudinal massage was performed for 10 seconds on both the right and then the left carotid by those experienced in performing carotid massage.

Patients with a normal carotid sinus massage proceeded to a head-up tilt table (HUT) test. The Italian protocol HUT test was used and should this test prove normal patients were invited to re-attend for a fasting front-loaded HUT test. A diagnosis of VVS was established when reproduction of either prodrome or syncope was experienced and was recognised by the subject as being in keeping with real-time syncope or unexplained falls previously experienced.

Unexplained Falls and Syncope assessment

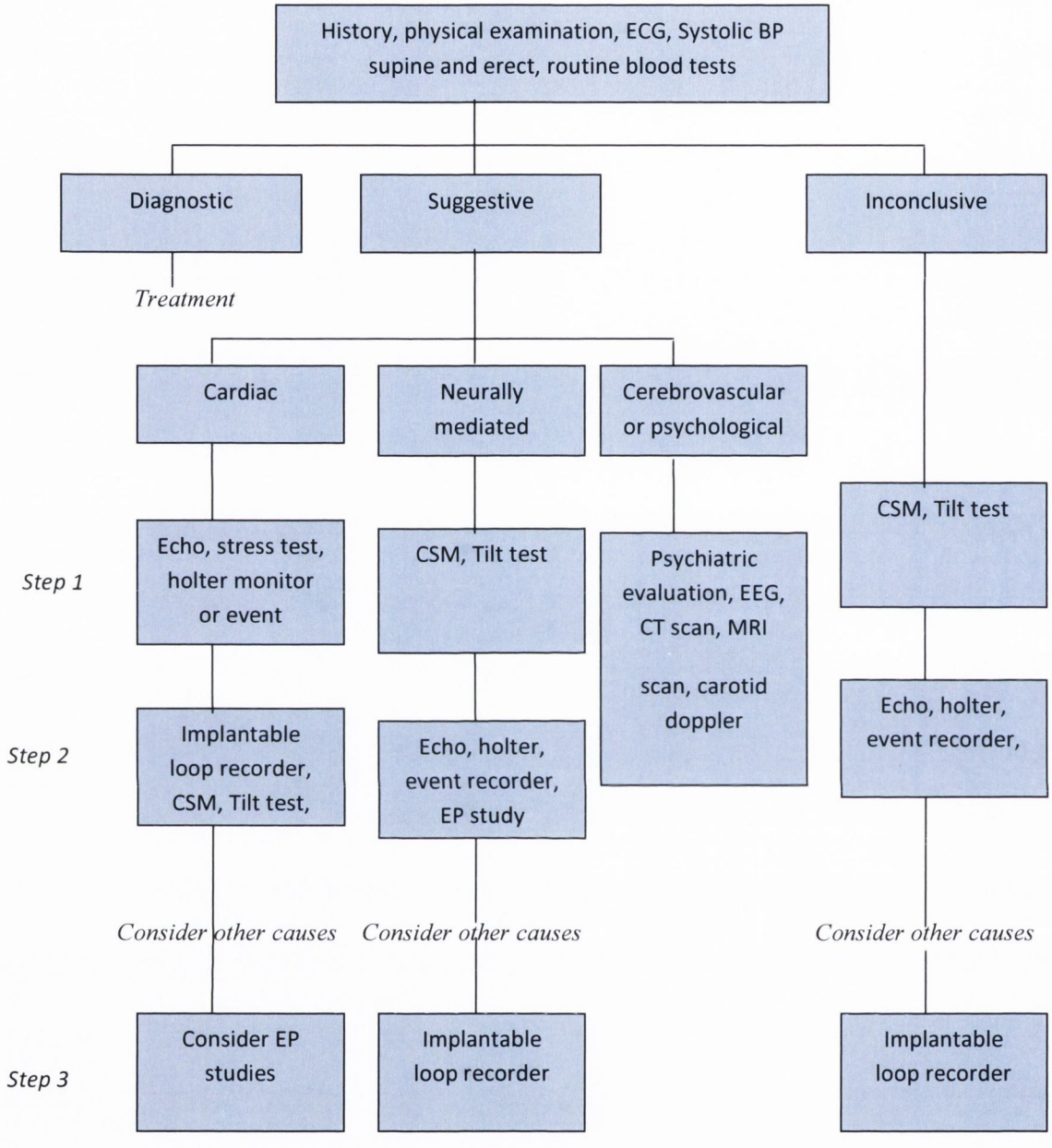


Figure 3.1: Proposed approach to the evaluation of syncope for all age groups.

BP=blood pressure; CSM=carotid sinus massage; EP= cardiac electrophysiological study; holter= ambulatory cardiac recorder; Echo= echocardiography; [214]

The main diagnoses elicited in the clinic are listed in Table 3.1:

Diagnosis	***Definition***
Orthostatic Hypotension (OH)	A drop of 20mmHg in systolic (SBP) and/or 10mmHg in diastolic (DBP) blood pressure within the first three minutes of orthostasis.[215]
Carotid Sinus Syndrome (CSS)	50 mmHg drop in systolic blood pressure (vasodepressor) and/or a 3 second ventricular pause (cardioinhibitory), during carotid sinus massage. [216]
Vasovagal Syncope (VVS)	Reproduction of prodromal symptoms or syncope induced by HUT associated with hypotension (vasodepressor) and/or bradycardia/asystole (cardioinhibitory). [103]
Cardiac arrhythmia	Supraventricular, ventricular or conduction disorder.
Structural Heart disease	Valvular defect such as Aortic stenosis or hypertrophic cardiomyopathy
Seizure	A seizure is characterised as an excessive asynchronous discharge of cerebral neurons leading to a clinical event.
Psychogenic	Episode of unresponsiveness in the presence of normal blood pressure and heart rate during HUT and not consistent with normal seizure activity [217]
Vestibular/vertigo	Abnormality in surroundings and impairment of balance secondary to middle ear pathology
Falls (gait or otherwise related)	An event whereby the individual unexpectantly comes to rest on the ground or another known level without any known loss of consciousness [51]

Table 3.1: Diagnoses and definitions

3.15 Inclusion and exclusion criteria for further participation in the study

Inclusion Criteria

- Participants had at least one unexplained fall or syncopal episode in the eighteen months prior to assessment
- Participants had an end diagnosis of VVS based on full reproduction of prodrome or syncope on HUT
- Participants were 16 years of age or older

Exclusion Criteria

- An alternative diagnosis was concluded at the end of testing such as a seizure or psychogenic syncope
- Inability to complete the questionnaire
- MMSE score of < 24/30 in those 60 years of age or older
- Inpatient referrals due to possibility of multiple co-morbidities at time of assessment
- Clinical diagnosis of VVS on history alone ie. without reproduction of symptoms demonstrated on a HUT test

Pathway to subject recruitment is shown in figure 3.2.

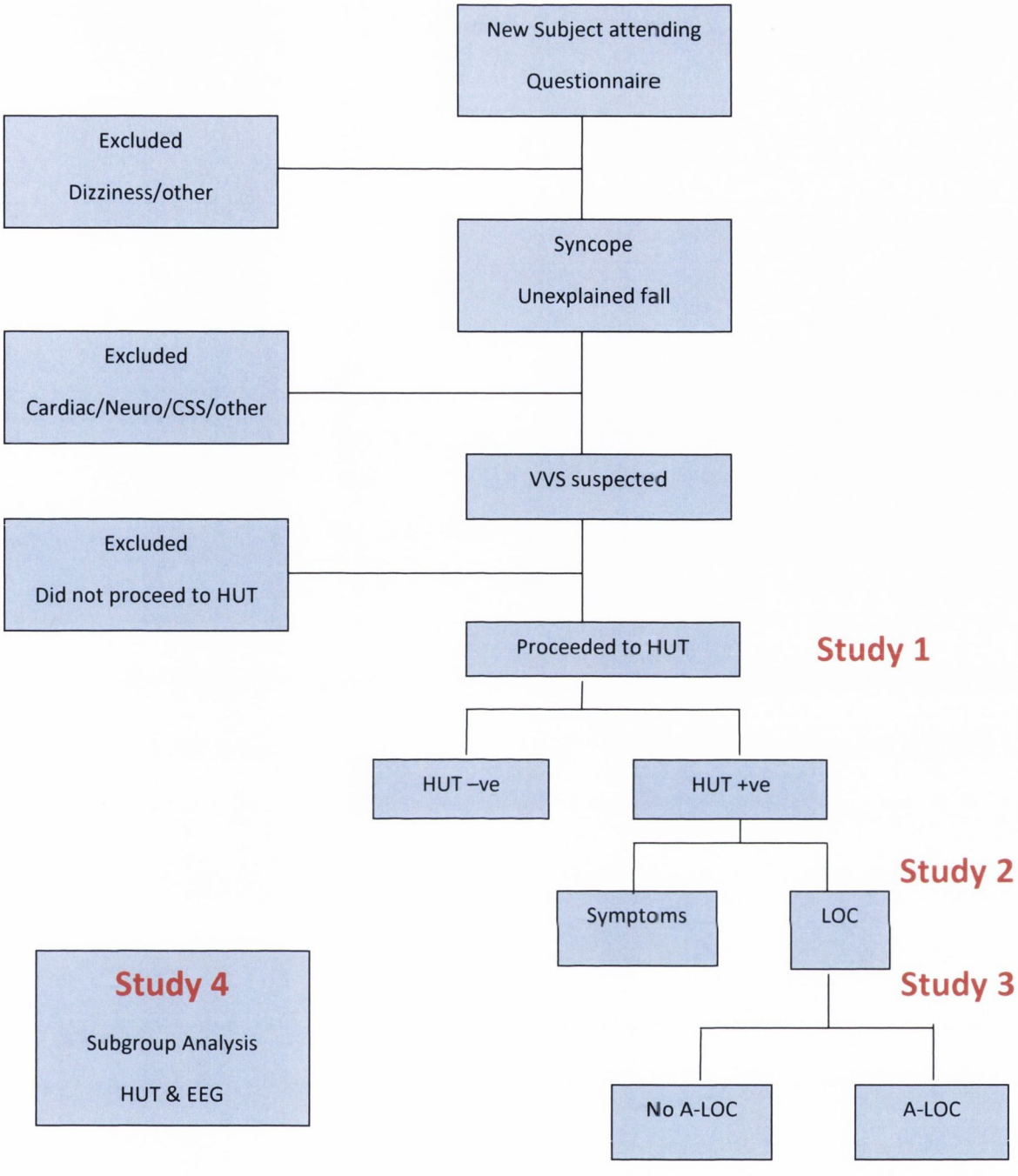


Figure 3.2: Pathway of subject recruitment.

HUT = Head-up-tilt; VVS = Vasovagal syncope; A-LOC = Amnesia for loss of consciousness; EEG =Electroencephalography

3.2 Baseline characteristics of subjects

3.21 Analysis of questionnaires

Information from questionnaires obtained from all participants were collected prospectively and transferred daily into an excel database. This database was continually updated when subjects returned for follow-up investigations with an end diagnosis also updated when known. Data on all those found to have a definite end diagnosis of VVS based on positive HUT were then transferred to SPSS 18.0 for further analysis.

3.22. Statistics

A histogram of ages represented in decades was then plotted for age distribution. Comparison was made between younger (< 60 years) and older (≥ 60 years) age groups of the various recorded characteristics associated with VVS using chi-squared (x2) test for categorical data. Odd ratios (OR) with 95% confidence intervals were calculated for clinical characteristics presented in 2 x 2 contingency tables. A two-tailed p-value of < 0.05 was considered statistically significant.

3.3 Haemodynamic measurements during VVS

This section describes the equipment (ie. Finometer®, tilt table) and the protocol used for the assessment of the patients' symptoms, and the haemodynamic response during tilting in the reproduction of VVS. It also explains reasons behind exclusion of unsuitable data.

3.31 Equipment

When VVS occurs it may involve sudden transient changes in circulation. Sphygmomanometry is therefore not suitable for evaluating sudden alteration in blood pressure in the setting of VVS. Although intraarterial measurements are more accurate, potential complications with this method can occur. The equipment used for this study is that of the Finometer® Pro device (Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com). (figure 3.3)



Figure 3.3: Finometer® pro equipment shown on the right with finger cuff attachment. Data as is depicted in real time on the computer screen on the left.

The Finometer® allows for measurement of finger arterial pressure non-invasively on a beat-to-beat basis and gives waveform measurements similar to that seen with intraarterial readings. Previous research analysing readings from intraarterial blood

pressure measurement and Finometer® readings have found acceptable correlation between both methods. [218-221]

The Finometer® can allow for several continuous measurements during tilt table testing including the following parameters;

- **Systolic blood pressure (SBP)**
- **Diastolic blood pressure (DBP)**
- **Heart rate (HR)**
- **Stroke Volume (SV)**
- **Cardiac output (CO)**
- **Total peripheral resistance (TPR)**

All HUT testing was carried out with full resuscitative equipment and a cardiac arrest trolley being present at all times.

3.32 HUT protocol

Italian protocol HUT (IPHUT)

The initial protocol used was that of the Italian protocol. [174] Patients were not required to fast or modify their lifestyle habits prior to testing and took their medications as normal on the day of testing. The test was explained in full to the patient prior to commencement both by the attending doctor and also by a specialist nurse who supervised the test throughout. Patients initially rested supine with both feet touching an end foot plate on a tilt table bed. The patient was secured with two horizontal straps; one above the waist

level and the second across the lower legs just below the knees. All testing occurred in a quiet clinical setting in individual curtain enclosed cubicles (*Falls and Blackout Unit*) at an ambient temperature (21-23°C). All tests were supervised by a specialist nurse with a clinical doctor in attendance.

The proper size cuff was applied to the index finger as advised by the Finapres manufacturer. [222, 223] Three sizes of cuff were available in total. Should finger arterial measurement prove difficult warming of the hand using warm water was instigated to improve signal pick up and the cuff was re-applied. After at least two minutes of continuous uninterrupted haemodynamic measurement, the blood pressures measured by Finometer® Pro were calibrated at baseline using the *Return to Flow* (RTF) calibration system. This involves the use of an oscillometric pressure cuff on the ipsilateral upper arm for an individual calibration of the reconstruction of the finger pressure signal to brachial level. [220] A hydrostatic height correction system was used to compensate for hand movements with respect to heart level during the study. [223] If any doubt occurred regarding baseline blood pressure measurements this was further cross checked on the contralateral arm with a separate semi automated oscillometric device (Omran). A difference of less than 20 mmHg in systolic blood pressure measurement between manual reading and Finometer reading was deemed acceptable in order for testing to proceed.

An automatic physiocal function intermittently calibrates finger arterial size at which finger cuff air pressure equals finger arterial blood pressure. Physiocal function was used to assess the signal quality prior to HUT. When the number of beats between physiocals reached 40, sufficient signal stabilisation was considered to be achieved. Prior to and during tilt table testing physiocal remained on. Once a marked blood pressure drop

occurred (< 90 mmHg Systolic) with either the presence or absence of symptoms, physiocal was switched off to ascertain a continuous recording during this hypotensive change. Should blood pressure increase again physiocal was switched back on, but remained off if hypotension persisted to the end of the test.

As well as beat-to-beat heart rate, three chest electrodes for heart rate monitoring provided direct ECG input into the Finometer® which displayed a continuous tracing of heart rate during the HUT. Furthermore ten ECG chest leads were attached separately to ECG equipment which contained a screen through which a continuous visible twelve lead electrocardiograph tracing was visible throughout testing and immediately alerted the clinical team to a bradycardic or tachycardic change in heart rate during testing or more importantly to any evidence of ischaemic change were this to occur.

Patients were educated prior to testing and advised that should they feel unwell during the test or should they experience any symptoms which they recognised from previous episodes they should verbalise this to the nurse in attendance immediately. Otherwise the test was conducted in silence. All patients rested supine in a quiet environment for a minimum of ten minutes prior to commencement of the test. As per the Italian protocol, the tilt bed was then tilted upright to a 70° angle with the patients head resting back on one pillow. (Figure 3.4)



Figure 3.4: HUT table bed in upright position during testing with equipment attached. GTN spray used demonstrated on the right.

The time at which the bed was tilted upright (ie. the start of testing) was marked using a specific *mark* button built into the Finometer® pro. Should the patient verbalise any symptoms reproductive or otherwise the *mark* button was pressed and written documentation was kept during the test to indicate the reasons for such a button being pressed. **(Appendix 3)** Following twenty minutes of unprovoked testing, 400mcg of sublingual glyceryl trinitrate spray was administered. The test was continued for a further 15 minutes or until symptoms or syncope occurred. Once significant hypotension occurred (< 90mmHg systolic) physiocal was switched off. Once hypotension of < 80mmHg systolic occurred patients were asked to count backwards from 10 to 1. The bed was tilted back to the supine position once significant symptom reproduction or loss of consciousness occurred and the patients' legs were raised upright resting on "bead bags"

with physical counter manoeuvres instigated to restore consciousness and cerebral perfusion. The patient was deemed to have VVS if reproduction of symptoms or syncope and recovery was recognised and confirmed by the patient following recovery. Vasovagal syncope is not always demonstrated with an initial HUT table test.

Front Loaded HUT (FLHUT)

Those patients with an initial normal Italian protocol HUT were invited to re-attend for a FLHUT. Patients were asked to fast from 12 midnight the night before but took their medications as normal. The test took place at 9am in a quiet environment at 21-23° C. The same equipment was used as per the IPHUT. The bed was tilted to a 70° angle. After 3 minutes in an upright position, 800mcg of sublingual glyceryl trinitrate spray was administered as opposed to 20 minutes in the IPHUT. The test continued for a further 20 minutes. Once again subjects were asked to voice any symptoms they were feeling and whether they recognised them as being familiar. The test ended at twenty three minutes or sooner if reproduction of symptoms or syncope occurred.

In a small proportion of cases, syncope occurred in the absence of symptoms. However if this was reproductive of real time syncopal episodes a diagnosis of VVS was confirmed.

3.33 Data analysis of haemodynamic parameters

Individual HUT files were exported to Microsoft Excel® spreadsheets with the Beatscope® 1.1a software. A one second averaging method was used for analysis. This was deemed appropriate as unlike orthostatic hypotension (OH) an abrupt haemodynamic change with little warning can occur in VVS and may be missed on 5 second averaging which has been more commonly used to analyse OH changes on active stand testing.

[224] The main blood pressure and heart rate recordings of interest were those at baseline, at time of symptom reproduction and at syncope. Marking of these points on HUT data was possible and correlation with written documentation of symptoms reported during testing was also studied.

1. Calculation of baseline haemodynamic values

The commencement of HUT was marked manually and by correction height method. The 60 seconds prior to automated height change represented the last minute of supine rest. Averaging of values in the first 30 seconds of this final minute prior to tilting upright was calculated. These values represented baseline haemodynamic values and were calculated for SBP, DBP, HR, SV, CO and TPR.

2. Calculation of haemodynamic values at time of symptoms

Values for SBP, DBP, HR, SV, CO and TPR at time of symptom onset were taken at the point marked which represented symptom reproduction. Averaging values over a period of time was not performed due to the abrupt nature of symptom onset which can occur in individuals with VVS.

3. Calculation of haemodynamic values at time of syncope

The point of syncope was the immediate point of tilt-back commencement. This was identified by automated height changes.

3.34 Exclusion criteria for HUT files

There were four main determinants for exclusion from end analysis which are listed

- Missing files

Files were saved incorrectly or lost from Beatscope® following HUT testing

- Finometer® Pro over reading of blood pressure measurements

Even in the setting of calibrated recording with Finometer® Pro, over reading and inaccurate readings in particular of systolic blood pressure do occur. If this occurred during the rest period prior to HUT, the equipment was stopped and restarted after relevant adjustments. However if differences in manual and finometer readings exceeded greater than 20 mmHg in systolic blood pressure measurement files were deemed unsuitable for accurate analysis.

- Failure of Finometer® Pro equipment

Where the equipment failed and cut out mid way through testing. While the recordings can be recommenced and haemodynamic values ascertained, the time to symptoms and time to syncope would remain inaccurate.

- Artefact, poor signal or excessive signal fluctuation

Rarely due to significant movement during testing particularly finger and wrist movement or due to anxiety, artefact occurred which deemed the file unsuitable for analysis.

3.35 Statistics

Subject groups were divided into group 1 (younger than 60 years of age) and group 2 (60 years of age or older). Relevant values were calculated for each subject using excel, and then transferred to SPSS 18.0 for further analysis. The data are given as mean values ± standard deviation (SD). Continuous variables were initially analysed for normality using the one-sample Kolmogorov-Smirnov test. Between group comparisons were made between group 1 and group 2; parametric data were analysed using t test (t-test) and nonparametric data using the Mann-Whitney U (MWU) test. A P-value of < 0.05 was considered statistically significant.

3.4 Assessment of Amnesia for loss of consciousness (A-LOC)

3.41 Protocol for A-LOC

If prodromal symptoms occurred prior to syncope in association with hypotension, patients were asked to repeatedly count backwards from 10 to 1 aloud. When loss of consciousness occurred, the tilt bed was returned immediately to the supine position. All HUT tests were supervised by both a doctor and nurse.

Subjects were not informed prior to HUT testing that they would be questioned on completion of the test on whether loss of consciousness had occurred. Agreed consensus by both the doctor and nurse in attendance that loss of consciousness had occurred was required. If agreement did not occur then the subject was considered not to have lost consciousness. All senior doctors and nurses were trained in the use of a standardised questionnaire at the start of the study to assess for A-LOC. **(Appendix 4)**

A standard protocol of questions to establish whether the subject was aware they had lost consciousness was administered once the subject was fully alert following HUT and blood pressure and heart rate had returned to baseline values. An open-ended question was initially asked to ascertain what the patient recalled happening; 'What happened to you?' followed by a more direct question 'Did you blackout?' If the patient denied loss of consciousness this was termed immediate amnesia. These questions were repeated 5 minutes later or when the patient was fully recovered or ambulant prior to leaving the clinic. If the subject again denied loss of consciousness this was termed delayed amnesia. If the subject was unsure whether or not they had lost consciousness they were deemed not to have A-LOC. The presence of immediate and delayed amnesia was clearly documented by the supervising doctor.

3.42 Analysis

Results were stored with other categorical data in Microsoft Excel® spreadsheets relating to presence or absence of A-LOC. Haemodynamic analysis was then performed in an effort to compare relevant points such as time of symptoms and syncope, baseline haemodynamic values and values at time of symptom onset and syncope. This analysis was done using the same methods as described in 3.33. Relevant values were also recorded in Excel® spreadsheets.

3.43 Statistics

Further analysis of data was carried out using SPSS 18.0 software. Categorical data relating to age and to the presence or absence of A-LOC was analysed using the Pearsons chi square and where appropriate Fishers exact test. Haemodynamic values during HUT

was initially interpreted using one second averaging and transferred from excel to SPSS 18.0 for further analysis. Comparison between two groups was then possible; group1 A-LOC and group 2 No A-LOC. Continuous variables were initially analysed for normality using the one-sample Kolmogorov-smirnov test. Parametric data was then analysed using t test and nonparametric data using the Mann-Whitney U test. Binary Logistic Regression analysis was then performed looking for independent predictors with A-LOC as the dependent categorical variable.

Results were expressed as mean ± SD unless otherwise indicated. P value of < 0.05 (two-tailed) was considered as significant.

3.5 Combined EEG and HUT assessments subgroup analyses

3.51 HUT equipment

Subjects who required a HUT test in order to confirm a diagnosis of VVS were invited on the first day of assessment to return on a separate day to undergo HUT testing. This occurred in a room on its own in a quiet environment with dimmed lighting at a temperature of 21-23° C. Medications were taken as normal on day of testing. On arrival subjects rested supine while Finometer® Pro and EEG equipment were being attached.

Blood pressure and heart rate were monitored non-invasively using Finometer® Pro as has been previously described methods 3.31. The IPHUT was the protocol used for this subgroup analyses.

3.52 EEG equipment

EEG was carried out using the XLTEX EEG system. Electrode placement spanned the frontal, fronto-temporal, parietal and occipital regions according to the 10-20 system for EEG recording. Further electrodes included one ground (Gnd) , 2 ECG, 2 electro-oculogram (EOG) and one reference noncephalic. (figure 3.5) The skin was prepared using 'nuprex' and the conductive paste 'elefix' was used for electrode attachment. EEG electrodes were connected using a Trex headbox to a portable laptop to record EEG which rested on a laptop stand beside the patient on the opposite side of the tilt bed to Finometer® Pro.

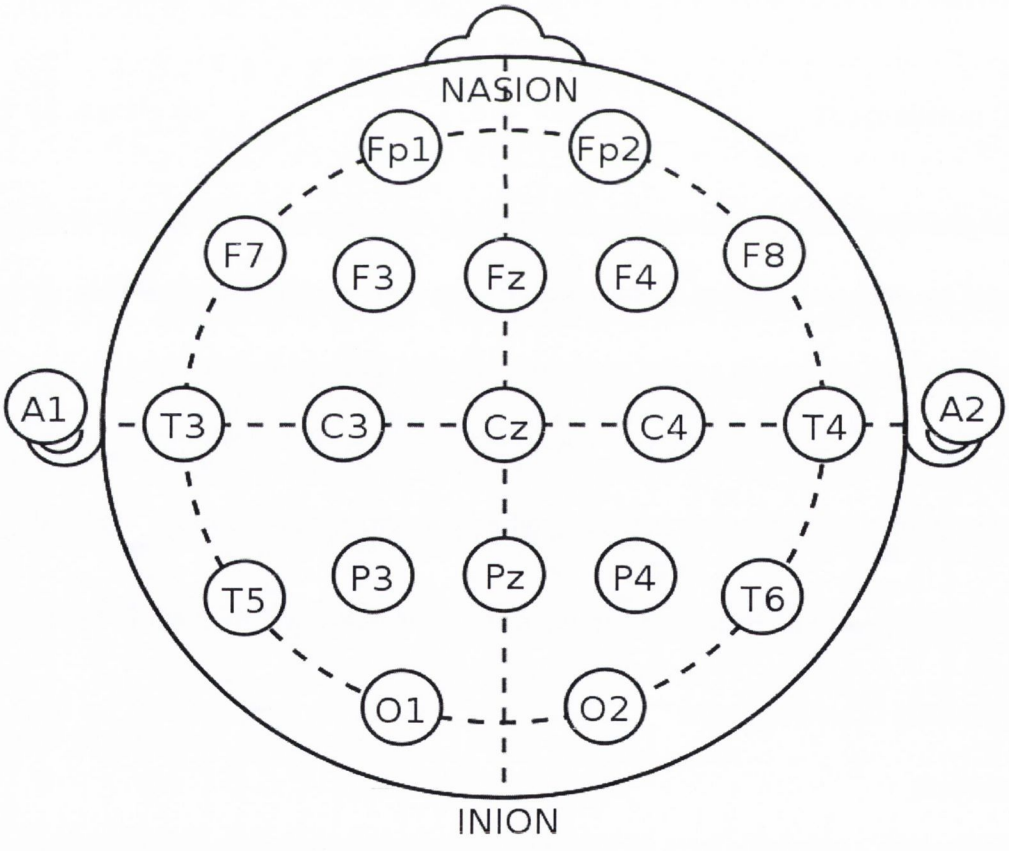


Figure 3.5: The 10-20 system or the 10-20 international system

The 10-20 system or the 10-20 international system is the internationally recognised method to describe and apply the location of scalp electrodes in the context of an EEG study. It is a method recognised as having reproducibility over time and best used for comparison between subjects within studies. Each letter identifies a cerebral lobe; F frontal: T temporal: P parietal: O occipital. C represents the centre. Each number represents the hemispherical location. Even numbers (2,4,6,8) represent the left hemisphere and odd numbers (1,3,5,7) represent the right hemisphere. Recording of data through these electrodes representing cerebral areas are then visible on the laptop screen as shown (Figure 3.6)

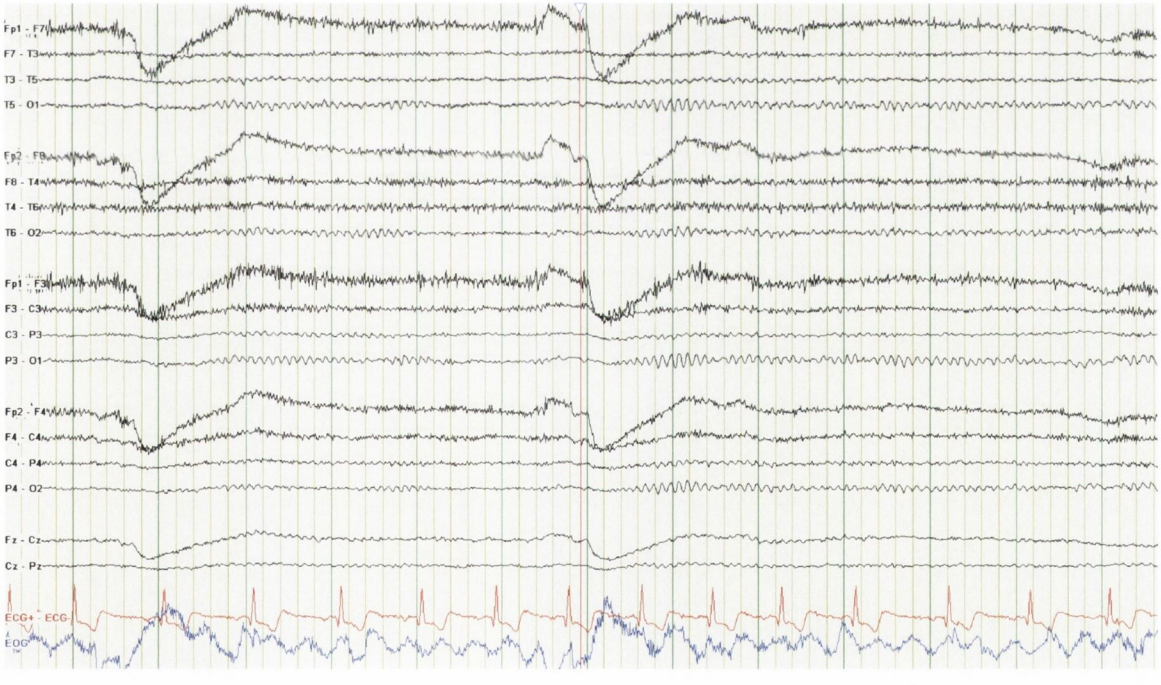


Figure 3.6: Normal baseline EEG

3.53 Protocol of combined HUT and EEG test

Once Finometer and EEG attachments were complete all patients were requested to rest quietly in a supine position with eyes closed for 10 minutes during which time baseline EEG, heart rate and blood pressure was recorded. Following 10 minutes resting supine the subjects were secured to the tilt bed using two secure straps, both feet resting on a secure foot plate. Simultaneous marking of relevant time points were performed using separate marking equipment of Finometer and of EEG. Following 10 minutes rest the HUT was tilted to a 70° angle and HUT protocol proceeded as per the Italian protocol (previously described methods 3.32). All patients had continuous 12 lead recording of ECG throughout testing. All tests were supervised throughout by a doctor, a nurse and an EEG technician. Marking occurred at the following time points:

- Start of rest
- End of rest
- Start of counting aloud at rest
- End of counting aloud at rest after 30 seconds
- Start of HUT
- Time GTN administered
- Any symptoms voiced aloud
- Time of first symptom reproduction first indicated by the patient
- Syncope

Additional comments or marks were added as required to indicate further symptoms or in the case of EEG, movement or restlessness which may add to artefact during recording. Syncope was defined as a transient loss of consciousness with short duration and quick recovery on the placement of the bed in a supine position. Definite loss of consciousness was deemed to have occurred only if witnessed by both the doctor and nurse in attendance. The main symptoms described were light-headedness, feeling warm, sweating, palpitations, blurred or dark vision and hearing disturbance.

3.54 Qualitative EEG analysis

All EEGs were inspected visually by both the investigator, and by a neurophysiologist experienced in the interpretation of EEG. Both were not blinded to symptom onset as this was marked on the EEG strip chart. Further independent EEG interpretation was then carried out by a second neurophysiologist for cross check and comparison, without the investigator being present. EEG at rest was interpreted for baseline abnormalities in waveform activity. Particular emphasis was placed on interpretation of any waveform change prior to reproductive symptom onset as marked on the strip sheet. The main waveforms seen on EEG are shown in figure 3.7.

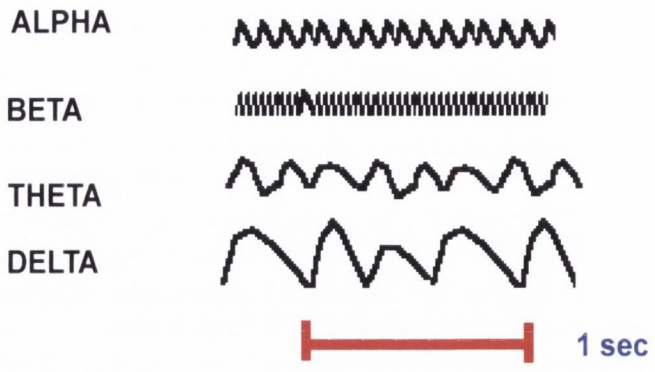


Figure 3.7: Brainwave frequencies as seen on EEG

The frequency of brainwaves are measures in hertz (Hz).

Delta waves (less than 3 Hz) occur in deep sleep or an inattentive state in the normal adult. They are abnormal in the awake adult. They can be focal with local pathology or diffuse with generalised pathology.

Theta waves (3.5–7 Hz) are normal in sleep at any age and are abnormal if they occur in excess in the awake state.

Alpha waves (8-13 Hz) are common in adults and more prominent in posterior rather than anterior leads. They are present with eye closure and relaxation. Alpha waves disappear with increased attention and are predominant in coma states.

Beta waves (greater than 13 Hz) occur predominantly anteriorly and are present in all age groups.

Gamma waves (26-100 Hz) occur with extremely high level cognitive functioning states.

3.55 Quantitative EEG analysis

Further detailed analysis of EEG then occurred. EEG data was acquired at a sampling rate of 200 hertz (Hz). The data were exported to MATLAB for processing. Data were filtered between 1Hz and 40Hz, with a band-stop filter at 50Hz to remove any remaining mains interference. All filters were equiripple FIR filters. The independent component analysis methods were adapted from the FASTER algorithm [225] and used to remove gross ocular artefacts. The EEGLAB software suite was used for data visualization and manipulation. [226] Data was analysed in the longitudinal bipolar reference montage.

A number of time-frames were identified for investigative analysis. These were five minutes, one minute and 30 seconds prior to symptom onset along with 30 seconds post symptom onset. (Figure 3.8)

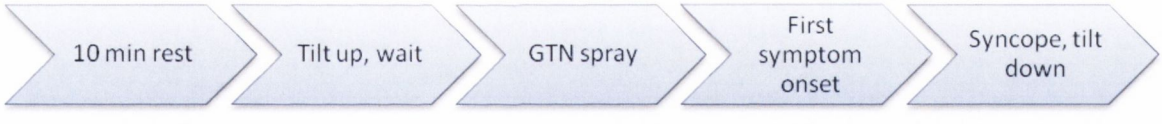


Figure 3.8: Timeframes of importance during combined HUT and EEG analysis

3.56 Statistics HUT

Data obtained using Finometer® Pro on blood pressure and heart rate was interpreted at one second intervals and converted to excel format prior to analysis of relevant timeframes as previously described in methods 3.33. Rest baseline values were averaged over the 10 minute rest period prior to HUT in this study to allow direct comparison with rest period of 10 minutes with EEG. This data was then transferred from excel to SPSS 16.0 for further analysis. Continuous variables were initially analysed for normality using

one sample Kolmogorov-Smirnov test. Data between 2 groups; Group 1 younger than 60 years of age and group 2 60 years of age or older was then analysed. Parametric data was analysed using students t-test and non-parametric data using the Mann-Whitney U test. Results are expressed as mean $\pm$ SD unless otherwise indicated. P value of < 0.05 (two-tailed) was considered as significant.

3.57 Statistics EEG

For analysis of EEG defined time-frames, the power spectrum was computed using Welch's method as implemented in MATLAB [227] and the mean power in the delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-25 Hz) and gamma (26-40 Hz) bands was calculated. To normalise these on a per-subject basis, these values were divided by the respective band values of the power spectrum calculated during the rest period. Thus the values were interpreted as the change in band power from rest in each of the time intervals of interest. These values were compared between subjects < 60 years of age and subjects > 60 years of age using 2-sample t-tests – which were performed in each frequency band, at each electrode, for each time interval, on the natural log-transformed power values. As powers are generally compared as ratios, the logarithmic transform was considered appropriate. Post-hoc correction for multiple comparisons was performed using the False Discovery Rate (FDR) method across channels. [228] The topographic distribution of the p-values were also taken into account when interpreting significance, such that spatially clustered significant electrodes were considered more likely to present true effects than single electrodes.

Chapter 4

Reported characteristics with VVS – Age related differences

Research Question: Do younger and older adults with VVS recall and report similar frequency and forms of prodrome prior to real time syncopal episodes?

Hypothesis: Younger adults report prodrome more frequently than older adults do with real time episodes of VVS and amnesia of symptom occurence in older adults may contribute to this difference.

4.1 Pathway of participant selection

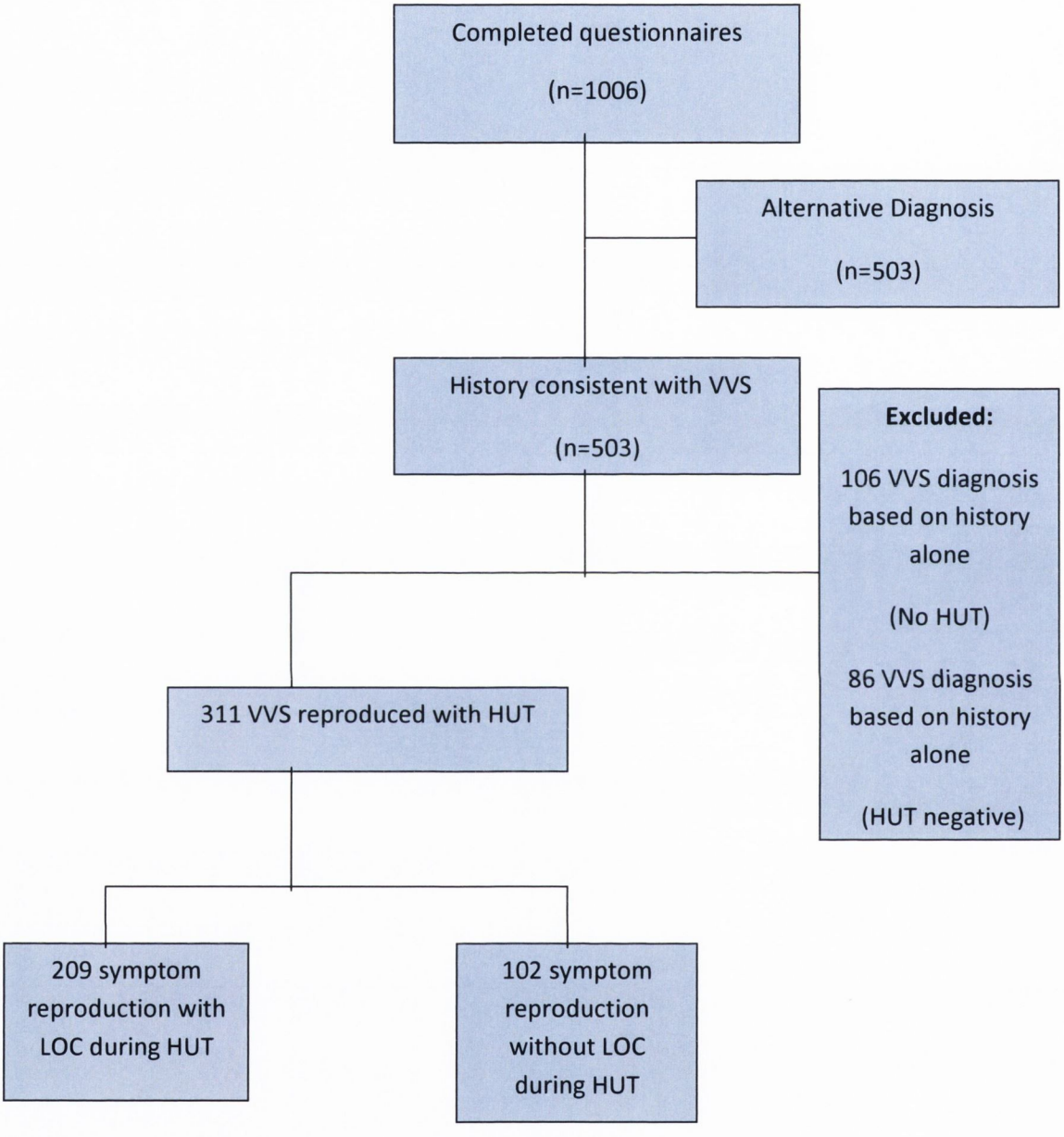


Figure 4.1: Pathway of those who completed a questionnaire and who proceeded to have reproduction of VVS with HUT

Questionnaires were completed by 1006 attendees to the unit. In total 506 (50.3%) were diagnosed with VVS. 311 (30.9%) had an end diagnosis of VVS which was confirmed with a positive HUT test (figure 4.1) and these individuals' questionnaires were analysed further.

4.2 Age distribution

Mean age (n=311) was 45.82 ± 20.08 years (range 16-87 years; median 45 years). Age distribution of those with confirmed VVS is depicted in Figure 4.2. In those attending the syncope unit there was a peak in age within the 2nd decade and again within the 5th and 6th decade. Eighty five percent of those with an end diagnosis of VVS had experienced a syncopal episode within 12 months of attendance. Subjects were then divided into groups, those < 60 years of age (n=219) (70%) and those ≥ 60 years of age (n=92) (30%). Mean age of those < 60 years of age was 35.42 ± 13.72 years (range 16-59; median 35 years) and mean age of those ≥ 60 years of age was 70.51 ± 7.18 years (range 60-87; median 70.5 years) (p=0.001).

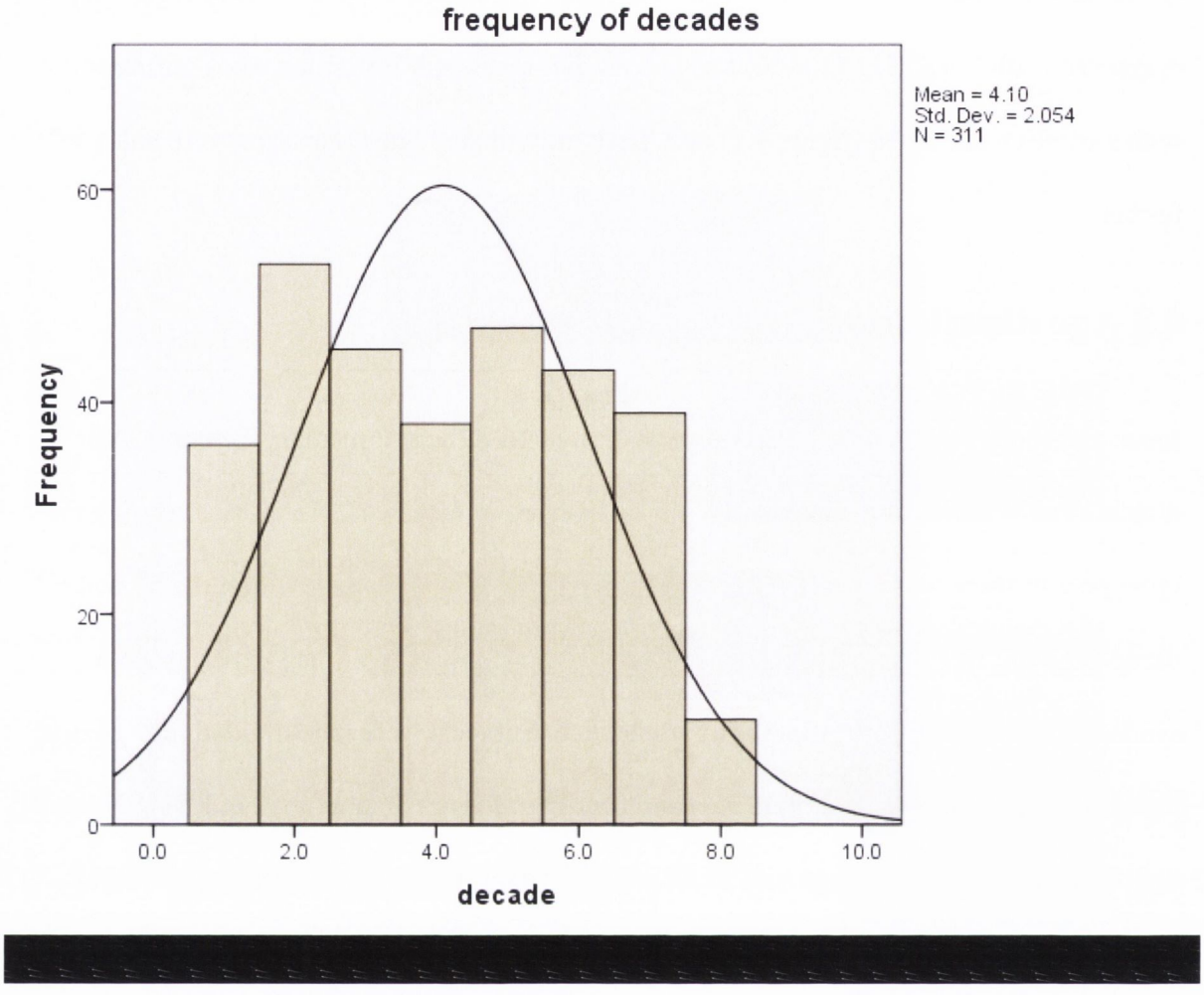


Figure 4.2: Histogram displaying age distribution per decade in those who had an end diagnosis of VVS (n=311). The eight columns (1-8) displayed represent increasing decades: 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79 and 80-89.

4.3 Baseline Characteristics

The baseline characteristics in both age-groups are shown in table 4.1. A low level of ischaemic heart disease (IHD) and cerebrovascular disease was reported in the older subjects in this study. Older subjects with VVS reported less history of migraine (16.3% vs 27.5%, p 0.04 OR 0.51 95% CI (0.27, 0.96)) or epilepsy (1.1% vs 5.5% p 0.12 OR 0.19 95% CI (0.02, 1.48)) compared to younger adults with VVS. However 7/12 (58%)

of those who reported a history of epilepsy at the time of questionnaire were later found to have an alternative diagnosis of VVS based on a positive HUT test and follow-up.

	<60 years (n=219)	*≥60 years (n=92)*	*P value*	*Odds ratio(95% CI) (Older versus younger)*
Female	141(64.7%)	61(66.3%)	0.78	1.08 (0.64,1.80)
History IHD	1(0.5%)	3(3.3%)	0.08	7.35 (0.75,71.60)
Previous MI	0(0%)	5(5.4%)	**0.002**	
Previous Epilepsy	12(5.5%)	1(1.1%)	0.12	0.19 (0.02,1.48)
Migraine	60(27.5%)	15(16.3%)	**0.04**	0.51 (0.27,0.96)
Cerebrovascular Disease	2(0.9%)	4(4.3%)	0.07	4.93 (0.89,27.41)
Family History of Syncope	54(24.7%)	3(3.3%)	**<0.001**	0.10 (0.03,0.34)
Witnessed LOC	194(89%)	66(72.5%)	**<0.001**	0.34 (0.18,0.63)
Aware had lost consciousness	154(70.6%)	67(72.8%)	0.70	1.11 (0.64,1.92)
Prodrome experienced with @ least one episode of LOC	180(84.1%)	60(69.8%)	**0.005**	0.44 (0.24,0.78)
Pre-syncope without LOC	166(76.1%)	48(52.2%)	**<0.001**	0.34 (0.11,0.57)
Unexplained Falls	87(39.9%)	33(36.3%)	0.55	0.85 (0.52,1.42)
Previous fracture with syncope	42(19.4%)	20(21.7%)	0.63	1.16 (0.64,2.08)
Antihypertensive medications	13(5.9%)	35(38%)	**<0.001**	9.73 (4.83,19.61)

Table 4.1: Baseline characteristics reported (Questionnaire) in those < 60 years and ≥ 60 years of age. [IHD Ischaemic heart disease; MI Myocardial infarction; LOC Loss of consciousness]

Older subjects were more likely to be on anti-hypertensives at the time of assessment (OR 9.73 95% CI (4.83, 19.61) $p < 0.001$) with the majority on diuretics followed by an ACE inhibitor or an Angiotensin 2 antagonist. (Table 4.2)

Anti-hypertensive medications	*<60 years (n=219)*	*≥60 years (n=92)*	*P value*	*Odds ratio(95% CI) (Older versus younger)*
B-blocker	6(2.7%)	3(3.3%)	0.73	1.19 (0.29,4.89)
Nitrates	0(0%)	1(1.1%)	0.30	
Diuretics	2(0.9%)	19(20.7%)	<0.001	28.24 (6.42,124.17)
ACE inhibitor	3(1.4%)	14(15.2%)	<0.001	12.92 (3.61,46.18)
Angiotension 2 inhibitor	3(1.4%)	14(15.2%)	<0.001	12.92 (3.61,46.18)
Calcium channel blocker	4(1.8%)	11(12%)	<0.001	7.29 (2.26,23.58)
Alpha blocker	1(0.5%)	5(5.4%)	0.01	12.53 (1.44,108.79)

Table 4.2: Antihypertensive medications in those <60 years and ≥60 years of age at time of presentation

Total number of lifetime syncopal episodes reported at time of presentation was significantly less in older adults in comparison to younger adults (Figure 4.3). One hundred and three (47%) of those < 60 years of age reported 6 episodes or more in comparison to 23 (25%) of those 60 years of age or older at time of attendance. Thirty three (15%) of those < 60 years reported more than 20 episodes in their lifetime at the time of assessment.

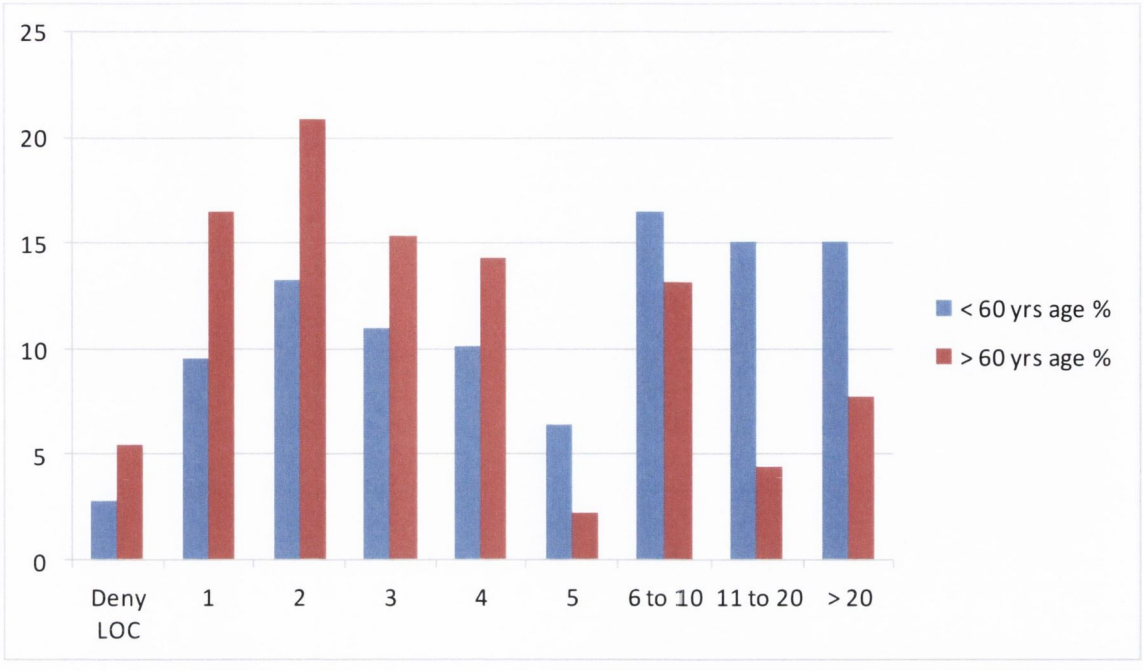


Figure 4.3: Syncope burden - number of total episodes of syncope reported at time of presentation to clinic. (n=219 < 60 yrs, n=92 ≥ 60 yrs)

Presyncopal episodes were also less frequent in those ≥ 60 years of age compared to younger adults, 48 (52%) vs 166 (76%) ($p<0.001$) OR 0.34 95% CI (0.11, 0.57). (Figure 4.4)

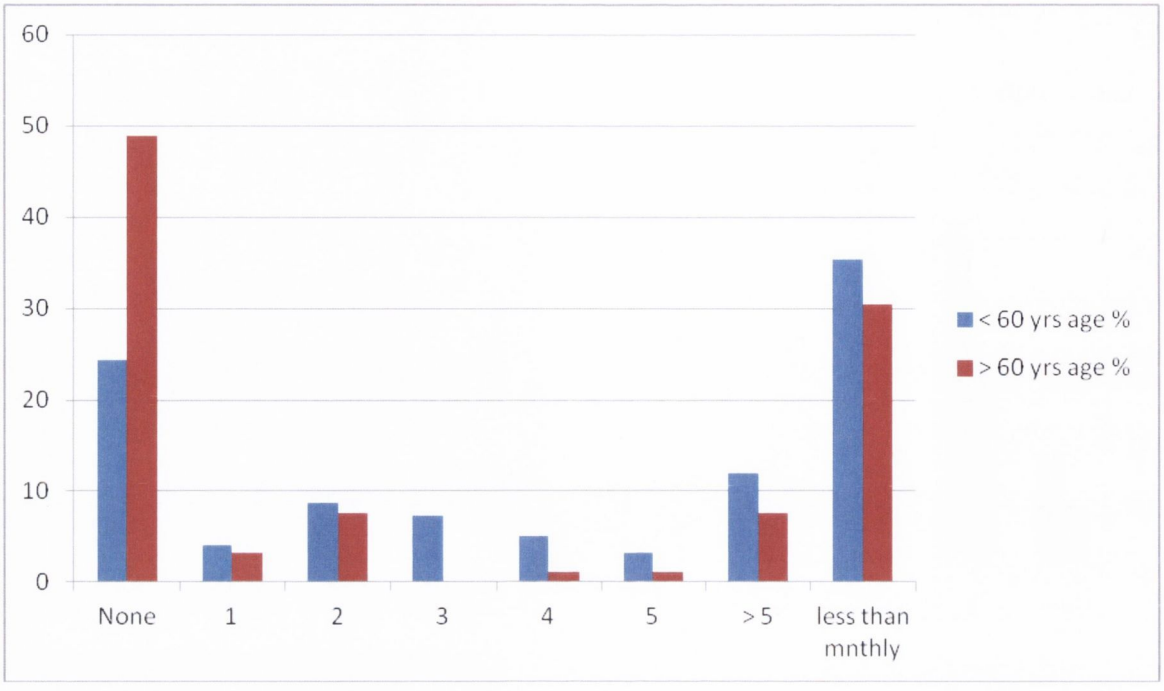


Figure 4.4: Presyncope burden – number of presyncopal episodes that did not proceed to loss of consciousness reported per month at time of presentation to clinic (n=219 < 60 yrs, n=92 ≥ 60 yrs)

A third of those 60 years of age or older, 28 (30.4%), reported a history of fainting in their teenage years or early twenties. Fifty nine (64%) of those 60 years of age or older reported that their first episode of syncope occurred at 50 years of age or older. The majority 149 (68%) of those < 60 years of age had their first syncopal episode before 30 years of age; most had first syncope between 10 and 20 years of age. (Figure 4.5)

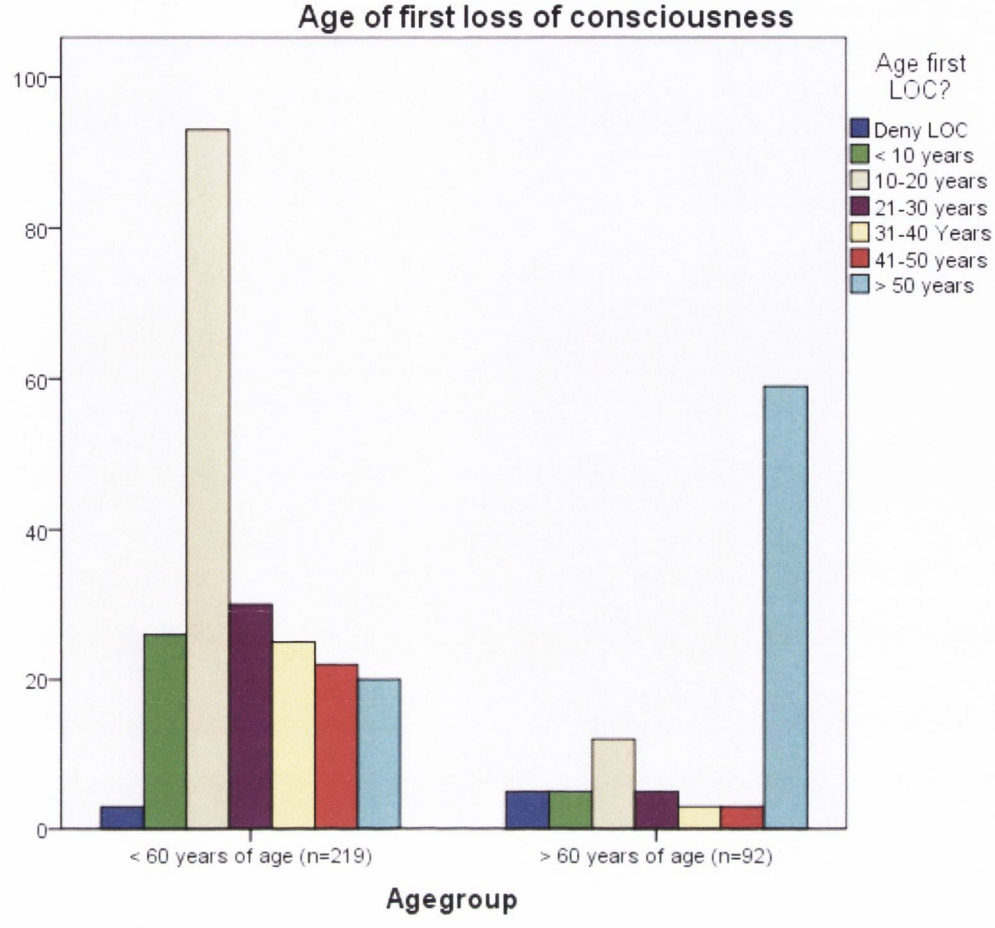


Figure 4.5: Age of first episode of loss of consciousness depicted in both age-groups

In those 60 years of age or older a peak in the same decade can also be seen in those who experienced syncope for the first time at a young age. Older subjects were ten times less likely to report a family history of syncope OR 0.10 95% CI (0.03, 0.34) $p < 0.001$.

4.4 Presenting Symptoms

Syncopal episodes were not witnessed with one third of older subjects (OR 0.34 95% CI (0.18, 0.63) $p < 0.001$) and prodrome was less common in older subjects (OR 0.44 95% CI (0.24, 0.78) $p = 0.005$). (Table 4.1)

	< 60 years of age (N=219)	*≥60 years of age (N=92)*	*P value*	*Odds ratio 95% CI (Older versus younger)*
Sweating	99 (45%)	29 (31.5%)	**0.023**	0.56 (0.33,0.90)
Palpitations	80 (36.7%)	9 (9.8%)	**<0.001**	0.19 (0.09,0.39)
Dizziness "Lightheadedness"	162 (74.3%)	54 (58.7%)	**0.006**	0.49 (0.30,0.82)
Chest pain	29 (13.3%)	1 (1.1%)	**<0.001**	0.07 (0.01,0.53)
Headache	37 (17%)	7 (7.6%)	**0.031**	0.40 (0.17,0.94)
Blurred Vision	75 (34.4%)	19 (20.7%)	**0.016**	0.50 (0.28,0.88)
Dark vision	44 (20.2%)	10 (10.9%)	**0.048**	0.48 (0.23,1.01)
Hearing disturbance	38 (17.4%)	4 (4.3%)	**0.002**	0.22 (0.07,0.63)
Paraesthesia "tingling sensation"	48 (22%)	5 (5.4%)	**<0.001**	0.20 (0.08,0.53)
A wish to lie down	116 (53.2%)	34 (37%)	**0.009**	0.54 (0.31,0.85)

Table 4.3: Significantly described prodromal symptoms more frequently recalled in those <60 years as opposed to those ≥60 years of age

	< 60 years of age (N=219)	*≥60 years of age (N=92)*	*P value*	*Odds ratio(95% CI)* *(Older versus younger)*
Nausea	78 (35.8%)	25 (27.2%)	0.142	0.67 (0.39,1.15)
Vomiting	15 (6.9%)	7 (7.6%)	0.82	0.89 (0.35,2.28)
Feeling Warm	90 (41.3%)	30 (32.6%)	0.152	0.69 (0.41,1.15)
Giddy sensation	17 (7.8%)	11 (12%)	0.243	1.61 (0.72,3.59)
"funny stomach sensation"	47 (21.6%)	25 (27.2%)	0.285	1.35 (0.77,2.38)
Yawning	11 (5%)	3 (3.3%)	0.489	0.63 (0.17,2.33)
Arm/Leg pain	20 (9.2%)	5 (5.4%)	0.363	0.57 (0.20, 1.56)
Neck/shoulder pain	22 (10.1%)	4 (4.3%)	0.118	0.41 (0.14,1.21)
Shortness of breath	41 (18.8%)	11 (12%)	0.14	0.58 (0.28,1.19)

Table 4.4: Prodromal symptoms equally described amongst those <60 years and those ≥ 60 years of age

4.5 Potential precipitating factors

Contributing trigger factors for syncope were for the most part similar in younger and older adults. Older subjects were more likely to report syncope in a church environment p = 0.002 which may simply reflect higher attendance in this environment. Older subjects were less likely to have VVS triggered by venepuncture or with the sight of blood OR 0.19 95% CI (0.06, 0.64) p = 0.002 or secondary to increased stress or anxiety OR 0.30 95% CI (0.13, 0.69) p = 0.003. (Table 4.5)

	< 60 years of age (N=219)	*≥60 years of age (N=92)*	*P value*	*Odds ratio(95%CI)* *(Older versus younger)*
Postprandial	17 (7.8%)	13 (14.1%)	0.112	1.84 (0.86,3.93)
Prolonged Standing	119 (54.6%)	47 (51.1%)	0.550	0.86 (0.53,1.40)
Church	32 (14.7%)	27 (29.3%)	**0.002**	2.43 (1.35,4.36)
Shopping environment	34 (15.6%)	7 (7.6%)	**0.058**	0.45 (0.19,1.05)
Crowded	52 (23.6%)	22 (23.9%)	0.991	1.00 (0.57,1.79)
Shower	26 (11%)	5 (5.4%)	0.098	0.42 (0.16,1.15)
Venepuncture/ Sight of blood	33 (15.1%)	3 (3.3%)	**0.002**	0.19 (0.06,0.64)
Alcohol	22 (10.1%)	2 (2.2%)	**0.018**	0.20 (0.05,0.86)
Micturition	9 (4.1%)	3 (3.3%)	0.718	0.79 (0.20,2.97)
Defecation	8 (3.7%)	3 (3.3%)	1.00	0.89 (0.23,3.43)
With exercise	20 (9.2%)	3 (3.3%)	0.095	0.34 (0.10,1.16)
Post exercise	24 (11%)	1 (1.1%)	**0.002**	0.09 (0.01,0.67)
Stress	47 (21.7%)	7 (7.6%)	**0.003**	0.30 (0.13,0.69)

Table 4.5: Precipitating factors reported to trigger VVS occurrence in those < and ≥ 60 years of age

For the majority in both age groups, syncope occurred when standing. However older subjects described fewer, episodes of syncope occurring directly when assuming an upright position from a seated position when compared to younger subjects OR 0.43 95% CI (0.25, 0.73) p = 0.001. Furthermore while older subjects did describe syncope in a seated position no significant difference was found when compared to younger subjects 43.5% vs 36.7% OR 1.33 95% CI (0.80, 2.17) p = 0.263. (Table 4.6)

	< 60 years of age (N=219)	*≥60 years of age (N=92)*	*P value*	*Confidence Interval*
Standing	174 (79.8%)	68 (73.9%)	0.251	0.71 (0.4,1.26)
From sit to stand	102 (46.8%)	25 (27.2%)	**0.001**	0.43 (0.25,0.73)
Seated position	80 (36.7%)	40 (43.5%)	0.263	1.33 (0.80,2.17)
Lying down	7(3.2%)	2(2.2%)	1.00	0.67 (0.13,3.30)

Table 4.6: Posture positioning at time of syncope occurrence reported in those < and ≥ 60 years of age

4.6 Consequences

Older subjects were less likely to report limb jerking OR 0.29 95% CI (0.12, 0.71) p = 0.005, fatigue OR 0.53 95% CI (0.38, 0.88) p = 0.013, and disorientation OR 0.30 95% CI (0.15, 0.62) p =0.001 than their younger counterparts but were more likely to report no symptoms at all at time of recovery from a syncopal event OR 1.66 95% CI (1.01, 2.78) p = 0.048. (Table 4.7) When questioned about awareness for loss of consciousness no significant differences were reported between younger and older subjects prior to HUT assessment OR 1.11 95% CI (0.64, 1.92) p = 0.70. (Table 4.1)

	< 60 years of age (N=219)	*≥60 years of age (N=92)*	*P value*	*Odds ratio (95% CI)* *(Older versus younger)*
Tongue-biting	8 (3.7%)	1 (1.1%)	0.216	0.28 (0.04,2.33)
Limb Jerking	42 (19.3%)	6 (6.5%)	**0.005**	0.29 (0.12,0.71)
Incontinence	19 (8.7%)	13 (14.1%)	0.152	1.72 (0.81,3.70)
Fatigue	107 (49.1%)	31 (33.7%)	**0.013**	0.53 (0.38, 0.88)
Disorientation	6 3(28.9%)	10 (10.9%)	**0.001**	0.30 (0.15,0.62)
No symptoms- Quick recovery	67 (30.7%)	39 (42.4%)	**0.048**	1.66 (1.01,2.78)

Table 4.7: Characteristics reported in those < and ≥ 60 years of age following an episode of VVS. Caution is needed in interpreting these results as less witness account is available in those ≥ 60 years of age and therefore recall in those ≥ 60 years of age may be less reliable despite normal MMSE results.

Neither group had a prevalence of reported unexplained falls above the other p = 0.55, nor in fracture rates with syncope or an unexplained fall p=0.63. However when fractures did occur older subjects did have more severe fractures (hip fractures) and were also more likely to have more than one fracture. (Table 4.8)

Fractures	*<60 years* *(n=219)*	*≥60 years* *(n=92)*	*P value*	*Odds ratio* *(95% CI)*
Wrist fracture	9(4.1%)	5(5.4%)	0.56	1.34(0.44,4.12)
Hip fracture	0(0%)	4(4.3%)	0.007	
Other fracture	31(14.2%)	15(16.3%)	0.61	1.18(0.60,2.31)

Table 4.8: Breakdown of fractures secondary to syncope reported at time of presentation to clinic

4.7 Summary of results

Older individuals had a greater number of unwitnessed syncopal episodes and reported fewer episodes of syncope at the time of presentation when compared to their younger counterparts. Older individuals with VVS reported less prodrome prior to syncope and were less likely to have their VVS precipitated by an emotional or stressful event. Vasovagal syncope occurred at any age with prolonged standing or sitting but occurred more commonly in younger individuals than older individuals when standing upright from a seated position. In this study, unexplained falls and injuries secondary to VVS were reported equally across both agegroups but the severity of injury sustained was greater in older individuals when it did occur.

Chapter 5

Haemodynamic parameters in VVS – Age related differences

Research Question: Do younger and older adults with VVS display similar haemodynamic characteristics during HUT at the time of first symptom or prodrome onset?

Hypothesis: younger adults have a higher prevalence of prodromal symptoms in VVS due to haemodynamic differences which are found at time of first symptom onset.

5.1 Pathway to subjects undergoing HUT

Subjects who completed the previously described questionnaire and for whom ECG, relevant cardiac investigation, active stand for postural hypotension or carotid sinus massage where appropriate, did not reveal a diagnosis, were then invited to complete a HUT table test. All subjects underwent an IPHUT which has been previously described in Methods 3.32. Relevant clinical observations were recorded as has been described in Methods Chapter 3.33. One second averaging was used for calculation of values. Values for baseline data, time of symptoms and syncope point were calculated as per Methods chapter 3.33. The test was considered positive if Syncope or pre-syncope were reproduced during HUT. Subject groups were divided into Group 1; < 60 yrs of age and Group 2; ≥ 60 yrs of age.

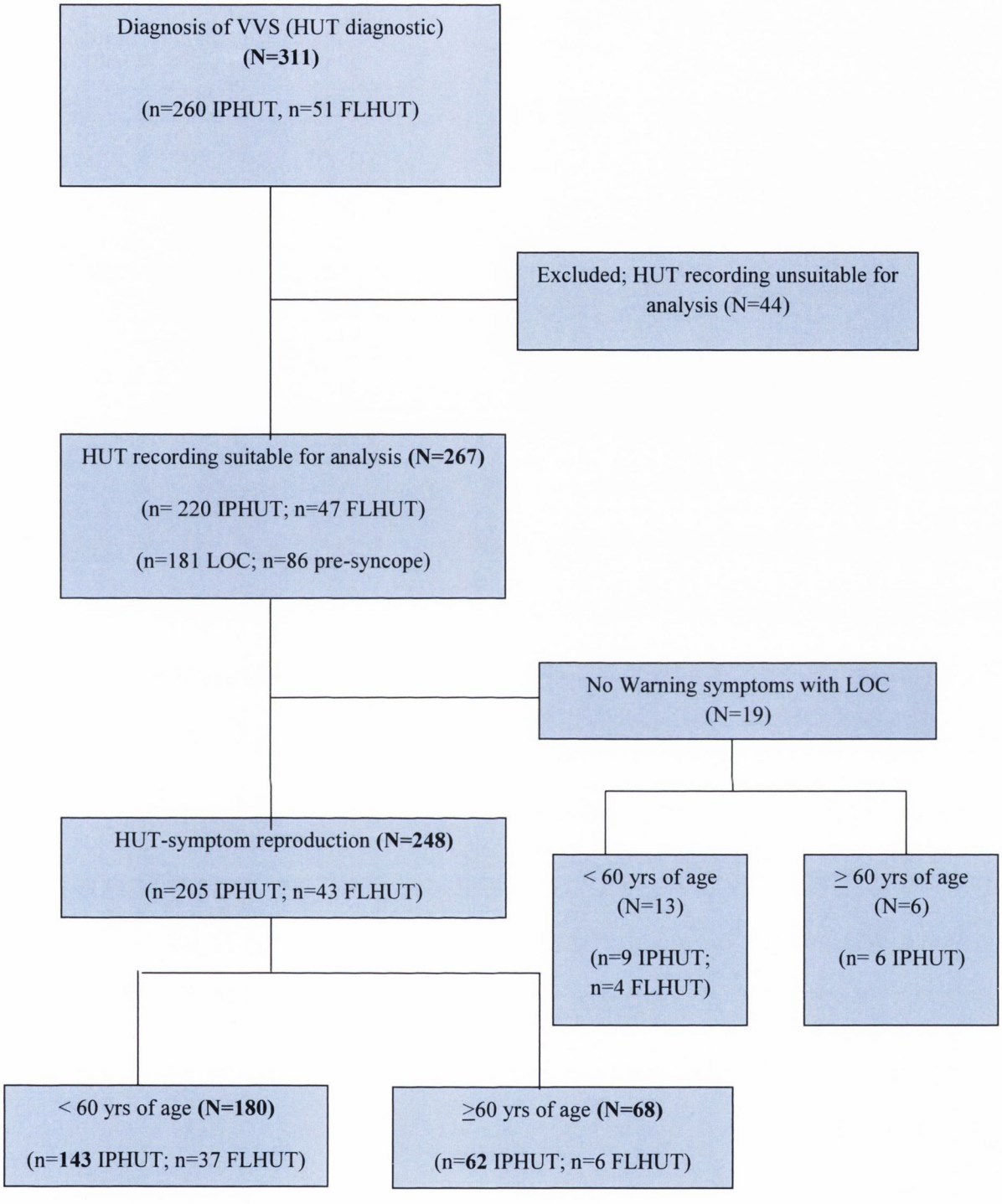


Figure 5.1: Reproduction of symptoms during HUT in different age-groups

(IPHUT – Italian protocol HUT; FLHUT – Front loaded HUT)

5.2 Results: Reproductive symptoms during HUT

5.21 Pre analysis IPHUT versus FLHUT

IPHUT is 35 minutes in duration with 400mcg of sublingual GTN @ 20 minutes. FLHUT is 23 minutes in duration with 800mcg of sublingual GTN given @ 3 minutes. In order to compare differences such as time to symptoms when analysing both age groups, differences between type of tilt test utilised needs to be addressed.

Total n=311	**<60 years (n=219)**	**≥60 years (n=92)**	**Total**
IPHUT	173 (79%)	87 (95%)	260
FLHUT	46 (21%)	5 (5%)	51

Table 5.1 Breakdown of those who had reproduction of symptoms by means of IPHUT and FLHUT.

79% of those < 60 years of age had an IPHUT as opposed to 95% of those ≥60 years of age. (**p=0.001**) OR 4.63 95% CI (1.78, 12.06) Similar breakdown was assessed following exclusion of unsuitable files and those who did not develop any symptoms during HUT.

Analysis of those who developed reproductive symptoms during HUT (n=248)

Total n=248 (symptoms during HUT)	<60 years (n=180)	≥60 years (n=68)	Total
IPHUT	143 (79%)	62 (91%)	205
FLHUT	37 (21%)	6 (9%)	43

Table 5.2: Breakdown of those who have reproduction of symptoms by means of IPHUT and FLHUT suitable for analysis

79% of those < 60 years of age had an IPHUT as opposed to 91% of those ≥60 years of age. (**p=0.03**) OR 2.67 95% CI (1.07, 6.67) The difference in duration of testing between both protocols would affect time to symptom analysis so age related haemodynamic data from IPHUT and FLHUT are presented separately.

5.22 IPHUT Analysis

Characteristics of those who developed reproductive symptoms on IPHUT (n=205) are shown in table 5.3.

	< 60 years of age (N=143)	≥60 years of age (N=62)	P value
Mean age years (median)	35.22 ± 14.20 (32)	70.23 ± 6.75 (70.5)	0.001 (MWU)
Time to symptoms(seconds)	1064.43 ± 479	1398.72 ± 396.43	**0.001** (MWU)

Table 5.3 Age and time to symptoms in different age groups (n=205) IPHUT

	< 60 years (N=143)	≥60 years (N=62)	P value
Baseline SBP (mmHg)	131.03±18.34	156.03±22.32	**0.001 (MWU)**
Baseline DBP (mmHg)	73.90±11.29	78.31±10.00	**0.005 (MWU)**
SBP at symptom onset (mmHg)	107.70±24.83	102.29±29.80	**0.024 (MWU)**
DBP at symptom onset (mmHg)	71.34±15.29	65.55±17.56	**0.006 (MWU)**
Decrease in SBP from baseline to time of symptom onset (mmHg)	23.33±28.56	53.74±35.43	**0.001 (MWU)**
Decrease in DBP from baseline to time of symptom onset (mmHg)	2.56±17.40	12.76±17.30	**0.001 (t test)**
Rate of change of SBP to symptom onset (mmHg/secs)	0.024±0.041	0.041±0.034	**0.001 (MWU)**
Rate of change of DBP to symptom onset (mmHg/secs)	0.001±0.018	0.006±0.009	**0.001 (MWU)**
Baseline HR (bpm)	69.16±11.20	66.51±10.10	0.10 (t test)
HR at time of symptom onset (bpm)	94.78±23.73	82.71±19.92	**0.001 (t test)**
Increase in heart rate from baseline to symptom onset (bpm)	25.61±20.64	16.19±16.32	**0.001 (t test)**
Rate of heart rate change to symptom onset (bpm/secs)	0.04± 0.06	0.02 ± 0.08	**0.001 (t test)**

Table 5.4 Blood pressure (BP) and heart rate (HR) differences in those < and ≥ 60 years of age at symptom onset on IPHUT (n=205)

5.23 FLHUT Analysis

Characteristics of those who developed reproductive symptoms on FLHUT (n=43) are shown in table 5.5

	< 60 years of age (N=37)	≥60 years of age (N=6)	P value
Mean age years (median)	38.7 ± 11.79 (40)	65.17 ± 3.55 (65.5)	0.001 (t-test)
Time to symptoms(seconds)	603.95 ± 305.37	682.33 ± 267.91	0.54 (t-test)

Table 5.5 Age and time to symptoms in different age groups (n=43) FLHUT

	< 60 years of age (N=37)	≥60 years of age (N=6)	P value
(Baseline SBP (mmHg)	133.03±15.43	157.30±24.10	0.056 (t-test)
Baseline DBP (mmHg)	76.10±9.65	83.56±10.21	0.14 (t-test)
SBP at symptom onset (mmHg)	107.73±29.42	105.33±48.17	0.91 (t-test)
DBP at symptom onset (mmHg)	72.57±17.80	69.00±24.97	0.75 (t-test)
Decrease in SBP from baseline to time of symptom onset (mmHg)	25.30±30.30	51.97±40.73	0.17 (t-test)
Decrease in DBP from baseline to time of symptom onset (mmHg)	3.54±15.62	14.56±21.62	0.28 (t-test)
Rate of change of SBP to symptom onset (mmHg/secs)	0.056±0.131	0.07±0.05	0.67 (t-test)
Rate of change of DBP to symptom onset (mmHg/secs)	0.002±0.025	0.015±0.022	0.22 (t-test)
Baseline HR (bpm)	69.62±11.31	66.55±11.08	0.55 (t-test)
HR at time of symptom onset (bpm)	96.54±24.47	90.67±16.23	0.47 (t-test)
Increase in heart rate from baseline to symptom onset (bpm)	26.93±20.08	24.12±8.17	0.56 (t-test)
Rate of heart rate change to symptom onset (bpm/secs)	0.054±0.437	0.039±0.0186	0.18 (t-test)

Table 5.6 Blood pressure (BP) and heart rate (HR) differences in those < and ≥ 60 years of age at symptom onset on FLHUT (n=43)

5.3 Results: Syncope during HUT

5.31 Pre analysis IPHUT versus FLHUT

Total n=181 (syncope during HUTT)	<60 years (n=125)	≥60 years (n=56)	Total (n=181)
IPHUT	104 (83.2%)	52 (92.9%)	156
FLHUT	21 (16.8%)	4 (7.1%)	25

Table 5.7 Proportion of those who developed syncope by type of HUT which were suitable for analysis

83.2 % of those < 60 years of age had an IPHUT as opposed to 92.9% of those >60 years of age. (**p=0.10**) OR 2.63 95% CI (0.86, 8.06) No significant difference was found between IPHUT and FLHUT in analysing parameters of those who developed syncope. (n=181)

5.32 HUT Analysis

	< 60 years of age (N=125)	≥60 years of age (N=56)	P value
Mean Age years (median)	34.4 ± 13.2 (32)	70.59 ± 7.29 (71)	0.001 (MWU)
Time to syncope (seconds)	1311.09 ± 480.72	1505.3 ± 562.44	0.029 (MWU)

Table 5.8 Age and time to syncope in different age groups (n=181)

	< 60 years of age (N=125)	≥60 years of age (N=56)	P value
Baseline SBP (mmHg)	131.72 ± 13.13	156 ± 23.04	**< 0.001 (t test)**
Baseline DBP (mmHg)	74.07 ± 11.66	79.34 ± 10.12	**0.004 (t test)**
SBP at time of syncope (mmHg)	59.86 ± 15.92	58.86 ± 12.75	0.723 (MWU)
DBP at time of syncope (mmHg)	37.06 ± 11.66	39.86 ± 9.5	0.118 (t test)
Decrease in SBP from baseline to time of syncope (mmHg)	71.86 ± 18.04	97.19 ± 26.08	**0.001 (t test)**
Decrease in DBP from baseline totime of syncope (mmHg)	37 ± 13	39.5 ± 10.46	0.173 (MWU)
Rate of change of SBP to syncope (mmHg/secs)	0.074 ± 0.094	0.079 ± 0.06	**0.006 (MWU)**
Rate of change of DBP to syncope (mmHg/secs)	0.04 ± 0.06	0.03 ± 0.03	0.595 (MWU)
Baseline HR (bpm)	68.43 ± 9.67	66.40 ± 10.87	0.211 (t test)
HR at time of syncope (bpm)	47.17 ± 21.35	57.96 ± 21.34	**0.002 (t test)**
Decrease in HR from baseline to time of syncope (bpm)	21.86 ± 22	8.43 ± 21.61	**0.001 (t test)**
Rate of HR change to time of syncope (bpm/secs)	0.03 ± 0.104	0.008 ± 0.028	**0.001 (MWU)**

Table 5.9 Blood pressure (BP) and heart rate (HR) differences in those < and ≥ 60 years of age who developed syncope (n=181)

5.4 Summary of results

Older individuals who experience VVS take a longer time to develop symptoms and syncope than younger individuals. Although older indivuals have a higher baseline systolic blood pressure they develop symptoms at a lower level of systolic blood pressure than younger individuals. There is however, no significant difference in the level of systolic blood pressure at the point at which syncope occurs between both age groups. The rate of drop in systolic blood pressure is faster in older individuals. Younger subjects with VVS develop a tachycardic response which is greater than their older counterparts at time of symptom onset but have an increased cardioinhibitory response at time of syncope which occurs at a faster rate than older subjects.

Chapter 6

Amnesia for Loss of Consciousness in Vasovagal Syncope

Research Question: Does amnesia for loss of consciousness (A-LOC) occur in VVS and is this solely an age-related phenomenon?

Hypothesis: A-LOC does occur in VVS and is more prevalent in older adults than younger adults and contributes to lack of prodrome recall and unexplained falls.

(a) What is the prevalence of A-LOC in VVS?

(b) Do baseline characteristics differ between those without and those with A-LOC?

(c) Do haemodynamic changes contribute to the absence or presence of A-LOC?

(d) What are the predictors for occurrence of A-LOC with VVS?

6.1 Background

Consecutive patients were recruited prospectively over a thirty month period from a dedicated Syncope unit in a tertiary referral teaching hospital as previously described in methods chapter 3.11. A diagnosis of VVS was established when reproduction of prodrome or syncope experienced during real-time syncope occurred with HUT testing. The Italian Protocol HUT (IPHUT) was used for investigation. If this test was negative, patients returned for a Front loaded HUT. (FLHUT) These protocols have been described previously in methods chapter 3. When loss of consciousness occurred, the tilt bed was immediately returned to a supine position. The method by which the presence of A-LOC was ascertained has been previously described in methods chapter 3.41. **(Appendix 4)**

6.2 Pathway to subject selection

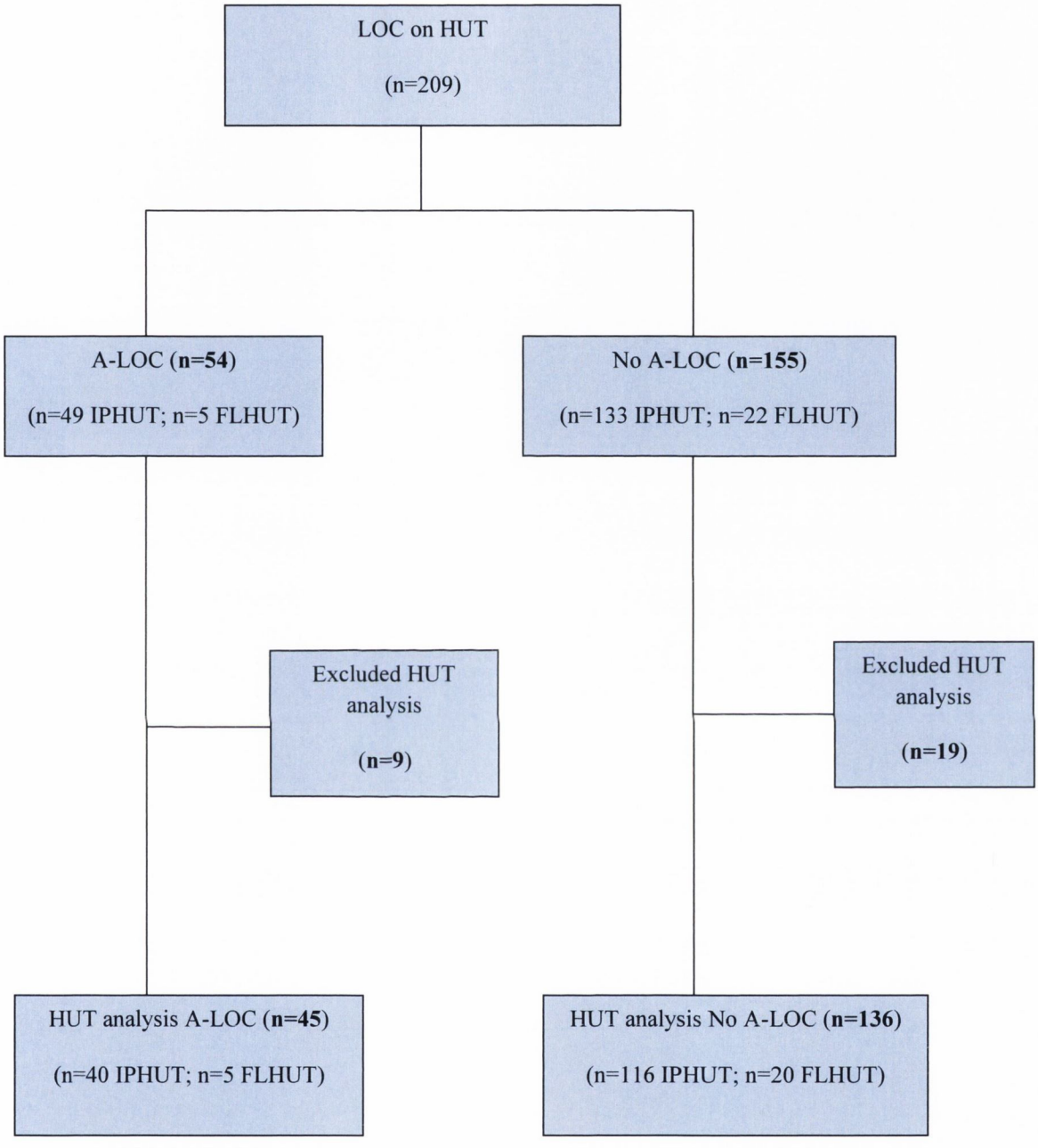


Figure 6.1: Flowchart demonstrating the breakdown of those without A-LOC and those with A-LOC following HUT and numbers excluded from HUT data analysis

6.3 Prevalence of A-LOC

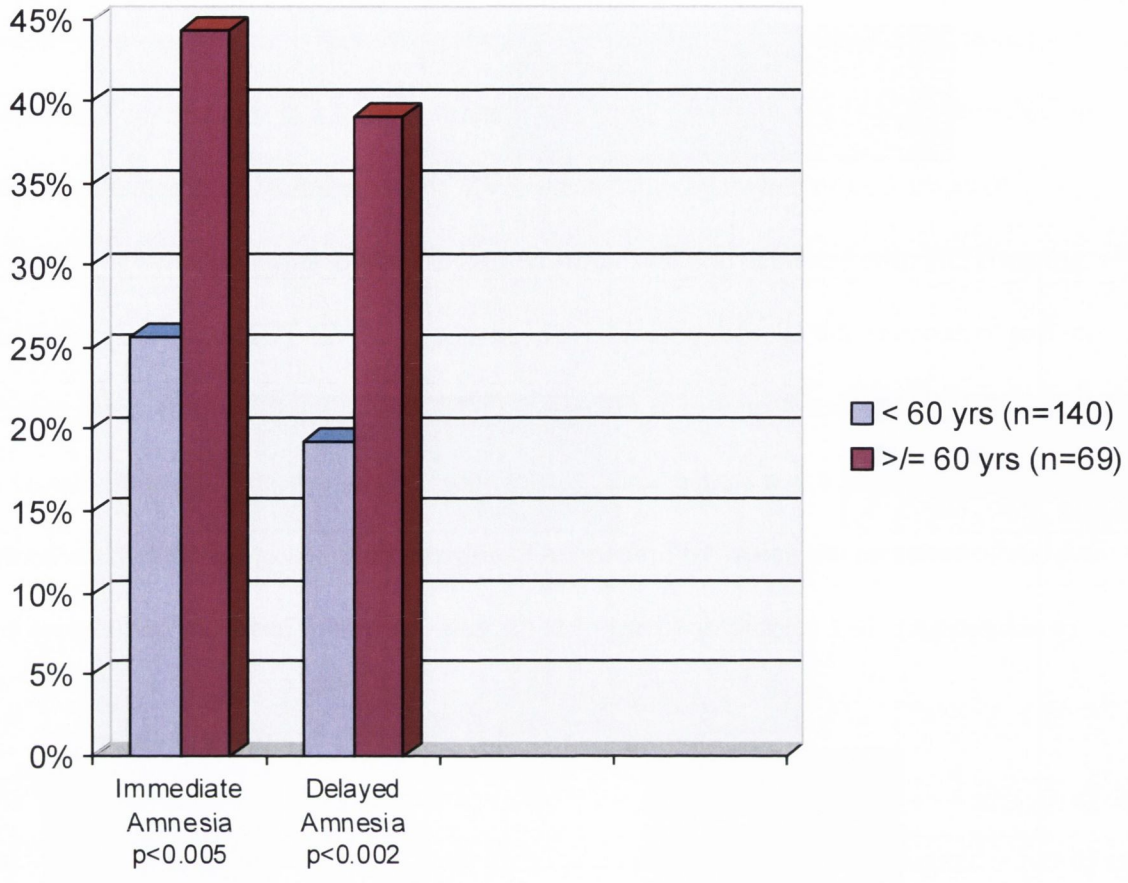


Figure 6.2: Prevalence of A-LOC in different age-groups.

31 (44.9%) of those ≥ 60 years of age had immediate A-LOC as opposed to 36 (25.7%) of those < 60 years. (p=0.005 OR 2.35 95% CI (1.28, 4.33). 27 (39.1%) of those ≥ 60 years of age had delayed A-LOC as opposed to 27 (19.3%) of those < 60 years of age (p=0.002 OR 2.68 95% CI (1.42, 5.10)

6.4 Baseline characteristics of those without and those with A-LOC

	No A-LOC (n=155)	*A-LOC (n=54)*	*P value*
Female sex	103 (66.5%)	34 (63%)	0.64
Mean age years	43.63 ± 19.56	54.98 ± 22.40	**0.003**
IPHUT	133 (86%)	49 (90%)	0.352
Reported prodrome with real-time syncopal episodes	132 (85.2%)	34 (63%)	**0.001**
History of reported unexplained falls	60 (39%)	24 (44%)	0.48
History of fracture with syncope	26 (17%)	17 (30.9%)	**0.03**
History of IHD	2 (1.3%)	2 (3.6%)	0.317
MMSE **(age ≥ 60 years)(n=69)**	28.67 ± 1.57	28.74 ± 1.94	0.404

Table 6.1 Clinical characteristics of those without A-LOC and A-LOC (N=209)

	No A-LOC (n= 26 fractures)	*A-LOC (n=17 fractures)*
Wrist Fracture (n=10)	5	5
Hip Fracture (n=3)	1	2
Other fracture (n=33)	20	13(overlap)

Table 6.2 Types of fractures obtained in those without A-LOC and those with A-LOC

	No A-LOC (n=155)	*A-LOC (n=54)*	*P value*	*Odds ratio 95% CI* *(No A-LOC versus A-LOC)*
Awareness of LOC with real time syncopal episodes (Yes)	125 (81.7%)	30 (54.5%)	**0.001**	3.72 (1.90,7.3)
Real time syncopal episodes witnessed (Yes)	134 (87.6%)	41 (74.5%)	**0.03**	2.40 (1.11,5.21)
Episodes of Pre-syncope experienced without LOC (yes)	107 (69.9%)	28 (50.9%)	**0.011**	2.24 (1.19,4.22)

Table 6.3 Previously reported characteristics with real time syncope (n=209)

	No A-LOC (n=155)	*A-LOC (n=54)*	*P value*	*Odds ratio 95% CI (No A-LOC versus A-LOC)*
Sweating	66 (43.1%)	19 (34.5%)	0.266	1.44 (0.76,2.73)
Palpitations	48 (31.4%)	10 (18.2%)	0.061	2.05 (0.96,4.43)
Dizziness	110 (71.9%)	31 (56.4%)	**0.035**	1.98 (1.04,3.75)
Nausea	62 (40.5%)	14 (25.5%)	**0.047**	2.00 (1.00,3.96)
Feeling Warm	61 (39.9%)	21 (38.2%)	0.826	1.00 (0.57,2.02)
Giddy sensation	14 (9.2%)	5 (9.1%)	0.990	1.00 (0.35,2.94)
Chest pain	13 (8.5%)	7 (12.7%)	0.361	0.64 (0.24,1.69)
"funny stomach sensation"	40 (26.1%)	14 (25.5%)	0.92	1.00 (0.51,2.10)
Yawning	7 (4.6%)	1 (1.8%)	0.684	2.58 (0.31,21.54)
Headache	23 (15%)	6 (10.9%)	0.449	1.45 (0.55, 3.76)
Blurred Vision	49 (32%)	12 (21.8%)	0.154	1.69 (0.82,3.48)
Dark vision	30 (19.6%)	4 (7.3%)	**0.034**	3.11 (1.04, 9.28)
Hearing disturbance	20 (13.1%)	6 (10.9%)	0.677	1.23 (0.46,3.24)
Paraesthesia	20 (13.1%)	7 (12.7%)	0.948	1.03 (0.41,2.59)
Arm/Leg pain	9 (5.9%)	4 (7.3%)	0.748	0.78 (0.24,2.70)
Neck/shoulder pain	11 (7.2%)	4 (7.3%)	1.000	0.98 (0.30,3.24)
Shortness of breath	23 (15%)	6 (10.9%)	0.449	1.45 (0.55,3.76)
A wish to ly down	82 (53.6%)	24 (43.6%)	0.205	1.49 (0.8,2.77)

Table 6.4 Individual prodromal symptoms reported by subjects without and with A-LOC with real time syncopal episodes (n=209)

	No A-LOC (n=155)	*A-LOC (n=54)*	*P value*	*Odds ratio 95% CI (No A-LOC versus A-LOC)*
Postprandial	18 (11.8%)	6 (10.9%)	0.87	1.08 (0.41,2.90)
Standing	73 (47.7%)	32 (58.2%)	0.183	0.66 (0.35, 1.22)
Church	29 (19%)	10 (18.2%)	0.9	1.05 (0.48,2.33)
Shopping	16 (10.5%)	5 (9.1%)	0.773	1.17 (0.40,3.35)
Crowded	34 (22.2%)	12 (21.8%)	0.951	1.02 (0.49,2.16)
Home	40 (26.1%)	11 (20%)	0.364	1.42 (0.67,3.01)
Shower	14 (9.2%)	5 (9.1%)	0.99	1.00 (0.35,2.94)
Venepuncture/ Sight of blood	25 (16.3%)	4 (7.3%)	0.115	2.49 (0.83,7.51)
Micturition	9 (5.9%)	1 (1.8%)	0.297	3.38 (0.42,27.27)
Defecation	5 (3.3%)	3 (5.5%)	0.438	0.59 (0.14,2.54)

Table 6.5 Individual precipitating factors previously reported with real time syncopal episodes in those without and those with A-LOC

6.5 Haemodynamic parameters in those without and those with A-LOC

6.51 Pre-analysis IPHUT versus FLHUT

Total n=181 *(syncope during HUT)*	*No A-LOC (n=136)*	*A-LOC (n=45)*	*Total*
IPHUT	116 (85%)	40 (89%)	156
FLHUT	20 (11%)	5 (15%)	25

Table 6.6 Breakdown of those without and with A-LOC who developed syncope by means of IPHUT and FLHUT (suitable for analysis)

85 % of those without A-LOC had an IPHUT as opposed to 89% of those with A-LOC. (**p=0.63**) OR 1.38 95% CI (0.49, 3.92) No significant difference was found between IPHUT and FLHUT in those who developed syncope. (n=181)

6.52 HUT analysis

	No A-LOC (n=121)	*A-LOC (n=41)*	*P value*
Time to symptom onset (seconds)	1045 ± 500	1242 ± 409	**0.037**
Time from symptom onset to syncope (seconds)	299 ± 394	237 ± 356	0.28
SBP @ symptom onset (mmHg)	108.27 ± 26.88	99.74 ± 34.16	0.10
HR @ symptom onset (bpm)	91.94 ± 21.6	82.95 ±20.2	**0.02**

Table 6.7 Analysis of symptom onset during HUT in those without A-LOC and with A-LOC (n=162)

	No A-LOC (n=136)	*A-LOC (n=45)*	*P value*
Time to syncope (seconds)	1318 ± 500	1531 ± 528	**0.05**

Table 6.8 Time to syncope in those without A-LOC and those with A-LOC (n=181)

	No A-LOC (n=136)	A-LOC (n=45)	P value
Baseline SBP (mmHg)	138 ± 19	143 ± 23	0.173 (MWU)
Baseline DBP (mmHg)	75.83 ± 10.31	75.33 ± 14.46	0.559 (MWU)
SBP at time of syncope (mmHg)	58.72 ± 14.62	62.07 ± 15.97	0.218 (MWU)
DBP at time of syncope (mmHg)	36.73 ± 10.86	41.56 ± 11.09	**0.012** (t-test)
Decrease in SBP from baseline to syncope (mmHg)	79.31 ± 22.24	80.84 ± 28.48	0.743 (t-test)
Decrease in DBP from baseline to syncope (mmHg)	39.10 ± 11.37	33.78 ± 14.19	0.04 (MWU)
Rate of change in SBP from baseline to syncope (mmHg/sec)	0.08 ± 0.09	0.06 ± 0.02	0.21 (MWU)
Rate of change in DBP from baseline to syncope (mmHg/sec)	0.04 ± 0.004	0.02 ± 0.01	**0.015** (MWU)
Baseline HR (bpm)	68.61 ± 9.34	65.35 ± 11.8	0.096 (t test)
HR at time of syncope (bpm)	48.17 ± 20.12	57.58 ± 25.44	**0.04** (MWU)
Decrease in HR from baseline to syncope (bpm)	20.44 ± 21.77	7.77 ± 22.81	**0.002** (t test)
Rate of change in HR from baseline to syncope (bpm/sec)	0.029 ± 0.101	0.007 ± 0.212	**0.001** (MWU)

Table 6.9 Blood pressure and heart rate parameters in those without A-LOC and with A-LOC (n=181)

6.6 Predictors for A-LOC in VVS

	B	*S.E.*	*Wald*	*df*	*Significance*	*Exp(B)*	*CI (Lower)*	*CI (Upper)*
Time to symptom onset (secs)	0.001	0.001	2.997	1	0.083	1.001	1.000	1.002
Change in HR from baseline to syncope (BPM)	-0.026	0.009	7.960	1	**0.005**	0.974	0.957	0.992
Prior Prodrome	-1.359	0.49	9.123	1	**0.003**	0.257	0.106	0.621

Table 6.10 Binary logistic Regression analysis with A-LOC as a dependent factor; Backward Wald: Step 5. Variables entered on step 1: Age, Prior prodrome, Prior fracture, Time to symptom onset, Time to syncope, Syncope HR, Change in HR from baseline to syncope, Rate of change in HR from baseline to syncope. This table shows results from step 5 logistic regression.

6.7 Results Summary

Of 1006 patients who completed questionnaires, 209 lost consciousness on HUT with an end diagnosis of VVS; (182 IPHUT and 27 FLHUT). In those who went on to lose consciousness (n=209); Mean age was 43.31 ± 20.78 (median age 44 ± 20.78) (range 16-87) years and 137 (66%) were female. 155 (74%) recalled and were aware of at least one episode of loss of consciousness while 54 (26%) denied or were unsure they had ever lost consciousness in their lifetime.

No disagreement occurred between observers on the presence or absence of LOC during HUT in the clinic. The overall prevalence of delayed A-LOC during HUT in the clinic was 54/209 (26%). Delayed A-LOC was more common in patients 60 years of age or older in comparison to those younger than 60 years (p=0.002) OR 2.68 95% CI (1.42, 5.10). Baseline characteristics of those with A-LOC and those without A-LOC are shown in Table 6.1. Mean age of those with A-LOC was 54.98 ± 22.40 yrs (median age 59.5 ± 22.41) (range 16-83 yrs). Mean age of those without A-LOC was 43.63 ± 19.56 yrs (median 41 ± 19.56 yrs) (range 16-87 yrs). Patients with A-LOC on HUT reported less awareness of prodrome with prior syncopal episodes. (p=0.001) and a higher incidence of fracture rate (p=0.03). In those who were 60 years of age or older, no difference in cognition was found between those with A-LOC and those without A-LOC.

Haemodynamic parameters of those patients who lost consciousness on HUT testing were further analysed. Of 209 patients, 28 were excluded from analysis. Reasons for exclusion were missing data, unsuitable quality of data for analysis, and insufficient dataset for symptoms. The remaining 181 datasets were suitable for analysis of whom 156 (86%) of patients had a positive IPHUT and 25 (14%) a positive FLHUT. Nineteen subjects had sudden LOC with no warning symptoms during HUT. Patients with A-LOC recognised

symptoms of hypotension later than those with no A-LOC. ($p=0.037$) No significant difference occurred in the time from symptom onset to time of syncope in those with A-LOC and those with no A-LOC. There was no significant difference in the degree of hypotension or in the rate at which hypotension occurred in order to achieve syncope, in those with A-LOC and those without A-LOC. Likewise the systolic blood pressure at the time of syncope was similar in both groups. Those with no A-LOC were found to have a slower heart rate at time of syncope ($p=0.04$) than those with A-LOC. Both the reduction in heart rate ($p=0.002$) and the rate at which this reduction occurred ($p=0.001$) was significantly greater in those with no A-LOC in comparison to those with A-LOC.

Logistic regression analysis was performed with A-LOC as the dependent variable. Age was not shown to be an independent predictor for A-LOC. Lack of a reported prodrome with prior syncopal episodes along with lack of a documented bradycardia on HUT were independent predictors for A-LOC, with increased time to symptom onset during HUT having a trend in significance for prediction of A-LOC.

Chapter 7

Qualitative and quantitative Electroencephalography during tilt induced Vasovagal Syncope

Research Question: Do changes in cortical activity occur prior to or at time of prodrome onset and if so does the degree of change differ, between younger and older adults?

Hypothesis: Cortical activity change ocurrs independent or prior to haemodynamic change and may contribute to absence or presence of prodrome and A-LOC in younger and older adults with VVS.

Results of EEG and HUT subgroup analysis

The methodology for data acquisition, data analysis and EEG protocol have been previously described in Methods section 3.5

7.1 Demographics

Fifty six subjects participated in the study (mean age 47±20 years, range 17-85), 23 male and 33 female. Head up tilt table test was performed for the first time at time of study, in all subjects. Reproductive VVS occurred in 22 subjects (39%). All 22 were suitable for data analysis. Thirty four other subjects with either normal HUT tests or confirmation of an alternative diagnosis were excluded from further analysis. Of these six subjects (11%) developed symptoms with or without presyncope during HUT but did not proceed to syncope, one developed postural orthostatic tachycardia syndrome, one asymptomatic orthostatic hypotension and one hyperventilation and anxiety symptoms. A further subject had a psychogenic response with a corresponding normal EEG. One subject had generalised spike wave activity on baseline EEG consistent with an epileptic focus and responded well to treatment for epilepsy on subsequent follow-up. Twenty three subjects (41%) had a normal HUT table test with no reproduction of symptoms at time of testing.

Analysis was performed on those who developed full reproductive VVS. The baseline demographics of those who experienced reproductive VVS during HUT are shown in table 7.1. Fourteen subjects were younger than 60 years of age (mean age 38 ± 13)(median age 37.5) and 8 subjects were > 60 years of age (mean age 73 ± 8.5)(median age 74.5) (p=0.001).

Age	*sex*	*Prior no. of syncopal episodes recalled*	*Anti-hypertensive medication (y=yes; n=no)*	*Handed*	*Known vascular disease*	*Haemodynamic response at time of syncope during HUT*
76	M	3	Y	Left	Diabetes	Vasodepressor
43	F	6-10	N	Right	-	Mixed Vasodepressor/cardioihibitory
21	F	2	N	Uknown	-	Vasodepressor
80	M	4	Y	Left	-	Mixed Vasodepressor/cardioihibitory
55	F	3	N	Right	-	Mixed Vasodepressor/cardioihibitory
58	M	4	N	Left	-	Vasodepressor
78	F	2	Y	Right	-	Vasodepressor
38	F	> 10	N	Right	-	Mixed Vasodepressor/cardioihibitory
63	F	2	N	Right	-	Vasodepressor
53	F	5	N	Unknown	Migraine	Mixed Vasodepressor/cardioihibitory
43	F	> 10	N	Unknown	-	Mixed Vasodepressor/cardioihibitory
22	F	> 20	N	Right	-	Vasodepressor
35	F	> 10	N	Right	Migraine	Pure cardio-inhibitory
26	F	> 10	N	Right	-	Vasodepressor
22	M	2	N	Right	-	Vasodepressor
61	M	2	Y	Right	-	Vasodepressor
73	M	6	Y	Unknown	Diabetes	Vasodepressor
28	F	> 20	N	Unknown	Migraine	Vasodepressor
85	M	4	Y	Left	-	Vasodepressor
37	M	6-10	N	Right	-	Pure cardio-inhibitory
68	M	2	N	Right	Stroke	Vasodepressor
52	M	2	N	Right	-	Mixed Vasodepressor/cardioihibitory

Table 7.1: Baseline characteristics of those who developed VVS during HUT (n=22)

7.2 Qualitative analysis EEG

On visible inspection of baseline resting EEG, 4 subjects had theta wave slowing, one subject had intermixed slow alpha with normal wave activity, and one subject (68 years of age) had a left temporal irregularity consistent with vascular change. All others had a normal resting baseline EEG. Twenty subjects experienced reproductive prodrome or symptom onset prior to syncope. No subject regardless of their age, displayed a change in EEG wave activity from baseline EEG wave activity prior to or at the time of symptom onset. During the progression of pre-syncope to syncope, previously well characterised EEG changes did occur. [151] These involved progressive theta wave slowing followed or mixed with delta wave slowing. A flat-line response occurred in some instances, mainly in younger subjects. Its presence depended on whether a cardio-inhibitory response of significant length occurred. An example of one such subject's EEG changes are shown in figure 7.1. Once syncope occurred and the subject had been placed in the recovery supine position with resumption of consciousness, reverse sequence of the above changes occurred to baseline EEG in all subjects.

Two subjects had no warning prior to syncope and had a pure cardio-inhibitory response at the time of syncope followed abruptly by hypotension during tilt-back. In both subjects this was characteristic of real-time episodes, one subject experiencing abrupt syncope with visible emotional stimuli. EEG showed corresponding abrupt flat-line activity in one while the other had 3-4 seconds of delta slowing prior to flat-line activity.

Qualitative reporting of all EEG recordings for 56 subjects are available in **Appendix 5.**

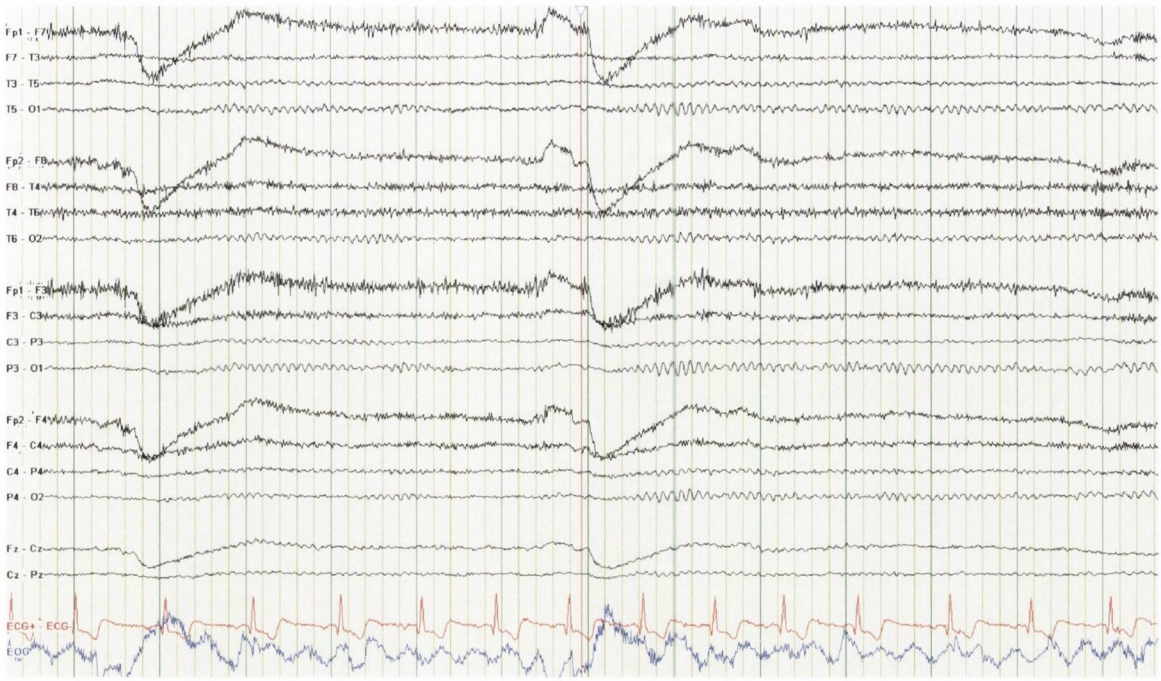


Figure (7.1A): Normal EEG at baseline

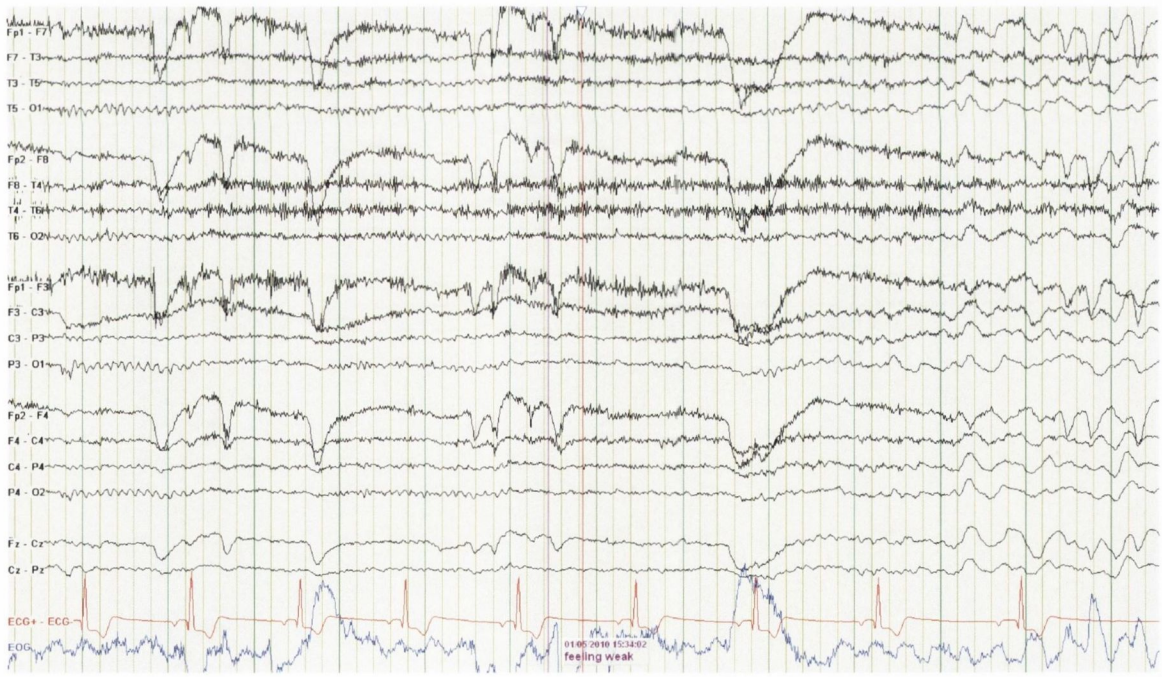


Figure (7.1B): Delta /Theta wave slowing following symptom onset with presyncope in association with a bradycardia depicted by the red ECG tracing.

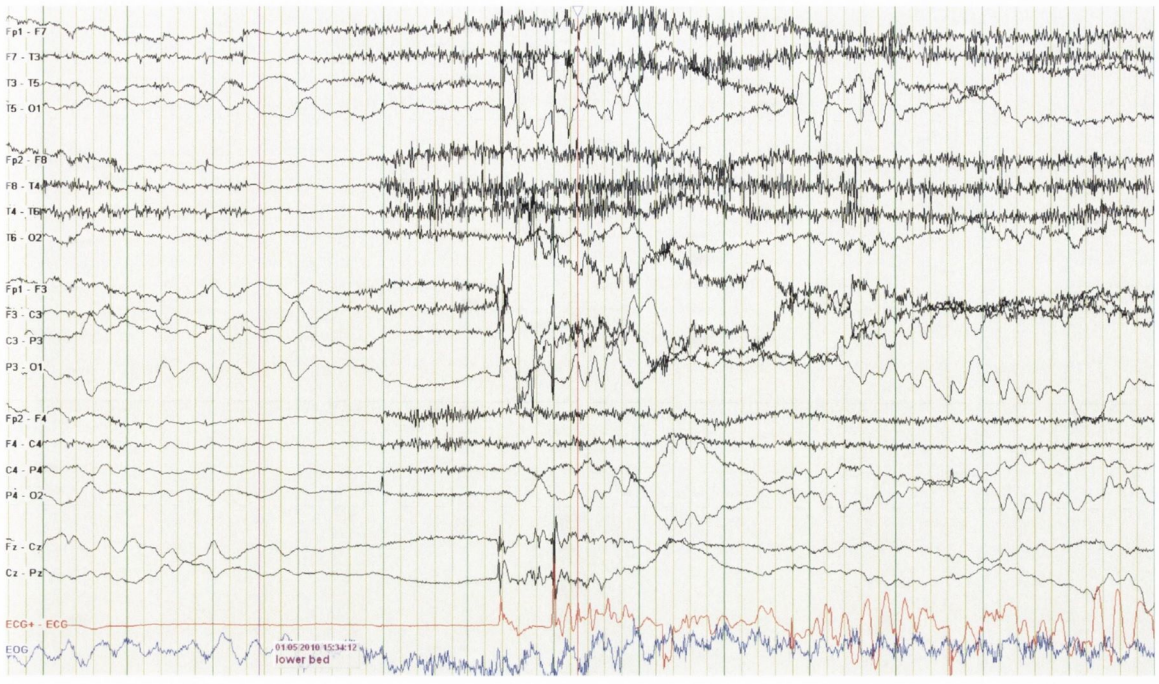


Figure (7.1C): Progressive EEG slowing to brief flat-line with simultaneous brief asystole. This is followed by interference with tilt-back following syncope.

7.3 Quantitative analysis EEG

Average baseline rest values over a 10 minute timeframe for systolic and diastolic blood pressure along with heart rate were calculated. Further average values were calculated over a 5 minute pre symptom period, 1 minute pre symptom period, 30 second pre symptom period and 30 second post symptom period and the difference in these values from rest values were calculated for each of these timeframes. Corresponding timeframe period analysis were calculated for alpha, beta, delta, theta and gamma band change from baseline values over the 10 minute rest period. An increase in delta band activity from rest values occurred in association with worsening hypotension and tachycardia prior to and following first symptom onset. No change occurred in other waveform bands. Figure 7.2 demonstrates in topographic format an increase in delta band for each of these timeframes for the whole group (n=22) with corresponding changes in blood pressure and heart rate shown. A decrease in SBP and increase in HR is seen to precede delta band increase as the timeframes progress.

	5 minutes pre-symptom vs rest	1 minute pre-symptom vs rest	30 seconds pre-symptom vs rest	30 seconds post symptom vs rest
↓ΔSBP(mmHg)	17.86±17.76	32.23±23.52	37.59±23.25	55.77±28.45
↓ΔDBP(mmHg)	0.5±9.22	8.5±12.47	12.27±13.05	25.91±19.33
↑Δ HR(bpm)	19.77±10.68	19.14±11.93	15.86±16.74	0.91±25.39

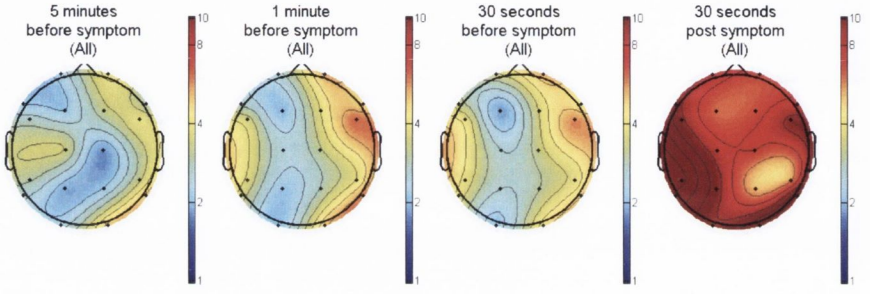


Figure 7.2 Topographic depiction of increase in delta band activity in different timeframes with corresponding change in Blood pressure and heart rate (n=22). SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HR = Heart rate; *The colour gradient signifies the level of increase in delta band change with blue signifying no change and red indicating a marked increase.*

7.4 Age-group comparisons in EEG waveform change

Comparison analysis between both age-groups (younger than 60 years of age and older than 60 years of age) for alpha, beta, delta and theta bands using the double banana (longitudinal bipolar) reference montage after log-transformation was performed. This was carried out for similar time frame periods of 5 minutes pre symptom onset, 1 minute pre symptom onset, 30 seconds pre symptom onset and 30 seconds post symptom onset

and levels of increase in comparison to baseline rest values were compared. A negative t value implies a significant increase in older with respect to younger subjects. (Table 7.2) The only change seen was that in the delta band range.

Frequency band	< 60 vs > 60 yrs, band power increase, 5 minutes pre-symptom vs. rest	< 60 vs > 60 yrs, band power increase, 1 minute pre-symptom vs. rest	< 60 vs > 60 yrs band power increase, 30s pre-symptom vs. rest	< 60 vs > 60 yrs, band power increase, 30s post-symptom vs. rest
Delta (1-4Hz)	0	13.64 (mean t= -1.9333)	**55.56 (mean t=-2.1385)**	0
Theta (4-8Hz)	0	0	0	0
Alpha (8-25Hz)	0	0	0	0
Beta (12-25Hz)	0	0	0	0
Gamma (25-40Hz)	0	0	0	0

Table 7.2 Longitudinal bipolar logarithmic stats. Percentage of significant channels (%) $p<0.05$ after FDR correction are shown. (Band wave changes on EEG in comparison to rest values in timeframes analysed, in different age-groups). (n=22)

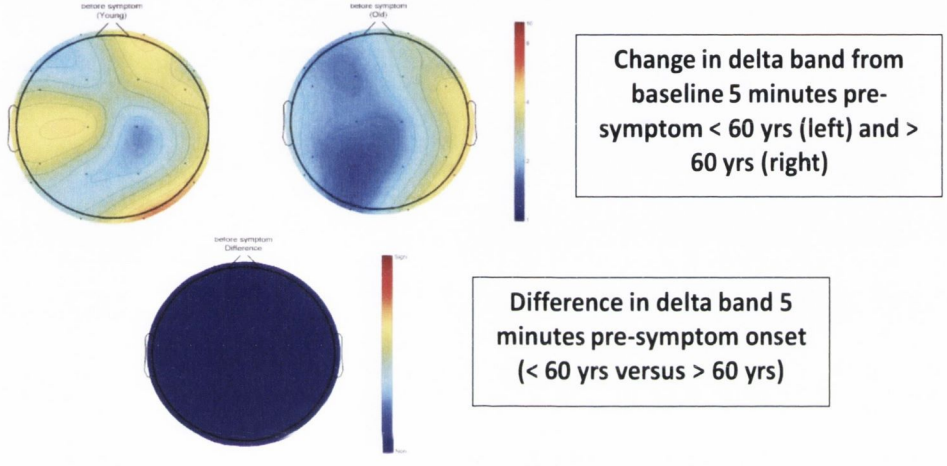
7.5 Age-group comparisons δwave and haemodynamic change

Increase in delta band activity for all timeframes is demonstrated in both age groups in topographic format. (Figures 3-6) The top two topographs depict the increase in delta wave in each age group individually from baseline while the topograph beneath depicts the difference in change in increase in delta wave between both age-groups for that particular timeframe. Corresponding blood pressure and heart rate changes from baseline values are described for the given timeframe for both age-groups in a table beneath each topograph depiction.

No significant difference exists between both age groups in this subgroup analysis in the level of SBP at which symptoms occur ie.the nadir SBP.

7.51 Five minute analysis pre symptom onset

No significant difference was found in blood pressure or heart rate change between both age-groups. Likewise no real increase in delta wave was noted in this time frame in either age-group when compared to baseline delta wave and therefore no significant difference existed between both age groups when comparing the increase in delta wave change.

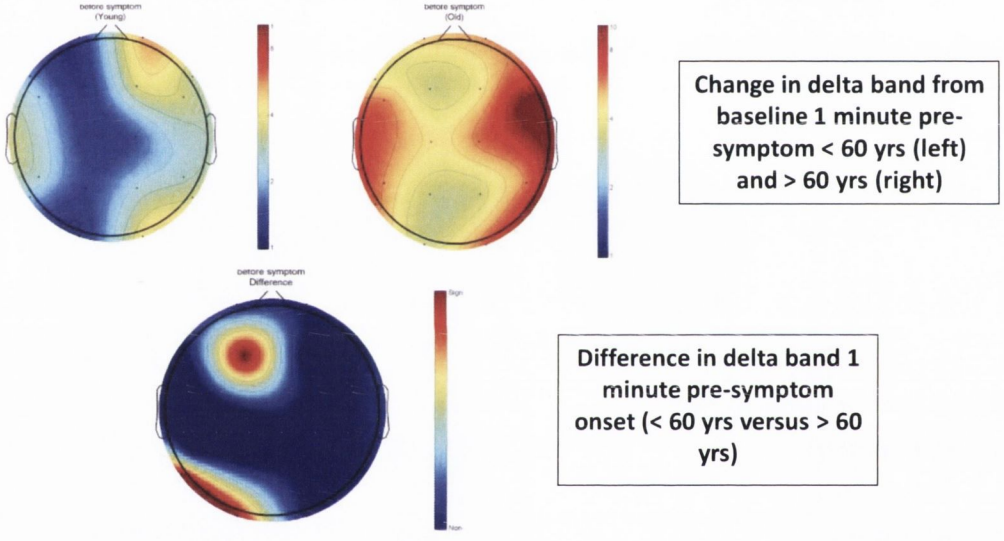


5 mins pre-symptom vs rest	<60 years	>60 years	P value
Δ ↓SBP (mmHg)	14.14 ± 11.22	23.87 ± 25.36	0.331
Δ↓ DBP (mmHg)	-1.79 ± 7.38	4.5 ± 11.19	0.184
Δ ↑ HR (BPM)	22.71 ± 10.35	14.63 ± 9.76	0.09
Nadir symptom SBP (mmHg)	94.14 ± 18.03	93.88 ± 32.23	0.98

Figure 7.2: Delta band activity change (red significant increase) and corresponding haemodynamic change 5 minutes pre symptom onset. (mmHg = millimetres of mercury; bpm = beats per minute)

7.52 One minute analysis pre symptom onset

No real increase in delta wave changes are seen in the younger age group but a marked increase depicted by increasing redness is shown in the older age group. A significant difference therefore exists between both age-groups in the delta band change and on topographic appearance shows early evidence of a left lateralisation in effect. No significant difference occurs between both age groups in DBP or HR. There is a greater fall in SBP in the older age-group but the difference is not found to be significant.

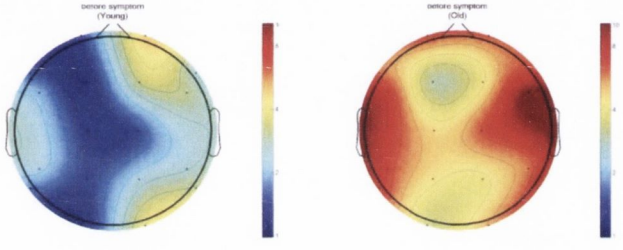


1 min pre-symptom vs rest	<60 years	>60 years	P value
Δ ↓SBP (mmHg)	24.36 ± 17.51	46.00 ± 27.36	0.07
Δ ↓DBP (mmHg)	5.07 ± 10.23	14.50 ± 14.42	0.131
Δ ↑HR (BPM)	20.93 ± 13.27	16.00 ± 9.04	0.48
Nadir symptom SBP (mmHg)	94.14 ± 18.03	93.88 ± 32.23	0.98

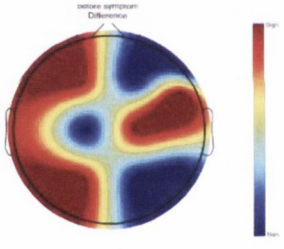
Figure 7.3: Delta band activity change (red significant increase) and corresponding haemodynamic change 1 minute pre symptom onset. (mmHg = millimetres of mercury; bpm = beats per minute)

7.53 Thirty seconds pre symptom onset

No increase in delta band is seen in the younger age group while a marked increase in delta band is seen in the older age group during this timeframe. The difference in increase in delta band from rest values between both groups is significant with this difference showing left lateralisation in effect. No significant differences are seen in haemodynamic values although the older age group does have a greater drop in SBP but less so than in the one minute timeframe measurements.



Change in delta band from baseline 30 seconds pre-symptom < 60 yrs (left) and > 60 yrs (right)



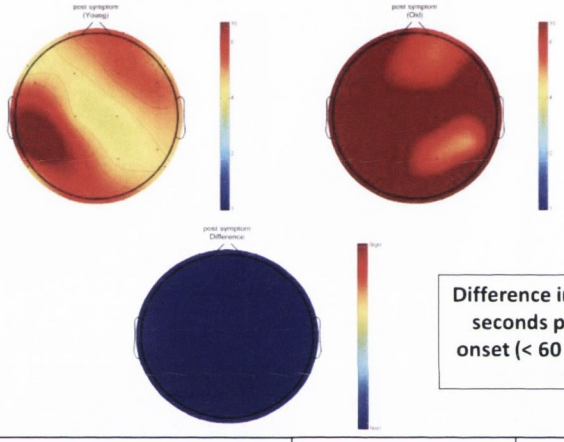
Difference in delta band 30 seconds pre-symptom onset (< 60 yrs versus > 60 yrs)

30 secs pre-symptom vs rest	<60 years	>60 years	P value
Δ ↓SBP (mmHg)	30.64 ± 19.37	49.56 ± 25.66	0.09
Δ ↓DBP (mmHg)	10.00 ± 11.75	16.25 ± 15.04	0.332
Δ ↑ HR (BPM)	15.00 ± 18.27	17.38 ± 14.75	0.743
Nadir symptom SBP (mmHg)	94.14 ± 18.03	93.88 ± 32.23	0.98

Figure 7.4: Delta band activity change (red significant increase) and corresponding haemodynamic change 30 seconds pre symptom onset. (mmHg = millimetres of mercury; bpm = beats per minute)

7.54 Thirty seconds post symptom onset

There is marked increase in delta band change in comparison to baseline in both age groups in the thirty seconds following first symptom onset. No significant difference is seen between either age group. Both age groups have a marked drop in SBP and DBP without any significant difference between both. Therefore both groups act similarly following symptom onset.



30 secs post-symptom vs rest	<60 years	>60 years	P value
Δ ↓SBP (mmHg)	58.00 ± 28.67	60.25 ± 28.87	0.644
Δ ↓DBP (mmHg)	30.57 ± 19.69	17.75 ± 16.79	0.125
Δ ↑HR (BPM)	30.57 ± 19.69	5.00 ± 32.17	0.625
Nadir symptom SBP (mmHg)	94.14 ± 18.03	93.88 ± 32.23	0.98

Figure 7.5: Delta band activity change (red significant increase) and corresponding haemodynamic change 30 seconds post symptom onset. (mmHg = millimetres of mercury; bpm = beats per minute)

7.6 EEG in those without and with A-LOC

7.61 Qualitative analysis

On visual inspection of EEG no differences were seen in those who had A-LOC (n=5) and those who did not experience A-LOC (n=17). No differences were seen in the time to recovery to baseline resting EEG between those who did and those who did not experience A-LOC.

7.62 Quantitative analysis

Similar analysis was performed using specific timeframes comparing those without and with A-LOC as was used for comparison between age-groups with symptom onset. No significant differences were seen.

	Percentage of significant channels (%) $p<0.05$ after FDR correction		
Frequency band	Band power increase, 5 minutes pre-symptom vs. rest	Band power increase, 30s pre-symptom vs. rest	Band power increase, 30s post-symptom vs. rest
Delta (1-4Hz)	0	0	0
Theta (4-8Hz)	0	0	0
Alpha (8-25Hz)	0	0	0
Beta (12-25Hz)	0	0	0
Gamma (25-40Hz)	0	44.44 (mean t=2.1694)	0

Table 7.3 A change in gamma power is seen in the 30 seconds prior to symptom onset. This increase in gamma power in the ALOC groups, most likely corresponds to less physical or eye movement in this group compared with the non-ALOC group.

7.7 Results Summary

Visual inspection or qualitative analysis of EEG does not reveal any change in cerebral activity prior to first symptom onset with VVS. Detailed quantitative analysis confirms an initial haemodynamic change in blood pressure and heart rate prior to symptom onset and prior to an increase in delta wave activity. Older individuals show a significantly greater increase in delta wave change from baseline values for the amount of hypotension experienced in the thirty seconds prior to symptom onset compared to younger individuals with VVS.

Chapter 8

Discussion

8.1 Reported characteristics with VVS – Age related differences

8.11 Discussion of results

In this prospective series of subjects with a confirmed diagnosis of VVS (n=311), a two third female preponderance occurred in both older (median age 70.5 years) and younger subjects (median age 35 years). Older subjects reported less syncope and presyncopal lifetime burden in comparison to their younger counterparts. Older subjects with an MMSE of 24/30 or above, reported less family history of syncope ($p<0.001$), were less likely to have a syncopal episode witnessed ($p<0.001$), were less likely to report prodrome prior to episodes of syncope ($p=0.005$) and were less likely to report presyncopal episodes.Commonly reported symptoms prior to VVS of lightheadedness, sweating, palpitations, blurred vision and hearing disturbance were reported more frequently in younger than older individuals. The sight of blood, emotional stress and crowded environments were more commonly reported as precipitants of VVS in younger than older subjects in this study. Syncope while in a seated position, occurred to the same extent in younger as in older individuals, but interestingly younger individuals fainted more commonly on postural change from a seated to a standing position than older individuals. This may reflect a sharper quicker fall in blood pressure in younger subjects on assuming the upright position while older subjects may experience a slower less abrupt decline in blood pressure. The significant difference in reporting of sequelae after syncope such as limb jerking, fatigue and disorientation may reflect a higher incidence of bradycardia and asystole experienced with younger subjects with VVS. Younger and

older subjects reported unexplained falls and fractures in equal rates but older subjects were susceptible to more severe fractures when they did occur.

8.12 Current literature

Two further studies comparing reported VVS characteristics between older and younger subjects have been published in 2010. The first by Duncan et al was a large retrospective observational study (n=1060) comparing those younger and older than 60 years of age with VVS. [182] Similar to our study, only subjects with HUT induced VVS were included. Unlike our study, older subjects had significantly more co-morbidities such as IHD which required adjusting for, in the analysis. Similar to our study a greater number of older subjects were on antihypertensive treatment at time of diagnosis. Individuals 60 years of age or older were less likely to present with episodes of presyncope compared to the younger age group as with our study. Following adjustments for co-morbidities, Duncan et al found that older subjects were less likely to present with dizziness OR 0.64 95% CI (0.46, 0.9) p<0.001 and palpitations OR 0.45 95% CI (0.28,0.72) . Both prolonged standing and change in posture were significantly greater precipitants reported in younger rather than older subjects. Duncan et al did find that older subjects did report a higher incidence of unexplained falls OR 2.33 95% CI (1.36, 4.32). This was no longer statistically significant when adjustments for comorbidities and sex were made. As in our study, no significant difference in fracture rates between younger and older subjects occurred OR 1.78 95% CI (0.89, 3.53).

The second study by Guida et al, reported on prodrome experienced with spontaneous VVS (n=743). [183] Sixty two percent (n=460) went on to have reproductive symptoms during HUT. When comparing three different age groups, subjects 65 years of age or

older reported a decreased number of syncopal episodes at time of presentation p=0.048 and less prodrome prior to syncope p<0.001 as in our study.

8.13 Study Limitations

Not all subjects completing a questionnaire had a witness account available, either at the time of a syncopal event/unexplained fall or during assessment in the clinic itself. Even if witness account was available for one syncopal episode, one assumed that all syncopal events took a familiar form. Subjects 60 years of age or older who scored 24 or greater on the folstein MMSE completed a questionnaire and were included in the study. The MMSE is a widely used crude test for testing cognitive function but may miss some individuals with mild or early cognitive impairment.

8.14 Conclusion

Caution is required when taking a history from an older subject with syncope. Once cardiac syncope is outruled, lack of prodrome in an older person prior to syncope does not exclude VVS as an underlying diagnosis. Diagnostic work-up of these subjects should include postural blood pressure measurement, carotid sinus massage where applicable, and a head-up tilt test to confirm diagnosis. Unexplained falls and injurious fractures have been previously reported in all age groups with VVS albeit in small numbers.This suggests that VVS is not as benign a condition as first thought and failure of older adults to recognise prodrome may be a major contributory factor to these injuries. Recently Anpalahan et al demonstrated that in a sample of 200 subjects admitted with unexplained or accidental falls, 26% of those with unexplained falls had a diagnosis of neurally mediated syncope. [44] Future research needs to focus further on the prevalence of VVS in older subjects presenting with unexplained falls and injury.

8.2 Haemodynamic parameters in VVS – Age related differences

8.21 Discussion of results

Symptom reproduction during HUT occurred in 160/187 (93%) of those < 60 years of age. Reported prodrome with real time syncope was 180/219 (84%) in those < 60 years of age. (Results 4.3 Table 4.1) Similarly symptom reproduction during HUT occurred in 62/68 (91%) in those ≥ 60 years of age. Reported prodrome with real time syncope was 60/92 (70%) in those > 60 years of age. (Results 4.3 Table 4.1) Therefore amnesia for recall of prodrome was present in both agegroups but more prevalent in those ≥ 60 years of age.

This study demonstrated that older subjects take longer to develop prodrome (1398.72 ± 396.43 vs 1064.43 ± 479 seconds p = 0.001) and syncope (1505.3 ± 562.44 vs 1311.09 ± 480.72 seconds p = 0.029) during VVS when compared to younger subjects. Although baseline systolic and diastolic blood pressures were higher in older subjects when compared to younger subjects (p=0.001, p=0.005), symptom reproduction occurred at lower systolic and diastolic blood pressures in older subjects when compared to younger subjects (p=0.024, p=0.006) with VVS. There were no significant differences however in the levels of systolic or diastolic blood pressures when syncope occurred in both age-groups (p=0.723, p=0.118). The rate at which systolic blood pressure drop occurred to time of prodrome and time of syncope was faster in older subjects when compared to younger subjects (p=0.001, p=0.006).

No significant differences were present in baseline heart rate in both age groups. Younger subjects developed a significant tachycardic reponse at time of symptom onset in comparison to their older counterparts (p=0.001) and at a faster rate change over time (p=0.001). Conversely younger subjects were significantly more bradycardic than their older counterparts at time of syncope (p=0.002) and this drop in heart rate occurred at a faster rate when compared to older subjects (p=0.001).

8.22 Current literature

This study confirms an increase in prodrome recognition particularly with older subjects during HUT in comparison to that reported with prior history taking. This corroborates previous work in the literature by Guida et al. [183, 184] Recently in 2010 even allowing for smaller numbers studied, Folino et al. found similar patterns to our study in haemodynamic response during HUT comparing responses in younger (n=41) and older subjects (n=24) prior to syncope.[100] Folino et al (2010) found that older subjects had a less striking rise in HR in the first twenty minutes of HUT in comparison to younger subjects together with a premature reduction in SBP and TPR. Younger subjects were found to have a more progressive and delayed reduction in SBP. This is confirmed in our study – older subjects had a faster rate of change in SBP when compared to younger. Rather than focussing on symptom onset as in our study, Folino et al studied haemodynamic change in the five minutes preceding syncope. Similarities can be seen to our results, as this timeframe for the most part would have incorporated time of first symptom onset. Younger subjects again displayed an initial increase in heart rate in the one minute preceding syncope prior to a steeper decrease.

Guida et al (2010) analysed recognition of prodrome during HUT in comparison to that reported during spontaneous episodes. Four hundred and sixty subjects in their study had

a positive HUT. No between-group differences in cardiovascular parameters at the time of prodrome onset were demonstrated. In contrast to our findings, although a lower SBP was demonstrated with older adults at time of first symptom onset, differences in SBP and HR levels at time of symptom onset between younger and older adults were not found to be statistically significant. Guida's study did not analyse time to onset of symptoms or haemodynamic changes leading to symptom onset.

This study again confirmed that although older subjects had a higher SBP at baseline that syncope occurs at the same level of SBP as younger subjects. This was also demonstrated in a smaller study by Giese et al in 2004 (n=42).[101] Although there was a trend for a higher SBP at time of syncope in those $\geq$ 60 years of age (n=7) this difference was not found to be statistically significant. Furthermore Giese et al had also commented on the fact that those $\geq$ 60 years of age tolerated upright posture for a longer period prior to syncope than did younger subjects which is in fitting with the results in our study.Other studies and reports have alluded to this phenomenan also.[105, 193, 229-232]

8.23 Study limitations

The time of first onset of prodrome during HUT was dependent on subjects verbalising aloud symptoms once they occurred. Subjects were educated prior to HUT on the importance of letting the supervising nurse or doctor know when these occurred. Sublingual nitrate can induce a tachycardia following administration. This usually occurs within three minutes of administration and prior to first reproductive symptom onset.

8.24 Conclusion

This study confirms the importance of HUT in securing a diagnosis of VVS in older subjects. The increased recognition of prodromal symptoms during HUT in older subjects in this study when compared to their reporting of prodrome with spontaneous episodes of syncope prior to HUT suggests that denial of symptoms in older subjects prior to syncope is not enough to outrule VVS as an underlying cause. Reproduction of symptoms during HUT is therefore important to sharpen recall and help to confirm diagnosis. HUT can play a vital role in educating older adults with VVS to recognise symptoms in an effort to prevent further syncope.

Older subjects present with specific haemodynamic changes that are induced by passive orthostatism when compared to younger subjects. Older subjects display less responsive sympathetic activity at time of both symptom and syncope onset ie. blunted increase in HR response and premature decrease in SBP. The ability of younger subjects to identify symptoms at an earlier time to older subjects is likely to be secondary to an increased tachycardic response to hypotension. Reflex sympathetic activity changes in aging have been previously studied. Reduced baroreflex sensitivity in men has been linked to systemic α1 adrenergic vascular responsiveness. [199] Reduced heart rate variability both at rest and in passive orthostatism has also been reported in older adults, while heart rate variability analysis during HUT in young adults displayed an increase in sympathetic activity prior to syncope. [97, 233]

In order to maintain cerebral autoregulation one would expect that syncope should occur at a higher level of SBP in the older adult with hypertension. A higher baseline SBP without a substantial upward shift of the lower limit of cerebral blood flow regulation

suggests that older adults exhibit a greater cerebral reserve for maintenance of consciousness than do their younger counterparts.

As in Folino's study in 2010, haemodynamic changes prior to first symptom onset in younger subjects may result from excessive sympathovagal reactions, while haemodynamic changes in older subjects are more likely due to increased central vagal activity with defective peripheral sympathetic activation.

8.3 Amnesia for loss of consciousness (A-LOC) in VVS

8.31 Discussion of results

This is the first prospective study to our knowledge investigating A-LOC in subjects with a diagnosis of VVS confirmed with reproduction of syncope on HUT. The prevalence of A-LOC in this study was 26% (54/209). This prevalence rate is consistent with previous reports on the prevalence of amnesia in patients with CSS. [2] However CSS is almost exclusively a disorder of aging found in those 50 years of age or older. In our series of subjects, although age was associated with a higher prevalence of A-LOC, 20% of cases occurred in a younger age group and age was not found to be an independent predictor for A-LOC. In older subjects there was no significant difference noted in MMSE scores (a traditional measure of cognitive function) in those without A-LOC and those with A-LOC. This is consistent with previous research observing A-LOC in CSS. [60]

In those who went on to have subsequent A-LOC on HUT, similar numbers of subjects reported a history of unexplained falls to those without A-LOC on HUT. However those with A-LOC in VVS were less likely to have reported warning symptoms with real time syncopal episodes (63% vs 85%) and were more likely to have had a fracture with a

syncopal episode or unexplained fall in the past (31% vs 17%). Time to syncope from symptom onset was not significantly different between both groups but those with A-LOC did develop symptoms later on HUT. There was no difference in blood pressure behaviour between both groups. This was also previously reported during observation of those with CSS and A-LOC which also reported same lengths of asystole in those with and without A-LOC in CSS. [60] However those with no A-LOC had a more marked and faster bradycardic response during HUT ie. a more pronounced vagal reaction. Therefore this study would suggest that A-LOC is more likely to occur in the setting of a predominant vasodepressor response in VVS.

Vasodepressor responses tend to be more gradual than cardioinhibitory and therefore one might expect more time for awareness of symptoms to occur and less likelihood of amnesia following syncope. However our study does not support this. Furthermore the drop in blood pressure or the rapidity at which the drop occurs does not influence the occurrence of A-LOC. Therefore the results of this study would suggest that other factors outside of cognition and haemodynamic change during VVS must play a role in the development of A-LOC in syncope.

8.32 Current Literature

It is more probable that the interaction of the autonomic nervous system with the cerebral cortex, subcortical areas and brainstem, in particular the amydala and hypothalamus which are associated with memory formation, plays some role. Selective hypoperfusion of these areas during hypotension may be contributory. Reduced parasympathetic activity has been previously reported in correlation with reduced regional cerebral blood flow in the amygdala-hippocampal complex during positron emission tomography in the setting of reduced memory task performance. [115] The actual pathway for this interaction remains unknown. Parry et al also demonstrated altered cerebral autoregulation in patients

with CICSS [234] and postulated that this may have a role in A-LOC. [60] A similar argument could be made for those with A-LOC in VVS. Another possible explanation is the neuro-endocrine response during VVS. A decrease in CA1 (a zone of densely packed pyramidal cells within the hippocampus) neuronal activity within the hippocampus has been shown to correlate with memory loss and hippocampal atrophy. [116, 117] Long term exposure to high cortisol levels have been implicated and shown to be inversely related to simple memory tasks. [118] Therefore the presence of A-LOC in VVS may also be influenced by cortisol release but more research is required to clarify its role if any in syncope related amnesia.

8.33 Study Limitations

Normal cognition is suggested by >24/30 MMSE score. MMSE is a global screen of cognitive function and a widely used test but is not sensitive enough to identify subtle changes in cognition. HUT does not always replicate real time syncopal episodes as internal loop recorder analysis in patients with VVS has demonstrated. [235] Assessing A-LOC with "real-time" syncope in those with internal loop recorders would be ideal but good witness account which is often unavailable would be required. It must also be acknowledged that those who develop loss of consciousness during HUT do not always demonstrate a similar haemodynamic response if the test is repeated. [236]

8.34 Conclusion

Vasodepressor responses are more commonly reported in older subjects on HUT as compared with younger subjects. [104] Although the mean age was higher in subjects with A-LOC, age was not an independent predictor on regression analysis. There were fewer older than younger subjects in our study (140 vs 69). A larger cohort of older adults may be required to provide sufficient power to test this hypothesis that A-LOC is

associated with increasing age. Our study also showed A-LOC in younger subjects. No studies however have assessed A- LOC in younger subjects in the setting of syncope previously but it has been alluded to in the literature. [63, 64, 237] It may therefore be more prevalent than first thought.

To date VVS has been commonly referred to as a benign phenomenon. In the setting of unexplained falls and injury or fracture, there is a tendency to investigate thoroughly for orthostatic hypotension and CSS but less so VVS particularly in the older adult. The association of VVS with unexplained falls resulting in injury has been reported previously. [42, 43] The presence of A-LOC in the setting of VVS further re-emphasises the need for a thorough work-up in individuals presenting with unexplained falls and syncope. Although haemodynamic change on HUT may not always fully represent real time events, the importance of reproducing symptoms during HUT in unexplained syncope or falls cannot be underestimated. The low reporting of prodrome prior to real time syncope/falls (63% vs 85% $p< 0.001$) and increased injury rate (31% vs 17.4% $p< 0.03$) further emphasises the importance and need for consideration of HUT in the setting of unexplained falls and syncope particularly in the older adult once other causes have been excluded.

A-LOC in the setting of neurally-mediated syncope is therefore not exclusive to patients with CSS, a syndrome found in older adults but also has an increased prevalence across all age-groups with syncope.

8.4 Qualitative and quantitative electroencephalography (EEG) during HUT induced VVS

8.41 Discussion of results

Previous combined EEG and HUT studies have focused on EEG changes observed during presyncope and syncope. Our study combining EEG and simultaneous non-invasive blood pressure and heart rate monitoring, concentrated in particular on cerebral and haemodynamic change just prior to and at the time of first reproductive symptom onset. Twenty two subjects experienced reproductive VVS during HUT. Differences from baseline resting blood pressure occurred from as early as 5 minutes prior to first onset of reproductive symptoms in these subjects. These haemodynamic changes followed by symptom onset were seen to precede any waveform change on initial visual inspection of EEG. When EEG changes did occur they did so in a bilateral and symmetrical fashion. Quantitative analysis however demonstrated a significant increase in delta band activity from baseline in those 60 years of age and older, compared to those younger than 60 years of age, in the one minute and in the thirty second timeframe prior to first symptom onset. This did not correspond to a significant hypotensive change between both age groups during the same timeframes. Furthermore the differences in delta band change from baseline between both age groups were seen to lateralise to the left hemisphere, a pattern which has been described previously. An increase in delta band activity reflects the non-attentive unconscious mind or trance like state. Delta band changes may well be representative of degrees of cerebral perfusion. We know that cerebral autoregulation differences exist between older and younger adults during hypotensive episodes. The left lateralisation change in delta band demonstrated between both age-groups may represent this change in autoregulation.

Correlation of left lateralisation and its relationship to cerebral autoregulation is unknown in the literature to the best of our knowledge.

8.42 Current Literature

Electroencephalography with combined HUT has provided a better understanding of simultaneous cortical brain activity at time of syncope.[157, 159, 161, 163] Many individuals experience prodrome or symptoms which herald the onset of VVS. It is this recognition of prodrome which enables individuals to abort further attacks, for example by assuming a rapid supine position, removing them selves from a specific trigger environment or commencing physical counter manoeuvres. [238] Older individuals tend to experience a shorter time interval between prodrome onset and syncope in comparison to younger individuals with VVS. [184] What potentiates this symptom onset remains unclear. Younger individuals demonstrate a tachycardia earlier than older individuals in response to hypotension during HUT table testing which could certainly explain this earlier prodrome onset. [100] This does not account for other scenarios such as abrupt syncope seen in response to emotional or visual stimuli more commonly described in younger individuals.

A primary cortical involvement in cardiovascular autonomic control has been proposed in previous research. Oppenheimer et al demonstrated increased vasodepressor and bradycardic responses with stimulation of the left insular cortex in those undergoing temporal lobectomy for epilepsy treatment while the converse was found for right insular cortex stimulation. [149] Further research suggested that acute left insular stroke may damage parasympathetic activity leading to an increase in basal sympathetic tone contributing to an increase in arrhythmia post stroke. [150] However recent studies do not support these conclusions.[239, 240]

Imaging studies in subjects experiencing VVS during HUT have attempted to further inform cortical association with blood pressure and heart rate change. Single photon emission computed tomography (SPECT) imaging of regional cerebral blood flow in 10 paediatric subjects who experienced VVS during HUT were compared with 10 subjects who did not experience VVS. [241] When all patients were evaluated together decreases in perfusion uptake were more widespread in the left hemisphere. However when tilt positive were compared to tilt negative, perfusion was significantly lower in the right peri-insular cortex in those with tilt negative result. The authors suggest that the right peri-insular involvement may explain initial early sympathetic predominance prior to syncope with further ischaemia in the peri-insular cortex then leading to rapid sympathetic withdrawal. One study using SPECT demonstrated a reduction in regional cerebral blood flow in adults with a history of VVS (mean age 36 years) during asymptomatic periods when compared to adults with no history of VVS. [242] Decreases in regional cerebral blood flow were demonstrated in a multitude of regions in the brain, however the authors make the point that it still remains unclear if these changes in cerebral blood flow are representative of cause or consequence of syncope.

8.43 Study Limitations

There are limitations to this study. No brain or carotid imaging were available for any of the subjects enrolled in this study and so knowledge of baseline cerebral perfusion particularly of older subjects within the group was not available. Transcranial Doppler studies were not performed. Cerebral vasoconstriction has also been implicated in the pathophysiology of VVS and additional knowledge regarding middle cerebral artery blood flow in such subjects at time of symptom onset would have added further to our observations. [92]

8.44 Conclusion

Left lateralisation predominance of such delta band change remains difficult to explain and larger syncope studies with combined neuro-imaging will be needed for further clarification. Interestingly 4 of the subjects in this study, 3 of whom were 60 years of age or older and one who was 58 years of age were left handed. All younger subjects questioned were right-handed. This could suggest a right parietal-temporal dominance in those subjects with more pronounced tendency to left delta wave lateralisation during hypotension.

The increase in delta band activity demonstrated in older subjects in this study prior to symptom onset when compared to younger subjects, may reflect further age related differences which have been previously described in relation to lack of symptom awareness with VVS. [34] This study demonstrated the added benefit of quantitative EEG to that of qualitative EEG when interpreting cerebral changes during VVS. Future research should concentrate on the use of combined quantitative EEG with TCD to better assist us in understanding cerebral changes in relation to haemodynamic change particularly in vulnerable older adults who are at risk of falls, injury and overall reduced quality of life.

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Dissemination of Thesis

Publications

Original Articles

Age related differences in qualitative and quantitative electroencephalography (EEG) during tilt induced Vasovagal Syncope (VVS)
O'Dwyer C, Nolan H, Langan Y, Connolly S, Reilly R, Kenny RA
(Currently in submission)

Amnesia for loss of consciousness is common in Vasovagal Syncope
O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA
Europace 2011 Jul; 13(7): 1040-5 E pub 2011 Mar 23

How well are European Society of Cardiology (ESC) guidelines adhered to in patients with Syncope?
O'Dwyer C, Hade D, Fan CW, Cunningham C, Kenny RA
Ir Med J. 2010 Jan; 103 (1): 11-4

Review Articles

Syncope Clinics and the Older Adult
O'Dwyer C, Kenny RA
Eur Ger Med 2010 Feb; 1 (1): 41-4

Abstract Papers

Electroencephalographic findings in different age-groups with vasovagal syncope
O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA

Abstract Published in: J Cardio Electrophysiol Oct 2011 Suppl, Vol 22
IJMS Sept 2011, Vol 180, Suppl 10

Does amnesia for loss of consciousness (A-LOC) occur with vasovagal syncope (VVS)?
O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA

Abstract Published in: J Cardio Electrophysiol Oct 2011 Suppl, Vol 22
European Geriatric medicine (EGM) Sept 2010, Vol 1

Prodrome and characteristics of younger and older adults presenting with vasovagal syncope (VVS)
O'Dwyer C, Rice C, Hade D, Byrne L, Fan CW, Kenny RA

Abstract Published in: Europace June 2010, Suppl 1, Vol 12
Age Ageing Jan 2010, Suppl 1, Vol 39
IJMS Sept 2009, Suppl 8, Vol 178

How well are European Society of Cardiology (ESC) guidelines on Syncope adhered to, in those referred to a dedicated Syncope Unit
O'Dwyer C, Hade D, Byrne L, Fan CW, Cunningham C, Kenny RA

Abstract Published in: IJMS Sept 2008, Suppl 9,Vol 177

Appendix

Appendix 1 Patient information and consent Forms

Patient Information Leaflet

Title of study:

Vasovagal syncope in the older adult.

Introduction:

Vasovagal syncope (often termed a benign faint), is caused by pooling of blood in the lower limbs after a period of standing. This causes a brief lack of blood flow to the brain which may cause someone to lose consciousness briefly. Some individuals will have a warning or feel unwell prior to this while others will have no warning at all. This is a common condition occurring in half of us at least once in our lifetime.

We are interested in categorising the different characteristics or warning which individuals with vasovagal syncope get in different age groups, and also in exploring in more depth why some develop a warning sensation and others do not, prior to losing consciousness.

Preparation:

At the time of participation in this study you will have undergone the following investigations:

- a consultation with a doctor involving a detailed questionnaire on symptoms surrounding blackouts or falls
- a routine examination of your cardiovascular and nervous system
- Routine blood tests if over the age of sixty years
- A memory (MMSE) test if over the age of sixty years
- A tracing of the heart using surface electrodes
- An active stand test for three minutes assessing blood pressure and heart rate
- In a minority over the age of fifty years, a carotid sinus massage

Procedures:

To further investigate your symptoms you have been asked to complete a Head-up tilt (HUT) test. This is the gold standard test for investigating vasovagal syncope. The aim of this test is to reproduce the same symptoms that you experienced prior to loss of consciousness or a fall. At the same time an EEG (electroencephalograph) may be carried out. This is a painless non-invasive method of monitoring the electrical activity of the brain. It is a safe and extremely common monitoring technique utilised in most hospitals world-wide, and can be performed at the bedside. EEG involves attaching electrodes with the use of a special gel directly to the scalp area. These electrodes (small sensors) are connected by small leads to the EEG recording device. EEG will enable us to continuously monitor your brains electrical activity during head-up tilt.

Your Doctor in the syncope unit will tell you whether or not to fast prior to HUT.

On attending you will be secured on a tilt bed in a supine position, and attached to leads monitoring both your heart rate and blood pressure.

EEG leads will be applied and attached to a separate monitor.

You will be tilted upright to simulate a standing position until symptoms are reproduced or until 35 minutes is completed.

If this test is negative, as per normal protocol you may be asked to return for a fasting head-up tilt for a shorter duration of twenty minutes with EEG recording.

Benefits:

Your cooperation is greatly appreciated, as results of these tests will help us to understand better the mechanisms underlying fainting conditions and in diagnosing conditions that cause fainting and falls in all age groups.

Risks:

The risks are as for a routine head-up tilt test.

You may experience dizziness, lightheadedness, nauseousness, a sensation that you will faint, and in some cases you may lose consciousness due to your blood pressure dropping or your heart rate slowing. Should the latter occur, you will immediately be put lying down to allow for quick recovery. As per standard testing you should avoid this test if you are pregnant or think you might be pregnant.

There are no harmful risks from the addition of electrodes to the scalp (EEG).You may experience some mild discomfort or irritation to the scalp and you will need to wash the gel from your hair on returning home. It is also advised to avoid putting additional hair products in your hair prior to attending the clinic to allow for easier placement of the electrodes.

Exclusion from participation:

There are no known exclusion criteria for performing an EEG as part of the investigation into your symptoms in addition to standard head-up tilt testing.

The standard exclusion criteria for performing a head-up tilt will be adhered to as per standard protocol . These include the following conditions - obstructive cardiomyopathy, aortic stenosis, myocardial infarction or a stroke within the previous 3 months, severe Carotid Stenosis or pregnancy.

Alternative treatment:

You do not have to be a part of this study to be treated. You may undergo a head-up tilt without EEG if you prefer as per normal protocol investigating your condition.

Confidentiality:

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

Compensation:

Your doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

Voluntary Participation:

You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study:

You understand that your doctor may stop your participation in the study at any time without your consent.

Permission:

This study has hospital Research Ethics Committee approval.

Further information:

You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Dr Clodagh O'Dwyer who can be telephoned at (01) 416 4105. If your doctor learns of important new information that might affect your desire to remain in the study, he or she will tell you.

PATIENT INFORMED CONSENT FORM

Title of research study: Vasovagal syncope in the older adult.

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study. I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:

SIGNATURE:

RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:

NAME OF SECOND WITNESS: SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:

Date:

(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

SJH / AMNCH RESEARCH ETHICS COMMITTEE

Appendix 2 Questionnaire

Questionnaire:

Prior to your assessment in the clinic, I would be grateful if you could take the time to fill in the attached questionnaire. The questions are all very relevant to the conditions surrounding causes for both Falls and Blackouts. We are continually trying to research the mechanisms behind these conditions in this clinic in an effort to improve treatment and quality of life for individuals.

Currently we are undertaking a research project looking at the various ways that these conditions may present. Your signed consent for us to use the information from this questionnaire as part of that research is much appreciated. Your identity will remain confidential and your name will not be published or disclosed to anyone outside this hospital.

Dr. Clodagh O' Dwyer

SPR Falls & Blackout Unit

Signature: _____Date:

QUESTIONNAIRE - Please circle relevant answers

Name:

Date of birth: Age:

Male Female

1) Have you ever lost consciousness in your life?

Yes No Not Sure

IF Definite NO go to Question 10

2) If Yes: Faint Seizure Blackout Not Sure

3) When did you last lose consciousness?

4) Last episode: < 12 months > 12 months

5) What age did you first blackout/faint? Please circle

<10yrs 10-20yrs 21-30yrs 31-40yrs 41-50yrs >50yrs

6) Do you know you have blacked out after the episode? Yes No

Does someone else have to tell you that you blacked out? Yes No

Did you faint as a young person? Yes No

7) How many episodes in total have you experienced? Please circle

1 2 3 4 5 6-10 > 10 >20

8) Do you get a warning prior to blacking out/fainting? Yes No

9) If yes have you also had episodes with no warning as well? Yes No

10) Do you get episodes where you think you will pass out but don't? Yes No

11) If yes to Q 10 how many per month? Please circle

1 2 3 4 5 >5 less frequent

12) If you get a warning please tick as appropriate below:

Sweating	Palpitation/heart racing
Light-headedness	Nausea
Vomiting	Feel Hot
Feel giddy	Chest pain
"funny feeling in stomach"	Yawning
Headache	Blurred vision
Dark vision	Hearing disturbance
Tingling/numbness	Pains in arms/legs
Pain in neck/shoulder	Short of breath
Feel the need to lie down	Other?

13) Does it ever occur while:

standing Getting up from sitting sitting Lying down

14) Does anyone comment on your colour at the time

Pale blue red No change

15) With Loss of consciousness do you have:

Tongue biting	Jerking of limbs
Incontinence	Fatigue/drowsiness
Disorientation	No symptoms

16) How long do you normally take to recover?

< 1 minute

< 5 minutes

5-30 minutes

> 30 minutes

17) Do symptoms tend to occur at a set time of day?

Morning Afternoon Evening Night-time No specific time

18) Do symptoms tend to occur at a set time of the year?

Spring Summer Autumn Winter No set time

19) Precipitating factors:-Please tick any relevant:

After a meal	After standing	At Church
Shopping	Crowded environment	At Home
In of after a Shower	Seeing Blood/Having blood taken	Stress/pressure
Alcohol related	Post micturition/urination	Post defecation
With Exercise	After Exercise	Coughing

20) Are episodes different now to when they 1st started? Yes No

21) Have these episodes been Witnessed? Yes No

22) Have you had falls ? Yes No

How many?

Do you associate these with : Please tick relevant:

tripping/slipping

Loss of balance

Unexplained

23) Have you had fractures? Yes No

If Yes: Wrist Hip Other

24) Do you live: Alone	With partner		With relative	Other
25)Do you walk :	Independently		With an aid	Chairbound
26)Do you drive :	Yes	No		
27) Have you a history of:	Heart attack		Angina	Irregular heart beat
28) Epilepsy		Yes	No	
29) Migraine		Yes	No	
30) Stroke		Yes	No	
31) Family History of blackouts		Yes	No	
32) Family History of sudden death		Yes	No	

To be filled by doctor:

MMSE (> age 60) =

CURRENT MEDICATIONS:

APPENDIX 3

TILT FORM

Falls and Blackout Unit - St James's Hospital

Patient Checklist

Name of person/s recording test :

Name:_____

MRN: _____

DOB: _____

Date: _____

Time: _____

Tilt Type	Tick Appropriate
Italian	
Front Loaded	
Plain	
Tilt to Symptoms	
Tilt to LOC	

	YES	NO
Verbal Consent		
Fasting am/pm		
Allergies		
Diabetic		
Pregnant		
Respiratory Conditions		
Headache today		
Migraine Hx		
Dentures/Caps/Crown/Oral Piercing/Gum (circle)		

Clinical Check:

ECG □

Intervals: PR ___ QRS_____

QTc ___Axis_____

Morphology: Pwave□

QRS complex □ Twave □

Relevant Information:

_____
_____
_____
_____
_____
_____
_____
_____
_____

DATE OF LAST LOC:_____

Symptom Check:	
Presence of Prodrome	
Weakness	
Dizziness	
Diaphoretic	
Vision Change	
Other:	

Accompanied Yes □ No□ Comment _____

Mode of transport home: Car/Bus/Train

Driver/Passenger *(Please circle appropriate)* Full

Machine and Equipment Safety CheckComplete□

BSL pre:

BSL post:

Time	BP	HR	CO	TPR	Aware	Symptom
Baseline						
30s						
60s						
90s						
120s						
3 min						
3.5						
4						
4.5						
5min						
5.5						
6						
6.5						
7						
7.5						
8						
8.5						
9						
9.5						
10min						
10.5						
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31.5						
32						
32.5						

14							33						
14.5							33.5						
15							34						
15.5							34.5						
16							**35**						
16.5							END						
17													
17.5							36						
18							36.5						

Press Mark- Start of Tilt, GTN, Symptoms and Syncope.

Please tick appropriate: **Italian Protocol HUT** ☐ **Front loaded HUT** ☐ **Plain HUT** ☐

Date	Drug (Generic name)	Dose	Route	Prescribers Signature	Given By	Time
	Glyceryl Trinitrate		SL			
	Paracetomol	1 gm	PO			
	Atropine	600mcg	IV			
	Normal Saline 0.9%		IV			

APPENDIX 4

POST LOSS OF CONSCIOUSNESS WITH HUT

Perform immediately and 5 mins post LOC.

Reassure patient but **Do not tell** patient they have blacked out or got weak while they are recovering

When Alert – **Immediately on recovery**
"What Happened"?

⇓ Not Sure?

⇓ I passed out?/Blacked out

Do you remember feeling weak?

⇓ Yes ⇓ No

Was this similar to prior episodes?

⇓ Yes ⇓ No

Do you think you passed out?

⇓ Yes ⇓ No⇒Amnesia

Is this what you normally experience ⇓ Yes ⇓ No

5 minutes post recovery
"What Happened"?

⇓ Not Sure?

⇓ I passed out?/Blacked out

Do you remember feeling weak?

⇓ Yes ⇓ No

Was this similar to prior episodes?

⇓ Yes ⇓ No

Do you think you passed out?

⇓ Yes ⇓ No⇒Amnesia

Is this what you normally experience? ⇓ Yes ⇓ No

APPENDIX 5

Visual Inspection EEG reporting

(A) End diagnosis VVS (n=22)

ID	Age	VASIS Grade	Waveform activity during 10 minute rest pre HUT	Waveform activity prior to and at time of first reproductive symptom	Waveform activity following symptom onset	Recovery Waveform pattern following tilt-back
506	76	1	Left temporal alpha slowing	No change from baseline waveform at rest	Bilateral symmetrical alpha slowing occurring 55 seconds post symptom onset Theta and delta slowing 11 seconds later and 9 seconds prior to syncope	Quick reversal of waveform sequence
521	43	2B	Normal	No change from baseline waveform at rest	Bilateral symmetrical alpha slowing occurring 48 seconds post symptom onset followed by theta/delta slowing and flatline for 70 seconds with syncope	Slow reversal of waveform sequence
523	21	3	Intermixed slow alpha slowing with normal waveform	No change from baseline waveform at rest	Bilateral symmetrical theta/delta slowing occurring 10 seconds post symptom onset for 12 seconds prior to syncope followed by flatline	Quick reversal of waveform sequence
575	80	2B	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta/delta slowing occurring 24 seconds post symptom onset for 166 seconds to syncope	Quick reversal of waveform sequence
634	55	2A	Normal	No change from baseline waveform at rest	Bilateral symmetrical alpha slowing occurring 48 seconds post symptom onset, followed by theta/delta slowing for 32 seconds prior to syncope	Quick reversal of waveform sequence

638	58	3	Normal	No change from baseline waveform at rest	No change from baseline waveform to syncope	Theta/delta slowing on recovery to baseline waveform
643	78	3	Bitemporal independent theta slowing	No change from baseline waveform at rest	Bilateral symmetrical theta/delta slowing occurring 10 seconds post symptom onset for 6 seconds to syncope	Quick reversal of waveform sequence
699	38	2B	Normal	No change from baseline waveform at rest	Flatline @ 14 seconds with syncope	Flatline for 20 seconds prior to normal recovery of baseline waveform sequence
728	63	3	Normal Interference of waveform with Blinking	No change from baseline waveform at rest	Bilateral symmetrical theta slowing occuring 55 seconds post symptom onset with delta slowing occurring 15 seconds later for 51 seconds to syncope.	Baseline waveform resumed 20 seconds after syncope
729	53	2B	Bitemporal Theta wave slowing multiple runs	No change from baseline waveform at rest	Bilateral symmetrical theta slowing occurring 30 seconds post symptom onset for 4 seconds followed by 10 seconds of delta prior to flatline at syncope	12 seconds of delta followed by 3-4 seconds of theta then baseline waveform resumed
789	43	2B	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing for 13 seconds post symptom onset, followed by 6 seconds of delta slowing and flatline to syncope	20 seconds interference associated with resuscitation and 20 seconds of delta prior to baseline waveform
793	22	3	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 44 seconds post symptom onset for 12 seconds, delta for 3-4 seconds, 10 seconds of flatline @ syncope	7 seconds of delta and 15 seconds of theta prior to return to baseline waveform
798	35	2B	Normal	No warning symptoms prior to syncope	Flatline for 10 seconds @ syncope	Delta/theta waveform for seven seconds complicated by 26 seconds of artefact, then 6 seconds theta waveform prior to return to baseline

799	26	3	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 3 seconds post symptom onset for 3 seconds, 17 seconds of delta and 16 seconds of flatline @ syncope.	8 seconds of delta waveform prior to return to baseline waveform
806	22	1	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta 39 seconds post symptom onset for 3-4 seconds, delta for 46 seconds, 15 seconds of theta and 12 seconds of intermixed theta/delta prior to syncope	11 seconds delta/theta waveform slowing prior to return to baseline waveform
822	61	1	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 155 seconds post symptom onset for 4 seconds, delta for 10 seconds to syncope	30 seconds of delta waveform slowing prior to return to baseline waveform
856	73	3	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 150 seconds post symptom onset for 7 seconds followed by 21 seconds of delta wave slowing followed by 8 seconds of flatline @ syncope	15 seconds of delta slowing prior to return to baseline waveform
874	28	1	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 58 seconds post symptom onset for 3-4 seconds and 7 seconds of delta to syncope.	3 seconds of theta slowing prior to return to baseline waveform
880	85	3	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta slowing 56 seconds post symptom onset for 3-4 seconds followed by 11 seconds of delta to syncope	Immediate return to baseline waveform

885	37	2B	Bursts of bilateral theta @ rest	No warning symptoms prior to syncope	Bilateral symmetrical theta wave slowing for 3-4 seconds 3-4 seconds of delta @ time of syncope	Immediate return to baseline waveform
887	68	3	Left temporal irregularity consistent with vascular change	No change from baseline waveform at rest	Bilateral symmetrical theta wave slowing 24 seconds post symptom onset for 13 seconds,followed by 3 seconds of delta wave slowing	4 seconds of delta wave slowing, 5 seconds of theta wave slowing prior to return to baseline waveform
889	52	2B	Normal	No change from baseline waveform at rest	Bilateral symmetrical theta wave slowing 26 seconds post symptom onset for 3 seconds, followed by 17 seconds of delta wave slowing to syncope	Artefact then return to baseline waveform

(B) VVS pre-syncope on HUT (n=6), POTS (n=1), Asymptomatic OH (n=1)

ID	Age	Waveform activity during 10 minute rest pre HUT	Waveform activity prior to and at time of first reproductive symptom
452	55	Normal	No change from baseline waveform at rest
615	28	Normal	No change from baseline waveform at rest
756	25	Intermittent temporal wave slowing	Some interference with movement, No change from baseline waveform at rest
774	70	Normal	No change from baseline waveform at rest
794	70	Left temporal slowing	Left temporal slowing, No change from baseline waveform at rest
884	23	Normal	Some interference with movement, No change from baseline waveform at rest
610	34	Normal	No change from baseline waveform at rest
879	69	Interference secondary to kyphosis	Interference as per baseline, No change from baseline waveform at rest

(C) No reproductive Vasovagal syncope during HUT

ID	Age	Waveform activity during 10 minute rest pre HUT	Waveform activity throught test
451	69	Occasional right temporal theta wave slowing	Occasional right temporal theta slowing
522	41	Left temporal theta wave slowing	Left temporal theta wave slowing
524	34	Normal	No change from baseline waveform at rest
573	25	Normal	No change from baseline waveform at rest
574	29	Normal	No change from baseline waveform at rest
595	33	Normal	No change from baseline waveform at rest
597	42	Muscle/movement artefact	Muscle/movement artefact
598	52	Left delta wave activity more than right	Left delta wave activity more than right
616	60	Normal	No change from baseline waveform at rest
617	77	Occasional runs of theta waveform	Occasional runs of theta waveform
639	34	Normal(drowsy)	Normal(drowsy)
683	25	Left temporal slowing	Left temporal slowing
694	38	Normal	No change from baseline waveform at rest
706	48	Normal	No change from baseline waveform at rest
741	62	Normal	No change from baseline waveform at rest
742	24	Eye Blinking, Normal	No change from baseline waveform at rest
743	30	Normal	No change from baseline waveform at rest
800	17	Normal	No change from baseline waveform at rest
814	20	Generalised spike/wave activity	Generalised spike/wave activity
818	49	Normal	No change from baseline waveform at rest
842	58	Left temporal theta	Left temporal theta
873	45	Normal	No change from baseline waveform at rest
881	83	Intermixed slowing bilateral theta/delta	Intermixed slowing bilateral theta/delta
890	25	Left temporal theta	Left temporal theta
896	22	Normal	No change from baseline waveform at rest
913	73	Normal	No change from baseline waveform at rest

Appendix 6 MMSE

Folstein Mini-Mental State Exam		
I. **ORIENTATION** (Ask the following questions; correct = ☑)	**Record Each Answer:**	(Maximum Score = 10)
What is today's date?	Date (eg, May 21)	1 ☐
What is today's year?	Year	1 ☐
What is the month?	Month	1 ☐
What day is today?	Day (eg, Monday)	1 ☐
Can you also tell me what season it is?	Season	1 ☐
Can you also tell me the name of this hospital/clinic?	Hospital/Clinic	1 ☐
What floor are we on?	Floor	1 ☐
What city are we in?	City	1 ☐
What county are we in?	County	1 ☐
What state are we in?	State	1 ☐
II. IMMEDIATE RECALL	(correct = ☑)	(Maximum Score = 3)
Ask the subject if you may test his/her memory. Say "ball, "flag," "tree" clearly and slowly, about on second for each. Then ask the subject to repeat them. Check the box at right for each correct response. The first repetition determines the score. If he/she does not repeat all three correctly, keep saying them up to six tries until he/she can repeat them	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐
		NUMBER OF TRIALS: _____
III. **ATTENTION AND CALCULATION**		
A. Counting Backwards Test	(Record each response, correct = ☑)	(Maximum Score = 5)
Ask the subject to begin with 100 and count backwards by 7. Record each response. Check one box at right for each correct response. Any response 7 or less than the previous response is a correct response. The	93	1 ☐
	86	1 ☐
	79	1 ☐

score is the number of correct subtractions. For example, 93, 86, 80, 72, 65 is a score of 4; 93, 86, 78 70, 62, is 2; 92, 87, 78, 70, 65 is 0.	72	1 ☐
	65	1 ☐
B. Spelling Backwards Test		
Ask the subject to spell the word "WORLD" backwards. Record each response. Use the instructions to determine which are correct responses, and check one box at right fore each correct response.	D	1 ☐
	L	1 ☐
	R	1 ☐
C. Final Score	O	1 ☐
Compare the scores of the Counting Backwards and Spelling Backwards tests. Write the greater of the two socres in the box labeled FINAL SCORE at right, and use it in deriving the **TOTAL SCORE**.	W	1 ☐
		FINAL SCORE_____ (Max of 5 or Greater of the two Scores)

IV. **RECALL**	(correct = ☑)	(Maximum Score = 3)
Ask the subject to recall the three words you previously asked him/her to remember. Check the Box at right for each correct response.	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐

V. Language	(correct = ☑)	(Maximum Score = 9)
Naming	Watch	1 ☐
Show the subject a wrist watch and ask him/her what it is. Repeat for a pencil.	Pencil	1 ☐
Repetition		
Ask the subject to repeat "No, ifs, ands, or buts."	Repetition	1 ☐
Three -Stage Command		
Establish the subject's dominant hand. Give the subject a sheet of blank paper and say, "Take the paper in your right/left hand, fold it in half and put it on the floor."	Takes paper in hand	1 ☐
	Folds paper in half	1 ☐
	Puts paper on floor	1 ☐

Reading		
Hold up the card that reads, "Close your eyes." So the subject can see it clearly. Ask him/her to read it and do what it says. Check the box at right only if he/she actually closes his/her eyes.	Closes eyes	1 ☐
Writing		
Give the subject a sheet of blank paper and ask him/her to write a sentence. It is to be written sponataneously. If the sentence contains a subject and a verb, and is sensible, check the box at right. Correct grammar and punctuation are not necessary.	Writes sentence	1 ☐
Copying		
Show the subject the drawing of the intersecting pentagons. Ask him/her to draw the pentagons (about one inch each side) on the paper provided. If ten angles are present and two intersect, check the box at right. Ignore tremor and rotation.	Copies pentagons	1 ☐

DERIVING THE TOTAL SCORE	
Add the number of correct responses. The maximum is 30.	TOTAL SCORE _____
23-30 = Normal / 19-23 = Borderline / <19 = Impaired	

CLOSE YOUR EYES

