



Amnesia for loss of consciousness is common in vasovagal syncope

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Aims

The aim of this study was to determine the prevalence of amnesia for loss of consciousness (A-LOC) in those who have a history suggestive of vasovagal syncope (VVS) and who develop syncope on head-up tilt (HUT) table testing. Furthermore, we wished to determine if A-LOC is an age-dependent phenomenon in VVS and whether haemodynamic parameters on tilting can predict for A-LOC.

Methods and results

Patients were recruited in a dedicated syncope unit and underwent neurocardiovascular evaluation as indicated under European Society of Cardiology guidelines to illicit a diagnosis of VVS. A set protocol of questioning occurred following induced syncope to determine the presence of A-LOC. The prevalence of A-LOC following syncope on tilting was 28% (44/159). Forty-two per cent of those ≥ 60 years of age vs. 20% < 60 years of age experienced amnesia post-induced syncope ($P = 0.003$). However, regression analysis did not show age to be an independent predictor for A-LOC. Blood pressure change between those without amnesia and those with amnesia showed no significant difference ($P = 0.687$). There was a significant difference in heart rate response; those experiencing amnesia had reduced bradycardic response on HUT compared with those without amnesia ($P = 0.001$).

Conclusion

Amnesia for loss of consciousness is common in VVS. Although more prevalent, it is not unique to older age-groups. Absence of syncope associated bradycardia during HUT testing predicts for A-LOC.

Keywords

Amnesia • Vasovagal syncope • head-up tilt Table test • Unexplained falls

Introduction

Amnesia for loss of consciousness (A-LOC) has been commonly described in the setting of neurological injury such as traumatic head injury, seizures or in the setting of transient global amnesia.¹ Syncope is defined as a transient spontaneous loss of consciousness, characterized by a loss of postural tone with a spontaneous recovery.² Neurally mediated syncope encompasses carotid sinus syndrome (CSS) and vasovagal syncope (VVS). Temporary reduction of cerebral blood flow occurs with syncope, including to regions which control memory such as the hippocampus and reticular activating system.³ The relevance of amnesia in the setting of neurally mediated syncope is important in the context of unexplained falls particularly in older adults.^{4,5} If an individual does not recall syncope, an inappropriate pathway of investigation may ensue and modifiable underlying causes

overlooked. Recurrent episodes increase further the risk of injury and fracture. In older adults witness account may only be available in up to 40% of persons with syncope or unexplained falls.⁶ A witness account is often the vital key in establishing whether a definite loss of consciousness has occurred. Without it, investigating the underlying aetiology of unexplained falls or drop attacks becomes a much more challenging task.

Thirty per cent of individuals with CSS and witnessed loss of consciousness have A-LOC during reproduction of symptoms in a clinical setting.⁷ A study assessing characteristics of patients presenting with unexplained falls vs. unexplained syncope reiterated this point. Ninety-five per cent of those presenting with unexplained falls had A-LOC during carotid sinus massage compared with 27% of those with syncope as a presenting symptom.⁸ This exposes the dilemma which exists when assessing an older faller who presents with both lack of warning and lack of witness account for events.

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Vasovagal syncope is often referred to as a more benign form of neurally mediated syncope. Although peak incidence occurs in teenage years, up to a 40% of unexplained recurrent syncope in older individuals is due to VVS.^{9,10} The low reported prevalence of VVS in the older population may in part be due to lack of history of prodrome, unavailable witness account, or the presence of cognitive deficits.

The prevalence of A-LOC in VVS is unknown. Case reports have alluded to its existence.¹¹ Although it is likely that cognitive deficits may have some role to play particularly in older persons, this is yet to be determined.¹² Lempert et al.¹³ demonstrate A-LOC in 2% of healthy young medical students in whom VVS was induced by a sequence of stooping and exaggerated valsalva manoeuvres. While orthostatic hypotension and CSS affect older adults in the majority, VVS occurs both in young and old and therefore enables analysis of the prevalence of A-LOC in all age-groups with syncope.

We suggest that A-LOC is also present in VVS and has a role to play in the context of unexplained falls. The main objective of this study was to establish the prevalence of A-LOC in VVS and to compare its prevalence both in younger and older age-groups. Furthermore, we wished to explore whether haemodynamic changes during VVS have a role to play in patients with A-LOC.

Methods

Study population

Consecutive patients were recruited prospectively over an 18-month period from a dedicated syncope unit in a tertiary referral teaching hospital. Source of referrals to this unit include accident and emergency, cardiology and neurology specialty referrals, general practitioner, and hospital physician referrals. All new patients 16 years of age or older, were invited to participate, gave informed written consent and completed a detailed questionnaire on the characteristics of presenting events (falls and syncope). In addition all patients had a full history taken, physical examination, 12-lead surface electrocardiograph (ECG), and assessment for postural blood pressure change on standing using finometer equipment. Cognitive testing using the minimal state examination (MMSE) was also completed in all patients 60 years of age or older. This is a 30-point questionnaire which assesses orientation, attention, executive function, and memory. Carotid sinus massage was performed in those 50 years of age or older who did not have contraindications and for whom the diagnosis remained unknown. If syncope remained unexplained patients proceeded to head-up tilt (HUT) testing. A diagnosis of VVS was established when reproduction of prodrome or syncope experienced during real-time syncope occurred with HUT testing. The study complied with the Declaration of Helsinki and was approved by the local Research Ethics Committee.

Inclusion and exclusion criteria

Participants had at least one unexplained fall/syncopal episode in the preceding 18 months. Patients were excluded if an alternative diagnosis was concluded at the end of testing such as seizure, cardiac, or psychogenic syncope. Those 60 years of age or older who were unable to complete an initial questionnaire or had an MMSE score of <24/30 were excluded from initial analysis.

Head-up tilt assessments

Head-up tilt testing was performed between 09:00 and 13:00 h. This occurred at a room temperature of 23°C. Patients were advised to take medications as normal on the day of testing. The Italian Protocol HUT (IPHUT) was used for investigation.¹⁴ If this test was negative, patients returned for a Front-loaded HUT (FLHUT).¹⁵ This took place at 09:00 h in the same environment and was preceded with an overnight fast of at least 12 h.

Italian Protocol head-up tilt

Patients rested supine for at least 10 min prior to testing. Continuous non-invasive beat-to-beat blood pressure monitoring was recorded during testing using finometer digital plethmography (Finapres-Philips). Continuous three-lead heart rate monitoring occurred throughout testing. All subjects had a 12-lead ECG that was recorded during symptom reproduction or change in blood pressure. Patients were secured to the tilt bed using two horizontal straps, feet rested on a secure foot plate. The bed was tilted to a 70° angle and patients were advised to voice any symptoms should they occur. At 20 min into testing if the patient remained asymptomatic 400 µg of Glyceryl trinitrate was administered sublingually. The function of glyceryl trinitrate is to enhance venodilation and venous pooling to precipitate VVS. The test was continued for a further 15 min or until symptom reproduction or loss of consciousness occurred.¹⁴

Front-loaded head-up tilt

Fasting subjects rested supine for 10 min prior to testing with beat-to-beat non-invasive blood pressure monitoring and heart rate monitoring as per Italian Protocol. The bed was tilted to a 70° angle. Three minutes into testing 800 µg of glyceryl trinitrate was administered sublingually. The test was continued for 20 min until symptom reproduction or loss of consciousness occurred.¹⁵

Assessment of amnesia for loss of consciousness

All HUT tests were supervised throughout by a nurse and doctor. When loss of consciousness occurred, the tilt bed was immediately returned to a supine position. If prodromal symptoms occurred prior to syncope, patients were asked to repeatedly count backwards from 10 to 1 aloud. Once the bed was supine the patients legs were raised upright with the addition of physical counter manoeuvres to expediate restoration of cerebral perfusion and consciousness.¹⁶

Patients were not informed prior to HUT that they were going to be questioned on whether loss of consciousness had occurred after the test. 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 patient was considered not to have lost consciousness. All senior doctors and nurses were trained in the use of a standardized questionnaire at the start of the study to assess A-LOC. A standard protocol of questions to establish whether the patient was aware they had lost consciousness was administered once the patient was fully alert and blood pressure and heart rate had returned to baseline recordings. 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 15 min later when the patient was fully recovered or ambulant prior to leaving the clinic. If the patient again denied loss of consciousness this was termed delayed amnesia. If the patient was unsure whether

or not they had lost consciousness they were deemed not to have A-LOC.

Statistics

Analysis of data was carried out using SPSS 16.0 software. Blood pressure and heart rate data during HUT was initially interpreted using 1 s averaging and transferred from excel to SPSS 16.0 for further analysis. Categorical data were analysed using Pearson's χ^2 and where appropriate Fisher's exact test. Continuous variables were initially analysed for normality using the one-sample Kolmogorov–Smirnov test. Parametric data were then analysed using *t*-test and non-parametric data using the Mann–Whitney *U* test. Binary logistic regression analysis was then performed with A-LOC as the dependent categorical variable.

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

Results

Of 800 patients who completed questionnaires, 387 went on to have a HUT test of whom 159 lost consciousness with an end diagnosis of VVS (137 IPHUT and 22 FLHUT) (Figure 1). In those who went on to lose consciousness ($n = 159$); mean age was 47.11 ± 21 (median age 45; range 16–87) years and 113 (71%) were female. Questionnaire information revealed that the mean number of syncopal episodes per lifetime was 4.5. One hundred and forty-two (89%) recalled at least one episode of loss of

consciousness while 17 (11%) denied or were unsure they had ever lost consciousness in their lifetime. For 39 (25%), at least on one occasion in the past, a witness had told them that they had lost consciousness of which they had been unaware.

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 44/159 (28%). Delayed A-LOC was more common in patients 60 years of age or older in comparison with those younger than 60 years ($P = 0.003$) CI 2.97 (1.44, 6.10) (Figure 2). Baseline characteristics of those with A-LOC and those without A-LOC are shown in Table 1. Mean age of those with A-LOC was 55 ± 22 years (median age 52.5; range 16–83 years). Mean age of those without A-LOC was 44 ± 20 years (median 41 years; range 16–87 years). 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 ($P = 0.02$). 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 (Table 1).

Haemodynamic parameters in those patients who lost consciousness on HUT testing were further analysed. Of 159 patients, 23 were excluded from analysis. Reasons for exclusion were missing data, unsuitable quality of data for analysis, and insufficient dataset for symptoms. The remaining 136 datasets were suitable

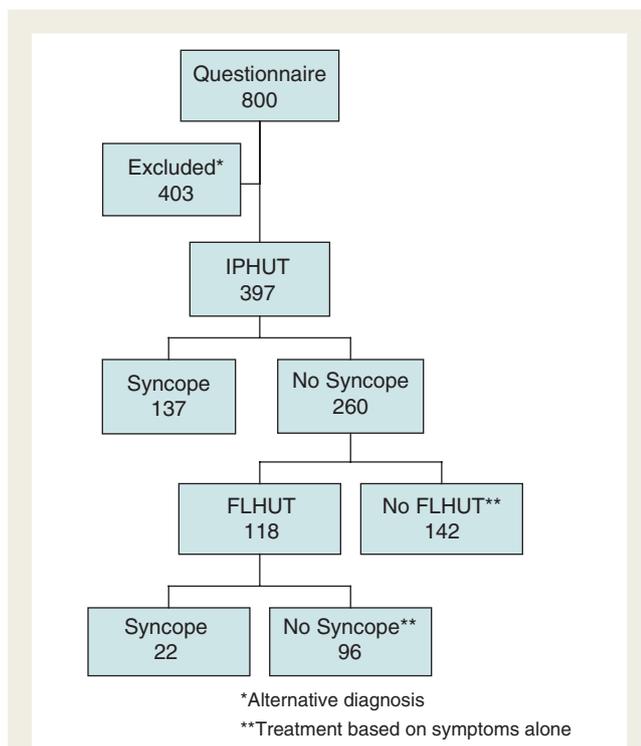


Figure 1 Pathway to head-up tilt. Figure showing pathway to Italian Protocol head-up tilt (IPHUT) and Front-loaded head-up tilt (FLHUT).

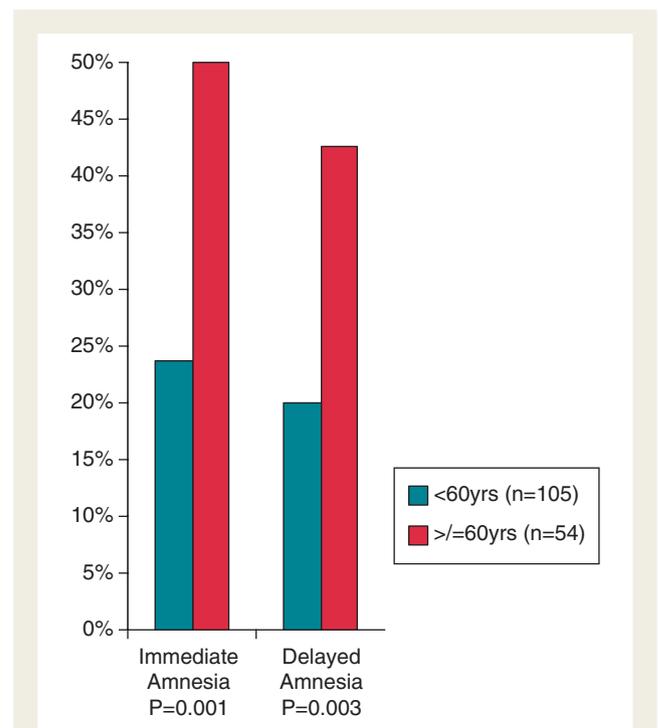


Figure 2 Amnesia for loss of consciousness (A-LOC) in different age-groups ($n = 159$). Twenty-five (23.5%) of those <60 years had immediate A-LOC compared with 27 (50%) of those >60 years ($P = 0.001$) CI 3.20 (1.59, 6.41). Twenty-one (20%) of those <60 years had delayed A-LOC compared with 23 (42.6%) of those >60 years ($P = 0.003$) CI 2.97 (1.44, 6.10).

Table 1 Clinical characteristics of those who lost consciousness on head-up tilt ($n = 159$)

	A-LOC ($n = 44$)	No A-LOC ($n = 115$)	P value
Mean age years	55.25 \pm 22.51	44 \pm 19.65	0.003
Female sex	30 (68%)	83 (72%)	0.619
Type of tilt—IPHUT	38 (86%)	99 (86%)	0.964
History of IHD	0%	3 (3%)	0.560
History of prodrome with real-time syncope	26 (59%)	98 (85%)	0.001
History of unexplained falls	19 (43%)	45 (39%)	0.67
History of fracture with syncope	15 (34%)	20 (17.4%)	0.02
MMSE (age > 60 years) ($n = 54$)	28.42 \pm 1.89 ($n = 23$)	28.95 \pm 1.63 ($n = 31$)	0.24

Table 2 Haemodynamic characteristics of those with syncope on head-up tilt ($n = 136$)

	A-LOC ($n = 36$)	No A-LOC ($n = 100$)	P value
Time to symptom onset (seconds) ($n = 123$)	1295 \pm 381 ($n = 33$)	1081 \pm 508 ($n = 90$)	0.058
Time from symptom onset to syncope (second) ($n = 123$)	207 \pm 308 ($n = 33$)	326 \pm 427 ($n = 90$)	0.153
Mean baseline SBP (mmHg)	144.48 \pm 24.25	138.55 \pm 20.1	0.153
SBP at the time of syncope (mmHg)	62.5 \pm 16.68	58.61 \pm 16.14	0.142
Change in SBP from baseline to time of syncope (mmHg)	81.98 \pm 29.27	79.94 \pm 24.75	0.687
Rate of change in SBP from baseline to syncope (mmHg/s)	0.06 \pm 0.02	0.07 \pm 0.05	0.581
Baseline HR (bpm)	65.11 \pm 12.13	68.58 \pm 9.88	0.09
HR at time of syncope (bpm)	59.92 \pm 25.83	47.3 \pm 20.87	0.004
Change in HR from baseline to time of syncope (bpm)	5.19 \pm 23.19	21.28 \pm 22.41	0.001
Rate of change in HR from baseline to syncope (bpm/s)	0.005 \pm 0.022	0.021 \pm 0.025	0.001

mmHg, millimetre mercury; SBP, systolic blood pressure; bpm beats per minute.

Table 3 Binary logistic regression analysis with A-LOC (Backward Wald)

	B	SE	Wald	d.f.	Significance	Exp(B)	CI (lower)	CI (upper)
Time to symptom onset (s)	0.001	0.001	2.769	1	0.09	1.001	1.000	1.002
Change in HR from baseline to syncope (bpm)	-0.03	0.01	8.770	1	0.003	0.970	0.951	0.990
Prior prodrome	-1.478	0.508	8.474	1	0.004	0.220	0.084	0.617

Variables entered on step 1: age, prior prodrome, prior fracture, time to symptom onset, baseline HR, 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.

for analysis of whom 117 (84%) of patients had a positive IPHUT and 19 (14%) a positive FLHUT. Thirteen subjects had sudden LOC with no warning symptoms during HUT. Patients with A-LOC recognized symptoms of hypotension later than those with no A-LOC ($P = 0.058$) (Table 2). 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 ($P = 0.004$) than those with A-LOC. Both the reduction in heart rate ($P = 0.001$) and the rate at which this

reduction occurred ($P = 0.001$) was significantly greater in those with no A-LOC in comparison with 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 (Table 3). Lack of a reported prodrome with prior syncopal episodes along with lack of documented bradycardia on HUT were independent predictors for A-LOC, with increased time to symptom onset during HUT having a trend in significance for the prediction of A-LOC.

Discussion

This is the first prospective study to our knowledge investigating A-LOC in patients with a diagnosis of VVS confirmed with

reproduction of syncope on HUT. The prevalence of A-LOC in this study was 28% (44/159). This prevalence rate is consistent with previous reports on the prevalence of amnesia in patients with CSS.⁷ However, CSS is almost exclusively a disorder of aging found in those 50 years of age or older. In our series of patients, 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 adults there was no significant difference noted in MMSE scores (a traditional measure of cognitive function) in those with A-LOC and those without A-LOC. This is consistent with previous research observing A-LOC in CSS.⁸

In those who went on to have subsequent A-LOC on HUT and those who did not, similar numbers reported a history of unexplained falls. However, those with A-LOC in VVS were less likely to have reported warning symptoms with real-time syncopal episodes (59 vs. 85%) and were more likely to have had a fracture with a syncopal episode or unexplained fall in the past (34 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.⁸ However, those with no A-LOC in VVS had a more marked and faster bradycardic response during HUT, i.e. 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 chance for 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, this study also confirms that other factors outside of cognition and haemodynamic change during VVS must play a role in the development of A-LOC in syncope. It is more probable 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. 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.¹⁷ The actual pathway for this interaction remains unknown. Parry *et al.*¹⁸ also demonstrated altered cerebral autoregulation in patients with cardioinhibitory CSS and postulated that this may have a role in A-LOC.⁸ 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 neuronal activity within the hippocampus has been shown to correlate with memory loss and hippocampal atrophy.^{19,20} Long-term exposure to high cortisol levels have been implicated and shown to be inversely related to simple memory tasks.²¹ 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.

There are limitations to this study. Normal cognition is suggested by >26/30 MMSE score. Mini-mental state examination is a global screen of cognitive function and a widely used test but is not sensitive enough to identify subtle changes in cognition. Head-up tilt does not always replicate real-time syncopal episodes as internal loop recorder analysis in patients with VVS has demonstrated.²² 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.²³

Vasodepressor responses are more commonly reported in older adults on HUT as compared with younger adults.²⁴ While the mean age was higher in patients with A-LOC, we did not find age as an independent predictor on regression analysis. There were fewer older than younger patients in our study (54 vs. 105). 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 patients. No studies however have assessed A-LOC in younger adults in the setting of syncope previously but it has been reported in the literature.^{13,25,26} 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 for VVS particularly in the older adult. This study would suggest that VVS may not be as benign as commonly reported. The association of VVS and unexplained falls resulting in injury has been reported previously.^{11,27} The presence of A-LOC in the setting of VVS further re-emphasizes the need for 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 (59 vs. 85%, $P < 0.001$) and increased injury rate (34 vs. 17.4%, $P < 0.02$) further emphasizes the importance and need for consideration of HUT in the setting of unexplained fall and syncope particularly in the older adult once other causes have been excluded.

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

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