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A dedicated investigation unit improves management of syncopal attacks (Syncope Study of Unselected Population in Malmö—SYSTEMA I)

Artur Fedorowski [1,2]*, Philippe Burri [1,2], Steen Juul-Möller [3], and Olle Melander [1,2]

[1]Center for Emergency Medicine, Skåne University Hospital, Entrance 33, Floor 5, SE 20502 Malmö, Sweden; [2]Lund University, Department of Clinical Sciences, 20502 Malmö, Sweden; and [3]Department of Cardiology, Skåne University Hospital, 20502 Malmö, Sweden

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Aims To investigate whether a systematic approach to unexplained syncopal attacks based on the European Society of Cardiology guidelines would improve the diagnostic and therapeutic outcomes.

Methods and results Patients presenting with transient loss of consciousness to the Emergency Department of Skåne University Hospital in Malmö were registered by triage staff. Those with established cardiac, neurological, or other definite aetiology and those with advanced dementia were excluded. The remaining patients were offered evaluation based on an expanded head-up tilt test protocol, which included carotid sinus massage, and nitroglycerine challenge if needed. Out of 201 patients registered over a period of 6 months, 129 (64.2%) were found to be eligible; of these, 101 (38.6% men, mean age 66.3 $\pm$ 18.4 years) decided to participate in the study. Head-up tilt test allowed diagnoses in 91 cases (90.1%). Vasovagal syncope (VVS) was detected in 45, carotid sinus hypersensitivity (CSH) in 27, and orthostatic hypotension (OH) in 51 patients. Twelve patients with VVS and 15 with CSH also had OH, whereas 25 were diagnosed with OH only. In a multivariate logistic regression, OH was independently associated with age [OR (per year): 1.05, 95% CI 1.02–1.08, $P = 0.001$], history of hypertension (2.73, 1.05–7.09, $P = 0.039$), lowered estimated glomerular filtration rate (per 10 mL/min/1.73 m^2: 1.17, 1.01–1.33, $P = 0.032$), use of loop diuretics (10.44, 1.22–89.08, $P = 0.032$), and calcium-channel blockers (5.29, 1.03–27.14, $P = 0.046$), while CSH with age [(per year) 1.12, 1.05–1.19, $P < 0.001$), use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (4.46, 1.22–16.24, $P = 0.023$), and nitrates (27.88, 1.99–389.81, $P = 0.013$).

Conclusion A systematic approach to patients presenting with unexplained syncopal attacks considerably increased diagnostic efficacy and accuracy. Potential syncope diagnoses have a tendency to overlap and show diversity in demographic, anamnestic, and pharmacological determinants.

Keywords Syncope • Orthostatic hypotension • Carotid sinus hypersensitivity • Tilt-table test • Antihypertensive agents

Introduction

Syncope is a common primary diagnosis at emergency departments (EDs) reported in ~1.5% of cases.[1–6] The management of suspected syncopal attacks (or transient loss of consciousness, T-LOC) is often challenging, especially when symptoms cannot be related to obvious cardiac, neurological, toxic, metabolic, traumatic, or infectious factors. Although anamnestic data and doctor's

* Corresponding author. Tel: +46 40 33 10 00, Fax: +46 40 33 62 08, Email: artur.fedorowski@med.lu.se

intuition may lead to correct final diagnosis, many patients leave EDs and hospital wards without knowing what really happened to them. In order to standardize the diagnosis and management of syncope, the European Society of Cardiology (ESC) has published guidelines,[7] but their practical implementation seems in general to be delayed. Meanwhile, those centres which have already established physical or virtual syncope management units report lower frequency of unexplained cases and reduced resource consumption.[8–10]

In the present trial, we decided to investigate a case series of emergency patients with unexplained T-LOC in a clinical setting, which lacks a systematic approach to this issue. The assessment of patients was based on a methodical application of the head-up tilt-table test (HUT) and cardiac arrhythmia evaluation, if appropriate, according to the present guidelines.

The aims of the study were: (i) to investigate how many patients attend ED because of suspected syncopal attack and receive the final diagnosis before being discharged from the hospital, (ii) to examine whether a systematic approach with application of HUT may improve the diagnostic process, and (iii) to study the frequency, characteristics, and determinants of dysautonomic/neurally mediated syncopal attacks.

Methods

Study location, duration, and population

The study was designed as a single-centre prospective case series. Patients were enrolled and investigated at the Skåne University Hospital, Malmö between September 2008 and May 2009.

Skåne University Hospital in Malmö is part of a regional tertiary hospital and serves an urban population of ~350 000 citizens. Emergency department at the study site takes care of ~200 patients per day, who are assigned to three main lines: internal medicine, surgery, and orthopaedics. Initially, all the patients go through a triage sector, and are successively directed to the proper line for diagnosis and treatment. Of these, about one-third are admitted to a short stay observation ward, or directly to one of the specialized hospital wards. During the present study, there were no specific syncope management guidelines for doctors working at ED, nor was there a specific unit or specialist to which suspected syncopal patients could be referred. The decision on how to manage patients presenting with T-LOC was incumbent on an individual doctor, who might consult a senior colleague if necessary.

Selection of patients

In this study, we decided to apply a multiple-stage model (*Figure 1*). First, patients presenting with a suspected syncope (T-LOC associated with the loss of postural tonus), traumatic fall of unclear origin with retrograde amnesia, or sudden-onset postural dizziness of unclear origin (suspected pre-syncope) were registered on a special list by the triage team. The team was instructed not to inform doctors working at ED about the registration. Then, the patients were transferred to a specific ED line for further assessment, treatment, admission, or dismissal from ED according to a doctor's decision.

In the next stage, a senior consultant, a specialist in cardiology and internal medicine (A.F.), collected the lists (every week or 2 weeks) and scrutinized the medical records of registered patients in order to select those who did not receive any final diagnosis, or were diagnosed with the term 'unspecific syncope' (R 55.9, ICD-10). Those with clinical signs and test results confirming cardiac (i.e. arrhythmia or structural disease), neurological, metabolic, toxic, and other definite aetiology of T-LOC were excluded, as were those with advanced dementia (arbitrarily or if mini mental test <15) and physical disability. The remaining patients were thereafter contacted and asked to participate in the study.

All participants gave written informed consent and the study was approved by the local Ethics Committee of Lund University.

Study protocol

Patients who responded positively to the invitation were investigated within 1–4 weeks at a dedicated HUT facility according to the

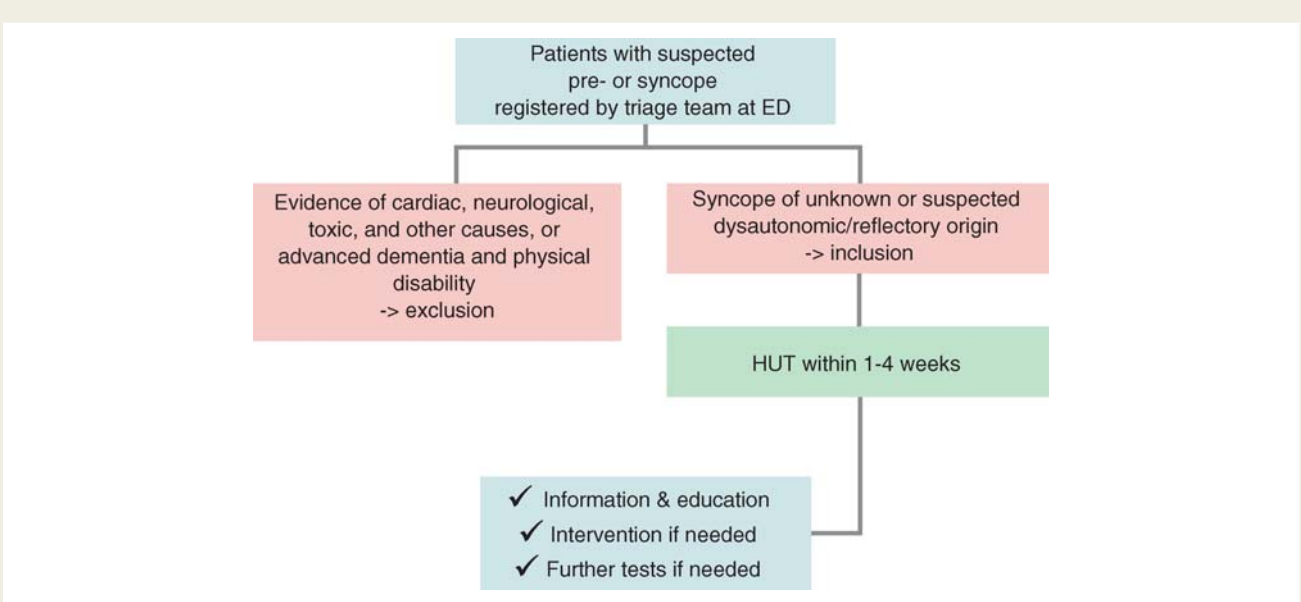

Figure 1 The general flowchart of the study.

protocol adopted from ESC guidelines,[7] including carotid sinus massage (the Newcastle protocol) and 20/15 min nitroglycerine test (the Italian protocol),[11] with addition of the active standing test if the initial orthostatic hypotension (OH) was suspected.[12] In selected cases (carotid bruits observed during admission or hospitalization), a carotid Doppler was performed prior to examination to exclude significant carotid artery stenosis (>70%). On the day of examination, study participants took their regular medication and fasted for 3 h before the test, although they were allowed to drink water *ad libitum*. They were also asked to fill in a questionnaire, which explored their past medical history, including the duration and frequency of syncope-related symptoms, and actual medication.

During examination, blood pressure (BP) and ECG were continuously registered using a validated non-invasive beat-to-beat BP monitor Nexfin HD (BMEYE B.V., Amsterdam, The Netherlands).[13]

Diagnostic criteria of orthostatic hypotension, carotid sinus hypersensitivity, and reflex syncope

The following diagnostic criteria were applied: (i) reproduction of symptoms (dizziness, light-headedness, pre- and syncope), if patients were able to recall conditions preceding syncope, and (ii) conventional criteria of OH, carotid sinus hypersensitivity (CSH), and reflex (neurally mediated) syncope (NMS).[7,11] Briefly, OH was defined as a sustained decrease in systolic BP (SBP) $\geq$20 mmHg and/or decrease in diastolic BP $\geq$10 mmHg, or SBP $<$ 90 mmHg within 3 min of HUT, CSH as a fall in SBP $\geq$50 mmHg and/or asystole >3 s, while NMS as a reproduction of syncope associated with a characteristic pattern of pronounced hypotension and/or bradycardia/asystole. Moreover, we decided to expand the definition of OH by adding delayed and initial OH to the study protocol.[7,12,14] The latter was determined by active standing if the anamnestic data were suggestive of this type of disorder. Finally, patients demonstrating NMS were divided into the classical and dysautonomic pattern according to BP dynamics preceding vasovagal reflex,[7,15] i.e. those with progressive BP fall prior to syncope were classified as dysautonomic.

If orthostatic challenge was positive in terms of conventional diagnostic OH criteria (SBP fall $\geq$20 mmHg), but patient did not reproduce symptoms or results were inconclusive, we usually proceeded with nitroglycerine provocation, if standing SBP >90 mmHg.

Management of test results

Patients who received their final diagnosis were informed and instructed how to cope with the syncopal attacks. The pharmacological treatment was modified at need (including discontinuing medication or starting a new treatment), and further tests were planned, if the investigator adjudged it necessary (e.g. 24 h BP or ambulatory ECG monitoring, echocardiography, etc.). Moreover, if the test results were negative and anamnestic data were suggestive of underlying cardiac arrhythmia, the patients were evaluated by a cardiac arrhythmia expert (S.J.-M.), as were those who demonstrated cardioinhibitory reaction (VASIS type II, especially IIB) during HUT. In selected cases, external or implantable loop recorder, and cardiac pacing were applied, according to the current ESC guidelines.

Estimation of kidney function

The estimated glomerular filtration rate (eGFR) was calculated according to Cockcroft–Gault formula: eGFR = (140 − age) × body weight (kg) × constant/plasma creatinine (μmol/L), where constant is 1.23 for men and 1.04 for women.

Estimated glomerular filtration rate was then corrected for the body surface area (BSA) and expressed as compared with the average-sized man (1.73 m^2), calculated as follows: $eGFR_{corrected} = eGFR \times 1.73\ m^2/BSA$, where BSA = weight $(kg)^{0.425}$ × height $(cm)^{0.725}$ × 0.007184.

Statistical analysis

Group-wise differences in continuous variables were compared using the *t*-test, and variables, which were not normally distributed, were log-transformed prior to the analysis. Dichotomous variables were compared using the χ^2 test. Thereafter, we performed a multivariate-adjusted (age, gender, and BMI) binary logistic regression analysis, entering OH, CSH, or NMS as the dependent variables, and covariates relating to patients' medical history, physical status, biochemical tests, and use of medication as independent variables, in order to identify independent determinants of OH, CSH, and NMS in the study population.

All calculations were performed using SPSS statistical software version 17.0 for Windows (SPSS Inc. 233 S. Wacker Drive, Chicago, IL, USA). All tests were two-sided and a $P < 0.05$ was considered statistically significant.

Results

As can be seen in *Figure 2*, out of 201 patients registered by the triage team over a period of approximately 6 months, 129 (64.2%) qualified for the study. One hundred and one patients (78.3%) responded positively to the invitation and were successively examined.

Seven (6.9%) of the included patients presented with suspected pre-syncope (sudden-onset dizziness) or unexplained traumatic fall only without an unambiguous syncope anamnesis, and 27 patients (26.7%) reported their first syncopal episode ever. The characteristics of the study participants are presented in *Table 1*. The mean age was rather high (~66 years), reflecting the fact that 54 patients (53.5%) were older than 70 years. Another significant observation was the high percentage (54.5%) of those reporting hypertension in their medical history. As can be seen in *Table 2*, almost one-third of study participants were on beta-blockers, and one-third were treated with renin–angiotensin–aldosteron system (RAAS) blockade [angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs)].

Ninety-one patients (90.1% of the study participants) obtained their final diagnosis on the basis of the test results. It should be emphasized that before the test was performed, none of them had received a specific diagnosis according to the medical journals and no information about the nature of syncope was given to these patients on their discharge from the hospital.

As shown in *Figure 3*, the diagnoses overlapped, but only one patient met the diagnostic criteria for all three disorders. The percentage of OH positive patients was relatively high (~50%), and of these 15 had lowest SBP $<$ 90 mmHg during orthostatic challenge. Twenty-five patients (24.8%) were diagnosed with OH only, and most of them could reproduce characteristic symptoms during HUT. Twelve patients demonstrated delayed OH (23.5% of all OH positive patients), whereas rapid (initial) OH was found in 11 study participants (10.9% of all participants). Among those with both OH and NMS ($n = 12$), nine patients demonstrated a dysautonomic pattern of vasovagal syncope, which actually meant

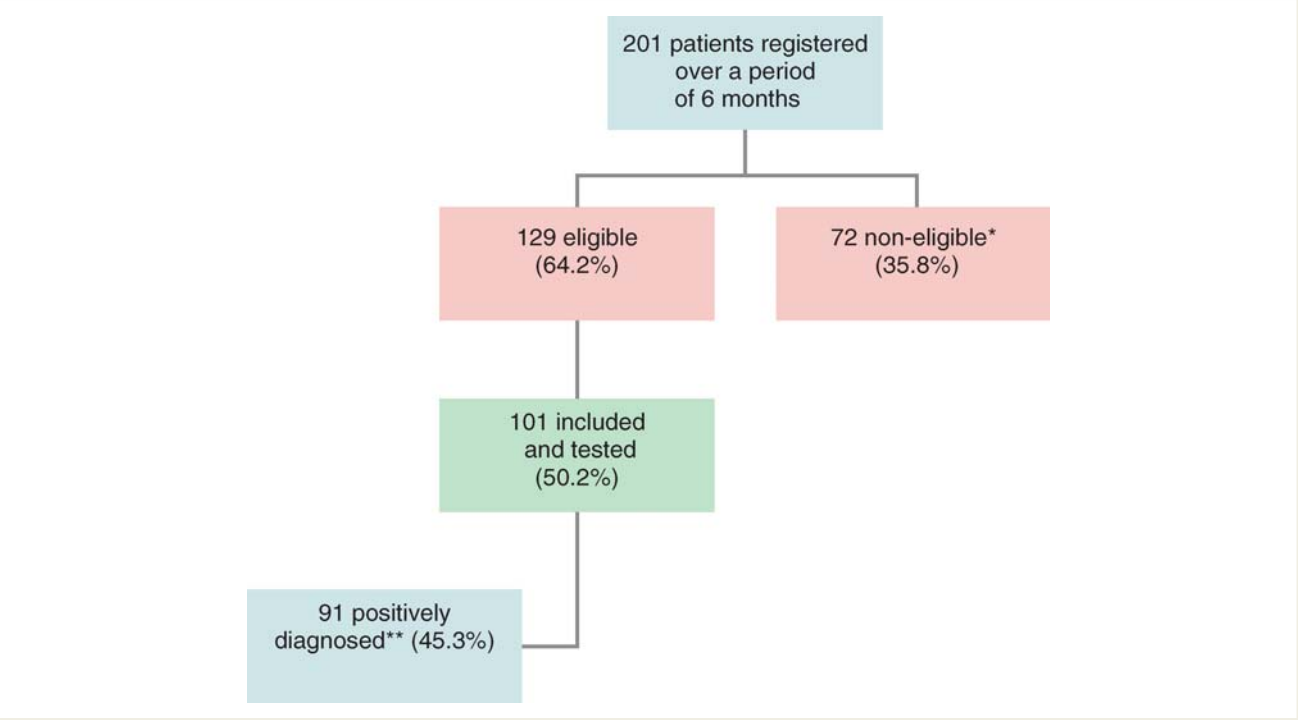

Figure 2 Overall results of the study. *Non-eligible: found to have cardiac, neurological, infectious, toxic, or other underlying causes, or incapable to undergo HUT (mentally or physically); **positively diagnosed: orthostatic hypotension, carotid sinus hypersensitivity, or vasovagal syncope.

Table 1 Characteristics of study participants (n = 101)

Covariate	Mean ± SD or percentage
Age (years)	66.3 ± 18.4
Gender (male, %)	38.6
BMI (kg/m^2)	24.6 ± 4.4
Current smoker (%)	12.2
History of hypertension (%)	54.5
History of MI (%)	11.9
History of stroke (%)	12.9
History of heart failure (%)	5.9
History of diabetes (%)	7.9
Atrial fibrillation (%)	5.0
Systolic BP, supine (mm Hg)	145.9 ± 27.5
Diastolic BP, supine (mm Hg)	74.7 ± 11.0
Heart rate, supine (b.p.m.)	70.3 ± 11.0
Estimated GFR (mL/min/1.73 m^2)	76.4 ± 34.6
Total cholesterol (mmol/L)	4.7 ± 1.1
HDL-cholesterol (mmol/L)	1.3 ± 0.4

Table 2 Drugs used by study participants (n = 101)

Medication	Percentage
Beta-blockers	30.7
Loop diuretics	12.9
Thiazide diuretics	18.8
Aldosterone antagonists	5.0
Potassium-sparing diuretics	4.0
Calcium-channel blockers	13.9
ACE-inhibitors	14.9
ARB	14.9
Alfa-blockers	2.0
Nitrates	5.9
Digoxin	3.0
Antiarrhythmic agents	2.0
Antidepressants	9.9
Thyroid hormone substitute	10.9
Statins	23.8

that orthostatic BP fall initiated the reflex syncope. In seven patients, this reaction was spontaneous (during the passive phase of HUT). Twelve out of 15 patients with both OH and CSH had the lowest SBP during orthostatic challenge <120 mmHg, but only two of them had lowest SBP <90 mmHg. Finally, in 10 patients, a pause >3 s was observed: seven in the NMS group (longest pause t = 46 s), and three in the CSH group. Three of them (two with CSH and one with severe NMS) received a pacemaker after being evaluated by a cardiac arrhythmia expert. The third patient with pause and CSH was on a high dose of beta-blocker during HUT and further tests were planned after

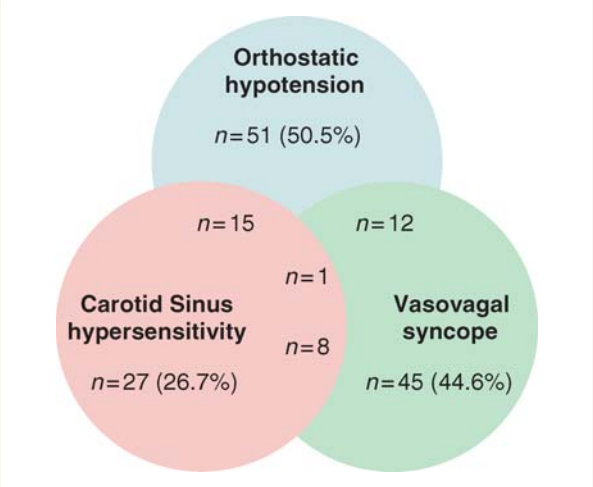

Figure 3 Frequencies and overlap of diagnoses.

Table 3 Independent predictors of orthostatic hypotension, carotid sinus hypersensitivity, and vasovagal syncope in a multivariate-adjusted (age, gender, and BMI) logistic regression model (n = 101)

Covariate	OR (95% CI)	*P*-value
Orthostatic hypotension		
Age (per year)	1.05 (1.02–1.08)	0.001
History of hypertension	2.73 (1.05–7.09)	0.039
Δ eGFR ↓ (per 10 mL/min/1.73 m^2)	1.17 (1.01–1.33)	0.032
Use of loop diuretics	10.44 (1.22–89.08)	0.032
Use of CCB	5.29 (1.03–27.14)	0.046
Carotid sinus hypersensitivity		
Age (per year)	1.12 (1.05–1.19)	<0.001
Use of beta-blockers	0.19 (0.05–0.73)	0.015
Use of ACE-I/ARB	4.46 (1.22–16.24)	0.023
Use of nitrates	27.88 (1.99–389.81)	0.013
Vasovagal syncope		
Age (per year)	0.96 (0.94–0.99)	0.002

modification of the treatment. Moreover, seven CSH positive patients who demonstrated a non-asystolic cardioinhibitory pattern (VASIS II A) were accepted for more comprehensible evaluation, including external or implantable loop recorder, as were six NMS patients with asystolic response during HUT.

In three of those who passed the test without conclusive results (n = 10), an alcohol intoxication was later proved after detailed scrutiny of medical records and discussion with patients. In the remaining cases, no definite diagnosis could be given, suggesting an accidental fall or trauma as the most probable aetiology.

As can be seen from *Table 3*, advancing age was a predictor of both OH and CSH, as was impaired renal function and a history of hypertension, but for OH only. In parallel, there were differences in relationships between various classes of drugs used by patients and these diagnoses. Loop-diuretics and calcium-channel blockers (CCBs) were associated with a higher probability of OH during HUT, and ACE-Is or ARBs, and nitrates, with CSH. Interestingly, the use of beta-blockers was associated with lower probability of CSH.

More than half (n = 53) of the study participants were admitted to the Hospital after suspected syncopal attack and registration by the triage team. In a multivariate-adjusted logistic regression analysis (age, gender, and BMI), the Hospital admission was predicted only by age [OR (per year): 1.04, 95% CI 1.01–1.07, P = 0.018]. As shown in *Table 4*, those admitted to the Hospital were most frequently examined by brain CT/MRI and/or telemetry. Although proportion of those discharged from ED (<12 h), who underwent brain imaging studies, was also high, in-hospital and ambulatory ECG monitoring was less used in this subgroup.

Discussion

The management of syncopal attacks at ED is often challenging. The results of our study add to the available evidence on the importance of specialized syncope units for the diagnosis and treatment of patients presenting at ED with T-LOC. Hospitals, which lack syncope units, risk incurring unnecessary healthcare costs and delays or errors in the diagnostic process. Some of study participants were referred to a cardiologist, a neurologist, or an otolaryngologist for further evaluation before being examined with our protocol. Moreover, they were referred for various additional tests and examinations, such as echocardiography, exercise ECG, Holter ECG monitoring, brain CT scans, or EEG, none of which yielded a conclusive result. Actually, in none of the study participants did these referrals and additional tests lead to a definite diagnosis, nor did any of the patients receive advice on how to deal with their problem. Thus, the current evaluation system, based only on spontaneous and instinctive doctors' decisions, was unable to manage adequately two-thirds of all suspected syncopal patients, although ~50% of them were admitted to the hospital.

The triage team registered approximately one patient per day with suspected pre- or syncope. Given that the number of patients attending ED was ~200 per day, the team probably failed to register between one and two out of three eligible individuals. Unfortunately, we were not able to review the medical records of all emergency patients owing to time limits.

The constant aging of the Swedish population was well reflected by the fact that ~50% of study participants were older >70 years. Among those who were positively diagnosed, approximately one out of two had a reflex syncope (with or without OH component), and one-fourth were found to have OH as the only underlying cause of fainting. Furthermore, one-fourth demonstrated CSH. These relatively high frequencies for OH and CSH seem logical in the light of demographic statistics (age ↑). The impressive total prevalence of OH (50.5%) may also be explained by the current diagnostic criteria, which classify individuals with SBP fall >20 mmHg as OH positive,[16] even if the lowest standing SBP value is distinctly above 90 mmHg (e.g. in hypertensive patients).

Orthostatic hypotension was predicted in accordance with previous studies[17–19] by history of hypertension, impaired renal

Table 4 Examinations performed on the study participants before head-up tilt test

Examination	All patients (n = 101)	Admitted (n = 53)	Discharged (n = 48)
Brain CT/MRI	52 (51.5)	30 (56.6)	22 (45.8)
Carotid Doppler ultrasound	9 (8.9)	8 (15.1)	1 (2.1)
Echocardiography	13 (12.9)	7 (13.2)	6 (12.5)
In-hospital telemetry	44 (43.6)	33 (62.3)	11 (22.9)
Holter monitoring	26 (25.7)	17 (32.1)	9 (18.8)
Exercise stress testing	4 (4.0)	1 (1.9)	3 (6.3)
Angiography (pulmonary/coronary)	5 (5.0)	4 (7.5)	1 (2.1)
Electroencephalography	9 (8.9)	4 (7.5)	5 (10.4)
Neurological consultation	6 (5.9)	2 (3.8)	4 (8.3)

Subgroups of those admitted to the hospital and discharged from the emergency department are presented separately. Percentages are shown in parentheses.

function, and use of loop diuretics and/or CCBs. In contrast, CSH was predicted by use of RAAS blockers and nitrates, the latter having recently proved to be associated with OH-related syncopal attacks.[19] Surprisingly, use of beta-blockers was a negative predictor of CSH, but the relatively small sample in our study warrants a verification of this finding.

These results support a theory proposed by other authors[20] that a dedicated syncope facility may considerably improve the management of patients presenting with T-LOC. Indeed, our positive experience with the specialized syncope evaluation team and systematic application of expanded HUT resulted in a decision to start a syncope management unit at the study site in a close cooperation with cardiac arrhythmia experts. The unit has access to all diagnostic tests that are recommended by the current ESC guidelines.

In conclusion, patients who present with T-LOC are a constant challenge at EDs. According to our study, up to 90% of otherwise unexplained cases can be properly diagnosed and managed by a specialized team, using such a cost-effective instrument as a tilt-test laboratory with adjacent facilities and closely collaborating experts. Most of the problematic patients demonstrate a reflex syncope (~50%), while others (often elderly >70 years) are usually affected by OH or CSH (~25% each). The diagnoses overlap chiefly because of a high overall prevalence of OH (~50%), which is frequently asymptomatic. Advancing age, history of hypertension, impaired renal function, use of CCBs, and loop diuretics are independent predictors of OH, while CSH is significantly associated with advancing age, use of nitrates, and RAAS blockers, and inversely with use of beta-blockers. A systematic approach to the patients presenting with syncopal attacks based on a dedicated investigation unit may dramatically improve the diagnostic rate, cost-efficiency, and therapeutic accuracy.

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