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Orthostatic Hypotension As Cause of Syncope in Patients Older Than 65 Years Admitted to Emergency Departments for Transient Loss of Consciousness

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Background. Syncope due to orthostatic hypotension (OH) refers to loss of consciousness caused by hypotension induced by the upright position; it is an important risk factor for fall-related physical injuries, especially in the elderly adults. We evaluated the prevalence of OH syncope and the clinical characteristics of patients older than 65 years with syncope due to OH in the Evaluation of Guidelines in Syncope Study 2 group population.

Methods. Two hundred fifty nine patients older than 65 years consecutively admitted to the emergency department because of loss of consciousness in a period of a month were submitted to a standardized protocol approved by the European Task Force for the diagnosis of syncope; all the patients were studied by a trained physician who interacted with a central supervisor as the management of syncope was concerned, using a decision-making software.

Results. Prevalence of OH syncope was 12.4%. Patients with OH syncope were more likely to be affected by Parkinson's disease and by other neurological diseases. ST changes and longer values of QTc were found in OH syncope group, and they took a greater number of diuretics, nitrates, and digoxin. In multivariate analysis, Parkinson's disease ($p = .001$) and use of nitrates ($p = .001$) and diuretics ($p = .020$) were independently related to OH syncope.

Conclusions. In patients older than 65 years, Parkinson's disease and neurological comorbidity are strictly related to OH syncope. Moreover, this study suggests the independent link between OH syncope and the use of vasoactive drugs, identifying the majority of cases as adverse drug reaction, a preventable risk factor for syncope and falls in the older population.

Key Words: Orthostatic hypotension—Older—Emergency department—Diagnosis—Adverse drug reaction.

CURRENT strategies for diagnosing and treating syncope vary widely among physicians and hospitals; this results in inappropriate use of diagnostic tests and a high rate of misdiagnosed or unexplained syncope. These considerations have led to the development of several diagnostic pathways and expert consensus statements (1–3); the "Guidelines on the Management of Syncope of the European Society of Cardiology (ESC)" (4,5) define the current standard for the management of patients with transient loss of consciousness, establish the most effective diagnostic pathway, give recommendations on indications and the interpretation of diagnostic tests, and provide indications for hospitalization and treatment. Interestingly, the Task Force included in its staff three geriatricians because it is well known that syncope and falls are fundamental matters for the elderly adults. One of the most important causes of syncope in the older patients is orthostatic hypotension (OH), which refers to loss of consciousness caused by arterial hypotension induced by the upright position. It occurs when the autonomic nervous system is altered, resulting in a failure of vasoconstrictor mechanisms, or when volume depletion occurs. Previous studies have revealed an increased prevalence of OH with age: In community-dwelling individuals older than 65 years, its prevalence is approximately 20%; in those older than 75 years, it is as high as 30%, whereas in frail elderly individuals living in nursing homes,

* The investigators in the Evaluation of Guidelines in Syncope Study 2 are listed in Appendix 1.

it is even higher, up to 50% or more (6). Just because it causes syncope, OH may be an important risk factor for fall-related physical injuries, especially in older patients, though this has not yet been demonstrated in prospective studies. The prevalence of syncope due to OH is not so clear: First, the relation between hypotension and a syncopal episode is sometimes difficult to establish, and second, multiple disorders may act synergistically to cause syncope. As a consequence, the prevalence of syncope due to OH varies widely from 4% to 24%, according to the different diagnostic criteria used by distinct authors (7,8).

The Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) group is a systematic population-based evaluation of management of syncope based on strict and rigorous adherence to the ESC guidelines (9). This study was born to provide all stakeholders (physicians, hospital and clinical governance managers, future research planners, etc.) with a frame of reference for their daily activity when dealing with syncope. Many studies define the prevalence of OH, but few describe the real prevalence of syncope caused by OH in patients referring to Emergency Departments because of loss of consciousness, particularly in those older than 65 years. Moreover, the existent studies apply nonhomogeneous methods, often putting together asymptomatic with symptomatic OH. Thus, the aim of the present study was to evaluate the prevalence of OH syncope and the clinical characteristics of older patients with syncope specifically caused by OH in the EGSYS-2 population.

Methods

The method's details of the EGSYS study have been already published elsewhere (9). Briefly, the study is prospective and included all the patients consecutively admitted to the emergency service of 11 general hospitals in Italy from October 4, 2004, to November 5, 2004, because of transient loss of consciousness that, on initial evaluation, was attributed to a syncopal condition or because a syncopal condition could not be excluded. Patients with a definite nonsyncopal cause of loss of consciousness on initial evaluation, those aged younger than 18 years, and those referred more than 24 hours after their episode were excluded.

Each recruiting hospital has a 24-hour emergency department and a cardiology ward with a coronary care unit and meets the requisites for the management of syncope set by the ESC guidelines (4,5). These include complete equipment for syncope evaluation (ie, phasic blood pressure monitoring, tilt testing, external and implantable loop recorder, 24-hour ambulatory blood pressure monitoring, 24-hour ambulatory electrocardiographic [ECG] monitoring, and autonomic function testing), on-site access to usual investigations (echocardiography, invasive electrophysiological testing, stress testing, cardiac imaging, computed tomography or magnetic resonance imaging, and electroencephalography), and on-site access to any therapy that may be required for syncope (ie, pacemaker and implantable cardioverter-defibrillator implantation, catheter ablation).

The study complies with the Declaration of Helsinki; the protocol was approved by the ethics committees of all participating hospitals, and all participants gave written informed consent.

Diagnostic Pathway and Management Strategy

All the patients underwent the diagnostic evaluation in strict adherence to the recommendations of the ESC guidelines (4,5); the diagnostic pathway is shown in Figure 1 (4). Briefly, all the patients were submitted to the initial evaluation concerning history, physical examination, 12-lead ECG, and the measurement of blood pressure in both lying and standing positions.

Vasovagal or situational syncope was diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation, and prolonged standing were associated with typical prodromal symptoms or syncope occurred during or immediately after urination, defecation, cough, or swallowing. Cardiac ischemia-related syncope was diagnosed when symptoms were present with ECG evidence of acute ischemia with or without myocardial infarction, independently of its mechanism; cardiac arrhythmia-related syncope was diagnosed when symptoms were associated with major arrhythmias. If the initial evaluation was not diagnostic, a cardiac cause was suspected when syncope was preceded by palpitations or occurred in the supine position or during exercise or when the clinical examination and/or 12-lead ECG was positive for heart abnormalities; in this case, the researchers followed the cardiac arm of the flowchart.

Conversely, a neurally mediated mechanism was suspected when predisposing factors, precipitating events, and accompanying symptoms were present and/or the patient had recurrent syncopal episodes over several years, and heart disease was excluded by means of history, physical examination, and ECG; in this case, the patient was submitted to neurally mediated tests. When the initial evaluation led to no certain or suspected diagnosis, the syncopal episode was defined as unexplained syncope. Because in these patients the likely diagnosis is neurally mediated, the tests for neurally mediated syncope (tilt testing and carotid massage) were performed. Once the evaluation was completed and no cause of syncope was determined, reappraisal of the workup was performed.

In order to maximize the application of the ESC diagnostic algorithm, two main issues were accomplished: the use of a decision-making software based on ESC guidelines (EGSYS software, Version 1.0) and the training of a designed physician in each hospital participating in the study, who interacted with a central supervisor as the management of syncope according to ESC criteria was concern.

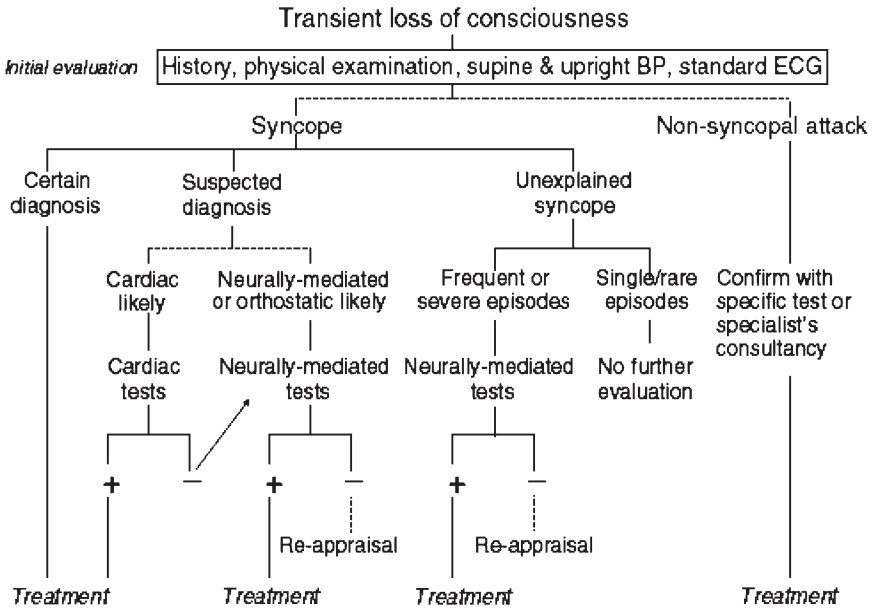

Figure 1. The flow diagram proposed by the Task Force on syncope to the evaluation of loss of consciousness based on the initial evaluation (4). Syncope: loss of consciousness caused by cerebral hypoperfusion; nonsyncopal attack: loss of consciousness due to other mechanisms; certain vasovagal/situational syncope: association of syncope with precipitating events (fear; pain; emotional distress; instrumentation; standing; and during or immediately after urination, defecation, cough, or swallowing); certain cardiacsyncope: symptoms associated with ECG evidence of acute ischemia with or without myocardial infarction or major arrhythmias; suspected neurally mediated syncope: presence of predisposing factors, precipitating events, and accompanying symptoms, and/or recurrent syncopal episodes over several years, and heart disease excluded by means of history, physical examination, and ECG; suspected cardiac syncope: syncope preceded by palpitations or in the supine position or during exercise, or when the clinical examination and/or 12-lead ECG was positive for heart abnormalities; unexplained syncope: no certain or suspected diagnosis at the initial evaluation. ECG = electrocardiogram.

In each hospital, an investigator usually involved in the management of syncope was designated and trained to run the study. Each day, the investigators were informed of every new admitted patient affected by loss of consciousness, followed the subsequent diagnostic flow of the patients, and gave advice in order to maintain strict adherence to the standardized workup. They were responsible for reviewing the patients' files and assigning the reported final diagnosis to one of the categories of the classification of loss of consciousness. Whenever discrepancies with the guidelines arose, they reevaluated the case with the central clinical monitors (cardiologists who were experts in syncope management—M.B. and R.M.), who had on-line access to the database. They daily supervised the entire process, verified adherence to the diagnostic pathway for all patients, and gave advice on any corrections deemed necessary.

Dropout criteria (patient's refusal, protocol violation, incomplete evaluation, incomplete records) were predefined. Minor deviations from the protocol, such as the execution of tests that were at risk of being inappropriate or that had been indicated for causes other than syncope (ie, trauma, underlying comorbidities, usual routine of the center), did not constitute a reason for dropout, but they were counted separately.

Diagnosis of OH Syncope

Orthostatic blood pressure measurements were recommended after 5 minutes of lying supine, were taken after 1 and 3 minutes of standing, and further continued if blood pressure was still falling at 3 minutes. A decrease in systolic blood pressure greater than 20 mm Hg or a systolic blood pressure less than 90 mm Hg was defined OH regardless of whether or not symptoms occurred (10). Syncope due to OH was diagnosed when there was a documentation of syncope or presyncope associated to the decrease of blood pressure defined previously. If the first-line evaluation was negative, or OH has caused no symptoms, OH syncope was eventually diagnosed during tilt testing when a fall in blood pressure within 3 minutes of tilt testing to 60° occurred in association with syncope or presyncope (11). Asymptomatic OH was diagnosed when a drop in blood pressure occurred from lying to standing position, but the patients did not complain symptoms of cerebral hypoperfusion (eg, blurred vision, vertigo, nausea).

Statistical Analysis

The analysis of data was performed using SPSS, 14th version (SPSS, Chicago, IL). The chi-squared test was used to compare proportions in univariate analyses of dichotomic variables and to calculate the odds ratios and the 95% confidence intervals. Student's t test for independent samples was used to compare continuous variables. Moreover, the median daily dose of drugs was calculated in 143 patients (55.2% of the population). Variables that were significantly associated with the outcome of interest in

Table 1. Clinical Characteristics of Patients Older Than 65 Years With and Without OHS

Characteristic	Without OHS (*N* = 227)	With OHS (*N* = 32)	*p*
Age, y	79.2 ± 7.1	81.2 ± 7.0	*ns*
Range	66–98	63–93	
Sex (male)	56.4	59.4	*ns*
Hypertension	55.5	62.5	*ns*
CHD	22.5	31.3	*ns*
Hypertensive HD	20.7	18.8	*ns*
Valvular HD	6.6	3.1	*ns*
Primary cardiomyopathy	1.8	0	*ns*
Other cardiac diseases	35.2	40.6	*ns*
Parkinson's disease	2.2	12.5	.003
Ischemic cerebral disease	13.7	21.9	*ns*
Other neurological diseases	11.9	25.0	.042
Diabetes	9.7	9.4	*ns*

Note: Data are expressed in percentage, except for age that is expressed as mean ± standard deviation. The diseases listed in the table were ascertained by clinical history. Other cardiac diseases: parossistic atrial fibrillation, past pacemaker implant; other neurological diseases: dementia and cognitive impairment, head trauma. CHD = coronary heart disease; HD = heart disease (hypertensive heart disease was defined as the presence of hypertension plus signs of left ventricular hypertrophy at electrocardiogram and/or echocardiography); OHS = syncope due to orthostatic hypotension.

univariate analyses, together with age and sex, were entered into a multivariate logistic regression model (backward stepwise) to assess their independent association with the outcome (syncope due to OH); the model also included variables that were not significantly associated to OH syncope but that were commonly known as clinically relevant (diabetes, ischemic cerebral diseases, ECG findings, type of drugs).

Results

Data regarding 259 patients older than 65 years consecutively admitted to the emergency department because of syncope (mean age 79.4 ± 7.1 years, 56.8% females) were analyzed. Overall, OH syncope was present in 32 patients (12.4%).

Syncope due to OH was established during the initial evaluation in 22 patients (8.5%). A diagnosis of OH syncope was also subsequently established in 10 patients who showed asymptomatic OH during the initial evaluation: 8 cases by means of tilt testing, which showed the typical pattern of late progressive OH, 1 case by means of 24-hour blood pressure monitoring, and 1 case with repeated orthostatic blood pressure measurement. Finally, 20 patients showed only asymptomatic OH (ie, not related to syncope or presyncope), so a diagnosis different from syncope due to OH was made at the end of the workup: neuromediated syncope (14 patients), carotid sinus syndrome (3 patients), arrhythmia (2 patients), and nonsyncopal loss of consciousness (1 patient).

Clinical characteristics and drugs taken (including drugs assumed during the past month) by patients with and without OH syncope are described in Tables 1 and 2, respectively.

Table 2. Drugs Assumed During the Past Month by Patients Older Than 65 Years With and Without OHS

	Without OHS (*N* = 227)	With OHS (*N* = 32)	*p*
Diuretics	24.7	37.5	.049
Ace inhibitors/sartans	44.1	43.8	*ns*
Calcium-channel blockers	11.0	21.9	*ns*
Beta-blockers	13.2	18.8	*ns*
Digoxin	6.6	18.8	.018
Antiarrhythmic drugs	7.9	12.5	*ns*
Nitrates	7.5	31.3	<.001
Antipsychotics	6.0	12.5	*ns*

Note: Data are expressed in percentage. OHS = syncope due to orthostatic hypotension; *ns* = not significant.

A normal ECG was found to be 37.5% in the group with syncope due to OH versus 43.2% in non–OH syncope group ($p = ns$); ST changes were found in 28.1% versus 19.4% ($p = .042$). A higher number of patients with longer values of QTc was found in OH syncope group (6.3% vs 0.4%, $p = .041$).

Five patients with diagnosis of syncope due to OH were correctly submitted to biochemical examination and to sinus carotid massage because of other comorbidities; nobody underwent cardiac evaluation (echocardiography, stress test, Holter ECG, intermittent loop recorder, coronarography), whereas tilt testing was appropriately executed in eight patients (25% of OH syncope patients). Neurological evaluation (cerebral tomography, electroencephalography) was correctly performed in two patients in whom the etiology of syncope due to OH was related to Parkinson's disease.

As shown in Table 3, the use of diuretics (mainly loop diuretics and hydrochlorotiazide) and nitrates was significantly related to syncope due to OH; this result was not dependent on the median daily dose; only very low doses of furosemide (<12.5 mg daily) were not related to OH syncope.

The recurrence of syncopal spells was significantly higher in patients with OH syncope (number of episodes in the whole life: 6.4 ± 5.7 vs 3.6 ± 4.8, $p = .040$).

Multivariate Analysis

Data are described in Table 3. Parkinson's disease was the only condition independently associated to syncope due to OH; no other cardiac (coronary heart disease, hypertensive

Table 3. Multivariate Analysis

	OR	95% CI	*p*
Parkinson's disease	10.91	2.645–45.05	.001
Use of diuretics	3.73	1.23–11.28	.020
Use of nitrates	5.20	1.99–13.61	.001

Note: Other variables included in the model: age, sex, ischemic heart disease, hypertension, hypertensive heart disease, valvular heart disease, myocardiopathy, other cardiac diseases, diabetes, ischemic cerebral diseases, other neurological diseases, electrocardiographic findings, type of drugs, daily dosage. CI = confidence interval; OR = odds ratio.

heart disease, valvular heart disease, myocardiopathy, others) or neurological (transitory ischemic attack stroke, others) diseases were found significantly related to OH syncope. As far as ECG findings were concerned, QTc and ST changes were not related to OH syncope in the multivariate model. The use of vasoactive drugs like diuretics and nitrates showed a strong link with syncope due to OH, independent of age, sex, daily dose, and cardiac and neurological diseases.

Discussion

By definition, decreased brain perfusion is common to all causes of syncope. Positional change from supine to standing causes a 300- to 800-mL shift in blood volume from the thorax to the lower extremities (12,13). Cerebrovascular autoregulation ensures that cerebral blood flow remains within a narrow range, regardless of systemic blood pressure. In patients with impaired vasoconstrictor compensatory reflexes, as occurs in older age and in different forms of autonomic failure like in Parkinson's disease, the increased downward pooling of the venous blood and the consequent reduction in stroke volume and cardiac output exaggerate the orthostatic decrease in blood pressure and lead to OH and symptoms of cerebral hypoperfusion shortly after orthostatic change (12). OH is one of the most frequent causes of syncope, ranging from 2% to 24% (8), but it is frequently underestimated, particularly in older patients, essentially because such patients infrequently undergo a standardized diagnostic protocol after a transient loss of consciousness. The diagnostic protocol derived from the ESC guidelines has been demonstrated to be applicable even beyond the age of 90 years in geriatric departments (14). In literature, the prevalence of OH and its relationship with older age are well known, but the number of patients with symptomatic OH is poorly studied, particularly in the emergency department. We found that OH caused syncope in 12.4% of our patients older than 65 years; as shown by our data, the mean age of patients with syncope due to OH is typically geriatric. OH is a major health problem in the elderly adults and affects up to one-third of the population aged 65 or above (15). OH can lead to functional disability with impairment of quality of life and to hospitalization for fall-related injury and is associated with adverse clinical outcomes (16,17). Falls and syncope are among the leading causes for which older patients seek hospital admission. The prevalence of unexplained or nonaccidental falls is higher in this group. Because syncope causes almost by definition falls and/or injuries, it is essential to prevent recurrence and to avoid further falls; as shown by our data, patients with OH syncope had a higher number of syncopal episodes in their lives.

As demonstrated by the present study, a correct collection of the clinical history and the first-step evaluation described in the ESC guidelines (4,5) for patients with syncope allow to avoid expensive examination (primarily cardiac and neurological tests). In the United States, a conservative estimate of total annual costs for syncope-related hospitalizations was $2.4 billion, with a mean cost of $5,400 per hospitalization (18). The diagnosis of syncope due to OH in the emergency department may avoid hospital admission, saving costs for the hospitalization itself.

Diagnosis of syncope due to OH was correctly performed by means of tilt testing in 25.0% of patients; this finding demonstrates the importance of tilt testing not only to support the diagnosis of vasovagal fainting but also to reveal OH that was not symptomatic at first-line evaluation. Moreover, the so-called delayed OH (a blood pressure drop that is evident after more than 5 minutes of standing) can be easily seen during tilt testing, in which the upright phase lasts at least 20 minutes (19).

In our study, patients with OH syncope are more likely to have heart diseases, as shown by data regarding ECG findings, but these patients also take medications active on the cardiovascular system. In multivariate analysis, syncope due to OH is strictly related to the use of vasoactive drugs, mainly diuretics and nitrates; this result is not dependent on daily dose. Indeed, many drugs are known to cause OH: antihypertensives, diuretics, cardiovascular, neurological, antiparkinsonian, and antidepressant medications (10,20). Drug-to-drug interactions may also induce syncopal events, particularly in older patients assuming a high number of drugs because of a great degree of comorbidity (21).

Derangement of cardiovascular homeostasis may be an important mechanism by which fall risk–increasing drugs induce adverse effects in the elderly adults, such as syncope; the withdrawal of drugs affecting baroreflex activity should be always considered to avoid the recurrence of syncope and falls (22).

Abnormal ECG findings are common in patients with syncope; they occur in about 90% of patients with cardiac cause of syncope but in only 6% of patients with neurally mediated syncope (23). A high number of cardiac abnormalities was found also among our patients with syncope due to OH; nevertheless, the multivariate analysis suggested vasoactive drugs, instead cardiac diseases themselves, as responsible of syncope for such patients.

In our study, we found that Parkinson's disease is strongly related to OH syncope, independent of age, sex, other comorbidities, and different kinds of drugs. In literature, there is evidence of association of OH with reflexive cardiovagal failure, reflexive sympathetic neurocirculatory failure, and extracardiac noradrenergic denervation in Parkinson's disease (24).

Conclusions

In the emergency departments, the systematic use of the ESC guidelines is useful to identify patients with syncope due to OH; for most of them, the diagnosis is easy, time

saving, and cheap because the execution of many expensive procedures is avoided. In patients older than 65 years, Parkinson's disease and neurological comorbidity are strictly related to OH syncope. Despite the relationship at the univariate analysis with ECG abnormalities, this study suggests an independent link between OH syncope and the use of vasoactive drugs; this relationship identifies syncope due to OH mainly as an adverse drug reaction, an identifiable and preventable risk factor for syncope and falls in the older population.

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Appendix 1

The following persons and hospitals participated in the EGSYS study: **Steering committee**: P. Alboni, F. Ammirati, M. Brignole, I. Casagranda, P. Cortelli, M. Disertori, R. Furlan, F. Giada, I. Iori, A. Lagi, M. Lunati, G. Mathieu, C. Menozzi, G. Micieli, C. Mussi, P. Ponzi, A. Raviele, G. Re, M. A. Ribani, G. Sandrone, A. Scivales, and A. Ungar. **Hospitals:** Policlinico S. Orsola Malpighi e Bellaria, Bologna: G. Re and M. A. Ribani; Nuovo Osp.S.Giovanni di Dio, Florence: A. Bartoletti, L. Bagnoli and P. Fabiani; Ospedale S. Maria Nuova, Florence: A. Lagi; Azienda Ospedale Università Careggi, Florence: A. Ungar, G. Masotti and S. Grifoni; Azienda Ospedaliera S. Martino, Genova: I. Ponassi and G. Baldi; Ospedali del Tigullio, Lavagna: M. Brignole, R. Maggi and P. M. Saggese; Ospedale Civile Umberto I, Mestre: F. Giada and A. Raviele; Azienda Ospedaliera L. Sacco, Milano: R. Furlan and M. Borella; Ospedale Estense, Modena: C. Mussi and G. Salvioli; Arcispedale S. Maria Nuova, Reggio Emilia: C. Menozzi and F. Quartieri; and Ospedale G. Salvini, Rho: G. Rovelli and F. Ferrari.