

Management of Syncope in Adults: An Update

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Syncope is a clinical syndrome characterized by transient loss of consciousness and postural tone that is most often due to temporary and spontaneously self-terminating global cerebral hypoperfusion. A common presenting problem to health care systems, the management of syncope imposes a considerable socioeconomic burden. Clinical guidelines, such as the European Society of Cardiology Guidelines on Management of Syncope, have helped to streamline its management. In recent years, we have witnessed intensive efforts on many fronts to improve the evaluation process and to explore therapeutic options. For this update, we summarized recent active research in the following areas: the role of the syncope management unit and risk prediction rules in providing high-quality and cost-effective evaluation in the emergency department, the implementation of structured history taking and standardized guideline-based evaluation to improve diagnostic yield, the evolving role of the implantable loop recorder as a diagnostic test for unexplained syncope and for guiding management of neurally mediated syncope, and the shift toward non-pharmacological therapies as mainstay treatment for patients with neurally mediated syncope. Syncope is a multidisciplinary problem; future efforts to address critical issues, including the publication of clinical guidelines, should adopt a multidisciplinary approach.

Mayo Clin Proc. 2008;83(11):1280-1293

ECG = electrocardiogram; ED = emergency department; EGSYS-2 = Evaluation of Guidelines in Syncope Study 2; ESC = European Society of Cardiology; ILR = implantable loop recorder; ISSUE = International Study on Syncope of Uncertain Etiology; NMS = neurally mediated syncope; OESIL = Osservatorio Epidemiologico sulla Sincope nel Lazio; SEEDS = Syncope Evaluation in the Emergency Department Study; SMU = syncope management unit; TLOC = transient loss of consciousness

Syncope is a clinical syndrome characterized by transient loss of consciousness (TLOC) and postural tone that is most often due to temporary and self-terminating global cerebral hypoperfusion.^{1,2} Implicit in this definition is the importance of distinguishing syncope from other nonsyncopal TLOC attacks and differentiating “true” from “apparent” loss of consciousness (Table 1 and Figure 1). Transient self-terminating interruption of global cerebral perfusion is the sine qua non that differentiates syncope from other nonsyncopal TLOC attacks, eg, seizures are due to a primary electrical disturbance of cerebral function and not cerebral hypoperfusion. Equally important is the need to distinguish syncope from apparent loss of consciousness events (so-called syncope mimics or *pseudosyncope*); the latter includes cataplexy, drop attacks, and perhaps even simple falls. Establishing a clear distinction between syncope and nonsyncopal TLOC or apparent loss of consciousness events at the outset of evaluation is not just a matter of semantics; it has practical implications for subsequent diagnostic evaluation and treatment.

The scale of syncope as a public health problem has been well documented. The Framingham study reported an incidence of 6.2 per 1000 person-years; cumulative incidence during 10 years was 6%.³ Because the number of patients in the midst of a faint at any given time is very small, estimates of syncope prevalence are based on the number of persons experiencing syncope during a given period of time (eg, 1 year). The prevalence of syncope varies from 15% in the pediatric population⁴ to 19% in an unselected adult population.⁵ In selected populations, the prevalence of syncope can approximate 40%.⁶ A common presenting problem in health care settings, syncope accounts for 1% of emergency department (ED) visits^{7,8} and 1% to 3% of hospital admissions.⁹⁻¹¹ Moreover, the substantial medical costs incurred in the management of syncope impose a considerable socioeconomic burden; in the United States, syncope-related expenditures approximate \$2 billion annually.¹²⁻¹⁴ Recognizing the scope of the problem, professional medical societies such as the European Society of Cardiology (ESC) have published clinical guidelines to direct a more effective management strategy.^{1,15} Position statements from other professional medical organizations¹⁶⁻¹⁹ and excellent reviews^{20,21} have also been published recently for the same purpose.

Our review does not present yet another diagnostic approach or treatment pathway for syncope. If interested in these matters, the reader is referred to Table 2, Figure 2,²² and the publications mentioned earlier. Instead, our review summarizes recent active research in the following specific areas germane to management of syncope in adults: syncope evaluation in the ED, effectiveness of a structured and standardized approach to syncope, role of the implantable loop recorder (ILR), and efficacy of nonpharmacological physical treatments.

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TABLE 1. Causes of Nonsyncopal Attacks (Commonly Misdiagnosed as Syncope)

Disorders without any impairment of consciousness
Falls
Cataplexy
Drop attacks
Psychogenic pseudosyncope
Transient ischemic attacks of carotid origin
Disorders with partial or complete loss of consciousness
Metabolic disorders, including hypoglycemia, hypoxia, hyperventilation with hypocapnia
Epilepsy
Intoxications
Vertebrobasilar transient ischemic attack

From *Europace*,¹ with permission from the European Society of Cardiology.

SYNCOPE EVALUATION IN THE ED

In recent studies, syncope has been shown to account for approximately 1% of ED visits^{7,8} and is the sixth most common cause for hospitalization of patients older than 65 years.^{23,24} Establishing a definitive cause for this common problem in the ED is hampered by its transient and episodic nature and by the fact that the affected patient has usually completely recovered by the time of examination. Moreover, multiple potential causes are present in 18% of patients with syncope.²⁵ The crux of syncope evaluation in the ED, therefore, is not to identify a precise cause but rather to decide which patients need to be hospitalized and which patients can be safely discharged with outpatient follow-up. Several factors govern this decision-making process, chief of which is the perceived risk of short-term mortality from malignant arrhythmias. This section discusses 2 efforts directed toward risk-stratification of syncope in the ED: syncope management units (SMUs) and risk prediction rules. The main findings of the principal syncope unit trials are summarized in Table 3.^{8,26-30}

SYNCOPE MANAGEMENT UNIT

Despite efforts to construct diagnostic protocols and pathways³¹⁻³³ to streamline syncope evaluation, hospitalization rates for syncope continue to be high, ranging from 26% to 60%.^{8,9,32,34} One strategy to reduce hospital admission is to establish an SMU in the ED that incorporates a multidisciplinary approach to syncope evaluation. The hypothesis that an SMU could improve diagnostic yield and reduce hospital admissions for patients with syncope was tested in the Syncope Evaluation in the Emergency Department Study (SEEDS), a prospective, randomized, single-center study in North America.³⁰

In this study,³⁰ patients who presented to the ED of a tertiary medical center with syncope were classified into high-, intermediate-, or low-risk groups for cardiovascular morbidity and mortality (Table 4). According to guidelines from the American College of Emergency Physicians,³⁵ high-risk patients were admitted and low-risk patients were discharged. Of the 103 patients with intermediate-risk profile who were enrolled in the study, 51 were randomized to the SMU group and 52 to standard care. The presumptive diagnosis was established in 34 (67%) of the patients randomized to the SMU group and in 5 patients (10%) randomized to standard care; hospital admission was required for 22 patients (43%) and 51 patients (98%), respectively. Additionally, actuarial survival and survival free from syncope were similar in both groups. The findings of this study provided evidence that the SMU improves diagnostic yield in the ED and reduces hospital admission without adversely affecting clinical outcomes.

What remains unsettled, however, is the extent to which SMUs can be implemented in community hospitals. The methodology used in SEEDS required close collaboration among emergency physicians, cardiologists, and cardiac electrophysiologists. In addition, patients randomized to

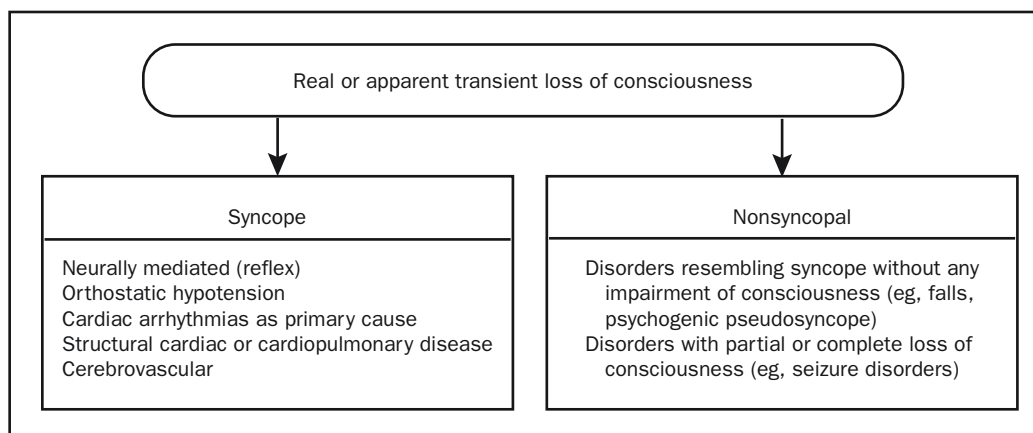


FIGURE 1. Causes of syncope and “nonsyncopal” spells. From *Europace*,¹ with permission from the European Society of Cardiology.

TABLE 2. Treatment for Cardiac Arrhythmia Causes of Syncope

Condition	Treatment
Sinus node dysfunction	Pacemaker
Atrioventricular (AV) conduction system disease (eg, high-grade AV block, complete AV block)	Pacemaker
Supraventricular tachycardia	Drugs (AV node blocking agents, antiarrhythmics) Catheter ablation
Ventricular tachycardia in the absence of structural heart disease (eg, outflow tract ventricular tachycardia, idiopathic left ventricular tachycardia)	Drugs (eg, verapamil for idiopathic left ventricular tachycardia) Catheter ablation if amenable and unresponsive to drugs Implantable cardioverter-defibrillator if drugs and catheter ablation have failed, especially if hemodynamically important
Ventricular tachycardia in association with structural heart disease	Implantable cardioverter-defibrillator with or without catheter ablation
Inherited channelopathies (eg, long QT syndrome, Brugada syndrome)	β -Blockers for long QT syndrome 1 Implantable cardioverter-defibrillator

SMU received continuous telemetry for up to 6 hours and had access to echocardiography, tilt-table testing, and electrophysiological consultation. The resources required to set up and maintain an SMU may be beyond the capacity of

most community hospitals, a situation that would confine the SMU only to tertiary medical centers.

In contrast to the situation in North America, the SMU in Europe is more established not only conceptually but

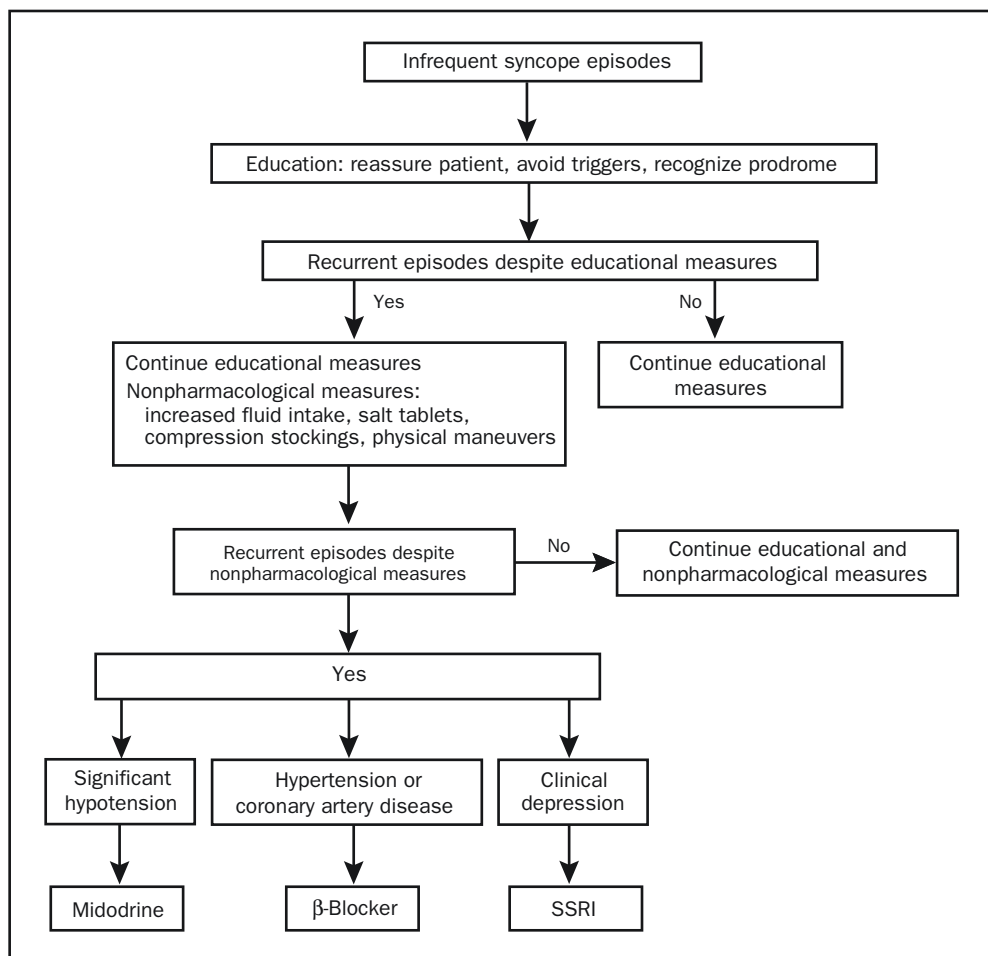


FIGURE 2. Flowchart showing recommended treatment of vasovagal syncope based on clinical scenario. SSRI = selective serotonin reuptake inhibitor. From *Expert Opin Pharmacother*,²² with permission.

TABLE 3. Summary of Counter-Pressure Maneuver and Syncope Management Unit Trials^a

Reference	Treatment/ intervention	Study design	Description of participants	Main findings/conclusions
<i>Counter-pressure maneuver trials</i>				
Krediet et al, ²⁶ 2002	Leg crossing/ muscle tensing	Single-arm trial	21 patients; recurrent syncope and positive findings on tilt-table test	Maneuver ↑ SBP and DBP during tilt testing Maneuver abolished prodromal symptoms and prevented loss of consciousness during tilt testing 11 of 13 patients who applied maneuver in daily life were free of syncope at 10 mo
Brignole et al, ²⁷ 2002	Handgrip	Single-blind, placebo- controlled, randomized, crossover, efficacy trial	19 patients; vasovagal syncope	Maneuver ↑ SBP during tilt testing; placebo ↓ SBP ($P=.008$) 63% in active arm vs 11% in placebo arm became asymptomatic ($P=.02$); 5% vs 47% developed syncope during tilt-induced onset of symptoms ($P=.01$)
van Dijk et al, ²⁸ 2006	Leg crossing, handgrip, arm tensing	Multicenter, prospective, randomized controlled trial	106 treated with PCM vs 117 control patients	Syncope recurred in 32% of patients treated with PCM vs 51% of control patients ($P=.004$) RRR with PCM, 39%; 95% CI, 11%-53%
Melby et al, ²⁹ 2007	Inspiratory impedance threshold device	Single-center, randomized controlled trial Active (impedance 7 cm H ₂ O) or sham (no inspiratory impedance) impedance threshold device	18 healthy volunteers and 22 patients with OH	Active treatment ↓ posture-induced drop in BP in healthy volunteers and patients with OH Active treatment ↓ posture-induced symptoms in patients with OH
<i>Syncope management unit trials</i>				
Brignole et al, ⁸ 2003	Syncope unit in the hospital	Prospective cohort study within a prospective registry 6 hospitals with syncope units (study group) vs 6 matched hospitals without syncope units (controls)	279 study group patients vs 274 control patients	Fewer hospitalizations (43% vs 49%; $P=NS$) and tests performed (mean ± SD, 3.3±2.2 vs 3.6±2.2; $P=NS$) among study vs control patients Study patients underwent 38% more CSM and 87% more tilt testing NMS was diagnosed in 56% of study patients vs 36% of control patients ($P<.001$)
Shen et al, ³⁰ 2004	Syncope unit in ED	Prospective, randomized, single-center study Syncope unit evaluation in ED (study group) vs standard care in ED (controls) for intermediate-risk patients	51 study group patients vs 52 control patients	Diagnosis was established in more study patients than control patients (67% vs 10%; $P<.001$) Study patients had fewer hospitalizations (43% vs 98%; $P<.001$) and higher actuarial survival (97% vs 90%; $P=.30$) than control patients Syncope unit in ED ↑ diagnostic yield and ↓ hospitalizations without affecting all-cause mortality

^a BP = blood pressure; CI = confidence interval; CSM = carotid sinus massage; DBP = diastolic blood pressure; ED = emergency department; NMS = neurally mediated syncope; NS = not significant; OH = orthostatic hypotension; PCM = physical counter-pressure maneuver; RRR = relative risk reduction; SBP = systolic blood pressure; ↑ = increases; ↓ = decreases.

also in practice.^{8,36} In an Italian study, the evaluation strategy for syncope in 6 hospitals equipped with in-hospital SMUs (study group) was compared with 6 matched hospitals (control hospitals) without such facilities.⁸ All 12 hospitals in the study were medium or large public general hospitals that had EDs and facilities for investigating syncope, including tilt-table testing, electrophysiological testing, prolonged electrocardiographic (ECG) monitoring,

and neurologic investigations. In contrast to SEEDS, the SMU in the 6 hospitals in this study were managed by cardiologists and not emergency physicians. Patients were referred to the SMU from the ED, inpatient services, and outpatient clinics. In this study, 279 patients presented with syncope to the SMU hospitals and 274 to the control hospitals. Only 30 patients (11%) were referred to the syncope unit for evaluation in the study group. Compared with the

TABLE 4. Emergency Department Risk Stratification of Patients With Syncope of Unknown Cause

High-risk group	Intermediate-risk group	Low-risk group
Chest pain compatible with acute coronary syndrome	Age ≥ 50 y	Age < 50 y
Signs of chronic heart failure	With history of	With no history of
Moderate/severe valvular disease	Coronary artery disease	Cardiovascular disease
History of ventricular arrhythmias	Myocardial infarction	Symptoms consistent with reflex-mediated or vasovagal syncope
Electrocardiographic/cardiac monitor findings of ischemia	Chronic heart failure	Normal findings on cardiovascular examination
Prolonged QTc (> 500 ms)	Cardiomyopathy without active symptoms or signs while taking cardiac medications	Normal electrocardiographic findings
Trifascicular block or pauses between 2 and 3 s	Bundle-branch block or Q wave without acute changes	
Persistent sinus bradycardia between 40 and 60 beats/min	Family history of premature (< 50 y), unexplained sudden death	
Atrial fibrillation and nonsustained ventricular tachycardia without symptoms	Symptoms not consistent with a reflex-mediated or vasovagal cause	
Cardiac devices (pacemaker or defibrillator) with dysfunction	Cardiac devices without evidence of dysfunction	
	Physician's judgment that suspicion of cardiac syncope is reasonable	

From *Circulation*,³⁰ with permission from Lippincott Williams & Wilkins.

control group, 12% fewer patients were hospitalized (49% vs 43%; $P=NS$) and 8% fewer tests were performed (mean \pm SD, 3.6 ± 2.2 vs 3.3 ± 2.2 per patient; $P=NS$) in the study group. Consistent with the recommendations of the ESC,¹⁵ the study group patients underwent echocardiography less frequently (11% vs 16%) and had fewer basic laboratory tests (75% vs 86%) and brain-imaging studies (17% vs 24%) but more carotid sinus massage (13% vs 8%) and tilt-table testing (8% vs 1%) than the control hospital patients. The authors of this Italian study concluded that the management of patients with syncope referred to hospitals with SMUs was in line with the recommendations of the ESC and substantially different from the management of equivalent hospitals without such specialized units. Moreover, the difference was observed despite the fact that only a minority of patients (11%) in the study hospitals were referred to SMUs, an observation that suggests the presence of SMUs per se was able to modify overall hospital practice.

Collectively, both the investigations in North America³⁰ and Italy⁸ demonstrate the potential of the SMU in providing high-quality and cost-effective care for patients with syncope. Despite this, SMUs are uncommon in North America. To address this lack of penetration, a 2005 survey³⁷ sampled 60 US and Canadian medical centers, 28 of which responded. Of those 28 medical centers, only 4 (14%) had SMUs. Most respondents, however, thought that SMUs would be helpful; reasons cited for the absence of SMUs included lack of leadership, resource limitations within medical centers, and absence of convincing published data regarding SMU effectiveness. Currently, the SMU may be at an evolutionary stage similar to that of the coronary care unit 40 years ago.³⁸

RISK PREDICTION RULES

Recommendations for hospitalization of patients with syncope have been provided by the ESC (Table 5)¹ and the American College of Emergency Physicians (Table 6).¹⁷ In

TABLE 5. Recommendations of the European Society of Cardiology for Hospitalization of Patients With Syncope

For diagnosis	For treatment
Suspected or known significant heart disease	Cardiac arrhythmias as cause of syncope
Electrocardiographic abnormalities suspected of arrhythmic syncope	Syncope due to cardiac ischemia
Syncope occurring during exercise	Syncope secondary to structural cardiac or cardiopulmonary diseases
Syncope causing severe injury	Cardioinhibitory neurally mediated syncope when pacemaker implantation is planned
Family history of sudden death	
Other categories that occasionally may need to be admitted	
Patients without heart disease but with sudden onset of palpitations shortly before syncope, patients with syncope in the supine position, and patients with frequent recurrent episodes	
Patients with minimal or mild heart disease when there is high suspicion of cardiac syncope	

From *Europace*,¹ with permission from the European Society of Cardiology.

recent years, intensive efforts have been made to incorporate elements of these recommendations into risk stratification schemes with the aim of quantifying more precisely short-term and long-term risks of serious morbidity and mortality. In this section, we review 2 such research efforts: the Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) risk score³³ and the San Francisco Syncope Rule.³⁹

OESIL Risk Score. The derivation cohort for the OESIL risk classification scheme consisted of 270 patients who presented with syncope to the EDs of 6 community hospitals in the Lazio region of Italy.³³ The investigators used data from the clinical history, physical examination, and 12-lead ECG to identify independent predictors of all-cause mortality within 12 months after the index evaluation. Multivariate analysis identified 4 independent predictors: (1) age greater than 65 years, (2) clinical history of cardiovascular disease, (3) syncope without prodrome, and (4) abnormal ECG findings. The OESIL score was computed as the simple arithmetic sum of the number of predictors present in each patient. The risk score had good discriminant ability; area under the receiver operating characteristic curve was 0.90, and mortality increased significantly as the score increased in the derivation cohort (0% for a score of 0, 0.8% for 1 point, 19.6% for 2 points, 34.7% for 3 points, 57.1% for 4 points).

The OESIL risk score was validated in 328 patients who presented with syncope to the EDs of 2 hospitals in Rome, Italy.³³ The area under the receiver operating characteristic curve in the validation cohort was 0.89, and a similar significant pattern of increased mortality with increased OESIL risk score was also noted in the validation cohort. These findings support the predictive ability of the OESIL risk score. The principal advantages of this risk score are its convenience (the risk score is a simple arithmetic sum of the independent predictors) and the ready availability of the information regarding the predictors to the emergency physician.

San Francisco Syncope Rule. The San Francisco Syncope Rule³⁹ differs from the OESIL risk score in at least 2 respects: first, it predicts not only mortality but also serious morbidity; and second, it predicts shorter-term (7-day) outcomes.

The derivation cohort³⁹ comprised 684 patients who presented with syncope to the ED of a university teaching hospital. The investigators considered 50 predictor variables from the clinical history, physical examination, laboratory tests, and 12-lead ECG. Outcomes of interest at 7 days after the initial evaluation included death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, clinically important hemorrhage, or any condition causing or likely to cause a

TABLE 6. Recommendations of the American College of Emergency Physicians for Hospitalization of Patients With Syncope

Older age and associated comorbidities ^a
Abnormal electrocardiographic findings ^b
Hematocrit <30 (if obtained)
History or presence of heart failure, coronary artery disease, or structural heart disease

^a Different studies use different ages as the threshold for decision making; age is likely a continuous variable that reflects the cardiovascular health of the individual rather than an arbitrary value.

^b Electrocardiographic abnormalities, including acute ischemia, dysrhythmias, or significant conduction abnormalities.

From *Ann Emerg Med*,¹⁷ with permission.

return ED visit and hospitalization. Twenty-six variables were found to be associated with a serious outcome on univariate analysis, and by recursive partitioning techniques, a rule was developed that consisted of 5 predictors: abnormal ECG findings, shortness of breath, hematocrit less than 30%, systolic blood pressure less than 90 mm Hg, or a history of chronic heart failure. This clinical prediction rule had 96% sensitivity and 62% specificity in predicting a serious outcome.

The San Francisco Syncope Rule has been validated in 2 different settings.^{40,41} The first validation study⁴⁰ was performed at the same institution as the derivation cohort. Of the 791 patients who presented with syncope to the ED and were prospectively enrolled in the validation cohort, 53 patients (7%) experienced serious outcomes 7 days after the ED evaluation. Overall, the rule was 98% sensitive and 56% specific, classifying 52% of patients as high risk and potentially decreasing hospital admissions by 7%. However, the lower limit of the 95% confidence interval for sensitivity was only 89%, necessitating further validation. The second validation cohort comprised 477 patients who presented with syncope to the ED of an academic, tertiary-care referral center.⁴¹ Of those 477 patients, 56 patients (12%) developed a serious outcome 7 days after the initial evaluation. Compared with the first validation cohort, the sensitivity and specificity of the San Francisco Syncope Rule were lower in this cohort: 89% vs 42%, respectively. The findings of the second validation study suggest that further validation is needed before this clinical prediction rule can be widely applied in EDs. This rule, however, has a distinct advantage: it is easy to remember by a simple mnemonic—CHESS (history of chronic heart failure, hematocrit of less than 30%, abnormal findings on ECG, shortness of breath, and a triage systolic blood pressure of less than 90 mm Hg).

In summary, a number of advances have addressed the need for structured, high-quality, and cost-effective evaluation of syncope in the ED. The theme of “structured” care will be reiterated in the next section as we

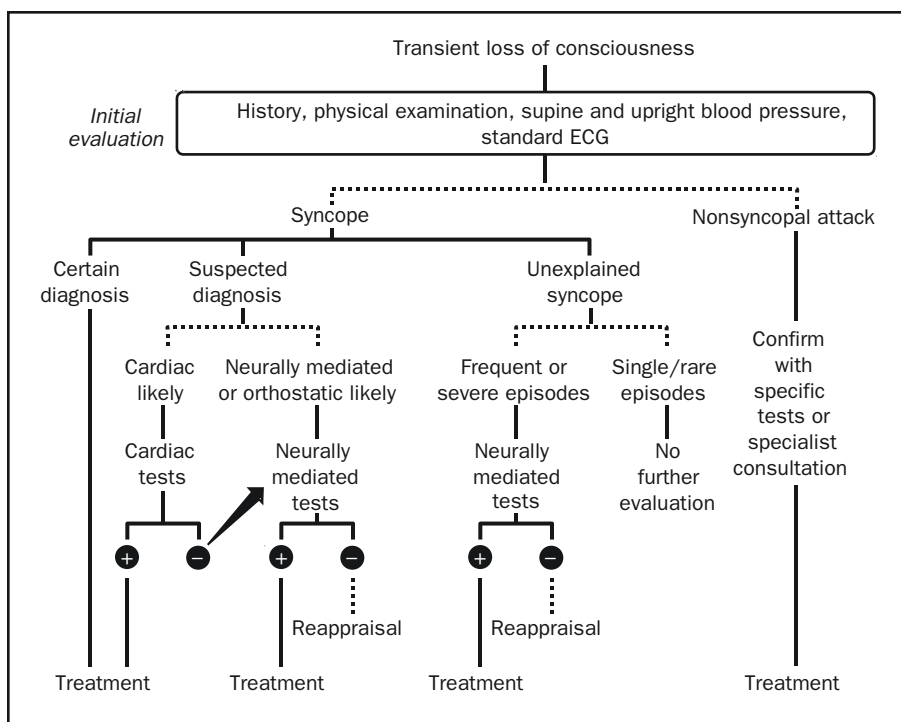


FIGURE 3. Flow diagram outlining an approach to the evaluation of loss of consciousness on the basis of the initial evaluation. Differentiating true syncope from other “nonsyncopal” spells is the first diagnostic step and affects the subsequent diagnostic strategy. Among cardiac investigations, echocardiography, prolonged electrocardiographic (ECG) monitoring, stress testing, electrophysiological study, and implantable loop recorder (ILR) are most useful. Among neurally mediated investigations, tilt test, carotid sinus massage, and ILR are most useful. From *Europace*,¹ with permission from the European Society of Cardiology.

discuss the effectiveness of guideline-based evaluation in settings other than the ED.

STRUCTURED AND STANDARDIZED APPROACH TO SYNCOPE

The importance of meticulous history taking in the evaluation of syncope cannot be overemphasized.^{1,18} According to the ESC guidelines,¹ history taking is a key component in the initial evaluation of syncope; other components include physical examination, which includes orthostatic blood pressure examination, and 12-lead ECG (Figure 3). Of course, history taking is subject to considerable variability and subjectivity that may limit its diagnostic yield. Efforts to standardize history taking by using a quantitative questionnaire may increase its diagnostic accuracy. In recent years, we have also witnessed investigations into the effectiveness of a systematic guideline-based approach to syncope.

STRUCTURED HISTORY TAKING

One of the earliest attempts to analyze historical elements quantitatively was undertaken by Calkins et al.⁴² Using a

structured questionnaire, they found that syncope due to ventricular tachycardia or atrioventricular block was associated with male sex, age greater than 54 years, 2 or fewer episodes of syncope, and a duration of warning of 5 seconds or less. Historical features that were predictive of neurally mediated syncope (NMS) included palpitations, blurred vision, nausea, warmth, diaphoresis, or lightheadedness before syncope; and nausea, warmth, diaphoresis, or fatigue after syncope. Four variables differentiated NMS from ventricular tachycardia or atrioventricular block with a sensitivity of 98% and a specificity of 100%: age, sex, duration of recovery period, and presence of mild or severe fatigue after syncope.

More recently, in a cohort of 341 patients evaluated for syncope, Alboni et al⁴³ correlated historical elements in a standard questionnaire with a cardiac cause of syncope. Presence of heart disease predicted a cardiac cause of syncope with 95% sensitivity and 45% specificity. Conversely, the absence of heart disease excluded a cardiac cause of syncope in 97% of patients. In the presence of heart disease, the most specific predictors of a cardiac cause were syncope in the supine position or during effort,

TABLE 7. Sensitivity and Specificity of Variables Predictive of Cardiac and Neurally Mediated Causes of Syncope, Stratified by Age of Patient

Variable	Sensitivity (%)	Specificity (%)
Patients <65 y		
Predictors of cardiac syncope		
Heart disease	85	83
≤2 Syncopal episodes	67	69
Absence of prodromes	37	84
Predictors of neurally mediated reflex syncope		
>2 Syncopal episodes	31	33
Any prodromes	81	37
History of presyncope	78	48
Diaphoresis	43	77
Absence of heart disease	83	85
Postprandial	15	100
Patients ≥65 y		
Predictors of cardiac syncope		
Heart disease	94	64
≤2 Syncopal episodes	66	49
Myoclonic movements	18	97
Occurs during effort	15	99
Occurs in supine position	7	99
Predictors of neurally mediated reflex syncope		
Diaphoresis (recovery)	25	86
Absence of heart disease	36	94
Supine/upright	5	95
Abdominal discomfort	7	99

From *Am J Cardiol*,⁴⁴ with permission from Elsevier.

blurred vision, and convulsive syncope. Significant predictors of a neurally mediated cause were duration of more than 4 years between the first and last syncopal episode, abdominal discomfort before syncope, and nausea and diaphoresis during the recovery phase. Age, however, may influence the diagnostic utility of the clinical history (Table

7⁴⁴). In a prospective evaluation of 485 consecutive patients with unexplained syncope, Del Rosso et al⁴⁴ found that the clinical features of cardiac syncope and NMS were very similar in patients aged 65 years or older (Table 7). In addition, the clinical history alone provided a diagnosis in 26% of patients younger than 65 years but in only 5% of patients aged 65 years or older. The low diagnostic utility of the clinical history in older patients is largely due to a higher prevalence of cardiac diseases in older patients.

Combining significant predictors of specific diagnostic categories to construct a point score can increase the diagnostic accuracy of history taking. One example is the study by Sheldon et al⁴⁵ that used a 118-item structured questionnaire to identify predictors that could distinguish syncope from seizures. Table 8 shows the diagnostic point score that was derived from the relative weights of each predictor.⁴⁵ Using a cutoff score of 0 or more to classify patients as having seizures resulted in an overall accuracy of 86%, sensitivity of 96%, and specificity of 84%. Adopting a similar approach, Sheldon et al⁴⁶ constructed a diagnostic point score for vasovagal syncope (Table 9). A point score of -2 or more classified a patient as having vasovagal syncope with an overall accuracy of 90%, sensitivity of 89%, and specificity of 91%.

Collectively, these efforts to quantify history taking systematize the process and increase its diagnostic accuracy.

GUIDELINE-BASED EVALUATION OF SYNCOPE

As Cicero noted, “Advice is judged by results, not by intentions.” The same can be said of clinical guidelines. To the extent that guidelines are implemented in the community and not only in academia where they are developed, they should produce measurable improvements in clinical

TABLE 8. Scoring System to Distinguish Syncope from Seizure

Question	Points (if yes)
At times do you wake with a cut tongue after your spells?	2
At times do you have a sense of déjà vu or jamais vu?	1
At times is emotional stress associated with losing consciousness?	1
Has anyone ever noted your head turning during a spell?	1
Has anyone ever noted that you are unresponsive, have unusual posturing, or have jerking limbs during your spells or have no memory of your spells afterwards? (score as yes for any positive response)	1
Has anyone ever noted that you are confused after a spell?	1
Have you ever had light-headed spells?	-2
At times do you sweat before your spells?	-2
Is prolonged sitting or standing associated with your spells?	-2

If a patient answers “yes” to a question, he/she is given the corresponding point score. A cutoff score of ≥0 classifies patients as having seizures with an overall accuracy of 86%, sensitivity of 96%, and specificity of 84%

From *J Am Coll Cardiol*,⁴⁵ with permission from Elsevier.

TABLE 9. Scoring System for Vasovagal Syncope

Question	Points (if yes)
Is there a history of at least one of the following: bifascicular block, asystole, supraventricular tachycardia, or diabetes?	-5
At times have bystanders noted you to be blue during your faint?	-4
Did your syncope start when you were aged 35 years or older?	-3
Do you remember anything about being unconscious?	-2
Do you have light-headed spells or faint with prolonged sitting or standing?	1
Do you sweat or feel warm before a faint?	2
Do you have light-headed spells or faint with pain or in medical settings?	3

If a patient answers “yes” to a question, he/she is given the corresponding point score. A point score ≥-2 classifies a patient as having vasovagal syncope with an overall accuracy of 90%, sensitivity of 89%, and specificity of 91%

From *Eur Heart J*,⁴⁶ with permission from the European Society of Cardiology.

cally relevant outcomes. Implicit in this statement are 2 questions: (1) How extensively can syncope guidelines be implemented? and (2) How does guideline-based evaluation compare with “usual” management?

These questions were most recently addressed by several Italian investigators.⁴⁷⁻⁴⁹ One study⁴⁷ sought to determine the appropriateness of hospital admissions and discharges from a single ED according to the ESC guidelines.¹ During a 2-year period, 566 patients with syncope (50%) were admitted and 558 (50%) were discharged. Of the 1124 patients with syncope, 440 (39%) met at least 1 criterion for hospitalization of the ESC guidelines, 393 (89%) of whom were admitted. In contrast, 511 (75%) of 684 patients without indication for admission were discharged. The appropriateness of the ED’s decision was 69% for hospital admission and 92% for discharge. These findings suggest that, despite the ESC guidelines, clinicians continue to err on the side of admitting rather than discharging patients with syncope when confronted with uncertainty.

To investigate this issue more rigorously, the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) group⁴⁸ developed an interactive Web-based decision-making system to help physicians follow the diagnostic pathway and the recommendations of the ESC guidelines. Additionally, trained core medical personnel were designated, both locally in each hospital and centrally, to verify and encourage adherence to the diagnostic pathway. Adherence to the ESC guidelines was evaluated prospectively in 11 general hospitals. The findings of this study were impressive: adherence to the guidelines was 86%, and a diagnosis was established in 98% of patients. These findings, however, have to be considered in the context of the considerable effort invested in professional education and software development. They probably define the “ideal situation” rather than a realistic benchmark that can be attained by most community hospitals.

Extending this line of investigation, the EGSYS-2 group compared the outcomes of patients managed according to the standardized-care pathway with patients managed according to usual practice in a prospective, controlled, multicenter study.⁴⁹ The standardized-care group comprised 745 patients and the usual-care group 929 patients. The standardized-care group had a lower hospitalization rate (39% vs 47%), shorter in-hospital stay (mean \pm SD, 7.2 \pm 5.7 days vs 8.1 \pm 5.9 days), and fewer tests performed per patient (median, 2.6 vs 3.4) than the usual-care group. The mean cost per patient and the mean cost per diagnosis were 19% and 29% lower in the standardized-care group. In conclusion, a standardized-care pathway significantly improved diagnostic yield and reduced hospital admissions, resource consumption, and overall costs.

The findings of both EGSYS-2 studies^{48,49} indicate that the ESC guidelines can be implemented widely in the clinical setting and provide a high-yield and cost-effective strategy for syncope management. These benefits, however, may be achievable only with specifically designed decision-making software and specially trained personnel.

ROLE OF ILR

Figure 3 shows a flow diagram for the evaluation of loss of consciousness on the basis of an initial evaluation that comprises history taking, physical examination, supine and upright blood pressure measurements, and a 12-lead ECG.¹ Among patients with true syncope, the initial evaluation categorizes patients as having a certain diagnosis, suspected diagnosis, or an unexplained syncope. In this framework, the role of the ILR is well established in the evaluation of unexplained syncope, particularly if other findings of conventional investigations (eg, tilt-table testing and electrophysiological testing) are normal. In this section, we discuss evidence that supports the superiority of ILR to conventional testing in patients with unexplained syncope and a role for ILR-based therapy in NMS. Indications and limitations of the traditional forms of rhythm monitoring, such as the Holter monitor and event recorder, have been reviewed extensively,^{1,50,51} and we refer the interested reader to these publications. The challenge of documenting infrequent or transient rhythm disturbances as potential causes of syncope by these traditional monitoring devices is self-evident.

CONVENTIONAL DIAGNOSTIC TESTING VS ILR

Initial clinical experience supported the ILR for evaluation of patients with unexplained syncope at the end of unsuccessful conventional testing.^{52,53} When ILR is used, correlation between syncope and ECG findings can be found in 34% of patients with unexplained syncope at the end of complete conventional investigations; bradycardia and asystole constituted 52% of recorded events.⁵²⁻⁵⁵ Testing the hypothesis that the ILR should be used before conventional testing in patients with unexplained syncope, Krahn et al⁵⁶ randomized patients with unexplained syncope to ILR with 1 year of monitoring or to conventional testing with an external loop recorder, tilt-table testing, and electrophysiological testing. Patients who had not obtained a diagnosis after their assigned strategy were offered crossover to the alternative strategy. A diagnosis was obtained in 14 (52%) of 27 patients randomized to the ILR compared with 6 (20%) of 30 patients who underwent conventional testing. Crossover was associated with a diagnosis in 1 (17%) of 6 patients undergoing conventional testing compared with 8 (62%) of 13 patients who completed pro-

longed rhythm monitoring. Overall, prolonged rhythm monitoring with the ILR was more likely to provide a diagnosis than was conventional testing (55% vs 19%). Twenty-two etiologies were diagnosed using the ILR: 14 bradycardia, 3 vasovagal, 3 tachycardia, and 2 seizures. Bradycardia was detected by the ILR in 14 patients compared with 3 patients who underwent conventional testing.

Several issues need to be emphasized with respect to these findings. First, this study excluded patients with a high pretest probability of NMS or ventricular arrhythmia as the cause of syncope. In other words, the ILR is most applicable as initial strategy in patients who do not have clinical features suggestive of NMS and do not have apparent heart disease. Second, the most common diagnosis obtained by the ILR that was infrequently obtained by conventional strategy was bradycardia. This is not surprising considering the low sensitivity of the electrophysiologic study for bradycardia.⁵⁷

In summary, the findings of the study by Krahn et al⁵⁶ support the ILR as initial strategy for recurrent syncope in patients without heart disease or features suggestive of NMS, particularly if bradycardia is suspected. The ILR, however, has an important limitation: in the absence of blood pressure information, NMS with predominantly vasodepressor response cannot be diagnosed. The ILR will likely have a greater role in the overall diagnostic scheme when blood pressure monitoring capability is available. Very recently, a new ILR with wireless telemetry capability that enables real-time continuous ECG monitoring has been approved by the US Food and Drug Administration (Sleuth; Transoma Medical, St Paul, MN).⁵⁸

ILR-BASED THERAPY FOR PATIENTS WITH NMS

Notwithstanding certain evidence^{59,60} suggesting that patients with cardioinhibitory tilt-positive NMS may benefit from cardiac pacing, this issue remains far from settled. Two issues that stand out in the controversy surrounding cardiac pacing and NMS are patient selection criteria and the potential role of the placebo effect in studies showing a benefit from pacing. In the most positive trials (Vasovagal Syncope International Study [VASIS]⁵⁹ and Syncope Diagnosis and Treatment [SYDIT] trial⁶⁰), patients had a cardioinhibitory response during tilt-table testing; such was not the case in the North American Vasovagal Pacemaker Study (VPS) II⁶¹ and the Vasovagal Syncope and Pacing (SYNPACE) trial.⁶²

It seems intuitive that patients with severe cardioinhibitory or asystolic response during tilt-table testing may benefit from cardiac pacing. However, response during tilt-table testing does not accurately predict type of response during actual syncope.⁶³ One possible solution is to use the ILR rather than the tilt-table test to classify type of NMS.⁴⁴

The International Study on Syncope of Uncertain Etiology (ISSUE) 2⁶⁴ was a prospective multicenter study that tested the efficacy of ILR-based evaluation and therapy in NMS. In this study, 392 patients with recurrent syncope due to likely NMS were implanted with the ILR and followed up until syncopal recurrence. Of these patients, 103 had a documented syncopal episode and were randomized to specific rhythm-guided therapy (53 patients [47 with pacemaker, 1 with implantable cardioverter-defibrillator, 4 with catheter ablation, 1 with antiarrhythmia]) or no specific therapy (50 patients). The 1-year recurrence rate in the 53 patients assigned to a specific therapy was 10% compared with 41% in patients without specific therapy. The 1-year recurrence rate in patients implanted with pacemakers was 5% compared with 33% before implantation. ISSUE 2, thus, represents a departure from tilt-table test-guided therapy on the premise that response to tilt-table testing does not predict a cardioinhibitory pattern recorded during subsequent spontaneous syncope.⁶³ However, in the absence of a blinded control group in ISSUE 2, one cannot rule out a placebo effect. This forms the basis of ISSUE 3, which will test the effectiveness of cardiac pacing for patients with NMS and asystole documented by ILR in a randomized, placebo-controlled trial.⁶⁵

NONPHARMACOLOGICAL PHYSICAL TREATMENTS FOR NMS

Encouraging data from clinical research on nonpharmacological physical maneuvers for NMS have shifted our focus away from pharmacotherapy for patients with the vasovagal form of NMS and for patients with various forms of orthostatic hypotension. Too often, promising results from small and uncontrolled studies on many pharmacological agents have not been replicated in larger, randomized, and placebo-controlled trials.²² In this section, we discuss the evidence in support of 3 nonpharmacological therapies: tilt training, counter-pressure maneuvers, and a novel impedance threshold device. The main findings of counter-pressure maneuver trials are summarized in Table 3.

TILT TRAINING

The beneficial effect of gravitational stress on the cardiovascular system to treat orthostatic intolerance was described as early as 1940 by MacLean and Allen.⁶⁶ Patients were recommended to sleep in a tilted head-up bed. This idea had since been borrowed and applied to patients with NMS. Using the same tilt table for diagnostic testing, tilt training subjects a patient with NMS to progressively prolonged periods of upright posture. The aim of this procedure is to condition the patient to better counter gravitational stress in a graduated fashion.

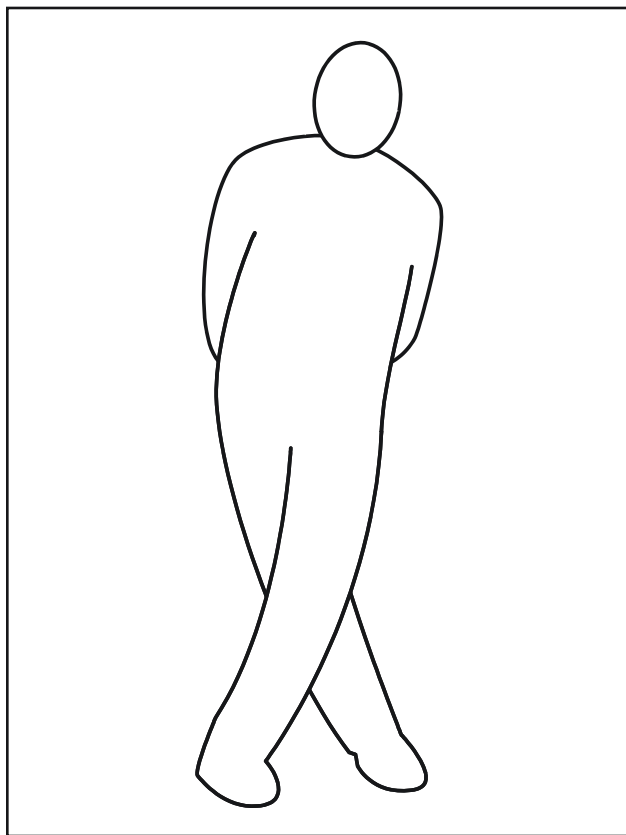


FIGURE 4. The leg-crossing maneuver consists of crossing the legs in standing position with tensing of leg, abdominal, and buttock muscles. The legs are firmly squeezed together.

One of the earliest studies of a possible beneficial effect of tilt training for NMS was that by Ector et al.⁶⁷ In this small study of 13 patients with recurrent NMS, tilt training resulted in complete disappearance of syncope in all patients. Tilt training was initiated in the hospital, and patients were instructed to continue with tilt training at home (30-minute session, twice daily). This study was limited by a small sample size, short follow-up period (mean \pm SD, 7.2 ± 4.9 months), and lack of a control group. This initial study was followed by a larger study (42 patients) with a longer follow-up period (mean \pm SD, 15.1 ± 7.8 months).⁶⁸ With tilt training, 36 patients were completely free of syncope; 1 patient had recurrent syncope, and 4 patients had presyncope. Although its findings were intriguing, the study once again lacked a control group. Moreover, patients are unlikely to adhere to this arduous therapy even if it is beneficial. One also wonders about its effectiveness once treatment is discontinued.

To address these issues, the same investigators followed up 38 patients for a mean \pm SD period of 43.0 ± 7.8 months; 29 patients (76%) had abandoned tilt training at the time of

assessment.⁶⁹ Of the 29 patients who abandoned treatment, 6 patients (21%) had syncope recurrence vs 1 (11%) of the 9 patients who continued treatment. Notably, when tilt training was resumed in the 6 patients who abandoned treatment, syncope again disappeared. Moreover, in 19 patients who abandoned tilt training after 1 year, no syncope recurrence was noted, suggesting that the disturbed autonomic reflex activity in these patients may have been restored by tilt training.

The findings of these studies are intriguing and warrant further investigation. It remains speculative whether tilt training can provide a durable beneficial effect after discontinuation of therapy.

COUNTER-PRESSURE MANEUVERS

Two recent clinical trials^{26,27} have shown that isometric counter-pressure maneuvers of the legs or arms are able to increase blood pressure during impending NMS, allowing patients to avoid or delay loss of consciousness. In the first clinical trial of 21 patients with recurrent syncope and positive tilt-table test results,²⁶ patients were instructed to perform leg crossing and muscle tensing for at least 30 seconds at the onset of a tilt-table-induced faint (Figure 4). The maneuver quickly increased mean \pm SD systolic blood pressure from 65 ± 13 mm Hg to 106 ± 16 mm Hg and mean \pm SD diastolic blood pressure from 43 ± 9 mm Hg to 65 ± 10 mm Hg, aborting prodromal symptoms and preventing syncope. At 10-month follow-up, 13 of 20 patients applied the maneuver in daily life and benefited from it.

Similarly, isometric arm exercise (Figure 5) was found to be effective in aborting impending NMS.²⁷ In a single-blind, placebo-controlled, randomized study, 19 patients with recurrent syncope were taught to perform handgrip

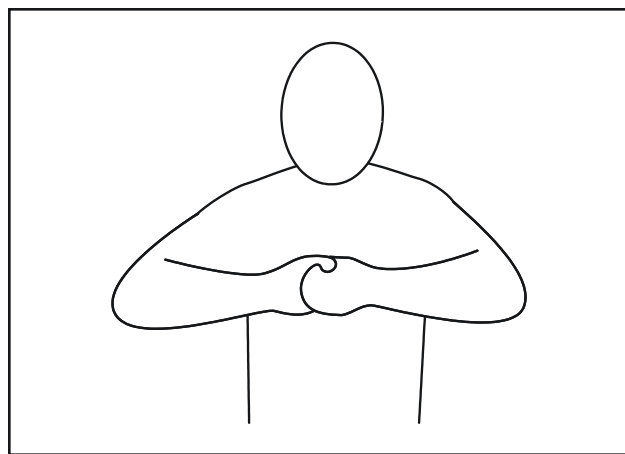


FIGURE 5. Arm tensing consists of isometric contraction of the 2 arms accomplished by gripping one hand with the other and concurrently abducting the arms.

and arm tensing during the prodromal phase of NMS. During the tilt study, the handgrip maneuver increased blood pressure, rendering 63% of patients in the active arm asymptomatic compared with 11% in the control arm. During 9 months of follow-up, the maneuver was performed in 95 of 97 episodes of impending syncope and was successful in 94 episodes (99%). In a longer follow-up (mean \pm SD, 14 \pm 6 months) study by the same investigators,⁷⁰ 260 episodes of syncope were reported by 19 patients. Arm tensing and/or handgrip were administered in 98.0% of cases and aborted syncope in 99.6% of cases.

The Physical Counterpressure Manoeuvres Trial (PC-Trial)²⁸ was a multicenter, prospective, randomized clinical trial that assessed the effectiveness of counter-pressure maneuvers in preventing NMS in a real-life setting. In this trial, 117 patients were randomized to conventional therapy alone, and 106 patients received conventional therapy plus training in physical counter-pressure maneuvers. During a mean follow-up of 14 months, 51% of the patients treated conventionally and 32% of the patients trained in physical counter-pressure maneuvers experienced syncopal recurrence; relative risk reduction was 39%. Syncope burden was also significantly less in the physical counter-pressure maneuver group compared with the control group ($P=.004$).

Given the ease of performing these maneuvers that encourage patient adherence and the compelling evidence attesting to their efficacy, counter-pressure maneuvers should be considered as first-line treatment for patients with NMS and recognizable prodromal symptoms.

IMPEDANCE THRESHOLD DEVICE

The impedance threshold device is a portable instrument that impedes the flow of air during inspiration, forcing the individual to generate a more negative intrathoracic pressure. Currently used to increase the effectiveness of cardiopulmonary resuscitation,⁷¹ it has been tested in one study on patients with orthostatic intolerance.²⁹ This study examined the hypothesis that the impedance threshold device can reduce blood pressure drop during postural change by generating a more negative intrathoracic pressure, hence increasing venous return and cardiac output. Eighteen healthy volunteers and 22 patients with orthostatic hypotension were randomized to either an active (impedance 7 cm H₂O) or sham (no inspiratory impedance) impedance threshold device. Compared with placebo, active impedance threshold device treatment significantly reduced upright posture-induced drop in blood pressure in both healthy volunteers ($P<.045$) and patients with orthostatic intolerance ($P=.0007$). In patients with orthostatic hypotension, inspiratory impedance also helped maintain standing blood pressure in a desirable range for 80 to 100 seconds, reducing upright posture-induced symptoms (eg, light-

headedness, dizziness). A subsequent study of 10 patients with orthostatic intolerance due to autonomic failure⁷² found that an impedance threshold device ameliorated upright posture-induced drop in blood pressure to the same degree as leg muscle tensing.

Larger studies are needed to confirm the efficacy of this novel form of therapy for orthostatic hypotension and to assess patient adherence to it. It would also be interesting to test the effectiveness of this device in patients with NMS.

CONCLUSION

Much has been accomplished in recent years to improve the evaluation process and treatment of patients with syncope. This review has summarized recent efforts to increase efficiency and reduce cost during ED evaluation, to increase diagnostic yield by implementing a structured and standardized approach, to define a more prominent role for the ILR, and to explore nonpharmacological therapies as first-line treatment for patients with NMS. Professional clinical guidelines, in particular the ESC guidelines, have had a major role in streamlining syncope management. However, many challenges and problematic areas remain. Given the multidisciplinary nature of syncope, future endeavors to tackle critical issues related to syncope, including development of professional clinical guidelines, should adopt a multidisciplinary approach.

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The Symposium on Cardiovascular Diseases will continue in the December issue.