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Review

Syncope in adults: Systematic review and proposal of a diagnostic and therapeutic algorithm

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ABSTRACT

This review aims to provide a practical and up-to-date description on the relevance and classification of syncope in adults as well as a guidance on the optimal evaluation, management and treatment of this very common clinical and socioeconomic medical problem. We have summarized recent active research and emphasized the value for physicians to adhere current guidelines. A modern management of syncope should take into account 1) use of risk stratification algorithms and implementation of syncope management units to increase the diagnostic yield and reduce costs; 2) early implantable loop recorders rather than late in the evaluation of unexplained syncope; and 3) isometric physical counter-pressure maneuvers as first-line treatment for patients with neurally-mediated reflex syncope and prodromal symptoms.

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1. Introduction

Syncope is a transient loss of consciousness often unwitnessed and accompanied by loss of postural tone, with rapid onset and full and typically quick recovery. A brief and abrupt decrease in or cessation of global cerebral blood flow is the basic mechanism.

Syncope is known to affect quality-of-life, to cause physical injuries, be challenging to manage and can be a harbinger of sudden death.

We present a systematic review on its relevance, classification and evidence-based management strategies and therapeutic approaches. New aspects presented in current guidelines are covered and we also propose a practical diagnostic and therapeutic algorithm.

2. Relevance

Syncope has a considerable medical and socioeconomic burden on the adult population. Its prevalence rises with advancing years: from 6.2 per 1000 person-years in middle age to 11 per 1000 person-years in 70–79 year olds, and to 19 per 1000 person-years in those over 80 years [1–3]. The age-adjusted incidence rate among patients with structural heart disease is about twice that among subjects without (10.6 vs. 6.4 per 1000 patient-years). The overall mortality and morbidity associated with syncope is 7.5%, with one-year mortality of 18% to 33% for cardiac syncope, which is noticeably greater than syncope of unknown origin and cerebrovascular syncope (less than 10%); whereas neurally-mediated reflex syncope is associated with the same mortality of comparably aged healthy individuals [1–3].

Syncope accounts for 1% of emergency department (ED) and urgent care clinic referrals; of these, ≈40% are hospitalized, resulting in excess of 200,000 hospital admissions annually in the U.S. [4–6]. The estimated costs for syncope-related hospitalizations in the year 2000 approached $2.5 billion, with a mean cost of $5400 per hospitalization [5]. The cost per-reliable diagnosis can be as high as $78,000, depending on the tests performed and their diagnostic accuracy. The average syncope patient visits a physician 10 times per-year and sees an average of 3.2 specialists [6–8].

Recurrences are frequent after an initial syncopal episode and the number of them during life is the strongest predictor. Indeed, a history of 1 or 2 episodes predicted a recurrence rate of 15% and 20% after one and two years, respectively; whereas 3 episodes predicted a recurrence of 36% and 42%, respectively [9]. Conversely, gender, severity of presentation, and presence or absence of structural heart disease have poor predictive value [9]. Recurrences have a substantial impact on patients' quality-of-life. They may develop excessive fear of dying and have difficulty returning to previous level of activities. Up to 76% of patients will change activities of daily living, 64% will limit their driving, and 39% will change employment. The functional impairment matches that of chronic low back pain, rheumatoid arthritis, chronic obstructive lung disease and depressive disorders [10,11].

Physical injuries are frequent complications of syncope occurring in ≈30% of patients admitted to EDs, of whom 5% experience severe trauma causing 1) skull or major bone segments fracture; 2) intracranial hemorrhage; 3) internal organ lesions requiring urgent treatment;

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and 4) retrograde amnesia or focal neurological defect [6,12]. Approximately 10% of falls in the elderly are caused by syncope and the cost to treat them exceeds $7 billion per-year in the U.S. [13,14].

3. Pathophysiological classification

Despite general elusiveness in the medical literature, syncope is and should be unquestionably classified on the origin of its pathophysiological mechanisms as shown in Table 1.

4. Neurally-mediated reflex syncopal syndromes

They refer to a diversity of clinical scenarios, generally described as vasovagal and situational, in which the triggers of abnormal neural reflexes are 1) fear of bodily injury; 2) painful or noxious stimuli; 3) venipuncture; 4) prolonged standing (e.g., soldiers fainting on parade); 5) heat exposure; 6) exertion; and 7) coughing, swallowing or straining while urinating or defecating. Patients frequently experience warmth, nausea, lightheadedness and pallor before syncope. However, they may not occasionally exhibit any symptom at all [15].

Three responses are generally seen: 1) cardioinhibitory; 2) vasodepressor; and 3) mixed response with features of both. The former results from increased parasympathetic tone and may be manifested by any or all of the following ECG findings 1) sinus bradycardia; 2) PR interval prolongation; and 3) advanced atrioventricular block.

The vasodepressor-hypotensive response is caused by "hypersensitivity" of the autonomic nervous system, which over-responds to different stimuli with orthostatic stress being one of the most common triggers seen in clinical practice.

Finally, reduced cardiopulmonary baroreceptor sensitivity may be a contributing factor for both cardioinhibitory and vasodepressor responses.

Table 1
Pathophysiological classification of syncope.

Neurally-mediated reflex syncope
Vasovagal
Situational (e.g., *coughing, swallowing or straining while urinating or defecating, excessive heat, pain, prolonged standing, exertion, venipuncture, fear of bodily injury*)
Carotid sinus syndrome
Orthostatic syncope and associated autonomic disorders
Primary autonomic failure syndromes (e.g., *pure autonomic failure, multiple system atrophy, Parkinsonian dysautonomia*)
Secondary autonomic failure disturbances (e.g., *alcohol, diabetes, amyloidosis, volume depletion*)
Drugs (e.g., *anti-depressives, phenothiazines, diuretics, β-and α-adrenergic blockers, vasodilators, nitroglycerin*)
Cardiac syncope
Arrhythmias (e.g., *sinus bradycardia<40 bmp while awake, sinoatrial block or pauses≥3 s, third-degree or high-grade or Mobitz type II atrioventricular block, VT, SVT*)
Genetic disorders (e.g., *long- and short-QT syndromes, ARVD/C, HOCM, Brugada syndrome, ECG early repolarization in infero-lateral leads*)
Pacemaker or ICD malfunction with cardiac pauses
Structural heart or cardiopulmonary diseases (e.g., *aortic stenosis, ischemic and non-ischemic or dilated cardiomyopathies, HOCM, pulmonary embolus, pulmonary hypertension, atrial myxoma, pericardial tamponade, MI/ischemia, aortic dissection*)
Drug-induced pro-arrhythmias (e.g., *antiarrhythmics, antipsychotics, antidepressants, antihistamines, antiinfectives, gastrointestinal agents*)
Cerebrovascular syncope
Migraines
Steal syndromes (e.g., *subclavian artery steal syndrome*)
Vertebrobasilar transient ischemic attacks
Non-syncopal attacks
Disorders with partial or complete loss of consciousness (e.g., *epileptic seizures, metabolic disorders, intoxications*)
Disorders without loss of consciousness (e.g., *falls, psychogenic pseudosyncope, cataplexy*)

VT, ventricular tachycardia; SVT, supraventricular tachycardia; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; HCOM, hypertrophic obstructive cardiomyopathy; ICD, implantable cardioverter defibrillator; MI, myocardial infarction.

4.1. Carotid sinus syndrome

It is an unusual type of neurally-mediated syncope. It is due to hypersensitivity of the afferent or efferent limbs of the carotid sinus reflex arc resulting in vagal activation and/or sympathetic inhibition, which leads to bradycardia and/or vasodilation. It rarely occurs in adults under 50 years and increases in prevalence with advancing age and in close relationship with accidental mechanical manipulation of carotid sinuses and can be reproduced by carotid sinus massage [16]. The test is considered positive if symptoms are produced immediately after the massage in the presence of asystole > 3 s and/or a fall in systolic blood pressure ≥ 50 mm Hg [16].

5. Orthostatic syncope and associated autonomic disorders

Orthostatic syncope occurs when the autonomic sympathetic vasomotor system is incapacitated and fails to respond to challenges imposed by the upright position causing hypotension. As Andresen D. pointed out, it is diagnosed when there is documentation of orthostatic hypotension associated with total loss of consciousness [17]. An asymptomatic decrease in systolic blood pressure of ≥ 20 mm Hg and decrease in diastolic blood pressure ≥ 10 mm Hg within 3 min of standing, defined as classical orthostatic hypotension, should not be taken as evidence for a cause of syncope if the medical history is inconsistent with such a diagnosis [17,18].

Orthostatic syncope may be due to primary or secondary autonomic disturbances. Primary forms include 1) pure autonomic failure; 2) multiple system atrophy; and 3) parkinsonian dysautonomia. The former is characterized by autonomic system dysfunction alone, while multiple system atrophy is characterized by both autonomic and somatic nervous system involvement, and finally parkinsonian dysautonomia develops over time in patients with Parkinson's disease.

Among the secondary forms, alcohol, diabetes, and amyloidosis are common causes as well as volume depletion in which the autonomic nervous system is not itself unbalanced, but is unable of maintaining adequate blood pressure due to reduced circulating volume.

Orthostatic syncope might also occur due to the effects of many drugs, mainly in the elderly, such as anti-depressives, phenothiazines, diuretics, β- and α-adrenergic blockers, vasodilators and nitroglycerin.

6. Cardiac syncope

The most common causes are arrhythmias, such as 1) severe sinus bradycardia (<40 bpm) while awake; 2) sinoatrial block or sinus pause ≥ 3 s; 3) third-degree atrioventricular block; 4) intermittent atrioventricular block (i.e., high-grade, Mobitz type II or type I in elderly); 5) sustained ventricular tachycardia; and 6) supraventricular tachycardia.

Other causes include 1) long- and short-QT syndromes; 2) Brugada syndrome; 3) arrhythmogenic right ventricular dysplasia/cardiomyopathy; 4) malfunction of implantable pacing and defibrillator systems; and 5) drug-induced pro-arrhythmias. However, we recommend, especially in men with a history of unexplained syncope and/or a familial incidence of sudden death at a young age, to assess the presence of early repolarization on ECG, particularly a J-point elevation of ≥ 0.1 mV in ≥ 2 leads in either the inferior (II, III, aVF) or lateral (I, aVL, $V_{4–6}$) territory or both. Indeed, strong evidence from recent literature suggests a significant link between this ECG pattern and occurrence of syncope and sudden death due to life-threatening ventricular arrhythmias as well as a heritable basis in the general population [19–21].