Syncope and Unexplained Falls in the Elderly

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7.1 Epidemiology and Healthcare Costs

Syncope, defined as a transient loss of consciousness (TLoC) due to a transient global cerebral hypoperfusion with a rapid onset, a short duration, and a spontaneous recovery [1], is a common clinical condition, but the estimation of its true incidence is challenging because different definitions were used in the few existing population epidemiological studies, and the incidence derived from specific clinical settings is probably an underestimate because most syncopal patients do not seek medical assistance.

In the first Framingham cohort, a first syncope episode was reported in 3 % of men and 3.5 % of women over a 26-year follow-up period (mean age 30–62 years) [2]. In the latest report of the Framingham offspring study, with a 17-year follow-up period, 10 % of the 7814 participants (mean age 51, range 20–96 years) reported at least one syncope. The incidence rate of the first syncope was 6.2 per 1000 person years, with a sharp increase after 70 years from 5.7 events per 1000 person years in men aged 60–69 to 11.1 in men aged 70–79 – equivalent to an estimated 10-year cumulative incidence of 6 % (Fig. 7.1) [3].

In an emergency department (ED) study [4], the mean age of patients referred with syncope was 71 years, with 60 % of patients being older than 65 years. Similarly, in a cross-sectional study on patients with syncope identified from the US

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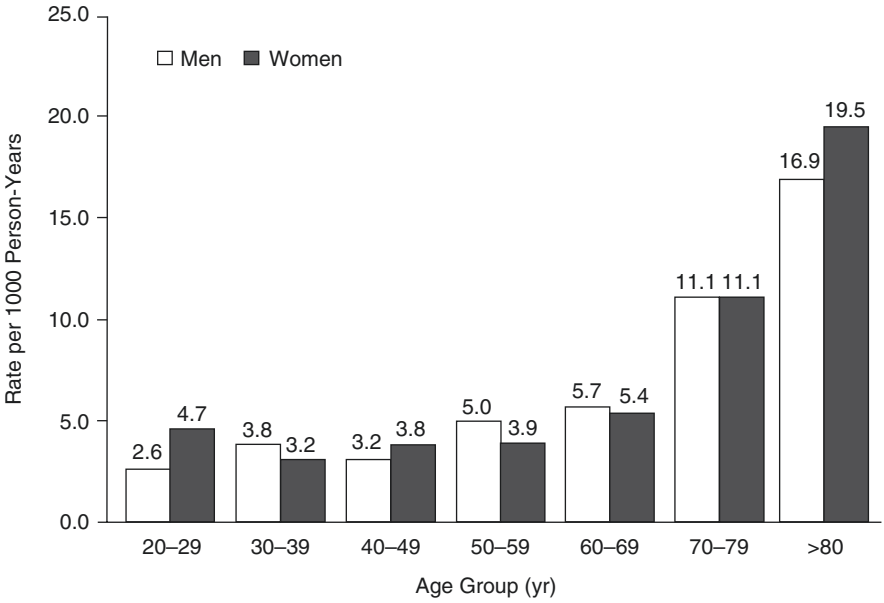

Fig. 7.1 Incidence rates of syncope according to age and sex (Reproduced with permission from Soteriades ES et al. [3])

National Inpatient Sample (NIS) database for the years 2000–2005, the mean age was 69 years; only 7.7 % of patients below the age of 40 suffered from syncope [5].

Underestimation of the problem, particularly important in the elderly, may be due to the overlap between syncope and other presentations such as falls. The incidence of syncope in older patients is thus likely to be considerably higher than current estimates, with attendant cost implications. Annual healthcare costs of syncope episodes in the United States have been estimated at $2.4 billion, with a mean cost of $5400 per hospitalization [6].

In 1999, falls accounted for 647.721 attendances at the UK accident and emergency departments and 204.424 hospital admissions in people aged 60 years and over, with cost implications approaching 1 billion pounds, the majority of which related to funding inpatient admissions [7]. Falling is indeed another major geriatric syndrome, with an age-related prevalence as for syncope (Fig. 7.2) [8], affecting mortality, morbidity, and institutionalization [9]. 34% of community-dwelling patients older than 65 years old and 50 % of octogenarians fall at least once a year [10]. 10% of hospital admissions are due to fall-related trauma [11]; 5–10 % of older patients experience fractures, concussions, and injuries [12]; and in about 1 % a hip fracture occurs, with a 20–30 % 1-year mortality and up to 50% loss of functional capacity [13]. In 30–70 % of fallers, a depressive syndrome develops, due to fear of falling and consequent disability [14].

Falls, which are not accidental, not related to a clear medical condition, or not drug induced, are defined as “unexplained” [15] and represent a relevant cause of hospital admission and increased healthcare costs [7]. Especially in older adults in whom the circumstances of a fall event cannot always be established, because of the

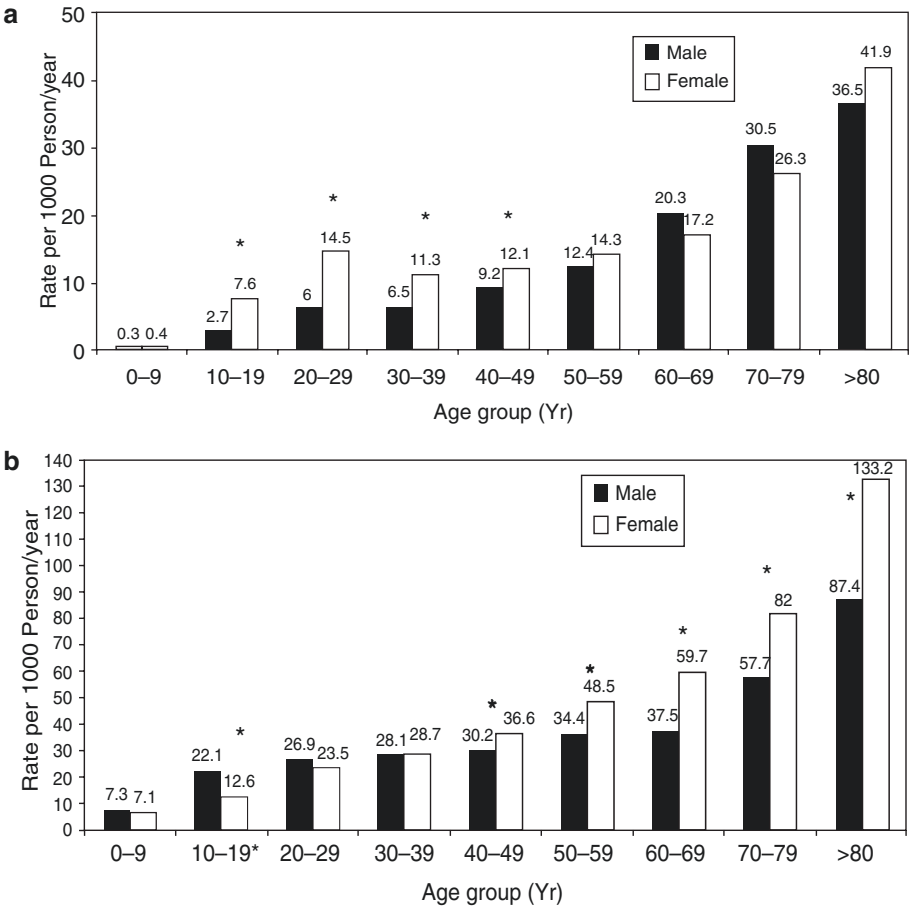

Fig. 7.2 (**a**) Prevalence of faints according to age; * indicates $P<0.01$; (**b**) Prevalence of falls according to age; * indicates $P<0.01$ (Reproduced with permission from Malasana G et al. [8])

lack of witnesses and amnesia for the episode, misdiagnosed syncope may underlie an unexplained fall. About 20 % of cardiovascular syncope in patients older than 70 years old presents as a fall, especially in patients with carotid sinus syndrome (CSS) and orthostatic hypotension (OH); more than 20 % of older patients with CSS complain of falls as well as syncope [16]. In a study of patients older than 60 years old admitted to the hospital because of a fall or syncope, fallers who had CSS during carotid sinus massage (CSM) showed retrograde amnesia for the loss of consciousness more frequently than patients with syncope [17]. Furthermore, over one third of fall events in patients in orthopedic wards are unexplained, particularly in those with depressive symptoms and syncopal spells [18], underscoring the importance of a comprehensive history and assessment at the very beginning of the medical pathway. In a recent systematic review of cardiovascular disorders and falls, positive associations were evident for low blood pressure, heart failure, cardiac arrhythmias, CSH, VVS and post prandial hypotension [19].

7.2 Pathophysiology

Syncope is caused by an inadequate supply of oxygen (<3 mLO_2/100 g tissue/min) and metabolic substrates to the brain, due to global and transient cerebral hypoperfusion [20]. Global cerebral hypoperfusion differentiates syncope from the other conditions which can mimic syncope, but without underlying cerebral hypoperfusion; such as epilepsy, hypoglycemia, transient ischemic attacks (TIA) in the vertebro-basilar region, intoxication, and episodes of apparent loss of consciousness, i.e., falls, drop attacks [1]. The functional integrity of the cerebral tissue strictly depends on oxygen supply, and in healthy subjects, cerebral autoregulation maintains a constant blood flow within a fairly wide range of pressures [systolic blood pressure (SBP) between 60 and 190 mmHg]. When SBP decreases below this threshold, brain perfusion decreases slowly and progressively, and if this hemodynamic status lasts for 8–15 s, ischemia and ultimately loss of consciousness will follow [1, 21].

Older adults are particularly exposed to syncope, because several factors differentiate them from younger adults. The effects of age-related pathophysiological changes have to be considered, such as reduced left ventricular compliance (which increases the susceptibility of cardiac output to preload and atrial contraction), altered control of blood volume, and decreased sensitivity of the baroreceptors. Moreover, diseases such as heart failure, diabetes, and chronic obstructive lung disease increase the risk of cerebral hypoperfusion. Finally, the differences in blood pressure (BP) adjustments during orthostasis between the young, which rely essentially on an increase in the heart rate (HR) and myocardial contractility, and the elderly, which rely more on an increase in peripheral resistance [22], can explain the attributable role of vasoactive drugs as precipitating factors for syncope in older patients [23]. The pathophysiological role of altered cerebral autoregulation in the elderly as a predisposing factor to syncope is debated. Serrador JM et al. [22] demonstrated that cerebral autoregulation is intact in elderly hypertensive subjects suggesting that otherwise healthy hypertensive elderly patients can safely undergo BP reduction, without concern for cerebral hypoperfusion. In older patients with syncope, there is evidence that cerebral blood flow velocity was lower than in younger subjects. However, autoregulatory indexes reflecting dynamic cerebral autoregulatory function were similar, either at supine rest or during tilt test (TT) [24]. Giese AE et al. [25] showed that in healthy individuals, age and baseline BP have only a minor effect on the lower limit of BP necessary to maintain consciousness. Higher baseline BP provides older individuals a greater BP "reserve" to maintain the consciousness compared to younger subjects. Further studies of unselected older populations are necessary to better understand the implications of cerebral blood flow, hypertension, orthostatic hypotension, and antihypertensive treatments. However, it is the case that age-related physiologic impairments of heart rate, blood pressure, and cerebral blood flow, in combination with comorbid conditions, concurrent medications, and neurohumoral adjustments, contribute to the increased susceptibility of older adults to syncope.

7.3 Etiology and Clinical Features

Neurally mediated disorders such as vasovagal (VVS), situational syncope, and CSS are the commonest cause of syncope in all age groups. Structural and arrhythmic cardiac syncope, as well as OH, increase with advancing age (Fig. 7.3) [4].

7.3.1 Vasovagal Syncope

VVS is commonly induced by triggers such as fear, pain, and instrumentation or is induced by orthostatic stress or hot environment. In older patients the presentation is often atypical. Syncope can also occur with uncertain stimuli or even apparently without triggers. Moreover, prodromes may be short and loss of consciousness starts abruptly, leading to falls and injuries [26]. However, more than 70 % of older patients with syncope complain of at least one symptom before loss of consciousness, with nausea, blurred vision, and diaphoresis being the most common in VVS, whereas dyspnea is more predictive of cardiac syncope [27]. The frequency of prodromes due to global cerebral hypoperfusion or to autonomic activation is lower in subjects >60. In one study during the syncopal phase, myoclonic movements were rarely observed in older subjects and absent in those >74 years [28]. A possible explanation is the less frequent occurrence of asystole in the elderly or slower reduction in SBP. Even during the recovery phase, the frequency of autonomic symptoms is lower in older subjects; thus, in the elderly the clinical features of VVS are very similar to those of cardiac syncope [28].

If VVS occurs when the patient is upright, he/she will fall thereby rendering clinical findings of syncope and falls very similar. In this context, retrograde amnesia has been demonstrated in patients with syncope induced in the laboratory; indeed, about 25 % of patients fail to recall their prodrome and TLoC during tilt-induced syncope [29].

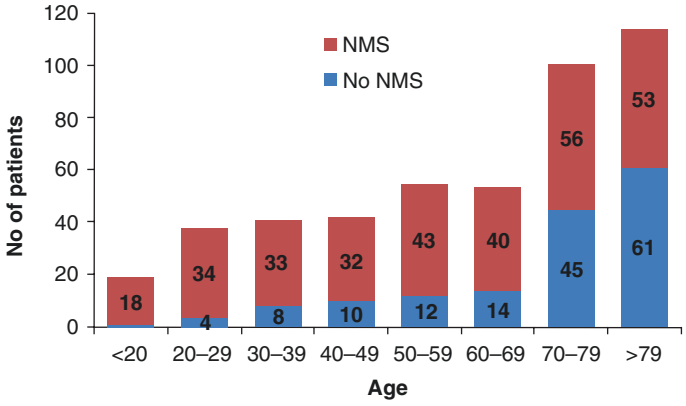

Fig. 7.3 Age distribution of neurally mediated syncope and other causes of syncope [4]. *NMS* neurally mediated syncope, *No NMS* no neurally mediated syncope

7.3.2 Orthostatic Hypotension

OH is traditionally defined as a fall in SBP from a baseline value ≥20 mmHg or diastolic BP (DBP) ≥10 mmHg or a decrease in SBP to <90 mmHg within 3 min of orthostatic position [1]. Since the magnitude of blood pressure drop also depends on baseline values, it was suggested that a drop of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension [30]. The rate of OH increases with advancing age, reaching 24.3 % in the eighth decade and 30.9 % in the ninth decade, as recently confirmed [31], [32]. In a study conducted on patients older than 65 years old consecutively referred to the ED for a TLoC, the prevalence of syncope related to OH was 12.4 % [33].

Initial OH is represented by a drop in SBP during the first 30 s of standing with quick and spontaneous recovery, which is detectable by beat-to-beat BP monitoring. This form of OH may have implications in older adults, particularly those on medications impacting cardiovascular control [34]. A recent study has found that 15 % of long-term care residents fall after rising to standing [35]. This represents a high-risk activity for older adults, and initial OH could potentially exacerbate this falling risk, although a recent population study suggests that initial OH is more benign than other subtypes [36].

C*lassic* OH is diagnosed with the active standing test within 3 min of orthostatic position. *Delayed* OH is characterized by a slow and progressive decrease of SBP on assuming the standing position. In this syndrome, hypotension can manifest clinically up to 30 min after the achievement of the upright position, and passive TT is necessary for the diagnosis [1].

Pharmacotherapy is the most common cause of OH in older individuals; alpha-receptor blockers, nitrates, or benzodiazepines and antidepressants [37], frequently used in older people, were found to be predictors of OH and associated with syncope and falls [31]. Other causes of OH are represented by primary autonomic failure (e.g., idiopathic Parkinson's disease and multiple system atrophy), secondary autonomic failure (e.g., diabetic and alcoholic autonomic neuropathy), and dehydration. Occasionally OH may be the presenting manifestation of malignancy or anemia, which should be considered in patients with OH and particularly in the older population [38].

Postural blood pressure decreases could cause a falling event. It has been suggested that 2–10 % of falls in older adults may occur secondary to impaired hemodynamic responses, and loss of consciousness is estimated to result in as many as 10 % of falls [39]. OH could also be linked to falls through indirect mechanisms. In many cases loss of consciousness is avoided, but increased fall's susceptibility remains through pre-syncope and associated physiological impairments [40]. Older adults with Parkinson's disease or diabetes mellitus and OH have poorer balance scores in comparison to those without OH [41, 42], and as poor balance is a known risk factor for falls, it has been suggested to increase this risk threefold [10].

Blood pressure impairments including OH, hypertension, and acute and chronic cerebral hypoperfusion are associated with impaired cognitive performance in older adults [43, 44]. This association has been recently confirmed in a large sample of the general population, where patients with OH showed a worse cognitive performance in the domains of memory, attention, and executive functions [45]. Frewen J et al. [46]

have shown an independent association between early OH and cognitive decline in patients with supine hypertension. A possible explanation is that high long-term BP levels, which are per se related to cognitive impairment, could be associated with OH, which in turn aggravates cognition. This latter is also a risk factor for falls [47]. Multivariable analyses suggest cognitive deficits increase falling risk threefold. Therefore, cognitive functioning could serve as an intermediary mechanism between BP impairment and falling risk in older adults [39].

7.3.3 Carotid Sinus Hypersensitivity and Syndrome

Carotid sinus hypersensitivity (CSH) can manifest as cardioinhibitory (CI-CSH) (asystole ≥ 3 s during CSM) or vasodepressor (VD-CSH) (a fall in SBP ≥ 50 mmHg during CSM) or mixed (M-CSH) and represents a positive response to CSM in an asymptomatic patient. CSH could indicate an abnormal reflex, which may have a role in predisposing to unexplained falls; in this condition syncope has to be taken into account, even if the clear dynamic of the event could not be recalled due to retrograde amnesia. Maggi R. et al. [48] have showed that CI-CSH in patients with a clinical diagnosis of suspected neurally mediated syncope was related to a long asystolic reflex detected by an implantable loop recorder (ILR) at the time of the spontaneous syncope.

When associated with syncope, CSH is defined as CSS [1]. The prevalence of CSS has been estimated to range from <4 % in patients <40 years to 41 % in those >80 years attending a specialized syncope facility [49]. CSS is frequent in older males with a mean age of 75 years and often evidence of cardiovascular disease; the related syncope has often little or no prodrome, with a consequent increased risk of traumatic fall. Syncope recurrence is common and is reported to be 50 % in 2 years. There is also a high mortality, which is considered to be related to comorbidities and age rather than CSS itself. When monitored, in CI-CSH patients the most frequently detected arrhythmia is sinus arrest without escape rhythm in 72 %. There is an association with sinus node disease in 21–56 % of the cases and with atrioventricular block in 21–37 % of the cases [49].

The most recent ESC guidelines on pacing [50] have proposed a 6 s cutoff for the CSM-induced asystole, because this latter, which causes symptoms in CI-CSH and M-CSH, is generally much longer than the historical 3 s cutoff value. On average, the duration of asystole to induce symptoms is 7.6 ± 2.2 s and the fall in BP is 63 ± 24 mmHg [51, 52].

7.3.4 Cardiac Syncope

Cardiac causes of syncope are highly represented in the older population (Fig. 7.3) [4].

Arrhythmias, structural heart disease, and pulmonary embolism are much more prevalent in older patients. In the Framingham study, cardiac syncope doubled the risk of death from any cause and increased the risk of nonfatal and fatal cardiovascular events, compared to those without syncope [3]. Short-lived syncope of abrupt

Table 7.1 EGSYS score. Point scores for the diagnosis of cardiac syncope [48]

Palpitations preceding syncope	4
Heart disease or abnormal ECG or both	3
Syncope during effort	3
Syncope while supine	2
Precipitating or predisposing factors or both[a]	−1
Autonomic prodromes[b]	−1

[a]Warm-crowded place/prolonged orthostasis/fear-pain-emotion
[b]Nausea/vomiting

onset and recovery, supine, during (rather than after) exercise or associated with palpitations or chest pain should be considered cardiac until proven otherwise. A past history of heart disease is an independent predictor of cardiac syncope with a sensitivity of 95 % and specificity of 45 % [53]. Cardiac syncope must be excluded in patients with known or suspected left ventricular systolic dysfunction (LVSD), valvular disease, and left ventricular outflow tract (LVOT) obstruction, in those with an abnormal surface electrocardiogram (ECG) and where the clinical context and concomitant investigations suggest pulmonary embolism. Neurally mediated cause of symptoms must not be assumed in any patient with these clinical and diagnostic features until a cardiac cause has been effectively excluded. The EGSYS score is a diagnostic score to identify cardiac syncope. Abnormal ECG and/or heart disease, palpitations before syncope, syncope during effort or in supine position, the absence of autonomic prodromes, and the absence of predisposing and/or precipitating factors were found to be predictors of cardiac syncope. To each variable a score from +4 to −1 was assigned according to the magnitude of regression coefficient (Table 7.1, [54]). A score >3 identified cardiac syncope with a sensitivity of 95 %/92 % and a specificity of 61 %/69 % [54].

7.4 Evaluation of the Older Patients with Syncope and Unexplained Fall

The diagnostic protocol proposed by the ESC guidelines on syncope [1] is well enforceable in older patients, and when applied, the rate of unexplained syncope decreases to 10.4 % [55].

7.4.1 Initial Evaluation

The initial assessment in older patients is aimed at considering, excluding, or identifying a cardiac cause of symptoms, given the high morbidity and mortality associated with these disorders in this age group.

The clinical history regarding the episodes should be pursued by a witness's account, for the relevant presence of retrograde amnesia in the elderly. Particular attention should be paid to the time of the day, season, relationship with meals,

nocturnal micturition, supine or upright position, drugs, duration of treatment, and time relationship between drug consumption and appearance of adverse effects. The clinical history should include the collection of systemic diseases, physical frailty, and locomotor disabilities. Details of cognitive status, social circumstances, injuries, impact of the event on confidence, and ability to carry out basal/instrumental activities of daily living independently should also be recorded [1].

However, the medical history has a limited value in the differential diagnosis between cardiac and neurally mediated cause of syncope in older patients [27]; thus, TT and CSM become essential in the diagnostic pathway.

The 12-lead ECG can be considered diagnostic and permits no further evaluation and institution of treatment, in cases of persistent sinus bradycardia <40 bpm in awake or repetitive sinus-atrial block or sinus pauses >3 s; Mobitz II second or third degree atrioventricular block, alternating left and right bundle branch block, ventricular tachycardia (VT), or rapid paroxysmal supraventricular tachycardia; non-sustained episodes of polymorphic VT and long or short QT interval; and evidence of acute ischemia with or without myocardial infarction [1].

The physical examination should include cardiovascular and neurological assessment, evidence of Parkinson's disease or other neurodegenerative conditions related to autonomic dysfunction. A careful observation of gait and standing balance is useful in the evaluation of the locomotor system and the consequent risk of falling.

The active standing test, which consists of the measurement of BP in the supine position and then immediately after changing from the supine to the upright position and after 1 and 3 min of orthostatic position, is a relevant diagnostic step, especially in older patients. OH is not always reproducible in older adults, especially when it is related to drugs or predisposing conditions; therefore, active standing tests should be repeated, preferably in the morning and/or "promptly" after the syncope [1].

Alpha-receptor blockers, nitrates, or benzodiazepines, frequently used in older people, were found to be predictors of OH; therefore, attention should be paid on the reevaluation of drug regimens in the presence of OH, in order to reduce the syncope recurrence [31].

The ESC guidelines on syncope [1] propose the execution of CSM during the first-line evaluation, because of the high prevalence of CSS as a cause of syncope and unexplained falls in the elderly.

The test is performed in a TT laboratory under continuous heart rate (HR) and beat-to-beat BP monitoring. CSM is conducted for 10 s, bilaterally, first in the supine and then in the upright position, on TT at an angle of 60°. The added diagnostic value of repeating CSM in the upright position has been well documented [56]. In order to assess the contribution of the VD component, CSM may be repeated after intravenous administration of 0.02 mg/kg of atropine, which eliminates vagally induced asystole, thereby unmasking the VD phenomenon [57]. This quantification of the VD component is clinically relevant, because it has been shown that pacemaker therapy is less effective when the VD effect is large, compared with predominant cardio-inhibition [58]. Transient ischemic attack or stroke

during the 3 months beforehand or critical carotid artery stenosis on Doppler ultrasounds performed in the presence of carotid bruits represents relative contraindications to CSM [59]. In such situation, a careful risk/benefit assessment must be undergone.

7.4.2 Second-Level Evaluation

7.4.2.1 Tilt Testing

TT is the best validated test for the clinical assessment of neurally mediated reflexes, has been validated in older subjects using the Italian protocol (300–400 mcg of sublingual nitroglycerine), is well tolerated, and has a similar positivity rate and specificity both in young and in older patients [60].

The test should be performed in the morning, in fasting state, and in a quiet and dimly lighted place. Briefly the test consists of 20 min of passive orthostatic position at an angle of 60° that is potentiated, if syncope does not occur, on administration of sublingual nitroglycerine (300–400 μg) with a further 15 min of observation at the same angle. The test is considered positive if symptoms reproducing those reported by the patient during spontaneous syncope are associated with hypotension, bradycardia, or both [61]. A recent meta-analysis [62] demonstrated that TT has a good overall ability to discriminate between symptomatic patients and asymptomatic control subjects, with a high specificity in most of the protocols investigated and a widely variable sensitivity. Pharmacological protocols have higher sensitivity and lower specificity than passive protocols. Moreover, nitroglycerine-stimulated TT has greater diagnostic capability in comparison to isoproterenol-stimulated TT [62]. However, Ungar A. et al. [63] showed that TT was unable to discriminate between cardiac and presumed neurally mediated syncope with the exception of an asystolic response which was highly specific. The test was indeed diagnostic in 56 % of presumed neurally mediated syncope and in 43 % of non-neurally mediated syncope patients and in 45–47 % of those with true cardiac arrhythmic syncope. A possible explanation of this discrepancy comes from a recent reinterpretation of TT, according to which the test could reveal a susceptibility to vertical posture stress as a "hypotensive susceptibility," which could cause syncope irrespective of the etiology and the mechanism of syncope itself [64]. The identification of hypotensive susceptibility makes TT a risk stratification tool, rather than a diagnostic one, for patients with recurrent, traumatic syncope and ECG documentation of spontaneous asystolic reflex syncope, as showed in the ISSUE 3 study [65], who could greatly benefit from pacing, especially when TT is negative, because of a pure asystolic mechanism [66].

TT can also be useful in guiding the differential diagnosis between syncope and unexplained falls, as recently confirmed that the positivity prevalence of TT and CSM was similar in patients who presented with these two conditions, suggesting that neuro-autonomic evaluation, through the standing test, TT, and CSM, should be routinely performed in older patients with unexplained falls [67].

7.4.2.2 Implantable Loop Recorder

ILR has been developed to provide ECG documentation of events that occur sporadically, as other technologies (ambulatory ECG and external event recorder) have a low rate of diagnosis due to the infrequent nature of events, such as syncope. The device is placed subcutaneously and has a retrospective (loop) memory which continuously records and deletes the patient's ECG, including a patient's activated function, through which the patient can activate the ECG storage as a result of symptoms and an automatic feature, which allows the capture of arrhythmic events without relying on patient's compliance or perception of symptoms. In pooled data from a consensus document [68], ILR provided an ECG-syncope correlation in about 35 % of patients during the lifetime of the device. Of these, 56 % had asystole or severe bradycardia. Similar findings were observed when ILR was inserted in patients with suspected neurally mediated syncope in an early phase after the initial evaluation or in unexplained syncope at the end of the conventional work-up.

Older patients are more likely to receive an ILR implantation than younger patients, because of the need for a precise diagnosis in case of structural heart disease or bundle branch block, which is almost exclusively present in patients ≥65 years, because of the limited value of the clinical history in the diagnosis of the causes of syncope, and finally because in the elderly the onset of syncope is sudden abrupt with little or no prodromes, justifying the need for ILR to detect the underlying mechanism and start a specific treatment [69]. ILR also has a high diagnostic value in conditions in which an initial diagnosis is only suspected, and the demonstration of an arrhythmic mechanism could definitively guide the therapy. Maggi R. et al. [70] showed that in highly selected older patients with an initial diagnosis of either likely epilepsy or unexplained falls, ILR gave a documentation of a relapse of their index attack and that, in about one-fourth of the patients, the final diagnosis was arrhythmic syncope. Moreover, ILR monitoring definitely excluded an arrhythmic cause, when the arrhythmia was not documented at the time of a spontaneous attack.

Different neurally mediated mechanisms can coexist especially in older people and be responsible for the genesis of syncope. In a population of 873 consecutive patients older than 65 years old, the rate of "complex diagnosis," namely, the presence of more than one diagnosis on standing test, TT, and CSM, was 23 %, and the most frequent association was between OH and VVS on TT in the 15.8 % of the cases [31]. It is therefore useful to run a comprehensive evaluation in every subject, without stopping at the apparently first etiological diagnosis.

7.5 Treatment

The treatment is based on risk stratification and identification of specific mechanisms leading to global cerebral hypoperfusion. An arrhythmic syncope may benefit from cardiac pacing, implantable cardioverter-defibrillators, and/or catheter ablation as well as, in the case of structural cardiac or cardiopulmonary disease, treatment directed at amelioration of the specific structural lesion or its consequences.

7.5.1 Neurally Mediated Syncope

Physical counterpressure maneuvers such as leg crossing, hand grip, or arm tensing can induce a significant BP increase during impending reflex syncope, but given the frequent absence or brief prodromes, particularly in older adults, these maneuvers are difficult to apply to this age group. Education and reassurance, modification or discontinuation of antihypertensive drugs, diuretics, nitrates, benzodiazepines, and alpha-receptor blockers, which are likely to be related to hypotension and falls, and avoidance of triggering situations are cornerstones of behavioral strategies. Disappointing results have been obtained by the use of various drugs in the context of neurally mediated syncope.

Cardiac pacing should be considered in patients with CI-CSS (class 2a, level B in the ESC syncope guidelines [1]). The ISSUE 3 study has demonstrated that pacing was effective in reducing the recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope, previously documented by an ILR [65]. Nevertheless 25 % of the patients had syncopal recurrence after 2 years, despite pacemaker therapy. The benefit of pacemaker therapy was not substantial in patients with a positive TT, speculating a hypotensive mechanism that cannot be prevented by cardiac pacing [66].

In a recent pragmatic study [71], a guideline-based diagnostic algorithm was proposed and the efficacy of cardiac pacing was assessed. Patients aged >40 years, affected by severe unpredictable recurrent reflex syncope, underwent CSM, followed by TT if CSM was negative, followed by implantation of an ILR if TT was negative. Those who had an asystolic response to one of these tests received a dual-chamber pacemaker.

The recurrence rate was similar in CSM+, TT+, and ILR+ patients and highly reduced in the year following implantation compared to the year before. The recurrence rate was also significantly lower than that observed in the group of patients with non-diagnostic test who had received an ILR, instead of a pacemaker. The guideline-based diagnostic algorithm proposed proved a clinical utility for the selection of candidates to cardiac pacing in everyday clinical practice.

7.5.2 Orthostatic Hypotension

Antihypertensive drug withdrawal (particularly beta blockers), extracellular volume expansion, and salt and water intake in the absence of hypertension are the principal treatment strategies. Elevating the head of the bed helps reducing nocturnal hypertension, with a more favorable distribution of body fluids and prevention of nocturnal micturition. Abdominal binders or compression stockings are useful against gravitational venous pooling [1]. Pharmacological interventions may become necessary when non-pharmacological measures fail to attenuate symptoms. Nevertheless, supine hypertension has to be considered as an adverse effect of pharmacological treatment.

Volume expansion may be achieved with 9-α-fluorohydrocortison, a synthetic mineralocorticoid, which increases plasma volume by renal sodium retention.

Peripheral vascular resistance is the limiting factor of 9-α-fluorohydrocortison treatment, resulting in dose-dependent supine hypertension. The alpha-agonist midodrine has been used, achieving a proper vasoconstriction of the peripheral vessels; nevertheless, its limitation is represented by a short half-life, which requires frequent dosing and limits a long-term compliance. Furthermore its use is related to adverse effects on urinary outflow, which requires special caution in older males [72].

Pyridostigmine is a cholinesterase inhibitor, which improves ganglionic transmission and vascular adrenergic tone in primarily upright position, mediating a slight increase in diastolic blood pressure during standing without worsening supine hypertension [73].

Droxidopa is an orally administered artificial amino acid converted both peripherally and centrally into norepinephrine. The enzyme responsible for the conversion, aromatic amino acid decarboxylase, is widely expressed, and so the administration of droxidopa increases norepinephrine even if postganglionic sympathetic neurons are not intact. The drug has received accelerated Food and Drug Administration (FDA) approval for the treatment of symptomatic OH, particularly in Parkinson's Disease. It has been recently demonstrated that droxidopa improved symptoms and symptom impact on daily activities, with an associated increase in standing SBP in patients with symptomatic OH due to different orthostatic intolerance syndromes, without worsening supine hypertension [74].

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