Neurally-mediated syncope

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Key words:
Carotid sinus massage; Pacing; Syncope; Tilt testing.

"Neurally-mediated (reflex) syncope" refers to a reflex response that, when triggered, gives rise to vasodilation and/or bradycardia; however, the contribution of each of these two factors to systemic hypotension and cerebral hypoperfusion may differ considerably. The initial evaluation may lead to a certain diagnosis in the case of classical vasovagal syncope and of situational syncope. Classical vasovagal syncope is diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing, are associated with typical prodromal symptoms. Situational syncope is diagnosed if syncope occurs during or immediately after urination, defecation, cough or swallowing. In the absence of a certain diagnosis, absence of cardiac disease, long history of syncope, syncope after sudden unexpected unpleasant sight, sound or smell, prolonged standing at attention or crowded, warm places, nausea and vomiting, post-prandial and post-exercise state suggest a neurally-mediated cause which needs to be confirmed by specific tests. Among them, the most useful are carotid sinus massage and tilt testing. In general, education and reassurance are the sufficient initial treatment. Additional treatment may be necessary in high-risk or high-frequency settings. Treatment is not necessary in patients who have sustained a single syncope and are not having syncope in a high-risk setting. It is valuable to assess the relative contribution of cardioinhibition and vasodepression before embarking on treatment as there are different therapeutic strategies for the two aspects. Even if evidence of utility of such an assessment exists only for the carotid sinus massage, it is recommended to extend this assessment also by means of tilt testing or implantable loop recorder. Tilt training and isometric leg and arm counterpressure maneuvers are indicated in patients with recurrent vasovagal syncope. Cardiac pacing is indicated in patients with cardioinhibitory or mixed carotid sinus syndrome and in patients with cardioinhibitory vasovagal syncope with a frequency > 5 attacks per year or severe physical injury or accident and age > 40 years. The evidence fails to support the efficacy of any drug.

(Ital Heart J 2005; 6 (3): 249-255)

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Definition and classification

"Neurally-mediated (reflex) syncope" refers to a reflex response that, when triggered, gives rise to vasodilation and/or bradycardia; however, the contribution of each of these two factors to systemic hypotension and cerebral hypoperfusion may differ considerably[1,2]. The triggering events might vary substantially in individual patients (Table I). The "classical vasovagal syncope" is mediated by emotional or orthostatic stress and can be diagnosed by history taking. "Carotid sinus syncope" is defined as a syncope which, by history, seems to occur in close relationship to accidental mechanical manipulation of the carotid sinuses, and which can be reproduced by carotid sinus massage. "Situational syncope" refers to those forms of neurally-mediated syncope associated with specific scenarios (e.g., micturition, coughing, defecating, etc.). Often, however, neurally-mediated reflex syncopes have "non-classical" presentations. These forms are diagnosed by minor clinical criteria, exclusion of other causes for syncope (absence of structural heart disease) and positive response to tilt testing or carotid sinus massage. Examples of non-classical vasovagal syncope include episodes without clear triggering events or premonitory symptoms.

The clinical spectrum of neurally-mediated reflex syncopes demonstrates much overlap between these clinical forms. The clinical features of situational, carotid sinus, tilt-induced and complex neurally-mediated syncope are very similar. Conversely, typical vasovagal syncope differs from other neurally-mediated syncopes not only in terms of its precipitating factors (fear, strong emotion, etc.), which constituted predefined diagnostic criteria, but also in the variety of its clinical features (lower age and prevalence of organic heart disease, higher prevalence of prodromal symptoms, and of autonomic prodromes, longer duration of prodromes, higher prevalence of symptoms during the recovery phase and lower prevalence of trauma)[3].

Table I. Classification of neurally-mediated (reflex) syncope.

Vasovagal syncope (common faint)
Classical
Non-classical
Carotid sinus syncope
Situational syncope
Acute hemorrhage
Cough, sneeze
Gastrointestinal stimulation (swallow, defecation, visceral pain)
Micturition (post-micturition)
Post-exercise
Post-prandial
Others (e.g., brass instrument playing, weight-lifting)
Glossopharyngeal neuralgia

Neurally-mediated syncope is the most frequent cause of syncope. In pooled data of four recent population-based studies including a total of 1640 patients[1,2], neurally-mediated syncope accounted for 50% of the causes of syncope.

Moreover, an abnormal reflex plays a role in causing syncope in different clinical settings where more than one pathophysiological factor may contribute to the symptoms. For instance, in the setting of valvular aortic stenosis or left ventricular outflow tract obstruction, syncope is not solely the result of restricted cardiac output, but may be in part due to inappropriate neurally-mediated reflex vasodilation and/or primary cardiac arrhythmias[4]. Similarly, a neural reflex component (preventing or delaying vasoconstrictor compensation) appears to play an important role when syncope occurs in association with certain brady- and tachyarrhythmias[5,6].

Diagnosis

The diagnosis of neurally-mediated syncope is made by typical history or positive response to tests and exclusion of other competing diagnoses (Table II).

History. The starting point for the evaluation of neurally-mediated syncope is a careful history, physical examination including orthostatic blood pressure measurements and a 12-lead ECG. In many patients without heart disease a definite diagnosis of neurally-mediated syncope can be made without any further examination. This is the case in the following situations:

- vasovagal syncope is diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing, are associated with typical prodromal symptoms;
- situational syncope is diagnosed if syncope occurs during or immediately after urination, defecation, cough or swallowing.

Under such circumstances, no further evaluation of the disease or disorder may be needed and treatment, if any, can be planned.

More commonly, the initial evaluation leads to a suspected diagnosis, when one or more of the features listed in table III are present. A suspected diagnosis needs to be confirmed by directed testing.

The diagnostic value of history decreases with advancing age. For example, history alone was able to define the diagnosis in 38% of patients aged < 65 years but only in 9% of patients aged > 65 years. Conversely, tests are particularly useful to confirm diagnosis in the elderly[7].

Carotid sinus massage. Carotid sinus syndrome is diagnosed in patients who have an abnormal response to carotid sinus massage (carotid sinus hypersensitivity) and an otherwise negative work-up for syncope. Carotid sinuses (alternatively right and left) are firmly massaged for 5-10 s. The site for massage is the anterior margin of the sternocleomastoid muscle at the level of the cricoid cartilage. Both a cardioinhibitory reflex and a vasodepressor reflex are usually evoked with the massage (mixed form) but their relative contribution varies. If an asystolic response is evoked, to assess the contribution of the vasodepressor component (which may otherwise be hidden), massage is usually repeated after intravenous administration of atropine (1 mg or 0.02 mg/kg body weight). A correct determination of the vasodepressor reflex component is of practical importance for the choice of pacing therapy which is more effective in dominant cardioinhibitory forms. A positive response is defined as a ventricular pause ≥ 3 s and/or a fall in systolic blood pressure ≥ 50 mmHg[8].

Table II. Investigations for neurally-mediated syncope.

Most useful
History
Carotid sinus massage
Tilt testing
Implantable loop recorder
Less useful
Adenosine triphosphate test
Eyeball compression test
External loop recorder
Holter monitoring

Table III. Clinical features suggestive of neurally-mediated syncope.

Absence of cardiac disease
Long history of syncope
After sudden unexpected unpleasant sight, sound, smell or pain
Prolonged standing or crowded, hot places
Nausea, vomiting associated with syncope
During or in the absorptive state after a meal
With head rotation, pressure on carotid sinus (as in tumors, shaving, tight collars)
After exertion

However, abnormal responses are frequently observed in subjects without syncope. The specificity of the test increases if reproduction of spontaneous syncope during carotid massage is a requisite for positivity of the test. The syndrome is misdiagnosed in half of the cases if the massage is not performed in the upright position[9]. There is a relationship between carotid sinus hypersensitivity and spontaneous, otherwise unexplained, syncope[10]. Carotid sinus syndrome is a frequent cause of syncope, especially in elderly males, ranging from 4% in patients < 40 years to 41% in patients > 80 years[9]. In a large population of 1719 consecutive patients (mean age 66 ± 17 years) with syncope of uncertain origin after the initial evaluation, carotid sinus hypersensitivity was found in 56% and syncope was reproduced in 26% of cases[9]. The response was cardioinhibitory in 46%, mixed in 40%, and vasodepressor in 14%. The main complication of carotid sinus massage is neurological, i.e. transient ischemic attack and stroke, its incidence ranging, in three studies, between 0.17 and 0.45%[9-11]. If there is a risk of stroke due to carotid artery disease, massage should be avoided. Therefore, carotid sinus massage is recommended in patients > 40 years with syncope of unknown etiology after the initial evaluation[1,2].

Tilt testing. By changing from the supine to the erect posture there is a large gravitational shift of blood from the chest to the venous capacitance system below the diaphragm. Failure of compensatory reflexes to orthostatic stress is thought to play a predominant role in a large number of patients with suspected vasovagal syncope. This forms the basis for the use of tilt testing.

Protocols. In 1986, the initial tilt protocol consisted of a passive phase of tilting with an inclination of 60º for 60 min[12]. In 1989 a drug challenge with isoproterenol (isoprenaline) was added[13]. After several protocol variations tested to maximize its diagnostic value, the most valuable seemed to be the "shortened" low-dose isoproterenol tilt testing, in which the rate of positive responses was 61% with a specificity of 92-93%[14,15]. In 1994 a drug challenge with nitroglycerin was proposed[16]. After several protocol variations, the most valuable seems to be a "shortened" protocol using 400 μg nitroglycerin spray sublingually after a 20 min baseline phase. Pooled data from three studies[17-19] show a positive response rate of 69% with a specificity of 94%.

To summarize, the widely accepted protocols consist of[1,2]:
• supine pre-tilt phase of at least 5 min when no venous or arterial cannulation is performed, and at least of 20 min when cannulation is undertaken;
• tilt angle 60 to 70°;
• passive phase ≥ 20 and ≤ 45 min;
• use of either intravenous isoproterenol or sublingual nitroglycerin for drug provocation if the passive phase has been negative. Drug challenge phase duration should be 15-20 min;
• for isoproterenol, an incremental infusion rate from 1 up to 3 μg/min, in order to increase the average heart rate by about 20-25% with respect to baseline, should be administered without returning the patient to the supine position;
• for nitroglycerin, a fixed dose of 400 μg nitroglycerin spray sublingually should be administered in the upright position;
• endpoint of the test is the reproduction of syncope or completion of the planned tilt duration including drug provocation.

In patients without structural heart disease, tilt testing can be considered diagnostic, and no further tests are needed when syncope is reproduced. In patients with structural heart disease, arrhythmias or other cardiac causes should be excluded prior to considering positive tilt test results. The clinical meaning of abnormal responses other than induction of syncope is unclear.

Responses to the tilt test. Experience from tilt testing showed that the vasovagal reaction lasts roughly ≤ 3 min before the loss of consciousness. A decrease in systolic blood pressure ≤ 90 mmHg is associated with symptoms of impending syncope reproducing the patient's previous experience and ≤ 60 mmHg is associated with syncope. Prodromal symptoms are present in virtually all cases of tilt-induced vasovagal syncope, which occurs, on average, 1 min after the onset of prodromal symptoms. During the prodromal phase, blood pressure falls markedly; this fall frequently precedes the decrease in heart rate, which may be absent at least at the beginning of this phase. During the syncopal phase, a cardioinhibitory reflex of variable severity (ranging from slight heart rate decrease up to prolonged asystole) is frequent and contributes to the loss of consciousness. Unusual response patterns include cases of chronotropic incompetence or of excessive heart rate rise (the so-called postural orthostatic tachycardia syndrome)[20].

Role of tilt test in the assessment of treatment effectiveness. Data from controlled trials showed that approximately 50% of patients with a baseline positive tilt test have become negative when the test was repeated under treatment or with placebo[21-23]. The mechanism of tilt-induced syncope was frequently different from that of the spontaneous syncope recorded with the implantable loop recorder (ILR)[24]. These data show that the use of tilt testing for assessing the effectiveness of different treatments has important limitations.

Complications. Tilt test is a safe procedure and the rate of complications is very low. The presence of prolonged asystole during a positive response cannot be considered a complication, since this is an endpoint of the test.

Adenosine triphosphate testing. Intravenous injection of adenosine triphosphate (ATP) has recently been proposed as a tool in the investigation of patients with unexplained syncope[25,26]. The test requires the rapid injection of a 20 mg bolus of ATP during ECG monitoring. Asystole lasting > 6 s or atrioventricular block lasting > 10 s is considered abnormal. ATP testing produces an abnormal response in some patients with syncope of unknown origin, but not in controls. ATP testing identifies a group of patients with otherwise unexplained syncope with definite clinical features and benign prognosis but possibly heterogeneous mechanisms of syncope[27]. The diagnostic and predictive value of the test remains to be confirmed by prospective studies.

Electrocardiographic monitoring (non-invasive and invasive). ECG monitoring is diagnostic when a correlation between syncope and ECG abnormality (brady- or tachyarrhythmia) is detected. Conversely, ECG monitoring excludes an arrhythmic cause when there is a correlation between syncope and no rhythm variation. Presyncope may not be an accurate surrogate for syncope in establishing a diagnosis and, therefore, therapy should not be guided by presyncopal findings[1,2].

The vast majority of patients have a syncope-free interval measured in weeks, months or years and therefore, symptom-ECG correlation can rarely be achieved with Holter monitoring. In an overview[28] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients (range between 1 and 20%) had a correlation of symptoms with arrhythmia. The true yield of conventional ECG monitoring in syncope may be as low as 1-2% in an unselected population. Therefore, Holter monitoring is indicated only in patients who have very frequent syncope or presyncope.

In one study[29], external retrospective loop recorders showed a relatively higher diagnostic yield in syncope, 25% of enrolled patients having syncope or presyncope recorded during the monitoring period up to 1 month. In a recent study[30], the external loop recorder yielded a low diagnostic value in patients with 3 ± 4 syncopal episodes (> 2) during the previous 6 months, no overt heart disease and negative tilt test. Therefore, the external loop recorder may be indicated in patients who have an intersymptom interval ≤ 4 weeks[1,2].

Patients with infrequent syncopes are unlikely to be diagnosed by the above systems. In such circumstances, consideration should be given to ILR. Pooled data from four studies[24,31-33] comprising 247 patients with unexplained syncope at the end of a complete conventional investigation, showed that correlation between syncope and ECG was found in 84 patients (34%); of these 52% had bradycardia or asystole at the time of the recorded event, 11% had tachycardia and 37% had no rhythm variation. The ILR may also be indicated in patients with suspected or certain neurally-mediated syncope presenting with frequent or traumatic syncopal episodes in order to confirm suspected bradycardia before embarking on cardiac pacing[24]. A classification of responses (Table IV) has recently been proposed by the ISSUE Investigators[34]. With ILR we have only ECG recordings but not any information about arterial blood pressure and other factors that are involved in causing syncope. Despite this limitation, the ISSUE classification has some pathophysiological implications which are helpful to identify neurally-mediated syncope. In types 1A, 1B, and 2 the findings of progressive sinus bradycardia, most often followed by ventricular asystole due to sinus arrest, or progressive tachycardia followed by progressive bradycardia and, eventually, ventricular asystole due to sinus arrest suggest that the syncope is probably neurally-mediated. In type 3B and 4A, mild rhythm variations reflect a participation of a cardiac reflex in the genesis of the loss of consciousness, the exact nature of which remains uncertain because of the lack of contemporary recording of blood pressure values with the available ILR technology.

Treatment

Patients who seek medical advice after having experienced a vasovagal faint require reassurance and education regarding the nature of the disease and the

Table IV. The ISSUE classification of ECG-documented spontaneous syncope[34].

Type 1. Asystole. RR pause ≥ 3 s
Type 1A. Sinus arrest:
Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest
Type 1B. Sinus bradycardia plus AV block
Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate
Sudden-onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate
Type 1C. AV block
Sudden-onset AV block (and ventricular pause/s) with concomitant increase in sinus rate
Type 2. Bradycardia. Decrease in heart rate > 30% or < 40 b/min for > 10 s
Type 2A. Decrease in heart rate > 30%
Type 2B. Heart rate < 40 b/min for > 10 s
Type 3. No or slight rhythm variations. Variations in heart rate < 30% and heart rate > 40 b/min
Type 3A. No variation or < 10% variation in heart rate
Type 3B. Increase in heart rate > 10% but < 30% and < 120 b/min; or, decrease > 10% but < 30% and > 40 b/min
Type 4. Tachycardia. Increase in heart rate > 30% or > 120 b/min
Type 4A. Progressive sinus tachycardia
Type 4B. Atrial fibrillation
Type 4C. Supraventricular tachycardia (except sinus)
Type 4D. Ventricular tachycardia

AV = atrioventricular.

avoidance of triggering events. In general, education and reassurance are sufficient for most patients. Modification or discontinuation of hypotensive drug treatment for concomitant conditions is another first-line measure for the prevention of syncope recurrences. Treatment is not necessary for patients who have sustained a single syncope and are not having syncope in a high-risk setting[1,2].

Additional treatment may be necessary in high-risk or high-frequency settings when[1,2]:
- syncope is very frequent, e.g. alters the quality of life;
- syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients to "high risk" of trauma;
- syncope occurs during the prosecution of a "high-risk" activity (e.g., driving, machine operation, flying, competitive athletics, etc.).

Non-pharmacological "physical" treatments are emerging as a new front-line treatment of vasovagal syncope. In highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of enforced upright posture (so-called "tilt training") may reduce syncope recurrence. However, this treatment is hampered by the low compliance of the patients in continuing the training program for a long period[35]. Two recent clinical trials[36,37] have shown that isometric counterpressure maneuvers of the legs (leg crossing), or of the arms (handgrip and arm tensing), are able to induce a significant blood pressure increase during the phase of impending vasovagal syncope, which allows the patient to avoid or delay losing consciousness in most cases.

Many drugs have been used in the treatment of vasovagal syncope (beta-blockers, disopyramide, scopolamine, clonidine, theophylline, fludrocortisone, ephedrine, etilefrine, midodrine, clonidine, serotonin reuptake inhibitors, etc.). In general, while the results have been satisfactory in uncontrolled trials or short-term controlled trials, long-term placebo-controlled prospective trials have failed to show any benefit of the active drug over placebo. Only two randomized double-blind well designed studies of medium size have been performed – one for etilefrine[23] and the other for atenolol[38] – and both were unable to show a superiority of the active drug vs placebo. Beta-adrenergic blocking drugs have failed to be effective in five of six long-term follow-up controlled studies[38-43]. Vasoconstrictor drugs are potentially more effective in orthostatic hypotension caused by autonomic dysfunction than in neurally-mediated syncope. Etilefrine proved to be ineffective[23]. To date there are not sufficient data to support the use of any other pharmacological therapy for vasovagal syncope.

Pacing for vasovagal syncope has been the subject of five major multicenter randomized controlled trials[44-48]. Three gave positive and two negative results. The two trials in which there was no statistically significant difference differed from the "three positive reports" in that both "paced" and "unpaced" groups had undergone pacemaker implantation (i.e., device inactive in the controls for the duration of the study). Putting together the results of the five trials, 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of the unpaced patients ($p < 0.000$). However, all the studies have limitations in particular concerning the pre-implant selection criteria of the patients who might benefit from pacemaker therapy. Therefore the role of pacing is not yet established.

Cardiac pacing appears to be beneficial in the carotid sinus syndrome and, although only one relatively small randomized controlled trial has been undertaken, pacing is acknowledged to be the treatment of choice when bradycardia has been documented[1,2]. Single-chamber atrial pacing is not appropriate for vasovagal syncope, and dual-chamber pacing is generally preferred over single-chamber ventricular pacing[10].

Conclusions

Evidence for therapy of neurally-mediated syncope is in general weak. Nevertheless, combining together the knowledge derived from several less rigorous studies and that derived from the epidemiology and pathophysiology of syncope, a Task Force of experts, as was that of the European Society of Cardiology[1,2], was recently able to draw some recommendations that can be used as conclusions of the present article. These are:
• in general, education and reassurance are sufficient for most patients. Modification or discontinuation of hypotensive drug treatment for concomitant conditions is another first-line measure for the prevention of syncope recurrences. Treatment is not necessary for patients who have sustained a single syncope and are not having syncope in a high-risk setting (class I recommendation);
• non-pharmacological "physical" treatments (tilt training and counterpressure maneuvers) are arising as a new first-choice treatment of neurally-mediated syncope (class II recommendation);
• there is evidence and general agreement that cardiac pacing is useful in patients with cardioinhibitory or mixed carotid sinus syndrome (class I recommendation);
• usefulness of the treatment is less well established and divergence of opinions exists among experts as regards cardiac pacing in patients with cardioinhibitory vasovagal syncope (class II recommendation);
• the evidence fails to support the efficacy of beta-blocking drugs (class III recommendation). Beta-blocking drugs may aggravate bradycardia in some cardioinhibitory cases;
• to date there are not sufficient data to support the use of any other pharmacological therapy for vasovagal syncope (class III recommendation).

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