CHAPTER 12  SYNCOPE AND ASSESSMENT OF AUTONOMIC FUNCTION IN CHILDREN

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Fainting or syncope can be a disabling condition, and these patients frequently seek medical attention. In the Framingham study the incidence of adults reporting at least one syncopal event during their lifetime was estimated at 3% (1). For children and adolescents the incidence of patients reporting a syncopal event in a U.S. registry was 71 per 100,000 (0.07%) and 126/100,000 (0.126%) for two 5-year observational periods (2). The incidence was higher in female than in male patients, with a peak at the age range of 15 to 19 years. In the same series the mortality and long-time survival of patients with syncope was not different from a general population.

CLASSIFICATION OF THE HEMODYNAMIC RESPONSE TO TILT TESTING IN NEURALLY MEDIATED SYNCOPE

Neurally mediated syncope can be classified according to the response to a tilt table test. Originally the response to tilt table testing was classified according to isolated or combined changes of heart rate and blood pressure. Sutton’s first definition referred to (i) a vasodepressor type, reflecting mainly a drop in blood pressure at the time of syncope without changes in heart rate; (ii) a cardioinhibitory type with a decrease in heart rate and/or asystole; and finally (iii) a mixed type reflecting both a decrease in heart rate and blood pressure (3). Recently a new classification has been proposed by the European Task Force on Syncope (4). Four hemodynamic types of syncope have now been described.

Type 1: Mixed type. Heart rate falls at the time of syncope but does not fall to <40 beats per minute for >10 seconds with or without asystole for <3 seconds. Blood pressure falls before heart rate falls.

Type 2A: Cardioinhibition without asystole. Heart rate falls to a ventricular rate <40 beats per minute for >10 seconds but asystole of >3 seconds does not occur. Blood pressure falls before the heart rate falls.

Type 2B: Cardiogenic with asystole. Asystole occurs for >3 sec. Blood pressure fall coincides with or occurs before the heart rate fall.

Type 3: Vasodepressor. Heart rate does not fall >10% from its peak at the time of syncope.

Two exceptions have been described:

Exception 1: Chronotropic incompetence. A <10% increase of heart rate during tilt testing.

Exception 2: Excessive heart rate rise. An excessive heart rate rise (i.e., >130 beats per minute) both at the onset of upright position and throughout its duration before syncope.

These different hemodynamic patterns reflect the complexity of the mechanisms behind the clinical picture of neurally mediated syncope. Moreover, the hemodynamic type of syncope may vary from one moment to another (5).

Although this classification was originally defined for classification of the hemodynamic type of syncope in adults, in children the same classification is used. However, in contrast to adults, in young patients different types of neurally mediated syncope have been observed. Some investigators reported a combination of bradycardia and hypotension (mixed type of syncope) at the onset of syncope (6–9) as being most common whereas others reported mainly vasodepressor response in young patients (10).

MECHANISMS AND PATHOPHYSIOLOGY OF SYNCOPE IN CHILDREN AND ADOLESCENTS

It has been estimated that the critical cerebral blood flow in young healthy persons is 60 mL/min/100 g tissue or about 11.4 mL of oxygen, assuming a normal hemoglobin value of 14 g/100 mL blood. Cerebral blood flow is maintained by autoregulation over a wide range of perfusion pressures. With a critical reduction in PO2 or an elevation of PCO2, reflexive cerebral vasodilation occurs. Syncope may occur with a transient failure in this reflexive mechanism, which protects the cerebral blood perfusion for some 8 to 10 seconds. Also, other factors such as dehydration may induce syncope (11).

Syncope typically is characterized by a sudden fall in arterial blood pressure, which is associated with light-headedness, dizziness, and loss of consciousness. A common explanation is the sudden pooling of blood in the splanchnic system or in the peripheral blood vessels, which leads to a dramatic reduction of the venous return to the heart. This induces vigorous ventricular contractions. The stretching of the myocardial C-fibers owing to inadequate ventricular filling sends an afferent signal to the brain. The brainstem may respond with a paradoxical cardioinhibitory or vasodilatory response (12). However, the complexity of this phenomenon is illustrated by the fact that neurally mediated syncope also occurs in patients who have had orthotopic heart transplantation in which cardiac afferent and efferent nerves are no longer intact. This shows that the cardiac mechanoreceptor theory (the so called Bezold–Jarisch reflex) is not the exclusive etiologic factor, although it probably is an important contributory factor.
Part III: Electrophysiology

SYNCOPE EVALUATION

Causes of Syncope

The causes of syncope in children are comparable with causes in adults. The most common cause is a functional disturbance in the baroreflex control of the arterial blood pressure. The abnormal reflex activity is characterized by a sympathetic withdrawal and excessive vagal tone. This leads to a critical impairment of cerebral blood flow. Other types of syncope, owing to structural heart disease, will not be discussed in this chapter. The reader is referred to other textbooks that deal with these issues (13). During neurally mediated syncope, afferent signals initiate a series of autonomic events in the medullary control areas that induce inappropriate vasodilatory, bradycardic, and in some instances, even asystolic responses. The resulting hemodynamic abnormalities can be classified according to a cardionhibitory, a vasodilatory, or a mixed type of response for heart rate and blood pressure as has been defined above. The pattern of response is not always reproducible because some patients may develop another type of syncope on a subsequent tilt test (5). Many adults and children may experience a syncopal event during their lifetime. Syncope occurs more frequently during adolescence than in earlier childhood (13). Some patients may have recurrent syncope. Thus, certain individuals are more susceptible to syncope.

A number of triggers have been shown to cause syncope (Table 12.1). However, the evoking factors are similar for children and adults.

General Overview of Diagnostic Tools

The starting point of the evaluation of patients with a history of fainting is to carefully seek the underlying cause. This will require a detailed medical history. For pediatric patients the medical history should include an interview of the child as well as the parents or relatives of the child. During the initial physical examination, blood pressure measurements should be performed in the supine and standing position to identify orthostatic hypotension. A 12-lead electrocardiogram is reasonable to exclude arrhythmia as a cause of syncope.

According to the guidelines of the European Society of Cardiology, further cardiac evaluation is recommended in patients with clinical symptoms that are suggestive of cardiac types of syncope. These features include the presence of structural heart disease, exercise-induced syncope, syncope preceded by palpitations, and or a family history of sudden death. Also, ECG abnormalities that suggest a cardiac cause of syncope may require further investigation. These may include, among others, atrioventricular block, interventricular block, sinus bradycardia (even asymptomatic), pre-excitation, and prolonged QT interval.

The recommended diagnostic tests are echocardiography, prolonged electrocardiographic monitoring, Holter monitoring, and exercise testing. Tilt testing also is considered a first-line diagnostic test, particularly in young (pediatric) patients.

Tilt Table Testing Methodology with Special Reference to Children and Adolescents

Tilt table testing is feasible in children as young as 6 years of age. One difficulty in young children is anxiety, which may occur when safety belts are applied. For adult patients a passive tilt test is 45 minutes at a tilt angle of 60 degrees (Westminster protocol) (14). For children, the same time is used. For children with neurally mediated syncope, the number of positive responders was different than that for adults at a tilt duration of 20 minutes but not at 30 minutes (15). Therefore, it could be that the orthostatic stress during tilt testing is different in children as compared with adults (11). The longer duration of the tilt as used in adults (45 minutes) may reduce the specificity of the test in children. For this reason, in pediatric patients shorter time periods could be recommended.

No uniform tilt table protocol exists. Some investigators use pharmacologic provocation for eliciting the susceptibility to neurally mediated syncope, whereas others use only a passive tilt. A considerable number of investigators have used isoproterenol infusion to decrease the duration of the tilt test protocol. However, although the use of pharmacologic stimulation increases the sensitivity of the test, the large number of false-positive responders decreases its specificity. Nitroglycerin also has been used (11).

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**TABLE 12.1**

TRIGGERS OF NEUROLOGICALLY MEDIATED REFLEX SYNCOPE IN THE YOUNG

- Emotional circumstances and pain, such as venipunctures, immunizations
- Prolonged motionless standing, especially in combination with warm temperature, confined spaces, crowded rooms ("church syncope")
- Fasting, lack of sleep, fatigue, menstruation, illness with fever
- Micturition
- Postexercise (i.e., after termination of long runs or vigorous bursts of activity during competitive sports)
- Hyperventilation and straining (self-induced syncope)
- Stretching
- Coughing
- Standing up quickly or arising from squatting
- Pronounced weight loss
- Certain medications, alcohol, and drugs (these need to be distinguished from intoxicated states, which can also cause loss of consciousness)

ASSESSMENT OF THE AUTONOMIC SYSTEM

In children and adolescents with neurally mediated syncope, it may be useful to assess cardiovascular autonomic function because syncope may be the result of a transient autonomic dysfunction (12,16,17). A considerable number of autonomic function tests have been proposed (13) (Table 12.2). In most of the tests, modulations of heart rate and/or blood pressure are assessed during provocative maneuvers. Some investigators have found it useful to assess the slope of heart rate versus blood pressure changes (16,17).

Beat-to-beat changes of heart rate are a complex interaction of respiration, vasomotor tone, body temperature, and central stimulation. Therefore, heart rate variability has been

<table>
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<th>TABLE 12.2</th>
<th>EXAMPLES OF CARDIOVASCULAR AUTONOMIC NERVOUS SYSTEM TESTS</th>
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<td>Measurement of Interest</td>
<td>Normal Response</td>
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<td>--------------------------</td>
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<tr>
<td>Baroreflex sensitivity (graded phenylephrine boluses)</td>
<td>Slope of R-R intervals + corresponding systolic BP</td>
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<tr>
<td>Cold pressor test</td>
<td>BP rise HR rise</td>
</tr>
<tr>
<td>Cuff occlusion test</td>
<td>BP drop</td>
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<tr>
<td>Isoproterenol test (graded boluses)</td>
<td>HR rise</td>
</tr>
<tr>
<td>Neuronal norepinephrine store (graded tyramine boluses)</td>
<td>BP rise</td>
</tr>
<tr>
<td>Sinus arrhythmia (control led breathing for 1 min)</td>
<td>HR variation</td>
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<tr>
<td>Valsalva maneuver</td>
<td>Phase IV/II RR ratio</td>
</tr>
<tr>
<td></td>
<td>Phase II HR rise</td>
</tr>
<tr>
<td></td>
<td>Phase IV HR drop</td>
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<td></td>
<td>Phase IV BP rise</td>
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</tbody>
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SNS, sympathetic nervous system; BP, blood pressure; HR, heart rate; NE, norepinephrine; CHF, congestive heart failure.

TREATMENT OF PATIENTS WITH NEURALLY MEDIATED SYNCOPE

General Treatment Issues

Before any medical treatment is started, the patients and/or their parents should be reassured and educated about the benign nature and excellent prognosis of syncope. The patients also should be advised to avoid situations that may trigger syncope (e.g., long standing, hot crowded environments; other mechanisms have included hot showers, hair dryers, hair combing, urinating while standing, and in church [see Table 12.1]).

Medical Treatment

The complexity of the pathophysiology of neurally mediated syncope is illustrated by the wide variety of medical treatments that have been proposed. A review of the proposed therapeutic options for adults is presented in Table 12.3. These therapeutic options include vagolytic drugs, beta blocking agents, fludrocortisone (to enhance plasma volume), serotonin reuptake inhibitors, and alpha agonists. These agents frequently have been prescribed as an initial treatment (11,13). However, the multitude of therapeutic options illustrate the unpredictable and unsatisfactory therapeutic results. These different therapeutic options are generally the same in children and adults. However, short-term and long-term follow-up of patients with neurally mediated syncope, treated by pharmacotherapy, has shown that a considerable number of patients continued to have syncope. Many trials have demonstrated that these drugs infrequently are ineffective and, in addition, have important side effects (4,10,13). In a review of the literature, Benditt et al. (19) observed 56% recurrence of syncope in adult patients treated with pharmacotherapy during a follow-up period of 18.5 months. Similarly, children have had a recurrence rate of 32% for a 3.5-year follow-up period (20). The recurrence rate was similar for patients with either a positive or a negative tilt test and also for both treated and untreated patients. Thus, medical treatment is unsatisfactory in many cases.

Nonpharmacologic Methods

Since pharmacological treatment may have important side effects in children, other treatment methods are preferred. Moreover, in children the compliance to a prescribed therapeutic regime may be problematic. Therefore, nonpharmacologic therapy should be chosen as first-line therapy. The parents and children must be educated about hygienic measures to prevent syncope. These include an increase of the daily amount of water intake (4,31,32). The intake of salt or sweet liquids without caffeine should be encouraged. Patients should be instructed to perform orthostatic maneuvers to improve venous return.

- Orthostatic maneuvers to improve venous return: Several maneuvers can abort syncope in children and adolescents. The patients and the parents can be instructed to learn these maneuvers that prevent the pooling of blood in the venous capacitance system. Syncope can be aborted if the patients cross their legs, stand on their toes, tense their leg muscles (34), or perform isometric arm exercises (35). Squatting can prevent the onset of loss of consciousness (34). It is helpful for the children and/or their parents learn these maneuvers.

- Electrolyte and water intake: Another preventive measure is to increase water, salt, and electrolyte intake. Studies in adult patients with orthostatic hypotension (36) have

| TABLE 12.3 |
| THERAPEUTIC OPTIONS IN THE TREATMENT OF NEURALLY MEDIATED SYNCOPE |

<table>
<thead>
<tr>
<th>Neurally Mediated Syncope</th>
<th>Therapeutic Options</th>
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<tr>
<td>Disopyramide</td>
<td>Salt and fluid supplement</td>
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<tr>
<td>Metoprolol, atenolol</td>
<td>Prevent hypoglycemia</td>
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<tr>
<td>Fludrocortisone</td>
<td>Blood pressure raising</td>
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<td>Theophylline, etilefrine</td>
<td>Maneuvers: Coughing</td>
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<td>Ephedrine, etilefrine</td>
<td>Leg crossing, squatting</td>
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<tr>
<td>Serotonin reuptake inhibitors: Fluoxetine, sertraline</td>
<td>Muscle contraction</td>
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<tr>
<td>Midodrine</td>
<td>Endurance training</td>
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<tr>
<td>Cardiac pacing</td>
<td>Avoid static position</td>
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<td></td>
<td>Sleeping in head-up bed</td>
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<td>Tilt training</td>
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shown that increased water intake (0.5 L/day) is effective for preventing syncope. Water drinking induces a pressor response that may be effective in the treatment of orthostatic hypotension. The same benefits can be expected in children and adolescents. The effect of water drinking can be enhanced by increasing the sodium content of the fluids (e.g., sport drinks), which have a volume-expanding effect.

Exercise training: Because moderate exercise training increases plasma volume, it can be speculated that exercise training may have a beneficial effect in the management of patients with neurally mediated syncope. However, some studies have shown that reduced orthostatic tolerance in athletes was due to an excessive vagal tone (39).

Studies in adults with neurally mediated syncope have used aerobic exercise training as a treatment. In normal volunteers, Mtimangi and Hainsworth (37) demonstrated that exercise training increased orthostatic tolerance. Hachul, et al. (38) compared three groups of patients with neurally mediated syncope treated with exercise training, tilt training, and pharmacotherapy. In this study, 40% of the patients treated with exercise training reported syncope recurrence versus 23.5% of the patients treated with pharmacotherapy (beta blockers, fluoxetine, and selective serotonin reuptake inhibitors [SSRI]). No recurrence of syncope was reported in the patients treated with tilt training.

Decreased orthostatic tolerance has been shown in physically inactive bedridden patients on one end of the spectrum and in competitive athletes on the other end. Exercise training has only a beneficial role when patients change from an inactive to a moderately active lifestyle. Competitive sport should be avoided in children and adolescents with a history of neurally mediated syncope.

Tilt Training

In an earlier study by Morillo et al. (21), a reduction in syncope was observed in patients who underwent repeated tilt tests. This study included a crossover design with oral disopyramide treatment and placebo. Sheldon et al. (22) reported a reduction in syncope after the performance of repeated diagnostic tilt tests. This suggests that together with conditioning of the baroreflex activity, a combination of factors such as natural history, counseling, and adoption of appropriate maneuvers will prevent syncope. However, these authors never used repeated tilt testing (tilt training) as a treatment for neurally mediated syncope. It was postulated that the frequency of syncope decreased in these studies because after several tilt tests, patients learned to recognize prodromal symptoms of syncope and could avoid situations that triggered syncope.

We also have observed that patients who have had repeated diagnostic tilt tests showed spontaneous improvement of tilt tolerance both during tilt table testing and during daily life. Therefore, we initiated a tilt training program (23). The patients were tilted daily on a tilt table to a 60-degree position (Westminster protocol). The patients had serial tilt tests (one per day) until syncope or signs of severe orthostatic intolerance occurred. Orthostatic tolerance was considered normal if the patients could sustain the test for at least 45 minutes. Therefore, the patients were discharged from the hospital and had to continue training at home. For safety reasons, it is recommended that patients start the therapy in a clinical setting with monitoring of the ECG and blood pressure. One limitation of this therapy, particularly in children and adolescents, may be the low compliance to the tilt training schedule (4). Therefore, it is mandatory that patients have ongoing evaluation at an outpatient clinic.

For standing training at home, the patients were instructed to stand with their feet 15 cm away from the wall and lean with the upper back against the wall. During the first 6 weeks, intensive tilt training therapy was required for two sessions per day. After 6 weeks, a tilt test was performed during an outpatient clinic visit. If this test was negative (normal duration of 45 minutes), the patients had to continue the therapy at home, but the frequency of the tilt training was reduced to one session per day. Other outpatient clinic visits with tilt tests were planned 3 months after the first outpatient test and then 6 months and 1 year after the first tilt training session. After 1 year of tilt training therapy, the frequency of tilt training was reduced (24).

In the field of cardiovascular rehabilitation, the treatment of neurally mediated syncope by repeated tilt testing is a new and fascinating therapy with promising results. In our cumulative experience of 222 patients who underwent tilt training therapy for neurally mediated syncope, we obtained a negative tilt test in every patient after an average of 2.9 ± 1.3 (median 2) sessions (25). Only 25% of the patients remained tilt positive and required three or more sessions. However, a negative response to tilt table testing could be obtained eventually in all patients. This was found in all types of neurally mediated syncope. Also, patients with the cardioinhibitory type of syncope, with long periods of asystole (mean 19.4 ± 13, minimum 5, maximum 60 s) became tilt-negative during consecutive tilt training. Therefore, it may be prudent to avoid pacemaker therapy in patients with neurally mediated syncope.

For 31 of 38 patients (82%) followed for an average of 43 ± 7.8 months, no syncope recurrence was reported (23). Syncope recurrence was observed only in patients who had discontinued the therapy. Nevertheless, there was a remarkable improvement in the clinical condition of the patients who became symptomatic again after early discontinuation of the tilt training therapy. When the patients reported recurrence of syncope, we simply advised them to resume the tilt training program and syncope disappeared again.

Pacemaker Therapy

In adult patients with the cardioinhibitory type of syncope, pacemaker therapy has been used to prevent the asystole. A reduction of syncope was observed in several studies (26–29), but many patients still developed recurrence of syncope (27,28). This was ascribed to the vasodepressor component of this disorder. Similarly, in children with the cardioinhibitory type of syncope, beneficial effects of pacemaker therapy have been shown in some studies, but recurrence of syncope also has been observed in several studies (30–32). However, because in many instances a vasodepressor component is also present, pacemaker therapy may not always be effective (33). Therefore, pacemaker implantation should not be considered as a first-line therapy in children with syncope.

PROGNOSIS

In adults who experienced a syncopal event, long-term follow-up studies have shown that syncope recurs at a rate of about 30% during a 30-month period (11,40). Similarly, in a long-term follow-up study of children and adolescents with neurally
mediated syncope, a recurrence rate of about 32% has been reported during a 46-month follow-up period (7). This recurrence rate was similar for patients with a positive or a negative tilt test and for both treated and untreated patients. The highest recurrence rate was found in patients with the most prior syncopal spells.

Although in patients with neurally mediated syncope and without structural heart disease the prognosis is benign, syncope recurrence can be harmful because it may lead to injuries, and it induces anxiety and loss of self-confidence. In patients with a cardiac cause of syncope, sudden death has been reported (11). Excess mortality has been found in patients with ventricular tachyarrhythmias and in patients with structural heart disease and malignant syncope. Moreover, excess mortality also has been found in patients with severe aortic stenosis and hypertrophic cardiomyopathy.

References