Neurally mediated syncope

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ABSTRACT - Neurally mediated or vasovagal syncope is the most common cause of transient loss of consciousness. Too excessive response to different triggers (emotional stress, scenes of blood, prolonged standing, etc.) results in brief and self-limiting loss of consciousness caused by a sudden drop in blood pressure with or without heart rate drop, which leads to transient brain hypoxia. Prior to the episode of syncope, the patient can have a sensation of nausea, sweating, pallor, and visual field narrowing. Although it is known that in the syncope background there is dysregulation of blood pressure control, the pathophysiology is still unclear. Blood pressure regulation involves complex afferent signals from the aortic arch processed by the central nervous system and efferent modulation of the heart and vascular system. Vasovagal syncope usually does not require treatment. However, in some cases to rule out other causes of fainting, such as arrhythmias, a broad diagnostic work-up is required, for which head-up tilt table test is most commonly used. Frequent vasovagal syncope adversely affects patient’s quality of life and pharmacological treatment with β-blockers, such as metoprolol, selective serotonin reuptake inhibitors and vascular constrictors like α-agonists can be administered. Other techniques to reduce hypotension are foot exercise, compressive stockings, increased fluid and salt intake. In more serious cases of vasovagal syncope with bradycardia or asystole, insertion of the electric pacemaker is an option.

Key words: bradycardia, head-up tilt table test, hypotension, neurally mediated syncope

INTRODUCTION

Syncope is a transient loss of consciousness with complete and fast recovery of consciousness and previous neurological functions. In general, it can be classified as vasovagal (situational, neurally mediated), cardiac or orthostatic syncope. Older patients are more prone to orthostatic syncope, carotid sinus hypersensitivity and cardiac syncope, while younger patients are more prone to vasovag-
gal syncope (VVS). Other syndromes with similar presentations are seizures, metabolic and psychogenic disorders, and acute intoxication.

Patients with frequent episodes have greater possibility of severe clinical disorders compared to patients with isolated syncope (1). VVS is a common problem in the population. About 3.5% of people experience one or more episodes of VVS in lifetime (2). Approximately 40% of cases remain undiagnosed, while 30% of patients experience recurrent episodes (3). The pathophysiology of syncope is a complex hemodynamic response with marked hypotension, bradycardia and loss of consciousness. Syncope is caused by baroreflex dysfunction, neuroendocrine response, and inadequate response of the central nervous system to stressor. Episodes of syncope in today’s lifestyle can cause discomfort and inconvenience for the patient. In most cases, medical history, physical examination and standard electrocardiogram (ECG) are sufficient for diagnosis (3). Although there are many different therapeutic measures to prevent syncope, its treatment is largely empirical and suboptimal, which is a result of heterogeneous patient population and the lack of controlled randomized trials (4). In most cases, detailed medical history is enough to determine the causes of fainting. The term ‘pre-syncope’ is used to describe a situation that resembles the prodromes of syncope, but is not followed by loss of consciousness. It is believed that the pathophysiological mechanisms of presyncope are the same as in syncope (5).

Epidemiology

Syncope is a common clinical disorder with the annual incidence of 1.3 to 2.7 per 1,000 inhabitants (2). Epidemiological studies indicate that approximately 40% of people in the general population have experienced at least one episode of syncope (6). Clinical studies show that the peak incidence of syncope is between 10 and 30 years of age (7). In younger patients, neurally mediated syncope is the most common cause, whereas in older patients cardiovascular causes are more frequent (8).

Etiology and pathophysiology

Physiological regulation of blood pressure consists of the afferent signals processed by the central nervous system, and the efferent modulation of the cardiovascular system (9). Normal regulation of arterial blood pressure is controlled by baroreceptors located in the aortic arch and carotid sinus. Afferent signals are transmitted from the aortic arch via vagal nerve and from the carotid sinus via glossopharyngeal nerve to the central nervous system. Distension of the vascular structures after cardiac systole results in discharge of afferent nerves that converge from the nucleus tractus solitarius to the brainstem. At this point, efferent sympathetic flow is inhibited and efferent vasovagal flow is increased (10).

The most commonly used model for the neurally mediated syncope is the Bezold-Jarisch reflex in which excessive venous load begins a chain of events that culminate in vasodilatation and bradycardia, which consequently leads to hypotension and loss of consciousness (11).

Excessive venous load of the lower extremities results in decreased ventricular volume, which activates sensory receptors in the inferoposterior wall of the left ventricle, which responds to pressure changes by increasing nerve outflow to the central nervous system via vagal nerve. Parasympathetic activity accompanied by vasodilatation and bradycardia increases (12). It is believed that different modulators of the central nervous system activity can cause vasovagal syncope. The potential mediators in the development of vasovagal syncope are serotonin, adenosine and opioids. The β endorphin level is increased in patients during syncope. Different clinical presentations of vasovagal syncope, variable outcome and syncope induced by the tilt-up test with drugs, such as isoproterenol, nitroglycerin and clomipramine indicate that complex pathophysiological mechanisms cause vasovagal reaction.

Neurohumoral theory

Experimental models have shown that the injection of serotonin into cerebral ventricular areas can cause similar sympathetic withdrawal response as in vasovagal syncope (13,14). Selective serotonin reuptake inhibitors (SSRI) can be successful in the treatment of vasovagal syncope (15). Some authors suggest that because the SSRI facilitate nerve transmission, they cause SSRI receptor down-regulation in the brainstem, which results in a blunted response to rapid shifts in the central serotonin levels (15-18).

Dysregulation of cerebral flow

More than 35 years ago, some authors suggested the patients with VVS to have abnormal cerebral vascular response to orthostatic stress, which may
be associated with the pathophysiology of this syndrome (19). This concept is supported by findings on cerebral vasoconstriction and reduced cerebral blood flow in patients with VVS.

**CLINICAL PRESENTATION**

History data on environmental factors are important for the diagnosis, since syncope is often caused by the sight or loss of blood, sudden stressful or painful experience, surgical manipulation or trauma. Precipitating symptoms and signs are pallor, weakness, yawning, nausea, hyperventilation, blurred vision and impaired hearing immediately before syncope. The patient falls in a horizontal position and after a few seconds or minutes returns to consciousness. While regaining consciousness, the patient may experience a feeling of weakness, but usually does not show signs of confusion. VVS is mostly associated with benign prognosis. A small proportion of patients have recurrent attacks of syncope, which can affect their quality of life, mainly due to frequent falls and injuries (20).

Although most patients show typical signs of VVS such as dizziness and full recovery after a few minutes, up to 30% of patients have an atypical presentation (21).

In case of a longer duration of cerebral hypoperfusion, cramping of body resembling epileptic seizures may occur (22). Patients often report fatigue, weakness, dizziness, sweating, blurred vision, tinnitus and loss of vision. Some patients experience trauma due to the fall, although severe traumatic injuries are rare.

Syncope in children is common. Most episodes are benign and neurally mediated. Only a small portion is potentially life threatening. Diagnosis is primarily achieved by medical history and standard ECG (23).

Patients with frequent syncope have a reduced quality of life, similar to that in patients with severe rheumatoid arthritis or chronic low back pain (24). Patients report difficulties in activities of daily living (71%), driving (60%), physical activity (56%) and walking (42%). Patients with syncope have a high incidence of psychological problems, especially anxiety and depression (25).

Neurally mediated syncope is associated with absenteeism from school in children and from work in adults (26). One retrospective study (27) collected data from medical records on the emotional impact of VVS and expressed stressful aspect. More than half (56%) had a history of mood disorder and 21% were taking psychotropic medications. Psychological problems include suicidal thoughts, depression, panic attacks and chronic anxiety, which is similar to the level of emotional symptoms in chronic patients.

**DIAGNOSTIC EVALUATION**

Therapeutic and diagnostic guidelines of the European Society of Cardiology define standards for the management of syncope and propose a model of organization for patient evaluation (23). Blood tests, cardiac workup (ECG, echocardiography, holter ECG), head-up tilt table test (HUTT), electroencephalography (EEG), transcranial vessel ultrasound and neuroimaging are diagnostic procedures for syncope. Despite all clinical tests, the cause of syncope remains undetermined in 30% of patients.

HUTT allows for reproduction of syncope and monitoring the patient’s physiological responses during syncope. Direct observation and documentation of symptoms during the test give a precise diagnosis and information for treatment and control of the symptoms (28). In patients with cardiac symptoms, echocardiography, stress testing, holter ECG, loop recorder and electrophysiological tests are recommended.

Tests for neurally mediated syncope are HUTT and carotid sinus massage, and in case of negative results, holter ECG and loop recorder. Patients with rare episodes of syncope probably have neurally mediated syncope and diagnostic tests are usually not needed (23).

Clinical characteristics related to the specific causes such as VVS are absence of cardiac disease, long-term history of syncope, provocation by unpleasant event, smell, sound or pain, prolonged standing, crowded, warm environment, nausea and vomiting. Presence of structural heart disease, appearance during exertion, chest pain and sudden death in the family are typical for cardiac syncope. Psychiatric evaluation is recommended when symptoms suggest somatization disorder, or if the patient has a psychiatric disease.

Basic laboratory tests are indicated in cases in which syncope is caused by the loss of circulating volume or in case of metabolic disorders. In patients with suspected heart disease, echocardiography, holter ECG and electrophysiological monitoring are recommended. For patients with chest pain
Table 1. VASIS classification (34) is used for interpretation of head-up tilt table test

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 – mixed</td>
<td>Both blood pressure (BP) and heart rate (HR) are reduced. BP reduction precedes HR reduction. HR decreases by &gt;10%, but HR does not decrease to less than 40 beats/min (Fig. 1)</td>
</tr>
<tr>
<td>Type 2 – cardioinhibitory</td>
<td>Decrease in both BP and HR, and BP decrease precedes decrease in HR. Type 2A: minimum HR is less than 40 (Fig. 2), type 2B: there is asystole for 3 seconds or more (Fig. 3)</td>
</tr>
<tr>
<td>Type 3 – pure vasodepressor</td>
<td>BP is decreased but HR does not decrease more than 10% (Fig. 4)</td>
</tr>
<tr>
<td>Chronotropic incompetence</td>
<td>No HR increase in spite of tilt</td>
</tr>
<tr>
<td>Excessive HR rise</td>
<td>This pattern is associated with postural orthostatic tachycardia (POT)</td>
</tr>
<tr>
<td>Positive carotid sinus massage</td>
<td>Test needs to be terminated due to one of the criteria after carotid sinus massage</td>
</tr>
</tbody>
</table>

Fig. 1. Head-up tilt table test in a 22-year-old female patient with a history of recurrent loss of consciousness during vaccination, standing in line and piercing. The circle in the heart rate line shows drop in heart rate and the arrow in blood pressure line shows minimal blood pressure values at the time of syncope.

Fig. 2. Head-up tilt table test in a 45-year-old female patient with recurrent syncope precipitated with pain. In circle: drop of heart beat, frequency less than 40 beats per minute. The arrow shows minimal blood pressure during syncope.

Fig. 3. Head-up tilt table test in an 18-year-old patient showing asystole (upper arrow) and lowest blood pressure (lower arrow). The patient complained of headache, dizziness and a feeling of confusion at that time.

Fig. 4. Head-up tilt table test in a 90-year-old patient with a history of hypertension and postprandial syncope. Note the decrease in blood pressure (arrow), without decrease in heart rate (circle) typical for the vasodepressor type of syncope.
typical for ischemia, stress testing, echocardiography and ECG are recommended. HUTT is also used for diagnosis of the postural orthostatic tachycardia syndrome (POTS). Cardinal criteria for this syndrome are symptoms of orthostatic intolerance and absence of orthostatic hypotension (29). For patients with syncope during or after exertion, echocardiography and stress testing are recommended as the first evaluation step. Cardiac pacemaker is recommended in patients with cardioinhibitory syncope with the frequency of seizures more than 5 per year (23).

**Head-up tilt table test**

HUTT helps the diagnosis of different types of dysautonomia. It is used in younger patients with no obvious or suspected heart disease with recurrent syncope of unknown origin, for distinction between syncope with myoclonic jerks and epilepsy, and for the evaluation of patients with unexplained falls or psychiatric disease (5).

Pharmacological agents are used for provocation of positive test results. Isoproterenol is often used to increase vasovagal response. Other agents used in tilt table testing are adenosine (vasodilator and direct activator of the sympathetic system), nitroglycerin and edrophonium (cholinergic activity) (4). The sensitivity of tilt-up test is 26%-80% and specificity 90% (30).

Patients should be in the horizontal position before testing and during HUTT under the angle of 60° to 80° for 30 to 45 minutes (30). If there is no pathological event and vital signs are normal, the test is repeated with pharmacological provocation. The most common protocol is infusion of isoproterenol or administration of sublingual nitroglycerin. The test is considered positive if the patient has a symptomatic decrease in systolic blood pressure and bradycardia. The room must be equipped with resuscitation equipment. Patients must not consume fluids for at least four hours and solid food for at least six hours before the test (32). During testing, the patient’s condition is monitored by ECG and continuous noninvasive blood pressure measurement. In patients older than 40 years with a history of syncope, carotid sinus massage is advised (33). The VAsovagal Syncope International Study (VASIS) classification (34) is used for interpretation of the HUTT (Table 1).

Pain provoked HUTT (PP-HUTT) is a test for confirmation of VVS. The subjects are tilted to 70° for a maximum period of 10 min or until symptoms occur. If there are no symptoms after the initial 10 min, a painful stimulus with subcutaneous insertion of 0.7 mm needle into the dorsum of the hand is performed. This test has a sensitivity of 65.9% and specificity of 89.7%. Compared to other tests, such as Calgary Syncope Symptom Score, it has a higher diagnostic rate and provides a rapid alternative to conventional methods (35).

**TREATMENT**

Treatment approaches are mostly empirical and symptomatic. Specific treatment cannot be made without knowing the cause of syncope. Major therapeutic innovations in recent years are isometric backpressure maneuvers and compression of lower limbs, while most of the drugs do not have great performance. The basis of the treatment of young patients with VVS is education about the potential causes of syncope. In elderly patients, specific treatment is often necessary. The main goal of treatment is to reduce the number of syncopes and psychological trauma.

The first step in the treatment should be an informative talk with the patient about the nature and prognosis of syncope. The patients need to be educated about avoiding heat, prolonged standing and decreased fluid intake. Substitute salt intake and isotonic drinks increase the circulating blood volume and thus venous return. Education includes information about prodromal symptoms and how they can be prevented by sitting or lying. Backpressure maneuvers such as clamping of the arms or leg crossing can inhibit the VVS by increasing the venous return (23).

Rare episodes of syncope with prodromal warning symptoms do not require intervention except for patient observation. In addition, it is important to maintain sufficient fluid and salt intake, especially during summer. Many drugs have been tested in the treatment of VVS, such as β-blockers, disopyramide, scopolamine, theophylline, ephedrine, midodrine, clonidine and SSRI, but there are no clear data on the gold standard therapy (22).

The most commonly used pharmacological agents are β-blockers, anticholinergics, disopyramide, adenosine receptor blockers, SSRI, α-adrenergic agonists, mineralocorticoids, anticonvulsants, and permanent pacemaker as a non-pharmacological treatment (5). These drugs are mainly symptomatic treatment and are often associated with side effects, which make them inappropriate in younger age groups. Fludrocortisone, midodrine and compres-
sion stockings are frequently used in the initial treatment of patients with borderline low pressure and the consequent orthostatic syncope. β-blockers have been the first choice in the treatment for a number of years. According to the guidelines of the European Society of Cardiology, β-blockers should not be used for the treatment of reflex syncope (5). Midodrine effects smooth muscle cells of arteries and veins without affecting heart rate and has no effect on the central nervous system (30). In three randomized, placebo-controlled trials, midodrine had a positive effect on reducing the frequency of symptoms, symptoms during HUTT and quality of life (35). SSRI, in contrast to the vasoconstrictor, can reduce the activity of the sympathetic nervous system (36). Some studies show that SSRI can reduce the incidence of VVS. Results showed that 17.6% of patients who received paroxetine had repeated syncope compared with 52.9% in the placebo group (37).

CONCLUSION

Vasovagal syncope is the most common cause of transient loss of consciousness, especially in younger patients. It is mostly associated with benign prognosis but if it recurs often, it greatly affects the patient’s quality of life. The diagnostic and therapeutic goal is correct diagnosis, reduction in the number of episodes, and better quality of life.

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Neuralno posredovana sinkopa

SAŽETAK - Neuralno posredovana ili vazovagalna sinkopa je najčešći uzrok prolaznog gubitka svijesti. Pretjerana reakcija na različite podražaje (emocionalni stres, vađenje krvi, dugotrajno stajanje i sl.) rezultira kratkim i prolaznim gubitkom svijesti uzrokovanim padom krvnog tlaka sa ili bez istovremenog pada srčane frekvencije i posljedičnom prolaznom cerebralnom hipoksijom. Česti prodromalni simptomi su osjećaj mučnine, znojenje, bljedilo, sužavanje vidnog polja. Iako je poznato kako je u podlozi sinkope disregulacija fiziološke kontrole krvnoga tlaka, patofiziologija tog poremećaja još je nejasna. Kontrola krvnog tlaka uključuje složene aferentne signale iz luka aorte koji se obrađuju u središnjem živčanom sustavu te eferentnu modulaciju srčane funkcije i funkcije vaskularnog sustava. Vazovagalna sinkopa obično ne zahtijeva liječenje. No, u slučaju kada treba isključiti druge uzroke gubitka svijesti, potrebna je šira dijagnostička obrada i tada se se najčešće koristi “head-up tilt table” test. Ćeste vazovagalne sinkope nepovoljno utječu na kvalitetu života te je tada moguće uvesti farmakološku terapiju β-blokatorima, npr. metoprololom, selektivnim inhibitorima ponovne pohrane serotonina ili vazokonstriktorima α-agonistima. Preporučuju se vježbe za donje ekstremitete, nošenje kompresivnih čarapa, povećani unos tekućine i soli u prehrani. U težim slučajevima vazovagalnih sinkopa s bradikardiom ili asistolijom postoji mogućnost ugradnje srčanog stimulatora.

Ključne riječi: bradikardija, head-up tilt table test, hipotenzija, neuralno posredovana sinkopa