THE PATHOPHYSIOLOGY OF VASOVAGAL SYNCOPE

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ABSTRACT
Vasovagal syncope, known also as neurogenic or neurocardiogenic syncope, accounts for about 30–40% of syncope cases of unclear origin and is the most common type of syncope among children and adolescents. Vasovagal syncope is defined as a state of temporary loss of consciousness with reduction of muscle tone followed by sudden, rapid and total return of consciousness. Vasovagal syncope is caused by a drop in blood pressure and/or reflex bradycardia which occurs as a result of emotional or orthostatic stress. Consequently, in understanding the mechanism of neurogenic syncope, most attention is paid to the dysregulation of sympathetic-parasympathetic autonomic nervous system.

The main objective of this study was to systematically review the pathomechanisms triggering a vasovagal reaction. The analysis is based on a review of the literature on this topic. Material was obtained using the library system ALEPH. The literature was obtained from databases such as PubMed, Medline and GBL. This study focused on the role of tilt testing in the diagnosis of vasovagal syncope as well as other tests used to assess the functioning of the autonomous control of the cardiovascular system in syncope.

KEYWORDS: vasovagal syncope, neurogenic syncope, tilt test

BACKGROUND
Sudden loss of consciousness is a common problem among children and adolescents and, in approximately 30% of patients, the cause cannot be determined. It belongs to the group of reflex syncopes, described as vasovagal, neurogenic or neurocardiogenic syncope. Episodes of vasovagal syncope consist of short-term and transient loss of consciousness that is accompanied by a decrease in postural muscle tone, followed by independent recovery of consciousness [1]. It is caused by a decrease in the blood supply to the central nervous system as a result of a reflex drop in blood pressure and/or pulse rate. Vasovagal syncope constitutes approximately 30% of all syncopes and is one of the most common reasons for loss of consciousness in children and adolescents. It is estimated that approximately 20–50% of healthy adolescents have experienced at least one episode of syncope. A characteristic feature of vasovagal syncope is the appearance of prodromal symptoms preceding the syncope such as nausea, anxiety, excessive sweating, pallor of the skin, changes in vision and hearing, and dizziness [2]. These clinical symptoms are typically associated with time spent in stuffy, hot, crowded areas, standing up or in a situation of emotional stress (e.g. the collection of blood) [3,4]. Pharmacotherapy is relatively ineffective in the treatment of vasovagal syncope and prevention and education to prevent syncope play an important role in its management. An important consequence of syncope is trauma resulting from collapsing, as well as fear and uncertainty which reduces patients’ quality of life. Despite numerous trials to elucidate the pathophysiology of vasovagal syncope, its main cause has yet to be clearly determined. The main objective of this study was to characterize the reflex regulatory mechanisms of the autonomic nervous system which play an important role in neurocardiogenic syncope.

AUTONOMIC NERVOUS SYSTEM IN THE PATHO-ETIOLOGY OF NEUROCARDIOGENIC SYNCOPE
It is believed that a key role in the pathogenesis of vasovagal syncope is played by the autonomic nervous system (ANS), which is responsible for controlling the functioning of the cardiovascular system. Correct functioning of the cardiovascular system is essential in the...
maintenance of homeostasis of the organism as a whole. The ANS has the primary role in the regulation of cardiovascular homeostasis. The autonomic system affects the reflex regulation and function of internal organs and is responsible for the adaptability of the body in variable conditions [5]. Its function is also to protect the body by inducing a defensive reaction of a fight and escape type, i.e. stimulation of the sympathetic nervous system in connection with the somatic system and an aversion response, i.e. activation of the parasympathetic nervous system with a simultaneous somatic inhibition. Neurocardiogenic syncope is triggered as a result of an interaction between sympathetic and parasympathetic nervous systems in the form of stimulating or inhibiting those systems. In reflex syncope, the reflexes are those of the autonomic nervous system, consisting of afferent and efferent nerve fibers, and the neural path (or reflex arc) that controls the reflex. The afferent pathway in neurocardiogenic syncope is composed of cranial nerves – vagus and glossopharyngeal nerves (impulses from mechanoreceptors of the cardiovascular system, gastrointestinal tract, urinary system and baroreceptors of the carotid sinus), trigeminal nerve, facial nerve and vestibulocochlear conduct (impulses from mechanoreceptors of the respiratory system), and nerves conducting impulses from chemoreceptors of the circulatory system (parasympathetic cardiac branches of the vagus nerve and sympathetic cardiac, cervical and thoracic nerves). Afferent impulses, carried by the vagus nerve from the circulatory system, are accumulated in the solitary nucleus in the medulla oblongata, which constitutes the center of the reflex arc of a neurogenic syncope. Impulses from the solitary nucleus are passed on, by means of an ascending path, to superior units, i.e. the diencephalon and cerebrum. Those nerve impulses then run via a descending path down from the centers of the superior units to centers of inferior ones, i.e. sympathetic and parasympathetic preganglionic neurons in the medulla oblongata [6]. This is where fluctuations in stimulation and inhibition of the sympathetic or parasympathetic system take place. Neurocardiogenic syncope is a physiological defensive reaction of the circulatory system, protecting it against excessive adrenergic stimulation, triggered by hypovolemia. Subsequently, syncope is a side reaction that is aimed at deflecting actions of the autonomic nervous system leading to an increase in catecholamines and excessive heart stimulation [1].

Taking pathogenesis into consideration, vasovagal syncope can be divided into syncope of a peripheral and central types. In the peripheral type, as well as in the central type, the afferent fiber of a vasovagal reaction is the same. The difference, however, is located in the efferent pathways of the autonomic nervous system. The peripheral theory by Oberg and Thoren recognizes that syncope is a consequence of a long-lasting motionless vertical position of the body. In an adult, within 10 seconds being in an upright position, about 500–1000 ml of blood moves into the venous system located below the diaphragm. Over the next 10 minutes, 700 ml of fluid is filtrated into the extravascular space, resulting in a significant decrease in blood pressure and filling of the heart cavities as well as drop in ejection volume [7,8]. Changes in hemodynamic conditions stimulate mechanoreceptors (in the left ventricle and auricles, in the aortic arch) and peripheral chemoreceptors of blood vessels [6]. A decrease in stroke volume and a reduction in venous return to the heart leads to the activation of the sympathetic system, which increases vasoconstriction of the vessels and the contractility of ventricles resulting in insufficient filling. As a result of ensuing tachycardia, activation of the parasympathetic system follows and mechanoreceptors in the left ventricle are triggered. They, in turn, activate the vagus nerve in the medulla oblongata via the afferent pathway. Consequent to this activation of the parasympathetic system, blood vessels dilate and the heartbeat slows. This causes a decrease of the brain’s perfusion and syncope [3]. This type of syncope presents itself mainly in situations where a person remains motionless (e.g. in a church, at the bus stop, at the school assembly) in a sultry, warm room for a long time. The loss of consciousness is preceded by vegetative, heralding symptoms, like dizziness, impaired vision, excessive perspiration, pale skin and nausea [2].

Similarly, prodromal symptoms are present in vasovagal syncope of the central type. According to James-Lange’s behavioral theory, somatic and behavioral changes and vasovagal reactions appear as a result of factors like pain, fear or emotions (Fig.1). The physiological background of vasovagal syncope of the central type is the occurrence of a reflex due to the stimulation
of sensory fibers (e.g. during blood collection) and the resulting activation of cortical and subcortical centers by neurohormones (endorphins) and neurotransmitters, which lead to a vasovagal reaction [1,6,9].

**Methods of Evaluating the Etiology of Syncope**

Table tilt test is one of the most commonly used clinical tests to evaluate the function of the autonomic system in children diagnosed with vasovagal syncope. The table tilt test, as a diagnostic tool of vasovagal syncope, was introduced in 1986 by Kenny et al. [10]. The tilt test is useful in the evaluation of the influence of the autonomic system on the occurrence of a vasovagal reaction because it enables the pathological vasovagal reaction to be recreated in controlled conditions [11,12]. Children and adolescents suspected of vasovagal syncope, after excluding other mental, cardiological and neurological causes (for example demonstrative syncope, heart defects, epilepsy and long QT syndrome) are suitable for the tilt test examination. The head-up tilt test is carried out in the morning hours in a warm, quiet room. There are numerous methods of executing the tilt test, which vary in the time taken for the examination, angle of the table and types of pharmacological provocation. Head-up tilt test can be passive or active. The former is most commonly performed according to the Westminster protocol, during which a patient is tilted to a 60° angle for a period of 45 minutes, and the later uses pharmacological provocation. Hemodynamic changes, which result from dominating influences of the sympathetic and parasympathetic systems, are documented during the course of the test, when blood pressure (most often using the method of beat to beat), and pulse are checked and ECG recorded [4,10–13].

The objective of the tilt test is to document hemodynamic changes preceding reflex syncope. During the tilt test, continuous and sequential changes in the autonomic system occur. These changes are correlated with the intensity of a stimulus, which, in this case, is the angle of tilting of the patient. It has been demonstrated that the heart rate drops at a rate which depends on the angle at which the table is tilted. Changes in heart rhythm during the head-up tilt are often used to evaluate the activity of subdivisions of the autonomic system [8]. At the time of the of tilt testing procedure, orthostatic stress occurs, where, owing to gravity, blood flows from venous bed below the diaphragm with a simultaneous decrease of venous return to the right ventricle. Initially, the sympathetic system is activated resulting in ventricles, which are insufficiently filled, increasing in contractility [3]. The result of stimulating the sympathetic system during the head-up tilt test is moderate tachycardia [8]. Paradoxically, mechanoreceptors in the left ventricle become stimulated and send an impulse to the vagus nerve in the medulla oblongata via type “C” afferent fibers. As a result of the misinterpreted blood pressure increase in the left ventricle, the parasympathetic system becomes activated. The consequence of this situation is hypotonia caused by blood vessel dilatation (vasodilatation) and reduced heart rate (bradycardia). Consequently, this results in cerebral hypoperfusion and the loss of consciousness [3,14].

In the course of the head-up tilt test, different mechanisms of neurocardiogenic responses are observed. According to VASIS classification (Vasovagal Syncope International Study) the following types of syncope can be distinguished:

1. **Type 1- mixed** – consists of lowering of the heart rate that does not reach the level of 40 bpm or reaches it for a period less than 10 seconds. If asystole occurs, it does not last more than 3 seconds. In the mixed type, the decrease in heart rate is preceded by a decrease in blood pressure.

2. **Type 2- cardioinhibitory** – in which 2 subtypes can be differentiated: If A (without asystole) when the heart rate drops below 40 bpm for a period of not longer than 10 seconds, but without the occurrence of asystole longer than 3 seconds. Although the blood pressure may increase, it consequently decreases before the drop in the heart rate. Subtype II B – (with asystole) when asystole occurs for more than 3 seconds with a decrease in blood pressure.

3. **Type 3- vasodepressive** – when syncope occurs as a result of lowering of the blood pressure and the reduction of the heart rate does not exceed 10% of the maximum value recorded throughout the test [13].

In patients with a positive outcome of the head-up tilt test, loss of consciousness usually takes place between the 10th and 30th minute of the test. Limited available diagnostic methods create difficulty in determining the influence of the autonomic system on the pathomechanism of syncope. Other methods used to assess the autonomic system, which at the same time record hemodynamic changes, are the head-up tilt table test, Valsalva maneuver, deep breath test and the carotid sinus pressure test [4,12,13].

The Valsalva maneuver is performed by moderately forceful attempted exhalation against a closed glottis. It is a non-invasive method of autonomic modulation of the cardiovascular system used to assess the integrity of baroreceptor reflexes of cardio-pulmonary and arterial systems, mainly to assess baroreceptor sensitivity. However, in addition to reflexes of the arterial baroreflex, reflexes such as low-pressure cardio-pulmonary baroreceptors reflexes, reflexes of chemoreceptors, Bainbridge reflex and central motor command are also triggered with conscious contraction of striated muscles. In order to obtain reliable results of the responsivity of baroreceptors, the Valsalva test needs to be performed repeatedly. Therefore, this test is not very useful in the evaluation of the sensitivity of baroreceptors [15].
The deep breath test involves deep breathing at a rate of 6 breaths / min controlled by a metronome for 3 min. This test mainly causes changes in the parasympathetic component of the autonomic nervous system in the form of its deceleration and activation. During the test, systolic blood pressure in the chest increases with a simultaneous adjustment in the length of the R-R interval. The test result is calculated using the I-E indicator which is the average difference of maximum and minimum heart rate during each 6 breaths per minute [16].

Another simple, non-invasive procedure is the Schellong test, performed at the patient’s bedside. It involves tilting the patient after 10–15 minutes of resting to an upright position, followed by the measurement of blood pressure at 1 and 3 minutes after the tilting, with the last measurement performed 10 minutes after tilting. When a drop in systolic blood pressure is at least 20 mmHg or the diastolic blood pressure is at least 10 mmHg during the first 3 minutes of the test, orthostatic hypotension is diagnosed. Whereas, if within the five minutes into the test, there is an increase in heart rate of more than 30 beats / min. or a heart rate of more than 120 beats / min., postural orthostatic tachycardia syndrome is diagnosed [17].

A less popular method used in the study of dysautonomia is the carotid sinus pressure test. Applying carotid sinus pressure for about 20–30 seconds causes the heart rate and blood pressure to naturally drop. Changes such as asystole lasting over 3 seconds or significant bradycardia triggered by the pressure are classified as pathological [18].

In children, the percentage of positive results of the passive tilt test is notably low and varies from 8% to 65%. However, after pharmacological provocation, the number of positive results increases from 57% to 80% [6]. Medicines used during the test are nitroglycerine, isoprenaline, edrophonium, adenosine and esmolol [12].

During the tilt test, the level of catecholamines increases. The main function of catecholamines in the human body is the stimulation of the mechanoreceptors of the heart, which increases its contractility and, as a result of a reflex reaction, hypotension and bradycardia occur. Research carried out by Kozlowski et al. on the use of esmolol in the tilt test showed the utility of this medicine in diagnosing syncope, especially in patients with permanent sinus tachycardia. Esmolol was demonstrated to have an unblocking influence on beta-adrenergic receptors, which are susceptible to endogenic levels of catecholamines such as epinephrine and norepinephrine. The resulting amplified body stress supports a positive test result [19]. Steward et al. reported that 75% of patients with vasovagal syncope had reduced systemic vascular resistance, of whom 23% had significantly reduced cardiac output. The authors used a Finometer to measure the cardiac output and systemic vascular resistance in the supine position and with the table inclined to an angle of 70°.

According to the authors, young patients with vasovagal syncope experience both reduced cardiac output and reduced vascular parenchyma, resulting in splanchnic vasoconstriction [20]. However, in Verheyden’s studies in patients with vasovagal syncope, during the tilt test both with and without the addition of nitroglycerine, and a significant decrease in blood pressure, a 50% decrease in cardiac output was recorded, but systemic vascular resistance remained unchanged [21].

Wei-Ting Lai and et. al. investigated the use of head-up tilt table testing in the management of neurocardiogenic syncope (NCS) in 79 children with a mean age of 12.4 years. The study showed neurocardiogenic syncope occurred in 65 patients and non-NCS in 14 patients. Isoproterenol infusion significantly increased the sensitivity of the test from 28% to 45% and was associated with a slight decrease in specificity from 93% to 86%. The authors concluded that the tilt test can be safely performed with a high specificity in children, with the sensitivity of tilt test improved by isoproterenol [22].

Other research into the pathomechanism of vasovagal syncope combines the tilt test with the monitoring changes in the brain (EEG, monitoring the flow in cerebral arteries using transcranial Doppler ultrasonography, measurement of oxygenation of the brain using near infrared spectroscopy -NIRS) and changes in peripheral hemodynamic parameters [22,23]. Studies conducted by Bosak et. al. analyzed changes in the interictal electro-encephalographic recording of 41 patients aged 29.8 years, with vasovagal syncope diagnosed on the results of passive tilt testing, where 40% of patients had generalized or focal slow activity (theta and delta). Results indicated the presence of changes in the interictal electroencephalographic recording, especially during hyperventilation. Patients with neurogenic syncope may be more sensitive to changes in PCO2 and PO2 induced by hyperventilation resulting in hyperventilation-induced changes in the EEG [24]. EEG, conducted during the tilt test, can be used to diagnose psychogenic or possibly epileptic causes of syncope. In a report by Kucinska and Werner, the tilt test made it possible to establish the correct cause of syncope in a 17-year-old patient during an alleged fainting episode when there were no changes in electrocardiogram, heart rate and blood pressure [25]. Psychogenic syncope, with a very similar clinical picture to neurocardiogenic syncope, is a child’s attempt to draw attention to psychological problems. The disturbed mental state may activate the nervous system resulting in vegetative symptoms and somatic diseases. Accurso et. al. have shown that loss of consciousness among people who experience syncope caused by anxiety during blood collection is due to the dysregulation of the autonomic nervous system. In assessing the etiology of syncope, the authors used a tilt test, during which the parameters of the heart rate and blood pressure were monitored for 15-minutes in a horizontal position and for 45 minutes in a vertical position, at a table tilt up to 70°. In addition, one person from the control group...
experienced syncope, which may indicate provocation of sympathetic-parasympathetic dysregulation following verticalization during the tilt test [26]. According to Fucá et al., in patients with vasovagal syncope and a positive tilt test result, 3 minutes before fainting, an increase in the heart rate was observed (which may indicate sympathetic activation), followed by a sudden decrease in HR during fainting. The authors showed that cardiac output during the tilt test decreased significantly which can be a significant marker for early detection of bradycardia in the majority of patients with vasovagal syncope [27].

Among the diagnostic tests for syncope, the most commonly used is the table tilt test. There are, however, some restrictions which can contribute to a false positive test result. Apart from pharmacological interventions, the angle the tilt table influences the accuracy of the tilt testing procedure. It is believed that angles above 60° increase the number of false positive results and that the reduction of the angle of tilt - angles below this value negatively affects its accuracy [28]. Another factor that determines the sensitivity of the tilt test is the time of the passive phase, with a longer passive phase, increasing diagnostic accuracy. In examinations of children, using this procedure, passive orthostatic stimulation is preferred, without pharmacological intervention. Moreover, there is no clear guidance in regard to the time of the test in order to maximize its accuracy. However, even though there is no uniformly accepted methodology for conducting head-up tilt testing, in the absence of alternative diagnostic tests for vasovagal syncope, it is extremely useful clinically in the assessment of neurocardiogenic syncope. Using another diagnostic device such as a Finometer during a tilt test is a non-invasive way of more fully characterizing arterial circulation, pressure variability, heart rate, cardiac output and systemic peripheral resistance [4,29,30].

**CONCLUSION**

Vasovagal syncope is caused by reflex dysfunction of the autonomic nervous system. The head-up tilt test is a valuable diagnostic tool in the diagnosis of neurocardiogenic syncope. With this procedure, the reflex interaction of the autonomic can be documented in interaction of the autonomic can be documented in head-up tilt testing, in the absence of alternative diagnostic devices. Vasovagal syncope is caused by reflex dysfunction of the autonomic nervous system. The head-up tilt test is a valuable diagnostic tool in the diagnosis of neurocardiogenic syncope. With this procedure, the reflex interaction of the autonomic can be documented in clinical assessment of vasovagal syncope, it is extremely useful clinically in the assessment of neurocardiogenic syncope. Using another diagnostic device such as a Finometer during a tilt test is a non-invasive way of more fully characterizing arterial circulation, pressure variability, heart rate, cardiac output and systemic peripheral resistance [4,29,30].

**REFERENCES**


