Neurocardiogenic syncope and associated conditions: insight into autonomic nervous system dysfunction

Nörokardiyojenik senkop ve ilişkili durumlar: Otonomik sinir sistemi işlev bozukluğuna bir bakış

Antoine Kossaify, M.D., Kamal Kallab, M.D.

Department of Syncope and Electrophysiology, ND Secours/USEK University Hospital, Byblos, Lebanon

Summary– Neurocardiogenic syncope is known to be associated with autonomic nervous system dysfunction, although the mechanism has not been entirely elucidated. In this study, we sought to highlight the pathogenic role of the autonomic nervous system in neurocardiogenic syncope and to review the associated co-morbidities known to have a dysautonomic basis. Herein we discuss migraine, orthostatic hypotension, postural orthostatic tachycardia syndrome, endothelial dysfunction, chronic fatigue syndrome, and carotid sinus hypersensitivity with a focus on the pathogenic role of the autonomic nervous system and any consecutive clinical implications. Other conditions, such as pre-syncopal heart rate acceleration and/or instability and pre-syncopal breathing instability, which occur during a tilt test, are discussed in the same perspective.

Özet– Nörokardiyojenik senkopun mekanizması hala tam olarak aydınlatılamamasına ragmen otonom sinir sistemi işlev bozukluğu ile ilişkili olduğu bilinmektedir. Bu yazıda nörokardiyojenik senkop patogenezinde otonom sinir sisteminin rolünü destekleyen en göze çarpıcı konuları araştırırken, temelinde otonom sinir sistemi bozukluğunun olduğu bilinen komorbid durumları da gözden geçidik. Bu amaçla otonom sinir sisteminin patogenezdeki rolü ve klinik çıkarımları üzerine odaklanarak migren, ortostatik hipotansiyon, postüral ortostatik taşikardi sendromu, endotel işlev bozukluğu, kronik yorgunluk sendromu ve karotis sinüs hipersensitivitesi tartışıldı. Tilt testi sırasında ortaya çıkabilen senkop öncesi kalp atımlarında hızlanma ve/veya instabilite ve senkop öncesi instabil solunum gibi durumlar da aynı perspektif içinde tartışıldı.

Patients presenting with syncope are often difficult to manage, especially if the episode was not witnessed. Neurocardiogenic syncope (NCS) is the most frequent cause of syncope, and treatment strategies are based on an incomplete understanding of its pathophysiology, although autonomic nervous system (ANS) dysfunction is known to be a major determinant.[1]

During a sustained upright posture under normal conditions, the decrease in venous return triggers a reflex sympathetic reaction that is counteracted by a balanced vagal reaction. Complex interactive processes involving cardiac output, peripheral vascular resistance, mean arterial pressure, metabolic factors, intravascular blood volume, and cerebrovascular resistance (with its intrinsic auto-regulation) maintain cerebral perfusion. A clinically significant deficiency in one or more of these processes may lead to syncope.[1]

Abbreviations:

ANS *Autonomic nervous system*
NCS *Neurocardiogenic syncope*

Current knowledge about the pathophysiology of NCS is still limited, although there are often common triggering factors such as excessive pain, heat, or fear, which are known to initiate an intense sympathetic reaction. In addition, orthostatis has been suggested as a main triggering factor, which leads to a reduction in venous return and activates the mechanoreceptors of the heart, resulting in vigorous myocardial contraction in relatively underfilled cardiac chambers. This process leads to a sudden reduction in the sympathetic tone as well as to parasympathetic overdrive, which precipitates the Bezold-Jarisch reflex, resulting in

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Correspondence: Antoine Kossaify, M.D. Chu-Nds-HND Secours Hospital, Jbeil PoB 3, Byblos, Lebanon.
Tel: +00 961 323 20 46 e-mail: antoinekossaify@yahoo.com

severe hypotension and/or bradycardia.[2,3] Vaddadi et al.[4] reported that there are many sympathetic nervous system phenotypes at the electrical, neurochemical, and cellular level in patients with recurrent NCS. Interestingly, they found a subnormal norepinephrine spillover during tilt testing in patients with low supine systolic blood pressure (<100 mmHg).

Many medical conditions have a physiopathological basis related to autonomic dysfunction. Some forms of NCS are known to be correlated with orthostatic hypotension and postural orthostatic tachycardia syndrome,[5] while some forms of migraine are also known to be associated with NCS.[6] The occurrence of pre-syncopal breathing instability[7] and heart rate acceleration during a tilt test have been associated with test positivity.[8,9] Fatigue is frequently encountered in patients experiencing syncope and postural orthostatic tachycardia syndrome.[10] In light of this, we hypothesize that ANS dysfunction represents a common etiopathogenic mechanism for many conditions, and accordingly, we sought to review and discuss autonomic dysfunction in the setting of NCS when associated with each of these conditions.

Autonomic dysfunction and NCS

NCS is defined as a syndrome in which the triggering of a neural reflex typically results in a self-limited episode of systemic hypotension characterized by both bradycardia (asystole or relative bradycardia) and peripheral vasodilation.[11,12] Knowing the patient's medical history remains a key diagnostic issue in the clinical approach to patients presenting with syncope of unknown origin,[13] and can also be used to identify associated conditions (e.g., migraine, orthostatic hypotension, depression) that may help in the assessment of NCS. Many tests (e.g., handgrip test, orthostatic presser response, Valsalva test, deep breathing test, postural test, heart rate variability) are available to assess autonomic function,[14,15] although head-up tilt testing remains the most clinically useful test for evaluating patients suspected to have NCS.

Head-up tilt testing is simple to perform, but has many limitations and lacks a uniform standardized protocol.[16,17] By triggering syncopal episodes in a controlled atmosphere, this test has allowed for a greater understanding of the mechanism of NCS and associated ANS dysfunction.[18] Many protocols for the tilt test have been proposed,[19] including the Westminster Protocol, which favors prolonged passive tilting,[20] and the Minneapolis[21] and Italian protocols, which use Nitroglycerin.[22,23] There is substantial evidence that the Italian protocol considerably increases the yield of tilt testing without significantly increasing false positive rates,[23] while isoproterenol provocation (Minneapolis) significantly increases the yield of false positive results, making its use on a routine basis questionable.[24]

Three types of hemodynamic responses during tilt tests have been described:[25] *type 1*, the classic vasovagal syncope pattern, which happens when an initial rapid and compensatory reflex adaptation to an upright position occurs (reflex tachycardia) followed by a steady-state condition with minimal decrease of tachycardia, until the abrupt onset of syncope; *type 2*, the dysautonomic vasovagal pattern, which occurs when the reflex tachycardia and adaptation to an upright position are absent, with a progressive fall in blood pressure until the occurrence of syncope; and *type 3*, the orthostatic intolerance pattern, which happens when a minimal progressive fall in blood pressure occurs similar to type 2, but without the occurrence of syncope. The clinical relevance of pre-syncope without bradyarrhythmias during tilt tests is still questionable, especially after nitroglycerin provocation.[26] Similarly, when a cardioinhibitory reaction occurs, different types of arrhythmias may be observed (sinus bradycardia, sinus arrest, junctional rhythm, or variable degree of atrioventricular block) and therefore the relevance of these arrhythmias is questionable when they are not associated with syncope.[27] All of these phenomena explain the substantial variations in the diagnostic yield of the head-up tilt test,[28] which is mainly related to the functional and dynamic pattern of the ANS, which may modulate each individual's susceptibility to exhibit NCS.[29]

NCS and associated conditions

a) Orthostatic hypotension

Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mm hg or a decrease in diastolic blood pressure of at least 10 mm hg within 3 minutes of standing or a head-up tilt of at least 60 degrees.[11] It has been well established that orthostatic hypotension is correlated with ANS dysfunction (functional or organic), and when prolonged and severe, may lead to syncope.[30] The decrease in

blood pressure results from the inability of the ANS to achieve appropriate reflex vasoconstriction and tachycardia during orthostatism. Orthostatic hypotension is more prevalent in the elderly because of the frequent decrease in physiological functions such as baroreceptor sensitivity, accordingly when orthostasis is prolonged and non compensated, it may lead to presyncope or syncope.

It is important to distinguish between reflex vasovagal syncope with abrupt vasodepressive reaction[31] and the dysautonomic response due to orthostatic hypotension, which is characterized by a gradual and progressive decrease in blood pressure that may ultimately lead to syncope. Sympathetic efferent activity is chronically impaired and vasoconstriction is deficient upon standing in autonomic failure that leads to orthostatic hypotension. Conversely, in patients with NCS, the failure of the efferent sympathetic system is functional and occurs episodically in response to a trigger.[32] Although they have distinct pathophysiological mechanisms, both dysautonomic and reflex syncope are often designated as NCS.[33] Nevertheless, adequate knowledge and an accurate diagnosis are critical for the management of each of these vasodepressive orthostatic disorders.

Patients with primary autonomic failure may require extensive autonomic function tests and should be seen by a neurologist. Their symptoms can be managed by increasing their salt and water intake. Patients with reflex syncope can sometimes be managed with a lifestyle change along with tilt training and may not initially need medical therapy. The objective of tilt training is to increase the patient's orthostatic tolerance and to raise his/her syncope threshold by modulating ANS reactivity to orthostatic stress.

b) Postural orthostatic tachycardia syndrome

Postural orthostatic tachycardia syndrome is defined as the presence of orthostatic intolerance symptoms for at least 6 months. These symptoms consist of a persistent heart rate acceleration of at least 30 beats per minute within 5 to 30 minutes upon assuming an upright posture in the absence of any secondary cause of tachycardia.[34] Dysautonomia is well-known to be implicated in the pathogenesis of this syndrome.[5]

In a study conducted on young patients[35] with chronic fatigue syndrome and postural orthostatic tachycardia syndrome, most of the patients were reported to have a positive tilt test, orthostatic tachycardia, and ANS dysfunction (characterized by decreased vagal baroreflex and potentiated sympathetic vasomotion).

In subjects suffering from NCS, an increase in cardiac and vascular sympathetic tone has been documented during orthostatism in the prodromal phase followed by an increase in vagal activity leading to exaggerated bradycardia/hypotension.[36] In addition, patients with orthostatic intolerance and postural orthostatic tachycardia may have a prolonged presyncopal phase during which the sympathetic nerve exhibits high activity.[37]

Stewart et al.[38] reported that patients with postural orthostatic tachycardia syndrome had a markedly increased heart rate, unstable blood pressure, and abnormal blood pooling in the lower extremities during orthostatic stress. Conversely, patients with organic autonomic failure had a persistent global dysautonomia (both sympathetic and vagal) that is independent of body posture. In this setting, beta-blockers should be an efficient treatment for both postural orthostatic tachycardia and NCS.

c) Migraine

Migraine is a condition characterized by recurring headaches, usually affecting one side of the head. Migraines have a multifactorial etiology, and dysautonomia has been suggested as a main etiologic factor.[39] A link between migraine and NCS has been reported.[6]

In a study to assess ANS dysfunction in patients with migraine,[40] the patients underwent many tests (Valsalva maneuver, sustained handgrip, cold presser test, head-up tilt test, deep breathing) and it was concluded that subjects suffering from migraine with aura had resting supine sympathetic hypofunction and intact parasympathetic function. More importantly, their sympatho-vagal imbalance was increased with head-up tilt.

Benjelloun et al.[41] reported that patients with migraine had a vagal hyperactivity and a deficiency of the alpha sympathetic system. He also reported that the dynamic fluctuations in ANS contribute to the development of aura and associated symptoms in migraine (e.g., phonophobia, photophobia, nausea and diarrhea). Endothelial dysfunction has been com-

monly described in patients suffering from migraine, but whether it is a consequence[42] or a causal factor[43] is still controversial.[44,45] From the clinical point of view, the association between migraine, endothelial dysfunction, and NCS should raise the issue of treatments used to protect endothelial function such as beta-blockers (also efficient on migraine) and angiotensin-converting enzyme inhibitors.

d) Breathing instability

Respiratory sinus arrhythmia is due to continuous and phasic alterations in the membrane potentials of pre-ganglionic autonomic motoneurons.[46] Breathing instability is a poorly defined breathing pattern that consists of variable breathing cycles and/or amplitude, which may be triggered by stress or anxiety. Porta et al.[7] reported that breathing instability occurs frequently during the pre-syncopal phase of a head-up tilt test, and that it consists mainly of a polypneic irregular breathing pattern. The resulting hypocapnia impairs middle cerebral artery flow, thus facilitating the onset of syncope. Lipsitz et al.[47] reported that during tilt testing, non-syncopal subjects had no change in respiratory dynamics during matched time periods of pre-syncope when compared with syncopal subjects. Accordingly, breathing instability may facilitate syncope. Ocon et al.[48] reported that the loss of the cardiovagal baroreflex along with thoracic hypovolemia is supplanted by respiratory reflexes with hyperpnea and breathing instability, which facilitates the occurrence of syncope.

Breathing instability during the pre-syncopal phase of the tilt test is a frequently reported phenomenon. The involvement of ANS in this phenomenon is obvious, and there is growing evidence suggesting that fluctuations of arterial pressure during pre-syncope result from the influence of respiration on sympathetic and vagal motoneurons.[49] Some investigators[50] have reported variable changes in respiratory patterns preceding symptoms of orthostatic intolerance, and these alterations often precede syncope. Other authors[51] reported that breathing instability during the pre-syncopal phase can cause baroreflex failure, which facilitates syncope.

The exact mechanism of breathing instability is poorly understood. However, there is growing evidence that it is related to ANS tone fluctuations,[7] and that it occurs in response to increased arterial CO_2.[52] with a marked accentuation of sympathetic tone (pre-syncopal phase) followed by a sudden shift of control to vagal tone (syncopal phase). During the pre-syncopal phase of the tilt test, there is a cerebral vasoconstriction,[53,54] which leads to a decrease in cerebral flow with a rise of arterial CO_2 triggering an abnormal breathing pattern and breathing instability. From the clinical point of view, the occurrence of breathing instability during the tilt test indicates the imminent occurrence of syncope. This allows the physician and personnel to be prepared to intervene adequately and promptly.

e) Heart rate acceleration, instability, and variability

Heart rate variability is a useful tool for the noninvasive evaluation of ANS activity. Abnormal heart rate variability is known to be related to ANS dysfunction, and this finding can help to predict the positivity of tilt testing.[55] In patients with NCS, the analysis of markers for ANS activity has shown an increased sympathetic tone with diminished or preserved parasympathetic activity just before the onset of syncope.[8,9]

Many authors[56] have demonstrated that the analysis of heat rate variability allows one to predict tilt test results during the five minutes preceding the onset of syncope. Other authors[55] reported that results of the tilt test can be predicted by analyzing the spectral parameters of heart rate variability during the first five minutes of the test. Mallat et al.[8] reported that an early sustained increase in heart rate during the first 6 minutes of the tilt test had a significant positive predictive value, while Lippman et al.[57] reported that the absence of a decrease in RMSSD (root mean square standard deviation) in response to orthostatic stress had 100% specificity and 41% sensitivity for predicting a positive test result. Julu et al.[58] described the phases of heart rate instability during the pre-syncopal period of tilt test as follows: after an initial heart rate acceleration (phase 1), there is a persistent tachycardia (phase 2), then heart rate instability (phase 3), followed by a cardioinhibitory response when syncope occurs (phase 4).

f) Endothelial dysfunction, carotid sinus hypersensitivity, and baroreceptor control

Tan et al.[59] found that carotid sinus hypersensitivity and orthostatic hypotension are likely to co-exist in individuals with positive tilt testing. More interesting-

ly, they reported that subjects with carotid sinus hypersensitivity had a significantly greater trend toward dysautonomic responses during tilt testing, and that this finding could be the result of an age-associated delay in sympathetic responses.

In a population with a mean age of 60±18 years presenting with syncope of unknown origin, Brignole et al.[60] found that carotid sinus syndrome - when performed both in the supine and in the standing position- was positive in 49% of cases and that the tilt test was positive in 48%. The authors therefore suggested that a common underlying neuroautonomic mechanism is present.

During orthostatic stress, an increase in the reflex sensitivity of the carotid baroreceptor plays an important role in maintaining adequate blood pressure. Failure of this baroreflex orthostatic modulation may be involved in the pathogenic process of NCS.[61] The male gender and increasing age were found to be independent factors of an increased likelihood of abnormal carotid sinus sensitivity.[62] The endothelin system is important for the regulation of cardiovascular homeostasis, and studies[63] have shown that endothelial function is strongly involved in the pathogenesis of NCS. Also, polymorphism of the 3A/4A gene coding for endothelin 1 has been found to predispose patients to syncope.[64]

Endothelial dysfunction is known to be involved in the pathogenesis of at least some forms of migraine.[44,45] Carotid sinus hyper- or hypo-sensitivity[65] in the elderly may simply be related to endothelial dysfunction, and this issue has important implications for the management of NCS in atherosclerotic patients.[43,66] Reduced carotid sinus compliance in arteriosclerotic patients may reduce afferent impulse in the baroreflex pathway, and this "relative deafferentation" may cause baroreflex postsynaptic hypersensitivity.[66]

Prolonged bed rest or any other condition causing a status of "weightlessness" may cause cardiovascular deconditioning, associating orthostatic intolerance, an increase in resting heart rate, and a decrease in physical capability. This phenomenon is due to a temporary impairment of endothelial function at the level of microcirculation, and is also a result of a significant decrease in the sensitivity of the spontaneous baroreflex.[67]

From the clinical point of view, when making a diagnosis of NCS in the elderly, it is essential to keep in mind that atherosclerotic changes in carotids and endothelial dysfunction affect the baroreceptors. This may play a significant role in the pathogenesis and severity of NCS, and management should accordingly target the involved processes.[68]

g) Other conditions associated with autonomic dysfunction

Many cardiac pathologies such as Brugada syndrome, atrial fibrillation, and long QT syndrome may be associated with autonomic nervous dysfunction. The main clinical hallmark of Brugada syndrome is the occurrence of polymorphic ventricular arrhythmias in the resting state and during sleep when the vagal tone is dominant. Also, ECG signs of Brugada syndrome may be unmasked or intensified by vagal stimulation. NCS has been described in patients with Brugada syndrome,[69] and there is increasing evidence that autonomic dysfunction contributes significantly to the arrhythmogenesis in the disease. New prognostic information with potential impact on the refinement of risk stratification and treatment algorithms in Brugada syndrome remains to be determined, and the proposed autonomic tests to identify patients at high risk are still undeveloped.[70]

Syncope in the setting of long QT syndrome is definitively a red flag, nevertheless data suggest that the vast majority of syncopal episodes in these patients are caused by NCS. ANS dysfunction has already been demonstrated in patients with long QT syndrome, but whether these patients exhibit more NCS than the general population remains to be demonstrated.[71,72] Finally, data[73,74] suggest that episodes of paroxysmal atrial fibrillation are provoked by changes in autonomic tone, and that abnormal heart rate variability is associated with autonomic imbalance and paroxysmal atrial fibrillation.[75]

Other conditions have been described in the setting of orthostatic intolerance and NCS, and these may be due to the expression of autonomic dysfunction and/or the consequence of the related psychosomatic effect.[76,77] Chronic fatigue syndrome[10,78] is frequently reported in patients subject to NCS, and it may be related to functional hemodynamic instability, such as postural tachycardia syndrome and/or orthostatic intolerance. Other symptoms preceding NCS or encountered during NCS and related to

ANS dysfunction may consist of diaphoresis, nausea, dysphonia, light-headedness, blurring of vision, and tremulousness.[77,79] Patients subject to NCS may also exhibit significant levels of anxiety, depression and pessimism. Whether these psychological profiles are a consequence of or simply co-morbid conditions has not been completely elucidated.[80]

Some prodromal symptoms are useful in predicting the trend of NCS progression. For example, the occurrence of diaphoresis in the prodromal phase predicts more syncopal or pre-syncopal spells during follow-up.[81] Finally, for management implications, and given the functional rather than organic pattern of ANS dysfunction in this setting, tilt training has been shown to be effective, and must be considered in the majority of patients before the initiation of medical therapy.[82]

Conclusion

In this review, we focused on the role of ANS in the pathogenesis of NCS and associated conditions. This may open new areas for future research in the management of NCS and associated conditions, which could improve the quality of life for patients.

Postural orthostatic syndromes, migraine, endothelial dysfunction, abnormal heart rate variability, and chronic fatigue syndrome are co-morbidities with potential dysautonomic etiology that are frequently encountered in patients with NCS. There is a wide heterogeneity of etiopathogenic factors underlying NCS and its associated co-morbidities. However, ANS dysfunction is a common pathway that should be regarded as dynamic and functional rather than as static and as an organic phenomenon in this setting. This issue is critical for better diagnosis and management of NCS and its associated conditions.

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Key words: Autonomic nervous system; Brugada syndrome; comorbidity; migraine disorders; respiration; syncope, vasovagal/etiology; tilt-table test.

Anahtar sözcükler: Otonom sinir sistemi; Brugada sendromu; eşlik eden bozukluk; migren hastalıkları; solunum; senkop, vazovagal/etyoloji; tilt testi.