The Elusive Pathophysiology of Neurally Mediated Syncope

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Syncope is defined as a sudden transient loss of consciousness and postural tone due to cerebral hypoperfusion. Although no permanent medical sequelae should result from syncope itself, isolated or recurrent events are often dramatic and disrupt the lifestyle of affected individuals. Syncope is a common clinical problem that affects up to 3.5% of the general population. Strikingly, in close to 40% of cases, the exact cause of syncope remains elusive, and ≈30% of affected patients will experience recurrent episodes.

Neurally mediated syncope (NMS) is a common type of syncope (Figure 1); clinical descriptions of it have been present in the medical literature for >100 years. Despite its prevalence, significant gaps in our understanding of its pathophysiology and treatment remain. The purpose of this review is to critically evaluate proposed theories that attempt to explain the pathophysiological mechanisms of NMS.

**Definition**

The development of arterial vasodilation in the setting of relative or absolute bradycardia characterizes NMS. This syndrome has also been known as vasovagal reaction, neurocardiogenic syncope, emotional fainting, or reflex syncope. Related processes include situational fainting (ie, shaving syncope), hyperadrenergic and hypoadrenergic conditions, and hypotensive reactions resulting from drug administration.

**Classification**

We have classified NMS into several categories. These include central (for example, occurring in response to strong emotional stimulation), postural (associated with the upright position), and situational (after the specific stimulation of sensory or visceral afferents). Another classification considers the final hemodynamic characteristics of the patient and includes categories such as vasodepressor, bradycardic, or mixed NMS. One other classification relates to the clinical characteristics of the syncope and its response to treatment. This categorization includes malignant NMS (evolving without a prodromal period or associated with prolonged asystole), recurrent NMS (repetitive or frequent syncope in a particular patient), and refractory NMS (does not respond to medical treatment).

Postural NMS typically develops while the subject is standing or walking, and it is much more frequent than the central and situational types. As determined using a referral population evaluated at the Syncope Unit at Vanderbilt Hospital, 94% of NMS cases fall into this category (unpublished data, R. Mosqueda-Garcia). Central NMS remains poorly characterized in humans. In susceptible individuals, emotional stimulation can activate ill-defined areas within the central nervous system that, in turn, trigger sympathetic inhibition and parasympathetic activation. Situational NMS relates to the specific stimulation of different and seemingly unrelated visceral, sensory-proprioceptive, or specialized afferents that result in hypotension and syncope. Examples include the types of syncope evoked by the hypersensitivity of carotid baroreceptors, rapid bladder distension, and gastrointestinal tract distention.

This review will discuss the pathophysiological aspects of postural NMS, without exploring the pathophysiology of the other types.

**Pathophysiology**

A person’s performance of vital and complex mental functions depends on an adequate cerebrovascular perfusion pressure which, under normal conditions, is preserved by cardiovascular reflexes such as the baroreceptor reflex. Changes in posture and physical exercise are among many activities that challenge cerebral perfusion and require the involvement of neurocardiovascular reflexes. For example, on standing, the increase of gravitational forces results in the pooling of blood in the lower extremities (Figure 2). After standing, between 500 and 800 mL of blood is trapped in the distensible veins below the level of the heart, plasma moves into the interstitial fluid, and venous return, cardiac output, and blood pressure (BP) decrease. These changes are detected by baroreceptors located in the arterial and cardiopulmonary regions. Information from the baroreceptors is then relayed to the central nervous system, where neuronal cell groups regulate reflex cardiovascular activity through changes in sympathetic and parasympathetic outflow. These changes attempt to restore BP and preserve cerebral perfusion during standing (Figure 2). Factors responsible for NMS are varied.
and not always evident; the exact pathophysiological mechanisms responsible for postural NMS have not been totally elucidated, as is discussed below.

Pathophysiological Mechanisms in Postural NMS

Often, NMS develops after the subject experiences changes in gravitational forces. One study suggested that an abnormality in the peripheral veins could result in exaggerated orthostatic pooling while standing. Supporting this is the observation of greater increments in calf venous volume with less variability during orthostatic stress in subjects prone to syncope. Others have shown decreased skeletal muscle tone in the lower extremities during upright tilt or a failure of reflex venoconstriction during exercise. In contrast, another study documented venoconstriction in the forearm or hand veins of patients with NMS during orthostatic stress. Also opposing the idea of exaggerated venous pooling in NMS patients are studies documenting similar decreases in central venous pressure during head-up tilt when compared with controls.

After the initiating events of syncope, a complex hemodynamic response develops, resulting in marked hypotension, variable bradycardia, and loss of consciousness. Several theories have been advanced to account for these hemodynamic events. They are critically evaluated below.

The Ventricular Theory

This theory suggests that when baroreceptors detect a decrease in BP, a reflex increase in efferent sympathetic activity develops. The increase in sympathetic tone enhances total peripheral resistance and produces positive chronotropic and inotropic cardiac effects. The presence of increased cardiac sympathetic stimulation in a setting of ventricular hypovolemia is thought to result in large pressure transients that are evoked by the contraction of the ventricular muscle on an “empty chamber” (Figure 3). The vigorous contraction of the hypovolemic ventricle, in turn, is thought to stimulate “ventricular afferents” in the left ventricle. Activation of these afferents might trigger an inhibitory response similar to that of the Bezold-Jarisch reflex, resulting in hypotension and bradycardia.

The ventricular theory was first proposed by Sharpey-Schafer, and it gained wide acceptance because it seemed to explain some clinical pathophysiological observations (ie, exertional syncope in aortic stenosis). In addition, this theory seemed to provide a rational basis for the combination of isoproterenol and tilt (in the diagnosis) and the use of β-adrenergic blockers (in the treatment) for NMS. Significant experimental observations, however, are not explained by this theory, and they challenge the concept of ventricular mechanoreceptors as responsible for the universal development of NMS.
Activation of Ventricular Mechanoreceptors

Recordings of Afferent Traffic

Studies by Oberg and Thoren\textsuperscript{16} seemed to provide an anatomical substrate explaining the development of NMS. These authors recorded increments in afferent vagal activity during the bradycardic effect evoked by vena cava occlusion. Detailed analyses of their results, however, indicate that only a minority of the ventricular afferents (\textapprox20\%) excited after vena cava occlusion also responded with excitation during the hemorrhagic event. Furthermore, they acknowledged that the vagal filaments recorded in their experiments were not randomly sampled, which lead to an overrepresentation of studied ventricular afferents.\textsuperscript{16} Overall, it was not clear if a “real” increase in ventricular afferent activity was present with decreases in ventricular load.

Sympathetic Withdrawal in Denervated Hearts

A direct challenge to the relevance of ventricular afferents came from studies demonstrating that the inhibition of sympathetic nerve activity evoked by hemorrhage remained intact, even with total denervation of the heart.\textsuperscript{17} In humans, NMS can be evoked in patients with heart transplants,\textsuperscript{18} a circumstance that is independent of autonomic reinnervation of the ventricle. Although it may be proposed that receptors in other cardiovascular regions may be excited by hypovolemia and trigger NMS, no experimental evidence of increased afferent traffic from other thoracic regions is yet available.

Ventricular Hypovolemia

Echocardiographic Determinations

The concept of circulating hypovolemia resulting from venous pooling and causing a decrease in filling return to the heart is one main postulate of the ventricular theory. Earlier reports found evidence of significant decreases in left ventricular dimensions.\textsuperscript{19,20} However, many of these studies were performed either in subjects without spontaneous NMS or after high doses of isoproterenol. More recently, others have demonstrated no significant decreases in cardiac chamber size or volume during tilt, at the time of presyncope, or during syncope in patients with well-characterized NMS.\textsuperscript{21} Similarly, others were unable to record significant changes in left ventricular end-diastolic or end-systolic dimensions.\textsuperscript{22}

Increased Sympathetic Tone

Plasma Norepinephrine Determinations

Another important premise of the ventricular theory is the presence of increased sympathetic tone. Attempts to evaluate sympathetic function with plasma norepinephrine in patients with NMS have produced contradictory results. Although some studies have reported moderate elevations,\textsuperscript{6,12,24,25} others have found normal or even decreased plasma norepinephrine levels preceding syncope. One detailed study of the sympathetic responses during tilt\textsuperscript{12} documented that when compared with controls, a blunted maximal increase in norepinephrine levels was observed in NMS patients (Figure 4).

In all, these dissimilar results\textsuperscript{6,12,20,23–25} may be explained by methodological limitations. Changes in synaptic norepinephrine only subsequently result in changes in norepinephrine levels in the peripheral circulation. This makes the time of blood sampling a source of significant variability. Likewise, changes in the rate of norepinephrine clearance or in spillover to the general circulation,\textsuperscript{26} which are likely to develop during hypotension, may also account for the variable concentrations of this neurotransmitter. Furthermore, the interpretation of plasma norepinephrine samples is meaningless without the proper consideration of associated hemodynamic factors.\textsuperscript{27} While standing, 2- to 3-fold increases in plasma norepinephrine are normal.\textsuperscript{27} However, similar increments in norepinephrine will be inappropriate in subjects experiencing hypotension.

Norepinephrine Spillover Determinations

Using total and cardiac norepinephrine spillover, some investigators have recorded decreases in norepinephrine release during syncope\textsuperscript{26} or blunted increases in the response to orthostatic stress in patients who subsequently developed syncope.\textsuperscript{25} Increases in sympathetic activity in these studies, however, cannot be completely excluded because these reports did not obtain temporal determinations of norepinephrine spillover.

Sympathetic Nerve Traffic Recordings

Microneurography has been used to study sympathetic responses in NMS because it can continuously assess neural sympathetic traffic. Initial reports presented only microneurographic tracings from either healthy volunteers\textsuperscript{28–30} or from one patient not suffering from postural NMS.\textsuperscript{31} These reports were anecdotal and did not account for the reciprocal relationship between BP and sympathetic outflow. More systematic studies in NMS patients have now clearly shown that muscle sympathetic nerve activity (MSNA) does not increase before syncope.\textsuperscript{12,32,33} In one of these studies,\textsuperscript{12} the investigators recorded MSNA in subjects who consistently experienced postural NMS, both spontaneously and during tilt. The
microneurographic responses of NMS patients were characterized by blunted MSNA increases during tilt followed by a progressive reduction until total disappearance a few seconds before syncope (Figure 5). In clear contrast, normotensive controls exhibited significant increases in MSNA in response to orthostatic stress that were well maintained for the entire period of tilt. Interestingly, in subjects who only experienced syncope while undergoing tilt (false-positive), the microneurographic response was apparently exaggerated, with a more sudden withdrawal before syncope (Figure 6). One important conclusion from this study was the concept that the sympathetic responses to orthostatic stress are entirely different in patients with spontaneous NMS and in subjects who experience syncope only during tilt. This indicates that many observations obtained from so-called vasovagal episodes in healthy control subjects cannot be readily extrapolated to patients with recurrent NMS.

Failure to record increases in MSNA preceding syncope has also been reported by others, either during tilt or during lower-body negative pressure (LBNP). Nevertheless, it can be argued that recordings of MSNA may not reflect the noradrenergic changes evoked in other relevant regions (ie, heart). However, it is important to note that at least one study documented decreases in the total, cardiac, and renal norepinephrine spillover of subjects experiencing NMS,26 which agrees with the microneurographic recordings discussed above. In addition, others have shown both a progressive decrease in subcutaneous blood flow, consistent with progressive sympathetic withdrawal before the onset of syncope,26 and a reduced cardiac sympathetic

Figure 5. Responses to tilt in a patient with recurrent NMS. The tracings correspond to recordings of integrated MSNA, BP, and heart rate (HR) obtained from a 38-year-old white woman in the supine position (0°) and at different tilt angles. Note the almost absent increase in MSNA at 15° and 30° and the progressive inhibition until total disappearance at 75°. The apparent MSNA increase at 45° and 60° developed in the presence of pronounced hypotension and is clearly blunted, as demonstrated by a comparison with responses obtained in normal subjects. The arrows indicate the time of syncope.

Figure 6. Hemodynamic and microneurographic responses of a subject with a negative history of fainting but an abnormal response to upright tilt. Abbreviations and layout as in Figure 5. The asterisk represents an artifact resulting from seizure-like activity during unconsciousness. The arrow indicates the time of syncope.
Spectral Analysis of Heart Rate Variability

During tilt, NMS patients exhibit increased vagal cardiac activity, with variable responses in cardiac sympathetic function. While some investigators have found that cardiac sympathetic tone increases before syncope, others have found the opposite or even evidence for both (increase or decrease, depending on the individual subject). Currently, it is not clear whether differences in methodology and/or the selection of patients may account for these discrepancies.

Manipulation of Sympathetic Tone

An attractive way to test the ventricular theory is to investigate whether sympathetic stimulation is an essential requirement for the development of NMS. The rationale behind this notion is that an increase in sympathetic outflow should worsen NMS, whereas a reduction in sympathetic tone could potentially prevent it. Recently, Mosqueda-Garcia et al demonstrated (contrary to what would have been expected with the ventricular theory) that the increase in sympathetic tone evoked by yohimbine enhanced orthostatic tolerance and prevented syncope in most NMS patients. Accordingly, a reduction in sympathetic tone by clonidine resulted in a worsening of the tilt-induced syncope. Overall, these results strongly indicate that increased sympathetic activity is not a prerequisite for the development of NMS, and alternative mechanisms should be sought to explain this syndrome.

Baroreflex Dysfunction Theory

Several other authors have advocated defective baroreflex function as a potential mechanism accounting for the development of NMS.

Carotid Baroreceptor Stimulation

Studies in animals have demonstrated that hemorrhage-induced sympathetic inhibition and hypotension could be prevented by the deafferentation of carotid baroreceptors. In humans, the stimulation of carotid baroreceptors resulted in smaller reflex heart rate responses in patients in whom hypotension was detected during a 20-minute tilt-table test. Another study indicated that individuals with a history of vasovagal reactions displayed greater baroreflex sensitivity. These 2 studies, however, did not use classic additional methods of testing baroreflex function, which would have complemented their observations.

Cardiopulmonary Baroreceptors

Sneddon and collaborators studied baroreflex function in patients with recurrent NMS and with positive or negative responses to tilt. Although no differences were seen for arterial high pressure baroreflexes between tilt-positive and tilt-negative NMS patients, the increase in forearm vascular resistance in response to LBNP was greater in the tilt-positive patients. They concluded that some NMS patients have augmented cardiopulmonary baroreceptor responses. Interpretations of these results, however, are hampered by the absence of a negative control group (subjects without a history of syncope and a negative tilt table test) and by their estimation of baroreflex responses using only vasopressor stimulation.

In a different study, Jacobs and colleagues reported that subjects experiencing syncope during 40 mm Hg of LBNP exhibited an already abnormal response to nonhypotensive negative pressures. This response was characterized by a failure of forearm norepinephrine spillover to increase. Their results indicate of an abnormal resetting of baroreflex function and/or altered responses of low-pressure baroreceptors.

Integrated Baroreflex Evaluation

Thomson et al performed a comprehensive assessment of baroreflex function in controls and in patients with spontaneous NMS (reproduced by tilt table examination). In NMS patients, cardiopulmonary receptor sensitivity was severely impaired, as indicated by the absence of forearm vasoconstriction or, in some subjects, by the development of paradoxical forearm vasodilation during nonhypotensive LBNP. When arterial baroreceptor sensitivity was investigated, a trend for reduced sensitivity was observed in NMS patients compared with controls.

Baroreflex abnormalities in NMS may be better documented by a definition of the entire sigmoidal baroreflex curve. Mosqueda-Garcia et al investigated baroreflex sensitivity on cardiac vagal and muscle sympathetic fibers by stepwise infusions of phenylephrine (linear and saturation parts of the curve) and sodium nitroprusside (threshold and linear parts). Subjects with recurrent NMS and positive tilt-table tests had reduced cardiac and sympathetic baroreflex responses when compared with controls (Figure 7). Other authors have also found pronounced reductions in baroreflex sensitivity in NMS patients with positive tilt reactions when compared with patients with negative tilt tests (Figure 8).
a subsequent report, the same authors found evidence of reduced vagal baroreflex gain during pressure reduction/elevation sequences but intact function with the pressure elevation/reduction algorithm. They indicated that patients who experienced NMS during tilt have subnormal vagal baroreflex responses to pressure changes below baseline but no evidence of vagal and sympathetic baroreflex malfunction during tilt. These later conclusions contrast somewhat with the observations discussed above. Although the reasons for these discrepancies are not clear, it is important to note that in the later article, the authors performed a different type of analysis (integrated evaluation over 3 mm Hg pressure ranges), did not have a “true” control group (all the study subjects had experienced spontaneous syncope; patients either fainted [positive] or not [control] during their tilt), and all but 2 of the presyncopal patients in whom microneurography was obtained required isoproterenol to induce syncope.

Some authors have suggested that baroreflex function is preserved but suddenly suppressed by a depressor reflex originating in the heart. In contrast, one study found significant spontaneous baroreflex function alterations in NMS patients on assumption of the upright position. This study demonstrated that when compared with controls, NMS patients have important reductions in the baroreflex correlation slopes between heart rate and systolic BP or between MSNA and central venous pressure during upright tilt.

Overall, most of the available articles report some type of baroreflex dysfunction that is thought to result in the inability to sense or compensate for changes in gravitational forces in subjects with NMS. The development of sympathetic withdrawal in NMS, however, may result from the paradoxical activation of baroreceptors. Some studies have shown baroreceptor resetting leading to sympathoinhibition during severe hemorrhage. In humans, plasma norepinephrine first increases and then decreases during progressive reductions of arterial BP. In agreement with the idea of baroreceptor resetting is the observation that the inhibition of MSNA declines during continuous electrical stimulation of the carotid sinus nerve in humans. Furthermore, the paradoxical activation of arterial baroreceptors has been documented at very low pressures.

### Reduced Blood Volume Theory

Some authors have proposed that reduced blood volume is present in NMS patients and that syncope can be prevented or reversed by the infusion of serum albumin or by antigravity suit inflation. These observations may explain the beneficial effects of a high salt intake or fludrocortisone treatment for the prevention or treatment of NMS. However, others have indicated that supine total blood volume does not predict the occurrence of NMS during tilt and that plasma volume changes are not different between syncope patients and controls.
controls. Overall, it seems that blood volume redistribution, rather than total blood volume, is more critical for the development of NMS.

**Neurohumoral Theories**

**Epinephrine**

Pronounced elevations of plasma epinephrine have been reported in NMS patients, and some investigators have suggested that epinephrine may play a role in the hemodynamic events of this syndrome. During NMS, a dissociation between the noradrenergic and the adrenomedullary response seems to develop. In these conditions, epinephrine may produce unopposed vasodilation, resulting in severe hypotension. Because isoproterenol has similar cardiovascular effects, one could postulate this as the rationale for its use in the diagnostic work-up of NMS. No experimental evidence, however, is available to support this possibility. In fact, authors have been unable to prove that epinephrine infusions in susceptible patients reproduce NMS. Furthermore, it is unclear whether epinephrine increases merely as a component of the stress response.

**Serotonin**

One group has proposed that selective serotonin reuptake inhibitors are successful agents for the treatment of NMS. These authors have indicated that serotonin surges may occur in humans before syncope and that these inhibitors will decrease the sensitivity of serotonin receptors, with subsequent prevention of NMS.

To date, no strong experimental evidence supports the involvement of serotonin in NMS. First, the basic studies showing an elimination of the vasodepressor reflex during hemorrhage used serotonin synthesis blockers or serotonin receptor blockers. Similar actions have not been reported with selective serotonin reuptake inhibitors. Second, it may be reasonable to speculate that in susceptible subjects, an initial increase in central serotonin levels would aggravate or increase the frequency of NMS. This has not been reported, despite the extensive use of these agents. Finally, studies in humans using serotonin receptor blockers do not show that syncope induced by tilt is prevented. Human studies with different subtypes of serotonin-receptor antagonists demonstrated a decreased tolerance to tilt, an acceleration of the development of hypotension, and a reduction of the sympathetic and adrenomedullary response to hypotension, without preventing syncope. Overall, the potential involvement of serotonin is highly speculative and has little experimental support.

**Renin, Vasopressin, β-Endorphin, Endothelin, and Nitric Oxide**

Other diverse humoral agents have been implicated in the pathogenesis of NMS. Increases in plasma levels of renin, vasopressin, β-endorphin, endothelin, or nitric oxide have been described before the onset of NMS. In some instances, however, pretreatment with specific receptor antagonists (ie, naloxone for β-endorphin) or with a nitric oxide synthase inhibitor did not prevent the provocation of syncope or the vasodilation associated with it. In other cases, the increases in plasma concentrations of these agents (ie, endothelin, vasopressin, and renin) have not been confirmed, and no evidence is available regarding the prevention of syncope with selective antagonists (ie, vasopressin and endothelin).

**Active Vasodilation Theory**

The hypotension observed in NMS has been proposed to result from cholinergic stimulation. Accordingly, the vasodilation observed during posthemorrhagic syncope disappears after cervical sympathectomy. However, the available recordings of MSNA do not support the presence of an active sympathetic-cholinergic mechanism. Furthermore, cholinergic blockade in individuals susceptible to NMS failed to prevent the hypotension.

More recently, Dietz et al proposed that the skeletal muscle vasodilation seen during syncope was greater than that caused by sympathetic withdrawal alone. Because cholinergic, nitric oxide, or epinephrine stimulation is not essential, they suggest that still-undiscovered mechanisms are responsible for the vasodilation observed in NMS. In contrast, others have argued that the disappearance of sympathetic vasoconstrictor nerve traffic to the skeletal muscle vascular bed is sufficient to explain vasovagal reactions. Overall, more experimental evidence is needed to support the involvement of “active” vasodilation in NMS.

**Respiration**

Frequently, patients developing NMS experience yawning and hyperventilation. Some studies demonstrated in presyncopal patients that increasing the depth of respiration results in an enhancement of BP oscillations. Furthermore, others have indicated that yawning and altered breathing patterns may result in an inhibition of sympathetic nerve activity or that the hypocapnia associated with hyperventilation enhances the vasodepressor response. More recently, however, one study indicated that vasomotor instability before syncope does not relate to alterations in respiration.

**Cerebral Blood Flow Dysregulation**

More than 35 years ago, some authors indicated that patients with NMS exhibited an abnormal cerebral vascular response to orthostatic stress, which may be implicated in the pathophysiology of this syndrome. Supporting this concept are the findings of cerebral vasoconstriction and reduced cerebral blood flow in NMS patients. In a more recent report, researchers speculated that abnormal baroreceptor responses initiated during the depressor response resulted in impaired cerebral autoregulation. These findings raise the possibility that abnormalities within the central nervous system play a pivotal role in the pathogenesis of NMS.

**Conclusions**

The exact mechanisms responsible for the development of NMS remain unresolved. The activation of ventricular afferents cannot explain many clinical and experimental observations. Furthermore, many postulates of the ventricular theory are not present in patients suffering from spontaneous recurrent episodes of NMS. The notion that NMS is a uniform
syndrome that can be reproduced in any healthy subject is also no longer believable. Although the ventricular theory may explain the development of hypotension and bradycardia in healthy subjects, other mechanisms are at play in patients with recurrent NMS. In patients with recurrent NMS, central or peripheral baroreceptor reflex abnormalities or alterations in neurohumoral mechanisms may play a pivotal role. Not only is more research needed to delineate the mechanisms responsible for this syndrome, but this research must be performed in actual patients with the disease. It will not be surprising if what we now call NMS is ultimately recognized as the final clinical expression of multiple different conditions that are still poorly characterized.

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