Neurohormones in Vasovagal Syncope: Are They Important?

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Vasovagal syncope (VVS), first described by Sir Thomas Lewis in the 1930s, results from a neurocardiogenic reflex-mediated inhibition of sympathetic activity, increase in parasympathetic activity, bradycardia, and hypotension that lead to peripheral and cerebral hypoperfusion, culminating in transient loss of consciousness and a cascade of associated symptoms.[1,2] VVS is often caused by orthostatic (upright) stress, or an emotional or painful trigger.[2] While manifestations may be similar irrespective of the trigger, no specific test has proven adequate to reproduce the reflex. VVS is episodic and difficult to predict. Head-up tilt-table testing (HUT) often used to evaluate patients is neither sensitive, nor specific in assessing VVS.[3,4] Despite its limitations, the method can provide valuable research and clinical insights[5,6]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Torabi et al[7] report results obtained from a careful and systematic study on a subset of a large population of consecutive patients, of whom 72% (827/1141) qualified for study, 56% (466/827) of those were diagnosed with VVS based on clinical assessment and/or HUT-testing, 37% (173/466) of those had VVS specifically without pharmacological stimulus, and 93% (161/173) of those had no missing data values. Venous blood samples were collected from all 827 patients while they were in the supine position (baseline) and after 3 minutes of HUT. The goal of the study was to determine whether circulating levels of several neurohormones, measured at baseline and early during HUT, are associated with shorter or longer time to VVS. Of those having a positive test for VVS, norepinephrine, C-terminal-pro-arginine vasopressin, C-terminal-endothelin-1, mid-regional-fragment of pro-atrial natriuretic peptide, and pro-adrenomedullin were measured in relation to time-from-tilt onset to VVS. To our knowledge, this is the first study to have analyzed so many neurohormones at 1 time in a large number of patients with suspected VVS, and thus we considered this report with interest.

The concept that shorter time-to-syncope during HUT might reflect greater VVS susceptibility (and vice-versa) seems reasonable.[6,8] Collection of blood samples at baseline (supine) and after 3 minutes of HUT in a relatively large number of subjects with demonstrated propensity toward VVS appears to be a good design to investigate whether early neurohormonal responses promote or protect against later VVS. The results of the study demonstrate that (1) older age, higher supine systolic blood pressure, and higher supine mid-regional-fragment of pro-adrenomedullin predict longer time-to-syncope. Supine levels of the other neurohormones were not associated with time-to-syncope; and (2) the increases in epinephrine and C-terminal-pro-arginine vasopressin measured after 3 minutes of HUT are associated with shorter time-to-syncope, suggesting that the early increases in epinephrine and vasopressin may trigger or contribute to occurrence of VVS. We commend the authors for tackling this challenging, long-standing question in a large clinical population. The results are of interest and will surely stimulate further research in this area. With that said, there are several limitations in the study to consider.

First, the novelty of the results is limited. Previous studies, including several by the authors of this article, have demonstrated effects of these neurohormones on cardiovascular responses to orthostatic stress in healthy subjects and syncopal patients. The evidence is strong that plasma levels of epinephrine and vasopressin increase early during HUT and predict later decreases in blood pressure and syncope.[9–14] Baseline and orthostatic levels of adrenomedullin, endothelin-1, and atrial natriuretic peptide (or their stable metabolites) have also been associated with susceptibility to VVS.[12,13,15–20]

A second limitation of the study by Torabi et al is the lack of a control group. Blood was apparently collected from the patients subjected to HUT who did not exhibit VVS, but the levels of neurohormones for those subjects were not reported. Data from even a subgroup of the 654 subjects would have strengthened the study. Why were these data not reported?

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Thirdly, discussion of possible mechanisms by which the changes in neurohormone levels influence blood pressure and orthostasis is lacking. For example, because adrenomedullin is known to cause vasodilation and natriuresis, it would seemingly promote syncope, rather than be protective against it. The mechanisms put forth in the Discussion are not compelling. While sensitization of cardiac vagal afferent reflexes by vasopressin was mentioned, the mechanism of action of epinephrine was not discussed. Beta-adrenergic receptor–mediated vasodilation and myocardial contractility-induced activation of sympathoinhibitory cardiac vagal afferents are likely mechanisms. Furthermore, data related to individual neurohormones were analyzed in isolation using linear regression. Potential interactions between 2 or more neurohormones were not evaluated. Multiple neurohormones may act in synergistic or antagonist ways to facilitate or prevent VVS. A multivariate analysis would have likely provided additional insight. Some studies suggest that neurohormones may preferentially influence the cardioinhibitory reflex over the vasodepressor reflex at syncope.[13,18,20] Thus, inclusion of heart rate and blood pressure data in the analysis might have aided interpretation of the findings. In addition, the discussion focused on the neurohormones that influenced orthostasis (epinephrine, vasopressin, and adrenomedullin). There was no discussion of the negative results found for the other peptides, especially for endothelin-1, and why results might have differed from previous studies. The finding that higher blood pressure is associated with longer times to syncope seems intuitive, but the author's explanation of a link to baroreceptor activity is not consistent with our knowledge of baroreceptor physiology. Lastly, as the authors suggest, there may be relative differences by age. This study does not represent what happens in younger patients, who are the great majority of those who have VVS. Thus, these data do not tell us about those who are most susceptible. While the linear regression analysis was adjusted for age and sex, we wonder whether effects of the various neurohormones on time-to-syncope hold true when analyzed within specific age groups or after separating data from males and females.

The quests to discover the pathophysiological mechanisms leading to VVS and identify biomarkers capable of predicting syncope continue. Torabi et al have opened our eyes to the potential complexities and dynamic relationships between several neurohormones and VVS. While the roles of epinephrine and vasopressin as possible triggers of VVS are apparent, the mechanisms by which other neuropeptides such as adrenomedullin and endothelin-1 influence orthostasis remain unclear. Studies to date, including the one by Torabi et al, have focused on correlating hemodynamics with measurements of neurohormones in blood. Most, if not all, of the neurohormones under consideration (eg, epinephrine, vasopressin, and endothelin) exert multiple actions on multiple target tissues, often binding to receptor subtypes with opposing effects on heart, vasculature, and nervous system. Future studies investigating effects of selective neurohormone receptor antagonists on orthostasis are encouraged.

Disclosures

Olshansky reports the following disclosures: Amarin: Chair of the DSMB of REDUCE IT, Boehringer Ingelheim: US Co Coordinator of GLORIA AF; Respironics: Consultant, Lundbeck: Consultant and Speaker. The remaining authors have no disclosures to report.

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