Autonomic dysfunction in patients with orthostatic dizziness

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Orthostatic dizziness is feeling dizzy or lightheaded when standing up. Hemodynamic orthostatic dizziness can be caused by autonomic dysfunction such as orthostatic hypotension or postural tachycardia syndrome. The interpretation of the autonomic function test results in patients with orthostatic dizziness is crucial for diagnosing and managing the underlying condition. The head-up tilt and Valsalva tests are especially important for evaluating adrenergic function in patients with hemodynamic orthostatic dizziness. However, it is important to note that autonomic function tests do not cover the entire diagnostic process, since their findings need to be considered along with the detailed history and physical examination results of the patient because various differential diagnoses exist for orthostatic dizziness. Ensuring appropriate treatment by interpreting the autonomic function test results can help to determine the improvement of and prevents falls from orthostatic dizziness.

Key words: Orthostatic intolerance; Dizziness; Hemodynamic; Autonomic nervous system; Orthostatic hypotension; Postural tachycardia syndrome

INTRODUCTION

Orthostatic dizziness refers to dizziness/vertigo during orthostasis, meaning it occurs when rising from a supine position to sitting or standing or from sitting to standing.¹ Orthostatic dizziness is one of the most frequent symptoms of orthostatic intolerance, which is the occurrence of symptoms upon standing that are relieved through recumbence.²-⁵ Orthostatic is a common type of dizziness, but its diagnosis can be challenging. Patients experience various symptoms, and the role of diagnostic tests is limited. Global cerebral hypoperfusion (hemodynamic orthostatic dizziness) is a well-known cause of orthostatic dizziness. Other causes of nonhemodynamic orthostatic dizziness are bilateral vestibulopathy, peripheral neuropathy, functional dizziness, orthostatic tremor, and gait disorders.⁶,⁷ The differential diagnosis of hemodynamic orthostatic dizziness is crucial because it can induce serious conditions such as autonomic disorders and systemic hypotension due to
bleeding. Diagnostic criteria have recently been developed for hemodynamic orthostatic dizziness/vertigo to help clinicians to understand the terminology related to orthostatic dizziness and to distinguish it from orthostatic dizziness with other etiologies. Orthostatic blood pressure (BP) and heart rate (HR) measurements are included in the definitive diagnostic criteria for hemodynamic orthostatic dizziness/vertigo since these are essential screening tests for autonomic dysfunction. Orthostatic hypotension (OH) and postural tachycardia syndrome (POTS) are commonly observed in patients with orthostatic dizziness. Neurogenic OH is often associated with neurodegenerative diseases such as multiple-system atrophy, Lewy body dementia, and primary autonomic failure, as well as peripheral autonomic neuropathies such as diabetes and chemotherapy-related autonomic neuropathies. Nonneurogenic OH is not caused by autonomic neuropathies, but rather by drugs, hypovolemia, deconditioning, or systemic infection. The pathophysiology of POTS is heterogeneous and remains unclear. POTS has been thought to be related to autonomic neuropathy, hyperadrenergic state, peripheral venous pooling, hypovolemia, and deconditioning. Antiganglionic acetylcholine receptor antibodies have been detected in some patients with POTS, which suggests a restricted form of autoimmune autonomic neuropathy. Other psychological factors such as depression and anxiety, or hyperventilation, may also contribute to its pathophysiology.

ADRENERGIC FUNCTION TESTS IN PATIENTS WITH ORTHOSTATIC DIZZINESS

Head-up tilt test: OH
OH is a sustained reduction in systolic BP (SBP) or diastolic BP (DBP) within 3 minutes of standing or tilting of at least 20 or 10 mmHg, respectively. Neurogenic OH from sympathetic adrenergic failure mediating peripheral vasomotor responses often indicates a classic OH pattern. Classic OH is a reduction in SBP or DBP within 3 minutes of standing or tilting of greater than 20 or 10 mmHg, respectively. It is important to discriminate neurogenic from nonneurogenic OH since the latter is a cardinal manifestation of cardiovascular sympathetic adrenergic failure. A decreased HR response to BP reduction is a useful surrogate marker of neurogenic OH. Neurogenic OH can be distinguished from nonneurogenic OH when the ∆HR/∆SBP ratio during the head-up tilt test (HUT) or active standing is <0.5 beats per minute per mmHg. However, this method might not be reliable if the patient has partial or early autonomic failure, a cardiac pacemaker, or is taking beta blockers. Delayed OH is a sustained BP reduction to the same degree as that in classic OH but occurring after 3 minutes from standing or the HUT. Delayed OH is also a frequent cause of orthostatic dizziness and is associated with milder abnormalities of sympathetic adrenergic function. Initial OH is a transient OH only examined during standing, and may be a common (but underrecognized) cause of syncope. Initial OH is defined as a transient decrease in SBP or DBP within 15 seconds of standing of >40 or >20 mmHg, respectively.

ADRENERGIC FUNCTION TESTS IN PATIENTS WITH ORTHOSTATIC DIZZINESS

Head-up tilt test: POTS
POTS is a condition with orthostatic intolerance and a sustained HR increase over 30 beats per minute or an absolute
HR of 120 beats per minute or greater within 10 minutes of standing or during a HUT.\textsuperscript{16} The minimum increment of HR should be 40 beats per minute for those aged 12-19 years.\textsuperscript{16} However, some patients may have a delayed accentuated increase in postural HR after 10 minutes from the onset of the standing or tilting test.\textsuperscript{25} Only 40% of the patients in a previous study exhibited classic POTS, and approximately 60% exhibited a late-onset HR increase after 10 minutes of the HUT.\textsuperscript{26} Clinicians must therefore be careful when diagnosing POTS using 10-minute HUT results. The diagnosis is based on the average rather than the peak HR during the HUT, so a HUT with beat-to-beat assessments of BP and HR is recommended for diagnosing POTS.\textsuperscript{23,27}

**Correlation between orthostatic symptoms and hemodynamic changes during HUT**

Orthostatic BP and HR measurements are the most important screening tests for autonomic dysfunction. The SBP changes during the HUT are more strongly correlated with orthostatic symptoms than are those in DBP.\textsuperscript{28} However, the degree of the BP reduction during the HUT is often not strongly correlated with orthostatic symptoms.\textsuperscript{29,30} The reproducibility of the HUT is higher in patients with more-severe and more-frequent orthostatic symptoms.\textsuperscript{31} Only about 50% of the patients with orthostatic intolerance in a previous study demonstrated changes in BP or HR during the HUT that fulfilled the criteria for OH or POTS, with only 25% of those patients being symptomatic during the actual test.\textsuperscript{32} Although the HUT is the most widely used method to identify sympathetic adrenergic failure, it can only detect moderate to severe generalized adrenergic failure due to its low sensitivity and reproducibility.\textsuperscript{5,17} In contrast, the Valsalva test has the advantage that it can detect milder forms of sympathetic adrenergic failure.\textsuperscript{5,33,34} Both techniques should therefore be combined in the thorough evaluation of sympathetic adrenergic function.\textsuperscript{34}

**Valsalva test in patients with orthostatic dizziness**

Due to the low reproducibility of the HUT, the Valsalva test is an important additional test to evaluate adrenergic dysfunction in patients with orthostatic dizziness. BP responses to the Valsalva test indicate the degree of underlying adrenergic failure. The pressure recovery time (PRT) is thought to be the most-sensitive index for defining neurogenic OH.\textsuperscript{35} The rho coefficient of the PRT in a study of 162 patients with varying degrees of adrenergic failure was 0.84, indicating that it was closely related to the severity of the adrenergic failure.\textsuperscript{36} However, the PRT could not differentiate the mild sympathetic adrenergic failure group from healthy controls in another study.\textsuperscript{32} The sympathetic index 3 (SI3), which measures the difference between BP at baseline and at the end of phase II, is the only index for differentiating all sympathetic adrenergic failure groups.\textsuperscript{17} In addition to the PRT and SI3, reduced or absent late phase II or blunted phase IV overshoot during the Valsalva test can be observed in neurogenic OH. These parameters represent sympathetic dysfunction and can help to differentiate between neurogenic and nonneurogenic OH.

The Valsalva test is sometimes helpful for assessing the hypovolemic or hyperadrenergic state in patients with POTS, since these patients have been found to have profound BP reductions during early phase II or exaggerated phase IV overshoot in response to the Valsalva test.\textsuperscript{37,38} Mild adrenergic impairment such as decreased late phase II, blunted phase IV overshoot, and mildly prolonged PRT can be observed in neuropathic POTS.\textsuperscript{38}

**OTHER AUTONOMIC FUNCTION TEST RESULTS IN PATIENTS WITH ORTHOSTATIC DIZZINESS**

Other autonomic function tests, including HR, deep breathing, the Valsalva ratio during the Valsalva test, and the quantitative sudomotor axon reflex test (QSART), are only valuable for evaluating combined autonomic dysfunction in patients with orthostatic dizziness. The QSART assesses patients with POTS for peripheral denervation. About half of the patients with POTS have slight autonomic neuropathy with a length-dependent pattern.\textsuperscript{39,40} Distal postganglionic sudomotor denervation can be demonstrated using the QSART\textsuperscript{41} or the thermoregulatory sweat test.\textsuperscript{42} The distribution of sudomotor denervation is often restricted to the feet and toes.

**CONCLUSION**

It is crucial to correctly diagnose orthostatic dizziness since
it may be a symptom of serious underlying conditions. Different causes of hemodynamic orthostatic dizziness can be identified using adrenergic function tests. The HUT is essential for detecting OH or POTS, but the Valsalva test is sometimes combined with the HUT due to its low reproducibility. The Valsalva test could be helpful for discriminating between neurogenic and nonneurogenic OH and for detecting mild adrenergic failure. The HR response to a BP reduction is also beneficial in identifying neurogenic OH if the ∆HR/∆SBP ratio is <0.5 beats per minute per mmHg. Understanding and correctly diagnosing orthostatic dizziness is essential, since it can manifest in underlying serious conditions.

Conflicts of Interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Dr. Lee serves on the editorial boards of the Research in Vestibular Science, Frontiers in Neuro-otology, and Current Medical Imaging Review.

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