The Causes of Postural Cardiovascular Disorders

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In this issue of *Hypertension*, Shibao et al describe a series of tests that elucidate mast cell activation as a novel cause of postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension (OH). Because blood pressure control systems are redundant, patients with OH often have more than a single cause of their postural symptoms, and elucidating these causes can be challenging. The study by Shibao et al illustrates this because all but one of their subjects were premenopausal females. Estrogen and histamine vasodilate, and the patients who developed POTS were predominantly those made more susceptible to excessive vasodilation by age and sex. There are so many syndromes that cause orthostatic symptoms that approaching the problem through differential diagnosis is needlessly difficult. Analysis of the cardiovascular physiology of patients with OH is a better way to elucidate etiology and is also more likely to reveal when there are multiple reasons for impaired blood pressure control.

The cardiovascular systems used to maintain blood pressure during upright posture are most simply pictured as a volume of fluid, a pump, vessels that resist fluid flow, and a system that regulates pump speed and resistance to flow. The corresponding anatomic parts of this system are blood volume, the heart, resistance blood vessels, and the autonomic nervous system. It is possible to test each of these components responsible for maintenance of blood pressure to determine the defect(s) causing POTS or OH. This simple physiological approach is useful in the outpatient setting to diagnose a single patient and in the clinical research laboratory.

Blood volume must be adequate for maintenance of blood pressure. When we stand, 300 to 600 mL of blood pools in our legs. When sympathetic innervation is impaired, an even greater volume of blood pools in the legs. Continued upright posture causes fluid to transude into our legs and feet, causing a 10% hemococoncentration. This rapid loss of blood volume into the legs diminishes cardiac preload and decreases cardiac output by half because the heart can only pump blood delivered by the veins. When blood volume is diminished by anemia, hypoalbuminemia, or dehydration, cardiac preload may fall critically low. Diminished blood volume presents a characteristic clinical picture with increased norepinephrine, renin, and aldosterone levels, a tachycardic response to standing and diminished pulse pressure on standing. All of these characteristics can be seen in the mast cell activation plus OH group of Shibao et al. In contrast to the other groups, that group decreased pulse pressure from 35 to 19 mm Hg on standing. Pulse pressure typically falls in patients with low blood volume because standing causes heart rate to increase while cardiac filling decreases, leading to a much smaller stroke volume. The sympathetic nervous response elicits tachycardia, vasoconstriction, and cool blue fingertips. If a vasodilator such as histamine is present, then reflex vasoconstriction may not be able to compensate for the low cardiac output, leading to OH. Low volume can be treated with salt, water, fludrocortisone, erythropoetin, desmopressin, or, in the case of hypoalbuminemia, with food.

Cardiac output is directly proportional to blood pressure, so it is surprising that congestive heart failure is an uncommon cause of OH. The poor cardiac output in heart failure usually does not cause OH because it is accompanied by increased peripheral vascular resistance, in part driven by increased sympathetic nervous activity. Cardiac preload is increased in congestive heart failure so that preload is adequate even during upright posture. However, when patients with congestive heart failure are treated with diuretics or nitrates, preload falls and they may develop OH. Patients with heart failure have taught us that when OH is caused by diminished cardiac output, the problem usually lies with diminished cardiac preload and not with impaired cardiac contractility.

The autonomic nervous system provides the major reflex mechanism that allows maintenance of blood pressure on standing. Autonomic failure usually divides into central nervous system diseases such as multiple system atrophy (Shy-Drager Syndrome) and peripheral neuropathies. Peripheral neuropathies are often seen with diabetes mellitus or uremia and tend to cause deterioration of the longest autonomic nerves. The vagus and sympathetic nerves to the legs show first damage. The vasovagal reflex can cause a brief withdrawal of sympathetic nervous tone with increased vagal activity. Because central and peripheral causes of autonomic defects generally have diffuse effects, they can be recognized by the many signs and symptoms they cause. Patients with autonomic defects may have defective sweating, poor temperature control, impaired papillary constriction, and poor sphincter tone. They tend to have constipation, difficult urination, impotence, impaired gastric motility, and diminished heart rate variability.

When normal subjects stand, heart rate increases and pulse pressure decreases as a consequence of higher diastolic and lower systolic blood pressure. Blood flow to the hands and feet decreases, and this leads to a change in the color of the palms and fingertips from pink toward blue that becomes visible after ~3 minutes of standing. In contrast, when subjects with autonomic insufficiency stand, they decrease...
diastolic blood pressure without the usual compensatory increase in heart rate. They not only fail to vasoconstrict their hands, they increase blood flow to the feet, with pink or red toes. All of this happens because of impaired norepinephrine release from their sympathetic nerves. This is reflected by a diminished plasma norepinephrine response to standing; norepinephrine should nearly double after 5 minutes of upright posture. The poor norepinephrine release is then reflected by poor renin and aldosterone response to standing. If blood pressure falls low enough, vasopressin levels may rise in response to the stress of hypotension.

Vasodilation from heat, acidosis, infection, bradynkinin, or histamine tends to cause POTS rather than OH. A similar response may be seen in patients who have hypertension treated with a single agent such as hydralazine or one of the dihydropyridine calcium channel blockers. The tachycardia without OH that follows arterial vasodilation occurs because arterial dilation increases blood flow, thereby increasing cardiac preload. The heart then has sufficient blood to pump and pumps more forcefully in response to increased sympathetic stimulation. This leads to the common symptom of palpitations among patients who are vasodilated. This type of response to vasodilation is nicely illustrated by the POTS group of Shibao et al, who were able to maintain blood pressure because increased cardiac output compensated for decreased peripheral vascular resistance. However, this system fails if blood volume is low. A short time spent in warm sunshine may be pleasant, but if we cannot replace fluids lost through sweating, hypotension and a feeling of weakness and lightheadedness ensue. The cardiovascular consequences are similar to those seen in the OH group of Shibao et al. Without sufficient blood volume, upright pulse pressure and blood pressure fall in vasodilated persons.

It is important to distinguish between arterial and venous dilation. Arterial dilation increases cardiac output but usually does not cause OH. Venodilation leads to poor cardiac output, which may cause hypotension. Venodilation causes symptoms very similar to volume depletion, because both act to diminish cardiac preload. The difference is dramatically illustrated by arterial and venodilator drugs. Hydralazine causes flushing, palpitations, and tachycardia. The addition of nitrates causes OH.

It is possible to use the classical approach of differential diagnosis for a patient with POTS and OH if the disease is attributable to a single cause. This classical approach fails when there are multiple causes of OH. Let us use the common example of the diabetic with mild autonomic neuropathy. That diabetic’s blood pressure is likely to be elevated in recumbent and standing postures. However, a mild infection can lead to vasodilation from fever and decreased volume from poor intake and glycosuria. The combination of decreased sympathetic nerve function, volume depletion, and vasodilation will cause OH. Without treatment directed toward the OH, the patient will be compromised until the infection has cleared and volume repleted.

Mast cell disorders did not cause OH in most of Shibao’s subjects because reflex sympathetic nervous activation enhanced cardiac output enough to maintain blood pressure. However, a patient with a disease that alters cardiovascular physiology will eventually experience other cardiovascular stresses, such as fever, dehydration, or drugs. At that point, the mild cardiovascular disease may manifest itself as OH, often reported to a physician as “feeling too weak to get up.” The most important postural cardiovascular tests described by Shibao et al are widely available and can often point toward cause and treatment.

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References

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