The Puzzle of Orthostatic Tolerance in Hereditary Sensory and Autonomic Neuropathy, Type IV

Neurogenic orthostatic hypotension is the most incapacitating feature of autonomic failure. Many afflicted patients are unable to leave the supine position without experiencing symptoms of orthostatic intolerance. These symptoms include not only dizziness and lightheadedness but also weakness and fatigue, visual blurring due to retinal or occipital lobe ischemia, dyspnea due to gravity induced pulmonary ventilation–perfusion mismatch, anginal chest pain due coronary hypoperfusion, and occipital and shoulder girdle discomfort (the "coat-hanger" headache) due to trapezius and posterior cervical muscle ischemia.[1]

Orthostatic hypotension is associated with substantial morbidity and mortality. The disorder leads to an estimated 80,000 hospitalizations annually in the United States[2] and is a risk factor for falls, hip fractures, and head trauma.[3] Several large-scale community-based epidemiological studies have shown that orthostatic hypotension is an independent predictor of mortality.[4,5]

The upright posture imposes a significant physiological burden on bipedal humans. On standing from a supine position, 500 to 1,000ml of venous blood pools in the lower extremities and splanchnic circulation. This hemodynamic stress provokes a compensatory reflex response initiated by the baroreceptors that results in decreased vagal nerve activity and increased sympathetic outflow.[6] Norepinephrine is released from vesicles within the terminal varicosities of sympathetic neurons, which leads to increases in peripheral resistance, venous return to the heart, and cardiac output, thereby countering the potential fall in blood pressure.[7]

Supine and standing plasma norepinephrine measurements provide a neurochemical measure of this compensatory reflex. The primary source of circulating plasma norepinephrine is spillover from sympathetic nerve terminals innervating blood vessels and, in healthy individuals, plasma norepinephrine levels double within 5 minutes of standing. Patients with central autonomic neurodegenerative diseases, such as the α-synucleinopathies, multiple system atrophy and Parkinson disease, typically have normal plasma norepinephrine levels when supine, whereas patients with pure autonomic failure, a peripheral autonomic α-synucleinopathy, typically have low supine plasma norepinephrine levels. In contrast to healthy individuals, in patients with neurogenic orthostatic hypotension, whether due to central or peripheral autonomic neurodegenerative diseases, the norepinephrine response to orthostatic change is usually markedly attenuated. The hallmark of neurogenic orthostatic hypotension is thus the failure to release norepinephrine appropriately in response to orthostatic stress.[8]

Herein lies the paradox. In this issue of *Annals of Neurology*, Norcliffe-Kaufmann and colleagues[9] report 14 patients with congenital insensitivity to pain with anhidrosis (CIPA), with undetectable or very low plasma norepinephrine levels that did not increase with the subject upright; despite this, upright blood pressure was maintained. In contrast, their patients with the peripheral autonomic α-synucleinopathy, pure autonomic failure, had severe orthostatic hypotension with, as expected, markedly abnormal supine and standing plasma norepinephrine levels (although not quite as low as those observed in the CIPA subjects).

CIPA, also known as hereditary sensory and autonomic neuropathy type IV, is a rare autosomal disorder characterized by anhidrosis, insensitivity to noxious stimuli, and motor and cognitive developmental delay.[10] The disorder is associated with missense, nonsense, frameshift, and splice-site loss-of-function mutations in the *NTRK1* (*TRKA*) gene that, in humans, encodes a high-affinity tyrosine kinase receptor for nerve growth factor (NGF). Deficient NGF-TrkA signal transduction leads to survival failure of NGF-dependent neurons. Consequently, CIPA patients lack Aδ and C primary nociceptive afferents and postganglionic sympathetic nerve fibers, leading to insensitivity to deep and superficial painful stimuli, impaired visceral pain perception, and impaired sympathetic innervation, most notably of the sweat glands.[11] Consistent with this, in a single-subject case report, a confocal microscopic study showed complete absence of cutaneous nerve fibers in the epidermis and almost complete absence of dermal fibers to blood vessels and arrector pili muscles. Intriguingly, in this report rare varicosities, not observed in controls, were present in the CIPA subject.[12]

A good study leaves the reader with more questions than answers. This one is no exception. Such questions include: Does the loss of postganglionic sympathetic neurons result in decreased norepinephrine reuptake, thereby prolonging the effects of the small amount of available norepinephrine? Could denervation result in exquisite supersensitivity to even very small amounts of norepinephrine? Do other neurotransmitters or neuromodulators participate in the pressor response? Is venous compliance decreased, limiting peripheral pooling? Do vestigial or secondary reflexes involved in orthostatic control such as the myogenic reflex and venoarteriolar reflex play a more prominent role? If epinephrine is involved in maintenance of orthostatic blood pressure, as suggested by the authors, do the vasoconstrictor effects of epinephrine dominate over the vasodilator effects in these patients? These questions could be answered in future studies. More extensive studies of dermal innervation, with systematic examination of the cutaneous vascular innervation, should also be performed on CIPA patients.

There are limitations to the study. Cognitive impairment prevented active participation in autonomic assessment of parasympathetic function and baroreflex function in most subjects. The experiments assessing the renin–angiotensin–aldosterone system and the effects of volume depletion were performed on a smaller subset of subjects. Adrenal release of catecholamines is not adequately assessed by a postural stress. This could be better tested, for example, by an emotional or standardized hypoglycemic stress.

These limitations do not detract from the many strengths of the paper. The authors have characterized autonomic cardiovascular control in this rare and challenging group of patients and have taken the first steps to understand the underlying mechanisms. Despite this, one is still left asking: How can they stand?

Potential Conflicts of Interest

Personal fees from Lundbeck and Chelsea Therapeutics, not related to the current work.

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