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*Editorial Comment*

# The Heart in Orthostatic Hypotension*

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Idiopathic orthostatic hypotension provides a vivid demonstration of the importance of the sympathetic nervous system in regulating cardiovascular function. Without sympathetic innervation of the heart and peripheral circulation, the marked decrease in venous return produced by upright posture causes a dramatic and unabated fall in blood pressure, leading to postural syncope. In the past 50 years, we have learned a great deal about the reflex neural mechanisms responsible for the normal circulatory adjustments to orthostatic stress and the pathophysiology of idiopathic orthostatic hypotension.

**Mechanisms responsible for cardiovascular adjustments during changes in posture in normal humans.** As a normal person assumes an upright posture, mean arterial pressure is maintained (though pulse pressure narrows) because of widespread activation of the sympathetic nervous system, causing reflex vasoconstriction, adrenomedullary release of epinephrine, activation of the renin-angiotensin system and increased heart rate and cardiac contractility (1). These autonomic adjustments to orthostatic stress are caused by a variety of reflex neural mechanisms that are initiated by several sets of sensory, or afferent, nerves.

First, certain inhibiting influences on sympathetic outflow are suppressed. The carotid sinus and aortic arch baroreceptors respond to a narrowing of pulse pressure by decreasing their inhibitory influence on sympathetic outflow (2). In the supine position, the tonic baroreflex restraint on sympathetic outflow is caused by "high pressure" sinoaortic baroreceptors and "low pressure" baroreceptors in the cardiopulmonary region (3–5). With an orthostatically induced fall in intracardiac filling pressure, these baroreceptors decrease their inhibitory influence on sympathetic outflow. As the upright position is assumed, both of these baroreflex mechanisms are engaged and their effects on peripheral vascular resistance are synergistic (6).

*Second, certain excitatory neural pathways are activated by standing.* The change in body position activates sensory nerves in the vestibular apparatus that reflexly increase blood pressure through an effect on the fastigial nucleus (7). The contraction of antigravity muscles activates a pressor reflex through stimulation of sensory nerves in the muscle interstitium (8). Muscle contraction increases venous return by causing compression of the leg veins (the "skeletal muscle pump"), a mechanical rather than a neural effect (9). Finally, the central neural drive associated with a voluntary change in body position may supplement the stimulation of central sympathetic discharge evoked by peripheral autonomic reflexes (10).

**Pathophysiology of idiopathic orthostatic hypotension.** Orthostatic hypotension may be hyperadrenergic or hypoadrenergic (11). *Hyperadrenergic orthostatic hypotension* is caused by marked hypovolemia; a normal sympathetic system, despite maximal stimulation, cannot compensate for a dramatic decline in venous return. In contrast, *hypoadrenergic orthostatic hypotension* is caused by a failure of sympathetic neural discharge to increase appropriately in response to a normal or modestly exaggerated postural decrease in venous return. This entity, described in the report of Kronenberg et al. (12) in this issue of the Journal, may result from abnormalities of the afferent or efferent limbs of the sympathetic nervous system. Although there have been isolated reports of hypoadrenergic orthostatic hypotension caused by baroreceptor dysfunction (13), most cases are caused by preganglionic or postganglionic defects in efferent sympathetic nerves (14). These abnormalities arise clinically as rare idiopathic disorders [for example, Shy-Drager syndrome (15), Bradbury-Eggleston syndrome (16)] or as secondary disorders in the setting of more common diseases such as diabetic autonomic neuropathy (17).

*Hypoadrenergic orthostatic hypotension is an "experiment of nature"* that has provided insight into the function of regional sympathetic nerves in the integrated control of the human cardiovascular system during changes in posture. For many years, failure of sympathetic vasoconstrictor nerves was thought to be the primary pathophysiologic abnormality in this condition (18,19). However, the absence of reflex peripheral vasoconstriction cannot be the only abnormality, because sympathomimetic arterial vasoconstrictor drugs do not correct the orthostatic hypotension even when given in doses that produce supine hypertension (16,20). Thus, in addition to defective peripheral vasoconstriction, hypoadrenergic orthostatic hypotension apparently is character-

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ized by impairment of cardiac output (21), possibly due to shrinkage of plasma volume caused by a salt-losing nephropathy (21–23) following renal denervation or to impairment of reflex increases in heart rate and cardiac contractility following cardiac denervation.

**Findings and significance of the present study.** In contrast to this traditional line of thought, Kronenberg et al. (12) report that cardiac contractility (measured noninvasively) is, surprisingly, *enhanced*, not depressed, in patients with idiopathic orthostatic hypotension. However, the finding of augmented contractility in patients with this disease does not prove that a deficiency in contractile performance plays no role in its pathophysiology. The failure of contractility, as well as of vascular resistance, to show an additional reflex increase during postural change still may contribute to the development of orthostatic intolerance in these patients. Nevertheless, the unexpected finding that cardiac contractility is augmented, not depressed, in the setting of cardiac denervation is a novel observation and calls for further research to elucidate its mechanism and pathophysiologic importance.

**Pathophysiologic speculation.** Enhanced ventricular contractility may be an adaptation to chronic denervation of the heart. When cardiac denervation is accompanied by denervation of the adrenal glands, kidneys and peripheral vasculature, as in idiopathic orthostatic hypotension, orthostatic tolerance is not maintained. In contrast, orthostatic tolerance is well maintained in patients with *selective* cardiac denervation due, for example, to cardiac transplantation (24). In heart transplant recipients, increased contractility may contribute to the maintenance of orthostatic tolerance. In these individuals cardiac denervation occurs in the setting of intact innervation of the adrenal glands, kidneys and peripheral vasculature.

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