Patients with deterioration of the autonomic nervous system can have unexpected or even paradoxical reactions to common cardiovascular drugs. For example, patients with severe neuropathy of the peripheral autonomic system can have a pressor response to phenylephrine eye drops and a paradoxical increase in blood pressure (BP) from the antihypertensive clonidine. Currently, the only approved therapy for postural hypotension in the United States is midodrine, an $\alpha_1$ agonist. The most common therapy is fludrocortisone, which causes sodium retention and sensitizes blood vessels to pressors. Both of these therapies raise BP irrespective of posture, so they can lead to recumbent hypertension. The pressor effect of midodrine is short lived, and it is customarily withheld in the evening. The pressor effect of fludrocortisone is long lived. Even combined therapy often leaves patients with symptomatic postural lightheadedness.

Arterial BP is controlled by negative feedback loops, especially the baroreflex (Figure). Stretch of the baroreceptor fires afferent nerves and initiates autonomic cardiovascular reflexes. The baroreflex is impaired by aging and hypertension as increasingly rigid blood vessels stretch poorly. When the baroreceptor is no longer stretched by high BP, it fails to input nerve signals to the brain stem, thus failing to either activate vagal cardiodepressor nerves or to withdraw outflow to sympathetic vasoconstrictor fibers. Patients with stiff baroreceptors from uncommon causes, such as neck radiotherapy, or common causes, such as atherosclerosis, have wide BP swings with exaggerated pressor responses to stress. Some will have symptomatic hypotension after a high carbohydrate meal. The wide BP swings characteristic of aging hypertensives are a manifestation of failure of the baroreceptor to activate the baroreflex loop to buffer BP through the autonomic nervous system. The baroreflex loop is also interrupted by diseases of the brain stem, such as multisystem atrophy, or by diseases of peripheral autonomic nerves. Both causes of autonomic failure lead to postural symptoms from low BP. Drugs that alter BP usually affect the baroreflex set point or sensitivity. For example yohimbine increases heart rate by decreasing the cardiovascular baroreflex.

Inhibitors of either the norepinephrine (NE) reuptake transporter (NET) or monoamine oxidase might be expected to raise BP by increasing intrasynaptic NE. They instead lower the BP of standing persons. This is because prolonged NE stimulation of $\alpha_2$ receptors inhibits sympathetic nervous outflow. The $\alpha_2$ receptors are stimulated by NE and clonidine and are blocked by yohimbine. Yohimbine increases plasma NE and BP in normal subjects and has a greater pressor effect in some patients with peripheral autonomic neuropathy. Yohimbine also interacts with several tricyclic antidepressants that block NET. The combination of clomipramine, nortriptyline, or desipramine with yohimbine can have a marked pressor effect. Yohimbine also counters the postural hypotension induced by tricyclic antidepressants. The therapeutic pressor effect of an $\alpha_2$ blocker combined with a NET inhibitor had not been studied in patients with postural hypotension because of autonomic disease before the report of Okamoto et al. Neuropathy of the peripheral autonomic nerves can lead to troublesome postural hypotension and may be the consequence of common illnesses, such as diabetes mellitus or parkinsonism. Peripheral neuropathy depletes stores of neuronal NE. Maximizing release of NE through precursors, such as droxidopa, or minimizing inhibition of NE release by inhibiting adenosine A1 receptors with caffeine or $\alpha_2$ receptors with yohimbine can be helpful. Okamoto et al in this issue of Hypertension report an unusually effective therapy for postural hypotension through the combination of the $\alpha_2$ antagonist yohimbine with the NET inhibitor atomoxetine. Inhibitors of NET ordinarily have only minor effects on BP, because their action to increase extracellular NE is counterbalanced by NE stimulation of $\alpha_2$ receptors both in the brain stem and on peripheral sympathetic nerves, inhibiting further neuronal exocytosis of NE. Blockade of $\alpha_2$ receptors with yohimbine permits full expression of the pressor effects of NET blockade. In patients with autonomic neuropathy, this caused a large increase in standing BP and, more importantly, lengthened the time that patients could stand. Although promising, this therapy requires further study before clinical application. Pressor drugs that improve hypotension in standing subjects commonly cause recumbent hypertension. That can be dealt with by use of short-acting agents that are withheld for several hours before patients lie down. The duration of the pressor effect from the combination of atomoxetine and yohimbine in subjects with normal hepatic metabolism is unknown. Both of these drugs are metabolized by CYP2D6 and CYP3A4, and a deficiency of these liver enzymes is not rare. Ten percent of normal subjects have no hepatic hydroxylation of yohimbine, leading to an exaggerated pressor response to the $\alpha_2$ blocker.

Therapies with a generalized pressor effect, such as midodrine and fludrocortisone, have direct pressor effects that are not withdrawn when subjects lie down. Droxidopa replaces
NE stores in dopamine β-hydroxylase deficiency and provides relatively normal BP regulation. Unfortunately, in autonomic failure, droxidopa gives identical increases in recumbent and standing BP, leading to recumbent hypertension that can limit therapy. On the other hand, the combination of an NET inhibitor with yohimbine enhances the normal actions of sympathetic nerves by blocking both NE reuptake and α2 downregulation of NE release. If the combination truly enhances the normal pattern of sympathetic nerve activity, it might lead to more effective maintenance of standing BP without causing significant recumbent hypertension. However, this potential advantage over current therapies for postural hypotension has not yet been studied. Thus, combined use of an NET inhibitor and yohimbine is promising but awaits further safety studies to determine duration of action and the incidence of recumbent hypertension.

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