Normal cardiovascular regulation requires intact baroreflex regulation. The efferent portion of the baroreflex arc, which is composed of parasympathetic and sympathetic nerves, is particularly important in this regard. Autonomic failure ensues when the efferent arc is interrupted. Neuronal degeneration within the brain or in the periphery,1,2 enzymatic defects in catecholamine synthesis,3 and autoimmune disorders4 can be causative. Common to all of these syndromes is debilitating orthostatic and postprandial hypotension. Some patients are unable to stand for more than a few seconds before presyncopal symptoms occur. Trivial stimuli, such eating, taking a hot shower, moderate physical exertion, or drinking small amounts of alcohol, can elicit hypotension in these patients. Less recognized is the fact that many autonomic failure patients are hypertensive in the supine position.5

Cardiovascular studies in autonomic failure patients can serve several purposes. First, these studies can provide deeper insight into human physiology and cardiovascular pharmacology, given the extreme phenotype exhibited by the patients. Many patients resemble laboratory “lesioned animals” or “knockout” models in their underlying pathology. Second, cardiovascular studies in autonomic failure patients may provide clues regarding treatment of orthostatic and postprandial hypotension. Finally, studies on supine hypertension in autonomic failure patients may provide mechanisms relevant to “garden variety” essential hypertension. Indeed, techniques to dissect autonomic cardiovascular regulation in rare patients with severe autonomic failure could be successfully applied to more common cardiovascular ailments.

One of the more puzzling findings in autonomic failure patients is that, even in severely affected patients, loss of efferent sympathetic function is rarely complete. Some residual efferent nerves appear to be disconnected from central nervous system input, making them truly “autonomic.” Residual sympathetic efferent fibers can be engaged through physiological and pharmacological stimuli. For example, when autonomic-failure patients drink 16 oz of tap water, blood pressure increases profoundly.6 The pressor response appears to be mediated through activation of an osmosensitive spinal sympathetic reflex mechanism7,8 and also occurs in healthy older subjects, albeit to a lesser degree.6

Residual sympathetic nerves can be exploited in the treatment of orthostatic and postprandial hypotension. Shibao et al9 manipulated residual sympathetic activity with yohimbine or pyridostigmine and with a combination of both drugs in patients with severe autonomic failure. The primary goal was gauging influences of these interventions on standing blood pressure. Yohimbine raises sympathetic activity through α-2 adrenoreceptor inhibition in the brain. In addition, yohimbine attenuates α-2 adrenoreceptor–mediated feedback inhibition of norepinephrine release from adrenergic nerve terminals in peripheral tissues.10 Pyridostigmine increases acetylcholine availability through acetylcholine esterase inhibition. Because acetylcholine is the main neurotransmitter mediating fast transmission in autonomic ganglia, pyridostigmine raises postganglionic adrenergic nerve activity among other actions. Both yohimbine and pyridostigmine have been applied previously in the treatment of symptomatic orthostatic hypotension when responses to nonpharmacological treatments were insufficient.11,12 Shibao et al9 included patients with peripheral and with central autonomic failure. Pure autonomic failure and Parkinson disease patients with autonomic failure composed the peripheral autonomic failure group. Most of the patients with probable central autonomic failure had multiple system atrophy. The main finding in the study was that yohimbine was more effective than pyridostigmine in improving orthostatic hypotension. Surprisingly, the combined use of yohimbine and pyridostigmine was not better than yohimbine alone.

In patients with intact baroreflex regulation, moderate yohimbine and pyridostigmine doses hardly raise blood pressure. Why then does blood pressure increase in patients with autonomic failure when given these compounds? That sympathetic stimulants such as yohimbine, pyridostigmine, or water cause more norepinephrine release in autonomic failure patients than in subjects with intact sympathetic nerves is highly unlikely. Indeed, water drinking increases plasma norepinephrine similarly in autonomic failure patients and in healthy subjects.6,13 Thus, a similar increase in endogenous norepinephrine produces a much greater blood pressure increase in patients. Autonomic failure patients are also extremely hypersensitive to exogenous α-adrenergic agonists.14 Similar increases in the sensitivity to α-adrenoreceptor agonists ensue when sympathetic and parasympathetic efferents are acutely interrupted through ganglionic blockade. Loss of baroreflex blood pressure buffering and increased vascular sensitivity may contribute to the pressor hypersensitivity.15

All of these observations are relevant for physicians caring for patients with autonomic failure because they directly
affect treatment decisions. Studies on residual sympathetic function in these rare conditions may also foster new concepts regarding hypertension-inducing mechanisms. In patients with peripheral autonomic failure, supine hypertension cannot be explained by sympathetic activity providing a model of entirely “nonneurogenic arterial hypertension.” In patients with central autonomic failure, supine blood pressure is massively reduced by infusion of α-adrenergic receptor antagonists or ganglionic blockers in moderate doses. Hence, residual sympathetic efferents “idling along” can drive supine hypertension in patients with central autonomic failure.\(^{16}\) The mechanism in part resembles the motor spasticity in patients with spinal cord injuries or strokes. Sympatholytic drugs at nighttime improve supine hypertension in patients with central autonomic failure.\(^{17}\) Could a subset of sympathetic efferent neurons also be disconnected from baroreflex restraint in people without autonomic failure? If so, could the mechanism contribute to essential hypertension? I believe the possibility deserves investigation. Indeed, the sympathetic nervous system has been rediscovered recently by the hypertension community stimulated by new therapeutic modalities, including carotid baroreflex stimulators and renal nerve ablation.\(^{18,19}\)

Autonomic failure patients provide a unique model elucidating human cardiovascular pharmacology, as evidenced by the study of Shibao et al.\(^{9}\) If a change in blood pressure with any given drug does not occur in a handful of autonomic failure patients, the chances that that particular drug could have relevant influences on vascular tone in other human subjects is highly unlikely. Much larger studies in healthy people would be necessary to arrive at similar conclusions. I suggest that autonomic-failure patients serve as a “magnifying glass” for human cardiovascular pharmacologists. The condition is also an excellent dissecting tool. Most physiological systems affecting blood pressure, such as the renin-angiotensin-aldosterone and the NO systems, are expressed in the brain and in peripheral tissues, where they may have opposing effects on blood pressure. Adrenoreceptors are also abundantly expressed in brain and peripheral tissues. This state of affairs makes it difficult to distinguish peripheral and central nervous system actions of cardiovascular medications. Because peripheral tissues are disconnected from central nervous autonomic control in autonomic failure patients, peripheral pharmacological responses can be selectively investigated. The approach has been successfully applied to investigate endogenous NO and norepinephrine transporter influences among other mechanisms.\(^{20,21}\) Finally, we have extensively investigated the phenomenon of baroreceptor-reflex buffering of blood pressure (not heart rate). Autonomic failure patients are models for failed baroreflex blood pressure buffering. A mendelian form of hypertension that we have studied extensively exhibits the same phenomenon.\(^{22}\)

Blood pressure buffering belongs to the phenotypes that warrant investigation.

Studies in patients with autonomic failure provided much insight for cardiovascular scientists through their willingness to participate in clinical research. One benefit for many autonomic failure patients has been a gradual improvement in symptomatic treatment over the years through a combination of physiological and pharmacological measures. Treatments addressing the disease cause are rare. Treatment with the norepinephrine precursor \(\text{L}-\text{threo-dihydroxyphenylserine (droxidopa)}\) restores sympathetic regulation in patients with genetic dopamine-\(\beta\)-hydroxylase deficiency.\(^{23}\) Removal of antibodies directed against ganglionic acetylcholine receptors can improve autonomic failure symptoms dramatically in affected patients.\(^4\) In most patients, autonomic failure results from hitherto for poorly understood neurodegenerative processes. Spending a week in a clinical research center to participate in a research project is much to ask from a patient with central autonomic failure with a life expectancy of months to a few years. Nonetheless, our insights were accrued from many patients willing to make this sacrifice to help others. The best way to return their favor is to seek disease mechanisms and better treatments halting disease progression.

**Disclosures**

None.

**References**


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