

## Dysautonomias: Clinical Disorders of the Autonomic Nervous System

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The term *dysautonomia* refers to a change in autonomic nervous system function that adversely affects health. The changes range from transient, occasional episodes of neurally mediated hypotension to progressive neurodegenerative diseases; from disorders in which altered autonomic function plays a primary pathophysiologic role to disorders in which it worsens an independent pathologic state; and from mechanistically straightforward to mysterious and controversial entities. In chronic autonomic failure (pure autonomic failure, multiple system atrophy, or autonomic failure in Parkinson disease), orthostatic hypotension reflects sympathetic neurocirculatory failure from sympathetic denervation or deranged reflexive regulation of sympathetic outflows. Chronic orthostatic intolerance associated with postural tachycardia can arise from cardiac sympathetic activation after "patchy" autonomic impairment or blood volume depletion or, as highlighted in this discussion, from a primary abnormality that augments delivery of the

sympathetic neurotransmitter norepinephrine to its receptors in the heart. Increased sympathetic nerve traffic to the heart and kidneys seems to occur as essential hypertension develops. Acute panic can evoke coronary spasm that is associated with sympathetic and adrenomedullary excitation. In congestive heart failure, compensatory cardiac sympathetic activation may chronically worsen myocardial function, which rationalizes treatment with  $\beta$ -adrenoceptor blockers. A high frequency of positive results on tilt-table testing has confirmed an association between the chronic fatigue syndrome and orthostatic intolerance; however, treatment with the salt-retaining steroid fludrocortisone, which is usually beneficial in primary chronic autonomic failure, does not seem to be beneficial in the chronic fatigue syndrome. Dysautonomias are an important subject in clinical neurocardiology.

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Drs. David S. Goldstein and Graeme Eisenhofer (Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke [NINDS], National Institutes of Health [NIH], Bethesda, Maryland): The notion that the sympathetic nervous system coordinates body functions probably originated with the second-century Greek physician Galen, who taught that nerves were hollow tubes distributing "animal spirits" in the body, thereby fostering concerted action, or "sympathy," of the organs. In 1552, Bartolomeo Eustachius first depicted the sympathetic nerves and the adrenal glands. Winslow reintroduced the sympathetic nervous system in 1732 to describe the chains of ganglia and nerves connected to the thoracic and lumbar spinal cord.

The functions of these structures remained unknown until the 19th century, when Bernard and others first reported the effects of sympathetic nerve stimulation. In 1895, Oliver and Schäfer described the potent cardiovascular stimulatory effects of adrenal extracts. Soon afterward—almost exactly a century ago—Abel and Takamine identified epinephrine ("adrenaline" in British and European countries) as the active principle of the adrenal gland.

Also in the late 19th century, Langley coined the term *autonomic nervous system* to denote the portion of the nervous system largely responsible for involuntary, unconscious functions of internal organs, in contrast with the portion responsible for voluntary, conscious, externally observable functions of skeletal muscle. Supporting this distinction, nerves projecting to internal organs arise from

ganglia outside the central nervous system, whereas nerves projecting to skeletal muscle arise from the anterior horns of the spinal cord. Langley introduced the term *parasympathetic nervous system* to denote the cranial and sacral portions of the autonomic nervous system, in contrast with the sympathetic nervous system, which originates from thoracolumbar ganglia.

Langley did not include the adrenal medulla in the autonomic nervous system. In the 1920s, Walter Cannon considered the sympathetic nerves and adrenal medulla as a functional unit—the "sympathico-adrenal" system (1). The parasympathetic nerves would subserve vegetative, energy-producing processes, such as digestion, during periods of quiescence and the sympathico-adrenal system energy-consuming processes during emergencies. The two systems would antagonize each other in maintaining "homeostasis," a word Cannon invented.

The concept of altered autonomic function as pathophysiologic is relatively new in clinical medicine, possibly dating from reports by Bradbury and Eggleston in the 1920s that demonstrated a neurogenic cause for postural hypotension (2). Humans absolutely require a functionally intact sympathetic nervous system to tolerate the "non-emergency" behavior of simply standing up. This explains why orthostatic intolerance constitutes a cardinal clinical manifestation of sympathetic neurocirculatory failure.

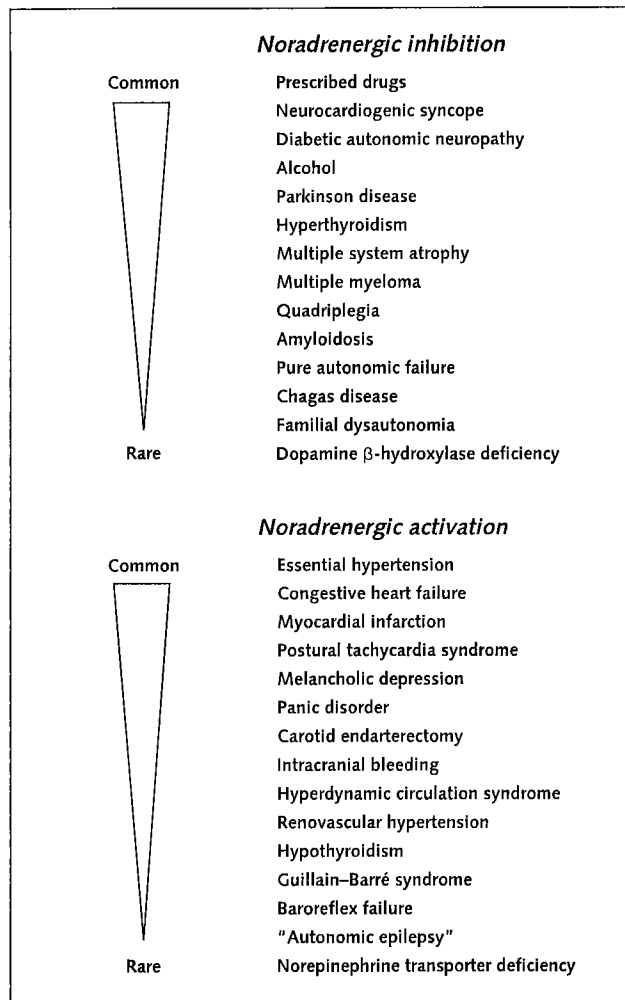
In more general terms, dysautonomia refers to a condition in which altered autonomic function adversely affects health (Figure 1). These conditions range from tran-

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Figure 1. Dysautonomias featuring altered sympathetic noradrenergic function.



In dysautonomias, altered function of the autonomic nervous system adversely affects health.

sient episodes in otherwise healthy people to progressive neurodegenerative diseases; from conditions in which altered autonomic function plays a primary pathophysiologic role to those in which it worsens an independent pathologic state; and from mechanistically straightforward to mysterious and controversial entities.

Norepinephrine (“noradrenaline” in British and European countries) is the main chemical messenger of the sympathetic nervous system. The messenger of the parasympathetic nervous system is acetylcholine. For thermoregulatory sweating, sympathetic nerves release acetylcholine as the main effector.

Modern clinical chemical methods can measure norepinephrine in human plasma (normal concentration is about 1.5 nmol/L). One might think that the plasma norepinephrine concentration would provide a means to assess sympathetic “activity”; however, several processes determine the relationship between sympathetic nerve traffic

and norepinephrine in antecubital venous plasma. These include the efficiency of neuronal reuptake of released norepinephrine, modulation of norepinephrine release by  $\alpha_2$ -adrenoceptors on sympathetic nerve terminals, local blood flow, and, as discussed later, clearance of norepinephrine from the circulation.

Norepinephrine is released into the bloodstream at the same time as it is removed from the bloodstream. Esler first applied the tracer dilution principle to estimate the rate of entry of norepinephrine into the bloodstream—the so-called norepinephrine spillover (3). Because of the relevance of this principle to presentations in this report, we discuss the underlying concepts here.

Because organs remove circulating norepinephrine as it passes through them, when a tracer amount of  $^3\text{H}$ -norepinephrine is infused, the concentration of  $^3\text{H}$ -norepinephrine in arterial plasma exceeds that in local venous plasma. There is less specific activity of  $^3\text{H}$ -norepinephrine (the amount of  $^3\text{H}$ -norepinephrine per unit of total norepinephrine) in the vein than in the artery because unlabeled endogenous norepinephrine enters the bloodstream in the organ. By quantifying the amount of dilution of the tracer, one can estimate the norepinephrine spillover from the organ.

Human plasma contains not only the catecholamines norepinephrine and epinephrine (with trace amounts of free [unconjugated] dopamine) but also two other catechols. Measurements of the other catechols can greatly enhance the interpretation of plasma norepinephrine levels in terms of sympathetic function (Figure 2). One catechol, 3,4-L-dihydroxyphenylalanine (levodopa or L-dopa), is the precursor of the catecholamines and the immediate product of the rate-limiting step in catecholamine biosynthesis. The regional rate of L-dopa spillover (usually estimated from the arteriovenous increment in plasma L-dopa levels, multiplied by the plasma flow) provides an index of norepinephrine synthesis in sympathetic nerves (4, 5).

Another catechol, dihydroxyphenylglycol (DHPG), is the main neuronal metabolite of norepinephrine (6). This catechol is produced by the action of monoamine oxidase on norepinephrine in the sympathetic axoplasm. Axoplasmic norepinephrine has two sources—leakage from storage vesicles and reuptake after exocytotic release. The neuronal uptake process is called uptake-1. Entry of DHPG into the bloodstream reflects both loss of norepinephrine from vesicles by leakage and reuptake of norepinephrine by uptake-1. Under resting conditions, most DHPG production is from the former mechanism. Local DHPG spillover (usually estimated from the arteriovenous increment in plasma DHPG levels, multiplied by the blood flow) has been used as an index of norepinephrine turnover in sympathetic nerves (6, 7). Thus, simultaneous assessments of norepinephrine, L-dopa, and DHPG spillovers provide information about related but different aspects of sympathetic noradrenergic function.

## CHRONIC AUTONOMIC FAILURE

Dr. David S. Goldstein (Clinical Neurocardiology Section, NINDS, NIH, Bethesda, Maryland): Orthostatic hypotension has been defined as a decrease in systolic pressure of at least 20 mm Hg or a decrease in diastolic pressure of at least 10 mm Hg within 3 minutes of standing or head-up tilt (8). Orthostatic hypotension usually results from depletion of blood or extracellular fluid volume or from a prolonged bedridden state and only uncommonly results from autonomic failure. Conversely, however, orthostatic hypotension constitutes a key manifestation of sympathetic neurocirculatory failure (9).

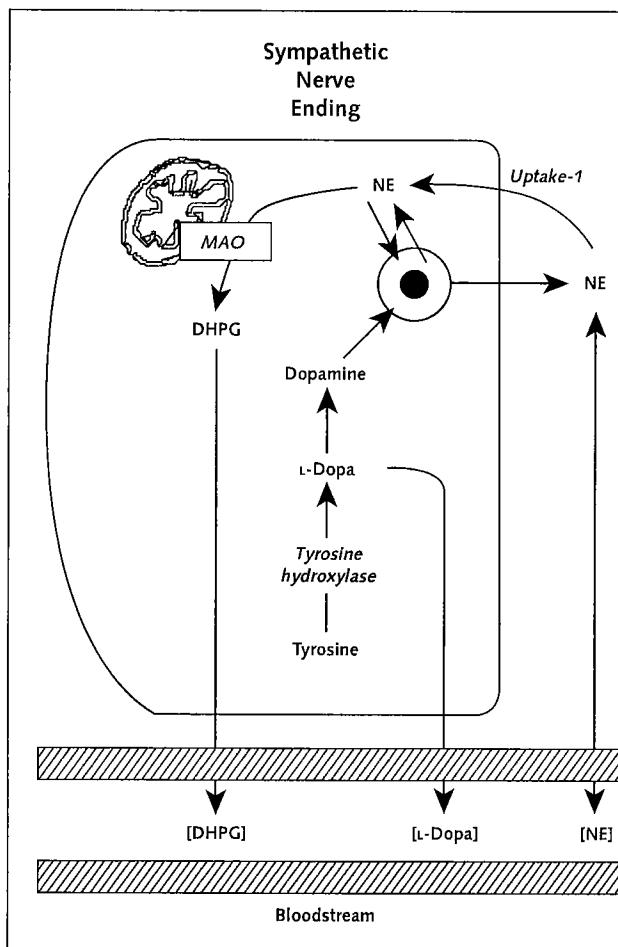
Most chronic autonomic failure occurs as a consequence of disease processes (for example, diabetes, amyloidosis, or multiple myeloma), toxic agents (for example, alcohol), or medications (for example, antidepressant, antipsychotic, antihypertensive, or antineoplastic drugs). Sometimes, autonomic failure dominates the clinical presentation and has no clear cause; this is called primary chronic autonomic failure.

Primary chronic autonomic failure in adults has been classified in terms of three clinicopathologic states (8, 10). Pure autonomic failure features orthostatic hypotension without symptoms or signs of central neurodegeneration. Multiple system atrophy, which includes a combination of autonomic failure and progressive central neurodegeneration, has been divided into parkinsonian, cerebellar, and mixed forms. Finally, autonomic failure can occur in association with Parkinson disease.

Multiple system atrophy can include parkinsonian features; thus, because patients with Parkinson disease can have autonomic failure, distinguishing the two conditions can pose a difficult diagnostic challenge. Patients with Parkinson disease usually respond to carbidopa-levodopa, whereas patients with multiple system atrophy usually do so to only a limited extent (8). This distinction does not always suffice, for two reasons. First, some neurologists may be reluctant to prescribe carbidopa-levodopa for a patient with Parkinson disease who already has orthostatic hypotension because such treatment might worsen the orthostatic hypotension. Second, some patients with multiple system atrophy improve when taking carbidopa-levodopa.

Recent neuroimaging techniques applied to the heart have clearly distinguished these two forms of chronic autonomic failure. Cardiac sympathetic nerves take up  $^{123}\text{I}$ -metaiodobenzylguanidine ( $^{123}\text{I}$ -MIBG) and 6- $^{18}\text{F}$ fluorodopamine, which radiolabel the vesicles in the terminals (11, 12). This allows visualization of the sympathetic innervation of the heart by scintigraphy or single-photon emission computed tomography after injection of  $^{123}\text{I}$ -MIBG (13) and by positron emission tomography (PET) after injection of 6- $^{18}\text{F}$ fluorodopamine (14). This visualization is independent of adrenoceptor binding; rather, it depends on active transport of the radioactive drug by the uptake-1 process, followed by vesicular sequestration.

Figure 2. Sources of plasma levels of catechols.

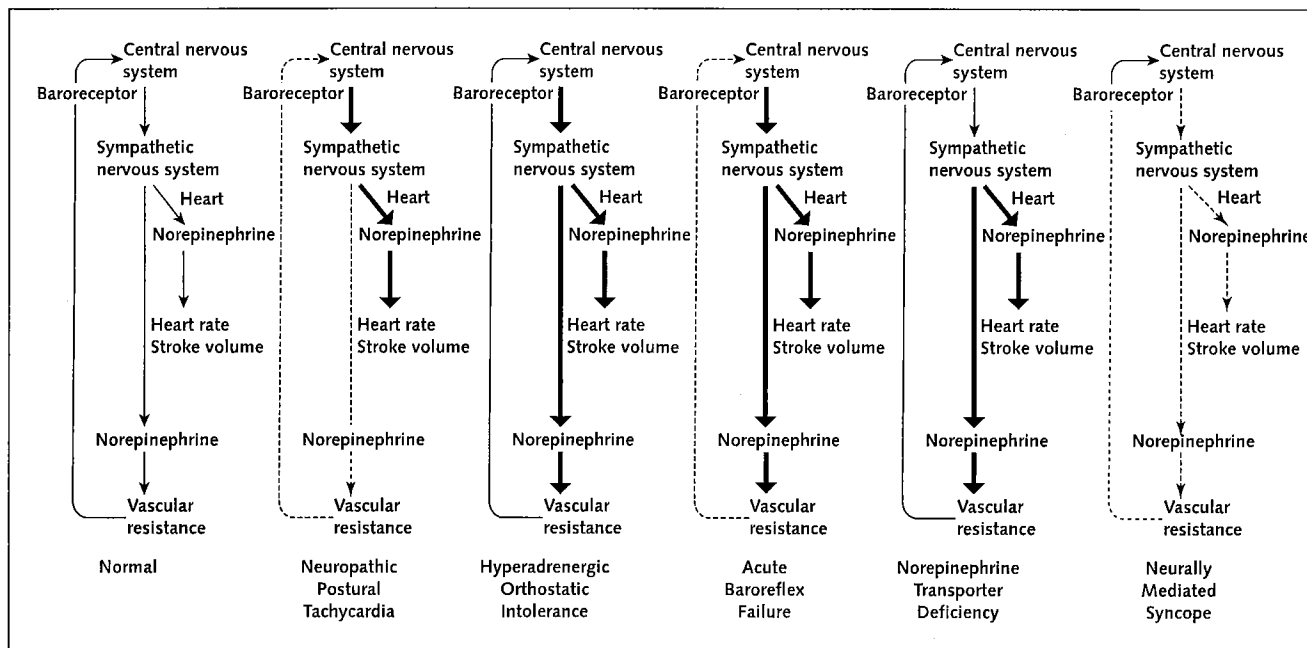


Norepinephrine (NE), dihydroxyphenylglycol (DHPG), and endogenous L-dopa are produced intraneuronally after uptake of tyrosine. Note that hypofunction of the membrane norepinephrine transporter, responsible for neuronal uptake of catecholamines via the uptake-1 process, should result in augmented responses of plasma norepinephrine levels and attenuated responses of plasma DHPG levels during sympathetic stimulation. MAO = monoamine oxidase.

Patients with multiple system atrophy of any subtype generally have intact cardiac sympathetic innervation and a large decrease in blood pressure in response to ganglion blockade with trimethaphan (15). In contrast, patients with Parkinson disease and autonomic failure have no detectable  $^{123}\text{I}$ -MIBG-derived (16–20) or 6- $^{18}\text{F}$ fluorodopamine-derived (21, 22) radioactivity in the left ventricular myocardium and a small or normal decrease in blood pressure in response to trimethaphan (Goldstein DS. Unpublished observations). Such patients also have markedly decreased or absent cardiac spillovers of norepinephrine, L-dopa, and DHPG, which provides neurochemical confirmation of a loss of sympathetic terminal innervation in the heart.

These differences point to a preganglionic lesion in multiple system atrophy and postganglionic lesion in Parkinson disease with autonomic failure. Separating sympa-

Figure 3. Regulation of sympathetic outflows to the heart and other parts of the body in orthostatic intolerance syndromes.



Thick lines represent increased activity, thin lines represent normal activity, and dashed lines represent decreased activity.

thetic denervation from deranged nerve traffic to intact terminals might be clinically important not only for diagnosis but also for treatment and predicting side effects of drugs. Patients with orthostatic hypotension from sympathetic denervation might not benefit from a sympathomimetic amine or  $\alpha_2$ -adrenoceptor blocker because the pressor effects of these drugs depend on releasable norepinephrine stores; however, such patients might benefit from midodrine, an orally acting  $\alpha$ -adrenoceptor agonist, or L-threo-3,4-dihydroxyphenylserine, which is converted to norepinephrine by L-aromatic amino acid decarboxylase, an enzyme found in many types of parenchymal cells. A patient with orthostatic hypotension from dysregulation of sympathetic outflows might be at increased risk for acute hypertension from herbal remedies, such as ma-huang and yohimbe bark, which release norepinephrine.

Future research about chronic autonomic failure should focus more on the pathogenic mechanisms of central and peripheral neurodegeneration and less on treatments of the orthostatic hypotension.

### AUTONOMIC FUNCTION IN CHRONIC ORTHOSTATIC INTOLERANCE

Dr. David Robertson (Clinical Research Center, Vanderbilt University School of Medicine, Nashville, Tennessee): Orthostatic hypotension and orthostatic intolerance are not synonymous. Patients with orthostatic hypotension, a clinical sign, typically have a rapid decrease in blood pressure exceeding 20/10 mm Hg and often cannot

stand for more than 1 or 2 minutes. Orthostatic intolerance, which generally occurs in much younger patients, rarely features rapid orthostatic hypotension, but delayed orthostatic hypotension can occur.

Orthostatic intolerance is common (23). Although formal studies about prevalence have not been done, we estimate that 500 000 Americans have this problem. In elderly persons, orthostatic intolerance can be a manifestation of cerebral hypoperfusion from carotid disease; however, most patients with orthostatic intolerance are young women between the ages of 15 and 45 years. They report dizziness, visual changes, head and neck discomfort, poor concentration while standing, fatigue while standing (as well as at other times), palpitations, tremor, anxiety, presyncope, and, in some cases, syncope.

In neuropathic postural tachycardia syndrome (Figure 3), orthostatic intolerance seems to be associated with a "patchy" dysautonomia, which results in orthostatic pooling of blood in the splanchnic and dependent circulations and activation of the remaining cardiac sympathetic system, causing tachycardia on standing (24). Orthostatic intolerance is also associated with deficient functioning of the renin-angiotensin-aldosterone system (25), acute baroreflex failure (26), and excessive extravasation during orthostasis.

Some patients have orthostatic intolerance associated with a primary abnormality of sympathetic nervous function, which results in augmented delivery of the sympathetic neurotransmitter norepinephrine to its receptors during orthostasis. We present the case of a family with

orthostatic intolerance for which we could identify a specific cause (27).

The index patient was a 33-year-old woman who had 15 years of exertional dyspnea and tachycardia on standing. She had typical orthostatic symptoms and occasional syncope. A pacemaker had been implanted, and the symptoms partially improved. The patient had been treated with  $\beta$ -adrenoceptor blockers, clonidine, and fludrocortisone.

In normal patients, peroneal muscle sympathetic activity approximately doubles during orthostatic stress, with an approximate doubling of the plasma norepinephrine concentration (28–31). In this patient, there may have been only an attenuated increase in sympathetic nerve traffic while standing; however, the plasma norepinephrine level increased by more than threefold.

To explore this dissociation, we evaluated plasma norepinephrine spillover and clearance by using the tracer dilution technique described earlier. We found reduced systemic norepinephrine clearance during various interventions.

We also measured the plasma level of DHPG, which, as noted earlier, is the intraneuronal metabolite of norepinephrine. In the supine posture, the plasma DHPG level was higher than the norepinephrine level (a normal finding), but with sustained upright posture, the plasma norepinephrine level increased by threefold, whereas the DHPG level increased minimally. This neurochemical pattern seemed unusual in this patient. Because increments in plasma DHPG levels during sympathetic stimulation depend largely on neuronal reuptake of released norepinephrine, we hypothesized that the patient had deficient function of the cell membrane norepinephrine transporter, which is responsible for inactivation of norepinephrine by uptake-1. Tyramine is a substrate for the norepinephrine transporter, and the pressor effect of tyramine depends on neuronal uptake of the sympathomimetic amine and displacement of norepinephrine from storage vesicles in sympathetic nerves. During tyramine infusion, we found that the patient had a blunted pressor response compared with other patients with orthostatic intolerance and normal persons.

The DNA sequence and polypeptide structure of the plasma membrane norepinephrine transporter protein are known (32). In our patient, we found a previously unknown polymorphism of the gene encoding this protein, which predicted a proline substitution for alanine at position 457 (27). Expression of the wild-type norepinephrine transporter in a cell line *in vitro* led to uptake of  $^3\text{H}$ -norepinephrine from the medium, whereas cells expressing the transporter with the proline-for-alanine substitution did not. Mixture of the two cell lines led to partial inhibitory effects, suggesting a dominant negative interaction. The pattern of altered upright plasma norepinephrine, DHPG, and heart rate cosegregated with the norepinephrine transporter mutation in this large family.

These findings indicate that deficiency of the plasma

membrane norepinephrine transporter can produce orthostatic tachycardia by amplifying delivery of norepinephrine to its receptors in the heart. We are studying the frequency of the proline-for-alanine substitution in other patients with orthostatic intolerance. We predict that mutations or polymorphisms of other monoamine transporters will also have clinically important manifestations.

### AUTONOMIC FUNCTION IN ESSENTIAL HYPERTENSION, PANIC DISORDER, AND CONGESTIVE HEART FAILURE

Dr. Murray Esler (Baker Medical Research Institute, Prahran, Victoria, Australia): Three conditions associated with altered autonomic function that adversely affects health are neurogenic essential hypertension, psychogenic ischemic heart disease, and congestive heart failure. In some patients with essential hypertension, chronic sympathetic nervous activation may be a primary causal mechanism. In panic disorder, acute episodes can evoke sympathetic neuronal and adrenomedullary activation and precipitate coronary artery spasm. In heart failure, chronically elevated cardiac sympathetic tone probably contributes to progressive deterioration of the myocardium and may serve as a target for therapy.

#### Neurogenic Essential Hypertension

Approximately 40% of patients with untreated essential hypertension have chronically increased cardiac and renal spillover of norepinephrine and increased rates of efferent sympathetic nerve firing in the outflow to the skeletal muscle vasculature (27, 33, 34). These alterations are most evident in relatively young patients. The sympathetic activation originates within the central nervous system and seems to be driven by noradrenergic projections from the brainstem to the forebrain (35).

Chronic sympathetic nervous activation contributes to hypertension by stimulating the heart and elevating cardiac output in the early phases; by neurally mediated vasoconstriction; and, in the kidney, by augmenting renin secretion and tubular reabsorption of sodium (27, 33, 34, 36, 37). The renal sympathetic activation may be of particular importance for the development of the hypertension. Interestingly, the three most commonly used nonpharmacologic therapies to reduce blood pressure (calorie restriction, weight loss, and exercise training) tend to inhibit sympathetic nervous system outflows (27).

A combination of high plasma norepinephrine levels with augmented pressor responses to yohimbine (38) or augmented depressor responses to clonidine (39) identifies patients in whom increased sympathetic nervous system outflows contribute to high blood pressure—termed hypernoradrenergic hypertension. A reasonable hypothesis for future testing is that laboratory profiling predicts long-term responses to different classes of antihypertensive agents.

