REVIEW ARTICLE

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Baroreflex Dysfunction

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THE AUTONOMIC NERVOUS SYSTEM INNERVATES ALL BODY ORGANS, including the cardiovascular system. Smooth muscle in arteries, arterioles, and veins and pericytes in capillaries receive autonomic innervation, which modulates vascular smooth-muscle tone and vessel diameter. Afferent sensory neurons with receptors monitoring local changes in the chemical and mechanical environment provide the information that allows the autonomic nervous system to regulate blood flow within every organ and redirect cardiac output to vascular beds as needed. The autonomic nervous system provides moment-to-moment control of blood pressure and heart rate through baroreflexes.[1] These negative-feedback neural loops regulate specific groups of both sympathetic neurons sending nerve impulses to the vasculature, the heart, and the kidney and parasympathetic neurons sending nerve impulses to the sinus node of the heart. We describe the main features of baroreflexes and the clinical phenotypes of baroreflex impairment.

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BAROREFLEXES

Baroreflexes enable the circulatory system to adapt to varying conditions in daily life while maintaining blood pressure, heart rate, and blood volume within a narrow physiologic range. Baroreceptors embedded in the walls of major arteries and veins and the heart elicit distinct reflexes.[2] They continuously signal to the nucleus of the solitary tract, located in the brain stem, through the vagus and glossopharyngeal nerves and are activated by stretch when blood pressure, blood volume, or both rise (Fig. 1). To counter the rise, baroreceptors evoke reflex inhibition of efferent sympathetic signals to splanchnic, skeletal-muscle, and renal blood vessels, causing vasodilatation. A concomitant increase in parasympathetic-nerve traffic to the sinoatrial node slows the heart rate. Conversely, when a change to a standing position is made, baroreceptors are unloaded, allowing vasoconstriction and tachycardia to buffer the fall in blood pressure that would otherwise occur. Not infrequently, there is initial orthostatic hypotension caused by a transient mismatch between cardiac output and peripheral vascular resistance, which quickly rebounds.

Arterial baroreceptors in the carotid sinuses and aortic arch sense pressure changes, and cardiopulmonary baroreceptors in thoracic veins and the heart sense changes in blood volume. Both arterial and cardiopulmonary baroreceptors inhibit efferent sympathetic neurons, leading to vasodilatation, but only arterial baroreceptors influence the heart rate. Arterial baroreceptors preferentially target the splanchnic circulation, and cardiopulmonary baroreceptors inhibit sympathetic renal outflow, reducing renin release and proximal tubular sodium reabsorption. Baroreceptor activation also suppresses vasopressin release and sodium appetite, increasing urine output (Fig. 1). Mechanosensing by arterial baroreceptors is mediated by the mechanically activated excitatory ion channels PIEZO1 and PIEZO2.[3]

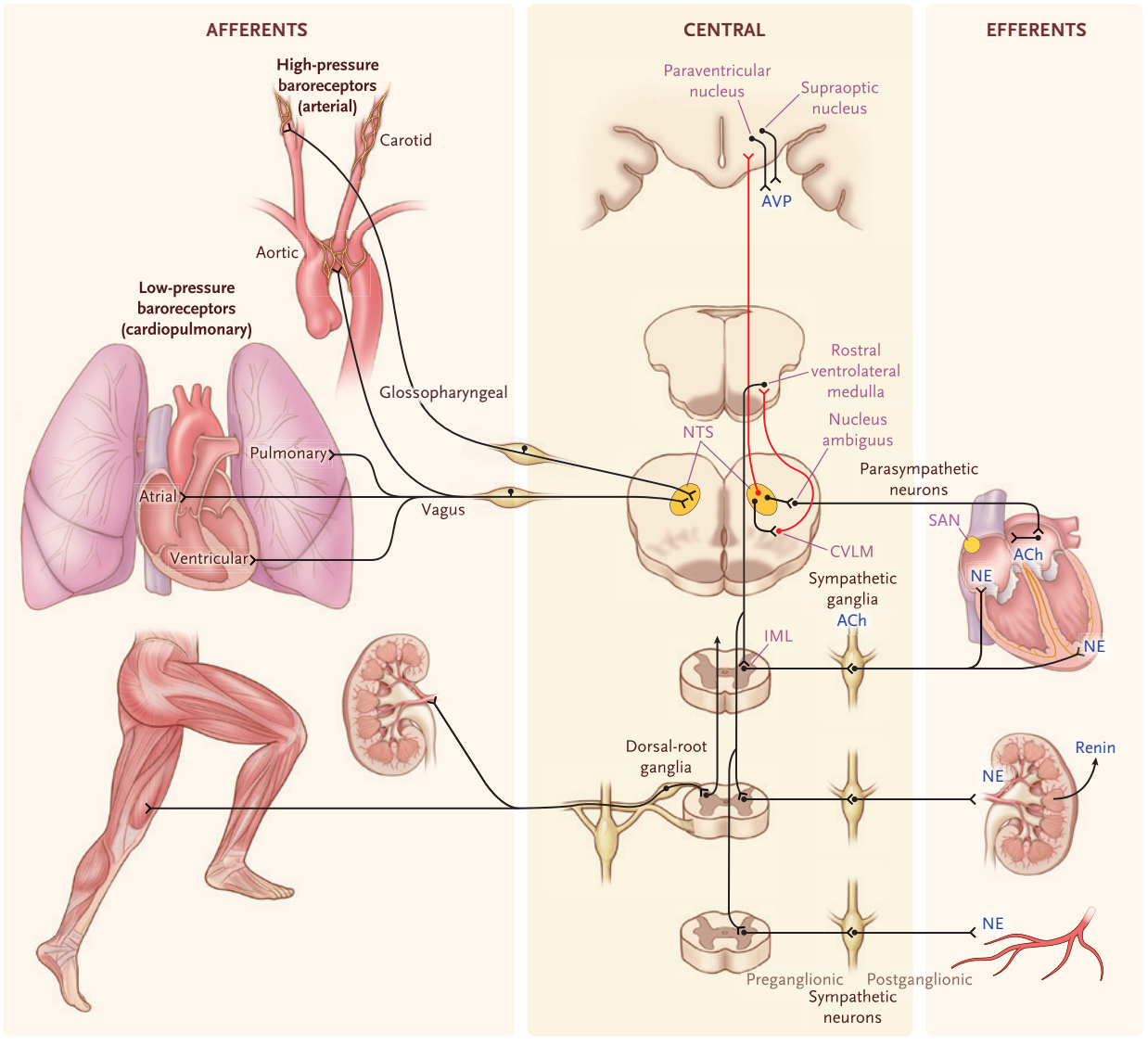


Figure 1. Neuroanatomy of Baroreflexes.

Afferent baroreflex mechanosensing neurons with axonal receptors in thoracic arteries (aortic arch and carotid sinuses) and the heart have their cell bodies in the nodose and petrosal ganglia (yellow ovals) of the glossopharyngeal and vagal nerves (nerves IX and X, respectively) and synapse with neurons in the brain-stem medulla oblongata at the nucleus of the solitary tract (NTS). From the NTS, there are three baroreflex pathways. The first is an inhibitory pathway that restrains sympathetic outflow to the vasculature. Through interneurons in the caudal ventrolateral medulla (CVLM), neurons in the NTS inhibit sympathetic (premotor) pacemaker neurons in the rostral ventrolateral medulla. The neurons in the rostral ventrolateral medulla are the source of sympathetic activity to the vasculature and are organized in groups that preferentially or exclusively control the movement of sympathetic efferent nerves to specific vascular beds. Axons of barosensitive neurons in the rostral ventrolateral medulla descend through the spinal cord and activate the two-neuron (preganglionic and postganglionic) sympathetic efferent pathway to skeletal muscle and mesenteric and renal vessels. The second pathway activates vagal efferents to slow the heart rate through a direct projection to preganglionic parasympathetic neurons in the nucleus ambiguus of the medulla, which activate postganglionic parasympathetic neurons to the sinoatrial node. The third pathway connects the NTS with the supraoptic nucleus) and the paraventricular nucleus in the hypothalamus, controlling arginine vasopressin (AVP) release from the pituitary. Also shown are renal afferents and muscle ergoreceptors (thinly myelinated group III and IV afferents), which reach the cord through the dorsal-root ganglia and have important modulatory effects on the baroreflex. ACh denotes acetylcholine, IML intermediolateral cell column, NE norepinephrine, and SAN sinoatrial node.

BAROREFLEXES DURING THE CARDIAC CYCLE, RESPIRATORY ENTRAINMENT, AND OTHER INPUTS

At rest, afferent baroreceptor discharge on the nucleus of the solitary tract maintains a tonic level of peripheral sympathetic inhibition and cardiovagal activation. In synchronicity with the pulse wave, afferent baroreceptor discharge increases with each systole and decreases during diastole, causing reciprocal changes in sympathetic and vagal efferent activity. Vagal efferent neurons also entrain with respiratory neurons and are inhibited during inspiration, giving rise to respiratory sinus arrhythmia. When the baroreflex pathways are damaged, these physiologic rhythms are lost or blunted.

The nucleus of the solitary tract also receives and integrates information from other sources, including peripheral and central chemoreceptors, renal mechanoreceptors and chemoreceptors through renal afferent nerves, muscle ergoreceptors (muscle afferents that are stimulated by muscle work) (Fig. 1), and respiratory neurons, as well as cortical and hypothalamic neurons. Increased input from chemoreceptors heightens sympathetic outflow in congestive heart failure, pulmonary hypertension, and chronic obstructive pulmonary disease,[4-6] and altered renal afferent activity may underlie sympathetic-nerve excitation in arterial hypertension.

BAROREFLEX IMPAIRMENT

Diseases affecting baroreflex neurons cause unstable blood pressure with acute symptoms of hypoperfusion or hyperperfusion. Lesions of afferent, central, or efferent baroreflex neurons result in distinct but overlapping cardiovascular phenotypes. Clinicians use the term autonomic failure when referring to diseased efferent baroreflex neurons, because other autonomic fibers are also frequently affected, impairing bladder, gastrointestinal, and sexual function. Baroreflex failure commonly refers to compromised afferent neurons, which affect cranial nerves IX and X but cause no additional autonomic deficits. Paroxysmal sympathetic hyperactivity, which occurs in patients with severe acquired brain injury, causes hypertension, diaphoresis, and tachycardia. Diffuse damage to white-matter tracts, including descending fibers from the right insula, and to other cortical areas that normally inhibit sympathetic activity, as well as maladaptive spinal cord plasticity, may explain these episodes.[7] In cervical or high thoracic spinal cord lesions, autonomic dysreflexia results in a similar phenomenon when stimuli from the viscera or skin trigger abnormal spinal sympathetic activation.[8,9] So-called functional autonomic disorders are encountered most frequently in the clinic and are not associated with any detectable nerve disease. The estimated prevalence in the United States of most of the disorders affecting baroreflexes is shown in Table 1.

EFFERENT BAROREFLEX FAILURE

Diseases affecting baroreflex sympathetic efferent neurons impair the release of norepinephrine at the neurovascular junction. Insufficient vasoconstriction on standing or exertion leads to orthostatic hypotension and symptoms of organ hypoperfusion, including lightheadedness or dizziness, visual blurring, and syncope. Dyspnea, subtle cognitive slowing, and fatigue are common and disappear in the supine position. Clinically, this disorder is defined by a sustained fall in blood pressure of at least 20/10 mm Hg within 3 minutes after assumption of an upright posture,[18] but in some cases, the fall in blood pressure is delayed, occurring after prolonged standing.[19]

Supine hypertension (blood pressure, >140/90 mm Hg) develops in 50% of patients with efferent baroreflex failure, probably as a result of the activation of residual sympathetic fibers and denervation supersensitivity.[20] Loss of the normal nocturnal profile of blood-pressure dipping impairs extracellular fluid-volume regulation. It is thought that abnormally elevated blood pressure throughout the night causes renal excretion of sodium and water (i.e., pressure natriuresis), resulting in overnight loss of extracellular fluid volume, with worsening orthostatic hypotension in the morning. However, lowering overnight blood pressure may not consistently reduce natriuresis.[21] Lack of sympathetic activation of renal tubular epithelia impairs sodium reabsorption[22] and may contribute to pressure natriuresis.[23] Long-term supine hypertension is associated with target-organ damage.

PREGANGLIONIC VERSUS POSTGANGLIONIC EFFERENT BAROREFLEX FAILURE

Impaired release of norepinephrine may be the result of disorders affecting peripheral postganglionic sympathetic neurons or the preganglionic

Table 1. Estimated Prevalence in the United States of Disorders Affecting Baroreflex Function.

Disorder	Prevalence or Incidence
Disorders without detectable nerve disease	
Neurally mediated (reflex) syncope	
Vasovagal syncope or situational syncope (i.e., syncope on micturition or defecation)	130 million people (40% of the population) have had ≥1 episode[10]
Carotid sinus syndrome and glossopharyngeal neuralgia	5–10% of patients with unexplained syncope[11]
Postural tachycardia syndrome	500,000[12]
Takotsubo cardiomyopathy	10,000 new cases/yr[13]
Disorders with pathological substrate	
Metabolic disorders	
Diabetes mellitus	20–30% of patients with type 1 or type 2 diabetes (about 25 million people)[14]
Porphyria	<1000 people
Neurodegenerative disorders	
Synucleinopathy	
Parkinson's disease	800,000 people[15]
Dementia with Lewy bodies	600,000 people[16]
Multiple-system atrophy	15,000 people
Pure autonomic failure	<10,000 people
Amyloid neuropathy	
Hereditary transthyretin amyloidosis	<5000 people
Acquired (AL [light-chain], AA, or wild-type transthyretin) amyloidosis	25,000 people
Acquired disorders	
Paroxysmal sympathetic hyperactivity caused by acute brain injury	150,000 people[7]
Spinal cord injury (T6 or above)	100,000 people[9]
Acquired afferent baroreflex failure	<10,000 people
Chemotherapy-induced and toxic autonomic neuropathies*	50,000 people
Autonomic neuropathies due to infectious diseases†	10,000 people[17]
Immune-mediated and paraneoplastic autonomic disorders‡	<5000 people
Rare genetic autonomic disorders (familial dysautonomia, dopamine–β-hydroxylase deficiency, mutations in *CYB561*, and others)	<1000 people

* Causes include antineoplastic agents, organic solvents, acrylamide, and heavy metals, as well as marine toxins (e.g., ciguatera and toxins from Irukandji jellyfish).
† The infectious diseases include human immunodeficiency virus infection, Chagas' disease, leprosy, and tetanus.
‡ Disorders in this category include the Guillain–Barré syndrome, limbic encephalitis, autonomic autoimmune ganglionopathy, paraneoplastic autonomic neuropathy, and acute autonomic and sensory neuronopathy.

and premotor neurons in the spinal cord and brain stem that activate them (Fig. 1). Although the lesions are different, the severity of orthostatic hypotension is similar. The supine plasma norepinephrine levels tend to be low in patients with postganglionic lesions but normal in patients with preganglionic or premotor sympathetic lesions (Fig. 2). In patients with postganglionic lesions, the pressor response to adrenergic agents is exaggerated because of adrenergic denervation supersensitivity, which is probably caused by an increased number of receptors.[24] Conversely, in preganglionic or premotor lesions, sympathetic postganglionic neurons are spared but are disconnected from central influences. In preganglionic but not postganglionic lesions,

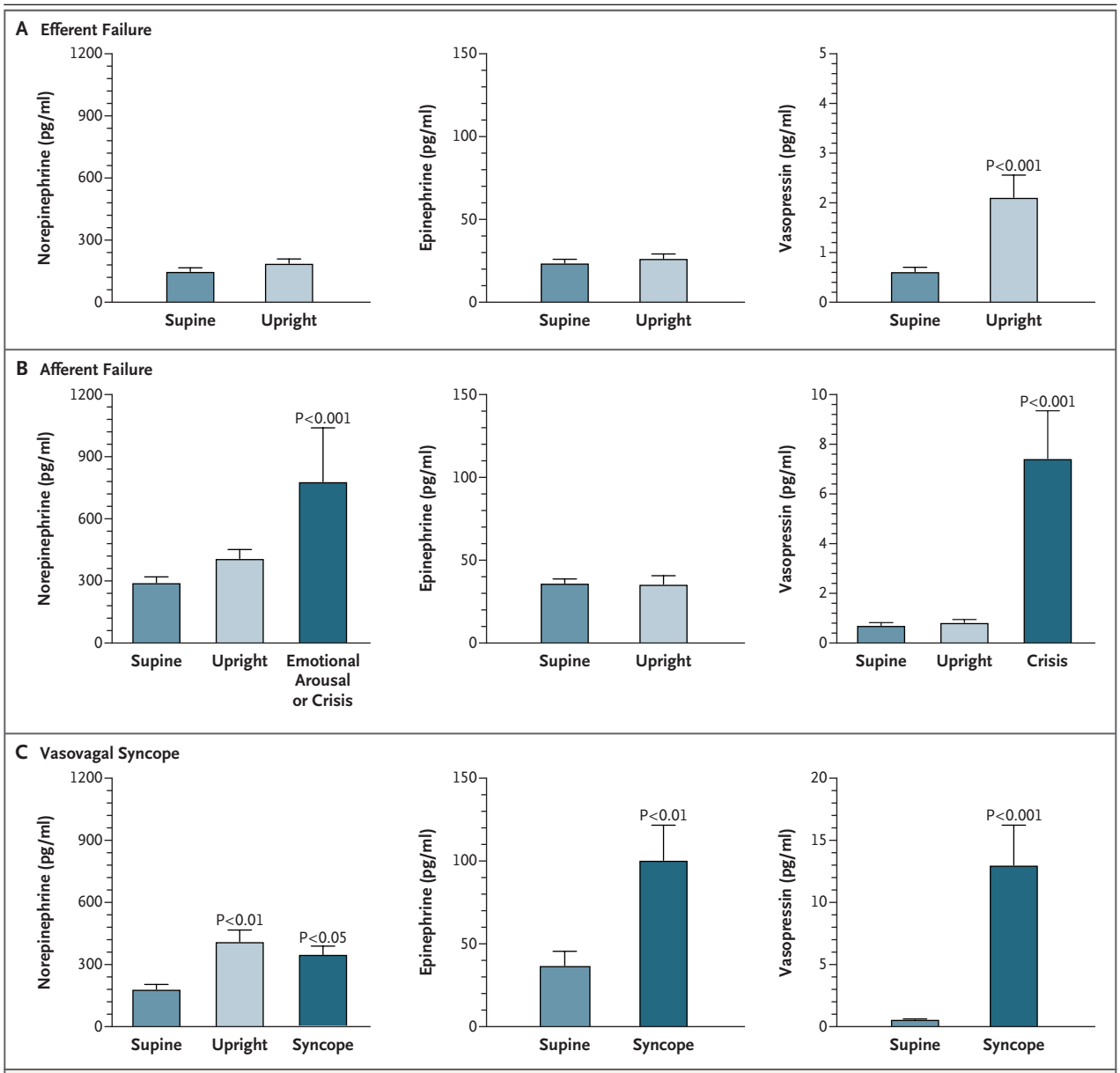


Figure 2. Neurohormonal Responses in Patients with Baroreflex Dysfunction.

Shown are plasma levels of norepinephrine, epinephrine, and vasopressin in 51 patients with efferent baroreflex failure (Panel A), 29 patients with afferent baroreflex failure (Panel B), and 63 patients with vasovagal syncope (Panel C). Also shown are plasma levels of norepinephrine and vasopressin at the time of emotional arousal or autonomic crisis in patients with congenital afferent baroreflex failure (Panel B) and norepinephrine, epinephrine, and vasopressin at the time of syncope in patients with vasovagal syncope (Panel C). T bars denote standard errors.

norepinephrine-reuptake inhibitors significantly increase norepinephrine levels at the neurovascular junction and raise blood pressure.[25]

CAUSES

Baroreflex efferent neurons are most often damaged by diabetes mellitus. The second most common cause is synucleinopathies (Table 1), including pure autonomic failure, Parkinson's disease, dementia with Lewy bodies, and multiple-system atrophy, which are caused by intracellular accumulation of misfolded α-synuclein in nerve tissue. Similarly, in light-chain and transthyretin amyloidosis, overproduced, misfolded amyloid

deposits are found in sympathetic neurons, but the deposits are extracellular.[26] Autoimmune mechanisms can also target sympathetic axons or block cholinergic transmission in autonomic ganglia.[27] Rare genetic mutations can impair norepinephrine synthesis or release, and toxic neuropathies can affect autonomic fibers of the baroreflex (Table 1).

The two most common synucleinopathies, Parkinson's disease and Lewy body dementia, have a predominantly postganglionic phenotype. Multiple-system atrophy is rare but much more aggressive, and it has a preganglionic phenotype, with postganglionic sympathetic neurons largely spared but compromised connections between the nucleus of the solitary tract and the hypothalamic nuclei regulating vasopressin release (Fig. 1).[28-30]

Baroreflex dysfunction can be the initial presentation of all synucleinopathies and may allow for early diagnosis, before the appearance of typical motor or cognitive deficits.[28] Prospective studies show that for patients with isolated efferent baroreflex failure (i.e., pure autonomic failure), the cumulative risk of a future diagnosis of Parkinson's disease, Lewy body dementia, or multiple-system atrophy is 10% per year.[28] Moreover, prospective, population-based studies of healthy persons have shown that a decrease in heart-rate variability or peak exercise heart rate carries an increased risk of a later diagnosis of Parkinson's disease.[31,32] It is suspected that these persons already had a synucleinopathy, solely affecting autonomic neurons at the time. Indeed, patients with incidental Lewy body disease at autopsy, with no signs of Parkinson's disease when they were alive, have abnormal synuclein deposits in the heart.

DIAGNOSIS

In clinical practice, particularly in the case of elderly patients, orthostatic hypotension due to neurologic (i.e., neurogenic) causes needs to be distinguished from common non-neurogenic causes (i.e., dehydration, hemorrhage, anemia, and medications). Diagnosis requires a careful history taking and physical examination (showing a sustained fall in blood pressure of at least 20/10 mm Hg with assumption of an upright posture after being in the supine position) and a 12-lead electrocardiogram or, when necessary, Holter monitoring to rule out cardiac arrhythmias.

A simple, bedside diagnostic test to distinguish neurogenic from non-neurogenic causes of orthostatic hypertension is the ratio of the increase in heart rate (in beats per minute) to the decrease in systolic blood pressure (in millimeters of mercury). Since the heart-rate response to hypotension is pronounced in patients with non-neurogenic orthostatic hypotension but is blunted in those with efferent baroreflex failure, a ratio below 0.5 indicates baroreflex failure and provides a sensitive and specific cutoff value during passive tilt and active standing.[33]

Laboratory autonomic testing in patients with efferent baroreflex failure shows a reduced or missing blood-pressure overshoot after the Valsalva maneuver and, frequently, reduced respiratory sinus arrhythmia. Measurement of plasma norepinephrine levels, in both the supine and standing positions, can help localize the site of the lesion and confirm the diagnosis. Prolonged tilt may be necessary in cases of delayed orthostatic hypotension. Once neurogenic orthostatic hypotension has been established, a careful neurologic examination to identify motor, sensory, or cognitive abnormalities could help to determine the underlying cause (e.g., synucleinopathy or diabetes).

AFFERENT BAROREFLEX FAILURE

Sympathetic activation is blunted in efferent baroreflex failure but is unrestrained and overactive in afferent baroreflex failure. Without mechanosensing afferent inputs, neurons in the nucleus of the solitary tract do not inhibit the premotor sympathetic neurons in the rostral ventrolateral medulla (an area of basal and reflex control of sympathetic activity), barosensitive sympathetic neurons are unrestrained, and the release of norepinephrine causes vasoconstriction, tachycardia, and increased blood pressure. Headaches, flushing, and agitation are common, and blood pressure is unstable throughout the day.[34] Orthostatic hypotension is part of the syndrome, but it is not always present. It is likely that central command and receptors outside the baroreflex system, including the vestibular otoliths, activate sympathetic neurons in the standing position.[35]

ACQUIRED AFFERENT BAROREFLEX FAILURE

Acquired afferent baroreflex failure is a complication of damage to the glossopharyngeal and vagal fibers due to radiotherapy to the neck, radical neck surgery for cancer, or rare tumors that affect the nucleus of the solitary tract. The disorder occurs after carotid endarterectomy or angioplasty involving damage to or stretch of the baroreceptors.[34] Symptoms may appear several years after surgery and sometimes herald tumor recurrence. The clinical severity of the disorder depends on the extent of the afferent lesion, which is variable. Afferent baroreflex failure is also well recognized in patients with the Guillain–Barré syndrome, who have wild swings in blood pressure with a relatively invariant heart rate. A lack of reciprocal heart-rate changes during changes in blood pressure is diagnostic. The same blunted heart-rate changes occur in laboratory animals with sinoaortic denervation and in mice lacking mechanosensing PIEZOs.[3]

CONGENITAL AFFERENT BAROREFLEX FAILURE

Familial dysautonomia (the Riley–Day syndrome) is a hereditary sensory and autonomic neuropathy due to a founder mutation that causes a splicing defect in *ELP1* in children with Jewish ancestors. Reduced levels of ELP1 (elongator complex protein 1) prevent the growth and survival of afferent neurons, including those involved in baroreflexes.[36,37] From birth, patients also have other features of glossopharyngeal and vagal dysfunction, including swallowing abnormalities and blunted hypoxic ventilatory drive. At times of stress, sympathetic activation is unopposed (i.e., baroreflexes are unrestrained and there are no parasympathetic responses), causing persistent hypertension, tachycardia, and flushing.[38] Fear, intense emotions, or illness can trigger the spillover of dopamine from sympathetic terminals, causing nausea, retching, and vomiting.[39] During these episodes (referred to as autonomic crises), patients can have inappropriate vasopressin release and hyponatremia for unknown reasons (Fig. 2).

As in acquired afferent baroreflex failure, direct recordings show that sympathetic efferent activity is no longer coupled to the cardiac cycle.[36] Complete failure of the baroreceptor afferents results in orthostatic hypotension with a paradoxical slowing of the heart rate that is not blocked by atropine, indicating that it is not mediated by activation of vagal efferents.[38] Slowing of the heart rate in patients with familial dysautonomia when they are in the standing position may be the result of decreased right atrial filling, as observed in denervated heart preparations. Increasing right atrial pressure increases the heart rate in the denervated heart, and increasing right atrial filling in patients with familial dysautonomia by placing them in the head-down position also raises their heart rate, perhaps revealing the intrinsic responses of a deafferented heart.[38]

CARDIOVASCULAR AUTONOMIC DISORDERS WITHOUT DETECTABLE NERVE DISEASE

The vast majority of patients seen in autonomic clinics (Table 1) have no detectable nerve disease. They report discrete episodes with symptoms and acute cardiovascular changes, but apart from these episodes, blood-pressure regulation appears to be normal.

VASOVAGAL SYNCOPE

Vasovagal syncope is triggered by a reflex that causes sympathetic inhibition and parasympathetic activation. The acute fall in blood pressure and heart rate causes transient loss (or near loss) of consciousness due to global cerebral hypoperfusion. Vasovagal syncope is very common in the general population, with the highest prevalence among teenagers, athletes, and the elderly. With a sufficient degree of orthostatic stress, vasovagal syncope can be induced in more than 75% of healthy people. It is not a predictor of adverse cardiovascular outcomes.[10] Although falling to the ground serves the physiological purpose of removing gravitational stress and immediately restoring cardiac output and perfusion to the brain, it can result in head trauma and bone fractures. Consciousness is regained rapidly, and there are no neurologic sequelae.[40]

The vasovagal reaction can be triggered by emotional, sensory, or hemodynamic stimuli (e.g., the sight of blood, colonoscopy, acute pain, prolonged standing in a warm environment, or dehydration), but triggers may not be immediately apparent. In some older men, the same reflex response occurs when turning the neck

generates pressure in the carotid area (i.e., carotid sinus syndrome). Susceptibility increases after the use of diuretics or vasodilators, including alcohol, marijuana, and alpha-blockers. The vasovagal reaction can occasionally be triggered while a person is sitting or lying down (e.g., during medical procedures).

In the prodromal phase, which usually lasts for 30 seconds or longer, sympathetic efferent activation and epinephrine release cause skin vasoconstriction, with facial pallor, diaphoresis, and piloerection, and nausea and gastric discomfort are common. These signs and symptoms of autonomic activation are an important anamnestic clue because they are present in vasovagal syncope but not in efferent baroreflex failure. At the time of syncope, sympathetic efferent activity ceases and norepinephrine levels fail to increase, but there is marked epinephrine release from the adrenal medulla, which is not under baroreflex control (Fig. 2). Hypotension causes hypoperfusion of the brain (including the retina) and sensations of lightheadedness, visual dimming, and muffled sounds. Hyperventilation, which begins in the prodromal phase, leads to hypocapnia, which constricts cerebral vessels and exacerbates the decrease in cerebral blood flow.[41] Vasopressin is released (Fig. 2), and high levels of circulating vasopressin contribute to facial pallor and the sensation of nausea. Plasma renin levels may also increase, probably through the renal pressor receptors.

Although direct vagal measurements in humans are not possible, muscarinic blockade with atropine prevents bradycardia during vasovagal syncope, supporting its vagal origin. Sympathetic withdrawal further adds to the lengthening of the heartbeat intervals, which is variable, ranging from milliseconds to more than 30 seconds of sinus arrest[42] (Fig. 3), sometimes prompting the use of pacemakers. Atropine prevents bradycardia but not syncope, underscoring the crucial role of vasodilatation. Parasympathetic activation may contribute to the vasodilatation through endothelial nitric oxide release.[43]

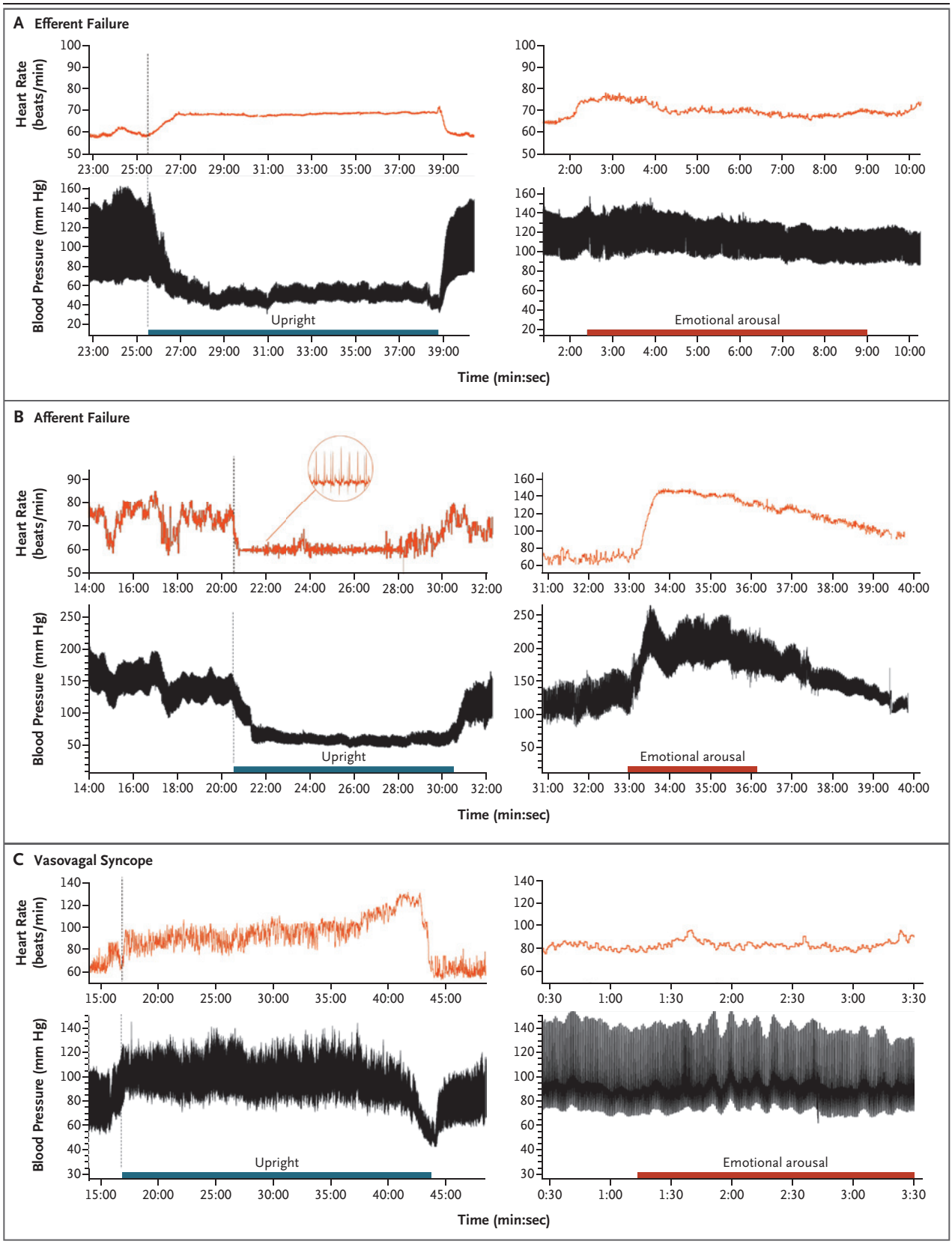
Figure 3 (facing page). Blood Pressure and Heart Rate in Patients with Baroreflex Dysfunction.

Panel A shows continuous blood-pressure and heart-rate recordings in a 70-year-old man with efferent baroreflex failure. In efferent baroreflex failure, blood pressure is in the hypertensive range when the patient is supine, and it falls immediately when the patient is upright, with minimal tachycardia. Blood pressure returns to baseline as soon as the patient returns to the supine position. Emotional arousal has no notable effect on heart rate or blood pressure. In Panel B, continuous blood-pressure and heart-rate recordings show afferent baroreflex failure in a 28-year-old woman. In this condition, blood pressure is unstable in all positions, and when the patient is upright, the heart rate slows. This patient has a pacemaker programmed to provide electrical stimulation only when the heart rate falls to 60 beats per minute or less (inset, showing pacemaker rhythm on electrocardiography). Blood pressure returns to baseline values on the patient's return to the supine position. Blood pressure and heart rate increase with emotional arousal and are markedly exaggerated owing to unrestrained sympathetic outflow. In Panel C, the recordings show functional baroreflex dysfunction (vasovagal syncope) in a 22-year-old woman. In cases of vasovagal syncope, the initial heart-rate and blood-pressure responses to an upright tilt are normal, followed by a sudden onset of bradycardia and hypotension, which are rapidly reversible on the patient's return to the supine position. The recording shows a typical cardioinhibitory response. Although vasodilatation is a constant feature, the slowing of the heart ranges from a few milliseconds (vasodepressor) to prolonged sinus arrest (cardioinhibitory). Blood pressure and heart rate remain unchanged during emotional arousal.

POSTURAL TACHYCARDIA SYNDROME

Postural tachycardia syndrome is characterized by marked tachycardia in the standing position, with no fall in blood pressure but with symptoms of sympathetic activation (palpitations, chest pain, shortness of breath, and anxiety).[18] The prevalence of this syndrome is high among young white women, the demographic group with the lowest orthostatic tolerance. Some subtle abnormalities in the baroreflexes have been reported, but data on their natural history are limited. Although no proposed mechanism applies to all affected patients, hyperventilation,[44] physical deconditioning or cardiac atrophy,[45] abnormal intravascular volume control, and defects in the cardiac norepinephrine transporter[46] may all play a role. The syndrome frequently coexists with joint hypermobility syndrome (Ehlers–Danlos syndrome, type III).[47]

Some patients have a stresslike neurohormonal response when upright, with high levels of epinephrine and norepinephrine in plasma (hyperadrenergic postural tachycardia syndrome). Underscoring the heterogeneous nature of the disorder, mild distal small-fiber neuropathies have also been reported (neuropathic postural



tachycardia syndrome). No correlation exists between the intensity of symptoms and the heart rate, and reducing tachycardia often does not alleviate symptoms.[48] Psychological stress may contribute to the hyperadrenergic phenotype. Increased anxiety and heightened somatic vigilance are not uncommon.[49]

The postural tachycardia syndrome is diagnosed when symptoms occur within 10 minutes after the patient has assumed an upright position, with an unexplained, sustained rise in the heart rate of 30 beats per minute (40 beats per minute in children).[18] The diagnosis is precluded by other findings that explain the tachycardia (e.g., fever, anemia, hyperthyroidism, or the use of diuretics, vasodilators, stimulant or sympathomimetic agents, norepinephrine-reuptake inhibitors, or β-adrenergic agonists). A related disorder is inappropriate sinus tachycardia, causing a resting heart rate above 100 beats per minute, with symptoms and palpitations that are thought to be due to faster pacing at the sinus node, β-adrenergic hypersensitivity, decreased parasympathetic activity, or a combination of these factors.[12]

OTHER DISORDERS WITH HEIGHTENED SYMPATHETIC ACTIVITY

Takotsubo cardiomyopathy is caused by abnormally increased sympathetic activity. Patients with this disorder are usually postmenopausal women, with neurologic or psychiatric disorders in more than 50% of patients but without clinically significant obstructive coronary artery disease.[50] Symptoms mimic an acute coronary syndrome, with acute chest pain, dyspnea, and sometimes syncope. Takotsubo cardiomyopathy can be triggered by physical or emotional stimuli, including acute pain and severe emotional distress. Anecdotally reported causes include pheochromocytoma and afferent baroreflex failure. Echocardiography shows ballooning of the left ventricle, resembling a Japanese octopus trap (*takotsubo*) with a narrow neck and round bottom. In the acute phase, catecholamine levels are high and heart-rate variability is reduced, suggesting a state of baroreflex imbalance. Rates of in-hospital shock and death among patients with takotsubo cardiomyopathy are similar to the rates among those with acute coronary syndromes.[50]

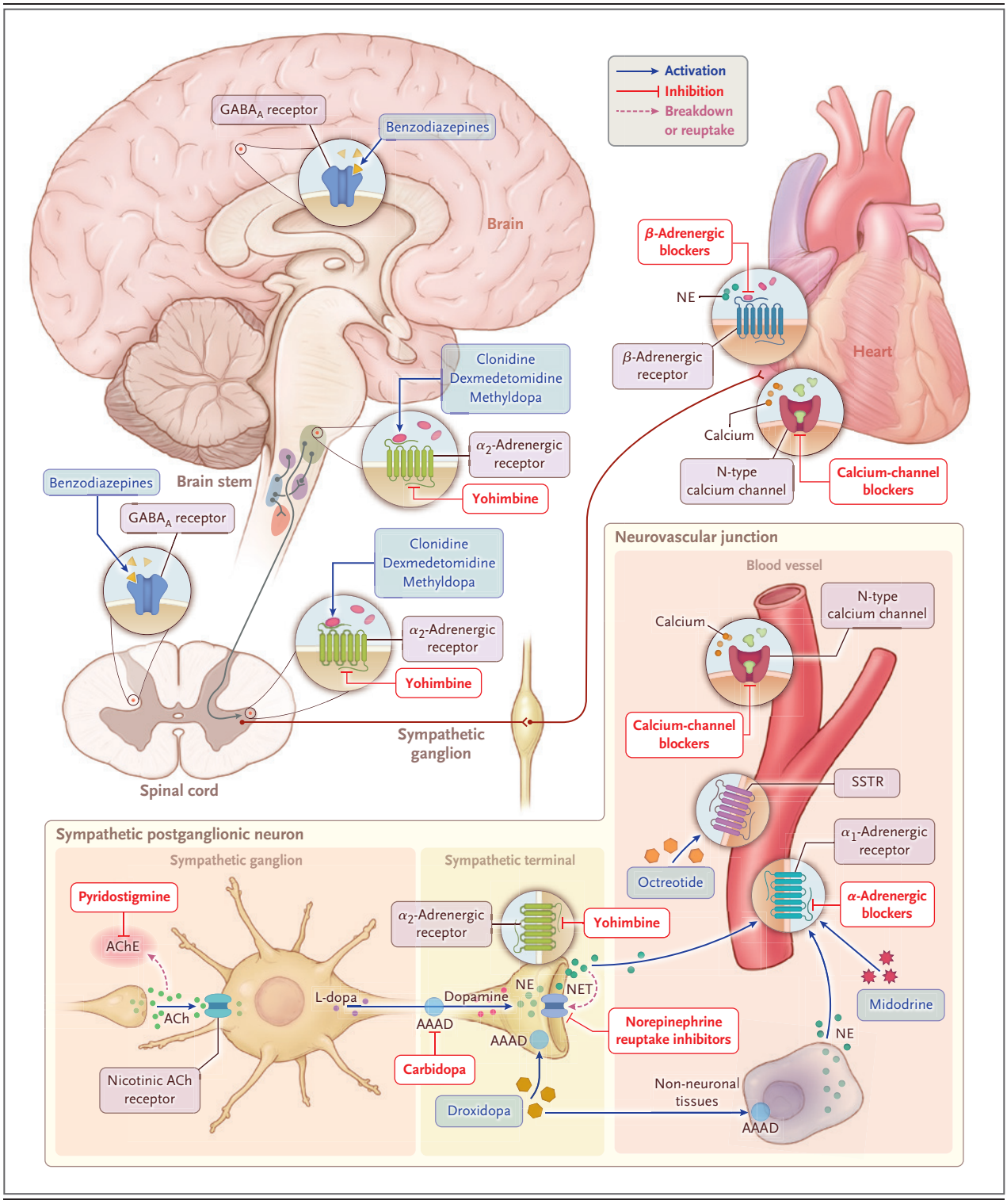
Figure 4 (facing page). Main Sites of Action of Pharmacologic Treatments for Afferent and Efferent Baroreflex Failure.

Pharmacologic treatments for neurogenic orthostatic hypotension act mainly at the level of the sympathetic postganglionic neurons. Pyridostigmine, midodrine, and droxidopa enhance sympathetic vasoconstriction through different mechanisms. By inhibiting the enzyme acetylcholinesterase (AChE), pyridostigmine augments cholinergic neurotransmission at the sympathetic and parasympathetic ganglia. Midodrine is converted to an α_1-adrenergic receptor agonist, causing vasoconstriction. Droxidopa is a synthetic precursor that is converted to norepinephrine (NE), the main postganglionic sympathetic neurotransmitter, causing vasoconstriction. Yohimbine, a blocker of central and peripheral α_2-adrenergic receptors, can enhance vasoconstriction in patients with preganglionic efferent baroreflex lesions. Octreotide, a synthetic somatostatin analogue that activates somatostatin receptors (SSTRs) and causes intense vasoconstriction of splanchnic blood vessels, has been used for postprandial hypotension. Fludrocortisone (not shown), a mineralocorticoid agonist, increases sodium and water reabsorption in renal tubules, thus expanding extracellular fluid volume. Pharmacologic treatments for afferent baroreflex failure combine centrally acting agents, including benzodiazepines, which activate γ-aminobutyric acid (GABA) receptors at multiple levels within the brain and spinal cord, and α_2-adrenergic agonists such as clonidine, dexmedetomidine, and methyldopa, which act at different regions of the brain and spinal cord. Calcium-channel blockers and α-adrenergic and β-adrenergic blockers can be used to dampen paroxysmal hypertension owing to their vasodilatory and bradycardic effects. Carbidopa, a reversible, competitive inhibitor of aromatic L-amino acid decarboxylase (AAAD), reduces production of dopamine and NE and appears to be useful for lessening blood-pressure variability. NET denotes norepinephrine transporter.

Although most patients survive and regain ventricular function, evidence of excessive sympathetic and blunted parasympathetic responses persists, and episodes may recur.[51]

TREATMENT OF BAROREFLEX DYSFUNCTION

Baroreflex dysfunction should be explained to the patient, and information should be provided about trigger avoidance, salt and water loading, physical training when fitness is low, the use of countermaneuvers at the onset of premonitory symptoms, and the avoidance of falls. In chronic baroreflex disorders, patients can withstand very low blood pressures because of an expanded



autoregulatory range. Symptoms usually appear when the mean blood pressure, when measured at the level of the heart, falls below 75 mm Hg.[52] Milder symptoms may go unrecognized, and in some cases of chronic efferent baroreflex failure, loss of consciousness can occur with little

Table 2. Pharmacologic Treatment of Baroreflex Dysfunction.*

Drug	Dose	Mechanism of Action and Comments	Level of Evidence	Side Effects
For orthostatic and postprandial hypotension				
Midodrine[57]	2.5–15 mg, 2–3 times/day; plasma level of the active metabolite peaks 1–2 hr after a dose; half-life is 3–4 hr	Prodrug converted to α_1-adrenergic receptor agonist; causes vasoconstriction and increase in peripheral vascular resistance, raises blood pressure without increasing heart rate; does not cross blood–brain barrier	1A	Piloerection, pruritus of scalp; can worsen supine hypertension and may cause urinary retention
Droxidopa[58]	100–600 mg, 2–3 times/day; plasma norepinephrine level peaks about 3 hr after a dose; monoexponential decline, with a half-life of 2–3 hr	Converted to norepinephrine by dopa-decarboxylase; more pronounced pressor response in patients with low plasma norepinephrine levels (<200 pg/ml) and those who do not take aromatic L-amino acid decarboxylase inhibitors (e.g., carbidopa or benserazide); efficacy has been evaluated for up to 12 mo; absorption slowed after high-fat or high-calorie meal	1A	Headache; can worsen supine hypertension
Fludrocortisone	0.05–0.2 mg, once/day; little benefit with higher doses	Activates mineralocorticoid receptors, resulting in sodium and water retention; increases blood pressure after 3–5 days of treatment	2B	Hypokalemia and ankle edema, supine hypertension; long-term complications include heart and renal failure and increased risks of hospitalization for any reason and sudden death during sleep
Atomoxetine[25]	10–18 mg, 2 times/day; plasma level peaks 1–2 hr after a dose; plasma half-life is 5.2 hr in patients with active metabolism and 21.6 hr in those with slow metabolism	Norepinephrine-reuptake inhibitor; prolongs bioavailability of norepinephrine at neurovascular junction; more pronounced pressor response in patients with high plasma norepinephrine levels; no long-term studies	2B	Piloerection, insomnia, reduced appetite
Pyridostigmine[59]	30–60 mg, 2–3 times/day; plasma level peaks 2 hr after a dose; half-life of 3–4 hr	Reversible acetylcholinesterase inhibition; enhances ganglionic cholinergic neurotransmission, stimulating release of norepinephrine; pressor effect is small; lowers heart rate; no long-term studies	1B	Increased gastrointestinal motility, urinary frequency, increased salivation, bradycardia
Yohimbine[60]	5.4 mg, 2–3 times/day	Central and peripheral α_2-adrenergic antagonist; more pronounced pressor response in patients with high plasma norepinephrine levels; no long-term studies	2B	Supine hypertension, headache
Acarbose[61]	50–100 mg before meals	Competitive inhibitor of alpha glucosidases in brush border of small intestines; reduces intestinal carbohydrate absorption and insulin-mediated vasodilatation; effective in reducing postprandial hypotension; minimal systemic absorption; no long-term studies	2B	Abdominal bloating, gas
Recombinant erythropoietin[62]	50 units/kg, 2–3 times/wk (subcutaneous injection)	Increases red cells, raises blood pressure, and reduces orthostatic hypotension, partly by binding nitric oxide	2B	Hypertension, influenza-like symptoms
Octreotide[63]	100 μg, 2–3 times/day (subcutaneous injection); half-life of almost 2 hr	Synthetic somatostatin analogue; potent vasoconstrictor of splanchnic vessels; only small studies	2B	Nausea, abdominal cramps, hyperglycemia
Desmopressin	0.05 mg, administered intranasally at nighttime; half-life of 1–2 hr	Synthetic vasopressin V_2 agonist; prevents water excretion, reduces nocturia, and increases blood pressure in the morning; only small studies	2B	Severe hyponatremia

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Indomethacin, ibuprofen, and caffeine	Dose varies	Only small studies, with inconsistent results	3B	Side effects vary
For supine (nocturnal) hypertension				
Sildenafil	25 mg at bedtime; plasma level peaks 60 min after a dose; half-life of 4 hr	Phosphodiesterase inhibitor	2B	Increases nocturnal natriuresis and can worsen orthostatic hypotension the next morning
Nitroglycerin	0.1 mg/hr (patch) at bedtime	Nitric oxide donor	2B	Increases nocturnal natriuresis and can worsen orthostatic hypotension the next morning
Nebivolol	5 mg at bedtime; plasma level peaks after 0.5–2 hr in patients with rapid metabolism and after 3 to 6 hr in those with slow metabolism	β-1 blocker; enhances vascular nitric oxide production	2B	Increases nocturnal natriuresis and can worsen orthostatic hypotension the next morning
Losartan	50 mg at bedtime; plasma level of active metabolite peaks in 3–4 hr	Type 1 angiotensin receptor antagonist	2B	Can worsen orthostatic hypotension the next morning; dry cough, rhinorrhea
Clonidine	0.1 mg at bedtime; plasma level peaks in 3–5 hr; half-life of 12–16 hr	α_2-Adrenergic agonist	2B	Can worsen orthostatic hypotension the next morning; gastroparesis, insomnia
Nifedipine	30 mg at bedtime (controlled-release tablet); plasma level peaks in 2.5–5 hr; half-life of 7 hr	Calcium-channel blocker; risk-benefit ratio should be individually assessed; medication should be administered only at bedtime	2B	Increases nocturnal natriuresis and can worsen orthostatic hypotension the next morning
For afferent baroreflex failure				
Diazepam	2.5–10 mg as needed; plasma level peaks 30–90 min after a dose; half-life 30–56 hr	GABA agonist; used to abort hypertensive episodes	4	Short term: increased risk of respiratory depression, urinary retention; long term: depression, addiction
Clonidine[34]	0.05–0.2 mg (oral)	α_2-Adrenergic agonist; used to abort hypertensive episodes	3B	Short term: gastroparesis and ileus; rebound hypertension can occur on withdrawal
Dexmedetomidine	0.2–0.4 μg/kg/hr, IV infusion	α_2-Adrenergic agonist; used to abort hypertensive episodes	3B	Short term: gastroparesis and ileus; rebound hypertension can occur on withdrawal
Methyldopa	250 mg (oral)	α_2-Adrenergic agonist; used to abort hypertensive episodes	3B	Short term: gastroparesis and ileus; rebound hypertension can occur on withdrawal
Carbidopa[39]	100–200 mg, 3 times/day	Reversible competitive inhibition of dopa-decarboxylase; blocks synthesis of dopamine and norepinephrine; reduces catecholamine-induced episodes of hypertension or retching	1B	Mild increase in gastrointestinal motility
Metoprolol	100–400 mg/day	Blockade of β-adrenergic receptors	3B	Short term: can worsen or unmask orthostatic hypotension and cause rebound hypertension
Prazosin	5–20 mg/day	Blockade of α-adrenergic receptors	3B	Short term: can worsen or unmask orthostatic hypotension and cause rebound hypertension

* GABA denotes γ-aminobutyric acid, and IV intravenous.

awareness, particularly in patients with cognitive deficits.[53] Treatment is aimed at preventing severe hypotension that might result in syncope. Discontinuing or reducing the dose of aggravating drugs (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and sleeping with the head of the bed elevated, to lower blood pressure and reduce overnight diuresis, are effective.[54] Abdominal binders target the splanchnic circulation and increase blood pressure.[55] Rapidly drinking 500 ml of water raises blood pressure as a result of an osmopressor sympathetic reflex and temporarily alleviates symptoms of orthostatic hypotension.[56]

Pharmacologic treatment of neurogenic orthostatic hypotension combines intravascular volume expansion and vasoconstrictor drugs (Fig. 4 and Table 2). Because orthostatic hypotension and supine hypertension typically coexist, the pharmacologic treatment of one usually exacerbates the other. Fludrocortisone induces an expansion of extracellular fluid volume, raising blood pressure. After approximately 2 weeks, plasma volume returns to normal (mineralocorticoid escape), but the pressor effect persists. Long-term use of fludrocortisone in high doses increases the risks of heart failure, renal fibrosis,[64] sudden unexpected death during sleep,[65] and hospitalization for any reason.[66] Pressor agents, such as the α-adrenergic agonist midodrine and the norepinephrine precursor droxidopa, are short-acting and relatively safe. The pressor response to droxidopa depends on the extent of postganglionic sympathetic neuronal loss and denervation supersensitivity to adrenergic agents.[24] Norepinephrine-reuptake inhibitors, such as atomoxetine, have a pressor effect when the peripheral sympathetic neurons are intact, in preganglionic or premotor sympathetic lesions such as multiple-system atrophy.[25] Patients with severe supine hypertension may need additional treatment with antihypertensive agents (Table 2), but such agents may worsen orthostatic hypotension the morning after administration.[20]

In patients with afferent baroreflex failure, benzodiazepines can dampen the hyperadrenergic states. However, because neurons in the glossopharyngeal nerve also provide sensory input from peripheral chemoreceptors, respiratory drive is often compromised, and benzodiazepines increase the risk of respiratory depression.[67] Other options include centrally acting α_2-adrenergic agonists (e.g., clonidine and dexmedetomidine) and the peripherally acting decarboxylase inhibitor carbidopa, which blocks the synthesis of dopamine and reduces downstream norepinephrine production, blunting catecholamine-induced hypertensive episodes (Fig. 4 and Table 2).[39]

In vasovagal syncope, low blood pressure and bradycardia can linger, and when the patient attempts to stand, loss of consciousness can recur. Reassuring the patient about the benign nature of the condition is important. In recurrent cases triggered by prolonged standing, midodrine[68] can be effective but beta-blockers are not.[12] Controversy surrounds the use of cardiac pacemakers, which may reduce the rate of recurrent cardioinhibitory carotid sinus syndrome.[69] Post hoc analysis of long-term studies showed that dual-chamber pacing may be effective in patients 40 years of age or older who have prolonged, spontaneous heart pauses, suggesting a bradyarrhythmic cause.[70] For patients with the postural tachycardia syndrome, no therapies have been uniformly successful. Recommendations include discontinuing all drugs that cause tachycardia. A regular, progressive exercise training program is probably the most effective approach, and addressing neuropsychological components can be helpful.[49,71]

A large observational study showed improved survival among patients with takotsubo cardiomyopathy who were treated with angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers but not with beta-blockers, for up to 1 year after an acute takotsubo event. These observational findings underscore the need for controlled trials.[13]

CONCLUSIONS

Baroreflex dysfunction is a treatable condition with multiple causes. It is most prevalent in functional disorders, which cause temporary states of autonomic imbalance and in which emotional components often play a role. Neurodegenerative, metabolic, autoimmune, traumatic, or toxic mechanisms can damage the neurons of the baroreflex. Recent developments in research on transthyretin amyloidosis show the potential for halting the progression of and reversing autonomic neuropathy by silencing protein production.[72,73] Similar strategies may work in the synucleinopa-

thies. Detection of efferent baroreflex failure may help identify patients in the initial stages of synuclein-mediated deposition for early disease-modifying treatments when available. In familial dysautonomia, correcting the splicing defect may normalize elongator complex protein 1 levels.[74,75] Whether this will restore afferent baroreflex function remains to be tested.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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