

Four Faces of Baroreflex Failure

Hypertensive Crisis, Volatile Hypertension, Orthostatic Tachycardia, and Malignant Vagotonia

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Background—The baroreflex normally serves to buffer blood pressure against excessive rise or fall. Baroreflex failure occurs when afferent baroreceptive nerves or their central connections become impaired. In baroreflex failure, there is loss of buffering ability, and wide excursions of pressure and heart rate occur. Such excursions may derive from endogenous factors such as stress or drowsiness, which result in quite high and quite low pressures, respectively. They may also derive from exogenous factors such as drugs or environmental influences.

Methods and Results—Impairment of the baroreflex may produce an unusually broad spectrum of clinical presentations; with acute baroreflex failure, a hypertensive crisis is the most common presentation. Over succeeding days to weeks, or in the absence of an acute event, volatile hypertension with periods of hypotension occurs and may continue for many years, usually with some attenuation of pressor surges and greater prominence of depressor valleys during long-term follow-up. With incomplete loss of baroreflex afferents, a mild syndrome of orthostatic tachycardia or orthostatic intolerance may appear. Finally, if the baroreflex failure occurs without concomitant destruction of the parasympathetic efferent vagal fibers, a resting state may lead to malignant vagotonia with severe bradycardia and hypotension and episodes of sinus arrest.

Conclusions—Although baroreflex failure is not the most common cause of the above conditions, correct differentiation from other cardiovascular disorders is important, because therapy of baroreflex failure requires specific strategies, which may lead to successful control. (*Circulation*. 2002;105:2518-2523.)

Key Words: baroreceptors ■ hypertension ■ tachycardia

An arterial reflex that maintains blood pressure homeostasis has been known since ancient times. The first reference to the baroreflex effect might have been noted in ancient Rome, where it was observed that pressing on the arteries of the neck in animals produced sedation.¹ Careful human studies in the 1940s indicated that the carotid sinus area represented one site for the location.²

Physiology

The arterial baroreflex prevents excessive fluctuations of arterial blood pressure. Regulation of the cardiovascular system by the baroreflex involves multiple components of the baroreflex arc.³ As demonstrated in Figure 1, baroreceptors in each carotid sinus send information about distention of the vessel wall to the brain stem via the glossopharyngeal nerve (cranial nerve IX). Other baroreceptors in the aortic arch and the great vessels of the thorax transmit similar information by the vagus nerve (cranial nerve X) to the same brain stem nuclei. Thoracic blood volume is also sensed by low-pressure receptors linked by the vagus nerve to the brain stem. The brain stem structure receiving this information is the *nucleus tractus solitarius* (Figure 1), which lies in the dorsal medulla at the level of the fourth ventricle. The *nucleus tractus solitarius* also receives cortical input derived from environmental stimuli. Neurotransmitters such as

glutamate and nitric oxide released in the *nucleus tractus solitarius* may lead to cardiovascular changes.⁴ The caudal ventrolateral medulla and the rostral ventrolateral medulla are crucial brain stem structures involved in the modulation of sympathetic outflow.⁵⁻⁷ It is well established that afferent nerve traffic from the thorax and abdomen also provides input to central cardiovascular centers after traveling with sympathetic nerves back to the spinal cord and then to medullary cardiovascular control centers.⁸ These afferents are less well understood at the level of clinical presentation and are beyond the scope of this review.

Physiological transduction of stretch is common to many tissues and organs, mediating light touch, hearing, and distention at visceral sites. The carotid sinus itself contains a stretch receptor. It has been proposed that the DEG/ENaC family of cation channels, which are responsible for touch sensation in *Caenorhabditis elegans*, are components of the baroreceptor mechanosensor.⁹ The expression of the γ subunit of ENaC in the fine baroreceptor nerve terminals innervating the aortic arch and carotid sinus is the first indication of the molecular identity of baroreceptor mechanotransduction. The role of this class of channels in baroreceptor function is supported by inhibition of baroreceptor activity with amiloride analogs, which are known to inhibit DEG/ENaC channels. Both β and γ subunits of DEG/ENaC have also been identified in mechanosensory structures in the rat footpad, which are believed to mediate light touch.¹⁰ The

Received January 29, 2002; revision received March 20, 2002; accepted March 21, 2002.

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Presented in part at the American Heart Association Satellite Symposium on Baroflex, Dallas, Tex, November 12, 2000.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000017186.52382.F4

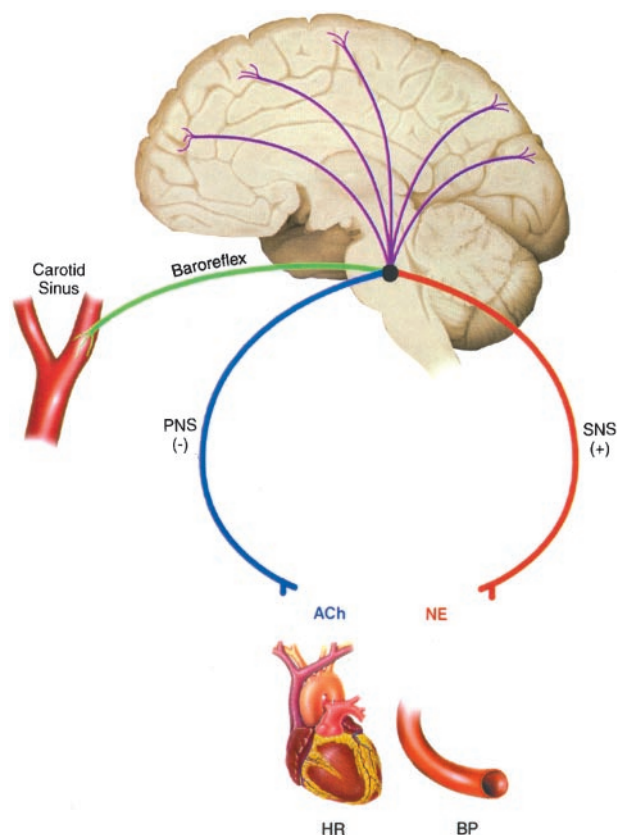


Figure 1. Normal baroreflex. Schematic representation of input from the carotid sinus to *nucleus tractus solitarii* via the glossopharyngeal nerves with additional cortical influences. Also represented is the output from the *nucleus tractus solitarii* to the heart and blood vessels via various sympathetic and parasympathetic nerve fibers. Intact baroreflex function leads to appropriate cholinergic and adrenergic influence on heart rate and blood pressure. PNS indicates parasympathetic nervous system; SNS, sympathetic nervous system; Ach, acetylcholine; NE, norepinephrine; HR, heart rate; and BP, blood pressure.

α subunit of ENaC is also present in osteoblasts, a cell type that responds to mechanical stimulation.¹¹

Problems Identifying Baroreflex Failure

Despite the voluminous data from animal studies and in vitro work, our understanding of the clinical manifestations of baroreflex impairment remains incomplete. There are several reasons for this. First, multiple cranial nerves transmit afferent baroreflex information to the medulla oblongata, including the right and left glossopharyngeal nerves and the right and left vagus nerves.¹² For clinical baroreflex failure to manifest, severe interruption of afferent input must be present. Subtler baroreflex impairment has commonly been described in human subjects with hypertension and in animal models, but usually with limited evidence for altered cardiovascular function in the basal state. It remains unclear how extensive baroreflex impairment must be to produce clinical baroreflex failure or whether impairment must be present in all or only a subset of involved cranial nerves.

Another problem in understanding baroreflex failure is the paucity of reported cases in the world literature. Until recently, there were not referral centers for autonomic disorders where groups of such patients could be studied in detail. Now that such facilities are available, we may expect more detailed elucidation of pathophysiology to emerge from future studies.

An additional level of complexity is the presence of both afferent and efferent nerve traffic in each of the cranial nerves involved in

TABLE 1. Baroreflex Failure Versus Autonomic Failure

Parameter	Autonomic Failure	Baroreflex Failure
Supine hypertension	++	+/-
Labile hypertension	-	+++
Orthostatic hypotension	+++	+/-
Postprandial hypotension	+++	-
Episodic tachycardia	-	+++

baroreflex function. The degree to which efferent nerves suffer collateral damage will no doubt have a significant impact on the clinical presentation of baroreflex lesions. This is particularly true when there is involvement of the vagus nerve.

Confusion also exists in the difference between baroreflex failure and autonomic failure. Some have used these terms interchangeably. But in reality, the cardiovascular manifestations of these two disorders are quite different (Table 1). The presentation of autonomic failure is dominated by orthostatic hypotension, whereas the presentation of acute baroreflex failure often resembles that of pheochromocytoma.

Focus heretofore has been on completeness of interruption of afferent baroreflex nerves in the presence of baroreflex failure. However, clinical studies have provided evidence for asymmetry in central control of cardiovascular function.^{13,14} Over the last two decades, Jannetta and Gendell¹⁵ have described arterial loops impinging on cardiovascular nuclei in the left brain stem as being the cause of unexplained hypertension in some patients. Future studies of baroreflex failure need to address whether left-sided baroreflex input elicits a disproportionate effect on cardiovascular regulation.

Causes of Baroreflex Failure

Abnormalities in the vascular baroreceptors, the glossopharyngeal nerve, their brain stem connections, or interruption of afferent nerves can all potentially lead to baroreflex failure (Table 2). Accidental trauma, trauma either from unilateral or bilateral carotid endarterectomy,^{16,17} or additional surgical therapy for pathology in the relevant anatomic areas, local tumor growth,¹⁸ and brain stem stroke¹⁹ are all recognized causes of baroreflex failure. In addition, patients with a genetic disorder predisposing them to tumors of chromaffin tissue tend to have tumor growth in structures close to the glossopharyngeal nerve and are thus particularly likely to provoke the complication of baroreflex failure. Present advances in surgical techniques of carotid body paraganglioma resection have helped decrease the mortality rates significantly, but the morbidity, especially in regard to postoperative cranial nerve dysfunction, remains high.^{20,21} Genetic linkage to 2 distinct chromosomal loci, 11q13.1 and 11q22.3-q23, has been reported for this autosomal-dominant disorder that is highly penetrant and influenced by genomic imprinting through paternal transmission.²² Radiation therapy of throat carcinoma may also have the side-effect of damage to cranial nerves,²³ and this damage tends to occur after an interval of months or, in some cases, years after the irradiation, perhaps reflecting local fibrosis as the intervening pathophysiology, whereby the nerves are damaged. Also, patients who have received radiotherapy for head and neck cancer may present

TABLE 2. Causes of Baroreflex Failure

Trauma
Surgery (carotid endarterectomy, carotid body tumor resection)
Brainstem stroke
Tumor growth, paragangliomata
Irradiation
Leigh's syndrome
Afferent sensory neuropathy
Genetic (hypertension-bradydactyly syndrome, Groll-Hirschowitz syndrome)

with lightheadedness or syncope attributable to baroreceptor damage.²⁴ A patient with impaired function of the nucleus tractus solitarius with no history of radiation, tumor, or trauma was ultimately found to have Leigh's syndrome.²⁵ Additionally complicating matters, a patient serendipitously taking intermittent clonidine reproducing the picture of baroreflex failure has been recently reported.²⁶ Two genetic disorders that seem to entail baroreflex failure have been described, Groll-Hirschowitz syndrome,²⁷ in which carotid sinus nerve dysfunction, sensory neuropathy, and duodenal diverticula occur, and a syndrome of autosomal-dominant hypertension and brachydactyly with loss of baroreflex buffering.^{28,29}

Clinical Manifestations of Baroreflex Failure

Hypertensive Crisis

The acute form of baroreflex failure is most often encountered in hospital settings, because it requires urgent treatment. Often patients have had surgical intervention, causing a loss of glossopharyngeal or vagus nerve function. Sometimes accidental injuries lead to acute baroreflex failure. If damage is isolated to the afferent limb of the baroreflex, the clinical presentation is severe, unremitting hypertension, tachycardia, and headache. The systolic blood pressure may exceed 300 mm Hg and is typically >250 mm Hg. Symptoms also include diaphoresis, the mechanism of which is not fully understood. Apneic spells may occur, especially in the first 48 hours of the postoperative period. Whether these apneic spells are related to concomitant loss of innervation of the carotid body or in response to narcotic analgesia for control of postoperative pain remains uncertain.

Volatile Hypertension

This is the most commonly encountered presentation of baroreflex failure. It may develop insidiously after a substantial period of time during which baroreflex function gradually declines. Alternatively, hypertensive crisis may evolve over days and weeks into the more chronic volatile hypertension phase. This phase is usually more or less permanent, although the pressor surges moderate over time. These patients display an interrupted afferent baroreflex input from the carotid sinus to the *nucleus tractus solitarius* with accompanied interrupted efferent parasympathetic output to the heart and blood vessels (Figure 2).

Abrupt sympathetic activation characterizes volatile hypertension. Thus, whereas baseline blood pressure may be normal to elevated, marked abrupt increases or surges of blood pressure lasting minutes to hours occur and are accompanied by tachycardia. These pressor surges are elicited by mental or physical stress,³⁰ during which sympathetic outflow is increased,³¹ and are characterized by dizziness or lightheadedness, palpitations, and severe headaches.³² Profuse sweating often occurs. Tremulousness, anxiety, and irritability are typical of these episodes, although in some cases, the irritability may trigger the pressor surge rather than vice versa. Mild and transient elevations in plasma glucose have also occasionally been seen. Intraocular pressure may also increase in baroreflex failure.³³ Plasma norepinephrine may increase to levels >1000 mg/mL, as encountered in pheochromocytoma.^{34,35} Values >2000 pg/mL are occasionally seen. Patients with volatile hypertension can have hypotensive valleys as well as pressor peaks, especially during periods of quiet, sedation, or sleep, when sympathetic outflow is diminished.³⁶

With time, the pressor peaks may attenuate somewhat and the depressor valleys may become a greater problem for the patient, but these changes in the character of baroreflex failure are often played out over many years. Nevertheless, because of the complexity of treating these polar shifts in blood pressure, frequent follow-up of patients is important to make certain they are at an optimal regimen at all times.

Orthostatic Tachycardia

Orthostatic tachycardia, defined as an increase in heart rate by >30 bpm from the supine to upright position, is one of the most common findings among patients referred to tertiary centers with complaints

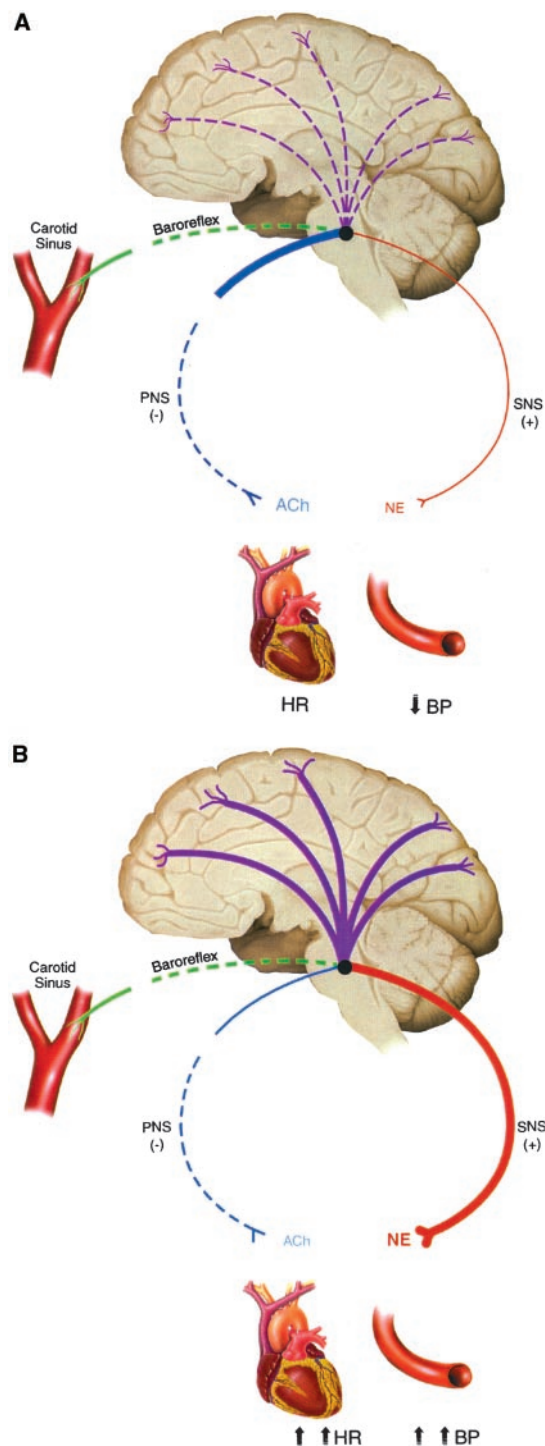


Figure 2. Baroreflex failure. Representation of interrupted afferent baroreflex input from carotid sinus to *nucleus tractus solitarius* with accompanied interrupted efferent parasympathetic output to heart and blood vessels. A, Quiet or resting state with less than normal cortical input resulting in diminished sympathetic efferent activity accompanied by lack of efferent parasympathetic activity. This causes a small decrease in blood pressure with no change in heart rate. B, Active or stressful state with more than normal cortical input resulting in increased sympathetic activity accompanied by lack of efferent parasympathetic activity. This results in a large increase in heart rate and blood pressure. Abbreviations as in Figure 1.

of orthostatic intolerance. Most patients referred for orthostatic tachycardia have neuropathic postural tachycardia syndrome³⁷ or some other cause for their symptoms rather than baroreflex failure. But this syndrome is also occasionally a presentation of clinical baroreflex impairment. In some cases, it may primarily reflect interruption of efferent right vagus nerve activity, leading to a loss of parasympathetic input to the sinus node, with a consequent increase in heart rate. In other cases, mild sympathetic activation may occur with stress and provoke tachycardia disproportionate to the increase in blood pressure. Occasionally, patients presenting with orthostatic tachycardia will ultimately progress to the volatile hypertension form of baroreflex failure. Other patients have remained stable for a prolonged period of time.

Malignant Vagotonia

Severe bradycardia and asystole attributable to increased parasympathetic tone are rarely encountered in baroreflex failure. More commonly, lesions lead to complete or near-complete destruction of afferent baroreflex input, producing denervation of the heart and cardiovascular system and tachycardia.

Nevertheless, patients with selective baroreflex failure (Jordan syndrome) possess interrupted afferent baroreflex input from the carotid sinus to the *nucleus tractus solitarius* with intact efferent sympathetic and parasympathetic output to the heart and blood vessels (Figure 3). They display malignant vagotonia with hypotension, bradycardia, and asystole.³⁸ Along with the hypertensive episodes encountered in the other forms of baroreflex failure, patients with this form may have episodes of hypotension with a systolic pressure <50 mm Hg. Accompanying symptoms include fatigue and dizziness, with possible progression to frank syncope. The most severe episodes tend to occur during early morning sleep. Episodes have also occurred after intravenous nitroprusside, sublingual nitroglycerin, and the stress of neurosurgery. Also observed in these patients are periods of asystole during rest, lasting for 20 seconds or more, mandating the placement of a cardiac pacemaker.

Differential Diagnosis of Baroreflex Failure

Because of the protean manifestations of baroreflex failure, the differential diagnosis can be extensive (Table 3). The most important consideration is usually pheochromocytoma, a condition that may mimic baroreflex failure in many ways, including impaired baroreceptor function.³⁹ In the usual situation, the diagnosis of baroreflex failure emerges from an unsuccessful work-up for pheochromocytoma. Other entities from which it must be distinguished include panic attack, generalized anxiety disorder,⁴⁰ migraine, pure autonomic failure,⁴¹ hyperthyroidism, alcohol withdrawal, and drug use (eg, amphetamines or cocaine). Renovascular hypertension frequently presents with volatility and brittleness and may particularly mimic baroreflex failure. There is a long list of entities that can produce orthostatic intolerance,^{42,43} and an equally long list of disorders that can present with bradycardia and syncope.⁴⁴

Despite the long differential diagnosis, key features of the history and examination of the patient with baroreflex failure make it possible to make the diagnosis. The most important finding is excessive excursion of heart rate during normal daily activities (confirming autonomic control of heart rate), coupled with absent bradycardia in response to a pressor such as phenylephrine or absent tachycardia in response to a depressor such as nitroprusside. In practice, the history of prior trauma exposure is usually the most important consideration in suspecting the diagnosis of baroreflex failure.

Therapy of Baroreflex Failure

The primary goal of therapy of patients with baroreflex failure is to reduce the frequency and magnitude of life-threatening surges in blood pressure and heart rate. A secondary goal of therapy is to attenuate symptomatic hypotensive episodes. In patients with selective baroreflex failure, pacemaker placement may be necessary. Innovative therapies have included a proposed bionic baroreflex system.⁴⁵

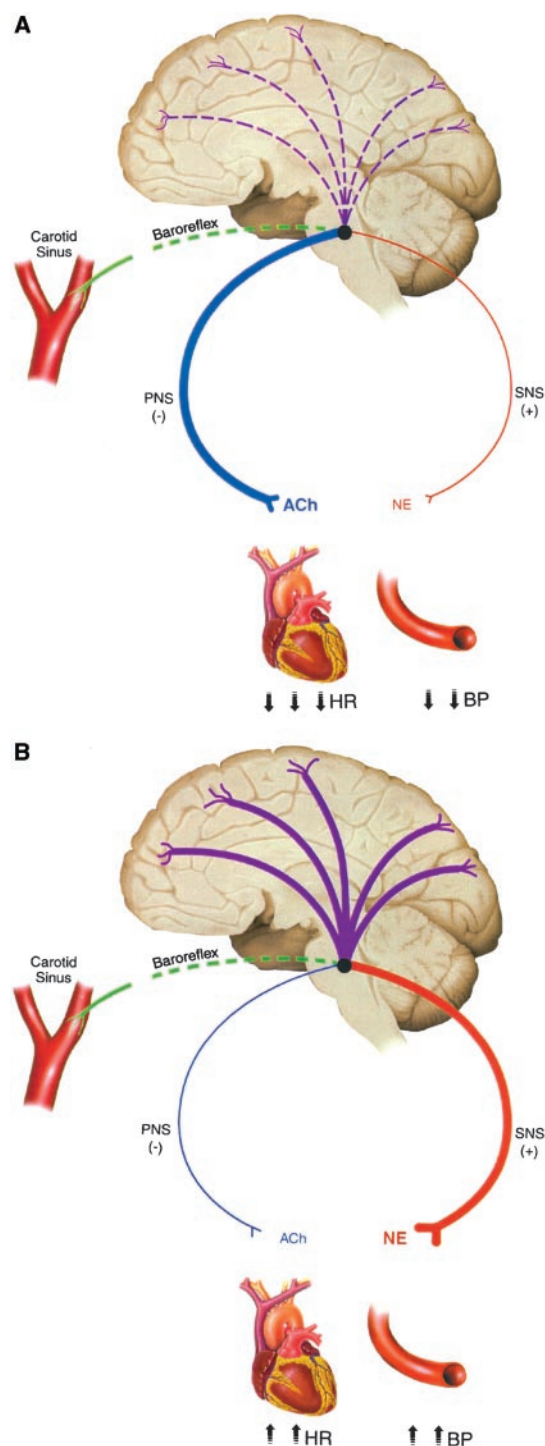


Figure 3. Selective baroreflex failure. Representation of interrupted afferent baroreflex input from carotid sinus to *nucleus tractus solitarius* with intact efferent sympathetic and parasympathetic output to the heart and blood vessels. The intact efferent parasympathetic limb is the crucial difference between this condition and that represented in Figure 2. A, Quiet or resting state with less than normal cortical input resulting in increased efferent parasympathetic activity and decreased efferent sympathetic activity. This results in a marked decrease in heart rate and large decrease in blood pressure. B, Active or stressful state with more than normal cortical input resulting in diminished efferent parasympathetic activity and increased efferent sympathetic activity. This results in a large increase in both heart rate and blood pressure. Abbreviations as in Figure 1.

TABLE 3. Differential Diagnosis

Pheochromocytoma
Syncope
Paroxysmal tachycardia
Orthostatic intolerance
Pure autonomic failure
Hyperthyroidism
Renovascular hypertension
Medications/drugs
Mast cell activation disorder
Carcinoid
Intracranial lesions
Alcohol withdrawal
Cerebral vasculitis
Page syndrome
Pseudopheochromocytoma
Migraine
Psychological disorders (panic attack, generalized anxiety disorder)

The pharmacological treatment of choice for blood pressure surges is clonidine (Table 4). Clonidine acts centrally and peripherally to attenuate sympathetic activation and limit the extent to which pressor surges can occur. The α -adrenoreceptor blocker phenoxybenzamine has been relatively unsuccessful in reducing the frequency of pressor surges, although the magnitude of surges (but not tachycardia) is controlled.⁴⁶ It may be that the sedative effects of the α_2 -adrenoreceptor agonists such as clonidine may assist the patients in preventing hypertensive episodes. In the case of clonidine, the inconvenience of frequent oral dosing can be avoided by using patch preparations. Most patients with baroreflex failure will require significant doses, whether oral or transdermal. To reduce the possibility of loss of a patch with consequent provocation of clonidine withdrawal, we sometimes use two No. 1 patches, one placed on Sunday and a second placed on Wednesday of each week, staggered this way to lessen the likelihood of inadvertent, complete discontinuation of clonidine.

In patients who have been well controlled for months to years, it is sometimes possible to modify treatment regimens from α_2 -adrenoreceptor agonists to benzodiazepines, such as diazepam. Although relatively high doses of benzodiazepines are required, patients often tolerate this extremely well.

Finally, because of the excessive levels of plasma norepinephrine encountered in this patient population, agents that prevent release of norepinephrine may also be helpful. Guanadrel, which inhibits the release of norepinephrine from peripheral sympathetic nerve end-

TABLE 4. Treatment of Baroreflex Failure

For blood pressure reduction
Clonidine 0.1 mg TID to 0.2 mg every 2 h
Guanadrel 10 mg BID to 20 mg TID
Guanethidine 10 mg QD to 30 mg QD
Diazepam 5 mg BID to 10 mg TID
For blood pressure elevation
Fludrocortisone 0.05 mg BID to 0.1 mg BID
Yohimbine 1.35 mg to 5.4 mg as needed
Dietary Salt
For prevention of bradycardia
Cardiac pacemaker

TABLE 5. Drugs Contraindicated in Baroreflex Failure

Tricyclic antidepressants*
Amphetamines
Monoamine oxidase A inhibitors
Cocaine
Prednisone
Tyramine-containing food and beverage

*Peripheral effect would be expected to raise blood pressure and heart rate; central effect would be expected to lower blood pressure and heart rate.

ings,⁴⁷ is particularly effective. It has a short half-life and therefore is very useful in instituting therapy. It is excluded from the central nervous system so that no central side effects may occur. Because of a longer half-life, 5 days at its site of action, guanethidine may provide a more efficacious and easy coverage regimen for the long-term. Like guanadrel, guanethidine is excluded from the central nervous system, which limits its side effects. Occasionally, patients experience diarrhea on moderate to high doses of guanethidine.

In some patients, prevention of hypotension is also required. This is quite different, because the hypotensive episodes are usually short lived and most agents have a longer half-life than the usual duration of these spells. Fludrocortisone may still be the best way to treat this problem, because patients with baroreflex failure may have reduced plasma volume. Generally, low doses are sufficient. Fludrocortisone requires time for its full effect, thus its dosage should not be increased more frequently than at 2-week intervals. In highly exceptional cases, where excessive α_2 -agonist effect has been elicited, with consequent prolonged hypotension, administration of the α_2 -adrenoreceptor antagonist, yohimbine, at modest doses (1 to 5 mg) will usually lead to improvement.

Finally, if severe bradycardia (<40 bpm) is detected or if the patient has concomitant evidence of significant heart block, the placement of a pacemaker may be necessary. This may free the clinician to use a broader range of pharmacotherapy to manage the pressor and depressor manifestations of the disease.

In addition to issues of therapy, avoidance of agents that may be harmful in baroreflex failure is also an important part of management (Table 5). Because the pressor surges depend on high synaptic norepinephrine concentrations, anything that causes those concentrations to be higher is generally contraindicated. Because 80% to 90% of synaptic norepinephrine is removed by the norepinephrine transporter,⁴⁸ blockade of this transporter by tricyclic antidepressants will potentiate the pressor effect of sympathetic activation. This may be particularly important in the heart, where up to 90% of norepinephrine removal is mediated by the norepinephrine transporter. Likewise, agents that reduce the breakdown of norepinephrine, such as monoamine oxidase inhibitors, should be avoided. Although not systematically studied, it would seem more appropriate to treat depression in patients with baroreflex failure with selective serotonin reuptake inhibitors than with tricyclic antidepressants or monoamine oxidase inhibitors. Other agents whose ultimate effect is to enhance norepinephrine availability, such as amphetamines and cocaine, should also be avoided. Although yohimbine has occasionally been used in situations where the effect of α_2 -agonists have led to excessive hypotension, in other circumstances it is likely to result in a profound pressor response and should therefore be avoided.

Conclusion

Baroreflex failure resembles many more common disorders, and its diagnosis is frequently missed. Baroreflex failure should be considered in the differential diagnosis of hypertensive crisis, volatile hypertension, pheochromocytoma, poorly controlled hypertension,⁴⁹ orthostatic tachycardia, headache, hyperhidrosis, bradycardia, and syncope. Important historical clues include medical, surgical, family, and pharmaceutical histories. History is usually crucial to making the

diagnosis. Baroreflex failure is particularly likely to develop in families with chromaffinomas, in patients after carotid artery surgery, in patients after throat irradiation, and in patients with neck injury. Correct diagnosis is important, because therapy in baroreflex failure is specific and usually quite effective.

Acknowledgments

This work was supported in part by National Institutes of Health grants RR00095, PO1 HL56693, and 1U01NS33460, NASA grant NAS 9-19483, and a grant from the Nathan Blaser Shy-Drager Research Program.

References

- Persson PB. History of arterial baroreceptor reflexes. In: Persson PB, Kirchheim HR, eds. *Baroreceptor Reflexes: Integrative Functions and Clinical Aspects*. Berlin, Germany: Springer-Verlag; 1991:1–8.
- Lampen H, Kezdi P, Koppermann E, et al. Experimenteller entzuegelungshochdruck bei arterieller hypertonie. *Z Kreislaufforschung*. 1949;38:577–592.
- Kezdi P. Baroreceptors in normotension. *Prog Brain Res*. 1977;47:35–42.
- Talman WT. Kynurenic acid microinjected into the nucleus tractus solitarius of rat blocks the arterial baroreflex but not responses to glutamate. *Neurosci Lett*. 1989;102:247–252.
- Sved AF, Ito S, Madden CJ. Baroreflex dependent and independent roles of the caudal ventrolateral medulla in cardiovascular regulation. *Brain Res Bull*. 2000;51:129–33.
- Taylor DG, Gebber GL. Baroreceptor mechanisms controlling sympathetic nervous rhythms of central origin. *Am J Physiol*. 1975;228:1002–1013.
- Chapleau MW, Abboud FM. Introduction. In: Chapleau MW, Abboud FM, eds. *Neuro-Cardiovascular Regulation: From Molecules To Man*. New York, NY: The New York Academy of Sciences; 2001:xiii–xxii.
- Montano N, Cogliati C, da Silva VJ, et al. Effects of spinal section and of positive-feedback excitatory reflex on sympathetic and heart rate variability. *Hypertension*. 2000;36:1029–1034.
- Drummond HA, Price MP, Welsh MJ, et al. A molecular component of the arterial baroreceptor mechanotransducer. *Neuron*. 1998;21:1435–1441.
- Drummond HA, Abboud FM, Welsh MJ. Localization of β and γ subunits of ENaC in sensory nerve endings in the rat foot pad. *Brain Res*. 2000;884:1–12.
- Kizer N, Guo X, Hruska K. Reconstitution of stretch-activated cation channels by expression of the α -subunit of the epithelial sodium channel cloned from osteoblasts. *Proc Natl Acad Sci U S A*. 1997;94:1013–1018.
- Fagius J, Wallin BG, Sundlöf G, et al. Sympathetic outflow in man after anaesthesia of the glossopharyngeal and vagus nerves. *Brain*. 1985;108:423–438.
- Hilz MJ, Dütsch M, Perrine K, et al. Hemispheric influence on autonomic modulation and baroreflex sensitivity. *Ann Neurol*. 2001;49:575–584.
- Zamrini EY, Meador KJ, Loring DW, et al. Unilateral cerebral inactivation produces differential left/right heart rate responses. *Neurology*. 1990;40:1408–1411.
- Jannetta PJ, Gendell HM. Clinical observations on etiology of essential hypertension. *Surg Forum*. 1979;30:431–432.
- Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke*. 1998;29:554–562.
- Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. *Surgery*. 1980;88:575–580.
- DeToma G, Nicolanti V, Plocco M, et al. Baroreflex failure syndrome after bilateral excision of carotid body tumors: an underestimated problem. *J Vasc Surg*. 2000;31:806–810.
- Phillips AM, Jardine DL, Parkin PJ, et al. Brain stem stroke causing baroreflex failure and paroxysmal hypertension. *Stroke*. 2000;31:1997–2001.
- Jansen JC, Van den Berg R, Kuiper A, et al. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer*. 2000;88:2811–2816.
- Netterville JL, Reilly KM, Robertson D, et al. Carotid body tumors: a review of 30 patients with 46 tumors. *Laryngoscope*. 1995;105:115–126.
- Milunsky J, DeStefano AL, Huang X, et al. Familial paragangliomas: linkage to chromosome 11q23 and clinical implications. *Am J Med Genet*. 1997;72:66–70.
- Robertson RM. Baroreflex failure. In: Robertson D, Low PA, Polinsky RJ, eds. *Primer on the Autonomic Nervous System*. New York, NY: Academic Press; 1996:197–201.
- Shapiro MH, Ruiz-Ramon P, Fainman C, et al. Light-headedness and defective cardiovascular reflexes after neck radiotherapy. *Blood Press Monit*. 1996;1:81–85.
- Biaggioni I, Whetsell WO, Jobe J, et al. Baroreflex failure in a patient with central-nervous-system lesions involving the nucleus-tractus-solitarii. *Hypertension*. 1994;23:491–495.
- Tellioglu T, Oates JA, Biaggioni I. Munchausen's syndrome presenting as baroreflex failure. *N Engl J Med*. 2000;343:581.
- Hirschowitz BI, Groll A, Ceballos R. Hereditary nerve deafness in 3 sisters with absent gastric motility, small bowel diverticulitis and ulceration and progressive sensory neuropathy. *Birth Defects Orig Art Ser*. 1972;8:27–41.
- Jordan J, Toka HR, Heusser K, et al. Severely impaired baroreflex-buffering in patients with monogenic hypertension and neurovascular contact. *Circulation*. 2000;102:2611–2618.
- Schuster H, Wienker TF, Toka HR, et al. Autosomal dominant hypertension and brachydactyly in a Turkish kindred resembles essential hypertension. *Hypertension*. 1996;28:1085–1092.
- Kuchel O, Cusson JR, Larochelle P, et al. Posture- and emotion induced severe hypertensive paroxysms with baroreceptor dysfunction. *J Hypertens*. 1987;5:277–283.
- Bishop VS. Carotid baroreflex control of blood pressure and heart rate in men during dynamic exercise [editorial]. *J Appl Physiol*. 1994;77:491–492.
- Aksamit TR, Floras JS, Victor RG, et al. Paroxysmal hypertension due to sinoaortic baroreceptor denervation in humans. *Hypertension*. 1987;9:309–314.
- Joos KM, Kakaria SK, Lai KS, et al. Intraocular pressure and baroreflex failure. *Lancet*. 1998;351:1704.
- Floras JS, Aylward PE, Victor RG, et al. Epinephrine facilitates neurogenic vasoconstriction in humans. *J Clin Invest*. 1988;81:1265–1274.
- Manger WM, Gifford RW. Catecholamine metabolism: biosynthesis, storage, release, and inactivation. In: Manger WM, Gifford RW, eds. *Clinical and Experimental Pheochromocytoma*. Cambridge, Mass: Blackwell Science; 1996:8–31.
- Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med*. 1993;328:303–307.
- Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med*. 2000;343:1008–1014.
- Jordan J, Shannon JR, Black BK, et al. Malignant vagotonia due to selective baroreflex failure. *Hypertension*. 1997;30:1072–1077.
- Hamada M, Shigematsu Y, Mukai M, et al. Blood pressure response to the valsalva maneuver in pheochromocytoma and pseudopheochromocytoma. *Hypertension*. 1995;25:266–271.
- Smit AJ, Wieling W, Karemaker JM. Clinical approach to cardiovascular reflex testing. In: Smit AJ, ed. *Impaired Baroreflex Function: Diagnosis and Treatment of Orthostatic Hypotension*. Amsterdam, The Netherlands: University of Amsterdam; 1998:17–29.
- Shannon JR, Jordan J, Diedrich A, et al. Sympathetically mediated hypertension in autonomic failure. *Circulation*. 2000;101:2710–2715.
- Jacob G, Shannon JR, Costa F, et al. Abnormal norepinephrine clearance and adrenergic receptor sensitivity in idiopathic orthostatic intolerance. *Circulation*. 1999;99:1706–1712.
- Stewart JM, Weldon A. Reflex vascular defects in the orthostatic tachycardia syndrome of adolescents. *J Appl Physiol*. 2001;90:2025–2032.
- Robertson RM, Medina E, Shah N, et al. Neurally mediated syncope: pathophysiology and implications for treatment. *Am J Med Sci*. 1999;317:102–109.
- Sato T, Kawada T, Shishido T, et al. Novel therapeutic strategy against central baroreflex failure: a bionic baroreflex system. *Circulation*. 1999;100:299–304.
- Robertson D, Hollister AS, Biaggioni I, et al. The diagnosis and treatment of baroreflex failure. *N Engl J Med*. 1993;329:1449–1455.
- Hoffman BB, Carruthers SG. Cardiovascular disorders: hypertension. In: Carruthers SG, Hoffman BB, Melmon KL, et al, eds. *Clinical Pharmacology*. New York, NY: McGraw-Hill; 2000:65–234.
- Esler M, Jennings G, Lambert G, et al. Over-flow of catecholamine neurotransmitters to the circulation: source, fate, functions. *Physiol Rev*. 1990;70:963–985.
- Reis DJ. The brain and hypertension: reflections on 35 years of inquiry into the neurobiology of the circulation. *Circulation*. 1984;70(suppl III):31–45.