Baroreflex Failure as a Late Sequela of Neck Irradiation

Yehonatan Sharabi, Raghuveer Dendi, Courtney Holmes, David S. Goldstein

Abstract—Combined chemotherapy and radiotherapy increase long-term survival in patients with head and neck tumors. Late complications of treatment, however, are being recognized increasingly. Surgery or radiotherapy of the carotid sinuses or brain stem can evoke labile hypertension and orthostatic intolerance from acute or subacute baroreflex failure. Here we report cases in which chronic baroreflex failure appeared to develop as a late sequela of neck irradiation. Three patients referred for autonomic nervous system function testing had labile blood pressure and chronic orthostatic intolerance that developed years after neck irradiation for cancer. In each patient, heart rate remained constant during performance of the Valsalva maneuver, suggesting baroreflex-cardiovagal failure. All 3 patients had virtually zero baroreflex-cardiovagal gain, quantified by interbeat interval–systolic blood pressure relationships after intravenous phenylephrine or nitroglycerine. Ambulatory blood pressure monitoring revealed highly variable blood pressure, with sudden pressor and depressor episodes, a characteristic feature of baroreflex failure. Cardiovagal efferent function, assessed by power spectral analysis of heart rate variability during slow, deep respiration, was normal. Sympathetic noradrenergic efferent function, assessed by cold pressor testing and plasma catecholamine levels during supine rest and orthostasis, was also normal or increased. These findings indicated a primarily afferent lesion. Carotid ultrasonography revealed intimal thickening and atheromatous plaques in all 3 patients. We propose that labile hypertension and orthostatic intolerance can develop as a late sequela of neck irradiation, due to chronic carotid baroreflex failure, which in turn is due to radiation-induced accelerated development of carotid arteriosclerosis. Splinting of carotid sinus mechanoreceptors in rigidified arterial walls would impede detection of alterations in blood pressure and thereby disrupt baroreflex regulation of cardiovagal and sympathetic outflows. (Hypertension. 2003;42:110-116.)

Key Words: baroreflex ▪ irradiation ▪ carotid sinus ▪ autonomic nervous system ▪ hypertension, secondary ▪ norepinephrine ▪ Valsalva maneuver

Treatment with combined chemotherapy and radiotherapy prolongs survival in patients with head and neck tumors. Cellular absorption of ionizing radiation generates toxic free radicals and leads to misrepair of DNA breaks, apoptosis, and cell death. Responses to radiotherapy occur in time frames of hours (nausea, vomiting), days (erythema), weeks (myelosuppression), months (fibrosis), and years (carcinogenesis). Among survivors of the cancer itself, late effects on “bystander” organs such as the thyroid and salivary glands have become increasingly prevalent, with secondary malignancies, infections, and cardiovascular disease increasing morbidity and mortality.1-3

In particular, after neck irradiation, long-term injury occurs commonly in the carotid arteries. Atherosclerotic and thrombotic complications have drawn the most attention.4-7 Among 910 patients who survived at least 5 years after irradiation of head and neck tumors, stroke occurred in ~6% and clinically significant carotid stenosis in 17%.8

Chronic inflammation and fibrosis of carotid arterial walls might lead to “splinting” of carotid sinus baroreceptors. Because these are stretch or distortion receptors, stiffening of the carotid sinus would be expected to lead to decreased gain of the arterial baroreflex.9 Nevertheless, few reports have noted baroreflex failure after neck or brain stem surgery or irradiation.10-12 Here we present 3 cases in which symptomatic baroreflex failure occurred, apparently as a late consequence of neck irradiation.

Because of the important role of the carotid sinus baroreflex in blood pressure homeostasis, acute and subacute failure of the baroreflex produces labile blood pressure, labile hypertension, and orthostatic intolerance. We predicted an analogous clinical picture in patients with chronic baroreflex failure. Carotid baroreceptor afferent nerve traffic tonically restrains sympathetic outflows, and patients with acute baroreflex failure tend to have high plasma levels of norepinephrine, the sympathetic neurotransmitter during standing. Release of sympathetic outflows from baroreceptor restraint would help explain why baroreflex failure does not typically manifest as orthostatic hypotension.13

To verify baroreflex-cardiovagal failure, we analyzed interbeat interval–systolic blood pressure relationships after bolus intravenous injection of phenylephrine and then nitro-
glycerine. Twenty-four-hour ambulatory blood pressure monitoring was used to identify blood pressure lability, a hemodynamic hallmark of baroreflex failure. To test the integrity of the cardiovagal efferent limb of the baroreflex, we conducted power spectral analysis of heart rate variability during slow, deep respiration, and to test the sympathetic noradrenergic limb, we measured blood pressure and plasma levels of catecholamines during orthostasis and blood pressure during the cold pressor test. Finally, to detect carotid atherosclerosis, which could splint carotid arterial baroreceptors and therefore constitute an afferent baroreflex lesion, we evaluated the carotid arteries by ultrasound.

Methods

Subjects

We studied 3 patients who were referred for autonomic nervous system function testing because of labile blood pressure and chronic orthostatic intolerance that developed years after neck irradiation for cancer.

Clinical Laboratory Testing

All of the patients were studied in a fasting state after lying supine for at least 30 minutes. Noninvasive measurements of beat-to-beat blood pressure and heart rate were done simultaneously by using a radial artery tonometric device (Colin 7000, Colin Instruments Co) and a finger pulse photoplethysmographic device (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation). Each patient performed a Valsalva maneuver, according to the following procedure. The patient blew into a plastic tube connected to a sphygmomanometer, maintaining a pressure of 20 to 30 mm Hg for 10 to 12 seconds. Beat-to-beat blood pressure and heart rate were recorded during and after the maneuver.

Orthostatic blood pressure and heart rate changes were recorded while the patient was supine and then after standing for 5 minutes. Blood was drawn from the indwelling intravenous catheter for measurement of plasma levels of catecholamines. Baroreflex-cardiovagal gain was estimated from relationships between interbeat interval and systolic blood pressure during a variety of manipulations. In phase II of the Valsalva maneuver, as systolic blood pressure falls, heart rate increases reflexively. Beat-to-beat systolic blood pressures and interbeat intervals were analyzed during phase II of the Valsalva maneuver, beginning with the peak pressure and ending with the nadir blood pressure. A scatterplot was constructed that related the interbeat intervals to the systolic pressures with a 1-beat delay from the previous heartbeat. Baroreflex-cardiovagal gain was defined by the slope of the regression line of best fit, in units of ms/mm Hg.

Baroreflex-cardiovagal gain was also measured by using the phenylephrine and nitroglycerine injection technique. After a bolus intravenous injection of phenylephrine, blood pressure increases and heart rate decreases reflexively. After a bolus injection of nitroglycerine, blood pressure decreases and heart rate increases reflexively. For phenylephrine injection, the patient was studied after lying supine for at least 30 minutes with an arm intravenous catheter in place. Noninvasive measurements of beat-to-beat blood pressure and heart rate were recorded as described previously. Phenylephrine (50 μg) was injected as an intravenous bolus, followed rapidly by a 5-mL flush of normal saline. The target increase in systolic blood pressure was 20 mm Hg. If the pressure did not increase by this amount, then 100 μg nitroglycerine was injected, with increasing doses until the criterion increase in pressure was attained. Blood was drawn through an arm indwelling venous catheter during supine rest and after 5 minutes of standing for assays of plasma levels of catecholamines.

Power spectral analysis of heart rate variability was conducted at baseline and then during and after slow, deep respiration (6 breaths per minute). Power spectral indices were calculated as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. An increase in high-frequency power during slow, deep respiration is considered a sign of increased cardiovagal activity. For cold pressor testing, the patient was at rest for 10 minutes. Then the left hand up to the wrist was placed in ice water for 1 minute. The patient was asked to report any pain. Blood pressure and heart rate were recorded before, during, and 5 minutes after the procedure. Imaging of the carotid arteries was conducted with high-resolution B-mode ultrasound. Carotid wall and intimal thicknesses were measured, and the carotid lumen was scanned for atheromatous plaques.

Ambulatory blood pressure monitoring was performed in all patients with the use of an oscillometric device (Dynapulse 5000A, Pulsemetric). Blood pressure and pulse rate were measured at 15-minute intervals during the day (7 AM to 10 PM) and at 30-minute intervals during the night (10 PM to 7 AM). The patient was instructed to keep a diary of daily activities and quality of night rest and to return with the device 24 hours later. The monitoring was done on a working day. The patients discontinued antihypertensive medications 2 to 4 days before the monitoring.

Results

Patient Descriptions

Patient 1

A 51-year-old white woman was evaluated for episodes of presyncope during standing. The patient had been healthy until 18, when she contracted Hodgkin’s disease. She was treated with neck irradiation and did well until the age of 26, when she had her thyroid removed for malignancy thought to be a long-term effect of the radiation she had received. She developed a left pleural effusion, presumably from radiation damage. Beginning about 2 years before evaluation, she suffered from bronchial asthma, extrinsic type. A year before evaluation, she underwent a bilateral mastectomy for left breast ductal carcinoma in situ, mainly as a preventive measure. Approximately 24 years after the radiation therapy and 2 months before the evaluation, she developed orthostatic intolerance without loss of consciousness, which was reliably alleviated by sitting down. The patient reported episodes of flushing, particularly over her neck and face, episodes of a racing heart rate, and fluctuating blood pressure. She partially associates these episodes to both emotional and physical stress; however, these episodes could occur for no apparent reason. At the time of the evaluation, her medications were levothyroxine, fluticasone, almeterol, and quinapril (which she stopped taking 4 days before the evaluation). She also reported heat intolerance and exercise intolerance, manifested by lightheadedness and shortness of breath. On physical examination, the patient appeared healthy. She had orthostatic hypotension. Her palms were warm and dry. She had decreased breath sounds and dullness to percussion bilaterally at the bases, especially on the right. Her neurologic examination was normal. Laboratory tests including complete blood count, electrolytes, standard kidney and liver function tests, mineral panel, and urinalysis were within normal limits, with the exception of a serum phosphorus level of 4.4 mg/dL.
Patient 2
A 57-year-old white woman was evaluated for orthostatic intolerance and episodes of lightheadedness after effort. Thirty-two years before these symptoms began, she had been diagnosed with Hodgkin’s disease, was treated with mantle field radiation therapy, and was considered cured. She suffered from several late complications of the radiotherapy, including pericarditis, pleuritis, hypothyroidism, and right coronary and bilateral carotid artery disease. She also developed right and then left breast cancer and underwent mastectomy and adjuvant chemotherapy several years before autonomic evaluation, at which time there was no clinical evidence of metastasis. The patient reported attacks of headaches and times when she felt “low blood pressure” after physical exertion. At the time of the evaluation, her medications were diltiazem, furosemide, enalapril, levothyroxine, and aspirin. On physical examination, she appeared chronically ill but in no distress. She had bilateral carotid bruits and systolic and diastolic heart murmurs. Decreased breath sounds were noted at the left lung base. Laboratory test results were normal, with the exception of a plasma glucose level of 123 mg/dL, serum urea nitrogen of 35 mg/dL, and uric acid of 7.2 mg/dL.

Patient 3
A 58-year-old white man was referred for orthostatic intolerance, dizziness, episodes of presyncope, and labile blood pressure. He suffered from type 2 diabetes and had a history of cigarette smoking. He had been diagnosed with type 2 diabetes 20 years previously. Initially he had been treated with oral hypoglycemic drugs and then with diet and exercise but no medications. During the last 7 years, he was taking insulin at various doses from 0 to 75 U/d. He had no signs of diabetic nephropathy, retinopathy, or neuropathy. At age 54 he was diagnosed with squamous cell carcinoma of the soft palate, which was treated with radiation therapy directed to the tumor, and adjuvant preventive radiotherapy to the neck and upper chest. Radiation-related complications began 4 years after the radiotherapy and included difficulty swallowing, slurred speech, lack of saliva production, and hypothyroidism. The patient reported episodes of headache, tachycardia, profuse sweating over the upper part of the body, and times when he felt that his heart rate and blood pressure were low. He felt that emotional stress could at least partly cause these symptoms. Medications at the time of evaluation included ferrous sulfate, omeprazole, levothyroxine, guaifenesin, and sertraline. On physical examination the patient appeared well. The buccal mucosa was dry. Chest auscultation showed coarse rhonchi and scattered basilar rales. A feeding gastrostomy tube was in place. Laboratory tests were normal, with the exception of a plasma phosphorous level of 4.7 mg/dL and serum glucose of 159 mg/dL. Serum albumin was 3.5 g/dL and sodium, 131 mmol/L.

Clinical Laboratory Results
All of the patients had no change in heart rate during phase II of the Valsalva maneuver (Figure 1). Baroreflex-cardiovagal gain therefore was zero. Values for baroreflex-cardiovagal determined by both the phenylephrine and nitroglycerine injection techniques also were virtually zero (Table 1). All of the patients had a blood pressure overshoot in phase IV of the Valsalva maneuver, though sometimes delayed. Patient 2 had
an increase in blood pressure at the end of phase II; in the other patients, the results were inconsistent. Patients 1 and 3 had unequivocal orthostatic hypotension (Table 2). Patient 2 had an orthostatic decrease in diastolic pressure exceeding 10 mm Hg but also had a concurrent increase in systolic pressure.

All 3 patients had obviously labile and fluctuating blood pressure (Figure 2), quantified by high standard deviations of the blood pressure readings (the upper 90th percentile of the normal population; Table 3). All had episodes of rapid increases in blood pressure >200 mm Hg. Patients 1 and 2 also had increased average heart rate. All 3 patients had episodes of rapid increases and decreases in pulse rate, paralleling the simultaneous blood pressure changes. Patient 1 attributed high blood pressure in the morning to waking up and domestic activities. Patient 2 reported an aggravating conversation that was concurrent with a large increase in blood pressure. Patient 3 noted lightheadedness while driving, at a time when the pulse rate had decreased to 48 beats per minute. All 3 patients, even in retrospect, also had episodes of fluctuating blood pressure and heart rate that were not associated with identifiable precipitants and were asymptomatic.

In Patient 1, plasma norepinephrine levels were normal during supine rest and increased normally during standing (Table 4). Levels of epinephrine and of the norepinephrine metabolite dihydroxyphenylglycol were also approximately normal. Patients 2 and 3 had high plasma norepinephrine levels even during supine rest, with lower than expected proportionate increments in response to standing.

Spectral analysis of heart rate variability showed an increase in high-frequency power during deep respiration (Table 5). In response to the cold pressor test, all patients had clear increases in blood pressure associated with smaller but nevertheless evident increases in heart rate (Table 5). All 3 patients had carotid atheromatous plaques, including at the carotid bifurcation. Carotid ultrasound showed mild bilateral intimal thickening (0.8 mm compared with 0.3 to 0.5 mm in normal subjects) in patients 1 and 2 and marked bilateral thickening (2.1 mm) in patient 3 (Figure 3).

**Discussion**

The present findings introduce the concept of baroreflex failure occurring as a late sequela of neck irradiation. All 3 patients had clear evidence for baroreflex-cardiovagal failure, as assessed by interbeat interval–systolic blood pressure responses to the Valsalva maneuver and by the phenylephrine and nitroglycerine injection techniques. All had symptoms of orthostatic intolerance and signs of labile hypertension that had developed years after undergoing therapeutic irradiation of the neck.

Acute disruption of the carotid arterial baroreflex causes lability of blood pressure, orthostatic intolerance, and symptoms such as headache, palpitations, diaphoresis, and emotional lability resembling acute anxiety or panic. In a study of
500 subjects referred for autonomic evaluation, only 11 were diagnosed with baroreflex failure. The spectrum of the clinical presentation is quite broad. The acute form is characterized by marked hypertensive episodes. The subacute form is characterized by labile blood pressure, orthostatic tachycardia or intolerance, and in cases of “selective” baroreflex failure, malignant vagotonia and severe bradycardia. Causes of acute or subacute baroreflex failure include carotid body tumors, surgery of the glossopharyngeal nerve, and neck irradiation. Regarding the latter, a case report described a patient with baroreflex failure after radiotherapy for naso-pharyngeal carcinoma. Evaluation of this patient revealed clear impairment of carotid body chemoreflexes, implicating direct local effects of the radiation.

The present results extend the concept of baroreflex failure to a chronic form, as a result of accelerated development of atherosclerosis in the region of the carotid sinus baroreceptors. Histopathologic studies have noted carotid atherosclerotic changes, thickening, and perivascular fibrosis after radiation, with intimal proliferation, hyaline deposition, and elastic layer fragmentation and increased collagen production, polymorphonuclear cell infiltration, and accumulation of foam cells and fibroblasts. Although no analogous histopathologic studies have focused specifically on the carotid sinus region, one might reasonably suspect the same types of changes, which would consequently attenuate afferent baroreceptor traffic in response to perturbations of blood pressure. The finding of carotid atherosclerosis in all 3 patients was consistent with the late development of a selective afferent baroreflex lesion from carotid arterial rigidification.

If such a mechanism were correct, then other components of the baroreflex arc, including parasympathetic cholinergic innervation of the heart and sympathetic noradrenergic innervation of the heart and blood vessels, should remain intact. We looked for clues about the integrity of efferent limbs of the baroreflex. Ambulatory blood pressure monitoring revealed episodes of relative bradycardia as well as episodes of extremely high blood pressure; cold pressor testing showed...

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NE indicates norepinephrine; EPI, epinephrine; DHPG, dihydroxyphenylglycol. Numbers in boldface indicate abnormal values. Normal mean values are based on 28 healthy volunteers, mean age 55 years old, with the assays done in our laboratory.
not only large pressor responses but also concurrent increases in pulse rate; and spectral analysis of heart rate variability demonstrated increases in high-frequency power as a function of respiration. These findings indicated intact parasympathetic cardiovascular function. Meanwhile, the pattern of blood pressure responses to the Valsalva maneuver, high plasma catecholamine levels during supine rest, increases in plasma catecholamine levels during orthostasis, and large cold pressor responses excluded sympathetic neurocirculatory failure. Taken together, the results therefore pointed to baroreflex failure from decreased afferent baroreceptor input to the brain, rather than loss of effector system functions.

The finding of a lack of heart rate responses to blood pressure changes, required to diagnose baroreflex failure, is not unique for this condition. Patients with autonomic failure also have deficient heart rate responses to blood pressure changes. Other aspects of the clinical and laboratory findings distinguish these conditions from baroreflex failure, because primary chronic autonomic failure features profound orthostatic hypotension and low plasma norepinephrine levels. 26

In a keynote article, Robertson et al 12 characterized the hemodynamic features of acute baroreflex failure as fluctuating and volatile. Jordan et al 20 introduced the notion of selective baroreflex failure. They studied a patient who had labile blood pressure and relative tachycardia with episodes of bradycardia. The afferent fibers of the baroreflex appeared to be preserved, whereas the efferent limb seemed defective. Our patients showed similar clinical features but apparently an opposite pathophysiologic mechanism, ie, selective baroreflex failure (intact efferent limb of the baroreflex).

Patients 1 and 2 were treated with angiotensin-converting enzyme, which improved their clinical status. The third patient, who had episodes of both high and low blood pressure, was advised that clonidine might help, but he preferred not to take any treatment.

Perspective

Surgery or radiotherapy of the carotid sinuses or brain stem can evoke acute or subacute baroreflex failure. Here we report cases in which neck irradiation appeared to elicit chronic baroreflex failure as a late sequela, manifested by labile hypertension and orthostatic intolerance. Because ultrasound imaging showed carotid intimal thickening and atherosclerosis, we propose that the chronic baroreflex failure resulted from encasement of baroreceptors in stiffened carotid sinuses walls. We believe that this phenomenon is underdiagnosed by cardiologists, neurologists, and radiation oncologists, at least partly because clinicians do not appreciate enough the possibility of this adverse long-term outcome, either when therapeutic options for neck malignancy are first considered or when, years after successful cure, the patient develops seemingly unrelated signs and symptoms of baroreflex failure. The results call for a prospective study about the incidence of this complication and its relationship specifically to carotid arterial rigidification. Meanwhile, we hope that neurocardiologic consultants and radiation oncologists will keep in mind the possibility of late-onset, iatrogenic baroreflex failure.

References


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