Case Report

Paroxysmal Hypertension Due to Sinoaortic Baroreceptor Denervation in Humans

TIMOTHY R. AKSAMIT, JOHN S. FLORAS, RONALD G. VICTOR, AND PHILIP E. AYLWARD

SUMMARY A 41-year-old man with a remote history of neck and mediastinal radiation was seen with severe paroxysms of hypertension, headache, and cutaneous flushing after bilateral carotid bypass surgery. Investigation revealed marked parallel fluctuations in blood pressure and heart rate and elevation of plasma norepinephrine to 1164 pg/ml during a paroxysm. We systematically evaluated his arterial and cardiopulmonary baroreceptor reflex function by assessing changes in heart rate, arterial pressure, and efferent muscle sympathetic nerve activity, which was measured directly by the microneurographic technique. Elevating resting arterial pressure from 130/88 to 164/100 mm Hg with phenylephrine or lowering it to 88/56 mm Hg with nitroprusside produced no reflex changes in heart rate or efferent sympathetic nerve activity. In contrast, decreases in cardiac filling pressures with lower body negative pressure produced a marked increase in sympathetic nerve activity. These findings indicate complete loss of the afferent limb of the arterial baroreceptor reflex but preservation of the cardiopulmonary baroreceptor reflex. They suggest that both carotid and aortic baroreceptors were impaired by the previous radiation and surgery. Despite the loss of arterial baroreceptor function, the patient did not have sustained hypertension. The paroxysms of hypertension appear to be due to spontaneous fluctuations in central sympathetic drive not buffered by arterial baroreceptors in a manner similar to that seen in sinoaortic-denervated animals. (Hypertension 9: 309-314, 1987)

KEY WORDS • arterial baroreceptor reflex • microneurography • sympathetic nerve activity

The arterial baroreceptor reflex is the principal control mechanism buffering acute changes in blood pressure.1 In experimental animals, elimination of the afferent baroreceptor input by sinoaortic denervation leads to increases in the lability of blood pressure, particularly in response to alerting stimuli.2,3 In humans, transient hypertension caused by baroreceptor dysfunction has been reported following carotid endarterectomy4-6 and surgical deafferentation of carotid baroreceptors,7 but the effects of chronic baroreceptor deafferentation in humans have not been described previously, presumably because there is redundancy of baroreceptor afferent input from both carotid and aortic receptors, so that loss of only one afferent pathway (e.g., carotid baroreceptor) does not produce a sustained impairment of arterial baroreceptor reflex function.8,10

In this report we describe a patient who was seen with paroxysmal hypertension, headache, and cutaneous flushing caused by total and permanent loss of arterial baroreceptor function. His condition is thus the human counterpart of experimental sinoaortic baroreceptor denervation in animals. The important features of this case study are 1) the demonstration of impairment of both carotid and aortic baroreceptor reflexes as a result of previous therapy, 2) the systematic assessment of both high pressure (arterial) and low pressure (cardiopulmonary) baroreceptor reflexes, and 3) the use of direct recordings of efferent muscle sympathetic nerve activity to assess baroreceptor function.

Case Report

The patient, a 41-year-old man, received radiation therapy (4570 rad) to the entire cervical area, partial mastoid area, high axillae, and superior mediastinum...
for reticulum cell sarcoma in 1961. In March 1985, symptomatic cerebrovascular disease developed. Severe, diffuse, ulcerative, occlusive carotid vascular disease was demonstrated at angiography. He underwent simultaneous bilateral aorto-internal carotid bypass using saphenous vein grafts in April 1985; the distal anastomoses were placed approximately 2 cm above the carotid bifurcations. There was evidence of extensive radiation damage to the skin, subcutaneous tissues, and carotid arteries. Following a protracted postoperative course, including an Enterobacter pneumonia and transient hepatitis, he recovered and was discharged from the hospital.

Five weeks later he had the first transient episode of pounding occipital headache, which began suddenly at rest and was followed by facial flushing, diaphoresis, and a nonpruritic erythematous macular rash over the trunk and arms. The next day, he had a similar episode during which his blood pressure, previously normal, was recorded at 230/130 mm Hg and his heart rate was 120 beats/min. The attack subsided spontaneously after 30 minutes. He was admitted for investigation.

Physical examination revealed a thin, anxious man. Blood pressure was 160/106 mm Hg supine and 120/90 mm Hg standing. Heart rate was 120 beats/min supine and standing. There were marked radiation changes of the skin over the neck and upper chest. Optic fundi were normal, and there was no cardiomegaly or other evidence of long-standing hypertension.

The patient continued to have two or three episodes of severe hypertension (systolic pressure > 200 mm Hg), headache, and flushing daily while in the hospital. Initially these responded to 10 mg of nifedipine administered sublingually with rapid relief of symptoms and fall in blood pressure toward normal (150/90 mm Hg), headache, and flushing daily while in the hospital. Thereafter 2 mg of phentolamine administered intravenously lowered his blood pressure from 186/126 to 138/88 mm Hg in 1 minute.

Investigations

Blood counts, blood chemistry values, electrocardiogram, chest roentgenogram, abdominal computed tomogram, and urinalysis results were normal.

Catecholamine Studies

The following values were obtained for catecholamine samples from an antecubital vein while the patient was normotensive and resting supine: norepinephrine, 360 pg/ml (normal 110–410 pg/ml); epinephrine, 56 pg/ml (normal <50 pg/ml); and dopamine <10 pg/ml (normal <30 pg/ml). Values for samples drawn during a hypertensive paroxysm were nor-epinephrine, 1164 pg/ml; epinephrine, 42 pg/ml; and dopamine, 28 pg/ml. A clonidine suppression test, with 0.3 mg of clonidine administered orally as described by Bravo et al., caused a fall in plasma catecholamines from the resting values to norepinephrine, 54 pg/ml; epinephrine, <10 pg/ml; and dopamine, <10 pg/ml accompanied by asymptomatic hypoten- 

A 24-hour urine collection obtained on a day when a paroxysm had occurred yielded normal values: vanil- llylmandelic acid, 4 mg/24 hr (normal, 0–8 mg/24 hr); catecholamines, 89 µg/24 hr (normal, 0–110 µg/24 hr); and metanephrines, 954 µg/g creatinine (normal <1200 µg/g). Values obtained during a 24-hour collection for 5-hydroxyindole acetic acid were also normal (0.3 mg/24 hr).

These investigations excluded a pheochromocytoma as the cause of his paroxysmal hypertension, but the elevated norepinephrine level and response to phentolamine suggested enhanced sympathetic neurogenic drive.

Bedside Assessment of Baroreceptor Reflex Function

Valsalva's maneuver produced a markedly abnormal heart rate response with an initial severe bradycardia rather than the expected tachycardia and a gradual recovery to normal. A noninvasive 24-hour blood pressure recording (Pressomatic II, Del Mar Avionics, Irvine, CA, USA) showed marked fluctuation in blood pressure (from 183/113 to 55/44 mm Hg) not accompanied by reciprocal reflex changes in heart rate.

Laboratory Assessment of Baroreceptor Reflex Function

Arterial pressure and central venous pressure were measured directly. Heart rate, measured by cardiac tachometer from the electrocardiogram, and respiratory excursions were recorded continuously along with arterial and central venous pressures.

Microneurography. Multiunit recordings of efferent postganglionic sympathetic nerve activity were obtained from a muscle nerve fascicle of the right peroneal nerve using the microneurographic technique described in a recent publication from our laboratory. Neurograms are acceptable as representing muscle sympathetic nerve activity when 1) electrical stimulation at the recording site causes a muscle twitch but no paresthesia, 2) afferent discharges are obtained when muscle afferents are stimulated by stretching tendons but not when cutaneous afferents are stimulated by stroking of the skin, 3) the neurograms show intermittent spontaneous activity that does not respond to alerting stimuli but increases with held expiration and lower body negative pressure. Previous studies have shown that these neurograms represent postganglionic efferent sympathetic nerve activity because 1) they are eliminated by ganglionic blockade, 2) they are eliminated by blockade of the nerve proximal to the recording site but not distal to it, and 3) they have a conduction velocity of 1 m/sec. These bursts are normally pulse-synchronous.

Arterial Baroreceptor Reflex. The arterial baroreceptors were stimulated by the elevation of arterial pressure with the infusion of phenylephrine (0.125–0.75 µg/kg/min) and unloaded by lowering blood pressure with nitroprusside (0.05–0.1 µg/kg/min).

Cardiopulmonary Baroreceptor Reflex. The cardiopulmonary baroreceptors were unloaded by application of lower body negative pressure incrementally, from −5 to −15 mm Hg. Measurements were made 1 minute after the application of lower body negative pressure.
The procedures were approved by the University of Iowa Committee on Human Investigation, and the patient gave informed, written consent.

Results of Investigations

Resting Parameters

There was a persistent resting sinus tachycardia of 120 beats/min. Blood pressure was extremely labile, showing marked spontaneous fluctuations with parallel rather than reciprocal changes in heart rate (Figure 1). Resting muscle sympathetic nerve activity was relatively high: 45 bursts/min. Further, the normal pulse synchronicity appeared to be lost in this patient (Figure 2A).

Reflex Responses

Arterial Baroreceptor Reflexes. Graded increases of mean arterial pressure up to +30 mm Hg with phenylephrine or graded decreases to −40 mm Hg with nitroprusside produced no reciprocal reflex changes in heart rate.
rate or efferent sympathetic nerve activity (Figure 2A). Changes in central venous pressure with these doses of phenylephrine and nitroprusside were less than 0.5 mm Hg. The normal reflex fall in heart rate and sympathetic activity with phenylephrine and the normal reflex increase in heart rate and sympathetic activity with nitroprusside are shown in Figure 2B.

Cardiopulmonary Baroreceptor Reflexes. Lower body negative pressure at —10 mm Hg lowered central venous pressure and arterial pressure and produced marked increases in efferent sympathetic nerve activity (Figure 3).

Valsalva's Maneuver. The patient showed a markedly abnormal response to Valsalva's maneuver. A precipitous fall in arterial pressure was accompanied by a bradycardia rather than the expected tachycardia. Arterial pressure then slowly recovered without the normal overshoot (Figure 4).

Discussion

This case study demonstrates the effects of bilateral sinoaortic denervation in humans, which presumably occurred secondary to mediastinal radiation and carotid bypass surgery. The interesting features are 1) the demonstration of the absence of arterial baroreceptor reflex control of heart rate and efferent muscle sympathetic nerve activity, 2) the preservation and importance of the cardiopulmonary baroreceptor reflex control of sympathetic nerve activity, 3) the lack of sustained hypertension, and 4) the clinical syndrome of paroxysmal hypertension, headache, and cutaneous flushing.

Arterial baroreceptors buffer changes in blood pressure by altering efferent autonomic tone. At rest, baroreceptor reflex afferents tonically inhibit efferent sympathetic discharge. Interruption of this tonic inhibition, as in sinoaortic baroreceptor–denervated animals, leads to marked lability of arterial pressure associated with increases in plasma norepinephrine. Transient arterial baroreceptor dysfunction in humans has been described previously following carotid endarterectomy, in Takayasu's arteritis, and following surgical deafferentation of carotid baroreceptors. Under these conditions, baroreceptor reflex impairments are transient rather than permanent, presumably because there is marked redundancy of baroreceptor afferents, particularly in the control of sympathetic nerve activity. Thus, the loss of carotid baroreceptor input does not appear to cause a long-term impairment in baroreceptor reflex control of sympathetic vasoconstrictor outflow so long as the aortic baroreceptors remain intact.

This patient demonstrated complete loss of arterial baroreceptor reflex control of both heart rate and efferent muscle sympathetic nerve activity, as evidenced by the lack of reflex responses to changes in arterial pressure produced by phenylephrine and nitroprusside. The spontaneous fluctuations in heart rate and the response of sympathetic nerve activity to lower body negative pressure demonstrate the integrity of the efferent autonomic outflow. We conclude, therefore, that the impairment of reflex responses to changes in arterial pressure was due to loss of afferent input from both carotid and aortic baroreceptors. Carotid baroreceptors were vascularly isolated as a result of carotid bypass surgery, and there may have been damage to afferent nerves during the anatomical dissection. The aortic baroreceptors presumably were damaged by mediastinal radiation.

In contrast to the impairment of arterial baroreceptor reflex control of the circulation, cardiopulmonary baroreceptor reflex function was preserved, as demonstrated by the brisk increases in sympathetic drive that occurred in response to decreases in cardiac filling pressures with lower body negative pressure.

The data from this patient have two interesting implications with regard to the contribution of cardiopulmonary and arterial baroreceptors in response to mild lower body negative pressure in humans. First, the responses support the view that the cardiopulmonary baroreceptor reflexes play a major role in the control of muscle sympathetic nerve activity, since lower body negative pressure produced large increases in muscle sympathetic outflow despite loss of arterial baroreceptor reflexes. Second, low levels of lower body negative pressure (—10 mm Hg) caused a fall in arterial pressure, which is not seen in normal humans with intact arterial baroreceptor reflexes. This finding suggests that arterial baroreceptors are involved in the response to low levels of lower body negative pressure and help to maintain arterial pressure during even mild levels of orthostatic stress.

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SINOAORTIC DENERVATION IN HUMANS/Aksamit et al.

FIGURE 4. Valsalva's maneuver. Note the markedly abnormal response to Valsalva's maneuver: a precipitous fall in arterial pressure was accompanied by bradycardia and a failure of arterial pressure to overshoot above baseline.

ment of efferent muscle sympathetic nerve activity. We believe this is the first time that pathological alterations of baroreceptor reflex function in humans have been demonstrated by this technique. Fagius et al. reported the effect of transiently anesthetizing the vagus and glossopharyngeal nerves on efferent sympathetic activity in two normal human subjects. They noted a marked increase in sympathetic activity and loss of pulse synchronicity that was accompanied by hypertension and tachycardia. In our patient with chronic deafferentation, resting activity (45 bursts/min) was high compared with the mean value for a group of normal subjects of similar age (25 ± 4 bursts/min). Because there is wide interindividual variation in muscle sympathetic nerve activity in the normal population (range, 12–55 bursts/min), it is not possible to state definitively that resting sympathetic nerve activity was abnormally high in this patient. There appeared to be loss of pulse synchronicity of the bursts of sympathetic activity, which has been suggested as a useful marker of impaired arterial baroreceptor afferent activity.

Despite loss of arterial baroreceptor function, the patient did not have sustained hypertension. He was seen with paroxysmal hypertension, headache, and cutaneous flushing. These symptoms and signs initially raised several diagnostic possibilities, including pheochromocytoma, carcinoid syndrome, and pseudoephochromocytoma. The normal resting plasma and urinary catecholamine levels and the clonidine suppression test results, together with the normal abdominal computed tomographic scan, appear to exclude the diagnosis of pheochromocytoma. There was no evidence for carcinoid syndrome or other causes of paroxysmal hypertension, as described by Kuchel. The mechanism of the paroxysmal hypertension appeared to be spontaneous fluctuations in sympathetic activity that were inadequately buffered by the arterial baroreceptor reflex system. Unfortunately, we were not able to directly measure sympathetic nerve activity during a paroxysm, but the elevation of plasma norepinephrine during an episode suggests enhanced sympathetic drive. The headache was closely related to the level of arterial pressure, possibly because of vasodilatation in the cerebral vascular bed. We are not certain of the mechanism producing the cutaneous vasodilatation; it may have resulted in part from an increased driving pressure, but there may also have been abnormalities in the autonomic control of skin blood vessels.

Because we concluded that the patient's symptoms were the result of excess fluctuations in central sympathetic nerve outflow, we used prazosin, an \( \alpha_1 \)-adrenergic receptor blocking agent, to control his symptoms. We considered clonidine, an \( \alpha_2 \)-adrenergic receptor agonist known to reduce sympathoneural outflow, but we were reluctant to use this agent because of concern for potential rebound effects. The patient improved clinically while taking prazosin (0.1 mg p.o., t.i.d.), with the episodes decreasing to one per week and satisfactorily managed with sublingually administered nifedipine. Nonetheless, we were still able to record marked fluctuations in systolic pressure from 80 to 160 mm Hg in follow-up study.

We believe this case study is the first demonstration of chronic sinoaortic denervation in humans and illustrates the clinical consequences of loss of this important neurocirculatory control mechanism.

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