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REPORTS ON HYPERTENSION

Primary Dysfunction of the Afferent Limb of the Arterial Baroreceptor Reflex System in a Patient With Severe Supine Hypertension and Orthostatic Hypotension

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A 33 year old man with a history of recurrent episodes of orthostatic dizziness since adolescence was noted to have a supine blood pressure of 200/120 mm Hg and a standing blood pressure of 90/60 mm Hg. Results of extensive laboratory studies for secondary hypertension were negative. Studies of the autonomic nervous system function revealed normal plasma catecholamines, cold pressor test and response to 4 minute 30% of maximal static handgrip contraction and an appropriate increase in heart rate on intravenous injection of atropine. In contrast, the heart rate response to phenylephrine and sodium nitroprusside infusion, carotid massage and graded neck suction with an airtight chamber was very abnormal, indicating marked dysfunction of the afferent limb of the arterial baroreceptor reflex system. Methyldopa decreased the supine hypertension and increased the standing blood pressure.

Carotid and aortic baroreceptors play an important role in the acute regulation of blood pressure (1). Orthostatic hypotension due to carotid baroreceptor and afferent nerve trauma as a result of extensive neck surgery has been previously reported (2). Although altered baroreceptor function has been implicated in essential hypertension (3,4), primary dysfunction of carotid baroreceptors or afferent nerves as a cause of supine hypertension and orthostatic hypotension has not been previously described. We report the case of a 33 year old man with marked dysfunction of the afferent limb of the arterial baroreceptor reflex system, probably of congenital origin, as a cause of severe supine hypertension and marked symptomatic orthostatic hypotension.

Case Report

History. This 33 year old, white man gave a history of recurrent episodes of postural dizziness first starting in his early teens; however, he had a normal seated blood pressure in 1970 (age 19) during an entrance physical examination for the U.S. Armed Forces. In November 1979 while still serving in the Army as an illustrator, he developed headache, fullness around the sinuses, visual disturbance and orthostatic dizziness and weakness, but never fainted. He denied seizures, head trauma or drug abuse. The supine blood pressure was noted to be 200/120 mm Hg. Evaluation at that time revealed a normal electroencephalogram and normal findings on spinal tap. In April 1980, he was admitted to an Army hospital for evaluation of hypertension and was found to have orthostatic hypotension with a decrease in supine blood pressure from 200/120 to 90/60 mm Hg on standing. Laboratory findings at that time included normal blood count, electrolytes, renal function, blood chemistry values, rapid sequence intravenous myogram, negative screening for pheochromocytoma and normal thyroid function, plasma cortisol, chest roentgenogram and electrocardiogram. A trial of propranolol lowered the blood pressure to 98/84 mm Hg supine and 40 mm Hg systolic in the standing position, making it impossible for the patient to stand. Propranolol was discontinued the next day. A repeat electroencephalogram was normal. He continued to have significant dizziness while standing. The renal arteriogram and bilateral renal vein renin levels were also found to be normal. Computed tomographic scans of the head, thorax and abdomen were reported to be normal.

In December 1980, the patient was hospitalized at the

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Cleveland Clinic where he was evaluated extensively for supine hypertension (blood pressure 170/134 mm Hg) and orthostatic hypotension (80/60 mm Hg). He was discharged with a diagnosis of "abnormal baroreceptor function." Because of his health, the patient was discharged from the Armed Forces in 1981 and has since lived in northern Wisconsin. He was first seen at the Wood Veterans Administration Medical Center Hypertension Clinic in March 1982. At that time, he was not taking any medications and, except for occasional dizziness, felt good. He denied symptoms of autonomic dysfunction such as anhidrosis, difficulty with erection or ejaculation or trouble with bowels or bladder. He does not smoke or drink alcohol. He underwent tonsillectomy and adenoidectomy at age 5 and was treated for pneumonia at age 12.

The patient's father has high blood pressure; one uncle had high blood pressure and died at age 38 of suspected myocardial infarction. His mother has diabetes. Three sisters are in good health; a brother who is 7 years younger has hypertension, but no orthostatic hypotension. The patient married in 1976 and has one son, born in 1978, who is in apparent good health.

Physical examination. On initial physical examination at this center, the patient weighed 70.2 kg at a height of 170 cm. Blood pressure was 148/112 mm Hg supine, 130/102 sitting and 114/86 standing, with heart rate remaining unchanged at 68 beats/min. He stuttered slightly. The remainder of the physical exmination was normal.

Laboratory findings. Urinalysis, complete blood count, routine serum chemistry values and electrolytes, plasma cortisol, plasma renin activity, plasma aldosterone level, chest roentgenogram, electrocardiogram, lower limb electromyogram and nerve conduction studies were normal. Plasma catecholamines at 0 and 60° head-up tilt were measured at the Cleveland Clinic in December 1980 and were normal (Table 1). Results of the tests performed at our center to evaluate the autonomic nervous system were as follows:

1. *Normal sympathetic efferent function:*
   a. *60 second cold pressor test:* 12 mm Hg increase in blood pressure
   b. *4 minute 30% of maximal static handgrip contraction:* 13 mm Hg increase in blood pressure
2. *Normal parasympathetic efferent function:*
   a. *intravenous injection of 2 mg atropine:* 30 beats/min increase in heart rate
3. *Abnormal tests of baroreflex function:*
   a. *40 mm Hg Valsalva maneuver:* there was no phase IV blood pressure overshoot, and a dissociation was observed between the normal inverse heart rate-blood pressure relation (Fig. 1)
   b. *phenylephrine infusion:* no decrease in heart rate despite 60 mm Hg increase in systolic blood pressure (Fig. 2)

Table 1. Plasma Catecholamines

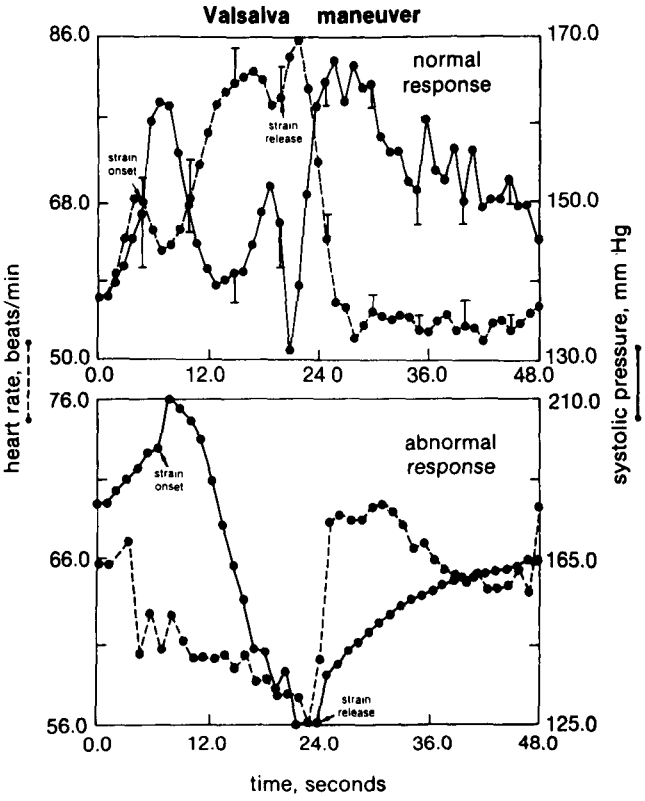
	Tilt		
	0°	60°	0°
BP (mm Hg)	130/90	80/60	170/134
HR (beats/min)	64	71	82
NE (ng/liter)	189 (200 to 500)	413 (400 to 1,500)	334
Epi (ng/liter)	25 (40 to 90)	81 (50 to 100)	32

Normal range in parentheses. BP = blood pressure; Epi = epinephrine; HR = heart rate; NE = norepinephrine.

   c. *sodium nitroprusside infusion:* no significant increase in heart rate despite a 20 to 30 mm Hg decrease in systolic blood pressure
   d. *carotid massage:* no change in heart rate
   e. *graded neck suction using an airtight chamber (5,6):* carotid baroreceptor gain of 0.94 ms/mm Hg as compared with the normal 2 to 6 ms of RR interval prolongation per mm Hg of applied suction.

Table 2 depicts the baroreceptor slopes for the neck suction, phenylephrine and sodium nitroprusside tests.

Figure 1. Beat by beat heart rate and systolic blood pressure responses to a 15 second, 40 mm Hg Valsalva maneuver. A normal reciprocal response between the blood pressure (**solid line**) and heart rate (**hatched line**) (mean ± standard error of the mean) of fifteen 20 to 29 year old healthy men is shown in the **upper graph**. The responses noted in our study patient (**lower graph**) reveal the absence of a reciprocal relation.



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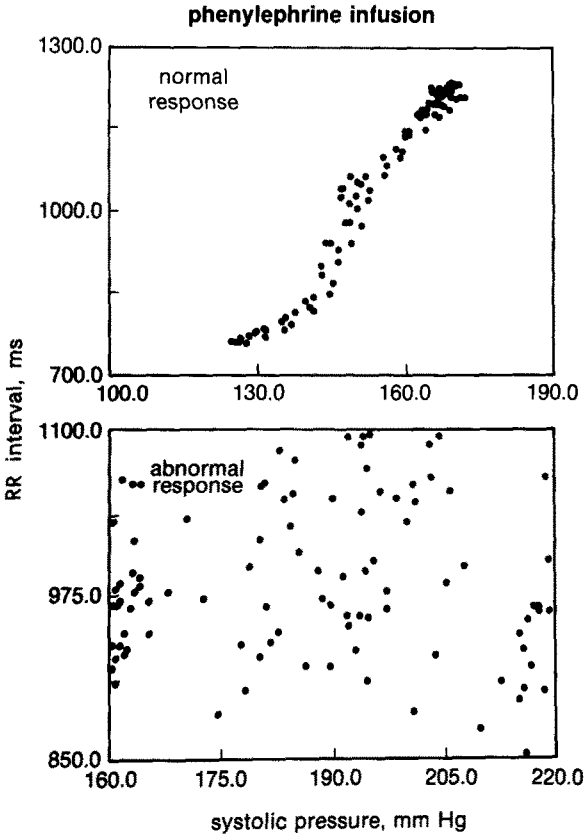

Figure 2. Beat by beat arterial baroreceptor-mediated RR interval responses to increase in blood pressure produced by intravenous phenylephrine in a healthy young man (**upper graph**). Responses of our study patient (**lower graph**) to systemic hypertension reveal abnormal (perhaps random) RR interval responses.

Hemodynamic findings. The effect of tilt on hemodynamic variables including stroke volume (measured using a Minnesota impedance cardiograph [7]) are shown in Table 3. The blood pressure decreased markedly on head-up tilt from 0 to 45° due to a decrease in the cardiac output. There was a slight increase in the heart rate and peripheral resistance, but not enough to compensate for the 50% reduction in stroke volume. The 70° head-up tilt further reduced the blood pressure, this time because of a decrease in peripheral resistance.

Treatment. The patient was advised to increase his dietary salt intake, sleep with the head of the bed tilted up, use leotard elastic stockings when leaving home and record blood pressure at home in the supine and standing positions. Despite these nonpharmacologic measures, he continued to experience dizzy spells with a decrease in standing blood pressure to 50 to 60/30 to 40 mm Hg. Fludrocortisone, 0.1 mg twice daily, was prescribed. On October 15, 1982, his blood pressure was 130/100 mm Hg supine, 98/64 sitting and 80/62 standing, with respective heart rates of 72, 68 and 80 beats/min. He felt dizzy and weak. Indomethacin, 25 mg three times daily, was added. On his December 6, 1982 visit to the hypertension clinic, he claimed he was feeling well except for occasional episodes of dizziness. The blood pressure was 160/110 mm Hg supine, 130/90 sitting and 130/80 standing with a heart rate of 60 beats/min in all three positions.

On February 17, 1983, he went to see his family physician in northern Wisconsin where he fainted in the doctor's office while standing in line to check in. On that day, his blood pressure was 200/150 mm Hg supine and 90 systolic in the standing position. His family physician discontinued indomethacin, continued fludrocortisone and added methyldopa, 250 mg three times daily, to control the supine hypertension.

He was seen on April 12 and August 28, 1983 in the hypertension clinic; he had continued to take fludrocortisone and methyldopa. His blood pressure on the August 28 visit was 152/114 mm Hg supine, 154/100 sitting and 138/90 standing. The corresponding heart rates were 62, 60 and 70 beats/min. However, the blood pressure measured at home had been in the range of 140 to 160/95 to 105 mm Hg supine and 110 to 130/70 to 90 mm Hg in the standing position. He also claimed to have been less dizzy and lethargic and thought that methyldopa had been the most helpful of all the drugs he had received. Clonidine, 0.1 mg twice daily, was substituted for methyldopa to see if it would be equally or more effective than methyldopa, but it caused the standing blood pressure to decrease to 40 mm Hg systolic, with little effect on the supine blood pressure. Methyldopa was reinstituted.

Table 2. Baroreceptor Slopes (ms/mm Hg)

	Normal Response* (n = 20)	Patient's Response
Test		
Neck suction	3.48 ± 0.7	0.94
Phenylephrine	25.78 ± 4.04	No significant slope
Sodium nitroprusside	13.37 ± 1.61	2.85

*Values are reported as mean ± standard error of the mean.

Discussion

Possible mechanisms of orthostatic hypotension. Maintenance of upright blood pressure requires an intact reflex system comprising baroreceptors, afferent nerve fibers, vasomotor centers, the sympathetic nervous system and effector organs (8). Lesions or drugs that interfere with the functions of the reflex arc at any of these levels can cause orthostatic hypotension. In our patient, based on a normal reponse to the cold pressor and isometric handgrip exercise tests, one can safely conclude that the sympathetic nervous system and the effector organs are intact. An appropriate increase in the heart rate on infusion of atropine suggests that the parasympathetic nervous system to the

Table 3. Hemodynamic Effects of Tilt in the Study Patient and Mean Values (±SEM) for 15 Normal Men Aged 20 to 29 Years*

Tilt	BP (mm Hg)	MAP (mm Hg)	HR (beats/min)	SV (ml)	CO (liters/min)	TPR (dynes·s·cm^{-5})
0°	166/112 (129 ± 2/72 ± 1)	130 (91.0 ± 0.4)	57 (56.8 ± 0 3)	100 (99.2 ± 2.4)	5.7 (5.66 ± 0.23)	1,828 (2,349 ± 44)
45°	112/80 (127.6 ± 2/78 ± 3)	91 (94.2 ± 2.5)	71 (70.6 ± 2 9)	53 (67.3 ± 0.4)	3.8 (4.7 ± 0.02)	1,962 (1,702 ± 12)
70°	104/68 (129.3 ± 2/84 ± 3)	80 (98.8 ± 1.7)	76 (78.9 ± 3.7)	51 (57.4 ± 0.6)	3.8 (4.4 ± 0.03)	1,665 (1,927 ± 17)

*Values for normal men are shown in parentheses. BP = blood pressure; CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; SV = stroke volume; TPR = total peripheral resistance calculated from the formula: TPR (dynes·s·cm^{-5}) = 80 × MAP (mm Hg) − CO (liters/min)

heart is also intact. On several occasions, this patient demonstrated mild tachycardia with head-up tilt or upright posture. Although orthostatic reflexes are primarily governed by baroreceptor reflexes, there is convincing evidence that the cerebellum and vestibular apparatus may also play a role (9). Thus, mild tachycardia with orthostatic stress and catecholamine increase with head-up tilt in this patient may be mediated through these nonbaroreceptor reflexes and possibly by cardiopulmonary reflexes.

The abnormal response to the Valsalva maneuver, phenylephrine and nitroprusside infusion demonstrates arterial baroreflex dysfunction. Furthermore, the lack of heart rate response to carotid massage and graded neck suction suggests dysfunction of carotid baroreceptors or the afferent nerves connecting them to the brain stem.

Etiology. The history of recurrent episodes of postural dizziness in adolescence indicates that the suspected deafferentation must be either congenital or precipitated by a childhood illness. Although the seated blood pressure was normal at age 19, supine or standing blood pressure was not recorded until the age of 29 when he became symptomatic with supine hypertension and postural hypotension. Inasmuch as we do not know the cause of the afferent limb dysfunction, we have labeled it a "primary" dysfunction.

Treatment. Treatment to normalize the patient's blood pressure has been very difficult, if not impossible. The use of agents such as fludrocortisone and indomethacin, which are recommended for orthostatic hypotension (10), proved insufficient to consistently increase the standing blood pressure. Methyldopa seems to have been successful, not only in lowering the supine blood pressure, but also in raising the standing blood pressure. A similar paradoxical effect on the upright blood pressure in patients with idiopathic orthostatic hypotension was previously reported by Robertson et al (11) using clonidine; however, in their experience, as in our patient, clonidine caused severe hypotension in a patient with baroreceptor dysfunction secondary to irradiation of the neck. Clonidine was supposedly effective in increasing the blood pressure in patients with idiopathic orthostatic hypotension through a direct alpha-agonistic effect on the peripheral blood vessels without the central antihypertensive action due to lack of a functioning sympathetic outflow. It is possible that methyldopa, through its metabolite alpha-methyl norepinephrine, which is a weak agonist of norepinephrine, blunted the central effects of high and low levels of norepinephrine on the vasomotor center's alpha-receptors and thereby reduced the drastic variation in supine and upright blood pressures in our patient.

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