Extreme Blood Pressure Fluctuations in a Patient With Intact Autonomic Reflexes and Intact Sodium Conservation

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ABSTRACT

A patient who had episodes of profound hypotension alternating with severe hypertension without an obvious precipitating cause is reported. The hypotensive episodes were accompanied by tiredness, syncope, bradycardia, and a low norepinephrine concentra-

tion while supine or standing. In contrast, the hypertensive episodes were associated with marked tachycardia, sweating, anxiety, abdominal pain, and very high levels of plasma norepinephrine concentration. Extensive investigations failed to support a diagnosis of pheochromocytoma. The testing of baroreceptor function and autonomic reflexes was normal. Blood pressure was not salt sensitive. It was concluded that this patient has a unique clinical syndrome of extreme fluctuation of blood pressure and sympathetic nervous activity yet intact cardiovascular reflexes and normal sodium conservation. The abnormal blood pressure regulation most likely has a central origin.

Key Words: Hypotension, hypertension, autonomic, function, baroreflex, norepinephrine

Blood pressure (BP) changes little with posture in normal human subjects because of baroreflex mechanisms that adjust the sympathetic and parasympathetic nervous discharge. The changes in heart rate that occur on standing up or lying down are due
for the most part to this baroreflex mechanism. Severe fluctuations in BP in the absence of changes in blood volume usually imply interruption in this baroreflex mechanism. For example, patients with autonomic failure experience severe orthostatic hypotension, sometimes accompanied by supine hypertension. The plasma catecholamine levels are normal or suppressed. Excessive release of catecholamines can occur with baroreflex failure or with pheochromocytoma and is associated with episodic or sustained hypertension. On other occasions, pheochromocytoma can cause hypertension alternating with hypotension and tachycardia. In this study, we describe a patient with episodes of hypotension alternating with hypertension without evidence of pheochromocytoma who has extreme fluctuation in plasma catecholamine levels, intact autonomic reflexes, and normal salt conservation.

CASE REPORT

Clinical History

Our patient is a 67-yr-old female retired bookkeeper. For 1 yr, she has had intermittent episodes that last several days at a time of orthostatic dizziness with syncope and falls, accompanied by weakness and lethargy. At these times, her systolic BP is typically 55 to 90 mm Hg with a heart rate of 60 to 70 beats/min. These symptoms alternate with episodes of headaches, sweating, palpitations, anxiety, nausea, vomiting, and abdominal pain. At these times, her systolic BP is typically 160 to 220 mm Hg with a heart rate of 100 to 160 beats/min. During the hypertensive or hypertensive episodes, there is little orthostatic fall in BP and standing is accompanied by an appropriate increase in heart rate. She has required frequent hospital admissions, averaging once a month, predominantly for hypotension. On one occasion, she had a syncopal episode, f.e., and fractured her left lateral malleolus. She denies flushing, diarrhea, visual symptoms, fever, chest pain, or shortness of breath. She was referred to our institution for a further work-up. In 1983, she was diagnosed to have sick sinus syndrome and a demand pacemaker was inserted. Cardiac catheterization at that time was normal. In 1986, she developed diabetes mellitus that was well controlled with insulin therapy. One year before presentation, she developed Staphylococcus aureus endocarditis, which was successfully treated with antibiotics. She is a nonsmoker, and she denies alcohol or illicit drug abuse. Her only regular medication at presentation was insulin (25 U of NPH in the morning and 12 U in the evening, and 12 U of regular in the morning).

Physical Examination

Physical examination during the first clinic visit when she was quite asymptomatic revealed a normal affect, a lying BP of 156/66, a lying heart rate of 78 beats/min, a standing BP of 126/78, and a standing heart rate of 96 beats/min. Examination of the optic fundi was negative for evidence of diabetic or hypertensive retinopathy. Otherwise, the examination was unremarkable including a normal neurologic examination.

Laboratory Investigations

Initial laboratory data revealed normal values for serum creatinine, BUN, electrolytes, urinalysis, creatinine clearance, and liver function tests. There was no evidence of hypoglycemia during repeated tests, and most blood sugar levels ranged between 80 and 200 mg/dl.

Cardiac Evaluation

She had a normal electrocardiogram, a normally functioning pacemaker, and an echocardiogram that revealed normal cardiac valves, and normal cardiac output while lying and after head-up tilt of 60 degrees. Neither head-up tilt nor isoproterenol infusion induced syncope.

Evaluation for Pheochromocytoma

Plasma catecholamines were measured on several occasions, particularly during the spontaneous episodes of hypertension and hypotension. On none of these occasions was she taking any medication. The plasma norepinephrine levels were remarkably variable and, as shown in Figure 1, correlated closely with the level of systolic BP. The normal range of plasma norepinephrine is 110 to 700 pg/mL. When her systolic BP was low, the plasma norepinephrine concentration was frequently below the limit of normal, whereas when it was very high, it was frequently well above the upper limit of normal. A clonidine suppression test was performed on two occasions to further investigate the diagnosis of pheochromocytoma (Figure 2). On one occasion (during a hypertensive episode), plasma norepinephrine was below normal and
remained suppressed throughout, whereas on the other occasion (during a hypertensive episode), the initial norepinephrine level was high, but was suppressed to normal after clonidine. A glucagon stimulation test was also negative. This result does not support the diagnosis of pheochromocytoma. Furthermore, whole-body computed tomographic scans (neck, chest, abdomen, and pelvis) revealed no lesion to suggest the presence of an adrenal or extra-adrenal mass. Serial venous sampling from the superior and inferior vena cava, femoral and internal jugular veins, and the right atrium did not show a significant difference in the catecholamine levels.

**Sodium Balance With Changes In Dietary Salt**

The patient was admitted to the Clinical Research Center (CRC) for 14 days to study the effects of changes in dietary salt on sodium balance and BP. During the first 7 days, the patient received a daily intake of 189 mEq of sodium, and during the following 7 days, it was reduced to 20 mEq. The BP was measured while lying and after head-up tilt of 60 degrees on the last day of each study period. Urinary sodium excretion was determined every 12 h. She developed a sudden episode of hypotension on the last day of high sodium intake that required an infusion of 0.154 M saline. As shown in Figure 3, sodium repletion or restriction failed to alter either the lying or the tilted BP. There was a rapid and appropriate reduction in sodium excretion during the salt restriction period (Figure 3). On the last study day, the effect of normal saline loading on BP and heart rate was tested. Initial lying and posthead-up tilt BP and heart rate were determined, and baseline hematocrit and catecholamine were measured. Two liters of normal saline was infused over a 2-h period, and BP and heart rate were measured again. Furosemide (40 mg) was given intravenously, and the BP and heart rate were determined after 2 h. A urine output of 500 mL was observed over a 2-h period after furosemide. Two liters of normal saline was infused again over the next 2-h period. No significant differences in BP or heart rate were observed after normal saline infusion or furosemide administration.

[Figure 2. Results of two clonidine suppression tests demonstrating changes in the systolic blood pressure (SBP) and plasma norepinephrine concentration after 0.3 mg of clonidine.]

[Figure 3. Heart rate (HR), systolic blood pressure (SBP), and sodium balance during changes in salt intake.]
Assessment of the Baroreflex Mechanism

Studies of the baroreflex mechanism were undertaken at the CRC. During these tests, the pacemaker was deactivated to properly assess the changes in heart rate. Valsalva's maneuver was performed with an intra-arterial recording by blowing into a tube connected to a pressure transducer to raise the intraoral pressure to 40 mm Hg for 20 s. There was a normal response of hypotension and tachycardia during forced expiration, followed immediately after the procedure by a transient overshoot of the BP (Figure 4) associated with bradycardia (54 compared with 110 beats/min). The baroreceptor reflex mechanism was further evaluated by graded infusions of phenylephrine and sodium nitroprusside, while monitoring the heart rate, to increase or decrease the systolic BP by 25 mm Hg, respectively. Phenylephrine was infused at a graded rate of 0.125 to 0.75 μg/kg per minute and nitroprusside was infused at a graded rate of 0.05 to 1.2 μg/kg per minute to increase or decrease the systolic BP by 25 mm Hg, respectively. These tests revealed appropriate increases in heart rate during a reduction in BP and decreases in heart rate during increases in BP (Figure 5).

Other Investigations

A drug screen was negative on three occasions. The Watson-Schwartz test and the measurement of δ-aminolevulenic acid and porphobilinogen excretion for porphyria were negative. Computed tomography of the brain and an electroencephalogram were both normal. A captopril test was negative with a postcaptopril plasma renin activity of 2.1 ng/mL per hour and plasma aldosterone of 5.5 ng/dL. Her plasma cortisol in the morning was normal at 9.8 μg/dL.

Management

The patient was treated with fludrocortisone, 0.1 mg twice a day, to combat hypotension and clonidine as required to manage hypertension, increased heart rate, and symptoms of catecholamine excess. Although there was a significant reduction in the frequency and the severity of the hypotensive episodes with the use of fludrocortisone, the hypertensive episodes became more frequent than before. However, clonidine was effective in controlling these episodes.

DISCUSSION

This patient presented with clinical features characterized by intermittent episodes of severe hypotension associated with a slow heart rate, alternating with episodes of hypertension associated with tachycardia and symptoms of catecholamine excess. Some of the diagnoses that were considered to explain the symptoms of labile hypertension with excess plasma catecholamines are summarized in Table 1. Although patients with pheochromocytoma usually present with intermittent or sustained hypertension, presentation with hypotension or alternating hypertension and hypotension has been previously documented (1–3). The mechanisms of orthostatic hypotension in pheochromocytoma include reduced plasma volume, impaired cardiovascular reflexes, and epinephrine-induced vasodilation in blood vessels to skeletal muscle. In a recent review, the clonidine suppression test was found to be 92% accurate in diagnosing pheochromocytoma (4). From the results of these extensive investigations and the favorable response to clonidine treatment, pheochromocytoma appears quite unlikely. Several rare causes for this patient's clinical condition were ruled out by appropriate evaluation and include: carotid sinus syndrome, vasovagal attacks, hypoglycemia, intracranial lesions or epileptic seizure, illicit or self-administered drug use, acute intermittent porphyria, mitral valve prolapse or other valvular lesions, renovascular hypertension, and underlying psychiatric disorder.

Lesions resulting in autonomic dysfunction may involve the afferent pathway, the central connections, the efferent pathway, the target organs, or a combina-
tion of these, depending on the disorder. The evaluation of a patient with suspected autonomic insufficiency includes multiple tests involving all organ systems. Therefore, the selection of the investigations should be designed to define the site of the lesion, depending on the clinical presentation. Figure 6 describes a simple algorithm for the initial evaluation of a patient suspected to have autonomic insufficiency. Further work-up will depend on the clinical presentation and the findings from the initial evaluation. Because our patient had evidence of abnormal BP regulation, an evaluation of the autonomic control of BP and cardiovascular reflexes was undertaken.

The autonomic nervous system is required for the normal regulation of body fluid. Defective renal sodium conservation during salt restriction was described in normal human subjects with the sympatholytic drug guanethidine (5). Sodium wasting was further shown in patients with autonomic failure. Although the defective sodium conservation was accompanied by subnormal aldosterone excretion, this is only partly responsible for this defect (6). In this patient, neither lying nor standing BP fell during sodium restriction. We studied sodium balance and BP in this patient during an alteration in salt intake, with 1 wk of normal sodium intake followed by a week of sodium restriction. As shown in Figure 3, appropriate sodium excretion occurred during a high salt intake and sodium conservation occurred during periods of sodium restriction. In addition, sodium restriction was not associated with postural hypotension or lower BP in comparison to normal sodium intake. Indeed, the patient actually developed a hypertensive episode during the high sodium intake. Clearly, there was no correlation between sodium intake and BP. Furthermore, no significant changes in BP or heart rate were observed after normal saline infusion or intravenous furosemide administration. Therefore, this patient does not have salt-sensitive BP, nor is the response to salt restriction suggestive of autonomic neuropathy (5–7). The hypotensive episodes cannot be ascribed to defective sodium conservation.

Both hypoadrenergic orthostatic hypotension and hyperadrenergic orthostatic hypotension have been described in different categories of patients with diabetes mellitus (8,9). Diabetic patients with hypoadrenergic postural hypotension usually have combined autonomic and peripheral neuropathy, with a lower than normal mean norepinephrine concentration in both the supine and the standing positions (10). Several studies have shown an association between peripheral and autonomic nerve dysfunction in long-term insulin-dependent diabetics (11,12). The absence of peripheral neuropathy and other features suggestive of autonomic neuropathy, such as gastrointestinal symptoms or defective sweating, argues against the diagnosis of diabetic autonomic neuropathy (12). Furthermore, the normal response to Valsal-
va's maneuver and appropriate heart rate changes with phenylephrine and sodium nitroprusside infusions effectively exclude a diagnosis of autonomic neuropathy due to diabetes mellitus. Patients with diabetes mellitus may also have hyperadrenergic orthostatic hypotension. The increased sympathetic activity in these patients has been attributed to a diminished intravascular volume or a vascular resistance to norepinephrine (9). All patients studied had subnormal blood volume, which may contribute to the orthostatic hypotension and enhanced catecholamine levels (9). In contrast, our patient had episodes of hypotension associated with low norepinephrine concentrations, whereas high norepinephrine concentrations were associated with episodes of labile hypertension. As shown in Figure 1, the BP was directly correlated with the plasma norepinephrine concentrations. This suggests that the high norepinephrine concentration may be a marker of enhanced sympathetic nervous system activity and may be causally related to the tachycardia and high BP, and not a response to a reduced blood volume. Furthermore, our patient had hypertensive episodes, which are not a feature of hypoadrenergic or hyperadrenergic orthostatic hypotension. Therefore, the clinical picture of this patient is not consistent with hypoadrenergic or hyperadrenergic orthostatic hypotension.

Baroreceptors in the carotid sinus, the aortic arch, and great vessels in the thorax transmit neural signals via the glossopharyngeal and vagus nerves to the brain stem. Abnormalities in the vascular baroreceptors, their neural connections, or the brain stem can lead to baroreflex failure. True baroreflex failure entails the loss of buffering of BP and is characterized by the volatility of BP and heart rate (13,14). In a recent study, Robertson et al. described 11 patients with baroreflex failure presenting with labile BP and hypertensive episodes accompanied by high levels of plasma catecholamines (15). However, our patient differs from those described previously (15–17), because she had prominent symptomatic hypotensive episodes. Moreover, she lacks a clinical cause, such as neck surgery, for baroreceptor damage. Additionally, she had an appropriate heart rate response to Valsalva's maneuver (Figure 4) and to induced changes in BP (5). Therefore, this patient appears to have an intact baroreflex arc.

The central autonomic network is an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioral responses (18). Bilateral lesions of the nucleus tractus solitarii in experimental animals abolish the baroreflex mechanism and result in fulminant neurogenic hypertension or chronic lability of BP (19). In humans, intraoperative stimulation of the insular, orbitofrontal, or anterior temporal cortex produces substantial changes in arterial pressure and heart rate (20,21). Structural lesions of the frontal or prefrontal cortex and amygdala may be associated with autonomic disturbances (22). The sudden onset of the episodes of hypotension and hypertension and the association with changing norepinephrine concentration in our patient with intact baroreflex mechanism suggest that the lesion is in the central integration of the sympathetic outflow. The presence of a normal baroreflex mechanism in our patient suggests that the lesion is above the level of the nucleus tractus solitarii. Environmental stress may be translated into increased sympathetic nervous activity via the limbic-hypothalamic-bulbar autonomic centers. In addition, acute environmental stress in spontaneously hypertensive rats elicits a prompt and sustained increase in arterial BP and heart rate (23). Our patient had no features to suggest mental stress or major psychiatric illness to explain her clinical condition. Although it is not possible to determine the exact site of lesion, the abnormal BP regulation in this patient appears to be of central origin.

Studies performed in this patient helped us to understand the underlying pathophysiology of her disease. The hypotensive episodes were more frequent and required more hospital admissions than the hypertensive episodes. The usual approach to the treatment of orthostatic hypotension is to expand plasma volume by administering fludrocortisone. Many patients with autonomic neuropathy have a normal plasma volume (24) but may become volume expanded during treatment with fludrocortisone. Several other pharmacologic agents such as prostaglandin inhibitors (25), somastostatin analogues (26), ergot alkaloids (27), and α1-adrenergic receptor agonists (28) have been used with variable success and side effects. Recently, erythropoietin has been reported to be useful in the treatment of orthostatic hypotension due to autonomic failure, although supine hypertension was a side effect in some patients (29,30). In our patient, fludrocortisone, 0.1 mg twice daily, helped to reduce the frequency of hypotensive episodes. The second aspect of the treatment of this patient was the hypertensive episodes associated with tachycardia and elevated norepinephrine levels, which are most likely centrally mediated. Animal studies have demonstrated that clonidine inhibits central sympathetic outflow, reduces the release of norepinephrine, and may have a vagomimetic action (31,32). In humans, clonidine reduced muscle sympathetic nerve activity and the sympathetic response to the cold pressor test without modifying the ability of the baroreceptors to respond to BP fluctuations (33). In our patient, clonidine suppressed norepinephrine concentration to normal during the clonidine suppression test (Figure 2). Furthermore, clonidine was effective in reducing the BP and heart rate in our patient during the hypertensive episodes when she was hospitalized. Therefore, we have used initial treatment with fludrocortisone on a regular basis to reduce the frequency of hypotensive episodes and clonidine intermittently to combat hypertension and tachycardia mediated by increased sympathetic outflow.

In conclusion, this patient presents with extremes
of BP without an obvious precipitating factor. The hypotensive episodes were associated with relative bradycardia, tiredness, and a low norepinephrine level that did not increase on standing. In contrast, the hypertensive episodes were associated with tachycardia, syncope, anxiety, sweating, and very high plasma norepinephrine levels that increase further on standing. She has intact autonomic reflexes and a BP that appeared quite insensitive to change in salt intake. This constellation of clinical findings appears not to have been described before.

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REFERENCES