Rapid Cyclic Fluctuations of Blood Pressure Associated with an Adrenal Pheochromocytoma

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SUMMARY We present a patient with an adrenal pheochromocytoma with an unusual pattern of periodic alternating hypertension and hypotension. Alpha-adrenergic blockade alone failed to affect this pattern, which was abolished only after fluid repletion. The efficacy of volume expansion in ultimately correcting the wide fluctuations of blood pressure implicates a possible reflex neurogenic mechanism for the cyclic changes in blood pressure attributable to intravascular volume contraction. (Hypertension 6: 281–284, 1984)

Key Words • adrenal • adrenergic blockade • catecholamines • hypertension • pheochromocytoma

Episodic rises in blood pressure in patients harboring pheochromocytoma are well known. However, rapidly occurring cyclical hypertension alternating with hypotension in such patients has rarely been documented. In one report, a catecholamine-secreting glomus jugulare tumor was associated with such a response. We report here a similar response in a patient with an adrenal pheochromocytoma. Alpha-adrenergic blockade with phentolamine alone did not control the blood pressure fluctuations, which finally abated only when volume replacement was instituted.

Case Report

History

This 67-year-old man had diabetes mellitus for 15 years. Two years earlier he had been admitted to a hospital for evaluation of precordial pain, episodes of sweating, weakness, and dyspnea associated with marked bradycardia. He was felt to have “sick sinus syndrome” and a permanent pacemaker was placed. Even after the placement of the pacemaker he continued to have symptoms, which were attributed to suboptimal functioning of the pacemaker. He was taking 28 units of Lente insulin for the diabetes mellitus but had not experienced hypoglycemia. During the 6 months preceding the first admission to our hospital he had short attacks of “rapid heart beat” and diaphoresis. A malfunction of the pacemaker was suspected, but when the demand rate was decreased from 72 to 60 bpm, symptoms persisted. Hypoglycemia was also considered, but adjusting his insulin regimen did not change the symptoms. Office blood pressure measurements had always been less than 140/90 mm Hg. On the day of his admission to the local hospital he had several bouts of vomiting associated with headache, pain over his left eye, profuse sweating, palpitation, and left infracostal pain. A diagnosis of acute myocardial infarction was considered.

Examination

The blood pressure on admission to the coronary care unit was 230/130 mm Hg, but fluctuated to as low as 120/60. Blood glucose concentration was 428 mg/dl. The patient was treated for a short time with hydrochlorothiazide, propranolol, and apresoline for the hypertension, but the blood pressure continued to fluctuate and he was transferred to the Indiana University Medical Center. On admission he was found to be diaphoretic, pale, with cool and clammy skin and was nauseated. At first it was thought that he became hypotensive when sitting, but hypotensive episodes occurred even when supine. His blood pressure was seen to fluctuate between 120/60 to 230/130 mm Hg with pulse rates ranging from 70 to 150 per minute. Fundoscopic examination was normal. A subcutaneous pace-
maker unit was in place over his right chest. Cardiovascular examination was otherwise unremarkable. Abdominal examination also revealed no abnormalities. There was no peripheral edema, and all pulses could be felt. The neurological examination was normal. Laboratory data revealed a hemoglobin of 19.4 g/dl, hematocrit 55.3%, and a white blood cell count of 18,600/mm³. The serum sodium was 138 mEq/liter, potassium 4.6 mEq/liter, BUN 34 mg/dl, creatinine 0.7 mg/dl, and glucose 297 mg/dl. The chest x-ray was normal, and the EKG showed nonspecific ST-T changes with an occasional, accelerated junctional rhythm.

In the intensive care unit his blood pressure showed rapid increases of systolic blood pressure up to 240 mm Hg and then decreased to as low as 60 mm Hg every 5 to 10 minutes in a recurring pattern (Figure 1 A). The pulse rate bore an inverse relationship to the blood pressure, decreasing to as low as 62 bpm during the hypertensive crises and increasing up to 134 bpm during the hypotensive periods. A tentative diagnosis of pheochromocytoma was made.

Treatment

The patient was given intravenous phentolamine, 1 mg at frequent intervals after an initial dose of 2 mg. After a total of 17 mg had been given the amplitude of the blood pressure swings had decreased some and by the time 25 mg had been given, the episodic pattern was less evident (Figure 1 B). An intravenous infusion of phentolamine was then started at the rate of 4 to 6 mg/hr. However, the cyclic variations in blood pressure returned, and we began to question the diagnosis of pheochromocytoma (Figure 1 C).

In view of the history of diuretic therapy earlier, profuse sweating, and recent vomiting with clinical suspicion of dehydration, we initiated an infusion of normal saline at the rate of 500 cc/hr under careful supervision. Within 1 hour, the episodic fluctuation of blood pressure tended to decrease (Fig. 1 D) and virtually disappeared after only several hours of fluid replenishment (Fig. 1 E). The infusion of normal saline and the phentolamine administration were continued, and the blood pressure stabilized between 110–120/80–90 mm Hg. Oral phenoxybenzamine was also started at this time in a dosage of 20 mg a day and later gradually increased to 50 mg a day in divided doses. The phentolamine infusion was tapered and discontinued over the next 4 hours. Repeat hemoglobin and hematocrit measurements subsequently showed normalization of those parameters (hemoglobin 16.2 g/dl and hematocrit 45.8%), with clinical improvement of the status of hydration. Total urinary VMA was 16.3 mg/24 hr and metanephrines were 2.8 mg/24 hr. Short collections of urine for determination of norepinephrine excretion rate during the first 48 hours and including sleep urine showed the rates to range from 26.6 to 92.7 µg/hr (normal up to 1.9 ± 0.05 µg/hr). Subsequently a CT-scan demonstrated a right adrenal mass and a selective arteriogram confirmed a vascular, 4 × 6 cm adrenal tumor.

After 1 month of therapy with phenoxybenzamine, during which the patient was asymptomatic, a right adrenal pheochromocytoma was removed. His symptoms have not recurred during 2 years of follow-up. The blood pressure has remained normal, and the sleep urinary norepinephrine excretion rate has returned to normal.

Summary

Blood pressure was monitored in our patient every 1 minute initially, then every 2 minutes using an Arteriosonde (Model 1214, Roche Medical Electronics). The diagnosis of pheochromocytoma was established by measurements of urinary metabolites of catecholamines and free sleep urinary norepinephrine excretion rate, localization by radiographic techniques such as arteriography and/or CT-scan, and eventually by the surgical removal of the adrenal tumor. Urinary norepinephrine was measured by radioenzymatic assay.

The cyclic variations of systolic and diastolic blood pressure prior to treatment, the responses to intravenous pulses of phentolamine, phentolamine infusion, and then the effect of fluid replenishment can be appreciated in Figure 1 (A-E). Although it seemed as though the marked periodic fluctuation of blood pressure tended to decrease soon after the initiation of fluid replenishment, it did not quite subside until several hours of fluid therapy (Figure 1 E). Direct measurement of volume changes was not available, but clinical evidence and the decrease of the initial high hemoglobin and hematocrit level suggest improvement of intravascular volume.

Discussion

The patient described in this report exhibited rapid fluctuations of blood pressure with a definite periodicity. Although paroxysmal hypertension in pheochromocytoma is well recognized, such episodes occur at irregular and often unpredictable intervals. Severe hypertension followed by hypotension and nocturnal episodes of hypertension has been described in patients with pheochromocytoma. The type of periodic changes seen in our patient is distinctly unusual. Despite earlier allusion to such oscillations of blood pressure by Howard and Barker, more recently Matsuguchi and colleagues have documented them clearly in a case report. They have attributed this unusual blood pressure response to the nature and site of the tumor, namely, glomus jugulare tumor.

The mechanism for these cyclic fluctuations of blood pressure in pheochromocytoma is not clear. Wave-like patterns of blood pressure changes can be produced in experimental animals under certain conditions and have been called Mayer waves. They probably result from a reflex mechanism involving either chemoreceptors or baroreceptors. Ferretti and associates have proposed that hemorrhagic hypotension and/or systemic acidosis by decreasing blood flow to the chemoreceptors might initiate the Mayer waves. A similar mechanism could be implicated in our patient, who developed hypovolemia from vomiting,
profuse sweating, and earlier diuretic therapy. Additionally, some untreated patients with pheochromocytoma are known to have a contracted blood volume.1 Hence, there was a strong basis for development of hypovolemia in our patient.

Alternatively, the hypertensive episodes may have been initiated by an ischemic response12-15 of the central nervous system (CNS). In such a setting, prompt bradycardia occurs secondarily from the intact and normally functioning baroreceptor mechanism.15 Such bradycardia may have caused hypotension and CNS hypoperfusion in our patient, especially in the presence of contracted intravascular volume triggering the CNS reflex again in a cyclical manner. This reflex CNS response is often associated with apnea, which was not evident in our patient. However, the conditions favoring the development of this CNS ischemia were present.

The frequency of the cyclic blood pressure changes was considerably slower in our patient than that seen in
experimental animals, either in the case of Mayer waves or CNS ischemic reflex. It is possible that species variation could account for such a difference. It has been demonstrated that a neurogenic mechanism is active in patients with pheochromocytoma despite excessive levels of circulating catecholamines. The reciprocal changes in pulse rate and blood pressure seen in our patient probably absolve an abnormal baroreceptor function as a mechanism for the cyclical hypertension.

The infusion of fluid and alpha-adrenergic blockade, but not the latter alone, terminated the cyclic blood pressure changes, possibly by improving the blood flow to the chemoreceptor zones or to the lower brain-stem areas. Further support for hypovolemia as a cause of hypertensive response may be found in the report by Cohn, who described episodic hypertension in three patients with evidence of hypovolemia. None of the patients in that report was shown to have pheochromocytoma, and volume repletion normalized the blood pressure. These unusual blood pressure responses were ascribed to hypovolemia-evoked neural discharges. Although in our patient volume measurements could not be undertaken before and after the treatment, some support for a role of volume repletion in stabilizing blood pressure lability is available to sustain our tenet. Repeat measurements of hematocrit and hemoglobin also indicated improvement of the fluid volume status in our patient. We cannot, however, dissociate an additive role of alpha-adrenergic blockade to volume repletion in bringing about the favorable result in our subject, since the former is known to cause intravascular volume expansion and enhanced blood flow to the tissues.

Initial events in our patient were likely to have been provoked by excessive secretion of catecholamines by the pheochromocytoma, but the subsequent events appear to have had a neurogenic basis. A lack of correlation between the blood pressure and plasma catecholamine levels in patients with pheochromocytoma has been reported by Louis et al. and Bravo et al. and may conceivably be related to a failure of instantaneous access of circulating catecholamines, in contradistinction to neurally released catecholamines to the vascular alpha adrenergic receptor sites or to complex interactions of catecholamines with other factors. If the proposed mechanism of this curious abnormality described in our patient is valid, then the results of treatment underscore the need for volume expansion in addition to alpha-adrenergic blockade in similar circumstances. To our knowledge, a detailed documentation of such an abnormal and unusual pattern of blood pressure variation in association with an adrenal pheochromocytoma and the effect of intravenous fluid therapy has not been previously reported.

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