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)

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 sub-optimal 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. Cardiov
vascular examination was otherwise unremarkable.
Abdominal examination also revealed no abnormali
ties. There was no peripheral edema, and all pulses
could be felt. The neurological examination was nor
mal. Laboratory data revealed a hemoglobin of 19.4 g/
dl, hematocrit 55.3%, and a white blood cell count of
18,600 cmmm. 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 pres
sure 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 virtu
ally disappeared after only several hours of fluid reple
tion (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 phen	olamine 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 symp
toms 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 Arterio
sonde (Model 1214, Roche Medical Electronics). The
diagnosis of pheochromocytoma was established by
measurements of urinary metabolites of catechola
mines 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 norepi
nephrine was measured by radioenzymatic assay.

The cyclic variations of systolic and diastolic blood
pressure prior to treatment, the responses to intrave
nous pulses of phentolamine, phentolamine infusion,
and then the effect of fluid repletion 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 replenish
ment, it did not quite subside until several hours of
fluid therapy (Figure 1 E). Direct measurement of vol
ume 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 periodic
ity. Although paroxysmal hypertension in pheochrom
cytoma is well recognized, such episodes occur at
irregular and often unpredictable intervals. Severe hy
pertension followed by hypotension and nocturnal
episodes of hypertension has been described in pa
tients with pheochromocytoma. The type of periodic
changes seen in our patient is distinctly unusual. De
spite earlier allusion to such oscillations of blood pres
sure by Howard and Barker, more recently Matsugu
chi 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 condi
tions and have been called Mayer waves. They
probably result from a reflex mechanism involving either
chemoreceptors or baroreceptors. Ferretti and associ
ates 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 pa
ient, 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. Hence, there was a strong basis for development of hypovolemia in our patient.

Alternatively, the hypertensive episodes may have been initiated by an ischemic response of the central nervous system (CNS). In such a setting, prompt bradycardia occurs secondarily from the intact and normally functioning baroreceptor mechanism. 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

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**Figure 1. Variations of systolic and diastolic blood pressure levels.**

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 neuronally 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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References

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