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Paroxysmal Hypotension Associated with Sympathetic Withdrawal
A New Disorder of Autonomic Vasomotor Regulation

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SUMMARY We evaluated a patient who had transient episodes of hypotension with clinical and laboratory features apparently distinct from previously recognized disorders of vasomotor regulation. In between his abrupt attacks of hypotension, the patient is asymptomatic and demonstrates normal autonomic modulation of heart rate and blood pressure in response to changes in body position, Valsalva maneuver, cold, and exercise. During periods of hypotension, his plasma norepinephrine falls markedly and he has blunted or absent responses to stimuli that normally have a pressor effect due to sympathetic efferent discharge. Mechanical or known hormonal disorders that produce episodic hypotension have been excluded by extensive testing. We suggest two possible causes for our patient’s paroxysmal sympathetic withdrawal: first, a centrally mediated inhibition of sympathetic discharge to peripheral resistance and capacitance vessels, but with no afferent stimulus reflexly producing sympathetic withdrawal readily evident; or second, an episodic release of an unknown endogenous compound with inhibitory effects upon central or preganglionic sympathetic neurons or upon postganglionic sympathetic neurons by a presynaptic inhibition of norepinephrine release.

HYPOTENSION associated with abnormal autonomic modulation of vasomotor function is a prominent feature of several neurologic disorders. One of the following mechanisms: episodic or variable vascular obstruction, abnormal activation of vasodepressor reflexes, abnormal episodic release of endogenous vasoactive substances, or had to remain supine to avoid syncope. The onset of the spells was not related to body position. There were no premonitory symptoms, no apparent periodicity, and no evident precipitating events (such as exertion, meals or emotional stress) associated with the episodes. He occasionally had bitemporal headaches during or after a period of hypotension, but had no other associated symptoms. He had no flushing of the skin. In between the episodes he was asymptomatic, with no orthostatic lightheadedness or abnormalities of sweating or micturition.

He first noted similar spells in 1971, though from that time until late 1978 they had been less frequent (one or two per month) and were shorter (5–60 minutes) than the more recent spells. Previous therapeutic trials of ephedrine, atropine and fludrocortisone acetate had been ineffective in preventing or moderating his symptoms.

His medical history included numerous episodes of superficial and deep thrombophlebitis of the lower extremities, dating from a deep-vein thrombosis during hospitalization for an appendiceal abscess at age 12 years, and including several vein-stripping procedures. In 1971 he suffered an angiographically documented pulmonary embolus despite systemic anticoagulation, and underwent percutaneous insertion of an umbrella filter device into his inferior vena cava. He also had a history of abuse of alcohol and minor tranquilizers and reported several hospital admissions for psy-
Hypotension was usually treated with diuretics. On physical examination he weighed 235 lbs and was 5'10" tall. His supine vital signs were pulse rate 72 beats/min and blood pressure 150/90 mm Hg, changing normally with standing to a pulse rate of 76 beats/min and blood pressure of 142/90 mm Hg. During a typical hypotensive spell (fig. 1) his blood pressure fell precipitously, to a range of 50/30 mm Hg to 80/50 mm Hg, usually with no change in heart rate or a slowing to a range of 48-68 beats/min. His periods of hypotension during hemodynamic monitoring ranged from 3 minutes to 2½ hours. During hypotension he remained oriented and conversant, though at times he appeared drowsy; his extremities remained warm; he did not become diaphoretic; his pupils were midposition and his pupillary responses to light were preserved; and his respiratory rate generally increased slightly, although he had no striking hyperventilation.

His skin showed stasis hyperpigmentation of the lower extremities. His head, eyes, ears, nose and throat were normal. His jugular venous pulsations were normal, as was his thyroid gland. He had bilateral carotid bruits, which were more prominent on the left. His left ventricular impulse was in the fifth left intercostal space, 12 cm from the midsternal line, and was normal. S₁ and S₂ were normal, and an S₄ gallop was present. No cardiac murmurs or other abnormal sounds were present. His lungs, abdomen, rectum, and genitalia were normal. The lower extremities showed superficial varicosities and 1+ peripheral edema. The peripheral arterial pulsations were normal. His neurologic examination was within normal limits.

Baseline laboratory data included a chest radiograph that was normal except for some calcification in the aortic knob and an ECG that showed nonspecific ST-T-wave changes only. His ECG was unchanged during hypotension. A complete blood count, urinalysis, serum electrolytes, urea nitrogen, blood sugar, and SMA-12 were within normal limits, except for a uric acid of 8.7 mg%. His prothrombin time was 12.3 seconds (control 11.8 seconds). Partial thromboplastin time was 32.3 seconds (control 39.8 seconds).

Other laboratory data included erythrocyte sedimentation rate (Westergren) 38 mm/hour fluorescent antinuclear antibody titer 1:160 with weakly speckled pattern, VDRL negative, hepatitis-associated (surface) antigen negative, rheumatoid factor negative, LE prep negative, thyroxine 9.8 mg/100 ml, RT3U 27%.

Radioisotope quantification of plasma volume by 125I-albumin was within normal limits. Plasma cortisol was normal. A toxic screen of plasma at the time of admission revealed only trace levels of benzodiazepine metabolites. Urinary excretion per 24 hours of 5-HIAA was undetectable, and of VMA was normal at 3.4 mg. Computerized axial tomography of the abdomen was normal.

### Laboratory Evaluation of Hypotensive Episodes

The hemodynamic characteristics of our patient's hypotensive episodes were studied in the cardiac catheterization laboratory and by continuous hemodynamic monitoring on the coronary care unit. Recordings of intra-arterial blood pressure during normotension and during typical hypotensive episodes are shown in figure 1. Hemodynamic measurements obtained in the catheterization laboratory before and during a hypotensive spell are listed in table 2. The initial pulmonary capillary wedge pressure of 18 mm Hg, observed in the catheterization laboratory, followed the injection of radiographic contrast media; more typical measurements during continuous hemo-
dynamic monitoring on the coronary care unit during normotension ranged from 8–14 mm Hg, and during hypotension ranged from 5–8 mm Hg.

Injections of contrast media into the right atrium revealed no evidence of right atrial myxoma, and no left atrial filling defects were noted during levophase. An echocardiogram was normal. Because we suspected intermittent venous obstruction of the inferior vena cava at the level of his umbrella device, pressure measurements above and below the umbrella were made and contrast injections were performed during normotension and during hypotension. There was no pressure gradient, and dye flowed freely across the umbrella during hypotension.

We tested our patient’s responses to a number of stimuli known to activate intrinsic autonomic responses in normal subjects. Unlike his normal circulatory responses to changes in body position while normotensive, during a hypotensive episode his blood pressure fell still further with changes from the supine to sitting position, evoking symptoms of presyncope, and he failed to elevate his heart rate with sitting.

Valsalva maneuvers during normotension elicited the expected fall in arterial pressure and tachycardia during the late strain phase, followed by the normal “overshoot” of blood pressure with slowing of the heart rate upon release (fig. 2A). During hypotension, these responses were markedly blunted (fig. 2B). The adequacy of the Valsalva maneuver in each instance was documented by a rise in intrathoracic pressure of at least 40 mm Hg for at least 10 seconds as recorded by a central venous catheter. Similarly, placing his hand in ice water during normotension evoked the normal pressor response (fig. 3A), while little effect was noted during a hypotensive episode (fig. 3B). Massage of either the left or right carotid sinus produced bradycardia during normotension, but did not produce hypotension; during hypotension, it produced slight sinus slowing or had no effect.
Plasma catecholamines were measured by radioenzymatic assay on blood obtained from an indwelling venous needle left in place at least 15 minutes before sampling. On 2 days, after blood samples were obtained while the patient was supine and his blood pressure was greater than 120/80 mm Hg, a hypotensive episode began. Repeat blood sampling was done 5–15 minutes after the onset of a fall in arterial pressure to levels less than 80/50 mm Hg. Each time hypotension was associated with a fall in plasma catecholamines.

**Figure 2.** Intra-arterial pressure recordings during Valsalva maneuvers. (A) Valsalva maneuver during normotension. Note the prominent "overshoot" of arterial pressure after the release of intrathoracic pressure. (B) Valsalva maneuver during hypotension. Note the absence of the "overshoot" phenomenon.

**Figure 3.** Intra-arterial pressure recordings during immersion of the right hand in ice water. (A) Ice water immersion during normotension. Note the rapid and sustained rise in arterial pressure, followed by a return to baseline after the cold stimulus was withdrawn. (Two minutes elapse at the break in the tracing.) (B) Ice water immersion during hypotension. Note the absence of a significant pressor effect. HR = heart rate.
nepinephrine to roughly one-half the resting value (fig. 4).

An electroencephalogram with nasopharyngeal leads was within normal limits during normotension and was unchanged during a hypotensive episode. Forearm venous plethysmography was monitored by standard techniques before and during a hypotensive episode, with results roughly paralleling the central hemodynamics during cardiac catheterization. Hypotension was associated with an abrupt fall in forearm vascular resistance (fig. 5). When this occurred, ice placed on the forehead, perhaps a more potent sympathetic stimulus than placing the hand in ice water, was associated with a slight, although blunted, pressor response. During normotension, a bicycle ergometer exercise test was unassociated with abnormalities in his ECG, and his heart rate and blood pressure responses to exercise were normal. His ventricular function as assessed by gated blood pool radionuclide angiography was normal both at rest and with bicycle exercise.

Response to Cardiac Pacing, Pharmacologic Agents and Biofeedback

Right atrial or right ventricular pacing (fig. 6) during a hypotensive episode did not correct the hypotensive state. Two types of drug studies were performed: acute i.v. or intranasal drug administration during a hypotensive episode aimed at correcting the hypotension and oral drug administration over a 72-hour period aimed at the prevention or modification of the hypotensive spells. Because of the marked spontaneous variation in the duration of his hypotensive spells, all acute interventions were performed several times. Neither i.v. atropine (2 mg), propranolol (5 mg), or isoproterenol (4 \( \mu \)g/min) produced a pressor response during hypotensive episodes (fig. 6B and 6C), although a cardioacceleratory effect of both atropine and isoproterenol did occur. With i.v. phenylephrine at an infusion rate of 75 \( \mu \)g/min, blood pressure returned to or above the normal range each of the three times it was tested (fig. 6D). A dose-response effect was observed for phenylephrine in that lower doses evoked smaller pressor effects. The doses of i.v. phenylephrine necessary to produce a pressor response were similar to those required for pressor effects in normal subjects. Thus, we did not observe the hypersensitivity to infused catecholamines that may be present in patients with idiopathic orthostatic hypotension. Intranasal phenylephrine (1%) solution in doses

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**Figure 4.** Plasma norepinephrine levels plotted against the systolic blood pressure at the time of blood sampling. Values during normotension are expressed as open squares and values during hypotension as open circles. The dotted lines connect determinations that were made serially within 1 hour of each other. The mean plasma norepinephrine during normotension (closed square) differed significantly from the mean value during hypotension (closed circle) at the p < 0.05 level by one-way analysis of variance. Vertical lines represent the SEM.

**Figure 5.** Heart rate (HR), blood pressure (BP), forearm blood flow (FBF) and forearm vascular resistance (FVR) before and during a hypotensive episode. Note the rapid decline in forearm vascular resistance occurring simultaneously with the fall in systemic arterial pressure. The application of ice to the forehead (arrow) produced a rise in vascular resistance and a slight increase in arterial pressure, though without returning arterial pressure to the normal range.
10 mg twice daily, induced any observable change in the frequency, severity or duration of the hypotensive episodes.

Biofeedback techniques and hypnosis were used to find clues to possible centrally mediated factors leading to his hypotensive episodes. Although a hypotensive spell occurred once during hypnosis, it could not be reversed during or in the hour after hypnosis, and voluntary induction or reversal of hypotension could not be reproducibly accomplished on other occasions. The patient denied any voluntary control over the episodes or any insight into psychological trigger mechanisms. Surreptitious drug administration was excluded by intra-arterial pressure recordings documenting numerous typical hypotensive episodes during sleep, during direct observation of the patient in the catheterization laboratory, and during direct visual monitoring of the patient by closed-circuit television in the coronary care unit.

Discussion

Our patient's hypotensive episodes appear to be different from previously reported disorders causing hypotension. During periods of normotension, he demonstrated normal autonomic vasomotor and cardiac chronotropic responses to standing, Valsalva maneuver, cold and exercise. His periods of hypotension were associated with signs of dramatic withdrawal of peripheral sympathetic efferent tone in both resistance and capacitance vessels. During hypotension his total peripheral vascular resistance and forearm vascular resistance fell markedly, his pulmonary capillary wedge pressure fell, he demonstrated blunted or absent responses to maneuvers that normally activate sympathetic neural reflexes, and he had an inappropriate bradycardia and an inappropriate absence of cutaneous signs, such as pallor or sweating, given the profound level of hypotension present. In addition, his plasma norepinephrine fell markedly with the onset of hypotension, and the hypotension could be readily corrected by i.v. phenylephrine, presumably through its effect upon postsynaptic vascular α-adrenergic receptors, but not by cholinergic antagonists, β-adrenergic agonists or antagonists, cardiac pacing, prostaglandin synthesis inhibitors, histamine antagonists, monoamine oxidase inhibitors, or antiepileptic medication.

We considered several possible causes for our patient's hypotensive spells. Anatomic loss of sympathetic neurons, inflammatory neuritis, or metabolic abnormalities, such as diabetes mellitus leading to autonomic insufficiency, were excluded by the highly transient nature of the hypotensive episodes, the absence of other neurologic dysfunction, and the absence of discernible metabolic abnormalities. In addition, he had no other clinical evidence for the neurologic disorders listed in table 1A that have been associated with hypotension. Centrencephalic epilepsy causing stimulation of pathways inhibitory to the peripheral release of norepinephrine was probably ex-

as high as 5 mg was ineffective in correcting the hypotension.

We attempted to prevent or modify our patient's hypotensive episodes with a variety of pharmacologic agents, with each drug administered orally in the stated dosages for at least 72 hours. Neither carbamazepine 200 mg for 1 day, 400 mg for 1 day, then 600 mg every day for 3 days, indomethacin 25 mg three times daily, ephedrine 25 mg four times daily, the combination of diphenhydramine 50 mg three times daily plus cimetidine 300 mg four times daily, nor translycypromine (monoamine oxidase inhibitor)

Figure 6. Effects of cardiac pacing and drugs upon blood pressure during hypotension. ECG monitoring and radial artery pressure (RAP) during hypotension before and during right ventricular pacing (A), before and 5-10 minutes after 2 mg of i.v. atropine (B), before and during i.v. infusion of 4 μg/min of isoproterenol (C), and before and during i.v. infusion of 75 μg/min of phenylephrine (D). The correction of hypotension by phenylephrine was confirmed twice during separate hypotensive episodes.
cluded by the normal electroencephalogram during hypotension and the lack of a therapeutic response to carbamazepine.

Intermittent vascular obstruction at the site of his inferior vena cava umbrella filter was excluded by angiographic studies. There was no evidence for right or left atrial myxoma, valvular heart disease, or hypertrophic subaortic stenosis. In addition, intermittent vascular obstruction alone could not explain the failure of the expected signs of reflex sympathetic stimulation to appear with the onset of hypotension.

Abnormal release of vasoactive substances producing vasodilatation and episodic hypotension has been observed in the situations cited in table 1B, but plasma or urine analyses, the failure of antagonist drug trials, or the lack of other expected concomitant clinical features excluded these known disorders.

The clinical and laboratory data suggesting episodic withdrawal of peripheral sympathetic tone in association with our patient's hypotensive spells are strong. However, the stimuli leading to sympathetic withdrawal were not identifiable, unlike the common form of vasodepressor syncope or the hypertensive syndromes of hypersensitive carotid sinus, micturition syncope, or cough syncope. Also, the duration of his hypotensive periods was often much longer than that observed in these syndromes. There was no evidence of a relationship between our patient's episodic hypotension and the other clinical abnormalities we observed — the history of psychiatric disturbances, the history of venous thromboembolic disease, the carotid bruits, the elevated uric acid, and the moderate antinuclear antibody titer.

We propose that one of two hypothetical mechanisms leads to the apparent withdrawal of sympathetic tone that accompanies the episodic hypotension noted in our patient.

First, the withdrawal of peripheral sympathetic vasomotor tone may be mediated centrally by reduced firing of afferent neurons from the medullary vasomotor centers. The primary stimulus that produces this centrally mediated sympathetic withdrawal could be from higher central nervous system pathways impinging upon the vasomotor centers of the brainstem, or from the activation of the afferent limb of an undescribed vasodepressor reflex, perhaps a sympathetically mediated analogy of the vagally mediated Bezold-Jarish reflex in laboratory animals. The opportunity to test this hypothesis must await either identification of a stimulus that produces hypotension in our patient or a method that allows us to record the rate of afferent sympathetic neuronal firing in our patient.

Second, an apparent sympathetic withdrawal could be produced by the episodic release of some unknown endogenous compound, perhaps a tumor product, with inhibitory effects either upon activation of central, pre- or postganglionic sympathetic neurons, or upon the release of norepinephrine from postganglionic nerve terminals, perhaps by stimulation of inhibitory presynaptic α-adrenergic receptors.

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