tachycardia and ventricular fibrillation in a young population. Circulation 60: 988, 1979

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

R. Sanders Williams, M.D., and Thomas M. Bashore, M.D.

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 disorders1-11 (table 1A). Other disorders may also lead to paroxysmal hypotension by one of three major mechanisms: episodic or variable vascular obstruction,18-22 abnormal activation of vasodepressor reflexes,23-26 or abnormal episodic release of endogenous vasoactive substances27-32 (table 1B).

We recently evaluated a patient with paroxysmal hypotension in whom extensive laboratory investigation revealed features that appear to be distinct from any recognized disorders of vasomotor regulation.

Case Report

A 50-year-old Caucasian man was referred to our Cardiovascular Laboratory for the evaluation of frequent episodes of presyncope associated with hypotension. His spells of lightheadedness occurred one to three times daily and lasted 1 minute to 4 hours. He 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 device33 into his inferior vena cava. He also had a history of abuse of alcohol and minor tranquilizers and reported several hospital admissions for psy-
TABLE 1. Disorders of Vasoconstrictor Control Leading to Hypotension

<table>
<thead>
<tr>
<th>A. Neurologic disorders with autonomic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathies: diabetes mellitus; alcoholic; acute intermittent porphyria; tabes dorsalis</td>
</tr>
<tr>
<td>Wernicke’s disease</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Holmes-Adie syndrome</td>
</tr>
<tr>
<td>Familial dysautonomia (Riley-Day)</td>
</tr>
<tr>
<td>Lesch-Nyan syndrome</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Disorders producing episodic hypotension (excluding cardiac dysrhythmias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent vascular obstruction</td>
</tr>
<tr>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Defective cardiac valve prosthesis</td>
</tr>
<tr>
<td>Pregnancy or large intra-abdominal tumor</td>
</tr>
<tr>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Idiopathic hypertrophic subaortic stenosis (IHSS)</td>
</tr>
</tbody>
</table>

Abnormal activation of autonomic reflexes |
Centrally mediated vasodepressor syncope |
Hypersensitive carotid sinus syndrome |
Micturition syncope |
Cough syncope |
? Aortic stenosis and ? IHSS |

Abnormal release of vasoactive substances |
Pheochromocytoma (epinephrine, dopamine, other amines) |
Carcinoid syndrome (serotonin) |
Systemic mastectomy (histamine) |
Anaphylactic shock (histamine, kinins, SRS-A) |
Septicemic shock (endotoxins) |
Hereditary angioedema (complement activation) |

| | | | | | |
| | | | | | |
| | | | | | |

Psychiatric evaluation and care. Although he denied alcohol or drug abuse in the 3 months before admission, he did note prominent symptoms of depression. He also gave a history of hypertension that had intermittently been 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 non-specific 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 129I-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-
An echocardiogram 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.1 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.

**Table 2. Hemodynamic Measurements Before and During a Hypotensive Spell**

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>158/84</td>
<td>78/46</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Arteriovenous oxygen difference (vol% )</td>
<td>5.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Cardiac output (Fick) (l/min)</td>
<td>5.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>Systemic resistance (Wood units)</td>
<td>16.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

**Figure 1. Intra-arterial pressure recordings during hypotensive episodes.** (A) Hypotensive episode in the catheterization laboratory. Tracings are not continuous. (B) Continuous monitoring of radial artery pressure. This tracing illustrates the typical abrupt swings in blood pressure, from normotension at left to profound hypotension, followed by a rapid return to normotension again. BP = blood pressure; HR = heart rate.
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.
norepinephrine 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 μg/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 μg/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
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 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 \( \alpha \)-adrenergic receptors, but not by cholinergic antagonists, \( \beta \)-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-

**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 \( \mu \)g/min of isoproterenol (C), and before and during i.v. infusion of 75 \( \mu \)g/min of phenylephrine (D). The correction of hypotension by phenylephrine was confirmed twice during separate hypotensive episodes.

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)
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 hypotensive 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 antiinflammatory 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-Jarisch 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 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.

Acknowledgment

The authors gratefully acknowledge the assistance and advice of Dr. John Baker and Dr. Jeffrey Medoff in the clinical evaluation of the patient; Dr. Redford Williams for the forearm venous plethysmography analysis and biofeedback efforts; Dr. Steven Grossman, Dr. J. Caulie Gunnels and Robin Sykes for the plasma catecholamine assays; and especially Dr. Joseph Greenfield and Dr. Eugene Stead for their advice during the laboratory evaluation of this patient and their review of the manuscript. We also thank Linda Ashley and Janice James for their assistance in the preparation of the manuscript.

References

R S Williams and T M Bashore

Circulation. 1980;62:901-908
doi: 10.1161/01.CIR.62.4.901

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/4/901