Baroreflex Failure in a Patient with Central Nervous System Lesions Involving the Nucleus Tractus Solitarii

Italo Biaggioni, William O. Whetsell, John Jobe, John H. Nadeau

Abstract Animal studies have shown the importance of the nucleus tractus solitarii, a collection of neurons in the brain stem, in the acute regulation of blood pressure. Impulses arising from the carotid and aortic baroreceptors converge in this center, where the first synapse of the baroreflex is located. Stimulation of the nucleus tractus solitarii provides an inhibitory signal to other brain stem structures, particularly the rostral ventrolateral medulla, resulting in a reduction in sympathetic outflow and a decrease in blood pressure. Conversely, experimental lesions of the nucleus tractus solitarii lead to loss of baroreflex control of blood pressure, sympathetic activation, and severe hypertension in animals. In humans, baroreflex failure due to deafferentation of baroreceptors has been previously reported and is characterized by episodes of severe hypertension and tachycardia. We present a patient with an undetermined process of the central nervous system characterized pathologically by ubiquitous infarctions that were particularly prominent in the nucleus tractus solitarii bilaterally but spared the rostral ventrolateral medulla. Absence of a functioning baroreflex was evidenced by the lack of reflex tachycardia to the hypotensive effects of sodium nitroprusside, exaggerated pressor responses to handgrip and cold pressor test, and exaggerated depressor responses to meals and centrally acting α2-agonists. This clinicopathological correlate suggests that the patient’s baroreflex failure can be explained by the unique combination of the destruction of sympathetic inhibitory centers (ie, the nucleus tractus solitarii) and preservation of centers that exert a positive modulation on sympathetic tone (ie, the rostral ventrolateral medulla). (Hypertension. 1994;23:491-495.)

Key Words • pressoreceptors • autonomic nervous system diseases • carotid sinus

Case Report

This patient was a 33-year-old man who had worked in the military aircraft building industry from age 21 to 31. He was in good health until approximately age 29, at which time he began to develop rapidly worsening eyesight requiring “frequent eyeglass prescription change.” Within several months of onset of visual symptoms, he began to notice occasional left-sided facial numbness, vague numbness in upper and lower extremities, decreased taste perception, and asymmetric decrease in temperature perception in all extremities. About 1 year later, he began to develop poor balance, staggering gait, slurring of speech, progressive memory loss, and general slowing of mentation, speech, and movement. Neurological examination demonstrated bilateral hyperreflexia and spasticity in upper and lower extremities, mild gait ataxia, and impaired mental status. Memory and concentration decreased gradually, with episodes of disorientation. He had to be stimulated to wake up and remained disoriented for several minutes, failed to recognize people, and displayed inappropriate behavior, such as urinating on the floor. There was no cogwheeling, inexpressive facies, or stooped posture. This unusual constellation of signs and symptoms was thought to reflect a toxic encephalopathy possibly related to a 10-year history of work-related exposure to chemical solvents, including toluene, ethyl acetone, and methyl ethyl ketone. The clinical manifestations progressed slowly, and approximately 1 year before his evaluation he developed markedly labile fluctuations in blood pressure, which prompted the current admission.
Changes in Blood Pressure and Heart Rate Produced by Physiological and Pharmacological Stimuli in the Index Case, In Healthy Subjects, and In Patients With Multiple System Atrophy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>SBP/DBP, mm Hg</th>
<th>HR, bpm</th>
<th>SBP/DBP, mm Hg</th>
<th>HR, bpm</th>
<th>SBP/DBP, mm Hg</th>
<th>HR, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva, phase II</td>
<td>-44/-15</td>
<td>10</td>
<td>-5±2/-11±3</td>
<td>37±3</td>
<td>-63±16/-15±4</td>
<td>8±1</td>
</tr>
<tr>
<td>Valsalva, phase IV</td>
<td>+17/+17</td>
<td>-2</td>
<td>+34±2/+21±2</td>
<td>-22±5</td>
<td>-37±12/-8±2</td>
<td>3±2</td>
</tr>
<tr>
<td>Isometric handgrip</td>
<td>+55/+35</td>
<td>12</td>
<td>+15±2/+14±1</td>
<td>7±2</td>
<td>4±3/2±1</td>
<td>4±2</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>+50/+30</td>
<td>+4</td>
<td>+15±4/+13±2</td>
<td>+6±3</td>
<td>5±3/6±3</td>
<td>6±1</td>
</tr>
<tr>
<td>Meal challenge</td>
<td>-14/-19</td>
<td>+3</td>
<td>-1±2/-3±2</td>
<td>+5±1</td>
<td>-44±8/-21±4</td>
<td>6±2</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>+38/+18</td>
<td>+23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside (0.8 µg/kg IV)</td>
<td>-45/-35</td>
<td>+4</td>
<td>-14±5/-8±2</td>
<td>22±5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine (1.6 mg IV)</td>
<td>-10/+2</td>
<td>+15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine (0.1 mg PO)</td>
<td>-33/-33</td>
<td>-11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Methylidopa (125 mg PO)</td>
<td>-32/-16</td>
<td>-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSA indicates multiple system atrophy (Shy-Drager syndrome); SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; and bpm, beats per minute.

*Data expressed as mean±SEM, n=8 for healthy control subjects and 19 for MSA patients.

The patient was taken off medications, admitted to the Elliot V. Newman Clinical Research Center, and fed a controlled diet containing 150 mEq sodium and 80 mEq potassium daily. Blood pressure was 172/120 mm Hg in the supine and 174/112 mm Hg in the upright positions. Heart rate increased from 72 to 84 beats per minute (bpm). Plasma norepinephrine was 496 pg/mL in the supine position and 514 pg/mL after 30 minutes in the upright posture. Plasma catecholamines were measured using a high-performance liquid chromatographic method, as described previously. While in the hospital and off medications, his blood pressure fluctuated from 90/70 to 200/150 mm Hg. Parallel changes in heart rate were observed. Physical examination was normal except for neurological involvement, characterized by bilateral spasticity and hyperreflexia with clonus in both ankles and equivocal Babinski sign. Speech was slow, with a slight scanning pattern. Mild cerebellar ataxia of gait was observed, and the patient complained of diplopia. Neurological and psychological testing revealed cognitive and sensorimotor dysfunction, with significant central nervous system impairment as evidenced by a Halstead Impairment Index of 0.7, and was interpreted as revealing a multifocal cognitive deficit without evidence of a primary dementia. Perceptual disturbances, especially tactile impairments, were prominent, consistent with bilateral parietal lobe dysfunction. General laboratory workup revealed mild anemia, with a hemoglobin of 129 g/L, corrected reticulocytes of 0.026, and normal total iron binding capacity, serum folate, and vitamin B12. Protein electrophoresis exhibited an abnormal band in the gamma region in serum and urine. Immunoelectrophoresis revealed a monoclonal gammopathy. Bone marrow showed increased plasma cells but was not diagnostic of multiple myeloma. A magnetic resonance imaging scan of the brain was unrevealing and showed no evidence of demyelinating disease. Cerebrospinal fluid was normal.

Autonomic function tests were performed as described previously. Blood pressure was monitored continuously through a catheter placed in the brachial artery and connected to a pressure transducer and signal conditioner (Gould carrier amplifier, Gould Inc.). The surface electrocardiograph signal was fed to a rate computer to monitor heart rate. The blood pressure response to Valsalva's maneuver was normal, with an intact blood pressure overshoot during phase IV (Table). There was a moderate increase in heart rate during phase II, but the expected reflex bradycardia during phase IV blood pressure overshoot was not observed. Sinus arrhythmia was impaired, with a heart rate ratio (fastest heart rate during inspiration divided by the slowest heart rate during expiration) of 1.06 (healthy control subjects, 1.41±0.06). Isometric handgrip (one third of maximal voluntary contraction for 3 minutes) and the cold pressor test (placing a hand in ice water for 1 minute) produced dramatic increases in blood pressure, from 180/105 to 235/140 mm Hg and from 165/105 to 215/135 mm Hg, respectively. Intravenous bolus injection of 0.8 µg/kg nitroprusside decreased blood pressure from 160/100 to 115/65 mm Hg. This decrease in blood pressure was not associated with the expected reflex tachycardia. Atropine (1.6 mg IV) increased heart rate from 75 to 90 bpm.

A standardized breakfast decreased blood pressure from 109/80 to 95/61 mm Hg. Smoking one cigarette increased blood pressure from 147/89 to 185/107 mm Hg. Small oral doses of the centrally acting sympatholytics clonidine (0.1 mg) and α-methylidopa (125 mg) produced significant decreases in blood pressure from 113/82 to 80/49 mm Hg and from 102/70 to 70/54 mm Hg, respectively (Table). Clonidine decreased plasma norepinephrine from 261 to 162 pg/mL.

The patient was initially treated with clonidine and was instructed to avoid nicotine and large meals. This approach was only partially successful. Three months after evaluation he was admitted to a local hospital with a 1-day history of increased confusion and disorientation. His mental status continued to deteriorate, and he developed fever and respiratory distress. Physical examination, chest radiogram, and routine laboratory work including cerebrospinal fluid analysis were unrevealing. A com-
puterized tomographic study of the head showed only slight dilatation of the ventricles. The patient’s condition continued to deteriorate until he died.

At autopsy, general examination revealed a right lower lobe pneumonia and moderate bilateral pulmonary congestion, findings that constituted the most likely cause of death. There was borderline left ventricular hypertrophy, acute congestion of liver and spleen, and small focal submucosal hemorrhages in urinary bladder and sigmoid colon. Examination of the brain revealed no gross evidence of cerebral cortical atrophy or cerebellar atrophy. The brain weight was 1550 g in the fresh state. Horizontal sections of the cerebrum in the fixed state exhibited multiple small infarctions that were distributed ubiquitously and bilaterally throughout the cerebral cortex, basal ganglia, and thalamus as well as in the midbrain, pons, and rostral medulla. Microscopic evaluation of sections of multiple brain regions demonstrated focal infarctions ranging in diameter from 10 μm to 2 mm. All infarctions were characteristic of old cystic microinfarctions containing scattered macrophages and lymphocytes surrounded by markedly fibrillary astrocytes. It was particularly striking to observe that this pattern of microinfarction and gliosis was prominent in the region of the NTS bilaterally (Figure). The larger of these (Figure, A and B) was approximately 1.5 mm in greatest diameter at the level of section, and it extended rostrocaudally approximately 2.0 mm. The smaller of the two NTS lesions (Figure, A and C) measured approximately 1.0 mm in mediolateral and rostrocaudal extent; this lesion was less cystic and exhibited greater fibrillary gliosis but bore prominent macrophages and lymphocytes. Neither lesion extended caudally below the level of the obex.

In addition to the focal microinfarctive changes, marked loss of neurons with associated gliosis was found in the thalamus, subthalamus, brain stem tegmentum, and substantia nigra bilaterally. In the substantia nigra, in addition to neuron loss and gliosis, there were numerous neuromelanin-bearing macrophages as well as abundant free extracellular neuromelanin. No evidence of Lewy body formation was observed.

Although gross examination of the spinal cord at multiple levels showed no abnormality, microscopic study showed prominent loss of nerve cells accompanied by reactive astrocytosis in the lateral horn on one side of the rostral thoracic spinal cord. No such pathological changes were found at the cervical, lower thoracic, or lumbosacral levels examined. Microscopic examination of several sympathetic chain ganglia showed no pathological change.

Discussion

The importance of the baroreflex in the regulation of blood pressure has long been recognized. The afferent limb of the baroreflex is composed of multiple baroreceptors located bilaterally in the carotid sinus and thoracic arteries. This redundancy of afferent receptors was thought to protect against baroreflex failure. However, virtually all previously reported cases of baroreflex failure have been due to damage of the afferent limb of the baroreflex (deafferentation), most often as a consequence of bilateral neck surgery or neck irradiation.1-4

In contrast to the redundancy of afferent baroreceptors, the central component of the baroreflex is limited to a few structures. Impulses arising from carotid and aortic baroreceptors all converge in the NTS, where the first synapse of the baroreflex is located.8 The NTS contributes to the regulation of sympathetic outflow in part through its inhibitory projections into the rostral ventrolateral medulla (RVLM). Activation of the RVLM results in increases in sympathetic outflow and blood pressure,9,10 and vasomotor neurons of the RVLM exhibit intrinsic pacemaker properties,10 suggesting that this region is positively involved in tonic sympathetic outflow. The NTS, on the other hand, can be considered an inhibitory vasomotor center. Stimulation of the NTS leads to inhibition of RVLM neurons, resulting in decreases in sympathetic outflow and blood pressure.11 Conversely, acute experimental lesions of the NTS lead to sympathetic activation and neurogenic hypertension as well as loss of baroreflex control of blood pressure.12 If animals are maintained through this acute period they can survive for long periods with a continuously labile blood pressure.13
The patient presented here showed the classic clinical and laboratory features of baroreceptor failure.1 Blood pressure fluctuated widely, with episodes of severe hypertension and tachycardia. Absence of a functioning baroreflex was evidenced by the lack of reflex tachycardia to increases or decreases in blood pressure, the lability of blood pressure, and the exaggerated pressor responses to isometric exercise or the cold pressor test can be explained by baroreflex interruption at the level of the NTS. On the other hand, other brain stem structures known to be involved in cardiovascular control, most notably the RVLM, were not affected anatomically. Two clinical observations suggest that the RVLM was also functionally preserved. First, the depresor effects of clonidine and a-methyldopa, which lower blood pressure at least in part by acting on the RVLM to inhibit sympathetic outflow,15 were intact and even exaggerated. Second, the pressor response to the cold pressor test was also conserved, and RVLM neurons have been shown to participate in the cardiovascular responses to nociceptive stimulation.16

Because lesions were also present in the substantia nigra, it could be proposed that this patient had multiple system atrophy (MSA, Shy-Drager syndrome). However, several findings argue against this possibility. MSA is most often seen during the sixth or seventh decade of life. In more than 60 patients with MSA evaluated by us, all were older than 50 years of age, with an exceptional case who was 45 years of age. The clinical picture of MSA is dominated by disabling bradykinesia and rigidity, profound orthostatic hypotension, and lack of the pressor responses to isometric handgrip and the cold pressor test. Hypertension can be observed in approximately 50% of severe cases17 but is seen only in the supine position and is sustained rather than labile. In contrast, bradykinesia and rigidity were not prominent in this patient, orthostatic hypotension was not observed, the pressor responses to handgrip and cold exposure were exaggerated (Table), and the hypertension was labile and worse during activity rather than in the supine position. Finally, the neuropathology of MSA is characterized by neuronal cell loss.18 The widespread microinfarctions and cellular infiltrates found in this patient have not been reported in MSA.

In addition to baroreflex failure, the clinical picture was characterized by a multifocal involvement of the central nervous system, confirmed at autopsy to correspond to multifocal microinfarctions of unknown etiology. The clinical presentation and history of possible toxic exposure raise the possibility of a toxic encephalopathy. We believe, therefore, that this represents a case of baroreflex failure of central origin. Even though we are not aware of previous reports of similar cases, it is likely that they occur in other central nervous system disorders but have not been documented. Neurogenic hypertension can certainly be seen as a complication of stroke19 and posterior cerebellar ischemia,20 but whether true baroreflex failure is seen in these cases is uncertain. The clinicopathological correlate in this patient suggests that the baroreflex failure can be explained by the unique combination of the destruction of sympathetic inhibitory centers (ie, the NTS) with sparing of centers that exert a positive modulation on sympathetic tone (ie, the RVLM).

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