Brain Stem Stroke Causing Baroreflex Failure and Paroxysmal Hypertension

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Background—Paroxysmal neurogenic hypertension has been associated with a variety of diseases affecting the brain stem but has only rarely been reported after brain stem stroke. The mechanism is thought to involve increased sympathetic activity and baroreflex dysfunction. We undertook microneurographic recordings of muscle sympathetic nerve activity (MNSA) during beat-to-beat blood pressure (BP) monitoring to investigate this hypothesis.

Case Description—We investigated a 75-year-old woman who developed paroxysmal hypertension (BP 220/110 mm Hg) after a large left-sided medullary infarct. The paroxysms were triggered by changes in posture and were accompanied by tachycardia, diaphoresis, and headache. Serum catecholamines were substantially increased (norepinephrine level, 23.9 nmol/L 9 days after stroke; normal level, 3.8 nmol/L), and heart rate variability, measured by spectral analysis, was decreased in both low- and high-frequency domains (0.04 and 0.06 ms², respectively; normal level, 0.14±0.02 ms²). MNSA was increased in frequency (61 bursts per minute; normal level, 34±18 bursts per minute), and the burst amplitude was not inversely related to diastolic BP. BP and MNSA responses to cold pressor and isometric handgrip stimuli were intact.

Conclusions—Extensive unilateral infarction of the brain stem in the region of the nucleus tractus solitarius may result in partial baroreflex dysfunction, increased sympathetic activity, and neurogenic paroxysmal hypertension. (Stroke. 2000;31:1997-2001.)

Key Words: baroreflex n hypertension n lateral medullary syndrome n stroke
Neurohormones
A 16-gauge cannula was placed in the right antecubital vein, and blood was withdrawn for catecholamine studies on 3 separate occasions on which the patient became symptomatic. Assay methods for norepinephrine, epinephrine, and arginine vasopressin have been previously described.8,9

Microneurography
The patient was positioned horizontally, and ECG electrodes were applied for continuous HR monitoring. A Finapres device was used for photoplethysmographic monitoring of beat-to-beat changes in BP. Microneurography recordings were made from the right superficial peroneal nerve over a 2-hour period with the use of the technique described by Valbo et al.10 Muscle nerve sympathetic activity (MNSA) was identified according to the following criteria: (1) short-duration bursts related to changes in BP; (2) no response to tactile or arousal stimuli; (3) low-threshold muscle twitch after electric stimuli; and (4) mechanoreceptor activity during muscle stretch.

HR Variability
Repeated 512-beat samples during a 2-hour period were analyzed with the fast Fourier transform, and 2 frequency domains were recognized: low (0.05 to 0.15 Hz) and high frequency (0.15 to 0.4 Hz), representing sympathetic and parasympathetic cardiac activity, respectively.11

Results
Neurohormones
Sampling on days 9 and 10 after admission demonstrated norepinephrine levels significantly increased at 23.9 and 13.2 nmol/L (normal, <3.8 nmol/L) and epinephrine levels mildly increased at 0.64 and 0.68 nmol/L (normal, <0.57 nmol/L), respectively. On day 18, norepinephrine remained increased at 12.6 nmol/L. Arginine vasopressin levels on each occasion were normal (<5 pmol/L).

Microneurography
On day 10, a satisfactory recording field was obtained with the patient resting supine and asymptomatic. At rest, HR varied between 60 and 67 bpm and BP between 170/98 and 208/106 mm Hg. MNSA was increased at 61 bursts per minute compared with control values (34 ± 18 bursts per minute), and the burst amplitudes were abnormally constant from beat to beat.12 There was a burst of activity for every heartbeat, and the amplitude of the bursts was not inversely related to diastolic BP (Figures 2 and 3). On occasion during the recording, there was a sudden and spontaneous withdrawal of MNSA for 2 heartbeats, followed by a rapid fall in BP over the next 10 beats (Figure 4). BP then recovered rapidly as MNSA resumed. BP and MNSA responses to cold pressor and isometric handgrip were intact (mean BP increases were 31 and 16 mm Hg, respectively), with only
minor increases in HR (4 and 0 bpm). Burst amplitude increased by 75% during both stimuli (Figure 5).

Low- and high-frequency HR variability values were decreased at 0.04 and 0.06 ms² compared with control values recorded previously in our laboratory (0.14±0.02 ms²).¹²

Discussion

This patient experienced recurrent episodes of severe, paroxysmal hypertension over a 20-day period after infarction of the medulla. Partial baroreflex failure causing intermittent disinhibition of brain stem sympathetic activity was thought to be the likely mechanism, supported by the following findings: (1) the attacks were accompanied by relative tachycardia, diaphoresis, and pallor and were triggered by passive movement; (2) sympathetic activity, measured by serum catecholamine levels and MNSA, was inappropriately increased; (3) the BP and MNSA responses to stimuli not mediated by the baroreceptors (handgrip and cold pressor) were relatively intact; (4) the inverse relationship between diastolic BP and MNSA amplitude was absent, consistent with peripheral barodeafferentation previously demonstrated in humans;¹³–¹⁵ (5) there appeared to be increased sensitivity of BP to sudden decreases in MNSA; (6) MRI demonstrated major infarction of the left rostral medulla in the area of the nucleus tractus solitarius and intermediate reticular zone, where all the baroreceptor afferents enter the brain stem;¹⁶ (7) electrolytic lesions to the nucleus tractus solitarius in the cat model were demonstrated by Reis¹⁷ to cause lability of BP and HR after postural changes; and (8) the generalized decrease in HR variability is also consistent with partial baroreceptor denervation, although this may be difficult to interpret in the setting of β-blockade.¹⁸

Medullary stroke associated with paroxysmal neurogenic hypertension has been previously reported, but the exact anatomic location of the infarcts and the mechanisms involved were not demonstrated.¹⁹,²⁰ Animal studies have demonstrated that baroreceptor afferents, carried by the ninth and tenth cranial nerves, terminate in the nucleus tractus solitarius, a paired nuclear structure lying dorsally in the rostral medulla oblongata.¹⁷ Inhibitory pathways extend to the rostral ventrolateral medulla, the tonic vasomotor center of the brain. Bilateral electrolytic lesions of the nucleus tractus solitarius in the cat result in marked variability and persistent elevation of BP. BP reactivity to a variety of environmental stimuli is also exaggerated.¹⁷ The abnormalities of BP control in the cat model of paroxysmal neurogenic hypertension are very similar to what we observed in our patient.

In the human, paroxysmal neurogenic hypertension has been most commonly described in association with diseases that diffusely affect the brain stem, such as tetanus, poliomyelitis, and syringobulbia.¹ Symptomatic lesions of the nucleus tractus solitarius are very unusual because of the rich vascularization in this region.²¹ Furthermore, the redundancy of
ever, in the absence of radiological confirmation of structural
residual function remained in the contralateral nucleus. How-
but because the baroreflex dysfunction was only partial, some
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takes effect. (3) If the contralateral solitary nucleus had been
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neurological functions that are under bilateral central control,
extent reflected in the findings we observed. (2) For
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infarcted tissue may not have extended to include that on the
closely situated in the medulla, and although the area of
delineated on conventional MRI. The 2 tracti solitarii are
area of functional tissue impairment may exceed the area
explana.22 The predominance of sympathetic activity and the
dysfunction of the infarction must generally be
either very selective or extensive in order to be symptomat-
ic.22 The predominance of sympathetic activity and the
decreased HR variability in our patient suggest that parasym-
pathetic responsiveness was also impaired, and this would be
consistent with an extensive lesion. Why an apparently
unilateral lesion should have resulted in a generalized distur-
bance of BP is uncertain, but we will postulate some possible
explanations. (1) In the acute phase of cerebral infarction, the
area of functional tissue impairment may exceed the area
delineated on conventional MRI. The 2 tracti solitarii are
closely situated in the medulla, and although the area of
infarcted tissue may not have extended to include that on the
right, potentially reversible ischemia may have impaired it to
an extent reflected in the findings we observed. (2) For
neurological functions that are under bilateral central control,
transient functional impairment may be evident in the acute
phase after unilateral damage, before central compensation
takes effect. (3) If the contralateral solitary nucleus had been
the site of previous subclinical damage, infarction of the
ipsilateral nucleus may result in abnormalities of BP control,
but because the baroreflex dysfunction was only partial, some
residual function remained in the contralateral nucleus. How-
however, in the absence of radiological confirmation of structural
impairment affecting the contralateral nucleus tractus soli-
tarius, these conclusions must be regarded as speculative.

The combination of paroxysmal hypertension, diaphoresis,
and increased serum norepinephrine levels raised the possi-
bility of pheochromocytoma,23 but this was considered un-
likely because of the following: (1) the paroxysms began only
after the stroke; (2) the BP had been previously controlled by
a β-blocker/thiazide combination; (3) the paroxysms lasted
only 5 minutes; (4) the paroxysms were associated with
relative tachycardia24; and (5) very high serum catecholamine
levels are not specific for pheochromocytoma and have been
demonstrated in baroreflex failure.25 No imaging studies of
the adrenals and sympathetic chains were undertaken.

Sudden falls in BP related to transitory sympathetic with-
drawal have not been previously reported in barodeafferen-
tation but may have been caused by decreased buffering of
other inhibitory inputs. Sympathetic activity generated in the
medulla may become more sensitive to stimuli from other
areas in the brain, such as the vestibular nuclei and the higher
centers during postural changes.26

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References
1. Montgomery BM, Newbery SC. The basilar artery hypertensive
5. Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac barosen-
concentrations in CSF and plasma of patients with cerebral infarction and
blood pressure variability in acute and subacute stroke patients with
8. Eisenhofer G, Goldstein DS, Stull R, Keiser HR, Sunderland T, Murphy
D, Koplin DJ. Simultaneous liquid chromatographic determination of
3,4-dihydroxyphenylglycol, catecholamines and 3,4-dihydroxyphenyl-
alanine in plasma and their responses to inhibition of monamine oxidase.
9. Sadler WA, Lynskey CP, Gilchrist NL, Espiner EA, Nichols MG. A
sensitive radioimmunoassay for measuring plasma anti-diuretic hormone
10. Valbo AB, Hagbarth KE, Torebjork HE, Wallin BG. Somatosensory,
proprioceptive and sympathetic activity in human peripheral nerves. Physiol
Rev. 1979;59:919–957.
11. The Task Force of the European Society of Cardiology and the North
American Society of Pacing and Electrophysiology. Heart rate variability:
standards of measurement, physiological interpretation, and clinical use.
Autonomic control of vasovagal syncope. Am J Physiol. 1998;274(Heart
13. Sundlof G, Wållin BG. Human muscle nerve sympathetic activity at rest:
outflow in man after anaesthesia of the glossopharyngeal and vagus
15. Fagius J, Wållin G. Microneurographic evidence of excessive sympathetic
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