Brain Stem Stroke Causing Baroreflex Failure and Paroxysmal Hypertension

A.M. Phillips, MRCP; D.L. Jardine, FRACP; P.J. Parkin, FRACP; T. Hughes, FRCR; H. Ikram, PhD

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 ■ hypertension ■ lateral medullary syndrome ■ stroke

Neurogenic hypertension has been demonstrated in animal models and is well known to occur in humans after subarachnoid hemorrhage, hydrocephalus, and stroke. Blood pressure (BP) is increased after stroke, particularly after lacunar infarction or hemorrhage and in patients with preceding hypertension. It is usually maximal on day 1 and may fall more during the first week in those with higher initial values. The mechanism may involve a transient increase in sympathetic activity or baroreflex dysfunction, although current evidence for this is unsatisfactory. Spectral analysis techniques, measuring heart rate (HR) and BP variability, suggest that baroreflex sensitivity is decreased after a cortical stroke. Serum catecholamine levels are raised in some patients during the first week.

In addition to being increased, BP may also become more variable after stroke. Paroxysmal neurogenic hypertension has been associated with a variety of pathologies affecting the brain stem but has only rarely been attributed to stroke. We describe a case of paroxysmal hypertension after left lateral medullary infarction and demonstrate, using microneurographic recordings of sympathetic activity, that the likely mechanism was partial baroreflex failure.

Case Report
A 75-year-old woman presented with sudden onset of slurred speech, double vision, and left-sided incoordination. She was on long-term treatment for essential hypertension consisting of cyclopenthiazide 0.5 mg daily and nadolol 40 mg BID. Examination findings were consistent with a left-sided lateral medullary syndrome and included the following: rotatory nystagmus on left gaze; left-sided Horner’s syndrome, facial hemianesthesia, and palatal palsy; and left-sided limb ataxia and contralateral loss of pain and temperature sensation. BP was 220/110 mm Hg (supine), and pulse was 70 bpm. Antihypertensive medications were continued, and the resting BP ranged from 140/90 to 190/90 mm Hg. She remained bedridden over the next 2 weeks and during that period experienced frequent attacks of paroxysmal hypertension (BP up to 220/110 mm Hg) accompanied by relative tachycardia (90 bpm), diaphoresis, pallor, and headache. Each episode lasted approximately 5 minutes and recurred up to 5 times per day. Episodes were usually precipitated by passive changes in posture, such as being turned to one side or helped to sit up.

Investigations
Blood count, biochemistry, chest x-ray, and ECG were normal. MR scan demonstrated a large left-sided infarct of the posterolateral medulla and cerebellum in the territory of the posterior inferior cerebellar artery (Figure 1).
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 photopletysmographic 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 ms$^2$ compared with control values recorded previously in our laboratory (0.14±0.02 ms$^2$).

**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$^{16}$; and (7) electrolytic lesions to the nucleus tractus solitarius in the cat model were demonstrated by Reis$^{17}$ 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
baroreceptor afferents terminating on the nucleus tractus solitarii is so great that the infarction must generally be either very selective or extensive in order to be symptomatic.\(^2\) The predominance of sympathetic activity and the decreased HR variability in our patient suggest that parasympathetic responsiveness was also impaired, and this would be consistent with an extensive lesion. Why an apparently unilateral lesion should have resulted in a generalized disturbance 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. However, in the absence of radiological confirmation of structural impairment affecting the contralateral nucleus tractus solitarius, these conclusions must be regarded as speculative.

The combination of paroxysmal hypertension, diaphoresis, and increased serum norepinephrine levels raised the possibility of pheochromocytoma,\(^2\) but this was considered unlikely 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 tachycardia;\(^2\) and (5) very high serum catecholamine levels are not specific for pheochromocytoma and have been demonstrated in baroreflex failure.\(^2\) No imaging studies of the adrenals and sympathetic chains were undertaken.

Sudden falls in BP related to transitory sympathetic withdrawal have not been previously reported in barodeafferentation 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.\(^2\)

Acknowledgments

The authors would like to thank Christine Mahon and the medical illustrations department of Christchurch Hospital for preparing the figures.

References

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doi: 10.1161/01.STR.31.8.1997
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/8/1997