Cardiovascular Autonomic Reflexes in Brain Infarction

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Background and Purpose  Increased sympathetic activity is associated with cardiovascular complications in stroke, but the role of the parasympathetic nervous system has not been carefully outlined. In the present study our purpose was to assess quantitatively autonomic cardiovascular disturbances in brain infarction by measuring cardiovascular autonomic reflexes.

Methods  We studied the autonomic regulation of cardiovascular functions prospectively in 40 patients with brain infarction (acute phase, 1 month, and 6 months) and in 55 healthy control subjects by recording heart rate and blood pressure responses to normal and deep breathing, the Valsalva maneuver, tilting, and isometric work.

Results  In the acute phase, heart rate responses to normal breathing, deep breathing, the Valsalva maneuver, and tilting were significantly (P<.05) impaired in both hemispheric and brain stem infarctions, thus indicating hypofunction of the parasympathetic nervous system. At 1 month heart rate responses to normal breathing (brain stem, P<.05), the Valsalva maneuver (brain stem, P<.01), and tilting (hemispheric, P<.05) were still significantly lower than those of the control subjects, but at 6 months significant suppression of the response was found only in tilting (hemispheric, P<.05).

Conclusions  These findings suggest that in addition to the previously well-established sympathetic hyperfunction, brain infarction also seems to cause parasympathetic hypofunction, which may be involved in cardiovascular and other known manifestations of autonomic failure associated with stroke.

Key Words: • blood pressure • heart rate • reflex

Lesions of the central nervous system frequently cause disturbances of cardiovascular1-4 and other autonomic functions.5-10 In ischemic brain infarction increased sympathetic tone leading to elevated levels of circulating catecholamines is associated with commonly encountered cardiac complications such as arrhythmias, electrocardiographic (ECG) changes, and ischemic heart damage.11-17 Increased sympathetic tone in the acute phase of brain infarction is related to impaired prognosis due to cardiac complications,14,16 but the duration of autonomic dysfunction and its stability have not been carefully investigated. Furthermore, possible changes in parasympathetic activity in brain infarction and their role in producing autonomic imbalance and cardiac complications are not yet understood.

Damage to the autonomic control of the cardiovascular regulatory system is currently assessed by standardized cardiovascular reflex tests based on changes in heart rate (HR) and blood pressure (BP) at rest and after certain stimuli.18,19 Abnormalities primarily reflect hypofunction of the sympathetic or parasympathetic nervous system.18,19 The presence of suppressed reflexes seems to be associated with serious complications and a significantly increased mortality rate in diabetics20 and alcoholics.21,22 Loss of HR variability has also been reported in peripheral neuropathies23 and in degenerative central nervous system diseases.24-30 However, to our knowledge there are no previous reports of stand-
lary syndrome of Wallenberg: Horner’s syndrome, limb ataxia, pharyngeal weakness, and facial sensory deficit on the side ipsilateral to the infarction and sensory deficits of the body and the limbs on the side contralateral to the infarction. Two additional patients with medullary infarction had ipsilateral Horner’s syndrome, bulbar paresis, dizziness, and contralateral sensory deficits of the body and the limbs. Six patients had pontine infarction resulting in either contralateral hemiparesis or impaired pain and thermal sensation, associated with bulbar paresis, external ophthalmoplegia, or ipsilateral facial sensory deficit.

Cerebral computed tomography (CT) was performed on all 40 patients on admission to the hospital and was repeated within 2 weeks if the first examination was negative. A hemispheric infarction was verified by CT in 18 patients and a brain stem infarction in 4 patients. The CT remained normal in 7 patients with clinical signs of hemispheric infarction and in 11 patients with signs of brain stem infarction even after repeated examination with contrast.

The control group consisted of 55 healthy subjects (29 men and 25 women; mean ± SD age, 49.5 ± 8.4 years; range, 26 to 69 years). None of the control subjects had any disease or took medication known to affect the autonomic nervous system.

Cardiovascular autonomic function tests were performed under standardized conditions between 2 and 10 days (median, 7) after the infarction and were repeated 1 and 6 months later. Thirty-six patients were available at the 1-month visit and 38 at the 6-month visit. HR and BP responses at rest and after stimulations were recorded under the following conditions and provocations: normal breathing, deep breathing, the Valsalva maneuver, tilting, and isometric work (handgrip). The ECG and breathing (nasal thermistor) signals were conveyed through an analog/digital converter with a sampling frequency of 320 Hz to a personal computer and were analyzed off-line using an automatic program package that allowed visual checking of the raw ECG and breathing signal.

The investigations proceeded as follows: first, the maximum contraction power (handgrip) of the patient’s healthy hand was measured three times with a dynamometer for the isometric work test. After a 30-minute resting period, the BP was measured three times using an automatic arm sphygmomanometer. Thereafter, with the patient lying in a supine position on the tilt table, five tests were performed in the following order:

1. **Normal breathing test.** The HR variation during normal breathing was recorded. The consecutive RR intervals for a period of 1 minute were measured from the ECG, and the SD of the intervals was used as the variable.

2. **Deep breathing test.** The HR variation during deep breathing (6 breaths per minute) was recorded. The mean ratio of the longest (expiration) to the shortest (inspiration) RR interval of five consecutive breathing cycles was calculated. The test was performed twice, and the higher RR interval ratio was used as the “maximum-minimum ratio.”

3. **Valsalva maneuver.** The HR response to the Valsalva maneuver was recorded. The ratio of the longest RR interval after blowing (at the pressure of 40 mm Hg for 15 seconds) to the shortest RR interval during blowing in the Valsalva maneuver was calculated. The highest ratio of three maneuvers was used as the “Valsalva ratio.” A small hole in the mouthpiece attached to a mercury manometer during the Valsalva maneuver guaranteed that thoracic pressure had to be used for blowing.

4. **Tilting.** The HR and BP responses to quick passive tilting (2 seconds, 90°) were recorded. The ratio of the longest RR interval around beat 30 (beats 20 to 40) to the shortest RR interval around beat 15 (beats 10 to 20) after tilting was used as the “30:15 ratio.” Systolic and diastolic BP were measured at rest, immediately after tilting, and at 2, 5, and 7 minutes after tilting. The difference between BP at rest and the lowest BP after tilting was recorded.

5. **Isometric work.** The maximum systolic and diastolic BP increase during isometric work (handgrip with 30% of the patient’s maximum power) was recorded. BP was measured at 1, 2, 3, and 4 minutes of work, and the result was compared with the resting BP. Male and female subjects were analyzed independently.

Cardiovascular autonomic reflexes have been shown to be dependent on both age and baseline HR. Therefore, the values of the HR and BP responses (after logarithmic transformation) were corrected for age and baseline HR separately for the patients and the control subjects using multiple regression analysis, as follows:

\[ \log(z) = a + bx + cy \]

where \( z \) is the predicted value and \( x \) and \( y \) are the predictor variables age and HR, respectively. The coefficients were chosen so that the sum of squares of residuals is the minimum. The significance levels for the comparisons between the patients and the control subjects were obtained using ANCOVA.

For further prospective analyses, the values of the responses in both groups were separately adjusted for the mean age (51.4 years) and the mean baseline RR interval (910 milliseconds) of the patients, and the differences were compared by ANCOVA.

### Results

The HR responses to the cardiovascular autonomic reflex tests for control subjects and patients in the acute phase of brain infarction are presented in the Figure. During normal breathing (panel a), deep breathing (panel b), the Valsalva maneuver (panel c), and tilting (panel d), the HR responses of the patients were significantly \( (P<.05) \) impaired compared with those of the control subjects.

The age- and baseline HR–adjusted values of the HR responses to the cardiovascular reflex tests for control subjects and hemispheric infarction patients during the 6-month follow-up period are shown in Table 1. In the acute phase after infarction, the HR responses of the patients were significantly suppressed compared with those of the control subjects in deep breathing \((P<.05)\), the Valsalva maneuver \((P<.05)\), and tilting \((P<.05)\). During the follow-up the HR responses improved. At 1 month and at 6 months, a significant difference \((P<.05)\) between patients and control subjects was still evident in tilting.

In patients with brain stem infarction, the suppression of the responses was even more pronounced than in patients with hemispheric infarction (Table 2). In the acute phase the HR responses of the patients were significantly lower than those of the control subjects in normal breathing \((P<.05)\), deep breathing \((P<.05)\), the Valsalva maneuver \((P<.001)\), and tilting \((P<.05)\). At 1 month a significant difference between patients and control subjects was found in normal breathing \((P<.05)\) and the Valsalva maneuver \((P<.01)\).

Table 3 presents mean baseline BPs of the patients and the control subjects in the acute phase, at 1 month, and at 6 months. In hemispheric infarction patients, the mean systolic BP was higher than that of the control subjects during the whole 6-month follow-up period, but the mean diastolic BPs were similar. No differences were found between the mean blood BPs of the brain stem infarction patients and those of the control subjects.
Scatterplots show SD of RR intervals during normal breathing (a), maximum-minimum (max-min) ratio (b), Valsalva ratio (c), and 30:15 ratio (d) (see "Subjects and Methods") in relation to age in control subjects and patients during the acute phase of brain infarction. The symbol □ indicates control subjects; ●, patients; ---, regression line in control subjects; -----, regression line in patients; x, age; y, baseline RR interval. In panel a, z = exp(2.795 - 0.018x + 1.69y) in control subjects and z = exp(2.261 - 0.029x + 2.79y) in patients; P < .05 at 50 to 69 years. In panel b, z = exp(0.388 - 0.004x + 0.08y) in control subjects and z = exp(0.343 - 0.006x + 0.16y) in patients; P < .05 at 42 to 69 years. In panel c, z = exp(1.219 - 0.012x + 0.01y) in control subjects and z = exp(0.741 - 0.010x + 0.02y) in patients; P < .05 at 33 to 58 years. In panel d, z = exp(0.380 - 0.004x + 0.00y) in control subjects and z = exp(0.102 - 0.003x + 0.18y) in patients; P < .05 at 30 to 57 years. Probability values refer to regression line of patients different from that of control subjects using ANCOVA.

The patients did not differ from the control subjects in their BP responses to tilting and isometric work in the acute phase or during the follow-up (Table 4).

Discussion

Cerebrovascular diseases frequently cause cardiovascular complications, presumably due to central autonomic dysregulation.14 These often prognostically unfavorable complications may be due to increased sympathetic tone, but the exact mechanisms behind this autonomic imbalance and the pathogenesis of these complications are still unclear.

The present series is the first prospective and quantitative study aiming to assess disturbances of cardiovascular autonomic regulation by using cardiovascular reflex measurements. The major finding of the study was the suppression of HR responses to parasympathetic stimuli in both patients with brain stem infarction and those with hemispheric infarction. This parasympathetic hypofunction seems to be most pronounced in the acute phase of brain infarction.

The values (mean ± SD) of both groups are adjusted for mean age and mean baseline heart rate of the patients (ANOVA).

*P < .05 different from controls by ANCOVA.
phase of infarction and is apparently not just a transient but a long-lasting phenomenon. However, the difference between the patients and the control subjects was not statistically significant in all age groups due to the limited number of very young and old patients. Our results suggest that the sympathetic hyperfunction related to acute brain infarction, which has been emphasized in previous studies, may be associated with concurrent parasympathetic hypofunction.

The central nervous system controls cardiac activity and vasomotor tone by a complex system of cardiovascular reflexes that regulate cardiac performance to meet the demands of the body even in rapidly changing circumstances. The reflex arc consists of three parts: the afferent autonomic pathway, the medullary and hypothalamic processing centers, and the sympathetic and parasympathetic efferent pathways. The sympathetic nervous system facilitates cardiac activity by increasing HR and contractility, whereas the parasympathetic nervous system has an inhibitory effect on the heart.36-38 The autonomic cardiovascular regulatory system operates by continuously balancing the sympathetic and parasympathetic systems. In addition to the basal brain structures, the cerebral cortex is also involved in the regulation of cardiac and vasomotor activity via the hypothalamus; thus, for example, emotional stress may cause excitation of the cardiovascular system.47-49 The role of the parasympathetic nervous system in producing cardiovascular disturbances in brain infarction is not as clearly defined as that of the sympathetic system. Experimental stimulation of the medullary cardioinhibitory neurons in the nucleus ambiguus, dorsal vagal nucleus,40 anterior and preoptic hypothalamic regions, orbitofrontal cortex, and insular cortex has evoked bradycardia and hypotension.41-43 Moreover, prolonged phasic stimulation within rat insular cortex resulted in atrioventricular and interventricular heart block, QT interval prolongation, ventricular ectopy, and death.44 In humans, Oppenheimer et al45 recently demonstrated that stimulation of the left insular cortex produces bradycardia, and stimulation of the right insular cortex produces tachycardia. The present findings of suppressed HR responses to various parasympathetic stimuli may reflect damage of the aforementioned brain stem vagal cardioinhibitory neurons or the disruption of the connections between brain stem and supratentorial vagal cardioinhibitory regions.

The effects of acute brain infarction on cardiovascular autonomic reflexes have not been systematically studied previously. Appenzeller and Descarries46 reported temporarily impaired baroreflex functions in patients with cerebrovascular diseases. In another series, respiratory sinus arrhythmia was "completely absent" in eight comatose patients with lesions of the central nervous system.47 Moreover, diminished respiratory sinus arrhythmia was recently reported in 20 of 27 patients with acute intracranial mass lesions (including three brain infarction patients).48 Abnormal cardiovascular responses are related to an unfavorable prognosis in diabetes mellitus20 and alcoholism.21,22 In one series of diabetics with symptoms of autonomic neuropathy and abnormal findings in autonomic function tests, the mortality rate was 56% after 5 years.20 In another series the 7-year survival of alcoholics with abnormal cardiovascular function tests was 66%, whereas the survival of alcoholics with normal test results was 91%.21 Similarly, increased sympathetic tone due to cardiac complications is prognostically adverse in acute cerebrovascular accidents.1,4 Therefore, a prospective study with a large number of patients should be carried out for establishing the prognostic value of abnormal cardiovascular reflexes in ischemic stroke.

In the present study no evidence was found for sympathetic dysfunction in the sympathetically medi-

### Table 2. Heart Rate Responses to Normal and Deep Breathing, the Valsalva Maneuver, and Tilting in Control Subjects and Patients with Brain Stem Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=55)</th>
<th>Acute Phase (n=15)</th>
<th>1 Month (n=23)</th>
<th>6 Months (n=24)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD of RR intervals (normal breathing)</td>
<td>33.1±2.0</td>
<td>26.2±2.8*</td>
<td>25.0±4.5*</td>
<td>30.0±3.1</td>
<td></td>
</tr>
<tr>
<td>Maximum-minimum ratio (deep breathing)</td>
<td>1.26±0.02</td>
<td>1.17±0.03*</td>
<td>1.20±0.04</td>
<td>1.25±0.06</td>
<td></td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.85±0.07</td>
<td>1.51±0.5‡</td>
<td>1.55±0.07†</td>
<td>1.64±0.07</td>
<td></td>
</tr>
<tr>
<td>30:15 ratio (tilting)</td>
<td>1.18±0.01</td>
<td>1.10±0.02*</td>
<td>1.13±0.02</td>
<td>1.14±0.02</td>
<td></td>
</tr>
</tbody>
</table>

The values (mean±SD) of both groups are adjusted for mean age and mean baseline heart rate of the patients (ANOVA).

*P<.05, †P<.01 different from control subjects by Student's t test.

### Table 3. Mean Baseline Systolic and Diastolic Blood Pressures in Control Subjects, in Patients With Hemispheric Brain Infarction, and in Patients With Brain Stem Infarction

<table>
<thead>
<tr>
<th>BP, mm Hg</th>
<th>Controls (n=55)</th>
<th>Acute Phase (n=25)</th>
<th>1 Month (n=23)</th>
<th>6 Months (n=24)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>131±16</td>
<td>143±16†</td>
<td>140±18*</td>
<td>141±17*</td>
<td>134±16</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78±10</td>
<td>82±11</td>
<td>80±10</td>
<td>79±10</td>
<td>75±10</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SD.

*P<.05, †P<.01 different from control subjects by Student's t test.
ated BP responses to tilting and isometric work. This observation does not contradict previous findings of increased sympathetic tone, however, because the test battery we used measures sympathetic hypofunction almost exclusively. Moreover, this methodology emphasizes parasympathetic rather than sympathetic effects. HR variation during normal and deep breathing, the Valsalva maneuver, and tilting measures predominantly parasympathetic function, although the sympathetic nervous system also plays a role in producing tachycardia in the Valsalva maneuver and tilting.18-19 BP changes in tilting and isometric work reflect sympathetic functions.18,19 In the present study the mean baseline systolic BP of the patients with hemispheric infarction was higher than that of the control subjects but within normal ranges. This phenomenon had no effect on HR responses.

In conclusion, we have demonstrated the suppression of HR responses to various parasympathetically mediated stimuli in patients with ischemic brain infarction. This suppression reflects the imbalance of the autonomic cardiovascular regulatory system and may be involved in prognostically unfavorable cardiac complications and other known manifestations of autonomic failure associated with stroke.

References

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