Suppressed Sympathetic Skin Response in Brain Infarction

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Background and Purpose: Autonomic failure is known to manifest commonly in stroke, but very little attention has been given to various features of sympathetic dysfunction such as sudomotor dysregulation in cerebrovascular diseases. In the present study, our purpose was to assess quantitatively sympathetic reflex activity in brain infarction by measuring the sympathetic skin response.

Methods: We recorded the sympathetic skin response to electric and auditory stimulations simultaneously on both hands in 58 patients with brain infarction and in 36 healthy control subjects.

Results: The response amplitudes were significantly decreased and the latencies prolonged in both hemispheral (n=49) and brain stem (n=9) infarctions compared with the control subjects. The amplitudes were diminished in both the acute and late phases of infarction, but the latencies were prolonged only in the acute phase.

Conclusions: Sympathetic dysfunction in brain infarction seems to be much more extensive than has previously been thought. In the present study, we have demonstrated impaired sympathetic skin responses, reflecting definite suppression of the reflex activity of the sympathetic nervous system. (Stroke. 1993;24:1389-1392.)

Key Words • autonomic nervous system • cerebral infarction • reflex

Cardiovascular complications,1-3 respiratory failure,4 and sweating dysfunction5-8 are frequently encountered manifestations of autonomic failure in cerebrovascular diseases. Although the exact pathogenesis of these disorders is uncertain, they have commonly been associated with increased activity of the sympathetic nervous system.1-3

Sympathetic skin response (SSR), based on changes of skin conductance levels in response to various stimuli, is a novel investigational method used in clinical practice to assess the reflex activity of the sympathetic sudomotor pathways.9,10 This method has proved to be useful in evaluating diabetic,11-14 amyloid,15 and other peripheral autonomic neuropathies,16 but its role in testing central autonomic dysfunction has not yet been established.17,18

Therefore, in the present study, we recorded the SSR in patients with brain infarction and compared the findings with those of healthy control subjects. Our purpose was to assess quantitatively the activity of the sympathetic nervous system in brain infarction and to evaluate the significance of the SSR as a reflection of central autonomic regulation in stroke.

Subjects and Methods

The study was carried out in the Department of Neurology, Oulu University Hospital, with the approval of the Ethics Committee of the Medical Faculty, University of Oulu, according to the principles of the Declaration of Helsinki. Informed consent was obtained from each subject.

Fifty-eight patients (41 men and 17 women; mean±SD age, 56.1±9.4 years; range, 30 to 71 years; mean±SD height, 169±8 cm) with clinical signs of brain infarction were included in the study. Patients with manifestations of other central or peripheral nervous system lesions and patients with any other disease known to affect the autonomic nervous system (eg, diabetes and alcoholism) were excluded. Thirty-nine of the 58 patients were investigated in the acute phase (within 14 days) and 19 in the late phase (from 6 to 12 months) of brain infarction.

Forty-nine of the 58 patients had neurological deficits clearly attributable to a hemispheral brain infarction in the internal carotid artery territory, 22 on the right side of the body and 27 on the left side. Twenty-four of them had severe motor deficits with complete hemiparesis, and 25 had mild hemiparesis with active movement against gravity. Sensory deficits on the paretic side of the body were found in 33 patients, accelerated tendon reflexes in 25, extensor plantar response in 37, flaccid paresis in 15, and spastic paresis in 15.

Nine of the 58 patients had clinical signs of brain stem infarction, all of them having the lateral medullary syndrome of Wallenberg.

Cerebral computed tomography verified a large cortical infarction in 31 cases, a small deep infarction in 10 cases, and a brain stem infarction in 3 cases. Even the repeated computed tomography with contrast remained normal in 8 cases in the group of patients clinically classified as small deep hemispheral infarcts and in 6
cases with brain stem infarct. None of the patients had cerebellar or occipital ischemic lesions.

Fifty-two of the 58 patients had no preexisting disease or medication known to affect the autonomic nervous system. Nine patients had arterial hypertension, 7 had coronary heart disease, and 3 had long-term atrial fibrillation. Sixteen patients were taking cardiovascular medication: diuretics in 8, β-adrenergic blocking agents in 6, digitals in 6, angiotensin converting enzyme inhibitors in 5, calcium entry blockers in 4, and nitroglycerin in 4.

All the patients were conscious during the examination. Two patients had decreased attention level due to large cortical infarction in the nondominant hemisphere. Body temperature and fluid balance of the patients were normal. A cannula for intravenous infusion, if needed, was situated far from the registration area.

The control group consisted of 36 healthy subjects (20 men and 16 women; mean±SD age, 53.5±8.5 years; range, 31 to 65 years; mean±SD height, 170±8 cm).

The experiment was performed under standard conditions in an illuminated and silent room with the temperature kept at 24°C to 25°C. During the experiment, the subject was kept awake and relaxed in a lying position. The SSRs were provoked by using two types of stimulation separately: an auditory click (0.1 millisecond, 120 dB) delivered to both ears, and an electric single square pulse (0.5 millisecond, intensity adjusted to 20% to 30% above the motor threshold) to stimulate the median nerve at the wrist of the nonparetic hand. Both types of stimulation were repeated four times and given at irregular rates with intervals of at least 60 seconds to prevent habituation.

Recordings were carried out using an electromyograph (Counterpoint, Dantec, Skovlunde, Denmark) with an amplifier gain of 0.1 to 2 mV per division and filter settings at 0.2 to 50 Hz. The time base of 0.5 millisecond per division allowed the analysis time of 10 seconds. The electrode (disc) connected to the negative input of the amplifier was attached to the palm, and the electrode connected to the positive input of the amplifier was attached to the dorsum of the hand at the standard location. The amplitudes and latencies of the SSR were recorded simultaneously on both hands, and the mean amplitudes and latencies of the four consecutive SSR recordings were included in the analysis. The amplitudes of the recorded waves were measured from peak to peak. The SSR was regarded as asymmetric when the amplitude of the response on one side was 50% or less of that on the opposite side.18

Statistical analyses were performed using the Wilcoxon matched pairs test to compare the SSR amplitudes and latencies of the contralateral side to the infarction with those of the ipsilateral side (patients) and the amplitudes and latencies of the right side with those of the left side (control subjects). The Mann-Whitney two-sample test was used for comparing the SSR amplitudes and latencies of patients with those of control subjects and also for comparing the amplitudes and latencies of the clinical subgroups with each other. The frequency of asymmetric SSRs of patients was compared with that of control subjects with the χ² test.

**Results**

A repeated SSR was elicited on both hands in all the control subjects and in 54 of the 58 patients (93%). In the control group, the SSR amplitudes and latencies showed no asymmetry. Therefore, the mean values of the right and left SSR amplitude and latency were used as reference values for each stimulation.

Table 1 shows the mean SSR amplitudes and latencies to electric and auditory stimulations in patients and control subjects. In patients with hemispheral brain infarction, the SSR amplitudes on both the contralateral and ipsilateral sides were significantly lower (electric, P<.001; auditory, P<.05) and the latencies markedly longer (electric, P<.01; auditory, P<.05) than those of control subjects. In patients with brain stem infarction, the SSR latencies were also markedly prolonged (contralateral side: electric, P<.01; ipsilateral side: electric, P<.01; auditory, P<.05), and the amplitudes were diminished (ipsilateral side: electric, P<.05; auditory, P<.01).

Table 2 shows the results of the SSR recordings in patients in the acute and late phases of brain infarction. Suppression of the SSR amplitude was obvious in both the acute and late phases of infarction, whereas prolonged latency of the response was found only in the acute phase.

The SSR amplitudes were significantly lower (P<.05) in patients with cortical infarction than in patients with small deep infarction, but the latencies were similar. The suppression of the response was not dependent on the side of the infarction or the cardiovascular medication used. Moreover, no significant correlation could be

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**TABLE 1. Mean Amplitude and Latency of Sympathetic Skin Response to Electric and Auditory Stimulations in Control Subjects and Patients With Brain Infarction**

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (mV)</th>
<th></th>
<th>Latency (s)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Electric</td>
<td>Auditory</td>
<td>Electric</td>
</tr>
<tr>
<td>Control subjects</td>
<td>36</td>
<td>2.4±2.2</td>
<td>1.6±0.9</td>
<td>1.53±0.20</td>
</tr>
<tr>
<td>Hemispheral infarction</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral hand</td>
<td>1.0±0.8*</td>
<td>1.0±0.8†</td>
<td>1.65±0.23†</td>
<td>1.69±0.29‡</td>
</tr>
<tr>
<td>Ipsilateral hand</td>
<td>1.1±0.9*</td>
<td>1.1±1.1‡</td>
<td>1.66±0.22‡</td>
<td>1.72±0.31‡</td>
</tr>
<tr>
<td>Brain stem infarction</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral hand</td>
<td>1.5±1.6</td>
<td>1.1±0.9</td>
<td>1.74±0.20†</td>
<td>1.72±0.27</td>
</tr>
<tr>
<td>Ipsilateral hand</td>
<td>1.1±1.4‡</td>
<td>0.6±0.7‡</td>
<td>1.69±0.15†</td>
<td>1.82±0.27‡</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<.001, †P<.01, ‡P<.05, different from control by Mann-Whitney two-sample test.
found between either the amplitude or the latency of the SSR and the following clinical signs of the patients: motor or sensory deficits, muscle tone, tendon reflexes, plantar response, and skin temperature of the hand.

In patients with brain stem infarction, the ipsilateral SSR amplitudes were markedly lower \( (P<.05) \) than the contralateral ones; but in patients with hemispherical infarction, the contralateral and ipsilateral SSR amplitudes were similar. The contralateral and ipsilateral SSR latencies did not differ significantly from each other in either of the patient groups (Table 1).

Although the mean values of the SSR amplitudes recorded simultaneously on the contralateral and ipsilateral hands did not differ from each other, the responses in individual subjects were often asymmetric. In the control group, the SSRs to electric stimulation were asymmetric in 2 (6%) and to auditory stimulation in 3 (8%) of the 36 subjects. In patients with brain infarction, the SSRs were asymmetric to electric stimulation in 16 of the 54 patients (30%, \( P < .05 \), compared with control subjects) and to auditory stimulation in 17 of the 54 patients (31%, \( P < .01 \)).

### Discussion

The SSR is a multisynaptic sympathetic reflex that may be evoked by a variety of internally generated or externally applied arousal stimuli.\(^9\)\(^{10}\) The afferent limb of the reflex arc is considered to consist of large myelinated cutaneous sensory fibers, auditory and optic nerves, and the efferent limb of the sympathetic sudomotor pathway.\(^9\)\(^{10}\) The central parts of the SSR reflex arc, however, are still incompletely known. The mesencephalic reticular formation and the posterior hypothalamus are considered the most important neural structures in generating the reflex,\(^{19}\)\(^{22}\) but the cerebral cortex also has a significant role in the modification of the response, regulating a subject’s attention via the corticoreticular pathways.\(^{23}\)\(^{24}\) It has also been suggested that a decreased attention state leads to response habituation with diminished amplitudes.\(^10\)

The present study is the first one aiming to assess quantitatively the disturbances of the SSR in cerebrovascular diseases. We have demonstrated a significant suppression and delay of the responses in the acute phase of both hemispherical and brain stem infarctions. In the late phase of infarction, the SSR amplitudes were still suppressed, but the latencies of the patients and those of the control subjects did not differ significantly from each other. The suppression of the response was more obvious in patients with large cortical infarction than in patients with small deep infarction, but it was not dependent on either the side of the infarction or the studied clinical signs of the patients.

Sympathetic sudomotor activity has scarcely been studied in central nervous system lesions. In Parkinson’s disease the latency of the SSR has proved to be increased,\(^17\) and in multiple sclerosis the SSR has been reported to be abnormal in 75% of patients.\(^18\) In spinal cord injuries, the sympathetic sudomotor tone has been shown to be reduced by using both the SSR\(^18\) and microneurographic methods.\(^25\) As for cortical lesions, the only available study\(^26\) is a series with neglect syndrome patients indicating abolished SSR in five of seven cases.

Our data suggest that the observed abnormalities of the SSRs in the present patients may be attributed to a central dysregulation of the response, because the patients had no diseases known to affect the peripheral parts of the reflex arc. Moreover, fluid balance and body temperature of the patients were normal, there were no skin abnormalities in the registration area, and intravenous cannulas were situated far from the registration area.

In brain stem infarctions, the disturbances of the SSRs are likely to be caused by destruction of the sympathetic sudomotor pathway, which descends from the hypothalamus via the mesencephalon,pons, and posterolateral medulla oblongata to the intermediolateral column of the spinal cord.\(^27\)\(^28\) Because the pathway is mainly uncrossed below the hypothalamus, a unilateral brain stem lesion may result in asymmetric suppression of the SSR. Previously, we have demonstrated with another cohort of brain stem infarct patients that interruption of this pathway results in hypohidrosis throughout the ipsilateral side of the body.\(^8\) It is possible that asymmetric SSR observed in the present study is related to this asymmetric sweating response. Moreover, asymmetric SSR has also been demonstrated in multiple sclerosis patients with clinical signs of brain stem lesions.\(^18\)

Our findings of abnormal SSRs in patients with hemispherical brain infarction and the previously reported abnormalities in patients with neglect syndrome\(^26\) may be associated with impaired attention caused by a deficit in ascending pathways (eg, from the reticular activating system), in descending corticoretic-
ular pathways, or in the cortex itself. Because these pathways project from the cortex bilaterally to the reticular formation, a unilateral cortical lesion may result in bilateral suppression and delay of the SSR.29

In addition to regulatory effects on attention, the cerebral cortex may also have contralaterally distributed facilitatory and inhibitory effects on the sympathetic sudomotor activity, but the exact mechanisms and affected cortical areas are not known.30 Increased sweating6,7 and elevated skin conductance levels31 in patients with cortical lesions are suggested to reflect the release of a cortical inhibitory effect on the sympathetic sudomotor system. The significantly increased frequency of asymmetric SSR in the present infarct patients may also reflect these cortical regulatory effects on the sympathetic sudomotor pathways. However, it is possible that the SSR and thermal sweating responses are dependent on different neuronal regulatory structures.

In conclusion, the spectrum of autonomic dysfunction associated with brain infarction seems to be more extensive and complex than has been thought previously. The present findings, obtained with recordings of the SSRs, suggest that, in addition to well-established sympathetic hyperfunction, brain infarction may also cause suppression of various sympathetic reflex activities.

References
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