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Sympathetic Skin Responses Evoked by Different Stimuli Modalities in Spinal Cord Injury Patients

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Objective. By using a combination of physiological and electrical peripheral nerve stimuli, the authors aimed to characterize the expected dysfunction of the circuits responsible for sympathetic skin response (SSR) in persons with spinal cord injury (SCI). *Methods*. The authors examined SSR induced in the hand and foot in 50 SCI patients and 15 age-matched and gender-matched healthy volunteers. SSR was induced by deep inhalation, unexpected acoustic stimuli, brisk hand muscle contraction, and median and peroneal nerve electrical stimulation (PNS). *Results*. SSRs to any stimulus modality were absent in hand and foot in patients with complete SCI above the T4 level. They were present in the hand and absent in the foot in complete SCI patients at levels between T4 and T11 for all stimuli modalities except PNS. The elicitability of SSR was lower with peroneal nerve stimulation than the other stimuli in hand and foot. The mean latency difference between SSRs of the hand and foot was significantly longer in patients than in controls, regardless of stimulus modality. The amplitude of SSR was larger in volunteers than in patients. *Conclusion*. SSR to various stimuli confirms the importance of supraspinal centers and the integrity of sympathetic descending pathways. Simultaneous recording of the SSR in the hands and feet provides information about the degree of sympathetic impairment possibly in the efferent pathway. To monitor spontaneous recovery or the efficacy of a drug or biological therapeutic intervention, changes in the latency delay between the hand and foot may be valuable.

Keywords: *Spinal cord injury; Sympathetic skin responses; Autonomic nervous system; Neuroplasticity*

Sympathetic skin response (SSR) is a simple, noninvasive electrophysiological test that examines the common efferent pathways of the sympathetic nervous system.[1,2] Centers of the cerebral cortex[2-5] and the brainstem[2,5,6] have been proposed as sites where sensory signals generate the SSR. Normal functioning of the autonomic nervous system relies on the integrity of the spinal cord, as the entire sympathetic outflow and a proportion of the parasympathetic outflow (sacral parasympathetic) pass through the spinal cord before supplying target organs. Pathways from the spinal cord to the sudomotor sweat glands of hands (palmar), feet (plantar), and the perineal skin region transmitted by preganglionic and postganglionic sympathetic nerve fibers can be evaluated using the SSR.

The analysis of the SSR response generated by supraspinal magnetic or electric stimulation allows for the assessment of eventual spinal cord lesions.[7,8] Latency measurements of SSR are of little value, because they mainly reflect the function of the efferent unmyelinated segment.[2] However, the spinal efferent pathways mediating the SSR are not completely known. In subjects with spinal cord injury (SCI), autonomic involvement varies depending on the site and the extent of the lesion.[9] Patients with SCI at various levels and of varying severity may have different patterns of abnormalities of the SSR. Indeed, changes in skin conductance may still be present in subjects with complete SCI to electric stimulation below the level of injury,[10] pointing to the possibility of autonomic reflex reactions organized in propriospinal centers.

We investigated the ability of physiological and electrical stimuli to elicit the SSR in persons with SCI and whether such stimuli are a reliable and useful tool for the assessment of sympathetic tract integrity along the pathways from higher autonomic centers to the sweat glands. By using a combination of physiological stimuli and electrical peripheral nerve stimuli, we aimed to understand whether there is afferent or efferent dysfunction in the circuit responsible for the SSR in SCI patients across various degrees of severity and spinal levels.

Method

Participants

Fifty patients with a mean age of 43.8 ± 13.1 years (range, 16-75 years; male/female, 39/11) were included in this study. Demographic patient characteristics and clinical level of the lesion are summarized in Table 1. According to the American Spinal Cord Injury Association (ASIA) Impairment Scale,[11] 16 patients had complete lesion (ASIA-A), 8 had ASIA-B, 9 had ASIA-C, and 17 had ASIA-D. Trauma was the main etiology.

Eleven patients were receiving antispasticity medication (baclofen), 2 were receiving antiepileptics for neuropathic pain (gabapentin, pregabaline), 3 were receiving antidepres-

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Table 1
Demographic Patient Characteristics and Clinical Level of the Lesion

	Controls	Patients
Number	15	50
Age (years)	37.2 ± 8.9	43.8 ± 13.1
Time since SCI onset (months)	—	107.1 ± 104.8
Sex (female/male)	3/12	11/39
ASIA (number)		
A	—	16
B	—	7
C	—	8
D	—	19
Etiology		
Traumatic	—	36
Nontraumatic	—	14
Level of lesion		
Above T4	—	21
Between T4 and T11	—	16
Below T11	—	13

Abbreviations: SCI, spinal cord injury; ASIA, American Spinal Cord Injury Association.

sant drugs (fluoxetine), and 4 were taking sedatives for sleep (diazepam, lorazepam).

Fifteen healthy volunteers (range, 26-57 years) served as controls. The age difference between both groups was not significant (Table 1). The study was approved by the local ethics committee of the Institute Guttmann, Neurorehabilitation Hospital, and all subjects granted informed consent.

Patients taking medication that could affect the autonomic nervous system, such as α-blockers, β-blockers, or anticholinergic agents, had their medication discontinued 12 hours before the study. SCI patients were frequently affected bilaterally and rather symmetrically, so we recorded and report results from the right side. If the SSRs were absent on the right side, we studied the left side to confirm the absent response.

SSR Test Procedure

We performed electrophysiological studies with the subject supine. Subjects were instructed to relax, but not to fall asleep. The ambient temperature was maintained between 22°C and 24°C. A Medelec Synergy electromyograph was used for recordings, using a bandpass of 0.1 to 100 Hz and a sensitivity of 0.5 to 2 mV per division. Sweep duration was 10 seconds. For the hand, the active electrode was attached to the palm and the reference electrode to the dorsum. For the foot, the active electrode was attached to the sole and the reference to the dorsum.

The stimuli used to induce the SSRs were deep inhalation (DI), acoustic bursts (AB), electrical median nerve stimuli at the wrist (MNS), peroneal nerve stimuli (PNS) at the ankle, and hand grip (HG). The duration of electrical stimulus was 0.5 ms. The stimulus intensity was set at 15 times the sensory threshold of the stimulated nerve. If no responses were obtained, stimulation intensity was progressively increased up to the maximum level (100 mA). Each stimulus was repeated 4 times. To reduce habituation, the interstimulus interval was at least 30 seconds.

Data Reduction and Statistical Analysis

In electrically induced SSRs, we calculated onset latency from stimulus delivery in hand. In all subjects, we measured the latency of hand and foot responses and calculated the latency difference between them. We measured response amplitude from peak to peak. If there was no identifiable SSR, response amplitude was considered "0" and no value was entered for response latency or for amplitude.

The response probability (%) to the total number of stimuli was calculated for each stimulus type, subjects group, and recording site. Patients who had complete lesion, above the T4 level, were not included for percentage SSR response in hand and foot, and patients with complete lesion, between levels T4 and T11, were not included for the calculation for percentage SSR response in foot. Data were expressed as mean ± standard deviation. All statistical analyses were performed using SPSS 13.0. Analysis of variance was used to compare latency and amplitude of responses in different groups. The level of significance was set at $P < .05$.

Results

All patients and healthy subjects were able to complete the experiments without difficulty. Figure 1A shows SSR responses evoked by deep respiration from a healthy volunteer and a representative patient graded ASIA-D with a C4 lesion level. Figure 1B shows SSR responses to MNS from a healthy volunteer and a representative patient graded ASIA-C below a T4 lesion.

Differences Between Patients and Healthy Volunteers

The mean latency of SSR in the hand was not significantly different between patients and healthy volunteers after MNS and PNS ($P > .2$). The latency difference between hand and foot SSRs was longer in patients than in healthy volunteers to all stimulus types ($F = 8.56$; $P < .001$; see Table 2 and Figures 1 and 2).

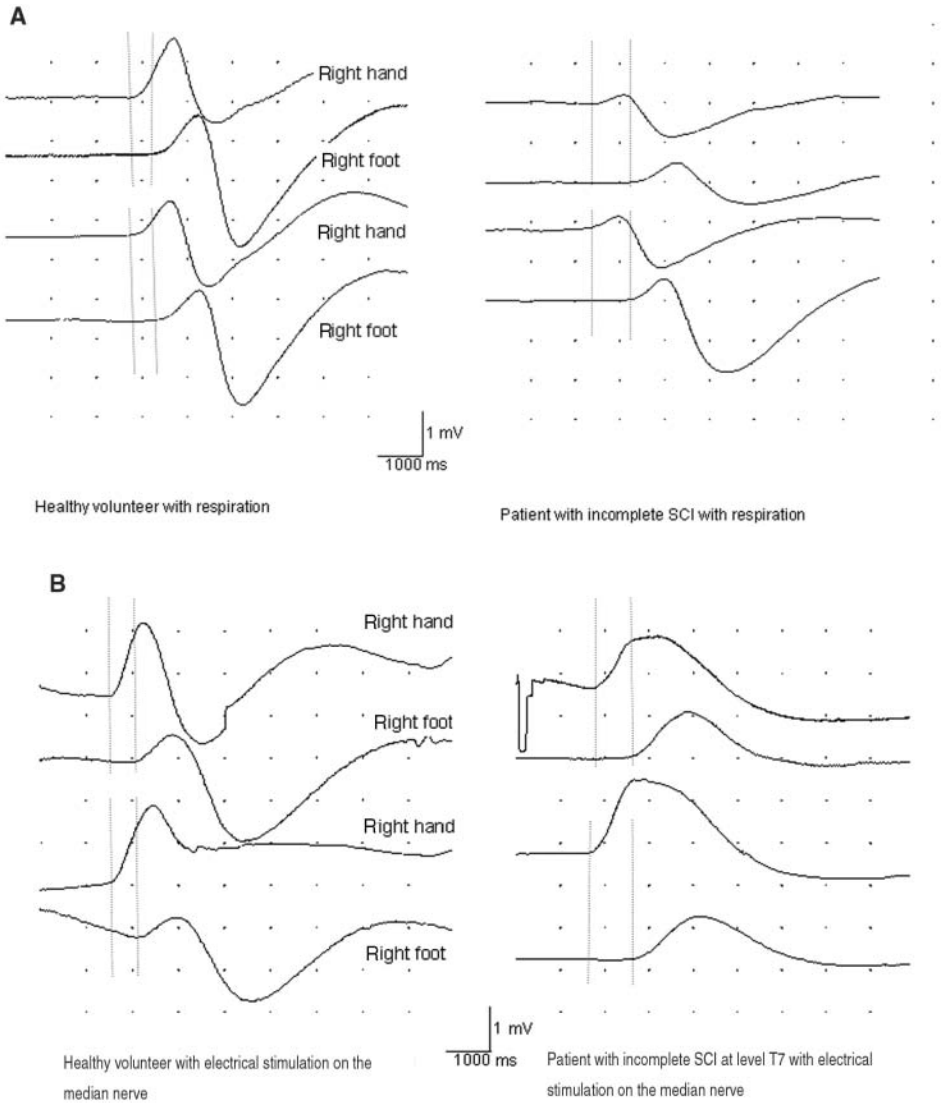
The amplitude of the SSR in the hand was larger in healthy volunteers than in patients, but the differences were not significant ($F = 1.86$; $P = .06$). However, the amplitude of the SSR in the foot was larger in healthy volunteers than in patients ($F = 2.94$; $P = .003$), and the differences were smaller in the SSR induced by HG ($P = .02$; Table 2).

Differences Between Complete Versus Incomplete Lesion

Only 3 patients with complete SCI had responses in the foot. Therefore, we did not carry out statistical analysis for SSR response.

Three complete SCI patients with lesions above T4 did not have an SSR in their upper and lower extremities. Ten complete SCI patients with lesions between T4 and T11 did not have an SSR in the lower extremity with any stimuli except peroneal nerve stimulation, which did not induce an SSR response in the upper or either lower extremity. Just 2 of 3 patients with complete SCI below the T11 level had an SSR in the upper and lower extremities with all stimulus modalities except with peroneal nerve stimulation, which did not induce any SSR response in the

Figure 1
Sympathetic Skin Responses (SSR)



Note: A, SSR responses evoked by deep inhalation from a healthy volunteer and a representative patient with SCI, ASIA-D, with C4 lesion. B, SSR responses to median nerve stimuli at the wrist (MNS) in a healthy volunteer and a representative patient with incomplete SCI, ASIA-C, below T6 lesion.

upper or either lower extremity. The other patient had an SSR in the hand but not in the foot to any stimuli.

Two patients with incomplete SCI at different levels, ASIA-D (C7 and T10), did not have an SSR in the lower extremity to any stimuli, or in the hand in the patient with a C7 lesion.

There were no statistically significant differences between subjects with complete and incomplete SCI for the latency of the hand SSR to MNS ($F = 0.14$; $P = .7$) or for the amplitude ($F = 1.2$; $P = .27$).

Differences Between Groups According to the Level of the Lesion

The patients were grouped according to lesion level (above T4, between T4 and T11, and below T11). The physiological stimuli (DI, AB, and HG) and electrical stimulation did not generate an SSR below the level of the lesion in patients with complete SCI. The SSR latency was similar with MN and PN stimulation ($P > .06$). In the comparison of latency difference between hand and foot SSRs at all levels, no differences were found ($P > .1$). However, the amplitude of the hand SSR to DI was significantly smaller in patients with a lesion level above T4 than in patients with other lesion levels ($P < .014$).

Differences According to Type of Stimuli

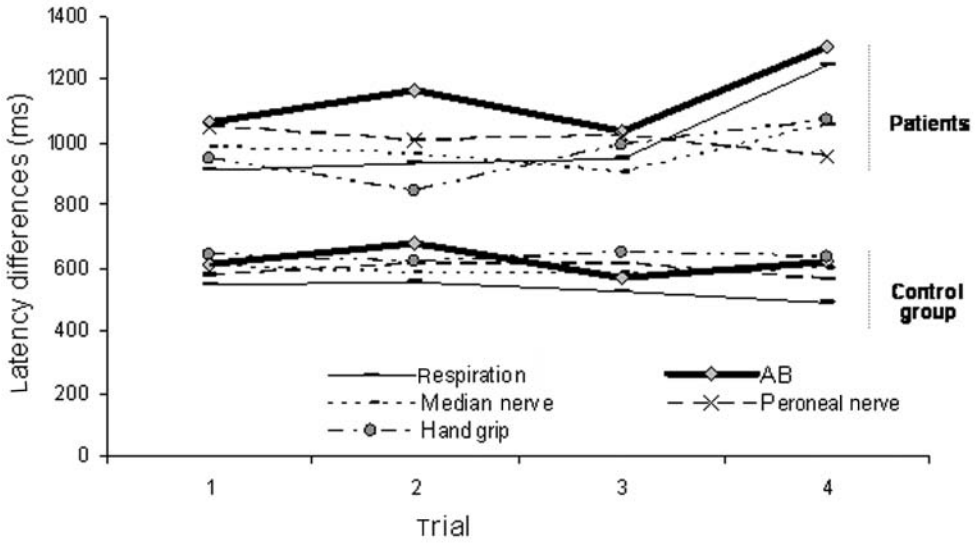
One patient with ASIA-D at level C4 had an SSR with DI and AB but not with MNS. The response probability of SSRs is shown in Table 2. Ninety-two percent of patients had an SSR in the hand to DI and MNS, whereas 65% of patients had SSR in the hand to PNS and 75% to HG (Table 2).

Table 2
Mean (Standard Deviation) of Latency, Latency Differences Between Hand and Foot, and Amplitude Evoked by Different Stimuli and SSR Response Probability

	Amplitude		Latency, Hands (ms)	Latency Differences, Hand – Foot (ms)	Response Probability	
	Hand (μV)	Foot (μV)			Hand	Foot
Respiration						
Patients	2110.6 (1546.2)	1157.4 (1559)		1034.2 (380.2)	91.5	55.5
Control	2325.4 (1480.7)	1956 (1343.7)		545.3 (106.1)	100	100
Auditory						
Patients	2456.4 (1801.2)	1509.5 (1450.5)		1080 (499.5)	85.9	53.4
Control	2933.5 (1318.3)	2378 (1601.8)		604.6 (181)	100	100
Stimulation of median nerve						
Patients	2555.5 (1718)	1585.5 (1365.7)	1573.8 (330.3)	1507.2 (515.5)	91.5	63.3
Control	3388.2 (2710.3)	2240.6 (1356.8)	1515.3 (173)	601.8 (101.1)	100	100
Stimulation of peroneal nerve						
Patients	1922.4 (1495.8)	1268 (1138.4)	1718.5 (333)	1126.9 (417.4)	65.5	46.1
Control	3154 (2242.8)	2539 (1143.3)	1641.6 (227.9)	598.9 (75.4)	100	100
With max force						
Patients	1813.9 (1269.9)	785.9 (478.7)		980.7 (322.2)	75.2	37.6
Control	2039.1 (1491.4)	1377.1 (1467.6)		657.9 (91.7)	100	100

Abbreviation: SSR, sympathetic skin response.

Figure 2
The Latency Difference Between Hand and Foot SSRs in Patients and in Control Subjects to All Stimuli



The intensity used for MNS and PNS was higher in patients (25.6 ± 20.3 vs 14.6 ± 4.8 mA; $P = .0027$) than in volunteers (76.7 ± 31.1 vs 30.7 ± 10.5 mA; $P < .0001$).

Maximum handgrip force was significantly reduced in patients than in healthy volunteers (24.2 vs 35.4 kilograms; $P = .02$).

Latency differences between hand and foot SSRs among all stimulus modalities were similar among subjects ($F = 0.265$; $P = .89$). However, the SSR amplitude obtained with DI and HG stimulations was smaller in the foot when compared with the hand ($P < .05$).

Discussion

The main finding of our study is the significantly larger difference between latencies of the SSRs recorded in the hand and foot in patients compared with healthy volunteers for different stimuli. The different stimuli caused very similar SSRs in patients with SCI, except for DI in the patients with lesions above T4 in whom HG produced smaller hand SSRs than in the rest of the patients.

None of our patients with complete SCI (ASIA-A) had an SSR in hand or foot to electrical stimuli applied below the

lesion, regardless of lesion level or stimulation intensity, which is in accordance with a previous report.[12] However, contrary to that study,[12] SSRs to electrical stimuli were present below the lesion in 4 patients with SCI of grade ASIA-B. These differences could be because of the different definitions of threshold used in the 2 studies. Preserved SSR in the palm to median nerve stimulation suggests normal sudomotor efferent tracts to the palm. Thus, absence of the palm SSR to peroneal nerve stimulation can be attributed to the involvement of afferent spinal pathways for the SSR. However, 2 patients with preservation of both motor and sensory function (ASIA-D) did not have SSRs in the foot to any stimuli, which suggests localized lesions on the efferent pathway of the sympathetic skin response to the lower limbs, although we could not exclude involvement of the afferent pathway.

Most patients with some preservation of motor and sensory functions (ASIA-C and ASIA-D) had SSRs in the hand and foot to all stimuli below the lesion. In those cases, although the hand SSR was smaller than in healthy volunteers, there were no significant differences in the SSR latency of the hand. Interestingly, however, the foot SSR was significantly delayed, leading to a significant increase in the latency difference between hand and foot SSR in patients compared with healthy volunteers. This suggests again a defect in the efferent pathway of the sympathetic tracts to the lower limbs in SCI patients.

The pathways innervating sweat glands in humans originate in the brainstem, hypothalamus, right and left medial prefrontal cortex, and right anterior insula.[13-15] Fagius and Wallin[16] considered that the latency of the SSR was derived from impulse conduction in an afferent arm, a central delay for sensorisympathetic coupling, and impulse conduction in the efferent tract. Hay et al[17] proposed that the efferent arm could be divided into preganglionic and postganglionic conduction times and sweat gland depolarization time. Wallin and Fagius[18] showed that the presence of neural activity may not always lead to a response. Methodological differences such as skin temperature, stimulus parameters, and stimulus significance may contribute to some response variation.[19] Kuppuswamy et al[15] showed that inhibition of cerebral activity with repetitive transcranial magnetic stimulation over dorsolateral prefrontal cortex, motor cortex, and cerebellum can cause the lengthening of the latency of SSR.

Clinical studies indicate that central neurons mediating sudomotor effects pass mainly through spinal cord segments and sympathetic ganglia T1-T6 to the upper limb and similarly through T8-T12 to the lower limb: lumbar lesions usually do not affect the sudomotor outflow to the limbs.[10,12,20,21] Reitz et al[10] showed that the SSR can be recorded in segments below the lesion, indicating that the descending pathway to sweat glands may be preserved despite the completeness of the motor and sensory lesion as judged by the ASIA criteria. However, the results of our study are compatible with those of Cariga et al,[12] with no response below the lesion to any physiological or electrical stimuli when there was a complete SCI.

The capacitive elements of the volume conductor may affect conduction in the sweat glands and may depend on the number of activated sweat glands.[22] This attribute could be explained by a new model based on the equivalent current dipole, a phenomenon caused by the Na^+ concentration gradient in the sweat.[22] When more sweat glands are activated, the equivalent current dipole develops more quickly and to a greater extent, leading to the generation of a large SSR with short latency. A small SSR with a long latency appears if only a small number of sweat glands are activated.[22-24] In our study, the lesser activation of the sweat glands because of the cord lesion may explain the latency delay in the foot in patients with SCI.

There are limitations to be considered when using physiological stimuli to elicit the SSR. The response to AB depends on intact hearing; all our subjects could hear the auditory stimulus (both ears) and none suffered from a hearing disability. The DI stimulus might be difficult to perform in some patients, such as those with upper cervical lesions, because of weakness of accessory respiratory muscles.[25] Of interest, the foot SSR response to DI was significantly smaller in our patients with high lesions.

Elicitation of the SSR in healthy subjects is independent of the type and location of stimulation.[20,26] Reitz et al[10] showed that the SSR following auditory and peripheral nerve (median and peroneal) stimulation occurred with the same pattern and with a similar latency, suggesting that common supraspinal descending sudomotor pathways mediated the SSR. Our studies indicate that all physiological stimuli led to a high incidence of SSRs, except HG, which was less effective in inducing the SSR and caused a smaller response than the rest of stimuli. This may be because of reduced handgrip force in patients with tetraparesis when compared with healthy volunteers.

Afferent and efferent spinal pathways mediating the SSR are not completely known. Preserved SSR suggests that some pathways are intact in the spinal cord, and this finding may indicate a favorable prognosis for motor recovery in SCI patients.[27] The data of Nair et al[28] showed a nonsignificant trend toward better motor outcome for subjects with spared SSRs. The differences between latencies of hand and foot SSRs may be an additional measurement of the defective efferent conduction in sympathetic pathways to the lower limbs in patients with SCI that could be considered in the assessment of indices of clinical/neurophysiological response of neurorehabilitation.[29] The possible involvement of the afferent pathway is not certain, however. Recording of the SSR will be of particular clinical relevance in monitoring the outcome of interventions designed to repair and improve spinal cord functions, especially in incomplete SCI lesions. To monitor spontaneous recovery or efficacy of therapeutic intervention in those patients, improvement in latency delay between hand and foot SSRs and increment of their respective amplitudes could provide valuable data.

In conclusion, our study investigated the SSR using physiological and peripheral nerve electrical stimuli in SCI patients. The SSR to various stimuli confirms the importance of supraspinal centers and the integrity of sympathetic descending pathways that are necessary to obtain an SSR. Simultaneous recording of the SSR in the hands and feet provides information on the degree of sympathetic impairment in SCI patients, which is currently not included in the ASIA and other functional and

physiologic SCI scales.[30-33] Using this test may be of particular clinical relevance in determining the completeness of the SCI lesion and in monitoring the outcome of interventions designed to repair and improve spinal cord functions, especially in incomplete SCI.[34] Assessment of the latency difference between hand and foot SSRs and of their respective amplitudes would provide valuable data to add to indices of spontaneous recovery or efficacy of therapeutic intervention in SCI patients.

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