CLINICAL STUDY

Sympathetic skin response: review of the method and its clinical use

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Abstract

Sympathetic skin response (SSR) represents a potential generated in skin sweat glands; it originates by activation of the reflex arch with different kinds of stimuli. The potential of rapid habituation after repeated stimuli is formed by biphasic or triphasic slow wave activity with relatively stable latency and variable amplitude. In healthy subjects younger than 60 years of age the response is always present in all extremities. SSR is most frequently used in diagnosing the functional impairment of non-myelinated postganglionic sudomotor sympathetic fibers in peripheral neuropathies. In this study a more complex and informative view on the anatomical and physiological substrates of SSR, its character, normal values and technique are presented, focusing on problems in evaluation of the response and factors that have influence on it. Based on personal experience normative latency and amplitude values of SSR in a group of 20 healthy individuals (x±SD), upper extremities: 1.48±0.80 sec., 444±167 µV, respectively; lower extremities: 2.06±0.93 sec., 203±87.4 µV, respectively) and recommendations for qualitative evaluation preference – the presence or absence of the response – over quantitative evaluation of latency and amplitude of the response in practical clinical use of the method are presented. *(Tab. 1, Fig. 2, Ref. 148.)*

Key words: sympathetic skin response, autonomic nervous system, autonomic dysfunction, neuropathy, non-myelinated fibers.

Autonomic nervous system, according to current knowledge, represents a complex structure with specific effects on each organ and system. Diagnostics of autonomic system disorders is therefore difficult. It is based on the accuracy of selection and interpretation of individual tests and their combination.

One of the methods for assessment of sympathetic fibers impairment in peripheral neuropathies as well as disorders of sympathetic system in other diseases is the evaluation of *sympathetic skin response (SSR)* (1). Similarly to other electrophysiological methods SSR has it's methodical and interpretational limits.

In this work it is attented, with respect to current knowledge, to present a more complex and informative view on anatomical and physiological substrate of sympathetic skin response, it's character, normal values and technique, factors that have influence on it and review of literature about its diagnostic use. Problematic technical aspects of the examination and means of response evaluation are discussed. Results from several years of our own experience using this method in diagnostics of diabetic neuropathy are also presented.

Definition, anatomical substrate and physiology of the sympathetic skin response

For the first time, the phenomenon of changes in skin potential following stimulation of special senses was described in 1890 by Tarchanoff. Subsequnetly after the method development, it's use particularly in physiological and psychological research has started (2, 3, 4).

Definition of this phenomenon was initially not unified. In 1970-ies the response was defined as either endosomatic, when electrical skin potential was recorded; or exosomatic when the

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change in electrical skin resistance was recorded after external stimulation by electrical current (4).

In the literature several terms are used such as electrodermal activity (4), electrodermal response (5), psychogalvanic reflex (6), galvanic skin response (7), peripheral autonomic surface potential (8) and the most frequently used – sympathetic skin response (SSR) (9). The term SSR represents electrical skin potential, i.e. endosomatic skin response according to an older classification.

The method of SSR recording was introduced into practice in electrophysiological laboratories by Shahani in 1984 and later by Knezevic and Bajada in 1985 (8, 9).

SSR is a change in potential recorded from the surface of the skin and represents a sudomotor activity. It is a result of polysynaptic reflex arch activation (10). The effectors of the reflex arch and most probably generators of potential change are activated eccrine sweat glands with cholinergic mediation.

The efferent part of the SSR reflex arch consists of myelinated sympathetic fibers of neurons from intermediolateral nucleus in TH1-L2 part of the spinal cord that terminate in paravertebral sympathetic ganglia. Postganglionic fibers are nonmyelinated (type C) and innervate the eccrine sweat glands. The central part of the reflex arch is not fully understood yet. It is presumably polysynaptic with a connection to the structures of hypothalamus, ventrolateral part of the brainstem, medial and basal parts of the frontal lobe and medial part of the temporal lobe (11–15).

SSR can be evoked by different types of stimuli. The stimulus modality determine the afferent tract of the SSR reflex arch. The most frequently used method – electrical stimulation of peripheral nerve in the extremity – activates the afferent part of the reflex consisting of thick myelinated sensory fibers (type II) and sensory spinal cord tracts ending in the brainstem (16). It is assumed that the afferent part of the reflex arch is selective and independent from somatic sensory tracts (17).

Technique of the sympathetic skin response examination

The technique of the SSR examination is not complicated and does not require any special instrumentation. The recommended standard guidelines are based on the method used by Shahani and Knezevic and Bajada (1). Standard surface silver (Ag-AgCl) electrodes are used for the recording. They should be placed on the sites with maximum eccrine sweat glands density – active electrode on the palm and the sole, respectively, reference electrodes on the dorsum of the hand and foot, respectively. The response was recorded also from perineum and genitals (18, 19, 20), from distal parts of the fingers, thumbs and toes (21, 22), as well as from proximal parts of the extremities (23). The response is processed by a standard electromyography with optional time base setting for 500–1000 ms per division, sensitivity setting 50–500 V/division and of filter bands availability in the range 0.1–2 Hz. Simultaneous bilateral recordings of the responses from both upper and lower extremities are recommended.

Single square – wave electrical stimulus with intensity of 10–30 mA and duration of 0.1–0.5 ms applied to peripheral nerve (the cathode oriented proximally) is used most frequently to evoke the response. With repetitive stimulation the inter-stimulus interval should not be more frequent than 1 per minute to minimize the phenomenon of habituation.

Most frequently, median and tibial nerves are stimulated contralaterally and ipsilaterally to the side of the recording (24–28), rarely peroneal nerve is stimulated (29). Stimulation of supraorbital nerve is preferred by some authors when monitoring SSR in focal cerebral lesions and spinal cord lesions to minimize the influence of the afferent part of the SSR reflex arch impairment (14, 28, 30–33). It was possible to record the SSR when dorsal penis/clitoridis nerve (34) and digitales proprii nerves of the hand were stimulated (35).

Shahani in his original work and later studies used deep inspiration as a stimulus to evoke the SSR (9, 36). The disadvantage of this kind of stimulation is the inability to determine the exact start of the stimulation even though concurrent recording of electromyographic activity from the diaphragm in the 8. intercostal space was preformed (37, 38).

Another frequently used stimulation modality was a clicking sound with intensity of 65–105 dB via biaural earphones (10, 39–42), or concurrent application of electrical and acoustic impulse (43–46).

The SSR was also provoked by magnetic stimulation in the region of C7 processus spinosus where direct stimulation of postganglionic sudomotor fibers C7 is presumed and also by direct magnetic stimulation of peripheral nerves and the brain. The highest response was observed in magnetic stimulation of contralateral motor cortex (47–51).

Sporadic information on the use of „startle stimulus“ (37, 38), laser stimulation of the skin (52, 53) or reflex hammer percussion on the sternum (54) was reported. Activation of afferent tracts for pain sensation is assumed.

Resende et al (55) used deglutination, blinking, skeletal movements, biting, light stimuli, vocalization as well as sphincter contraction to provoke SSR.

Characteristics of sympathetic skin response, normal values:

a) Shape of the response

SSR has a form of slow triphasic, biphasic or rarely monophasic wave exposing inter-individual as well as intra-individual variations of the shape, latency and amplitude by repetition (2, 10, 56–58). On the lower extremities it is usually biphasic (Fig. 1).

There are two types of the response according to the polarity of the waveform with the maximum amplitude: P-type with maximum positive deflection; N-type with maximum negative deflection. In healthy subjects the P-type of SSR is more frequent (58).

In our group of healthy subjects (n=32, 19 women, 13 men, age 18–54 years, average 31.4±10.5 years, median 29.5) the P-type waveform was recorded in 27 subjects (84 %) and N-type waveform in 5 subjects (26 %) (Fig. 2).

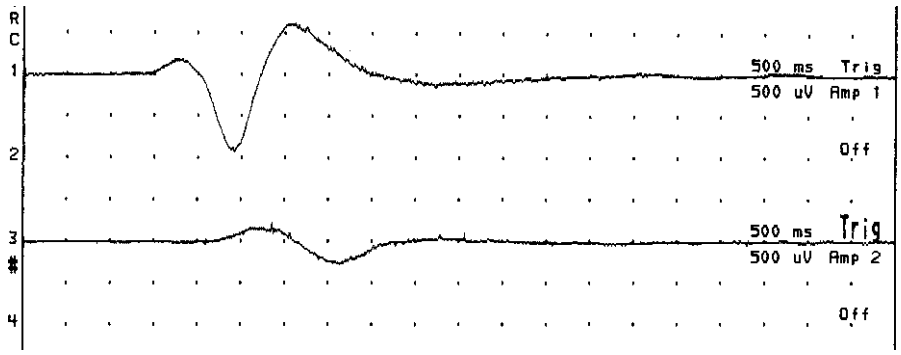

Fig. 1. Sympathetic skin response recorded from upper (1) and lower (3) extremities.

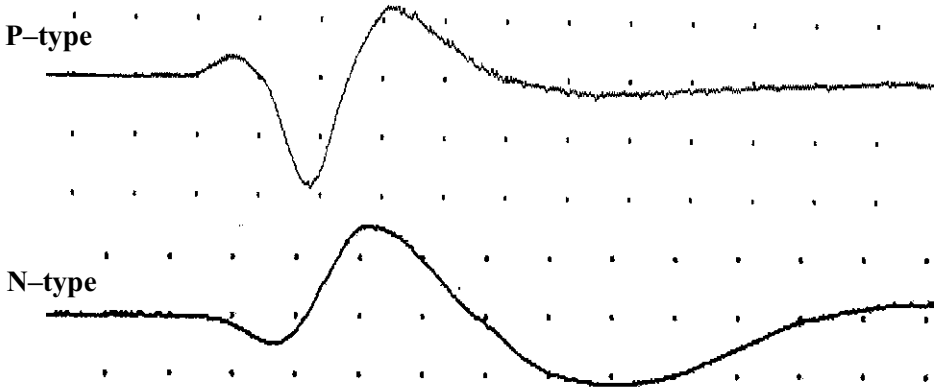

Fig. 2. P-type and N-type waveform of sympathetic skin response.

b) Latency and amplitude of the response

The latency of SSR is measured from the stimulation artifact to the first deflection from the baseline; the amplitude is measured from the peak of the first deflection to the peak of the next one (peak to peak). In healthy subjects the latency from the hands is significantly shorter than from the legs (9, 10, 59) and amplitude is significantly higher from the hands compared to the legs (59, 60). No intra-individual side differences in latency or amplitude of SSR were observed (10, 13, 31, 61). Normative latency and amplitude values of SSR from upper and lower extremities are summarized in the Table (Tab. 1).

c) Reproducibility of the latency, amplitude and shape of the response

SSR exposes intra-individual variation in the range of 2––44 % for amplitude and 2–22 % for latency according to different literature data (56, 62, 63).

In our group of 10 healthy subjects a 5.5 % average variation coefficient value from two measurements for latency from both upper and lower extremities and 48 % and 50 % for amplitude from upper and lower extremities, respectively were observed.

SSR shape variation at repeating examination was 23.9 % in healthy subjects and it did not change even in patients with diabetes mellitus (58, 64).

Factors with influence on sympathetic skin response

When evaluating the sympathetic skin response several factors should be taken to account, as they could by different means influence the response characteristics.

a) Habituation

There is a decrease in SSR amplitude observed after repetitive stimulation. This habituation phenomenon depends on the number of stimuli applied and on the total examination time. Aramaki et al observed a significant decrease in the amplitude after the 3rd consecutive stimulus (61). Ellie et al observed that the degree of habituation depended on the duration of the examination. They observed that the average SSR amplitude after 60 min was equivalent to 50 % of the SSR amplitude at baseline. A significant drop in the amplitude was observed after approximately 15–20 minutes of the examination. Habituation appeared earlier after regular application of consecutive stimuli in short intervals. Therefore, a limitation of 15 minutes per test and irregular application of the stimuli (frequency more than 1 per minute) is recommended (1, 10).

b) Gender, age, height

There are different opinions concerning the influence of age on SSR.

Tab. 1. Normal values of sympathetic skin response latency and amplitude in healthy subjects.

n	Upper extremities	(±SD)	Lower extremities	(±SD)	Author
	Latency (sec)	Amplitude (μV)	Latency (sec)	Amplitude (μV)	
40	1.39±0.10	912.8±605.5	2.00±0.16	480.28±283.82	Denišlič (80)
50	1.45±0.23	678±553	2.02±0.23	268±247	Aramaki (60)
100	1.47±0.16	449±429	1.92±0.21	147±122	Drory (65)
30	1.50±0.08	310±180	2.05±0.10	140±80	Elie (10)
30	1.52±0.13	479±105	2.07±0.16	101±40	Knezevic (8)
30	1.36±0.11	730±630	1.97±0.20	430±390	Žgur (95)
45	1.342±0.108	228.1±103.3	-	-	Baba (56)
50	1.42±0.11	563±424	-	-	Toyokura (58)
35	1.24±0.16	914±372	1.88±0.20	441±214	Tzeng (88)
32	1.48±0.80	444±167	2.06±0.93	203±87.4	Kučera

Comparing the SSR amplitude and latency values in 100 healthy subjects, Drory et al found in elderly a statistically significant decrease in amplitude, but no influence on the latency (65). Opposite to this, Baba et al did not observe an age-dependent significant decrease in SSR amplitude in 45 healthy subjects (56).

Using the qualitative criteria for SSR evaluation, i.e. the presence or absence of SSR, Drory et al found in the group of healthy subjects over 60 years of age a 50 % and 70 % absence of SSR from upper and lower extremities, respectively. In the group under 60 years of age the presence of SSR was 100 %. However, Braune et al observed a 100 % presence of SSR even in the group over 60 years of age (66).

Monitoring the correlation of the amplitude and latency with age revealed a strong negative correlation of SSR amplitude with age observed by some authors (63, 65). However, Braune et al did not find this correlation in a group of 50 subjects (66). The non-dependence of SSR latency on age was reported concomitantly by several authors (38, 66, 67).

Some authors have reported a presence of a height-dependence of SSR latency (9, 10, 23, 56, 67), but it has not been observed by others (8, 38, 63).

c) Modality of the stimulation used

Ellie et al did not find any significant differences in the SSR latency and amplitude using an acoustic stimulation, electrical stimulation of the median nerve contralateral to the site of the recording and concurrent application of both stimulations. (10, 43). The same was observed by Satchell and Seers (68). Denišlič and Meh did not observe any significant differences in the SSR latency and amplitude using electrical stimulation and mechanical stimulation – percussion with a reflex hammer on the sternum (54). Shahani et al, on the other hand, found a significantly higher SSR amplitude values evoked by deep inspiration compared to electrical stimulation of the peripheral nerve (9). Kira et al observed an increase in the SSR amplitude after forced exspiration compared to inspiration and electrical stimulation (69). More complex review of the literature data on SSR is absent.

d) Body temperature

The SSR latency and amplitude are dependent on the body temperature and the relation is linear. This is most probably caused by a change in the conduction of postganglionic non-myelinated fibers and by an influence on neuroglandular connection (63, 70). Stability of the room temperature (around 26 °C) and 15–20 minutes stay of the person to be examined in a room with this temperature prior to examination are regarded as sufficient measures. Local warm-up of the extremities is not recommended as it could cause a depolarization of the sweat glands and so a decrease in SSR amplitude (10, 71).

Means for evaluation of the sympathetic skin response and its parameters

There is still no consensus in the scientific literature dealing with SSR about the evaluation and processing of the responses recorded. Two different evaluation attitudes of the SSR have been presented. The qualitative evaluation accepts only the absence of SSR as a pathological sign (17, 26, 32, 38, 57, 61, 72–78). However, with this evaluation, a risk of false negative results can not be excluded (79). The other group of authors favors the quantitative evaluation. Some of them prefer the latency parameter due to its lower variability (2, 40, 45, 54, 73, 80, 81). The others prefer only the amplitude measurement. They cast doubt on uncertainty of marking the exact beginning of the slow initial deflection from the baseline (56, 82).

There exists no opinion consensus either about the selection of the response to be evaluated, or the selection of the mathematical processing of the responses after repetitive stimulation.

Some authors used the method of *averaging* number of responses (8, 9, 54). The validity of this average response is, however, influenced by habituation and SSR shape variation (56).

Some authors selected the *absolute* amplitude and latency value evaluation of the first evoked response, which has, also according to our experience, the highest amplitude and shortest latency. This option minimizes the habituation phenomenon (83).

One group of authors performed a number of SSR measurement and they used the absolute amplitude and latency values of

the response with the highest amplitude and shortest latency for evaluation (27, 44, 84).

The other group selected the *average* amplitude and latency value from a number of consecutive measurements (25, 13, 22, 37, 85–87), or they have evaluated the *average* amplitude and latency value from consecutive SSR examinations with the highest amplitude and shortest latency (29, 82, 88–90). Literature data on systematic evaluation of the above mentioned attitudes is still absent.

In our laboratory, the qualitative evaluation of SSR abnormalities is preferred. Recording concomitantly from all extremities, the absence of SSR from at least two extremities after electrical stimulation followed by a deep inspiration is considered abnormal.

Use of the sympathetic skin response in diagnostics of autonomic functional disorders

a) Lesions of the peripheral nerves and nerve roots

In the clinical neurological practice evaluation of the SSR is used particularly in the diagnostics of autonomic disorders in patients with peripheral neuropathy. Most frequently the SSR is used for diagnosis of thin unmyelinated fibers lesions in diabetic neuropathy (8, 9, 36, 39, 59, 63, 72, 74, 75, 82, 88, 91–99) and uremic neuropathy (77, 89, 100–105).

Abnormal SSR was detected also in familial amyloid neuropathy (106), alcoholic neuropathy (26, 107, 108) and lepromatose neuropathy (109, 110).

The absence of SSR was found in 5 out of 15 patients with hereditary motor and sensory neuropathy type I (111). Measurements of SSR were used for differentiation between type III and type IV of hereditary sensory autonomic neuropathy; in type IV neuropathy with clinically characteristic anhidrosis the response was absent (112). The absence of SSR was observed also in acute and chronic inflammatory neuropathies with autonomic dysfunction (113, 114).

Abnormality of SSR was observed in HIV-positive patients in the early asymptomatic stages of the disease (115).

In carpal tunnel syndrome the response was characterized by a lower amplitude (21, 116–119); in root compressions at level L5 and S1 no changes of SSR were observed (120).

SSR was clinically used in diagnostics of autonomic disorder in reflex sympathetic dystrophy by measurement of amplitude decrease and latency prolongation (90, 121, 122).

b) Central nervous system disorders

In clinical studies, abnormalities of SSR were found in more than 50% of patients with multiple sclerosis. It is considered a sign of a lesion of the central sympathetic pathways (30, 42, 84, 123–126). According to several authors the sensitivity of SSR is comparable with sensitivity of the evoked potentials (43, 83).

Prolongation of latency and decrease in amplitude of SSR were observed in patients with Parkinson's disease and Parkinsonian syndrome (35, 40, 46, 54, 66, 127–129).

In amyotrophic lateral sclerosis the SSR was absent in 40 % of 25 patients (25) and prolongation of latency and decrease in amplitude was present (130, 131).

Abnormalities of SSR were present in patients with cervical myelopathy (32) and syringomyelia (86).

SSR was abnormal in the majority of patients with Shy Drager syndrome, sporadic olivo-ponto-cerebellar atrophy (OPCA) and striatonigral degeneration, on the other hand, it was normal in patients with familial OPCA, sporadic cerebellar atrophy and familial cerebellar atrophy (31).

Abnormalities of SSR were found in Wilson's disease (132, 133), Huntington's disease (134, 135), Duchenne's muscular dystrophy and other dystrophies (37, 134).

The sympathetic skin response was studied also in patients with hemispheric and brainstem cerebral strokes. Shwalen et al observed bilateral prolongation of latency and a decrease in amplitude of SSR in 24 patients with ischemic stroke in the vascular region of cerebral media artery without evident lateralization (41). Similar observations were reported by Korpelainen et al in hemispheric as well as brainstem strokes (13). Linden and Berlit observed more frequent bilateral abnormalities of SSR in brainstem strokes and more significant abnormalities contralaterally to the site of the lesion (14). On the other hand, Obach et al found more significant decrease in SSR amplitude in the upper extremity ipsilaterally to the site of the lesion in the region of lateral medulla oblongata (33).

Reports about changes in SSR in epilepsy are rare (137).

c) Other diseases

Efforts have been made to use the sympathetic skin response in diagnostics of sympathetic impairment in erectile dysfunctions (18, 19, 34, 67), sclerodermia (61), Sjögren syndrome (76), autoimmune vitiligo and primary autoimmune hypothyroidism (138), psoriasis and vitiligo (139), depression and psychosis (140, 141), Behcet disease (142), rheumatoid arthritis (143), Fabry disease (144, 145) and botulism (146).

SSR could be useful even as a method of efficacy assessment of surgical or chemical sympathectomy (85) and nerve regeneration after surgical procedure (147).

Péréon et al used SSR in monitoring of acoustic threshold in patients with cochlear implant (148).

The method of sympathetic skin response recording can be considered technically simple and realizable using standard electromyographic instrumentation. It is critical to strictly follow the standard examination procedure and take all known influential factors into account in interpretation of the results. In the clinical practice it is useful to prefer the qualitative evaluation of the SSR abnormalities, i.e. the absence of SSR. In the view of current knowledge it is possible to consider SSR measurement as a useful complementary method in neuropathy diagnostics when lesions of thin non-myelinated fibers are supposed.

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