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Is There Any Sympathetic Skin Response (SSR) Abnormality in Raynaud Phenomenon?

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Abstract

Objectives: Sympathetic skin response (SSR) is a technique for assessment of the damage of peripheral neuropathies and the disorders of the sympathetic system. This study aimed to evaluate SSR among patients with Raynaud phenomenon (RP). ***Methods:*** Between January 1, 2015 and December 30, 2018, about 20 patients with RP and 20 healthy subjects as the control group were recruited from patients referring to the Outpatient Clinics of Shiraz medical University. All the participants were clinically examined, and the SSR was performed using a standard protocol. SSR is abnormal when the latency is prolonged and/or the amplitude reduced. ***Results:*** Raynaud's group consisted of 19 women (95 %) and 1 male (5%). 3 patients (15 %) with primary Raynaud's phenomenon (PRP) and 17 patients (85%) with secondary Raynaud's

phenomenon (SRP). The control group consisted of 16 women (80%) and 4 males (20%). The mean age of the Raynaud's group and control subjects was 43.1±9 and 36.7±8.6 years, respectively. The SSR to the electrical stimulus was absent in 3 patients (PRP patients). The total median nerve mean latencies in the upper limb were 1.9±0.57 and 1.19±0.52 seconds for the Raynaud's group and control groups, respectively ($p < 0.001$). These findings revealed significantly prolonged SSR latencies in the Raynaud's group, while the mean amplitude showed no significant differences in both groups ($p = 0.756$). ***Conclusion:*** Absence or prolonged latency of SSR was associated with the disorders of the unmyelinated axons in the sympathetic system. Our findings suggested the disorders of unmyelinated axons in Raynaud's phenomenon.
Keywords: Raynaud Disease; Autonomic Nervous System; Electrodiagnosis; Sympathetic Fibers; Nerve Conduction.

Advances in Knowledge

- As this study is conducted in Iran, it will increase the individuals and physicisns' awareness of to Raynaud's phenomenon (RP).
- Absence or prolonged latency of sympathetic skin response was associated with the disorders of the unmyelinated axons in the sympathetic system such as Raynaud's phenomenon.

Application to Patient Care

- SSR test is recommended to be used for evaluating the sympathetic status and the symptoms in patients with RP.

Introduction

In Raynaud phenomenon (RP), when one is exposed to cold weather or stress, a sequence of pallor, cyanosis, and redness is manifested, which can be painful and leads to recurrent vasospasms in the digits.[1, 2] PR is divided into primary Raynaud's phenomenon (PRP) and secondary Raynaud's phenomenon (SRP). The criteria of PRP include a symmetric presentation of this phenomenon without tissue necrosis, ulceration, or gangrene, when secondary causes are ruled out.[3] SRP occurs in association with the underlying diseases, including neurological disorders and mixed connective tissue disorders (MCTDs).[3] Sympatholytic drugs and reduction

of emotional stress are useful in RP treatments; it has been suggested that Autonomic Nervous System (ANS) dysfunctions may lead to RP.[1] To evaluate a patient presenting with RP, a physician should request the required laboratory data and imaging studies after complete history taking and physical examination. These assessments are essential tools in broader evaluation of RP symptoms .[4] To manage the phenomenon, patients should consider lifestyle modification, keep the affected figure warm, and stop taking vasoconstricting drugs like nicotine. Hughes et al. reported that only 16% of the participants with RP stated that partially one current medication was effective to prevent or control RP attacks.[5]

Sympathetic skin response (SSR) is a simple and noninvasive test that reveals an interaction between the surrounding epidermal tissue and the sweat glands. Because it is a multisynaptic reflex, its waveform amplitude and latency are variable. SSR involves electric stimulus of a peripheral nerve and record from the surface electrodes on the hands and feet for studying the neural activity of type C unmyelinated fibers. It is a reliable indicator of sudomotor sympathetic function to evaluate the patients with somatic and autonomic neuropathies.[6, 7]
Most of the recent studies have assessed the large myelinated fibers and have not measured the thin myelinated or unmyelinated fibers such as the sympathetic fibers within the peripheral nerve.[8] There are few studies that evaluate the ANS effect electrophysiologically in RP. In this study, we evaluated SSR in patients with RP to assess the sympathetic dysfunction in patients with RP.

Methods

The present study included 20 patients with PRP and SRP in the period between January 1, 2015 and December 30, 2018. The patients were recruited from those referring to the Outpatient Clinics of Physical Medicine and Rehabilitation and Rheumatology of Shiraz University of Medical Sciences. The control group included 20 healthy participants without any medication affecting the ANS. Written informed consent was taken from all participants to be enrolled in our study. The ethics committee of Shiraz University of Medical Sciences approved this study (ID: IR.SUMS.REC. 1387.S4254).

Inclusion criteria were the patients diagnosed with PRP and SRP if they had definite sensitivity to cold with classic color sequence triad in their hands and according to previously published criteria.[9] Patients were selected at least six months after the onset of the symptoms. These patients were recruited from those referring to the outpatient clinics of physical medicine and rehabilitation and rheumatology.

Exclusion criteria were the patients with endocrine diseases such as diabetes mellitus, thyroid diseases and metabolic diseases; those with scars, ulcers or gangrene of the hand fingers, neurological disorders, other mixed connective tissue disease, history of cancer, any type of peripheral neuropathy; and the patients who used drugs that affect the ANS (e.g. tricyclic antidepressants, clonidine, ergotamine and serotonin-receptor agonists, B blockers, oral contraceptives).

At first, general clinical and neurological examinations were performed for all subjects in a half dark and silent room with a temperature of 23°-26°C and the humidity between 30 and 35%".[10] SSRs with an intensity between 15-25 mA were used to assess the sympathetic activity in 20 patients with RP and 20 controls. The skin temperature was kept above 32°C in all patients. One electromyographic apparatus, Medelec Synergy electromyography instrument (VIASYS Healthcare UK, manor way, old-working, Surrey, UK), was used for all patients and the control group by the same physiatrist.[10] A sweep speed of 500 ms/div, sensitivity of 200-1000 mv/div and filtering of 0.5 kilohertz (KHZ) were used.[14]

The subjects were conscious, silent and fixed in a supine position to diminish movement artifacts. Before performing the test, the procedure was explained for all the participants. "For the median nerve SSR, the active electrode was attached to the base of the second finger in the palmar surface and the reference electrode was placed in the dorsal aspect of the hand. Stimulating electrodes were placed on the wrist area between the Palmaris longus and flexor carpi radialis tendons. A ground electrode was located proximal to the active electrode with respect to the cathode's location"[10] (Figures 1 and 2).

To record the SSR, we used the minimum stimulation intensity which was needed and increased it in the subsequent stimulation. The stimuli were given at irregular intervals of more than 65 seconds to avoid considerable habituation. Latencies and amplitudes of the waves were measured. The latency of SSR was measured in seconds from the stimulation artifact onset to the onset of the first deflection from the baseline; the amplitude was measured in microvolt from the peak of the first deflection to that of the next one (peak to peak). Three recordings were performed for each limb and the average responses were used for analysis.[11] Absent response was considered as an abnormal test. Median and Tibial nerve compound muscle action potential (CMAP) and median and sural sensory nerve action potential (SNAP) were done for all subjects for assessment of any peripheral neuropathy (e.g. carpal tunnel syndrome). Only the reproducible responses with no movement artifact were chosen for analysis.[12]

The statistical package SPSS, version 18, was used to analyze the data. Arithmetic mean and standard deviation of the data were determined using T-test and Mann Whitney's U test. Chi-square test was utilized to compare the responses from the Raynaud's and control groups. P values less than 0.05 were considered significant.

Results

The present study consisted of 20 RP patients [19 females (95%) and 1 male (5%)]. The patient's mean age was 43.1±9 years. The control group consisted of 16 females (80%) and 4 males (20%). The mean age of the control subjects was 36.7± 8.6 years. Any underlying disease was not found in 3 patients (15%) of the Raynaud's group (PRP). However, 17 patients (85%) had a history of underlying disease such as systemic sclerosis 14 (70%) and Rheumatoid arthritis 3 (15%) (SRP). All of the PRPs had abnormal SSR latency and amplitude tests (100%).

The mean latencies for SSR of the right and left median nerves lasted 1.86± 0.55 and 1.79±0.5 seconds in the Raynaud's group, and 1.117±0.5 and 1.21± 0.6 seconds in the control group, respectively. Also, the total median nerves mean latencies in the upper limb was 1.9±0.57 and 1.19±0.52 seconds for the Raynaud's and control groups, respectively. Comparisons in both groups demonstrated significant differences for SSR mean latencies with $p<0.001$. However, the

comparison of SSR mean amplitudes in both groups did not show a significant difference (p = 0.756) (Table 1).

All individuals had normal Median and Tibial nerve compound muscle action potential (CMAP) and median and sural sensory nerve action potential (SNAP) although any peripheral neuropathy such as carpal tunnel syndrome or peripheral polyneuropathy was excluded.

Discussion

The aim of the present study was to investigate electrophysiologic alterations of the sympathetic nervous system in RP patients. There are some conditions associated with abnormal SSR such as lesions of the peripheral nerves as well as those of the nerve roots (diabetic neuropathy, familial amyloid neuropathy, alcoholic neuropathy, lepromatose neuropathy).[8] Additionally, abnormality of SSR was observed in carpal tunnel syndrome and complex regional pain syndrome.[7, 13] Measures have been taken to utilize the SSR in diagnosis of sympathetic damage in some rheumatologic disorders, such as scleroderma, Sjogren, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, and RP as well as in urologic diseases such as chronic prostatitis.[14-17] To the best of our knowledge, literature lacks adequate data regarding ANS evaluation in patients with RP. Neurologic changes in RP are doubtful.

When used clinically, SSR has many limitations. Latency and amplitude of the signal response are different in a single individual and even more diverse when studying in population. Adding the habituation phenomenon to letters makes it challenging to calculate SSR normal parameters.[18, 19] One study on the clinical use of SSR reports lower amplitudes response in the contralateral side than the side of common peripheral nerve stimulation. This might happen due to greater excitation dispersion of the afferents arc.[19] When studying the role of sympathetic fibers in mononeuropathies, one can bypass obtaining absolute reference values dilemma, using the unaffected side as an internal control by comparing the parameters between the two sides. Thus, the ratio of values between two side values can be calculated.[18, 19] Based on previous studies, to identify the abnormal response in amplitude and latency of SSR, we made a comparison between patients and normal individuals.

Our result showed that PRP had abnormal SSR latency and amplitude, which was similar to a previous study carried out by Mondelli et al. They reported sympathetic dysfunction in PRP. They stimulated the ulnar nerve in the upper limb, but we stimulated the median nerve that has more sympathetic fibers. They found a significant delay in SSR latency in the patients with PRP. Additionally, they did not measure the SSR amplitude; they measured the area because it had a good accuracy of total sympathetic excitability of the nerve.[20]

According to a study carried out by Charkoudian, the sympathetic nervous system, via both peripheral (local) and central system mechanisms, plays a critical role in the pathogenesis of primary and secondary RP.[21] Pancera et al. investigated the sympathetic hyperactivity in systemic sclerosis and PRP. Subjects with PRP had normal heart rate changeability and more activity of sympathetic fibers.[15] In another study, PRP was compared with SRP in systemic sclerosis. Both groups had a decrease in Calcitonin gene-related peptide (CGRP), endothelium–1 flare, and Prostaglandin production 9.5 (PGP). These findings indicate that there is a general vascular hyperactivity in these conditions that probably reflect a primary vascular disorder.[22]

Gosk-Bierska et al. in a study on 20 patients with SRP noted a significant low SSR amplitude and significant long latency in those suffering from SRP in their palms and sole. In patients with SRP, no relationship between SSR and microangiopathy was found; this confirms that these two processes occur independently in patients with SRP. They concluded that normal peripheral nerve function with impaired ANS suggested the central origin of SRP. Abnormal SSR habituation might also result from the central mechanism.[23]

Gledhill in another study showed ANS dysfunction in 9 patients with SRP with cardiovascular autonomic dysfunction. The heart rate response to deep breathing, Valsalva and standing were measured before and after the triiodothyronine administration. The amplitude was decreased in three patients, and mild slowing of conduction velocity in six patients was observed (less than 20%). Test results showed the considerable improvement of ANS function after administration of triiodothyronine.[24]

Using median nerve stimulation, Badry et al. compared the SSR in 21 patients with systemic sclerosis (SSc) and 39 patients with RA to SSR in 60 healthy participants. They found increased latency and reduced amplitude in SSc and RA patients. The SSR of SSc patients was significantly prolonged in latency and showed reduced amplitude when compared to RA patients. Additionally, 6 SSc patients had increased SSR latency without manifestations of polyneuropathy. They concluded that patients with SSc and RA suffered from ANS dysfunction with more effects in SSc patients.[25]

Saba et al. evaluated the ANS changes in RA patients. The SSR amplitude was decreased and SSR latency was prolonged in RA patients compared to the control group. Additionally, there were no statistically significant differences between the patients with different disease activity of RA as well as functional disability of RA and SSR latency and amplitude .[26]
Another stydy of SSR in 30 RA patients showed that SSR were abnormal in 6 patients. They did not include the amplitude as a diagnostic criterion because it too variable even in the patients. They found frequent abnormalities in SSR in patients with RA whether there was a clinical symptom of ANS or not.[27]

Our findings are in line with those of previous studies; there was no significant abnormality in SSR amplitude between the patients and controls. Most studies did not consider the amplitude as a valid measure of normality versus abnormality.[20, 27] Also, there was no relationship between the type of SSR abnormality and intensity of autonomic impairment. In one study, in reflex sympathetic dystrophy, the mean amplitude and onset latency of SSR in the involved limb was greater and shorter than that the uninvolved limb. [7] These findings support the crucial role of ANS dysfunction in RP.[28] Overall, in our study, the individuals in the Raynaud's group presented with abnormal SSR with the mean latency, which suggests no significant differences between the groups in skin innervation.

In pathophysiology, lack of SSR represents the failure of polysynaptic system to propagate the impulses to the end organs. Increased latency in SSR may originate from milder neuropathic damage or may originate from loss of thicker axons, changes in cholinergic fibers and/or sweat glands, and synaptic transmission interruption through the central processing.[23] Since there was

no evidence of afferent somatic fibers, central nervous system, or sweat glands disease in our study, it is suggested that the source of SSR latency abnormalities might be the sympathetic efferent nerves.

PRP is more common in women than men; thus, many published studies failed to match gender in the control and case groups.[20] By matching gender between the case and control groups, we tried to omit this bias.

Performing the SSR test in rheumatology patients helps us detect autonomic disorders early. Thus, the patient can receive appropriate treatment for potential complications. (For example, cardiovascular or skin disorders such as dry skin or excessive sweating - or neurological disorders such as dizziness and imbalance).[27] It could be beneficial to regulate the drugs that affect the autonomic system in RP patients. Also, using SSR test for better management of underlying autonomous system-related symptoms helps one to optimally control the RP symptoms.[20] ANS dysfunction is one of the etiological factors linked to the development of microvascular manifestations of RA and SSc, which may play a role in developing pain symptoms in these diseases.[7]

This study had some limitations, such as sample size (n=20). This was just an observational report, which requires validation with randomized criteria and a larger sample size. Moreover, some patients with SRP use anti-hypertensive drugs and we could not discontinue the medication. These medications may alter the SSR. The test is very sensitive and requires complete relaxation during the examination; thus, there is a need for some special techniques and patients' cooperation. We recommend further studies with a larger sample size and clinical trials to better evaluate the SSR parameters.

Conclusion

Absence or prolonged latency of SSR was associated with the unmyelinated axons disorders in the sympathetic system. Our findings confirm the role of the disorders of unmyelinated axons and sympathetic nervous system in Raynaud's phenomenon.

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Conflict of Interest

The authors declare no conflicts of interest.

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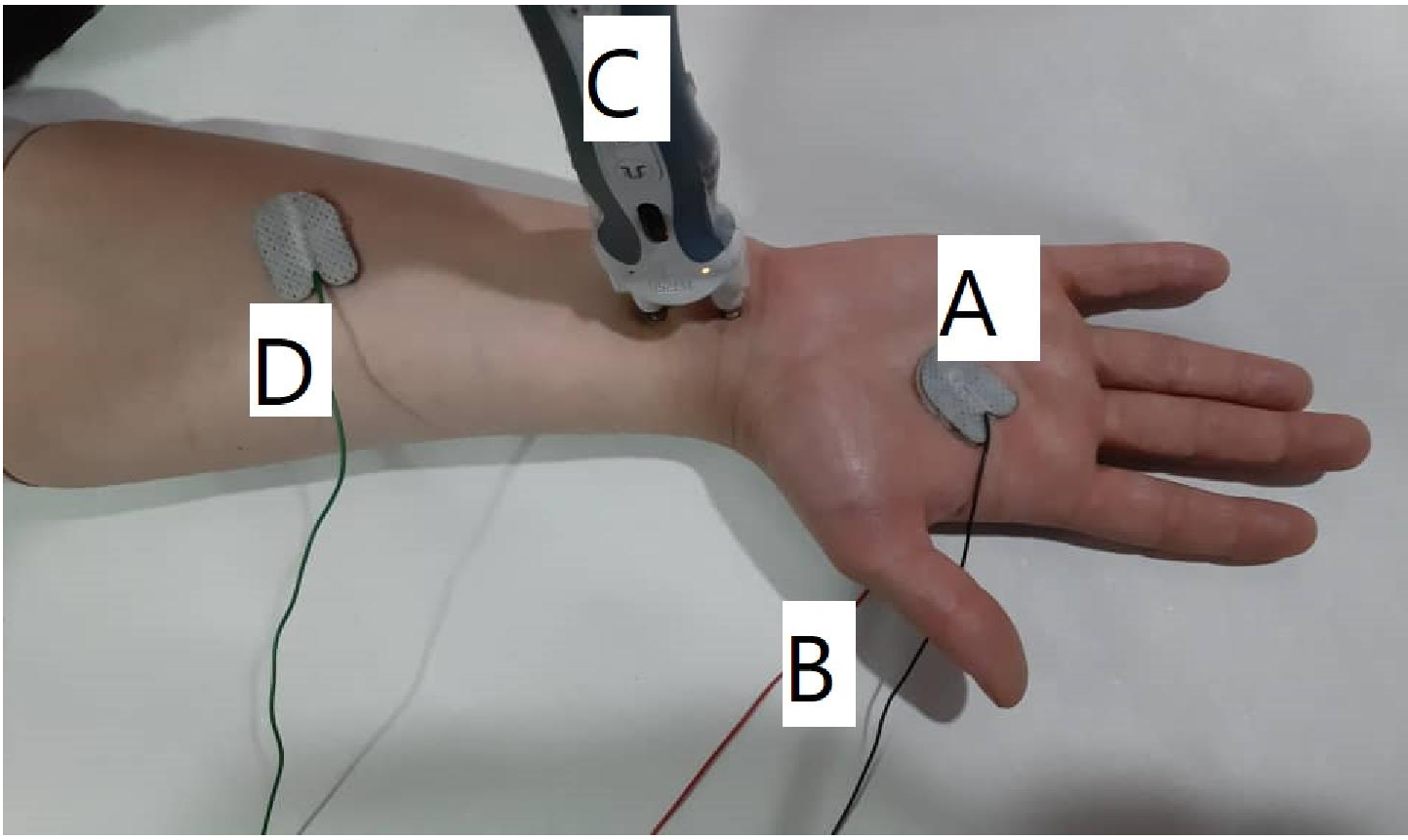

Figure 1: The sites of recording sympathetic skin response from the median nerve **A:** Active electrode on the hand; **B:** Reference electrode on the dorsal aspect of the hand, **C:** Ground electrode on the forearm and **D:** Stimulate median nerve on the wrist.

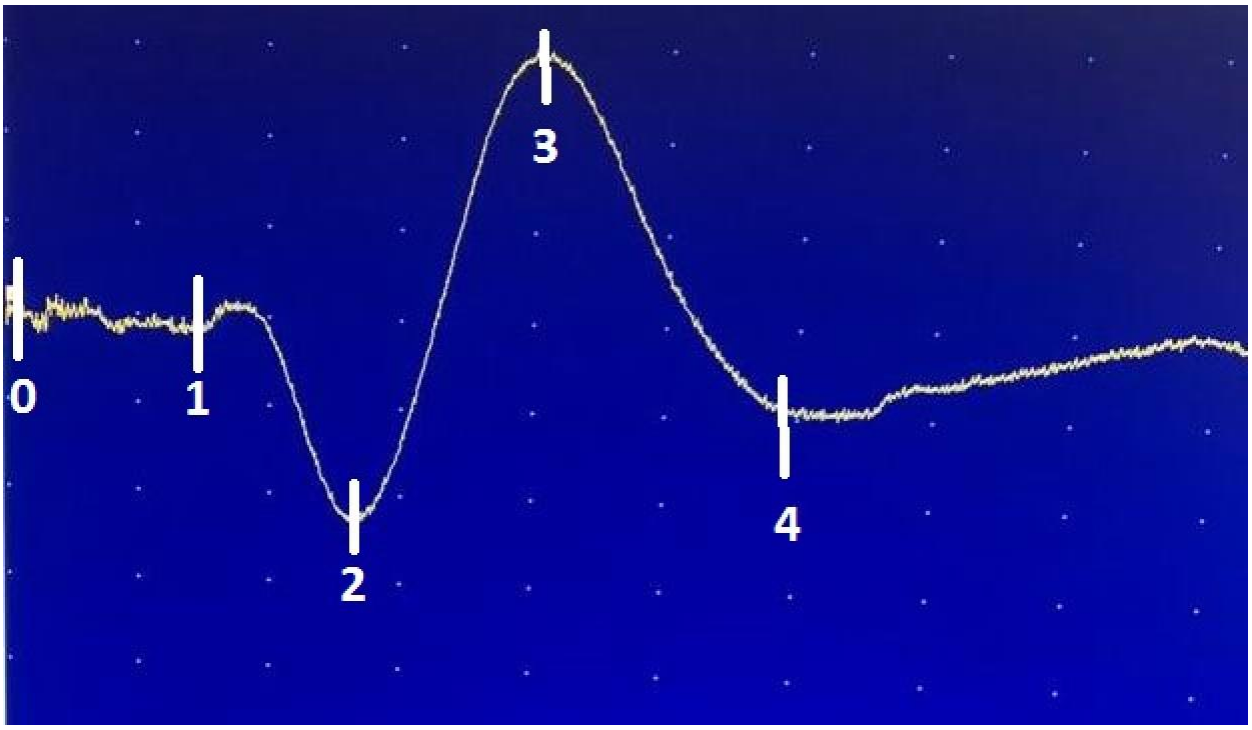

Figure 2: The sympathetic skin response waveform. 0-1: onset latency(s); 2-3: peak to peak Amplitude(µV); 1-4: The total duration of sympathetic skin response(s).

Table 1: Comparison of sympathetic skin response between the Raynaud's and control groups

Parameters (mean± SD)	Raynaud's group (N = 20)	Control group (N = 20)	P-value
Latency (s)			
Right median nerve	1.86± 0.55	1.11± 0.5	<0.001
Left median nerve	1.79± 0.49	1.21± 0.65	<0.002
Upper limbs	1.90± 0.57	1.19± 0.52	<0.001
Amplitude (mV)			
Right median nerve	1.14± 0.89	0.93± 0.48	0.358
Left median nerve	0.85± 0.5	1.01± 0.50	0.318
Upper limbs	0.94± 0.7	1.00± 0.50	0.756

mV = millivolt; S = second; SD = standard deviation.

P-values of <0.05 were considered significant.