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Investigation of autonomic dysfunction in primary Raynaud's phenomenon with sympathetic skin response (SSR), R-R interval variation (RRIV) and composite autonomic symptom score (COMPASS)-31

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Abstract

Background: In this study, we aimed to investigate the autonomic dysfunction in patients with primary Raynaud's phenomenon with using sympathetic skin response (SSR) as a neurophysiologic test, R-R interval variation analysis and composite autonomic symptom score (COMPASS)-31 questionnaire. *Methods:* Palmar SSR to median nerve electrical stimulation was recorded in 38 patients with 36 healthy age and sex-matched control subjects. The SSR was recorded from the palmar surface of both left and right hands for patients and control groups. The amplitudes and latencies formed as a result of electrical stimulation were calculated and compared between the two groups. Additionally, R-R interval variability was examined during normal breathing, deep breathing, standing up and Valsalva maneuver in both groups. Furthermore, we asked to complete the COMPASS-31 questionnaire, a validated tool to assess symptoms of autonomic dysfunction. And by calculating total COMPASS-31 scores, the relationship between the two groups was investigated. *Results:* The Raynaud's phenomenon and control groups were similar in age (37.4 ± 11.6 vs. 34.9 ± 13.0 years), had identical gender ratios and similar body mass index (24.5 ± 6.1 vs. 25.7 ± 4.6%). Palmar SSR to median nerve stimulation of RP patients shows significantly delayed latency (1890 ± 146) (p=0.03). And no difference between amplitudes in comparison to the control group. In the patient and control groups, R-R interval measurements were evaluated during rest and deep breathing, standing up and Valsalva maneuver. When the R-R interval measurements of the patient and control groups at rest and deep breathing were compared, there was no statistically significant difference between the groups. In addition, COMPASS-31 questionnaire scoring system was applied to both groups. The mean COMPASS-31 score was higher in patient group (22.8 ± 13.8), than from healthy controls (8.9 ± 7.8) (p=0.02)
Conclusions: Autonomic dysfunction plays a role in the etiology of Raynaud's phenomenon, due to latency prolongation in the sympathetic skin response and significant difference between COMPASS-31 tests, and these tests can be used in the diagnosis stage of this disease.

Keywords: Raynaud's phenomenon, sympathetic skin response, autonomic dysfunction

INTRODUCTION

Raynaud's phenomenon is characterized by recurrent vasospasm of the fingers and toes after exposure to cold and emotional stress. Community-based surveys estimate Raynaud's may be present in 5-20% of women and in 4-14% men.[1] It is a relatively common but often unrecognized clinical syndrome causing characteristic color changes in the digits as a result of vasospasm. Classically it includes triphasic

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color change; whitening, cyanosis and redness.[2] The pathogenesis of Raynaud's phenomenon is not fully understood. However, it includes abnormalities of the blood vessel wall and neural control mechanisms and intravascular factors, including platelet activation and oxidative stress.[3] The diagnosis is based on the detection of typical attacks. The purpose of the treatment is to reduce the number and severity of the attacks and to prevent loss of the fingers and toes and tissue damage. The treatment of Raynaud's phenomenon is conservative. Supportive approach consists of protection of body temperature, use of gloves and socks, smoking cessation, emotional stress reduction and exercise.

Sympathetic skin response (SSR) is a potential generated by sweat glands in response to a variety of stimulation.[4] This technique records changes in skin conductance after activation of sweat glands in areas of the skin that are rich in eccrine glands (commonly palmar and plantar sites) under the neural control of sympathetic cholinergic fibers.[4] SSR potentials can be recorded in response to various stimuli, for example, electric peripheral nerve stimulation, acoustic stimulation, or magnetic stimulation of nerves or the brain. Furthermore, R-R interval variation (RRIV), a measure of the heart rate variability is a simple and reliable test used for the evaluation of parasympathetic nervous system autonomic functions of the heart. Measurement of R-R interval variability (RRIV) is a sensitive test for detection of cardiac autonomic neuropathy.[5]

The composite autonomic symptom score (COMPASS)-31 is a self-administered 31-item questionnaire that quantifies self-reported autonomic symptoms. It is an abbreviated version of the 164-item COMPASS assessment tool.[6] The COMPASS-31 was validated in a cohort of patients with small fiber neuropathy, and was previously used to quantify self-reported autonomic symptoms in multiple sclerosis, diabetic neuropathy, and fibromyalgia.[7]

In this study, we analyzed the results of SSR, R-R interval and COMPASS-31 tests to investigate autonomic dysfunction in the etiology of RP.

METHODS

This prospective study included 38 patient adults (24 males, 14 females; mean age 35.2 ± 10.6 years) and 36 healthy adults (18 males, 18 females; mean age 33.9 ± 11.0 years) for the control group. There was no significant difference between the demographic and clinical characteristics of all patients. Autonomous functions were investigated by performing SSR, RRIV and COMPASS-31 tests to all participants. Patients with major diseases such as diabetes mellitus, central or peripheral nervous system diseases, kidney or liver failure, chronic obstructive pulmonary disease, heart failure, cardiac arrhythmia, and those using drugs affecting the nervous system were excluded. A written informed consent was obtained from each patient. The study protocol was approved by the institutional Gulhane Ethics Committee of Health Science University (No: 19-203, Date: 28-05-2019). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Electromyography

To assess ANS (autonomic nervous system) functions, SSR and RRIV were measured using a Dantec Keypoint four channel electromyography (EMG) equipment in the EMG lab. Electrophysiological tests were performed in a semi-dark quiet room. The tests were performed between 11 a.m. and 15 p.m. after the subjects had a light meal. To maintain a skin temperature of 22 ° C to 25 ° C, participants were admitted to the procedure room at least 15 minutes before testing. Filters of EMG apparatus were 16-80 Hz, sensitivity (200-1000 microV / D) and sweep speed 500 ms / D. Four groups were recorded at rest, during deep breathing (6 breaths / minute), standing up, and Valsalva maneuver. Electrocardiographic traces were obtained at rest and during deep breathing, standing up, Valsalva maneuver, and RRIV values were automatically calculated by the computer and expressed as a percentage (heart rate change) using the formula below: RRIV = (RR maximum –RR minimum) × 100 / RR mean (the difference between the shortest and longest RR is given as a percentage of the average of all the maximum and minimum peaks for 1 minute). This RRIV method is the algorithm described by Stalberg *et al*.[8] RRIV responses at rest and deep breathing were considered abnormal when they were out of two standard deviations from the age-adjusted mean.

The latency and amplitude of the response were recorded. SSR latency was measured from the beginning of the stimulus artifact to the starting point of the first negative deviation of the signal baseline, and the SSR amplitude was measured from top to top. If there was no consistent voltage change using 50 mV sensitivity after three attempts at maximum stimulus intensity, the response was deemed to be absent. At least 5-10 SSRs were recorded and averaged under certain stimulation

/ recording conditions. Although the response amplitudes were considered pathological when more than two standard deviations below the mean amplitude of the control group, latencies were considered pathological when they were more than two standard deviations above the mean latency of the control group.

The composite autonomic symptom score (COMPASS)-31

The COMPASS-31 is a self-administered 31-item questionnaire that quantifies self-reported autonomic symptoms.[11] The scale includes 31 items evaluating autonomic function areas (orthostatic intolerance, 4 items; vasomotor, 3 items; secretomotor, 4 items; gastrointestinal, 12 items; bladder, 3 items; pupillomotor, 5 items). The scoring system consists of calculating the raw area scores obtained by adding the scores obtained for the questions in each area. Final domain scores are obtained by multiplying the raw score by a weight index. The total score is the sum of all domain scores and ranges from 0 (normal) to 100 (worst condition). In simple yes or no questions, no 0 points, yes 1 point was evaluated. All questions regarding the frequency of symptoms were rarely or never 0 points, occasionally or sometimes 1 point, often or "often" 2 points, almost always or continuously 3 points. All questions regarding the severity of symptoms were evaluated as 1 point for mild, 2 points for moderate and 3 points for severe.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows program (version 15 SPSS; Chicago, IL, USA) was used for statistical analysis. Normality assumption of variables were determined using the Kolmogorov-Simirnov test. Student's t test was used for comparison of variables with normal distribution while Mann-Whitney U test was used for comparison of variables with non-normal distribution. Descriptive statistics for continuous variables were expressed as mean±standard deviation and median (minimum-maximum). And p values of 0.05 or fewer were considered significant. And latency of SSR value in predicting occurrence of RP was analyzed using receiver operating characteristic (ROC) curve analysis.

RESULTS

This prospective study included 38 patient adults (24 males, 14 females; mean age 35.2 ± 10.6 years) and 36 healthy adults (18 males, 18 females; mean age 33.9 ± 11.0 years) for the control group. All patients had a palmar SSR to median nerve stimulation for both palms. Average latency and amplitude of palmar SSR to median nerve stimulation for the two examined groups (control group, RP group) are given in Table 1. The average latency of SSR in the RP group was 1890 ± 146 (ms) and 1443 ± 142 (ms) in the control group. The average amplitude of SSR was 1.31 ± 0.8 (mV) in the RP group and 1.46 ± 1.1 (mV) in the control group. It is noted that there is significantly delayed latency of SSR potentials in patient groups when compared to the control group. It is noted that there is significantly delayed latency of SSR potentials in RP group when compared to the control group. (p: 0.03) In ROC curve analysis, the area under the curve (AUC) value of latency of SSR was 0.749, (with a 95% CI: 0.639-0.860) (Figure 1). For prediction of RP, an optimal cut-off value for latency of SSR level was 1845 ms with a sensitivity of 73 %, specificity of 61%. However, there was no significant difference between the amplitudes of both groups. (p: 0.16)

When R-R interval measurements of the patient and control groups (R%, D%, D%/R%, D%–R %) were evaluated, a statistically significant difference between groups was not determined (p= 0.13, p=0.24, p=0.32, p=0.14) (Table 2). Furthermore, the study included 38 consecutive patients with RP and 36 control

Table 1: Average values of SSR in the two groups (RP group and control group)

	RP group (N = 38)	Control group (N = 36)	P values
Average latency of SSR (ms)	1890 ± 146	1443 ± 142	0.03*
Average amplitude of SSR (mv)	1.31 ± 0.8	1.46 ± 1.1	0.16

SSR sympathetic skin response, RP Raynaud's phenomenon *Statistically significant

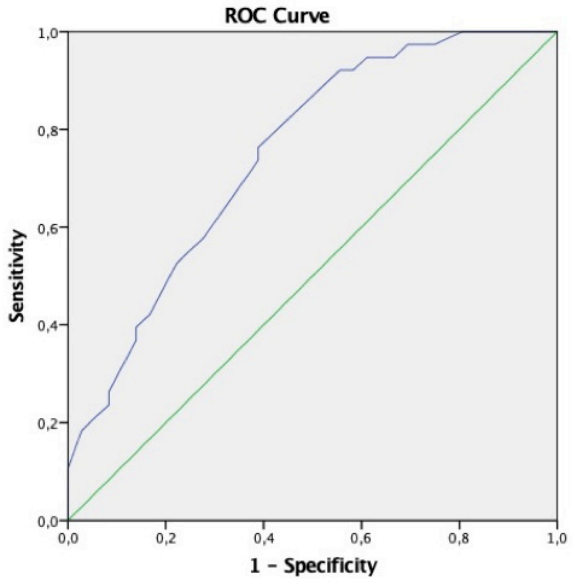

Figure 1: Receiver operating characteristic (ROC) curves of SSR latency

group who were recruited and completed the COMPASS-31 questionnaire. With this test, evaluation was made in subgroups of orthostatic, vasomotor, secretomotor, gastrointestinal, urinary, pupillomotor. Patients with RP have higher total COMPASS-31 scores than control group (Table 3).

DISCUSSION

The etiology of the Raynaud's phenomenon is not fully known. In the physiopathology of Raynaud's phenomenon, theoretically, three main factors are focused on vasoconstriction, increased blood viscosity and microcirculation disorder (impaired current due to abnormal expansion of the terminal vascular bed).[12] The general conceptual confusion about Raynaud syndrome is caused by the various etiological factors suggested and the many factors suggested as a treatment method. Mechanisms thought to play a role in pathophysiology; changes in the number, organization, or effects of postsynaptic and presynaptic alpha and beta adrenergic receptors; stimulation interaction of the sympathetic nervous system with up-regulation; insufficient control or release of various vasoactive substances such as calcitonin-gene bound peptide, nitric oxide, endothelin, serotonin and prostaglandin.[13]

Persistent or recurrent vasospastic symptoms often occur after sympathectomy. The reason for this is the defect in the response to the circulating catecholamine in the vascular wall as well as the receptor denervation hypersensitivity. The clinical relationship between Raynaud's phenomenon and migraine pains, variant angina and pulmonary hypertension indicates that there is an ordinary vasospastic mechanism in more than one artery bed.[14] In Raynaud's phenomenon, all treatments are symptomatic and there is no curative treatment. 90% of patients are treated by avoiding cold and tobacco use, no need for medication. The remaining 10% group is

Table 2: Means of R-R interval measurements of RP group and control group

	RP group (N = 38)	Control group (N = 36)	P values
Normal breathing (R%)	21.25±5.22	22.95±5.09	0.13
Deep breathing (D%)	37.15±8.38	33.15±6.27	0.24
D%-R%	18.21±1.88	15.21±1.68	0.32
D%/R%	1.64±0.79	1.44±0.81	0.14

RP Raynaud's phenomenon; (R%) normal breathing, (D%) deep breathing

Table 3: COMPASS-31 questionnaire scores and subdomain scores in RP group and control group

	RP group (N = 38)	Control group (N = 36)	P values
Orthostatic	7.6 ±3.8	2.6 ± 5.8	
Vasomotor	2.8 ± 1.7	0.3 ± 0.1	
Secretomotor	5.7 ± 3.8	1.5 ± 2.4	
Gastrointestinal	6.9 ± 4.9	3.2 ± 2.7	
Urinary	2.6 ± 1.6	0.5 ± 0.7	
Pupillomotor	1.9 ± 1.1	1.1 ± 0.9	
Total COMPASS-31	22.8 ± 13.8	8.9 ± 7.8	P=0.02*

RP Raynaud's phenomenon

treated with calcium channel blockers, where the results are slightly better than others and 50% symptomatic improvement is achieved. Cervicothoracic or digital sympathectomy can be tried as a last alternative approach in cases where other treatment methods fail. However, as a result, this phenomenon has not been fully elucidated and definitive solutions have not been produced for its treatment.[15]

There are not many studies in the literature investigating autonomic dysfunction in Raynaud's phenomenon and similar diseases. In this disease group whose etiology has not been elucidated in general, there are studies using sympathetic skin response, R-R interval analysis, and COMPASS-31 test in the literature for autonomic dysfunction research.

In their study, Badry *et al*.[4] compared palmar SSR in systemic sclerosis and rheumatoid arthritis case groups. Palmar SSR to median nerve stimulation (of systemic sclerosis patients and rheumatoid arthritis patients) showed significantly delayed latency and reduced amplitude in comparison to the control group. SSR of systemic sclerosis patients has significantly delayed latency and reduced amplitude when compared to RA patients.

Pancera *et al*.[16] investigated heart rate variability in patients with scleroderma and primary Raynaud's phenomenon. Heart rate variability was reduced and sympathetic output increased in patients with systemic sclerosis. Subjects with primary Raynaud's phenomenon were characterized by normal heart rate variability and by some degree of sympathetic hyperactivity.

In several studies, autonomic dysfunction research was carried out with COMPASS-31 test in different patient groups. This non-invasive and easy-to-apply test continues to be used as an illuminating parameter in disease etiology today. Adler *et al*.[7] investigated the selectivity of the COMPASS-31 test in patients with systemic sclerosis in their study. The mean COMPASS-31 score in this cohort was 24.9 ± 15.5, higher than COMPASS-31 scores from previously published healthy controls (8.9 ± 8.7). Compared to patients with mild or absent GI disease, patients with significant GI disease had higher scores across several subdomains of the COMPASS-31, including orthostatic intolerance (median 10.0 vs 0, p = 0.006) and secretomotor dysfunction (median 6.4 vs 4.3, p = 0.03).

In our study, we tried to illuminate the etiology of the Raynaud's phenomenon with three parameters. In the literature, there is no study in the phenomenon of Raynaud where these three parameters are combined. As a result of the study, the latency prolongation we found in the sympathetic skin responses in the RP group and a significant difference compared to the control group confirm the presence of autonomic dysfunction in the etiology of the disease. No significant difference was found between amplitudes between patient and control groups, similar to previous studies. Furthermore, with COMPASS-31 test, a significant difference between the patient groups is confirming autonomic dysfunction in Raynaud's phenomenon for etiology.

In conclusion, the mechanism and pathophysiology of Raynaud's phenomenon is still unclear; the etiology of the disease is likely to be multifactorial. Our study has confirmed that autonomic dysfunction is part of the pathophysiology. The tests to elucidate autonomic dysfunction will help to confirm the diagnosis.

DISCLOSURE

Conflicts of interest: None

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