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How Can Follow-Up of Patients with Raynaud Phenomenon be Optimized?

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Background: Raynaud phenomenon (RP) is common worldwide and presents diagnostic and therapeutic difficulties. We aimed to share our experience with optimizing of patient follow-up by using the cold-stimulation test (CST).




Material/Methods: Data of 81 patients admitted with RP symptomatology were collected. Demographic data and symptoms were recorded. A scale was used for determining the severity of disease at pre-treatment and post-treatment. CST was performed to all patients at pre-treatment and post-treatment for assessment of treatment efficiency in follow-up. Results were analyzed with the SPSS for Mac 20.0 program.

Results: All the patients were male. Mean age was 22.3 ± 2.14 (19–29). Mean duration of symptoms from onset to present was 4.59 ± 2.85 years. There were statistically significant differences between pre-treatment and post-treatment hand temperatures measured by CST ($p < 0.001$). However, there were no statistically significant differences between pre-treatment and post-treatment severity scores of patients ($p = 0.135$).

Conclusions: To quantitatively determine the treatment efficacy, CST may be used instead of asking simple questions of patients.

MeSH Keywords: **Cold Temperature • Diagnosis • Peripheral Vascular Diseases**

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Background

Raynaud phenomenon is a common health problem characterized by episodic cyanosis, swelling, and pallor on both upper and lower extremities with cold exposure. Its prevalence variously estimated at 3.3% to 22% [1]. This group of disorders predominantly affects females [2].

In the history of this disorder, researches have described many etiologic factors, but, to date, neither an objective, quantitative diagnostic tool, nor an objective follow-up method has been defined [3].

In this study, we aimed to find an optimized method for the follow-up of patients with Raynaud phenomenon.

Material and Methods

In this retrospective study, we aimed to describe an optimized method for the follow-up of patients with Raynaud phenomenon, and to compare its' efficacy with a verbal complaint severity scale. Our local ethics committee approved the study (Ethics approval number 1291).

Patient's selection

Between August 2012 and July 2013, data of 81 patients with Raynaud phenomenon symptomatology were collected. Systemic evaluation including blood examinations, capillaroscopy, and Doppler ultrasonography are routinely performed in our clinic to exclude secondary etiologic factors. Therefore, in this study we included only patients with primary Raynaud phenomenon. Demographic data, concomitant disorders (such as hypertension, diabetes mellitus, renal insufficiency, and thoracic outlet syndromes), and type and duration of symptoms were recorded.

Cold stimulation test

In our center, testing of patients' response to cold stimulation is mandatory due to our national regulations. Therefore, we routinely apply the cold stimulation test (CST) to all of our patients presenting with the Raynaud phenomenon symptomatology. CST is performed at room temperature (26°C). All patients are only allowed to wear their shirts, without additional jackets or coats throughout the test. All measurements of CST are performed with the patient's hand at the level of the heart. A Sonatemp™ 400/700 Monitor (Sheridan Catheter Corp. Argyle, NY, USA) device was used for temperature measurements. According to our protocol, application of the CST is as follows: 1. Hand temperatures of the patients are measured with a probe, which is inserted between the pulp of the

first and second distal phalanges. 2. The most affected extremity is immersed into the +4°C iced-water for 20 seconds. 3. After drying the hands, the fingertip temperature is measured again at 5th, 10th, 15th and 20th minutes, with the same technique as detailed before. 4. The rewarming time to initial temperature is also recorded.

We recently defined an assessment scale of CST in our previous paper [3]. The assessment scale for CST is given in Table 1.

In order to evaluate the effectiveness of the medical treatment, we routinely use a verbal complaint severity scale (VCSS) described in our previous study [4].

Medical treatment

According to our clinical protocol, we routinely use the combination of pentoxifylline 1200 mg/d bid (2×600 mg) as a vasodilator molecule, nifedipine 60 mg/d bid (2×30 mg) as a calcium-channel blocker, and acetylsalicylic acid 300 mg/d (1×300 mg) as an antiplatelet agent. Beside these medications, all of the patients are advised to protect themselves from cold as much as possible.

Patients were informed about the possible adverse effects of these medications.

Statistical analysis

SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL) was used for statistical evaluation. Descriptive results were expressed as mean ± standard deviation for normally distributed continuous variables and median values for abnormally distributed continuous variables. Categorical variables were reported as numbers and percentages. Before analyses, Kolmogorov-Smirnov test was used for analyzing the distribution pattern of data. Comparisons of the parametric values were performed with the t-test for normally distributed groups and with Mann-Whitney U test and Wilcoxon signed ranks test with abnormally distributed groups. Pearson's chi-square test, Fisher's exact test, and McNemar-Bowker test were used for the comparisons of categorical variables.

A p value of <0.05 was considered as statistically significant with a 95% confidence interval.

Results

Patients' characteristics

Military service is an obligatory duty in Turkey for every young male. Since this study was performed in a military hospital, all

Table 1. Assessment scale for cold stimulation test.

Stage	Rewarming time (minute)	Assessment	Potential diagnosis
0	0–10	Normal	Healthy person
I	11–15	Mild disturbed	Otherwise healthy person
II	16–20	Moderate disturbed	Mild vasospastic disorder
III	21–30	Serious disturbed	Moderate vasospastic disorder
IV	≥31	Serious disturbed	Serious vasospastic disorder

Table 2. Patients' demographic data.

Age (year)	22.3±2.14 (19–29)
Gender (male/female)	81/0
Smoking (n)	56
Co-morbidity (n)	
Hypertension	2
Diabetes mellitus	0
Renal insufficiency	0
Vasculitis	0
COLD	0
Other	0
Symptoms	
Cyanosis (n,%)	66 (81.4%)
Coldness (n,%)	50 (61.7%)
Numbness (n,%)	47 (58%)
Hyperhidrosis (n,%)	45 (55.5%)
Hand swelling (n,%)	32 (39.5%)
Burning sensation (n,%)	19 (23.4%)
Pain (n,%)	9 (11.1%)
Duration of symptoms (year)	4.59±2.85

of the patients were young males; 56 out of 81 patients (69.1%) are heavy smokers (17 patients >10 years). Cold-aggravated cyanosis (66 patients, 81.4%), coldness (50 patients, 61.7%), and

numbness (47 patients, 58%) were the most frequent symptoms. The other complaints were as following: hyperhidrosis (45 patients, 55.5%), cold aggravated swelling (32 patients, 39.5%), burning sensation (19 patients, 23.4%) and pain (9 patients, 11.1%); 57 of patients (70.1%) had 3 or more complaints mentioned before, while only 1 patient had all complaints above. Mean duration of symptoms from onset to present was 4.59±2.85 years. None of the included patients were observed to have adverse effects associated with medications. Demographic data of patients are given in Table 2.

Verbal complaint severity scale

According to VCSS, patients were categorized into 3 groups. Before the treatment, 11 patients were in VCSS I, 32 patients were in VCSS II, and 38 patients were in VCSS III. After the treatment, when those patients were questioned again, there were no statistically significant differences between before and after treatment VCSS. However, 4 patients changed their scores after the treatment. One patient in VCSS I declared as VCSS II and 3 patients in VCSS III declared as VCSS II. VCSS distribution of patients is given in Table 3.

Temperature changes

There was a significant decrease in hand temperatures after cold exposure in both pre-treatment and post-treatment periods. Then, hand temperatures were increasing slowly with different parabolas. Pre-treatment parabola appeared to have a concave curve, which means that the temperature increased gradually. Post-treatment parabola appeared like a convex curve, which means that temperature increased quickly, and

Table 3. Verbal complaint severity scale distribution of patients.

Verbal Complaint Severity Scale	Before treatment		After treatment		p value
	n	%	n	%	
I	11	13.6	10	12.3	0.135
II	32	39.5	36	44.4	
III	38	46.9	35	43.2	

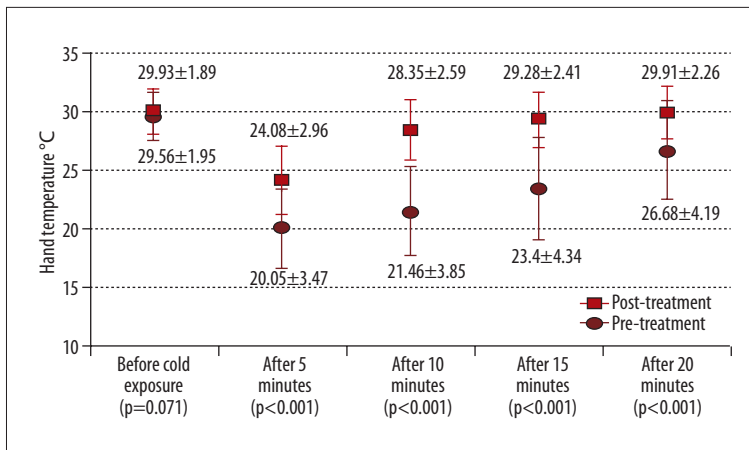


Figure 1. Changes of the hand temperatures during cold stimulation test.

Table 4. Comparing of rewarming time at pre-treatment and post-treatment periods.

	Definition	n	Mean (minute)	Standard deviation	p value
Rewarming time	Pre-treatment	81	26.67	9.68	<0.001
	Post-treatment	81	19.48	8.27	

Table 5. Distribution of patients according to assessment scale.

Stage	Before treatment		After treatment		p value
	Mean time (minute)	n	Mean time (minute)	n	
0	0	0	8.5 ± 0.9	8	<0.001
I	13.6 ± 1.08	10	12.5 ± 1.3	19	
II	18 ± 1.51	15	17.5 ± 1.16	23	
III	25.1 ± 2.3	30	24.3 ± 3.05	21	
IV	38.5 ± 5.4	26	35.7 ± 3.6	10	

continued almost at this level. The changes in hand temperatures during the CST are given in Figure 1.

There were statistically significant differences between pre-treatment and post-treatment hand temperatures at each measurement (p<0.001) except initial values (p>0.05).

When the results of CST for every measurement time point were separately analyzed, the following results were found:

1. At 5th minute measurements, there was 4.0 ± 2.9°C increase when compared to pre-treatment values (p<0.001).
2. At 10th minute measurements, there was 6.9 ± 3.1°C increase when compared to pre-treatment values (p<0.001).
3. At 15th minute measurements, there was 5.9 ± 3.4°C increase when compared to pre-treatment values (p<0.001).
4. At 20th minute measurements, there was 3.2 ± 3.3°C increase when compared to pre-treatment values (p<0.001).

In addition, there was a 7.2 ± 4.4 minutes decrease in rewarming time to initial temperature at post-treatment period compared with pre-treatment values, which was also statistically significant (p<0.001).

A comparison of rewarming times at pre-treatment and post-treatment periods is given in Table 4. According to assessment scale of CST results, the distribution of included patients in the present study is given in Table 5.

Discussion

Since the first description of Raynaud phenomenon, several diagnostic tools and treatment methods have been used. However, neither a definitive diagnostic tool nor an obvious curative treatment method has been defined [5], primarily

due to the complex etiopathogenesis, which is still not understood completely.

The second cause of this diagnostic problem may be the subjectivity of patients' symptoms. Most RP patients complain about cyanosis and numbness, which is often aggravated with cold exposure [6]. These symptoms are quite inadequate for definitive diagnosis, but secondary forms of this disorder, mostly based on an underlying disease, can be diagnosed with more objective tests [6,7]. In this respect, objective diagnosis for primary forms of RP is often not possible.

Several diagnostic tools for definitive diagnosis have been defined: observation of triphasic color changes of hands and fingers, measurement of finger systolic blood pressure or finger-brachial index, plethysmography, capillaroscopy, Doppler ultrasonography, and, rarely, more invasive techniques such as arteriography [2,3,8]. Most of these tools require special conditions, such as special technicians, devices, and sometimes laboratory conditions. However, even though they could be performed once for diagnosis, none of them could be used for follow-up, because of the above-mentioned features [9].

In addition to these problems, assessment of treatment efficacy in the follow-up period is the other important problem, which also mainly depends on subjectivity of patients and their symptoms. Most patients consider that all treatment modalities, independent of their types, are ineffective. However, if we could find a user-friendly, objective test to follow up these patients, we can evaluate their progress and document it; then we can convince the patients about the progress of their status.

In our study we used verbal complaint severity scale (VCSS) for patient self-expressed feelings, such as their ideas about the treatment efficacy and the progress of the disease; 11 patients were categorized in VCSS I at pre-treatment and 10 patients were categorized in VCSS I after treatment. Thus, it seems that 1 of these 11 patients probably thought that their complaint became worse in the follow-up period. However, 3 patients in VCSS III before treatment were categorized in VCSS II after treatment, which probably means that their symptoms improved with treatment, but none of these changes were statistically significant and none were quantitative, obvious, and re-measurable. In this regard, CST seems to be helpful for quantitative and objective follow-up of patients with RP.

In our study the quantitative data of CST such as temperature changes and decreases in rewarming time were statistically significant. When we analyzed these parameters of CST, besides the accuracy of our test, we also observed variable patterns of rewarming and rewarming time. Following a decrease in hand temperature after the cold stimulation, we observed

significant differences in rewarming patterns between the 2 groups (Figure 1). The concave curve of pre-treatment figures in the rewarming period shows that the temperature increases slowly at the beginning, then there was a gradually increase in rewarming rate, which suggests that vasospasm lasts longer. In contrast, the convex curve of post-treatment figures in the rewarming period shows that the temperature increased quickly at the beginning, and then reached initial temperature slowly, which suggests that vasospasm duration was shorter than in the former period.

When our results were analyzed and compared objectively, there were 2 parameters that can be used for follow-up of patients. One of them is patients' verbal complaint severity scale and the other is the result of CST. We analyzed data from the 4 patients who had changed their verbal complaint severity scale after treatment as a subgroup, and we compared their CST results independent from the study group. In paired correlations, we found that there were no statistically significant differences between measured temperatures or rewarming times before and after treatment ($p>0.05$). We also found that there were no statistically significant differences in the other remaining patients who considered that no improvement was observed within the treatment protocol ($p>0.05$). These results mean that if the follow-up period assessment depends only on "patients' expression", researchers would have to reach a conclusion about treatment (positive or negative); however, these results would be far from real conclusions.

Conclusions

We form 2 main conclusions from this study. First, the cold stimulation test can be used as an objective and quantitative test, especially for follow-up of patients under treatment when it is performed with certain criteria like in our study. Second, although the patients have expressed that there is no change after treatment, the study results revealed that the treatment were objectively effective. Although more extensive studies are necessary, based on our results, we conclude that CST with certain criteria seems to be a much more objective, quantitative, easy to use, and scientific method than "patients' self-expression" for follow-up of patients with RP, regardless of treatment methods.

Study limitations

This study was performed in a military hospital; therefore, all of the patients were male. For this reason, it may be difficult to make a generalized conclusion for both sexes from these results. There is a need for further research in broader populations.

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