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CONDITIONAL THERAPY IN RAYNAUD'S PHENOMENON(U) ARMY
RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA
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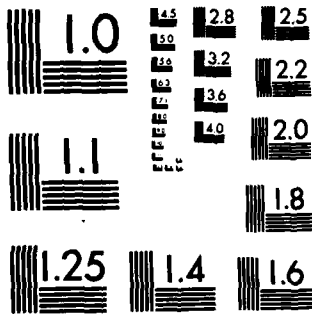
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Author(s) Jared B. Jobe, Donald E. Roberts, and James B. Sampson

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For many years controversy has existed over the pathophysiology of Raynaud's phenomenon (RP). When Maurice Raynaud initially described the phenomenon which now bears his name, he postulated that the peripheral vasospasms were the result of sympathetic overreactivity [1]. However, Lewis [2] theorized that the problem was attributable to local fault of the arteries, whereas others have attributed it to increased blood viscosity [3]. It is not unlikely that RP is the result of multiple factors.

Because the sympathetic nervous system is alterable by behavioral techniques, many researchers have attempted to treat RP using conditioning techniques. This approach is all the more prevalent due to the adverse side effects and equivocal results associated with pharmacological and surgical intervention in RP treatment [4, 5].

Operant Conditioning and Relaxation Research

The most widely known methods of behaviorally increasing blood flow to the periphery are operant conditioning, usually involving biofeedback, relaxation, meditation, autogenic training, hypnosis or a combination of these methods [6-8]. Surwit et al. [6] compared biofeedback plus autogenic training to autogenic training alone and found increases in digital skin temperature and decreases in vasospastic attacks; the combination of feedback and autogenic training was no more effective than autogenic training alone. A follow-up study one year later [9] indicated that although subjects continued to report fewer vasospastic episodes, skin temperature on a cold stress test had deteriorated to pre-treatment levels.

Another study [10] found small changes in digital skin temperature using feedback combined with hypnosis, although hypnosis alone produced no change. Keefe et al. [11] found that progressive muscle relaxation, autogenic training, and autogenic training plus feedback all increased digital temperature and decreased vasospastic episodes equally well. In addition, Graebert et al. [12] found that feedback plus suggestion produced increases in digital skin temperature, although neither method by itself was effective. On the other hand, Jacobson et al. [13] found that muscle relaxation training alone was more effective than muscle relaxation plus feedback, although both groups increased digital skin temperature. These studies suggest that biofeedback and relaxation techniques are often effective in the treatment of RP, although it is difficult to isolate the factors that contribute to the increases in digital skin temperature. Furthermore, the long term effectiveness of these techniques has not been demonstrated.

Classical Conditioning Research

An alternative to treating RP by operant conditioning is classical or Pavlovian conditioning. Initial research in classically conditioned vascular responses was done by Tsitovich (cited in Bykov [14]), who obtained a conditional vascular response (CVR) by combining a neutral pipe sound with local cooling of the skin in man. After 24 pairings, the sound alone elicited vasoconstriction. Bykov [14] also describes research done by his colleague Rogov. He used heat (47°C) or cold (4°C) as uncondition-

al stimuli (US) applied to the hand via water circulating in hollow metal bases, and a variety of conditional stimuli (CS). Rogov found that 20-30 combinations of CS and US elicited CVRs to warming and cooling of the skin, and that 70-90 such combinations were required to produce a stable CVR. Figar [15] summarized the literature on conditional circulatory responses and recommends a warm stimulus of 43-45°C as US for obtaining vasodilatation in the extremities. More recently, Hayduk [16] obtained a vasodilative CVR in normals. The US of 38°C warm water was applied to the hand in a room maintained at -8°C. Twenty-one to 31 conditioning trials were required to obtain a CVR.

Initial pilot work in the use of Pavlovian conditioning as a treatment for RP was conducted by Marshall and Gregory [17] at the Arctic Medical Research Laboratory of the U.S. Army Research Institute of Environmental Medicine (USARIEM). Three subjects with idiopathic RP and five subjects with nonspecific cold hypersensitivity, who showed no evidence of causal disease, participated in the study. The patients were exposed to 0°C in a cold room for eight minutes wearing indoor clothing while their hands were immersed in a container of warm water ($42 \pm 2^\circ\text{C}$). The US was the warm water and the CS was the cold room. Patients received one trial per day, three days per week for two weeks for a total of six treatments. Pre- and post-treatment evaluation consisted of peripheral nerve conduction velocity measurements and digital skin temperature response in a warm room ($26 \pm 3^\circ\text{C}$) and in a cold chamber ($0 \pm 2^\circ\text{C}$) for eight minutes while dressed in normal indoor clothing. Each patient treated during the winter demonstrated improvement in either digital skin temperature or nerve conduction

velocity during cold exposure. Five patients treated during the summer showed less improvement. Nerve conduction velocity showed small, but consistent improvement in all five cases, whereas skin temperature improved in only three of the five cases. All patients treated experienced subjective improvement during cold exposure, reporting absence of vasospastic color changes and disappearance of skin necrosis (if present).

Results of the Marshall and Gregory [17] study indicated that classical conditioning therapy was a potential alternative to traditional drug and surgical therapy. The study did not, however, employ a no-treatment control group. The results of the Marshall and Gregory study were expanded by Jobe, Sampson, Roberts, and Beetham [18], in a study conducted from October-March. Seventeen subjects with idiopathic RP and eighteen healthy volunteers with normal response to cold were compared. Physical and laboratory examination of all subjects with RP were within the normal limits: criteria for diagnosis were those of Allen and Brown [19].

Eight patients with RP were given 27 classical conditioning treatments, three per day, three times per week for three weeks for a total of 27 treatments. Treatments consisted of 10-minute whole-body simultaneous exposure to 0°C (CS) while both hands were immersed in a 43°C water bath (US). Patients were dressed in light coveralls and boots. Nine patients with RP served as no-treatment controls, but later received treatments. Normal subjects also received treatments and served as no-treatment controls. The week before and the week following treatments all subjects (treatment and no-treatment) received a single 10-minute, whole-body exposure to cold (0°C) while dressed in light coveralls and boots (pretest and

posttest, respectively). The dependent measure was the mean digital temperature of the dominant hand during the last minute of the cold exposure.

Patients with RP who were treated had superior digital skin temperatures after 10-minute exposure to 0°C on the posttest compared with untreated patients with RP (Figure I). Digital temperatures of treated patients with RP were not different from normal subjects on the posttest, although they did differ on the pretest. Several patients with RP were retested up to four months later and exhibited no loss of their increased responses to cold. After the no-treatment patients with RP subsequently received treatments, their results indicated that 13 of 17 showed improvement of at least 1.0°C (Table I). Improvement in digital temperature averaged 2.2°C.

Subjective reports from the patients with RP indicated that the treatments were effective. Patients reported that their recovery from vasospastic episodes was faster, that their hands were warmer, and that their attacks occurred with less frequency and were less severe. A follow up one year later was conducted and 9 of the 16 patients with RP reported continued positive effects of the treatment.

Patients with RP were not different either from normals or the test norms on two measures of emotional stability.

The results of the Jobe et al. study [18] confirmed and expanded the results of the Marshall and Gregory [17] study and indicated that classical conditioning therapy is a viable, long-lasting alternative to more traditional medical treatments of RP.

A comparison was then performed of the effectiveness of classical con-

ditioning therapy in relation to a combination of biofeedback and relaxation therapy for idiopathic RP [20]. An additional goal was to determine whether increasing the number of classical conditioning treatments would increase the magnitude of the CVR. Two male and 12 female volunteers were studied from January - March. All patients were diagnosed as having idiopathic RP according to the criteria of Allen and Brown [19]. One subject did not complete the study. The week before treatments began and during the week following treatments, all patients received a single whole-body exposure to 0°C for 10 minutes while dressed in light coveralls and boots (pretest and posttest, respectively). The dependent measure was the mean digital skin temperature of the dominant hand during the 10th minute of cold exposure.

The six subjects in the classical conditioning group received three treatments per day, three days per week for six weeks for a total of 54 treatments. As in the previous study, each treatment consisted of a 10-minute simultaneous whole-body exposure to 0°C while the hands were immersed in warm water (43°C). The patients were dressed in light coveralls and boots.

The eight subjects in the biofeedback-relaxation group received three treatment sessions per week for six weeks, each session lasting 45 min - 1 hr. The subject, dressed in street clothes, sat in a warm (24°C) sound-proofed room and listened to relaxation tapes while receiving electromyograph feedback from the frontalis area of the head for 8 sessions and thermal feedback from the middle finger of the dominant hand for 10 sessions. Each subject in the biofeedback group received a copy of the

last tape and was asked to practice at home. Individual characteristics of the patients are presented in Table II.

Both groups showed significant increases in digital skin temperature from the pretest to the posttest, but posttest differences between groups were not significant. The classical conditioning group increased an average of 3.9°C and the biofeedback-relaxation group increased an average of 4.1°C. Subjective data favored the classical conditioning patients, who reported less pain during attacks at the conclusion of the treatments and reported less severe attacks one year later. As in the first study, patients with RP did not differ from the test norms on two measures of emotional stability.

Patients with RP given 54 classical conditioning treatments in this study increased digital temperature 3.9°C on the posttest compared to 2.2°C for patients in the previous study who received 27 treatments. Classical conditioning also appeared to have a more enduring effect than biofeedback-relaxation based on follow-up data. The latter result is consistent with results of Keefe *et al.* [9] who reported that patients treated with biofeedback and/or autogenic therapy returned to baseline levels one year later.

Impressive results were obtained using classical conditioning therapy under controlled laboratory conditions using commercially available water heaters-circulators and an arctic chamber. However, if the therapy is to have widespread utility, effectiveness must be demonstrated under less stringent circumstances, preferably using naturally occurring ambient cold and hot tap water. The goal is for patients with RP to treat themselves

at home with occasional visits for evaluation to a medical treatment facility.

Runge [personal communication, May 10, 1982] had 10 patients with RP who treated themselves at home with classical conditioning using naturally occurring cold and hot tap water during March, 1982. Three patients had systemic lupus erythematosus, four had progressive systemic sclerosis, one had polymyositis, one had rheumatoid arthritis, and one had mixed connective tissue disease. Four patients noted no change, the other six rated their improvement from 12-52mm on a 100mm analog scale. The mean improvement for all 10 subjects was 15.5mm. No objective measures were used. Patients reported the program simple to follow and only one patient had any problems.

Encouraged by Runge's results, we conducted a study to more formally evaluate the effectiveness of classical conditioning as a home treatment for RP [21]. Two male and twelve female patients with RP, who showed no symptoms of causal disease, were studied. Two of the subjects had had a mild frostbite injury preceding their initial vasospastic episodes. Four subjects who began the treatments did not return for follow up evaluation (posttest).

The study was conducted during November and December. Prior to the initiation of treatments, all patients came to the arctic chambers and received a 10-minute whole body exposure to cold (0°C) while dressed in light coveralls and boots (pretest). The stress test was repeated one or two days following the completion of treatments (posttest). Once again the dependent variable was the mean digital skin temperature during the

last minute of exposure. Patients were instructed to condition themselves at home using three treatments per day, every other day for 18 days for a total of 54 treatments over a five-week period. They were instructed to dress in indoor clothing, to fill a container with 43-45°C water, to go outside and to immerse both hands to the wrists for 8-10 minutes (subjects were given a thermometer to measure the water temperature). Patients were asked to return indoors between treatments and adjust the water temperature. A log was used by the patients to keep track of the treatments.

The patients reported completing between 48 and 60 treatments. Mean digital temperature on the posttest was significantly higher than on the pretest with a mean increase of 3.4°C (see Table III). All ten subjects demonstrated an increase in excess of 1.0°C, with two patients improving by more than 6.0°C. There were no measured differences between RP patients and the psychological test norms on two measures of emotional stability.

Results of this study compared favorably with the earlier laboratory studies with improvement averaging 3.4°C with 48-60 treatments compared to 3.9°C with 54 treatments and 2.2°C with 27 treatments in the laboratory.

DISCUSSION

Results of experimental studies have been presented which demonstrate the effectiveness of classical conditioning as a treatment for RP. Classical conditioning therapy avoids the problem of side effects of pharmacological therapy and the loss of nerve function secondary to

sympathectomy.

Effective conditioning was obtained in as few as 6 trials in one study [17] and in our program in as few as 27 trials [18]. Other research [14-16] has indicated that a vasodilatative CVR can be obtained in as few as 20 trials but that 70-90 trials are necessary for stable responding [14-15]. There may be several reasons why conditioning occurs more rapidly in our research: First, our subjects were aware of the conditioning process we were attempting to perform, i.e., the CS-US relationship. Baer and Fuhrer [22-23] have demonstrated that difficult differential conditioning occurred only in subjects who could accurately verbalize the CS-US relationship. Therefore, it is possible that conditioning was facilitated by the patients' awareness. Secondly, patients with RP may be easier to condition than other individuals, i.e., they may be what are referred to as "excitatory" individuals. These individuals may have RP as a result of excessive vasoconstriction being classically conditioned to cold (we do not however, hypothesize that sympathetic overreactivity is the sole component in RP). Thus, effective counter-conditioning is more likely to occur with these subjects.

The most exciting prospect, given these findings, is that classical conditioning has several advantages over other behavioral therapies for RP. First, research has shown that conditioning by biofeedback extinguishes upon withdrawal of treatment [9, 20], even though we gave subjects tapes to use at home. Biofeedback-relaxation requires consistent practice to maintain control, but classical conditioning appears to require only periodic "booster training" to maintain conditioning. Secondly, biofeed-

back usually requires "suggestive" subjects; classical conditioning appears more applicable to a wider range of patients. Finally, classical conditioning therapy does not require expensive equipment and can be safely applied in the patient's own home.

Home treatment of RP using classical conditioning was shown to be as effective as laboratory treatment and may be more resistant to extinction than laboratory treatment for two reasons. First, home treatment avoids the artificial environment of the laboratory, and as a result, there is less stimulus generalization decrement during the extinction process which follows the conclusion of treatments. Secondly, the conditioning may be more resistant to extinction because the different ambient temperatures used as the CS will theoretically result in conditioning to each of these CS and therefore less stimulus generalization decrement will occur to the multiple stimuli (cold temperatures), encountered by the patient during extinction.

Of particular interest, because of the medical literature, is evidence which indicates that patients with RP are not different as a group from normals based on two measures of emotional stability. This result is in contrast to the widely supposed notion that patients with RP are emotionally unstable [24].¹

¹Psychological explanations are common in the medical literature, where there are no "physical" explanations of the disease or ailment.

Future Research

There is still much to explore in the study of classical conditioning therapy for RP. The nature of the CS and US, as well as the timing and frequency all need to be examined. Research on the use of multiple temperatures as CS to strengthen long-term conditioning, for example, is one of the many variables that is worthy of further research. Other research is needed to determine whether the treatment regimen can be compressed into a shorter time period, using more treatments per day, and treating patients for consecutive days instead of every other day. The goal is to find procedures that are most effective in the shortest possible time frame.

Another goal is to explore the application of the treatment to individuals who have suffered a previous cold injury such as frostbite whether or not they exhibit RP. Thus far, subjects with previous frostbite and RP have been successfully treated. If the treatment is successful for frostbitten subjects, it will have widespread applicability for the military and industry.

Finally, we are very encouraged by the results of these studies and think that classical conditioning has great potential as a treatment mode for RP. More independent studies are needed to reach our goal of designing a treatment program that is as simple and effective as possible for wide-spread application to individuals with various forms of vasoconstrictive disorders.

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All participants in these studies gave their free and informed consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Human Volunteers in Research

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TABLE I
Individual Data of Raynaud's Afflicted Subjects

Subject	Age/Sex	Years Since Onset	Smoker	Mean Digital Temperature	
				Before Treatments	After Treatments
	<u>yrs</u>	<u>n</u>		<u>°C</u>	
1	38/F	3	Yes	14.2	16.4
2	32/F	7	Yes	9.6	10.4
3	40/M	3	Yes	8.7	9.9
4	33/F	5	No	8.1	9.7
5	54/F	24	No	10.5	13.8
6	44/F	9	Yes	13.2	13.9
7	46/F	3	No	7.0	8.3
8	54/F	10	No	8.7	9.0
9	46/F	10	No	12.5	15.0
10	34/F	9	Yes	10.2	11.0
11	33/F	10	Yes	8.5	12.8
12	34/M	2	No	9.5	12.4
13	42/F	5	No	9.0	10.1
14	34/M	15	No	11.7	15.9
15	33/F	24	No	11.7	13.1
16	62/M	18	No	14.2	16.7
17	51/F	5	No	8.1	10.6

TABEL II

Individual Data of Raynaud's Afflicted Subjects

Subject	Age/Sex	Years Since Onset	Smoker	Family History of Raynaud's Disease ¹	Mean Digital Temperature Before Treatments	Mean Digital Temperature After Treatments
Classical Conditioning Group						
	<u>yrs</u>	<u>n</u>			<u>°C</u>	
C2	36/F	3	No	No	6.2	10.5
C3	47/F	10	No	S	5.9	9.1
C4	36/F	7	No	S	12.3	12.3
C5	28/F	5	No	No	3.5	8.1
C6	44/F	7	No	A	4.7	11.1
C8	51/F	12	No	No	5.4	10.0
Biofeedback-Relaxation Group						
B1	20/F	10	No	GP,P,A,C	5.3	7.3
B2	45/M	17	Yes	No	8.3	13.2
B3	17/F	2	No	GP	5.4	12.2
B4	43/F	22	No	O	6.3	12.1
B5	61/M	15	No	No	9.5	12.5
B6	42/F	2	Yes	No	8.0	9.3
B7	68/F	36	No	C	5.3	10.9
B8	14/F	7	No	GP	8.1	11.1

¹A - Aunt
C - Cousin
GP - Grand Parent
O - Offspring
P - Parent
S - Sibling

TABLE III

Individual Data of Raynaud's Afflicted Subjects

Subject	Age/Sex	Years since Onset	Smoker	Family History of Raynaud's Disease ¹	Number of Treatments Completed	Mean Digital Temperature	
						Before Treatments	After Treatments
	<u>yrs</u>	<u>n</u>				<u>°C</u>	
R1	22/F	6	No	No	54	6.5	8.1
R3	28/F	5	No	S	48	8.1	9.7
R4	47/F	3	No	No	54	8.3	12.1
R5	28/F	7	No	No	54	6.2	7.7
R8	42/F	20	No	No	57	4.5	9.4
R9	45/F	4	No	C	54	6.0	12.2
R11	54/F	3	Yes	No	54	5.4	12.0
R12	36/F	8	No	No	60	6.9	10.1
F1	33/M	5	No	No	51	9.9	11.1
F2	20/M	2	No	No	54	11.3	14.4

¹S-Sibling
C-Cousin

Figure and Table Captions

Figure 1. Mean digital temperatures at 10 minutes exposure to 0°C air of treated and not treated (control) subjects with and without Raynaud's disease. [From J.B. Jobe, J.B. Sampson, D.E. Roberts, & W.P. Beetham, Jr. Induced vasodilation as treatment for Raynaud's disease. Annals of Internal Medicine, 1982, 97, 707.]

Table I. Individual Data of Raynaud's Afflicted Subjects. [From J.B. Jobe, J.B. Sampson, D.E. Roberts, & W.P. Beetham, Jr. Induced vasodilation as treatment for Raynaud's disease. Annals of Internal Medicine, 1982, 97, 707.]

Table II. Individual Data of Raynaud's Afflicted Subjects.

Table III. Individual Data of Raynaud's Afflicted Subjects

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