Physiological Mechanisms of Temperature Biofeedback

Robert R. Freedman

Lafayette Clinic and Wayne State University

Research on the physiological mechanisms of finger temperature biofeedback with normal subjects and Raynaud's disease patients is reviewed. Studies conducted in the author's laboratory have shown that feedback-induced vasodilation is mediated through a non-neural, β-adrenergic mechanism rather than through reductions in sympathetic nervous system activation. In contrast, feedback-induced vasoconstriction is mediated through the traditional, sympathetic nervous pathway. When used with primary Raynaud's disease patients, feedback-induced vasodilation has achieved reductions in reported symptom frequency ranging from 66% to 92% in controlled investigations. Future research directions are discussed.

KEY WORDS: temperature biofeedback; Raynaud's disease; adrenergic receptors; sympathetic nervous system.

PHYSIOLOGICAL CONTROL OF FINGER BLOOD FLOW

The digital vasculature is almost entirely cutaneous and plays a fundamental role in the regulation of body temperature. The palmar surface and tip of the finger are rich in arteriovenous anastomoses (or shunts) which function in parallel with the capillary bed (Figure 1). These shunts

1Research conducted by the author was supported by research grants Nos. HL-23828, HL-30604, and AG-05233 from NIH. I am grateful for the collaboration of the following colleagues during the 14 years of work reported here: Peter Ianni, Dena Norton, Paul Wenig, Subhash Sabharwal, Maureen Mayes, Nagraj Desai, Michael Morris, Peter Migály, and Stewart Vining.

2Address all correspondence to Robert R. Freedman, Ph.D., Lafayette Clinic, 951 E. Lafayette, Detroit, Michigan 48207.

have the capacity to rapidly vary their lumen size and rate of blood flow in response to changes in external temperature. This is accomplished mainly through sympathetic adrenergic vasoconstrictor nerves (Figure 2). Body cooling causes reflex finger vasoconstriction through increased neural activity, and conversely, body heating produces vasodilation through withdrawal of this activity. Finger capillary blood flow is somewhat affected by sympathetic nervous system (SNS) activity, though to a lesser extent than arteriovenous shunt flow (Coffman, 1972). There are no known vasodilating nerves in the human finger, although such nerves do exist in the skin of the forearm (Shepherd, 1963).

Finger blood flow is also controlled through the interactions of circulating vasoactive substances with alpha- and beta-adrenergic receptors to produce vasoconstriction and vasodilation. Circulating catecholamines, released from the adrenal medulla and from other nerve endings “upstream,” act at alpha-adrenergic receptors to produce vasoconstriction. These alpha receptors are probably closer to the lumen than those that respond to norepinephrine released from sympathetic nerve endings. Alpha and beta receptors have been divided into two subtypes based on their relative sensitivities to different agonists. A beta-adrenergic vasodilating mechanism has recently been discovered in the finger by injecting isoproterenol, a synthetic beta-adrenergic agonist, into the brachial artery.
Fig. 2. Control of digital blood flow. Reflexive cooling causes digital vasoconstriction through the liberation of norepinephrine (NE) from sympathetic nerve endings, which can be reduced by indirect heating. Injection of tyramine causes vasoconstriction by displacing NE from the nerves. Vasoconstriction can also be caused by the interaction of circulating NE or synthetic agonists such as phenylephrine (PHENYL) or clonidine (CLON) with alpha-1- and alpha-2-adrenergic receptors. Synthetic beta-adrenergic agonists such as isoproterenol (ISO) cause vasodilation through interaction with beta-receptors. Reactive hyperaemia produces vasodilation through the accumulation of unknown compounds during ischaemia. (From Freedman, 1989.)
and then blocking this effect with propranolol, a beta-adrenergic antagonist (Cohen & Coffmann, 1981). However, an endogenous ligand that acts at these beta receptors has not yet been found.

The sensitivities of vascular adrenergic receptors change according to temperature and represent one means of local control of blood flow. Other local influences include changes in blood gases and metabolism, myogenic tone, and the axon reflex (Vanhoutte, 1980).

**SELF-CONTROL OF FINGER BLOOD FLOW — STUDIES IN NORMAL SUBJECTS**

Early investigations of self-induced vasodilation combined the effects of procedures such as finger temperature biofeedback, monetary rewards, and suggestions of thermal imagery. For example, Taub and Emurian (1976) reported an uncontrolled study in which 9 subjects were trained to increase and 12 subjects were trained to decrease hand temperature using feedback. Subjects were also encouraged to use thermal imagery and nine subjects received monetary rewards for changes in temperature. The authors stated that clear evidence of learning usually occurred within four sessions and that the average temperature change per session was approximately 1.2°C. Two subjects, selected on the basis of superior performance, were given additional training to increase and decrease temperature and showed changes of 5°C to 7.7°C.

Two controlled studies, subsequently performed by Surwit, Shapiro, and Feld (1976), failed to demonstrate significant elevations in finger temperature using biofeedback and monetary rewards. In the first study, two groups of 8 subjects each received training to either increase or decrease finger temperature. Half the subjects in each group received 7 training sessions and half received 11 sessions. Although the decrease group produced significant temperature declines (-2.0°C), the elevations shown by the increase group (0.25°C) were nonsignificant. Varying the number of training sessions had no effect. The authors hypothesized that the poor performance of the increase subjects might have been due to their approaching maximal finger temperature levels. They therefore trained 8 additional subjects in a cooler (19.5°C) environment in order to reduce basal levels of finger temperature. However, this procedure did not improve performance. Significant within-session changes in heart and respiration rates did not occur in either study.

Three controlled studies by Keefe did find significant temperature increases using finger temperature feedback and other procedures. In the first study (Keefe, 1975), two groups of 4 subjects each were instructed to
either raise or lower the temperature of their finger in comparison with their forehead. All subjects received 12 sessions of temperature feedback training, each consisting of a 5-minute baseline and a 10-minute feedback period. Data analyzed from the final training session showed significant finger temperature increases (+1°C) and decreases (−0.8°C) relative to forehead temperature. In the second study (Keefe, 1978), six groups of 10 subjects each were randomly assigned to receive various combinations of temperature feedback, thermal suggestions, and response-specific instructions. Subjects received five daily training sessions (10-minute baseline, 10-minute training) and two follow-up sessions, 1 and 2 weeks later. Subjects given either feedback and response-specific instructions, feedback and thermal suggestions, or no feedback and thermal suggestions were able to produce significant increases (+0.8°C to 1.1°C) in finger temperature by the third training session and to maintain this ability during the two follow-up sessions. In the final investigation (Keefe & Gardner, 1979), subjects given brief temperature feedback training sessions again demonstrated significant within-session temperature increases by the third session. Increasing the number of training sessions to 20 did not increase the magnitude of the response, which was approximately 1.3°C.

For finger temperature self-control to be of practical value it presumably must be replicable without the use of feedback instrumentation. The first study to examine the ability to increase finger temperature in the absence of feedback was conducted by Stoffer, Jensen, and Nesset (1979), although they did not examine the ability to perform this task prior to training. Twenty-four subjects were instructed to increase finger temperature using either contingent feedback, false feedback, or no feedback. During five 13-minute training sessions the contingent- and false-feedback groups produced significant temperature elevations (+0.5°C). During the posttraining test of voluntary control without feedback, only the contingent feedback group could increase digital temperature significantly (+0.4°C).

Two studies conducted by the author (Freedman & Ianni, 1983b) were designed to assess the ability to increase finger temperature without feedback as well as outside the laboratory and to determine if physiological relaxation is necessary for feedback-induced vasodilation. In the first experiment, 32 subjects were assigned randomly to receive six sessions of finger temperature feedback, frontalis electromyogram (EMG) feedback, autogenic training, or simple instructions to increase finger temperature. Each session consisted of a 16-minute baseline period, a 24-minute training or instructions period, and a final 16-minute baseline. The ability to increase temperature voluntarily without feedback was tested before training, after training, and outside the laboratory during ambulatory monitor-
In addition to finger temperature, heart rate, respiration rate, frontalis EMG, and skin conductance level were recorded continuously during each session.

In the pretraining voluntary control session subjects' finger temperature declined, demonstrating that peripheral vasodilation did not occur prior to training. During training, subjects receiving temperature feedback showed significant increases in finger temperature during the first 12 minutes of the first session only, an effect not shown by the other subjects. During the subsequent five training sessions, significant temperature elevations were not shown by any group. Subjects as a whole showed within-session declines in heart rate, respiration rate, and frontalis EMG level. During the posttraining test of voluntary control in the laboratory, only the temperature feedback group produced a significant elevation in digital temperature. In the final voluntary control test, conducted outside the laboratory, no temperature increases were found. Thus evidence for having trained the response through biofeedback was found upon removal of the feedback as long as subjects were asked to vasodilate in the same environment in which they were trained. It appears, however, that the response was not robust enough for generalization to occur.

It was hypothesized that finger temperature elevations produced during temperature feedback might be time limited or that excessive session length might impede training. Kluger and Tursky (1982) also found that feedback-induced temperature increases peaked early in the session and subsequently declined. We therefore performed a second experiment in which the training periods were shortened from 24 to 16 minutes and the final baseline period eliminated. Sixteen subjects were assigned randomly to receive either finger temperature feedback or simple instructions to increase finger temperature. Half the subjects in each group received either 6 or 10 training sessions. As in the previous study, subjects were unable to raise their finger temperature when requested to do so prior to training. However, during training, temperature feedback subjects consistently increased their finger temperature (+0.42°C, $p < .05$), while those receiving instructions only experienced no increase. Increasing the number of training sessions from 6 to 10 had no effect. Subjects in the instructions-only group showed significant declines in heart rate and muscle tension during training, while temperature feedback subjects did not. During the first posttraining voluntary control test, only the temperature feedback subjects demonstrated significant increases in digital temperature (+0.56°C). There were no group differences on other physiological measures. During a similar test performed outside the laboratory with ambulatory monitoring, only these subjects again showed significant finger temperature elevations. These increases were of substantially larger magnitude (2.41°C) than those
produced during prior sessions. Thus, shortening the session length resulted in a robust laboratory training effect and also enhanced generalization of the response to an extralaboratory setting. Subjects as a whole showed significant heart rate declines during this session.

As opposed to biofeedback, considerably less research has been done on the use of relaxation procedures to increase finger temperature in normal subjects. Bouydewyns (1976) found significant increases in finger temperature while subjects listened to brief tape-recorded relaxation instructions; these changes were not correlated with measures of skin conductance level or heat rate. Blizard, Cowings, and Miller (1975), however, failed to find significant temperature elevations in six sessions of autogenic instructions for hand warming.

Comment

From the preceding studies it is reasonable to infer that small but significant elevations in finger temperature can generally be produced by normal subjects using temperature feedback, a conclusion shared by other reviewers (King & Montgomery, 1980). Furthermore, subjects can retain this response over time (Keefe, 1978) and produce it without feedback (Stoffer et al., 1979) and outside the laboratory (Freedman & Ianni, 1983b).

Subjects seem to acquire the temperature feedback response within a few training sessions and the magnitude of this response does not increase with additional training (Freedman & Ianni, 1983b; Keefe & Gardner, 1979; Surwit et al., 1976). Also, it appears that temperature elevations occur shortly after the activation of feedback and may be time limited (Freedman & Ianni, 1983b). Reasons for this temporal limit are not known. The notion of a temporal limit to training is supported by the fact that previous studies reporting significant finger temperature increases during temperature feedback utilized training periods of 15 minutes or less (Keefe, 1978; Keefe & Gardner, 1979; Kluger & Tursky, 1982; Stoffer et al., 1979; Taub & Emurian, 1976), whereas studies failing to find this effect used periods of 24 minutes or longer (Surwit, 1977; Surwit et al., 1976).

It also appears that relaxation, at least as indicated by decreased heart rate, respiration rate, frontalis EMG, or skin conductance level, is not necessary for the vasodilation shown by temperature feedback subjects. In our first study (Freedman & Ianni, 1983b) there were no group differences in these measures; however, only the temperature feedback subjects produced significant temperature elevations during any session. In the second experiment, instructions-only subjects showed significant
declines in heart rate and frontalis EMG level during training, yet they could not raise their finger temperature. In contrast, temperature feedback subjects were able to vasodilate despite small increases in heart rate and EMG. Other studies have not found evidence of physiological relaxation during temperature biofeedback (Stoffer et al., 1979; Surwit et al., 1976; Taub & Emurian, 1976).

Little evidence exists to suggest that normal subjects can increase finger temperature through autogenic training, although only two controlled studies have examined this issue directly (Blizard et al., 1975; Freedman & Ianni, 1983b). Vasodilation through other procedures, such as progressive relaxation, warrants investigation.

**RAYNAUD'S DISEASE**

Raynaud's disease is a disorder of the peripheral vasculature in which episodic vasospasms occur in the fingers, toes, and occasionally, in the nose and ears. The symptoms are triggered by cold and/or emotional stress (Freedman & Ianni, 1983a) and are characterized by blanching followed by cyanosis and rubor.

Although the etiology of Raynaud's disease is unknown, two major theories have attempted to explain it. Raynaud (1888) felt that sympathetic nervous system hyperactivity caused an increased vasoconstrictor response to cold, while Lewis (1929) hypothesized a "local fault" in which small peripheral blood vessels were oversensitive to local cooling.

Data regarding Raynaud's hypothesis have been inconsistent. Peacock (1959a) found that the average hand blood flow of Raynaud's disease patients was abnormally low during baseline conditions but rose to normal levels after sympathetic release by body warming. However, the failure of others (Downey & Frewin, 1973; Fagius & Blumberg, 1985) to find increased sympathetic vasoconstriction to reflexive cooling provides substantial evidence against this theory. Peacock (1959b) also found increased levels of circulating catecholamines in Raynaud's disease patients, which he interpreted as evidence of increased sympathetic activity. However, these findings were not replicated in several other studies of patients with Raynaud's disease or Raynaud's phenomenon secondary to scleroderma (Kontos & Wasserman, 1969; Mendlovitz & Naftchi, 1959; Sapira, Rodnan, Scheib, Klaniecki, & Rizk, 1972; Surwit et al., 1983).

We recently compared finger blood flow (FBF) responses of Raynaud's disease patients and normal subjects to dose-ranging brachial artery infusions of phenylephrine, an $\alpha_1$ agonist; clonidine, an $\alpha_2$ agonist; isoproterenol, a $\beta$ agonist; and tyramine, which causes vasoconstriction
by releasing norepinephrine from sympathetic nerve endings (Freedman, Sabharwal, Wenig, Desai, & Mayes, 1989). Twenty-eight patients with idiopathic Raynaud's disease, 24 women and 4 men aged 22 to 69, were screened to see if they met the Allen and Brown criteria, and had negative antinuclear antibody tests, normal nailfold capillaries, and normal finger blood flow (FBF) responses to a maximum vasodilation test. In the latter procedure, subjects were subjected to total body heating and peripheral reactive hyperemia, to verify the patency of finger blood vessels. They were matched by age and baseline FBF levels with 24 normal women and 5 normal men, aged 22-66. Subjects were supine in a 23°C room while FBF was measured with venous occlusion plethysmography and the above four compounds given by pump, in successively doubling doses, through a brachial artery catheter. The doses employed did not change blood pressure or heart rate. ANOVAs showed that phenylephrine caused dose-related vasoconstriction ($p < .005$) that was greater in the patients than the normals ($p < .002$). Similarly, dose-related vasoconstriction produced by clonidine ($p < .02$) was greater in patients than in normals ($p < .05$). There were no significant differences in responses to isoproterenol or tyramine. Thus, equal levels of circulating catecholamines would cause a greater degree of peripheral vasoconstriction in Raynaud’s disease patients than in matched controls.

Regarding Lewis' theory, some studies have found increased vasoconstrictive responses to cold in Raynaud’s patients (Chucker, Fowler, Motomuja, Singh, & Hurley, 1971; Jamieson, Ludbrook, & Wilson, 1971), whereas others have not (Downey & Frewin, 1973; Miller & Walder, 1972). Lewis' evidence (1929) was based on the induction of vasospastic attacks in locally cooled fingers which had been anesthetized or sympathetically denervated. However, it is likely that most of his patients had advanced forms of the disease and that their vascular changes were therefore of a secondary nature (Halperin & Coffman, 1979).

We recently tested Lewis' theory in a controlled laboratory investigation (Freedman, Mayes, & Sabharwal, 1989). Using a combination of environmental and local cooling, we induced vasospastic attacks of Raynaud's phenomenon in 9 of 11 patients with idiopathic Raynaud's disease and in 8 of 10 patients with scleroderma. Two fingers on one hand were anesthetized by local injection of Xylocaine and the effectiveness of nerve blocks was verified by plethysmography. The frequency of vasospastic attacks in nerve-blocked fingers was not significantly different from that in the corresponding intact fingers on the contralateral hand. These findings show that the vasospastic attacks of Raynaud’s disease and phenomenon can occur without the involvement of efferent digital nerves and argue against the etiologic role of sympathetic hyperactivity.
Freedman

BEHAVIORAL TREATMENT OF RAYNAUD'S DISEASE

Given the vasoconstrictive nature of the symptoms of Raynaud's disease and the ability of normal subjects to learn to increase peripheral blood flow using behavioral techniques, it was logical to employ behavioral procedures in the treatment of this disorder. The first investigations in this area were single-case studies. Using blood volume feedback from the big toe, Shapiro and Schwartz (1972) produced complete relief of Raynaud's disease symptoms for 1 year in one patient using 10 training sessions. A second patient terminated treatment prematurely and showed neither control of blood flow nor amelioration of symptoms. Surwit (1973) treated a patient with severe Raynaud's disease with over 50 sessions of finger temperature feedback. The patient was able to increase her average basal skin temperature from 23°C to 26.6°C with partial symptom relief. Jacobson, Hackett, Surman, and Silverberg (1973) treated a patient who was refractory to drug treatment, using combined hypnosis and thermal biofeedback. After eight treatment sessions, the patient was able to increase his finger temperature 4.3°C with substantial symptom relief that was maintained at a 7½-month follow-up. In a well-controlled single-case study, Blanchard and Haynes (1975) showed an advantage of feedback over nonfeedback training sessions for control of finger temperature. The patient was able to consistently increase her hand temperature at least 1°C and experienced substantial symptom relief that persisted at 2-, 4-, and 7-month follow-ups.

In the first controlled study of behavioral treatments for Raynaud's disease (Surwit, Pilon, & Fenton, 1978), 30 patients were randomly assigned to receive either autogenic training alone or in combination with temperature feedback. Half the subjects in each group received twelve 45-minute laboratory training sessions while half received home training and three instructional group meetings. In addition, for a 1-month period, half the subjects served as a waiting-list control group for the other half and then received treatment. All subjects were instructed in a response generalization technique in which they practiced hand warming many times each day using visual aids as reminders. Subjects as a whole showed significant improvement in response to a cold stress test and reported fewer attacks after treatment. However, the decline in symptom frequency reported by treated subjects (32%) did not differ significantly from that reported by the waiting-list controls (10%). There were no significant differences between subjects who received autogenic training alone and those who also received biofeedback or between subjects trained at home and those trained in the laboratory. Also, subjects' heart rates were significantly higher during the posttreatment cold stress test than during the
Physiological Mechanisms of Temperature Biofeedback

pretreatment test. One year later the cold stress responses of 19 follow-up subjects returned to pretreatment levels, although reported symptom frequency remained improved (Keefe, Surwit, & Pilon, 1979). In a subsequent study (Keefe, Surwit, & Pilon, 1980) of 21 patients, no outcome differences were found among those receiving progressive relaxation, autogenic training, or a combination of autogenic training and tempera-ture feedback; patients as a whole showed significant improvements in response to the cold stress test and in reported symptom frequency. All patients were treated at home in that study.

Jacobson, Manschreck, and Silverberg (1979) treated 12 Raynaud's disease patients with 12 brief sessions of progressive relaxation alone or in combination with temperature feedback. Patients generally showed tempera-ture elevations during training and rated themselves as improved; how-ever, there were no outcome differences between the two groups.

Up to this time, no controlled group study had been conducted in which patients were treated with temperature biofeedback alone. There-fore, this was the approach chosen by the present author. In one investiga-tion (Freedman, Lynn, Ianni, & Hale, 1981), six patients with Raynaud's disease and four with Raynaud's phenomenon received twelve 56-minute training sessions of finger temperature feedback. Patients showed sig-nificant reductions in symptom frequency that were maintained for a 1-year follow-up period. Small but significant elevations in finger temperature were found during training and were not accompanied by physiological relaxation. In fact, increased finger temperature was correlated significantly with increased respiration rate, skin conductance level, and frontalis EMG activity.

In a review of the literature on transfer of training in biofeedback, Lynn and Freedman (1979) concluded that transfer will tend to be minimal when the training stimulus is nonrepresentative of the population of stimuli to which the response is to be transferred. Since the Raynaud's disease patient must be able to control finger blood flow in cold conditions as well as in the comfortable laboratory environment, a study was performed in which a cold stimulus was introduced during temperature feedback training (Freedman, Ianni, Hale, & Lynn, 1979). Six Raynaud's disease and two Raynaud's phenomenon patients first received six temperature feedback training sessions as described above. During six subsequent sessions, a ther-mal cooling device was applied to the finger that was being monitored for feedback. The temperature of this device was decreased from 30°C to 20°C at a rate of 1°C per minute and then held at 20°C for 10 minutes. The addition of this device, of course, greatly increased the difficulty of finger temperature elevation during feedback. However, patients again showed
significant reductions in attack frequency, which were maintained throughout the following year.

In a subsequent investigation (Freedman, Ianni, & Wenig, 1983) we tested the relative efficacy of standard temperature feedback and temperature feedback under cold stress in a controlled manner. Thirty-two Raynaud's disease patients were assigned randomly to receive ten 32-minute training sessions in either one of these procedures, autogenic training, or frontalis EMG feedback. The last procedure was chosen to control for the effects of receiving feedback of any physiological information and to assess the role of relaxation in treatment. In addition, since emotional stress is a factor in some Raynaud's attacks (Freedman & Ianni, 1983a), cognitive stress management was employed with half the patients in each group. Patients were tested for the ability to increase temperature without feedback prior to treatment, after treatment, and 1 year later. This was done both with and without cold stress. All vasospastic attacks were recorded for 1 month before and 1 year following treatment. In addition, patients received ambulatory monitoring of finger temperature, ambient temperature, and ECG for 24 hours prior to treatment and at the 1-year follow-up evaluation.

During training, subjects receiving temperature feedback (TEMP) or temperature feedback under cold stress (TEMPCS) showed significant increases (0.60°C) in finger temperature, whereas those receiving EMG feedback or autogenic instructions did not (Figure 3). EMG and autogenic subjects showed significant declines in muscle tension and reported stress and nonsignificant declines in heart rate, whereas the other groups did not. During posttraining cold stress and voluntary control tests, the temperature elevations of the TEMP subjects were superior to those of the other three groups. One year later, however, the TEMPCS group showed the best performance (+0.5°C) on the voluntary control test. The change shown by the TEMP group (+0.3°C) was still significant but smaller than that shown previously. Final temperatures during the follow-up test were related significantly to the number of reported attacks. Decrements in reported symptoms were greatest for the TEMPCS group (92.5%), next greatest for the TEMP group (66.8%), followed by the autogenic group (32.6%), and the EMG group (17.0%). During 1-year follow-up Medilog recordings, greater finger-ambient temperature differences were needed to produce attacks in TEMP and TEMPCS subjects compared to EMG and autogenic subjects. The addition of cognitive stress management had no significant effects on any procedure. Data subsequently obtained from the TEMP and TEMPCS subjects show that their reported symptom reductions were retained 3 years after treatment (Freedman, Ianni, & Wenig, 1985).
Fig. 3. Finger temperatures averaged across training sessions. TEMP, finger temperature feedback; TEMPCS, finger temperature feedback under cold stress; EMG, frontalis EMG feedback; AUTO, autogenic training. (From Freedman, Ianni, & Wenig, 1983.)

Only one other controlled investigation of biofeedback treatment for Raynaud's disease has been published to date (Guglielmi, Roberts, & Patterson, 1982). Thirty-six patients were assigned randomly to receive 20 sessions of training in temperature feedback, EMG feedback, or to a no-treatment control group. Since the study was conducted in a double-blind manner, neither the patients nor the therapists knew which type of feedback was being given. Neither the EMG nor the temperature feedback groups showed evidence of acquiring their respective responses. There were no group differences in reported attack frequency during treatment.

At this point in time, several controlled studies of behavioral treatments for Raynaud's disease had been published. The first 3 (Jacobson et al., 1979; Keefe et al., 1980; Surwit et al., 1978) tested the relative efficacy of relaxation procedures alone and in combination with temperature feedback and did not find differences in treatment outcome among conditions. The double-blind study of Guglielmi et al. (1982) also found no outcome differences among groups given temperature feedback, EMG feedback, or a no-treatment control procedure. The most likely explanation for the
failure of these studies to find group differences in treatment outcome is their failure to demonstrate group differences in finger temperature training effects. In contrast, the next study (Freedman et al., 1983) found group differences in both treatment outcome and the acquisition of digital vasodilation. Subjects given temperature feedback alone or under mild cold stress acquired the ability to voluntarily increase finger temperature and reported highly significant reductions in symptom frequency; those given autogenic training or EMG feedback did not learn to vasodilate and reported only modest symptom reductions. Some of the physiological mechanisms underlying the effects of different behavioral treatments are discussed below.

MECHANISMS OF BEHAVIORAL TREATMENT

We have shown in normal persons (Freedman & Ianni, 1983b) and in Raynaud's disease patients that the effects of temperature feedback are physiologically different from those of autogenic training, frontalis EMG feedback, or simple instructions to increase finger temperature. Temperature feedback produces digital vasodilation without bradycardia or decreased muscle tension, whereas the other techniques do produce bradycardia and lower EMG levels but not increased finger temperature. Recent research has uncovered a physiological mechanism that may explain increased digital blood flow in the absence of decreased generalized physiological arousal. It was previously thought that vascular control of digital blood flow resulted solely from sympathetically mediated alpha-adrenergic vasoconstriction. However, recently an active beta-adrenergic vasodilating mechanism has been identified in the human finger (Cohen & Coffman, 1981). We have show that this mechanism is operative during temperature feedback in both normal persons and patients with Raynaud's disease by local beta-blockade of the vasodilation with intraarterial infusions of propranolol (Freedman, Sabharwal, Ianni, Desai, Wenig, & Mayes, 1988).

We first randomly assigned 18 patients with idiopathic Raynaud's disease and 16 normal subjects to receive ten sessions of temperature feedback or autogenic training using the methods of the previous study (Freedman, Ianni & Wenig, 1983). Following training, in a separate session, a catheter was placed in the right brachial artery using a local anaesthetic and connected to two Harvard infusion pumps, one containing 0.9% saline solution, the other containing propranolol, a beta-adrenergic antagonist. Saline was infused at a rate of 2 ml/min throughout the experiment except when indicated below. The pumps were housed in a sound-proofed box and con-
trolled remotely by the experimenter from the polygraph in a separate room. Finger blood flow was measured in both hands with venous occlusion plethysmography, and capillary blood flow was recorded by injecting 2 μCi of Na\(^{131}\)I subcutaneously in one finger-pad on the right hand and measuring its disappearance with a scintillation counter.

After a 20-minute adaptation period and 16 minutes of baseline recordings, the temperature-feedback signals or autogenic tape were activated. After 6 minutes the infusion was switched from saline to propranolol (0.5 mg/min) for 2 minutes, then saline for 4 minutes, propranolol (same dose) for 2 minutes, and saline for 4 minutes. These changes occurred without the subject’s knowledge. Significant bilateral vasodilation occurred in the temperature-feedback subjects and was significantly reduced by propranolol in the infused but not the control hand. The magnitudes of these effects were not significantly different in the Raynaud’s disease and normal subjects. However, capillary blood flow increased significantly during feedback in the patients but not the normal subjects. There were no significant blood flow changes at all in the patients or normals who received autogenic training. There were no significant heart rate or blood pressure changes in the temperature-feedback group; the autogenic group showed a significant decline in heart rate during the autogenic instructions. Thus, a beta-adrenergic mechanism is involved in feedback-induced vasodilation.

The only known efferent vasomotor nerves in human fingers are adrenergic; neurogenic vasoconstriction is caused by the interaction of released norepinephrine with postjunctional alpha-adrenergic receptors. Our finding of a beta-adrenergic mechanism in temperature biofeedback thus raised the question of whether feedback-induced vasodilation is neurally mediated. Since it is possible to block the digital nerves by local injection of an anaesthetic, a method was available to test this hypothesis. Since digital nerve blockade raises finger blood flow to near ceiling levels, we reduced it to midrange by infusing norepinephrine (NE) (0.25 μg/min), into the right brachial artery. To control for all of the manipulations, we measured blood flow in 3 fingers: right, nerve-blocked + NE; right, no block + NE; left, no block, no NE. We then repeated the propranolol infusion of the previous study (Figure 4). In two separate studies of normal subjects (N = 8, N = 9) and a subsequent study with Raynaud’s disease patients (N = 10), we found that vasodilation produced by temperature feedback was not attenuated by nerve blockade or norepinephrine, but was reduced by propranolol. This also occurred for capillary blood flow in the patients, but not the normal subjects. Thus, the beta-adrenergic vasodilating mechanism of temperature feedback does not appear to be mediated through the digital nerves.
Fig. 4. Blood flow (FBF) in three fingers during last 4 minutes of baseline period and subsequent temperature feedback period. Nerves in right second finger (R Block) were anesthetized. During baseline period FBF did not significantly change (NS). When feedback was activated FBF in all three fingers increased significantly ($p < 0.005$). Propranolol (PROP) infused into right brachial artery (0.5 mg for 2 minutes) caused significant ($p < 0.01$) reduction in FBF in infused hand (*) but not left hand. (From Freedman et al., 1988b.)

To further examine possible changes in sympathetic nervous system activity during temperature feedback and autogenic training, we recently measured plasma levels of epinephrine and norepinephrine during these procedures (unpublished data). An I.V. needle was inserted into a vein on the forearm and connected to a Cormed blood withdrawal pump through special, nonthrombogenic tubing. The pump was located in an adjacent room, so that blood could be collected without observation by the subject. Plasma levels of epinephrine and norepinephrine were subsequently analyzed by the HPLC-EC method.

Thirty-one patients meeting the Allen and Brown criteria for idiopathic Raynaud's disease were randomly assigned to receive eight 32 minute sessions of finger temperature feedback ($N = 16$) or autogenic
training \((N = 15)\) over 28 days. Sessions were structured in the same manner as those of our previous studies (Freedman et al., 1983a, 1988b). Women logged their menstrual cycles for 2 months prior to study. Half of each group began and finished training between cycle days 5 and 7 (follicular), the other half between days 22 and 24 (luteal). During sessions 1 and 8, blood was continuously drawn with a Cormed pump and subsequently analyzed, in duplicate 4-minute samples, by HPLC.

During training, significant temperature elevations were shown by feedback patients \((p < .001)\) but not by autogenic patients. There were no significant effects whatsoever for NE and E for either group. A power analysis showed that the sample size was more than adequate to detect such effects, if they existed. Small but significant elevations in heart rate, skin conductance level, and systolic and diastolic blood pressures were shown by subjects overall; there were no group differences for any measure. These findings do not support the role of decreased sympathetic activation in behavioral treatments for Raynaud's disease.
Our finding that feedback-induced vasodilation is mediated through a non-neural, β-adrenergic mechanism raised the question of whether feedback training for vasoconstriction is mediated through a sympathetic nervous pathway. Nine normal subjects received temperature feedback vasoconstriction training in which feedback was delivered only during periods of successful performance (Freedman, Morris, Norton, Masselink, Sabharwal, & Mayes, 1988). In a subsequent session, the nerves to one finger were blocked with a local anesthetic while finger blood flow was recorded from this and other fingers. Vasoconstriction occurred during feedback in the intact fingers but not in the nerve-blocked finger and was accompanied by increased skin conductance and heart rate (Figure 5). These data demonstrate that temperature feedback vasoconstriction training is mediated through an efferent, sympathetic nervous pathway.

CONCLUSION

Replicated, controlled investigations have demonstrated that normal persons and those with idiopathic Raynaud’s disease can significantly increase finger temperature and blood flow using temperature biofeedback. This effect occurs early in the training process and can be sustained after the removal of feedback. In Raynaud’s disease patients, vasodilation occurs in the finger capillary bed, as demonstrated by radioisotope clearance studies. These patients report declines in symptom frequency from 67% to 92%, which persist for at least 2 to 3 years following treatment. Comparable improvements are not reported by patients given autogenic training. Contrary to popular belief, feedback-induced vasodilation is not achieved through reductions in sympathetic nervous system activation. Early studies in our laboratory did not find expected reductions in heart rate, skin conductance level, or reported arousal in Raynaud’s patients or normal subjects given temperature feedback. We subsequently demonstrated that feedback-induced vasodilation is not mediated through sympathetic nerves but, rather, through a β-adrenergic mechanism. Consistent with these findings, we have most recently found that plasma levels of norepinephrine and epinephrine do not significantly change during temperature feedback or autogenic training in Raynaud’s disease patients.
In contrast to the above findings, feedback-induced vasoconstriction is mediated through the expected sympathetic nervous pathway. In normal subjects we showed that feedback-induced vasoconstriction was abolished by selective digital nerve blockade but maintained in intact fingers. Thus, feedback-induced vasodilation and vasoconstriction are mediated through fundamentally different physiological mechanisms.

There are many remaining questions in the search for a complete understanding of the mechanisms underlying temperature biofeedback, such as the ligand producing digital vasodilation and the cognitive and brain mechanisms involved. Hopefully, we and others will further delineate these in the course of future research.

REFERENCES


