PAPERS AND SHORT REPORTS

Role of cold and emotional stress in Raynaud's disease and scleroderma

ROBERT R FREEDMAN, PETER IANNI

Abstract

Research on the aetiology of Raynaud's disease and phenomenon has been hindered by the difficulty of provoking attacks in the laboratory. A study was therefore conducted in which digital and ambient temperatures, electrocardiograms, and stress ratings were obtained during ambulatory monitoring in patients with idiopathic Raynaud's disease, Raynaud's phenomenon secondary to scleroderma, and in normal subjects. In Raynaud's disease about one third of the vasospastic attacks were associated with tachycardia and increased stress ratings without declines in ambient temperature. In contrast, cold alone was enough to provoke most attacks of Raynaud's phenomenon in scleroderma.

Chronically increased stress ratings in patients with scleroderma and increased muscle tension in anticipation of a cold stimulus suggest that these patients have different patterns of stress responses from those with Raynaud's disease.

Introduction

The symptoms of Raynaud's disease and phenomenon consist of episodic vasospasms in the fingers and toes precipitated by cold or emotional stress, or both. When these attacks occur in the presence of identifiable pathological processes the term Raynaud's phenomenon is used. This is the case for a variety of diseases such as scleroderma, where Raynaud's attacks occur in over 95% of patients.[1] When the attacks occur in the absence of identifiable pathological processes the term Raynaud's disease is used. In either case the aetiology is unknown, although several theories have been put forward to explain the underlying mechanisms. Raynaud[2] originally hypothesised an overactivity of the sympathetic nervous system leading to an increased vasoconstrictor response to cold or intense emotion, while Lewis[3] postulated a "local fault," in which precapillary resistance vessels were hypersensitive to local cooling.

Raynaud's concept of autonomic overactivity was similar to that of Selye,[4] who emphasised the "repeated elicitation of the generalised alarm reaction" in the development of stress related disorders. This reaction consists of increased heart rate, muscle tension, skin conductance, and peripheral vasoconstriction. While Selye emphasised the generalised alarm reaction, subsequent workers called for studies on the differential patterns of responses to various types of stressors in contrasting groups of patients.[5]

Although much laboratory work has been done on the effects of cold in Raynaud's disease and phenomenon,[6-13] less attention has been paid to the role of emotional stress. Mittelmann and Wolff presented data from one patient showing that a combination of low environmental temperature and emotional stress was necessary to provoke an attack.[14] Graham showed cutaneous vascular changes in three patients with Raynaud's disease during discussions of disturbing life events.[15] In a recent study of 838 Raynaud's attacks,[16] 188 (22·4%) were reported to be caused by emotional stress.

Research on the aetiology of Raynaud's disease and phenomenon has been hindered by the inability reliably to produce attacks in the laboratory.[6] In the present study, therefore, vasospastic attacks were obtained in naturally occurring conditions of cold and emotional stress while physiological responses were recorded using ambulatory monitoring procedures. One component of the stress response, tachycardia, was measured by recording an electrocardiogram on one channel of a Holter type recorder. It was also desirable to obtain patients' ratings of subjective emotional stress experienced immediately before attacks and at other points throughout the day. In a previous investigation[16] in patients with Raynaud's disease ratings of subjective emotional stress made on a 0-100 scale were significantly higher before attacks than during

Lafayette Clinic, 951 East Lafayette, Detroit, Michigan 48207, USA
ROBERT R FREEDMAN, PHD, director, behavioural medicine laboratory

Department of Psychology, Wayne State University, Detroit, Michigan, USA
PETER IANNI, MA, psychologist

Correspondence to: Dr Robert R Freedman.

asymptomatic periods. Similar findings were obtained using a psychometric measure of anxiety, which was significantly correlated ($r=0.75$; $p<0.001$) with the subjective estimates of stress. The 0-100 measure of subjective emotional stress has been shown to be sensitive to stress induced by films,[17] imagined scenes,[18 19] and natural events occurring over extended periods of time[20] and to correlate with measures of heart rate,[17 18] skin conductance,[17 18] and peripheral blood flow.[19] Since this emotional stress scale could be easily used by patients throughout the day and is significantly correlated with objective psychometric and physiological measures, it was employed during ambulatory monitoring in this study. It was also desirable to obtain physiological responses to cold which were not technically feasible with ambulatory monitoring. We therefore recorded skin conductance, muscle tension, and other physiological measures during baseline and cold conditions in a controlled laboratory environment.

Subjects and methods

We studied two men and 22 women meeting the American Rheumatism Association criteria for progressive systemic sclerosis[21] and having serological test results positive for antinuclear antibody and negative for ribonucleoprotein and Sm antibody. In addition, all were required to have bilateral Raynaud's phenomenon unrelated to other causes, such as exposure to vinylchloride or obstruction of the thoracic outlet. Four men and 28 women with primary idiopathic Raynaud's disease who met the criteria of Allen and Brown,[22] had serological test results negative for antinuclear antibody, and had nailfold capillaries with no evidence of connective tissue disease[23] were also studied. Control subjects were recruited through newspaper advertisements requesting normal volunteers for psychophysiological studies; they were paid a nominal fee. They were judged to have no evidence of any physical disorder after giving a history and completing an extensive questionnaire. The group consisted of four men and 18 women. The ages and sex ratios of the three groups were not significantly different. Informed consent was obtained from all subjects according to procedures approved by the facility's institutional review board.

APPARATUS

All laboratory physiological measures were recorded on a Grass model 7D polygraph, digitised, and simultaneously printed each minute on two Med Associates DIG 900 printers. Skin temperature, skin conductance level, and electromyographic responses were converted to digital pulses by resetting integrators. Skin temperature was measured from the distal end of the middle finger of the dominant hand using a Yellow Springs No 729 thermistor and "Thermivolt" bridge circuit. The absolute accuracy of this system was 0·05°C calibrated against a National Bureau of Standards certified glass thermometer in a stirred water bath. Skin conductance level was recorded from the fourth and fifth fingers of the dominant hand using a 0·5 volt constant voltage circuit and Beckman standard surface electrodes filled with 0·05M NaCl paste. The frontalis electromyogram was recorded using two Beckman surface electrodes placed 2·5 cm above each eyebrow and 10 cm apart, with a ground electrode midway between them. The electrocardiogram was recorded using a standard lead I configuration. R waves were detected by a Schmitt trigger and the resulting rate shown each minute on one of the printers. Similarly, respiration rate was measured using a nasal thermocouple and Schmitt trigger and printed every minute.

The cold stimulus was a 2·5 cm square Pelletier principle thermoelectric module which could be set by the experimenter to any temperature between 0° and 50°C with an accuracy of 0·1°C. Temperature was regulated by a thermistor on the stimulus side of the module, which provided feedback to an electronic regulator controlling the current to the module.[16]

Ambulatory monitoring was performed using a Medilog (Oxford Medical Instruments) cassette recorder worn by the subject on a belt. Skin temperature was measured from the distal end of the middle finger on one hand using a Yellow Springs No 729 thermistor and recorded continuously on one channel of the Medilog. Ambient temperature was recorded on a second channel of the Medilog using a Yellow Springs No 729 thermistor attached 4 cm away from the dorsal side of the wrist of the same hand and insulated from body heat by a specially constructed Plexiglass shield. An event marker button and time code generator were mounted on the side of the recorder and connected to a third channel. The electrocardiogram was recorded on the fourth channel using disposable electrodes in a lead II configuration. All data were recorded on Maxell UDC 120 cassette tapes and replayed on an Oxford PB-2 playback unit and Siemens-Elema Mingograph chart recorder. Accuracy of temperature measurement with this system was 0·1°C.

PROCEDURE

Cold stress—This laboratory test was conducted in a soundproofed, temperature and humidity controlled room maintained at 23°C. Subjects sat upright in a large reclining chair with their hands and arms kept on armrests. After attachment of the transducers each subject was allowed to adapt to the laboratory for 10 minutes. Data were then recorded during a 16 minute baseline period, a 16 minute cold stress period, and a 16 minute recovery period. During the second 16 minute period the middle phalange of the subject's dominant middle finger rested on the cold stimulus, whose temperature decreased from 30°C to 20°C at a rate of 1°C/min for 10 minutes and was then maintained at 20°C for six minutes. The edge of the stimulus was 1 cm from the thermistor used to measure the temperature of the finger.

Ambulatory monitoring—Within two weeks of the cold stress procedure subjects wore the Medilog recording apparatus described above from 1000 to 2200 hours on two consecutive days. Subjects were instructed not to sleep during the recording periods. Three identical Medilog recorders were used in this study. Whenever possible one subject from each group was recorded simultaneously to control for possible effects of the weather. The average daily outdoor temperatures during recordings were not significantly different among the three groups. At the end of each recording hour an event diary was completed describing the activities of the preceding hour and a rating of perceived emotional stress made on a 0-100 scale, where zero represented no stress at all and 100 represented as much stress as could possibly be imagined. Stress was defined as an aversive emotional state, similar to anxiety or tension. An hourly tone produced by the time code generator on the recorder prompted subjects to fill out the diary. Patients with Raynaud's disease and scleroderma were also instructed to press the event marker button each time a vasospastic attack occurred. An attack was defined as blanching of one or more fingers with or without cyanosis or rubor. An additional diary entry was made for each attack, including a 0-100 rating of stress experienced *just before the attack*, a visual description of the attack, and the cause, time, and place of the attack.

DATA ANALYSIS

All data were analysed using repeated measures analyses of variance and Newman-Keuls post hoc tests unless otherwise noted.[24] For Medilog recordings, finger and ambient temperatures were measured at each hourly point on the chart records and at each vasospastic attack as indicated by the patient's activation of the event marker. Heart rate was counted for the minute preceding each hourly point and the minute preceding each event mark. Stress ratings were obtained from the diaries. Average daily outdoor temperatures for each recording day were obtained from the National Climatic Center in Asheville, NC. The minimum level of statistical significance for all analyses was 0·05.

Results

During the laboratory cold stress test the average finger temperatures of the patients with Raynaud's disease (27·1°C) were significantly lower than those of the patients with scleroderma (29·2°C; $p<0.05$) and those of the normal subjects (30·0°C; $p<0.01$). The temperatures of the latter two groups were not significantly different. The cold stimulus produced significant declines in finger temperature ($p<0.0001$), although the magnitudes of decline were not different ($p>0.9$) for the three groups (fig 1). The frontalis electromyographic responses of the patients with scleroderma

increased significantly ($p<0.01$) at the onset of the cold stimulus and decreased ($p<0.01$) when it was stopped (fig 2). Significant changes were not shown by the other two groups. Average respiration rates in the scleroderma group (18·02 cycles/min) were significantly ($p<0.05$) higher than those of the patients with Raynaud's disease (16·02) and the normal subjects (16·06) but did not change significantly during the session. There were no significant group differences in heart rate or skin conductance level.

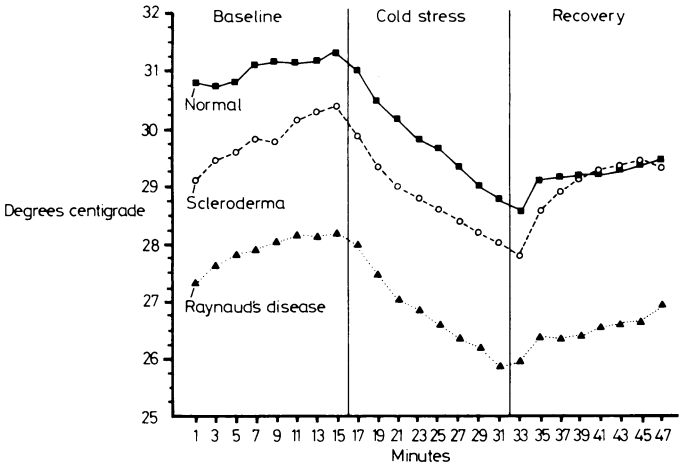

FIG 1—Finger temperature responses to thermal stimulation.

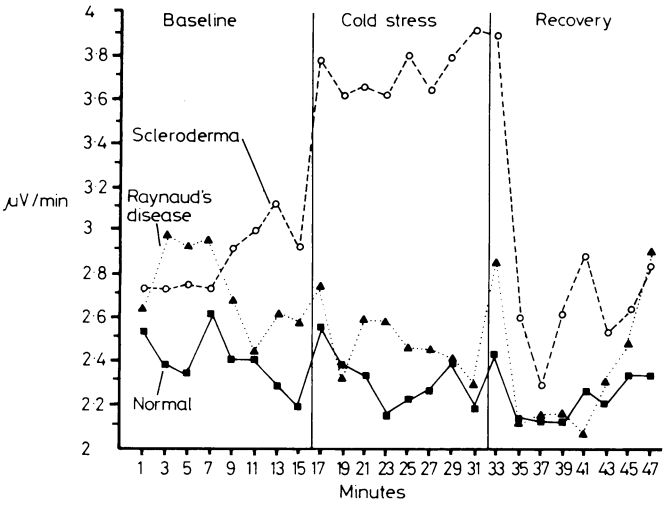

FIG 2—Frontalis electromyographic responses to thermal stimulation.

Average finger temperatures during Medilog recording paralleled those obtained in the laboratory. Patients with Raynaud's disease had significantly lower temperatures (26·8°C) than had the patients with scleroderma (29·0°C; $p<0.05$) and the normal subjects (30·2°C; $p<0.01$); temperatures of the latter two groups were not significantly different. Average temperatures during Medilog recording and during the cold stress session were significantly correlated ($r=0.38$; $p<0.01$). Average stress ratings of the patients with scleroderma during Medilog recording (34·2) were significantly higher than those of the patients with Raynaud's disease (23·4; $p<0.05$), which were in turn significantly higher than those of the normal subjects (13·5; $p<0.05$). There were no group differences in average ambient temperature or heart rate during Medilog recording.

Forty six vasospastic attacks were recorded in 16 patients with scleroderma, and 56 attacks were recorded in 12 patients with Raynaud's disease. Data obtained at the point of each attack were compared with those from the hour preceding and the hour after each attack. Significant ($p<0.01$) declines in finger and ambient temperatures accompanied attacks in both groups of patients (fig 3). Although reductions in finger temperature occurred in most attacks in the scleroderma (93·5%) and Raynaud's (82·1%) groups, declines in ambient temperature occurred less frequently ($\chi^2=5.57$; $p<0.02$) in attacks in the Raynaud's disease group (65·9%) than in attacks in the scleroderma group (87·0%). Significant ($p<0.05$) tachycardia occurred in most (76·1%) attacks in the scleroderma group but not in the Raynaud's disease group. Significant ($p<0.05$) tachycardia

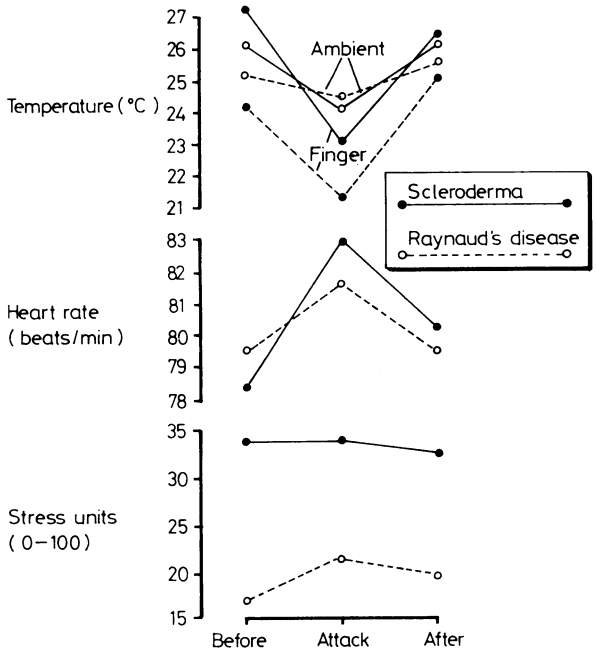

FIG 3—Finger temperature, ambient temperature, heart rate, and stress ratings before, during, and after vasospastic attacks.

(3·5 beats/min) did accompany those Raynaud's disease attacks which occurred above the average rating of stress. This occurred in 37% of the attacks. In patients with Raynaud's disease attacks occurring above the average stress rating were associated with higher finger temperatures than those occurring below it (22·7°C *v* 20·2°C; $p<0.05$; Student's *t* test); this was not so in the patients with scleroderma.

Discussion

In this investigation patients with Raynaud's disease had significantly lower finger temperatures and higher levels of reported stress than normal subjects. Significant increases in stress were reported in conjunction with vasospastic attacks in these patients. (It should be noted that the patients were instructed to estimate the amount of stress that they were experiencing just before the attacks.) Increases in stress ratings and heart rate occurred in 39% and 37% of attacks in the Raynaud's disease group. Declines in ambient temperature were not detected during 34% of attacks in that group. It is thus reasonable to infer that about one third of the attacks in our patients with Raynaud's disease were precipitated by emotional stress. This is consistent with the fact that emotional stress causes tachycardia and digital vasoconstriction[25 26] in normal subjects and with findings that anxiety and subjective ratings of stress are higher in patients with Raynaud's disease during symptomatic than asymptomatic periods.[16] In our study Raynaud's disease attacks which occurred above the average stress rating were accompanied by significantly higher finger temperatures than those occurring below it. Hence the addition of an emotionally stressful stimulus may cause an attack at a level of blood

flow which was insufficient to produce an attack in the absence of stress. Mittelmann and Wolff found an analogous relation in one patient with Raynaud's phenomenon in the laboratory.[14]

In contrast to the vasospastic attacks of Raynaud's disease, those occurring in scleroderma were almost always accompanied by declines in ambient temperature but not by increases in reported stress. Thus cold alone appears to be enough to trigger most attacks of Raynaud's phenomenon in scleroderma. The continually raised stress ratings of the patients with scleroderma reflect chronic and significant emotional stress. Other diseases, such as cancer, are associated with emotional stress[27 28] and it is not unreasonable to consider that a similar relation exists in scleroderma. The tachycardia accompanying Raynaud's phenomenon in scleroderma may indicate stress reactions which are caused by these attacks or by cold but are not discriminated by the patients.

Consistent with the hypothesis that patients with scleroderma have a different cold stress response from that of patients with Raynaud's disease are the results of our laboratory thermal stimulus procedure. There, exposure to a mild thermal stimulus produced increased frontalis muscle tension only in the patients with scleroderma. Since this increase occurred when the stimulus was warmest (30°C) and the average finger temperature of the patients (29·9°C) was near the point of thermoneutrality for skin,[29] it is unlikely that cold by itself caused this response. More probably this increase in muscle tension indicates a stress response to the threat of cold exposure. Tension of the frontalis muscle increases in response to the threat of electric shocks[30] and during difficult cognitive tasks.[31] If patients with scleroderma associate exposure to cold with tissue damage or pain, or both, it is possible that the expectation of this stimulus would be stressful.

Average levels of heart rate and skin conductance did not differ among the three groups in our study. Thus during non-attack periods evidence of generalised sympathetic hyperactivity (or hypoactivity) was not obtained in either group of patients. This does not agree with the results of Fries,[32] who found sympathetic hypoactivity as evidenced by increased skin resistance—that is, decreased conductance—in patients with scleroderma and those with Raynaud's phenomenon alone. This disparity may be explained by a methodological difference. Fries employed a simple ohmmeter to measure skin resistance rather than a constant current or constant voltage circuit. It has been shown[33] that failure to control the amount of current through the skin results in non-linear measurements in subjects with high skin resistance. We avoided this problem by using a constant voltage circuit. The higher average respiration rate found in our patients with scleroderma is most easily explained by impaired pulmonary function rather than by stress or increased sympathetic activity.[34]

In conclusion our investigation, using ambulatory monitoring techniques, verifies previous anecdotal evidence that the vasospastic attacks of Raynaud's disease are precipitated by cold or emotional stress, or both. In contrast, almost all attacks of Raynaud's phenomenon in scleroderma could be explained by cold provocation alone. It is possible that, since our patients with scleroderma experienced most of their vasospastic attacks in response to cold stress, the conditioning history of these patients is different from that of patients with Raynaud's disease, who may have attacks in the absence of cold. Thus patients with scleroderma show an aspect of the alarm reaction, increased muscle tension, before cold exposure, while patients with Raynaud's disease show no such response. Further research on the underlying mechanisms of vasospastic attacks, emotional stress, and scleroderma may elucidate relations among these entities.

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