Increased cutaneous vasoreactivity to cold in anorexia nervosa

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Summary
1. Hand blood flows in healthy young men and women and in patients with anorexia nervosa were measured in a warm environment by using venous occlusion plethysmography. The mean core temperature of each of the three groups was similar, but the male control subjects and the anorexic patients had significantly higher peripheral blood flows than the female control subjects.

2. Blood flows were determined in the hand after 6 min localized cooling of it at varying temperatures. The female control subjects and the majority of the anorexic patients had blood flows which were similar for a given temperature, and lay between the higher values of the male control subjects and the low values of the remaining anorexic patients.

3. Those patients whose vascular responses to cold were exaggerated were characterized clinically by severe and persistent signs of ischaemia of the extremities during subsequent rehabilitation, unlike the majority of patients whose peripheral circulation rapidly improved.

4. Cold thermal stimuli evoked marked falls in blood flow of the contralateral (non-cooled) hand in the male and female control subjects, but these responses were attenuated or absent in the anorexic patients. An altered set-point for vaso-motor thermoregulation in anorexia nervosa could explain these findings.

5. Plasma and whole-blood viscosity and erythrocyte deformability measured in a sample of the patients studied were similar to the values obtained from a sample of the control subjects.

6. It was concluded that the cutaneous vasoconstrictor responses to cold in the majority of the anorexic patients studied were quantitatively normal. The mechanism of the response, however, was different in that the vessels themselves were unusually reactive to cold. Increased cutaneous vasoreactivity to cold could contribute to the severe peripheral hypoperfusion observed in some anorexic patients.

Key words: anorexia nervosa, body temperature, cold, hand blood flow, Raynaud's phenomenon, thermoregulation, venous occlusion plethysmography.

Introduction
Cold hands and feet and peripheral cyanosis are common physical features of anorexia nervosa. Core temperatures of anorexia patients in the malnourished state are often subnormal and would be expected to evoke high levels of cutaneous vasoconstrictor tone as part of a thermoregulatory response to limit loss of body heat [1]. Certain observations on anorexic patients, however, suggest that the degree of peripheral vasoconstriction cannot always be fully accounted for by a low core temperature. Thus many patients who are observed during rehabilitation in hospital continue to display signs of peripheral vasospasm and are troubled by numb, blue extremities on cold exposure long after return of their body temperatures to normal. Moreover, Davies et al. [2] observed that hyperthermia induced in anorexic patients by exercise was, in a cool environment, associated with little rise in hand temperature. Thus the control of the peripheral blood flow of these patients seemed to be unusually sensitive to the
cool local temperatures. The incidences of Raynaud’s phenomenon and acrocyanosis have been reported to be higher in anorexia nervosa than in the general population [3], and there is evidence that in these syndromes the vessels of the extremities of some patients are abnormally sensitive to cold [4, 5].

These observations led us to postulate that the cutaneous circulation of the extremities of some anorexic patients might be more sensitive to the constrictor effect of localized cooling than normal. We have tested this hypothesis in the present study by measuring the change in hand blood flow produced by various degrees of localized cooling, and comparing the results obtained from anorexic patients with those from controls. By simultaneously measuring the change in blood flow produced in the contralateral (non-cooled) hand by the cold stimulus, it has been possible to estimate the extent to which the altered responses in anorexia are due to reflex rather than direct local effects. Since an abnormal blood viscosity has been demonstrated to occur in some patients with Raynaud’s phenomenon [6], the possibility that altered blood rheology contributes to the peripheral hypoperfusion of anorexic patients has also been examined in the present study.

Subjects and methods

We studied 14 patients (one male, 13 females) all within 10 days of their admission to the acute psychiatric ward. All conformed to the diagnostic criteria for anorexia nervosa described by Russell [7], and presented the vasoconstricted cyanotic extremities typical in the illness. Routine biochemical, haematological and radiological investigations had been performed before the tests to exclude systemic illnesses associated with vasoconstrictor syndromes. The mean age of the patients was 17 years and their mean weight was 38 kg. When studied, each was taking regular meals and none was receiving medication. Twenty healthy young adults (10 males, 10 females) acted as control subjects. Their mean weight was 60 kg and mean age was 20 years. None smoked or was taking medication at the time of the study.

Each study was performed in the morning on fasted subjects in a climactic chamber at 30°C (±1°C) ambient. Blood was taken from six patients (one male, five females) and six control subjects (one male, five females) for estimation of the following: packed cell volume, plasma and whole-blood absolute viscosities with the Contraves viscometer [8] at low and high shear rates (0.69, 2.3 and 94.0 s⁻¹ at 37°C), erythrocyte deformability [8] and plasma potassium and glucose concentrations. The following measurements were then performed on all 34 patients and control subjects. 1. Hand blood flow. This was measured simultaneously in both hands by a venous occlusion plethysmography technique modified from that of Barcroft & Swan [9]. Both plethysmographs were perfused with water at a constant flow and at a thermostatically controlled temperature. Blood flow was usually measured with both plethysmographs perfused with water at 32°C, though the water in the left plethysmograph could be rapidly varied between 12 and 32°C. 2. Temperature of the left index finger. A thermistor applied to the palmar surface of the finger was read to 0.1°C. 3. Mean skin temperature. Skin temperature was measured at six sites with a thermistor and weighted average of these values derived to obtain the mean skin temperature [10]. 4. Core temperature. A sublingual thermistor placed in the tightly closed mouth was used to estimate core temperature. The sublingual site is generally regarded as providing a less reliable estimate of core temperature than the other sites commonly chosen, i.e. rectal, tympanic or oesophageal, but none of the latter was acceptable to the patients. In a previous study [11] we showed that sublingual temperature was as valid an estimate of core temperature in malnourished subjects as for those of normal weight. Since the present study was designed to compare responses of patients with those of control subjects we have utilized sublingual temperatures, though it is accepted that these may not provide absolute values of core temperatures.

Initially the temperature and flow values rose in the warm environment until a plateau was achieved, at which point the values of core temperature, mean skin temperature, initial left index finger temperature and initial mean hand flow (the average of both hands) were measured. The left plethysmograph was then perfused at a constant rate with water at a lower preselected temperature for 6 min at which time hand flow was measured synchronously in both hands at 30 s intervals. The average of three values obtained at these intervals immediately after the cooling period was recorded for each hand as the flow at the final temperature of the plethysmograph, the latter being measured by a thermistor in the effluent. Note was made of the temperature of the left index finger at this temperature. Having restored the temperature of the left plethysmograph to 32°C, and after waiting for hand flows and finger temperature to return to initial values,
we repeated the procedure at a different pre-selected perfusion temperature. In certain patients, where the response to cooling was clearly grossly abnormal, the procedure was repeated at a third perfusion temperature.

After the study, as each patient regained weight she was examined regularly by an observer who had no knowledge of the laboratory findings. At each clinical assessment, evidence of improvement of the peripheral circulation was judged by noting the colour, temperature and sensory function of the patients' extremities. A final clinical assessment was made just before discharge, no patient being included in the results of the study who did not ultimately achieve her predicted standard weight.

Statistical analysis

Results are expressed as means ± SEM with ranges and the significance of differences was calculated by Student's t-test for unpaired data. Values of $P < 0.05$ were considered significant.

Results

The rheological and biochemical data obtained from the two subgroups of patients and control subjects are shown in Table 1. Absolute whole-blood viscosity values are presented for each of the three shear rates, together with the values corrected to a standard packed cell volume of 45%, eliminating cell population variation which affects viscosity. No significant differences between the two subgroups in the means of any of the measured variables were obtained.

Table 2 presents the data obtained from the temperature, hand flow and hand volume measurements of all the male and female control subjects and of all the patients. The initial hand flows of the male control subjects and anorexic patients were similar and both were significantly higher than those of the female control subjects (both $P < 0.02$). Mean skin temperatures of the male control subjects were significantly lower than those of both the female control subjects and the patients (both $P < 0.01$). The mean skin temperatures of the patients did not differ significantly from those of the female control subjects. The hand volumes of the female control subjects were similar to those of the patients, and both were significantly less than those of the male control subjects (both $P < 0.01$). Core temperatures and initial index finger temperatures were similar in all three groups.

Fig. 1 (male and female control subjects) and Fig. 2 (patients) depict the values for blood flow obtained in the left (cooled) hand after 6 min perfusion plotted against final plethysmograph temperature (water temperature). Lines of regression, calculated from the data, are plotted for the two control groups on Fig. 1 and for nine of the anorexic patients (eight females, one male) in Fig. 2. An analysis of variance to compare the lines of regression for female control subjects and this group of patients failed to show a significant difference between the two responses ($F = 0.22$, $P > 0.1$). The responses of the remaining five female patients to cold stimuli were clearly exaggerated and each of these patients was exposed to three different stimulus intensities. Their responses are plotted as the lower group in

<table>
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<tr>
<th>Table 1. Values of physicochemical measurements made on blood from six control subjects and six patients with anorexia nervosa</th>
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<td>Results are means ± SEM with ranges in parentheses.</td>
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<td>Control subjects (five females, one male)</td>
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<td>Packed cell volume (%)</td>
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<td>Plasma viscosity (cP) *</td>
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<td>Erythrocyte deformability †</td>
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<td>Plasma potassium (mmol/l)</td>
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<td>Plasma glucose (mmol/l)</td>
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* cP (centipoise) = 10⁻⁴ N s m⁻².
† Results from five patients.
TABLE 2. Core and cutaneous temperatures, hand volumes and blood flows of control subjects and patients with anorexia

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<th>Control subjects</th>
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<td>Mean initial hand blood flow (ml min⁻¹ 100 ml⁻¹)</td>
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N.S., Not significant (P > 0.05).

Fig. 1. Hand blood flows after 6 min localized cooling at various water temperatures. ●, Male control subjects; ○, Female control subjects.

Fig. 2, and the calculated line of regression clearly differs from that of the other members of the anorexic group. The results of the clinical observations performed independently after the laboratory study showed that these five patients, unlike the majority of those tested, continued to be troubled with cold hands during their admission and on discharge still had evidence of a vasoconstrictor syndrome.

Fig. 3 shows the change in flow occurring in
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12 14 16 18 20 22 24 26 28

Water temperature (°C)

0 2 4 6 8 10 12 14 16

Blood flow in cooled hand (ml min⁻¹ 100 ml⁻¹)

Fig. 2. Hand blood flows after 6 min localized cooling at various water temperatures. □, Anorexic patients (five females) with persistently cold extremities; ■, anorexic patients (eight females, one male) whose peripheral circulation showed clinical improvement with weight gain.

Discussion

The peripheral hypoperfusion underlying the cold cyanosed extremities of the anorexic patient has generally been considered to be entirely vasoconstrictive in origin. Blood flow is, however, also dependent on viscosity, and an abnormally high blood viscosity in anorexic patients could contribute to the hypoperfusion, particularly if the increase was more marked at low temperatures. Such a mechanism has been implicated in the pathophysiology of Raynaud's syndrome and an increased whole-blood viscosity measured at 37°C has been reported in studies on patients with Raynaud's disease [6, 12]. In addition, an association between peripheral ischaemia and a low erythrocyte deformability has been described [8]. In the present study, however, there were no significant differences in the values for whole-blood viscosity or erythrocyte deformability obtained from the six anorexic patients or the six control subjects (Table 1). This indicates that altered haemorheology is unlikely to have contributed to the peripheral ischaemia observed in the patients we studied.

The blood flow responses observed in the present study have been attributed solely to changes in cutaneous vascular resistance. Due to the nature of the experimental technique which necessitated bilateral venous occlusion, it was not possible to measure brachial arterial blood pressure during the flow measurements. In a previous study (P. Luck & A. Wakeling, unpublished work) involving 10 malnourished anorexic patients (one male, nine females) under similar environmental conditions (30°C) we observed no significant changes in the mean arterial blood pressures of the patients on 6 min immersion of a gloved hand in stirred water at 15°C. A similar lack of blood pressure response was obtained in
10 sex-matched control subjects on cold immersion. These results suggest that hand cooling over the range of temperatures employed in the present study might not be expected to alter mean blood pressures significantly in any of the groups investigated, though this evidence, it is admitted, is only indirect.

Abnormally low values for plasma glucose and potassium concentrations have been reported previously in anorexia nervosa [13]. Both these factors may affect circulatory responses. In the present study, however, the anorexic patients were taking regular meals and, as Table 1 shows, plasma concentrations of glucose and potassium in the anorexic subgroup were similar to those of the control subjects. Thus neither hypokalaemia nor hypoglycaemic sympathoadrenal stimulation could account for the altered responses observed in the anorexic patients.

Moderate localized cooling of the skin (down to 14°C) normally causes vasospasm of the subjacent vessels accompanied by a generalized cutaneous vasoconstriction of lower intensity and shorter duration. Cold directly stimulates cutaneous vessels to constrict, but the power of the response is augmented by local sympathetic vasomotor activity [14, 15]. Thus the cutaneous vasospasm induced by localized cooling has two interacting components. The vasoconstrictor responses observed in the non-cooled hands have been used here to determine the extent to which the local responses to cooling result from reflex effects, thereby separating these two components.

**FIG. 3.** Change in blood flow of non-cooled hand after 6 min contralateral cooling at various water temperatures. ●, Male control subjects; ○, female control subjects; □, anorexic patients (entire group).
Fig. 1 clearly shows a shift to the left for male control subjects of the blood flow responses to direct hand cooling. The reduced responsiveness in males is well documented [16] and is probably due to lower levels of cutaneous sympathetic discharges (and therefore lower sympathetic potentiation of the cold stimulus) which obtain in men compared with women at similar body temperatures [17]. The change in flow of the non-cooled hand which reflects the increase in vasomotor discharge reflexly evoked by cooling was often evanescent and did not permit differences in male/female sympathetic responses to be distinguished (Fig. 3). However, the initial hand flow was significantly higher for men than for female control subjects, signifying lower initial sympathetic vasomotor activity in the men.

Fig. 2 shows that the effect of local cooling on the hand flow of anorexic patients was similar to that of the female control subjects (upper plots) or more pronounced (lower plots). Further evidence that the effect of cold in causing local vasospasm was on average more potent in the patients than the female control subjects is provided by a comparison of the index finger temperatures observed in these two groups when matched for plethysmograph temperature (Fig. 4). Finger temperatures were on average lower for the patients than the female controls and, since the hand volumes were similar in both groups (Table 2), blood flows must on average have been lower.

Fig. 3 shows, however, that the cold stimuli in the patients were associated with little or no generalized increase in vasoconstrictor tone as measured by the vasoconstrictor responses of the non-cooled hands. To account for the quantitatively similar local response to cooling in the absence of generalized vasoconstriction, it is postulated that a qualitative difference exists and this represents an increase in the reactivity to cold of the vessels themselves. The significance of this altered vasoreactivity is suggested by the marked sensitivity to cold exhibited by the group of five female patients whose responses form the lower plots (□) of Fig. 2. The results of the clinical observations performed independently after the laboratory study showed that these five patients, unlike the larger group of patients, continued to be troubled by cold extremities throughout their
admission and when discharged were all noted as still having signs and symptoms of a vasoconstrictor syndrome.

The mechanism underlying the increased vaso-reactivity to cold of anorexic patients is unknown. It was not possible in our study to include a further group of control subjects with no known psychiatric history who had experienced a similar degree of recent starvation to the patients. Thus we cannot exclude the possibility that the altered responses described may result directly from malnutrition. However, we suggest that the degree of clinical severity of the vasoconstrictor syndrome of the patients was related directly to the level of the increase in cutaneous vasoreactivity. The stability of the clinical features of the five patients described above after weight gain therefore suggests that factors other than malnutrition may operate to promote the altered vascular responsiveness of the disease.

The foregoing observations allow a simple formulation to be made about the disturbances of control of the peripheral circulation which can occur in the disease, and may explain some of the puzzling observations described earlier in this paper. At room temperature it has been shown that the subnormal core temperature of the malnourished anorexic patient evokes a high level of sympathetic vasomotor discharge to the skin [11]. Potentiation of this sympathetic activity by the abnormal vasoreactivity to cold discussed above would intensify the resulting vasoconstriction and produce the typical ischaemic extremities of the anorexic patient. These patients in whom cutaneous vasoreactivity is grossly abnormal would continue to exhibit excessive peripheral vasospasm on cold exposure despite elevation of metabolic rates and core temperatures to normal. Finally, the selective vasoconstriction of the extremities observed in some patients during hyperthermia induced by exercise [2] can be explained by abnormal sensitivity of the cutaneous vessels of the extremities to the cool temperature of the environment.

The reflex vasoconstrictor responses which occur in the non-cooled hands (Fig. 3) are components of the thermoregulatory reactions evoked by changes in cutaneous temperature. Analysis of these responses in the patients and the control subjects might therefore provide evidence of a thermoregulatory disturbance in anorexia nervosa, such as has been postulated to occur in the disease [18]. Hammel et al. [19] have shown that a thermoregulatory response \( R \) is proportional to the difference between the actual hypothalamic temperature \( T_h \) and the set-point temperature \( T_{set} \) at which internal body temperature is regulated: \( R \propto (T_h - T_{set}) \).

The set-point temperature is adjustable and influenced by several factors including input from cutaneous thermal sensors. Wenger et al. [20] have studied the relation in man between thermoregulatory blood flow \( F \) and core \( T_c \) and mean skin temperatures \( T_{sk} \). Applying their results to the adjustable set-point model gives Eqs. (1) and (2),

\[
F = a(T_c - T'_o) \quad (1)
\]
\[
T'_o = T_o + b (33^\circ C - T_{sk}) \quad (2)
\]

where \( T'_o \) is the adjustable core set-point temperature for vasodilatation, \( T_o \) is a constant term representing the core temperature vasodilator threshold computed for a mean skin temperature of 33\(^\circ\)C, \( a \) is a constant factor representing the sensitivity of the flow to changes in core temperature and \( b \) is a constant factor representing the sensitivity of the set-point adjustment response to changes of mean skin temperature from 33\(^\circ\)C. Thus changes in mean skin temperature may be considered to evoke flow responses by shifting the core set-point temperature, thereby generating an error signal \( (T_e - T'_o) \).

From the above it follows that the reduction in flow evoked in the non-cooled hand by contralateral cooling, in the present study, is determined by: (1) the change in core temperature produced by the cold stimulus; (2) the intensity of the cold stimulus, which will determine \( T_{sk} \); (3) the value of the constant \( b \), which will determine the rise of the set-point for a given fall in \( T_{sk} \).

Core temperatures of the anorexic patients were similar to those of both control groups in the present study (Table 2). Moreover, changes in core temperature were never observed during any period of cooling, suggesting that this factor cannot explain the altered responses of the patients. Similarly, the attenuated responses of the patients cannot be attributed to a reduced intensity of the cold stimulus, since skin temperatures measured at the finger of the cooled hands of the patients were similar to or lower than those of the control groups of subjects when matched for plethysmograph temperatures (Fig. 4), and the patients' hand volumes were similar to those of the female control subjects (Table 2).

An abnormally low sensitivity, \( b \), of the set-point adjustment response to changes in mean skin temperature in anorexic patients could explain our findings. This could account for the attenuated reflex responses observed in our study and could explain the results of Freyschuss et al. [21]. They showed that patients with anorexia nervosa exhibited reduced thermoregulatory vasodilatation when exposed to indirect radiant heating compared with control subjects. There exists, however, a different mechanism by which
the diminished vasoconstrictor reflex responses of our patients can be explained. In a previous study [11] we showed that the core temperature for thermoregulatory vasodilatation at a mean skin temperature of 33°C was lower for anorexic patients than for control subjects. A low value for $T_c$ in Eqn. (2) might cause an attenuation of the vasoconstrictor response to a peripheral cold stimulus by generating a high error signal $(T_c - T'_c)$ in favour of vasodilatation. The diminished vasoconstrictor responses to cutaneous cold stimuli observed in normal subjects with elevated stimulus by generating a high error signal $(T_c - T'_c)$ in favour of vasodilatation. The diminished vasoconstrictor responses to cutaneous cold stimuli observed in normal subjects with elevated core temperatures would be analogous to the above, though the high central error signal here is different in origin. Further information regarding the relation between thermoregulatory blood flow and core and peripheral temperatures is required before a decision can be made between these alternative mechanisms, though it is equally possible that a combination of both contributes to the thermoregulatory disturbances of the disease.

Acknowledgments
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