
The effect of a 48 h fast on the thermoregulatory responses to graded cooling in man

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Summary

1. The thermoregulatory responses to graded cooling were measured in 11 healthy male subjects after a 12 h fast and after a 48 h fast. The cooling stimulus was produced by changing the temperature of the skin of the trunk and legs with a water-perfused suit. Five levels of skin temperature from 35.5 to 24°C were applied on each occasion.

2. After a 12 h fast, core temperature was maintained during cooling. This maintenance of core temperature was associated with an increase in metabolic rate and a reduction in blood flow to the hand and to the forearm.

3. After 48 h of fasting, the subjects could not maintain core temperature during cooling, and a decrease of 0.36±0.05°C occurred as the suit temperature was reduced from 35.9 to 24°C. Metabolic rate was slightly higher after the 48 h fast than after the 12 h fast, but similar increases in metabolic rate were observed during cooling.

4. Vasoconstriction in the hand was initially less after a 48 h fast than after a 12 h fast, but at the lowest suit temperature, hand blood flow was similar, and low, on both occasions. After 48 h of fasting, forearm blood flow was elevated at all suit temperatures, being approximately twice the level recorded after the 12 h fast.

5. Venous plasma noradrenaline levels did not change during cooling after the 12 h fast, whilst after 48 h of fasting a significant increase in noradrenaline level was observed at the lowest suit temperature.

6. The results of this study provide further evidence that fasting induces an impairment of autonomic reflex mechanisms, but it is not clear whether this is due to a suppression of sympathetic nervous activity.

Key words: fasting, metabolic rate, peripheral blood flow, plasma noradrenaline, thermoregulation.

Introduction

From work in rats there is evidence that underfeeding causes inhibition of sympatho-adrenal activity, while overfeeding has a stimulant effect [1]. In the former case there is a decrease in systemic arterial blood pressure, particularly in spontaneously hypertensive rats [2]. Recent observations in normal human subjects indicate that acute underfeeding reduces sympathetic efferent activity and blood pressure [3] and that acute starvation impairs the control of blood pressure [4]. Such an effect could explain the hypertensive effect of dieting in obese individuals [5].

If restricted energy intake has a widespread effect on sympatho-adrenal activity then it is feasible that thermoregulation would be compromised under these circumstances due to impaired cutaneous vasoconstriction and/or thermogenesis. We have examined these possibilities in the present work.

Methods

Subjects

Eleven male subjects (aged 22-34 years) took part in the study after giving their written, informed consent; the investigation had been
approved by the Medical School Ethical Committee. None of the subjects was obese (body fat was estimated from the sum of four skinfold thicknesses [6]) or on medication of any kind. Each subject was studied on two occasions: once after an overnight fast (12 h) and once after a 48 h fast during which time only water or low-calorie carbonated drinks (One-cal, Energen Ltd) and sodium chloride (85 mmol/24 h) were consumed.

Protocol

Thermoregulatory responses to graded cooling were assessed by using a water-perfused suit [7] connected to a Churchill Thermocirculating pump (05/CTVCM) to change the skin temperature of the legs and trunk. At each of five different levels of skin temperature, measurements of core temperature, metabolic rate, peripheral blood flows, arterial blood pressures and heart rate were made.

Experiments were performed in a temperature-controlled laboratory (25°C), with subjects resting supine on a bed, wearing shorts and the water-perfused suit, and covered with a blanket. Both arms were outside the suit and blanket to enable peripheral blood flows and blood pressure to be measured. Core temperature was recorded in the left ear with a zero-gradient aural thermistor [8]; heart rate was recorded from the ECG and blood pressures were measured by auscultation in the left arm. Blood flows in the right forearm and left hand were measured by means of venous occlusion plethysmography using a mercury-in-silastic strain gauge around the forearm [9] and a water displacement chamber set at 34°C for the hand [10]. A cannula (venflon) was placed in a vein in the left antecubital fossa and was maintained patent by the infusion of 0.154 mmol/l sodium chloride solution (0.3 ml/min).

Measurements of respiratory gas exchange were made with a continuous flow system such that the subject's head was enclosed in a canopy through which room air was drawn at approximately 60 litres/min (with an industrial vacuum cleaner, Electrolux Z 73). The flow rate of the gas leaving the canopy was measured with a mass flowmeter (EAHL 5X, Teledyne Hastings-Raydist, Hampton, Virginia, U.S.A.) and the gas was then drawn through mixing chambers [11] before being continuously sampled for oxygen (Servomex OA540, Taylor Instrument Analytics Ltd, Crowborough, Sussex, U.K.) and carbon dioxide (901 MK II, PK Morgan Ltd, Chatham, Kent, U.K.). The gas analysers were calibrated with standard gases (compressed air and a gas mixture containing 20% oxygen and 1% carbon dioxide) that had previously been measured with a Lloyd-Haldane apparatus. The electrical outputs from the analysers were recorded on potentiometric recorders. The mean concentrations of oxygen and carbon dioxide were determined from planimetry of the chart recordings and metabolic rate was then estimated according to Weir [12].

The suit was perfused with a mixture of antifreeze and water (30% v/v Thermocal B, Cargo Fleet Chemical Co, Stockton, U.K.) at flow rates between 1.2 and 1.6 litres/min, but the actual flow rates were not measured throughout every experiment. The temperature of the fluid flowing into the suit was measured with a thermocouple (copper-constantan; reference junction in melting ice) connected to a potentiometric recorder (BS316, 12 channel recorder; Bryans-Southern, Mitchum, Surrey, U.K.). Each experiment started with the suit inlet temperature at 35.0-35.6°C. This suit temperature was chosen to represent a thermoneutral environment. In preliminary experiments we had established that core temperature and peripheral blood flow were stable during at least 1 h exposure to this suit temperature and all values were similar to those obtained when subjects wearing shorts only were exposed to still, dry air at 30-31°C (the thermoneutral zone for adult subjects). A 20 min period of equilibration was allowed before the measurements of cardiovascular variables and metabolic rate were made and (from seven subjects) a blood sample was taken. The suit inlet temperature was then reduced in four steps of approximately 3°C each; a period of 10 min was necessary before a stable inlet temperature was achieved at each step; after a further 10 min, during which time skin temperatures were stable, measurements of metabolic rate and peripheral blood flow were made and a blood sample was taken.

The blood samples were immediately centrifuged at 4°C and the plasma was removed and stored at −80°C before determination of noradrenaline content by high-performance liquid chromatography with electrochemical detection [13].

Statistics

The responses to cooling were analysed with the Wilcoxon matched-pairs signed-rank test.

Results

Core temperature (Fig. 1)

When the suit was perfused with water at 35.5-35.9°C, there was no significant difference
Fasting and thermoregulation

Fig. 1. Effect of reducing the perfusion temperature of the suit on core temperature after a 12 h fast (●) and after a 48 h fast (○). Values are mean ±1 SEM, n = 11. Core temperature was maintained during cooling after a 12 h fast. After a 48 h fast core temperature fell during cooling and was significantly lower than after a 12 h fast at the lowest suit temperature (*P < 0.05).

between core temperature after a 12 h fast and after a 48 h fast. After a 12 h fast, reductions in suit temperature to a final value of 24°C produced minimal disturbance of core temperature [mean fall in core temperature was 0.03 ± 0.05 (SEM)°C]. In contrast, when the subjects had fasted for 48 h there was a progressive decrease in core temperature when the suit temperature was reduced; overall, core temperature fell by 0.36 ± 0.05°C (P < 0.01).

In Fig. 2 the percentage body fat (estimated from skinfold measurements) is plotted against the change in core temperature which was recorded between the highest and lowest suit temperatures on the two occasions. After a 12 h fast there was no correlation between the change in core temperature and the percentage fatness (r = -0.23, NS). In contrast, after a 48 h fast there was a significant correlation (r = 0.93, P < 0.01) between these variables, the thinnest subjects showing the greatest reduction in core temperature.

Metabolic rate (Fig. 3)

After a 12 h fast, metabolic rate was 5.10 ± 0.18 kJ/min when the suit temperature was 35.6°C. As the perfusion temperature was reduced, metabolic rate rose to 5.74 ± 0.23 kJ/min at a suit temperature of 23.9°C (Fig. 3a). This rise in metabolic rate was not accompanied by visible shivering, but no recordings of ECG activity were made.

Following a 48 h fast, metabolic rate was 5.41 ± 0.14 kJ/min when the suit temperature was 35.9°C (P < 0.05 compared with the corresponding value after a 12 h fast). Metabolic rate rose with each reduction in perfusion temperature, such that with a suit temperature of 24°C the metabolic rate was 6.33 ± 0.26 kJ/min (P < 0.05 compared with the corresponding value after a 12 h fast). At this lowest suit temperature, shivering was observed in some of the subjects.

Although the pattern of change of metabolic rate relative to suit temperature appeared to be similar on the two occasions, this occurred against the background of different changes of core temperature. Thus, when the metabolic rate responses were considered in relation to core temperature (Fig. 3b), a different pattern was observed after the 48 h fast compared with that after the 12 h fast. After a 12 h fast, the marked increase in metabolic rate during cooling of the skin was associated with very small changes in core temperature. In fact, the first reduction in suit temperature was accompanied by a slight increase in core temperature and a small increase in metabolic rate. In contrast, after a 48 h fast there was very little change in metabolic rate during the initial stages of cooling, when core
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6.2 0.4 5 5.2 5.0

Suit temperature (°C)

5.0 5.2 5.4 5.6 5.8 6.0 6.2 6.4

Metabolic rate (kJ/min)

24 26 28 30 32 34 36

(a)

FIG. 3. Effect of reducing suit perfusion temperature (a) on metabolic rate after a 12 h fast (●) and after a 48 h fast (○). Values are mean ± 1 SEM, n = 11. After a 12 h fast, metabolic rate rose progressively as the suit temperature was reduced. After a 48 h fast, metabolic rate was significantly higher than after a 12 h fast at the highest and at the lowest suit temperatures (*P < 0.05). In (b), the metabolic rate at each of the five suit temperatures is plotted against the core temperature recorded at each suit temperature, for the 12 h fast (●) and the 48 h fast (○).

when the suit temperature was 35.6°C. A decrease in the suit temperature to 32.9°C was accompanied by a slight reduction in hand blood flow (to 12.1 ± 1.7 ml min⁻¹ 100 ml⁻¹ of limb, P < 0.05 compared with the value at a suit temperature of 35.6°C). The most marked decrease in hand blood flow occurred as the suit temperature was then reduced to 26.4°C (hand blood flow, 2.9 ± 0.9 ml min⁻¹ 100 ml⁻¹ of limb, Fig. 4a).

Following the 48 h fast, hand blood flow was similar (at all perfusion temperatures) to that recorded after a 12 h fast. There was no change in hand blood flow after the first reduction in suit temperature (13.7 ± 2.0 at 35.9°C compared with 13.5 ± 2.1 ml min⁻¹ 100 ml⁻¹ of limb at 32.6°C) but thereafter, hand blood flow fell as suit temperature was reduced (Fig. 4a).

In both phases of the experiment, the decreases in hand blood flow were due to marked increases in vascular resistance; the absolute values were not different on the two occasions (6.9 ± 0.8 up to 88 ± 12 arbitrary units after 12 h fasting vs 7.9 ± 1.3 up to 130 ± 30 arbitrary units after 48 h fasting).

Although resting hand blood flow and the responses to a reduction in suit temperature were similar after fasts of 12 and 48 h, this was against the background of the different responses of central body temperature to the procedure under the two conditions. Thus the pattern of change of hand blood flow relative to central body temperature was different after 12 h and 48 h fasting (Fig. 4b).

Forearm blood flow. After a 12 h fast, forearm blood flow was 3.3 ± 0.3 ml min⁻¹ 100 ml⁻¹ of limb at a suit temperature of 35.6°C and did not change as the suit temperature was reduced to 29.7°C. Further reduction in suit temperature was accompanied by a decrease in forearm blood flow, to 2.5 ± 0.3 at 26.4°C and to 1.8 ± 0.2 ml min⁻¹ 100 ml⁻¹ of limb at 23.9°C (Fig. 4c). This decrease in forearm blood flow was due to an increase in vascular resistance from 31.9 ± 3.5 (arbitrary units) at 29.7°C to 56.3 ± 6.8 at 23.9°C.

After a 48 h fast, forearm blood flow was significantly higher than after a 12 h fast at all suit temperatures (P < 0.01); this was due to significantly lower vascular resistance after a 48 h fast (P < 0.01). As the suit temperature was reduced from 35.9 to 29.2°C there was an insignificant increase in forearm blood flow from 6.6 ± 0.9 to 7.2 ± 1.5 ml min⁻¹ 100 ml⁻¹ of limb. Thereafter, reductions in suit temperature were accompanied by decreases in forearm blood flow (to 4.9 ± 0.7 at 26.3°C and to 3.7 ± 0.5 ml min⁻¹ 100 ml⁻¹ of limb at 24°C, Fig. 4c) and increases in vascular resistance.

Peripheral blood flows (Fig. 4)

Hand blood flow. After a 12 h fast, hand blood flow was 14.4 ± 2.3 ml min⁻¹ 100 ml⁻¹ of limb temperature had decreased by 0.16°C, whereas in the later stages of the experiment a further fall in core temperature of 0.19°C was accompanied by a marked increase in metabolic rate.

Peripheral blood flows (Fig. 4)

Hand blood flow. After a 12 h fast, hand blood flow was 14.4 ± 2.3 ml min⁻¹ 100 ml⁻¹ of limb
The different pattern of response of forearm blood flow to the experimental procedure on the two occasions is accentuated by considering the relation between forearm blood flow and central body temperature (Fig. 4d).

Heart rate and blood pressure

After a 12 h fast, progressive cooling was accompanied by a decrease in heart rate, from 66.8 ± 2.6 (at 35.6°C) to 56.4 ± 2.6 beats/min (at 23.9°C), and an increase in blood pressure from 113 ± 3/69 ± 2 to 122 ± 5/79 ± 2 mmHg. After a 48 h fast, a similar pattern of change in heart rate was observed during cooling, but the absolute levels were significantly (P < 0.05) higher than after a 12 h fast (74.7 ± 2.7 beats/min at a suit temperature of 35.9°C, 62.7 ± 4.3 at 24°C). At each suit temperature, the diastolic blood pressures after a 48 h fast were similar to the...
values recorded after a 12 h fast, but systolic blood pressure was significantly elevated after a 48 h fast (123 ± 2 mmHg at 35.9°C, 133 ± 6 at 24°C; *P* < 0.05 for both values when compared with the corresponding values after a 12 h fast).

**Plasma noradrenaline (Table 1)**

After a 12 h fast, venous plasma noradrenaline values fell slightly, but insignificantly, as the suit temperature was reduced from 35.6 to 32.9°C. Thereafter, the plasma noradrenaline levels remained at approximately 1 nmol/l as the suit temperature was reduced further.

After a 48 h fast the plasma noradrenaline levels were similar to those measured after a 12 h fast, except at the lowest suit temperature when the values after a 48 h fast (1.78 ± 0.78 nmol/l) were significantly higher than those after a 12 h fast (1.05 ± 0.25 nmol/l, *P* < 0.05).

**Discussion**

The main finding from the present study was that during cooling of the skin, central body temperature was less well-maintained after a 48 h fast than after a 12 h fast. There was an indication that this abnormality was more marked in the individuals with less body fat (i.e. the less well insulated). However, the fall in central body temperature was not due to impaired heat production, since this variable had higher values under all conditions in the 48 h fasted compared with the 12 h fasted state. Interpretation of these data is complicated by the observation that with the lower suit temperatures some subjects shivered when fasted for 48 h whereas they did not do so after a 12 h fast.

The observation that resting heat production was increased after a 48 h fast compared with a 12 h fast is inconsistent with the proposition that sympato-adrenal activity is reduced by underfeeding. However, it is feasible that the elevation in heat production occurred in response to a factor other than sympato-adrenal activity. For example the fasted state could have rendered the subjects more responsive to some non-specific stress imposed by the conditions in which the measurements were made. However, this is unlikely since all subjects were well acquainted with the methods used before they participated in this study, and several had fasted in previous studies. An increase in metabolic rate during the first few days of underfeeding was seen in the early studies of Benedict et al. [14], who used continuous, direct calorimetry.

The finding that venous plasma noradrenaline levels were not significantly reduced following the longer fast also indicates that sympato-adrenal activity may not have been decreased. This interpretation is reinforced when one considers the forearm blood flow values on the two occasions. After a 48 h fast the forearm blood flow was approximately double the value recorded after a 12 h fast, thus the similar venous plasma noradrenaline levels might have reflected different rates of noradrenaline release from the sympatetic nerves. The only significant difference in plasma noradrenaline levels was seen at the lowest suit temperature, when higher values were recorded in the 48 h fasted state. However, since central body temperature was lower under these conditions the ‘drive’ for sympato-adrenal activity was probably greater and thus assessment of relative sympato-adrenal activity under the two conditions is difficult. Furthermore, a dissociation between sympathetic nervous activity and plasma noradrenaline levels has been demonstrated [15, 16], but it is not known whether this applies to the present experimental situation.

From our experiments the fall in central body temperature with cooling in the 48 h fasted state could be explained by the increased forearm blood flow, which is consistent with reduced sympathetic efferent activity. However, this effect was not generalized because baseline hand blood flows were similar in the 12 h and 48 h fasted states. But in the 48 h fasted state there was an indication that reflex vasoconstriction in the hand was im-

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**Table 1. Venous plasma noradrenaline levels (nmol/l, mean ± 1 SEM, n = 7) during cooling after a 12 h fast and after a 48 h fast**

<table>
<thead>
<tr>
<th>Suit temperature (°C)</th>
<th>Plasma noradrenaline (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.6-35.9</td>
<td>1.76 ± 0.50</td>
</tr>
<tr>
<td>32.6-32.9</td>
<td>1.00 ± 0.21</td>
</tr>
<tr>
<td>29.2-29.7</td>
<td>0.90 ± 0.15</td>
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<tr>
<td>26.3-26.4</td>
<td>1.10 ± 0.22</td>
</tr>
<tr>
<td>23.9-24.0</td>
<td>1.05 ± 0.25</td>
</tr>
<tr>
<td>12 h fast</td>
<td></td>
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<tr>
<td>48 h fast</td>
<td>1.46 ± 0.41</td>
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<tr>
<td></td>
<td>1.04 ± 0.19</td>
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<tr>
<td></td>
<td>1.12 ± 0.16</td>
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<tr>
<td></td>
<td>1.36 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>1.78* ± 0.28</td>
</tr>
</tbody>
</table>

* Significantly different from the value after a 12 h fast, *P* < 0.05.
paired since the initial cooling step evoked no change in blood flow, whereas there was a significant response after the 12 h fast.

With cooling, under both conditions, the reduction in hand blood flow occurred earlier than the reduction in forearm blood flow. Since reflex vasoconstriction in the forearm in response to cooling is confined to skin [17], then these observations are consistent with cutaneous vasoconstriction in hand and forearm being mediated by mechanisms with different thresholds.

We have commented elsewhere [14] on the increased forearm blood flow following a 48 h fast and the fact that this observation is not consistent with volume depletion consequent upon starvation. In that study we were unable to localize the increased forearm blood flow to cutaneous or muscular beds. However, in the present study the maximum reduction in forearm blood with cooling was 1.5 ml min\(^{-1}\) 100 ml\(^{-1}\) of limb after a 12 h fast whereas it was 2.9 ml min\(^{-1}\) 100 ml\(^{-1}\) of limb after a 48 h fast. If we can assume that body cooling causes reflex vasoconstriction only in the skin of the forearm under the two conditions then it follows that at least part of the elevated forearm blood flow in the 48 h fasted state must have been through skin. If this cutaneous hyperaemia occurred also in the trunk and legs it could readily explain the increased heat loss observed in the 48 h fasted state.

Disturbances of thermoregulation have been observed in at least two other situations of undernutrition, both involving chronic underfeeding rather than acute starvation. Malnourished infants have been shown to be unable to mount a thermogenic response to cold exposure and hence their core temperature falls [18]. This impairment of thermoregulation disappeared after the infants had been refed and was attributed to an atrophy of their main thermogenic tissues (brown adipose tissue) due to a low food intake [18]. However, recent studies in animals have shown that underfeeding also decreases the level of sympathetic efferent activity to brown adipose tissue [19], thus, the deficient thermogenesis in the chronically undernourished infants may have been due to the ineffective stimulation of a reduced mass of tissue.

The second example is in patients with anorexia nervosa, who have an enhanced response to local cooling but show impaired reflex hand vasoconstriction when the contralateral hand is cooled [20]. It is not known whether this impaired thermoregulatory reflex is a reversible consequence of the undernutrition or whether it is secondary to hypothalamic damage in these patients.

In summary, the present study has demonstrated that a 48 h fast impairs thermoregulation in young healthy subjects. When considered together with our previous demonstration that fasting impairs blood pressure regulation in similar subjects, it would appear that a generalized disturbance of autonomic function occurs as a consequence of such fasting. A complication of these studies is that, with regard both to blood pressure regulation and temperature regulation, autonomic function was disturbed and blood pressure and body temperature were poorly controlled, but there was no reduction in venous plasma noradrenaline levels. Although this could be interpreted as indicating that the activity of the sympathetic nervous system is unaffected by fasting, direct assessments of sympathetic nervous activity, noradrenaline kinetics in the forearm and in the whole body, and end-organ sensitivity to catecholamines, must be made before any firm conclusions can be drawn. It remains to be established whether more prolonged periods of less severe undernutrition impair autonomic function in a similar manner, but it is interesting to note that thin undernourished, elderly patients admitted to hospital with fractured femur have lower core temperatures than normal weight elderly patients with similar fractures [21].

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### References


