A paradoxical increase in resting energy expenditure in malnourished patients near death: the king penguin syndrome

Daniel Rigaud, Jacqueline Hassid, Alain Meulemans, Anne Thérèse Poupard, and Alain Boulier

ABSTRACT
Background: The metabolic expression of extreme starvation on the verge of death is unknown in humans.
Objective: The objective was to compare the resting energy expenditure (REE) of 5 extremely malnourished dying patients [body mass index (in kg/m\(^2\)): 9.77 ± 0.1] with that of 16 less-malnourished anorexia nervosa (AN) patients.
Design: REE was measured by indirect calorimetry and body composition was measured by anthropometry and dual-frequency bioelectrical impedance analysis. Fasting serum insulin, thyroid hormone, and catecholamine concentrations were also determined.
Results: At the start of refeeding, REE was high in each of the 5 extremely malnourished dying patients, whereas it was low in the 16 AN patients (\(\bar{x}\) ± SD: 5174 ± 391 kJ/d compared with 3844 ± 619 kJ/d; \(P < 0.05\)). The high REE value in the 5 extremely malnourished dying patients was associated with almost no fat mass (FM), high urinary nitrogen loss (16.4 ± 2.9 g/d), low serum fatty acid concentrations (0.36 ± 0.23 mmol/L), and low or normal serum insulin, thyroid hormone, and catecholamine concentrations. During the first 2–4 wk of refeeding, REE and nitrogen loss decreased, whereas fatty acid concentrations increased in each of the 4 surviving patients; REE and urinary nitrogen output increased in the 16 AN patients.
Conclusion: In malnourished persons near death, there is an increase in REE and in protein catabolism. The reason for this increase is unknown but could relate to consumption of the last mobilizable muscle mass and to diseased cellular membranes. Am J Clin Nutr 2000;72:355–60.

KEY WORDS Resting energy expenditure, malnutrition, oxygen consumption, anorexia nervosa, women

INTRODUCTION
Resting energy expenditure (REE) decreases after a few days’ starvation in animals (1, 2) and humans (3, 4) and remains low during long-lasting starvation (3, 4) and marasmic malnutrition (5, 6). This may be due to the decrease in fat-free mass (FFM) associated with weight loss and to the better metabolic efficiency associated with low energy intakes. When refeeding is initiated, both REE and diet-induced thermogenesis increase, which exemplifies how energy metabolism can adapt (5, 7).

The metabolic expression of extreme malnourishment in persons near death is unknown. Le Maho’s research team described, in the king penguin Aptenodytes patagonicus (8) and in rats (9, 10), successive phases of energy expenditure and protein breakdown during prolonged starvation. During the initial phase, which lasted several days, a decrease in protein utilization was observed. The second phase, lasting several weeks, was characterized by an important sparing of visceral and muscle proteins. During the terminal phase (ie, the last few days before death), an important increase in protein oxidation and breakdown was again observed.

No such data are available for humans. In a 15-y study of refeeding extremely malnourished dying patients, only a few patients with a body mass index (BMI; in kg/m\(^2\)) < 10 have been seen at our unit. The paradoxical REE, body composition, and metabolic and hormonal data of 5 extremely malnourished women near death and of 16 malnourished female anorexia nervosa (AN) patients were measured and compared.

SUBJECTS AND METHODS
Subjects
There were 3 groups of women: 5 extremely malnourished dying patients, 16 severely malnourished AN patients, and 16 healthy subjects. Three of the 5 dying patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders (4th ed) criteria for AN (11). The 2 other dying patients had AN related to severe depression. The patients were hospitalized at the Nutrition Unit, Bichat-Claude Bernard Hospital (Paris), because they were extremely malnourished and unconscious. The patients or members of their families reported that the patients were physically inactive, had consumed very little food for several weeks, and had been confined to bed for several days because of muscle weakness.

The AN patients and healthy subjects served as control subjects (Table 1). The control subjects were recruited by advertisement at Bichat University, Paris. The AN patients had BMIs between 12 and 16 and the healthy subjects had BMIs between

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TABLE 1
Physical characteristics of 5 extremely malnourished dying women, of 16 malnourished anorexia nervosa (AN) patients, and of 16 healthy subjects.*

<table>
<thead>
<tr>
<th></th>
<th>Dying patients (n = 5)</th>
<th>AN patients (n = 16)</th>
<th>Healthy subjects (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29.8 ± 9.3 (21–45)</td>
<td>25.2 ± 3.9 (19–32)</td>
<td>23.8 ± 4.1 (20–29)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>24.5 ± 1.1 1</td>
<td>38.1 ± 5.7 56.1 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>(% of preillness weight)</td>
<td>48.3 ± 3.1 64.4 ± 5.2</td>
<td>101.1 ± 3.8</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>9.77 ± 0.1 2</td>
<td>13.6 ± 1.1 21.2 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>By SFT</td>
<td>24.3 ± 2.1 35.5 ± 5.2</td>
<td>43.1 ± 5.9</td>
</tr>
<tr>
<td>By BIA</td>
<td>24.9 ± 2.1 34.1 ± 4.9</td>
<td>42.7 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>By SFT</td>
<td>0.15 ± 1.0 2.5 ± 2.1</td>
<td>13.0 ± 2.1</td>
</tr>
<tr>
<td>By BIA</td>
<td>0.12 ± 1.3 4.2 ± 2.7</td>
<td>13.4 ± 3.5</td>
<td></td>
</tr>
<tr>
<td>Muscle circumference (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td>12.2 ± 1.2 13.6 ± 1.6</td>
<td>21.3 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>24.3 ± 3.5 30.3 ± 3.7</td>
<td>44.1 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>Calf</td>
<td>20.4 ± 2.1 24.0 ± 1.6</td>
<td>31.9 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Urinary creatinine (mg/d)</td>
<td>382 ± 153 702 ± 83</td>
<td>1283 ± 162</td>
<td></td>
</tr>
</tbody>
</table>

* ± SD; range in parentheses. SFT, skinfold thickness; BIA, bioelectrical impedance analysis.

1 Significantly different from the 2 other groups, P < 0.05.

2 n = 16.

19 and 25. The AN patients and healthy subjects were matched for age (±2 y) with the 5 dying patients. The research protocol was explained to the subjects, who gave informed, written consent. The study protocol was in accordance with the guidelines of the Bichat Hospital Ethical Committee.

Resting energy expenditure

One of the 5 dying patients died after the first REE measurement. The 4 remaining patients were more extensively studied. REE (expressed as kJ and kcal/d) was measured every 2 wk during refeeding in the 2 groups of patients and once in the healthy subjects. The first REE measurement was made at the start of refeeding after the subjects had fasted for 10 h. In the 4 dying patients and in 3 of the AN patients, water and electrolyte deficits were corrected by 1500–2000 mL intravenous infusions containing 5% glucose (75–100 g/d), saline, potassium (4–6 g/d), phosphorus, and mineral and vitamins (100 mg vitamins B-1, B-6, and niacin; vitamin C; and polyvitamins). Refeeding of the 4 remaining dying patients began on the second day, at the low rate of 2090 kJ (500 kcal)/d, via continuous enteral nutrition (CEN) through a pediatric nasogastric tube. No feeding was allowed by mouth. Shortly after the first REE measurement was made, these 4 patients received 4180 kJ (1000 kcal)/d by CEN for 2 d (6270 kJ (1500 kcal)/d) between days 5 and 8. Subsequently, each patient was advised to increase her food intake to obtain a body weight gain of 150 g/d during the first 2 wk of refeeding. The 16 AN patients were refed orally as well as by CEN and had a weight gain of 150–200 g/d. Each patient consumed a low-sodium diet.

The procedure used to measure REE was described in detail previously (12). Briefly, the subjects fasted overnight (tube and oral feeding was interrupted at 2200 the night before) and then were placed in a quiet, ventilated room (22.7 ± 0.5°C). After 30 min of bed rest, including 15 min under a ventilated hood, to stabilize gas exchanges, REE was recorded for 20 min between 0830 and 1000. The subjects remained in a supine position throughout the procedure, holding the hood in which air flow was monitored according to the respiratory rate.

Oxygen consumption and carbon dioxide production

Oxygen consumption (\(V_O^2\)) and carbon dioxide production (\(V_CO^2\)) were measured online by using open-circuit indirect calorimetry with a ventilated-hood system (12), which consisted of 2 paramagnetic analyzers for oxygen, 2 infrared analyzers for carbon dioxide, and a mass flow meter to determine precise airflow rates. \(V_O^2\) and \(V_CO^2\) were calculated as being the difference between expired gases and room gases. Corrections for nonprotein respiratory quotient and REE were made by subtracting the \(V_O^2\) from the \(V_CO^2\) for protein oxidation from urinary nitrogen output. The reproducibility was >96%. REE was calculated according to the method of Ben Porat et al (13).

Body weight and body composition

Body weight was measured every 2 d while the subjects were fasting. Body composition was assessed each week by measuring skinfold thicknesses at the biceps, triceps, suprailiac, and subscapular sites (14) and every 2 wk by conducting 2-frequency (5 kHz and 1 MHz) bioelectrical impedance analyses (BIA) (15) with a portable 2-electrode analyzer (IMP BO 1; l’Impulsion, Caen, France). In addition, muscle circumferences of the brachia and thigh (at the middle of the limb segment) and of the calf at the largest site (16, 17) were measured every 2 wk; the skinfold thickness at each site was subtracted. Muscle mass was estimated every 2 wk on the basis of the mean of 3 consecutive 24-h urinary creatinine outputs by using an analytic procedure based on the Jaffé procedure (18).

Other measurements

Energy intake was estimated daily by one dietitian from a 7-d food record and on the basis of the volume remaining in the enteral feeding bottles (7). Urinary nitrogen was calculated weekly by chemiluminescence (17) on the basis of the mean of 3 consecutive 24-h measurements. Serum fatty acid concentrations were determined by gas chromatography with use of a CP-SIL 8 CB (0.12 μm) column (19). Serum albumin and transthyretin were measured by laser nephelometry (20). Serum sodium, potassium, calcium, phosphorus, zinc, and magnesium and red blood cell magnesium concentrations were measured by using a Technicon SMA 6 (Technicon, Paris). Every 2 wk, serum thyroid hormone (free triiodothyronine and thyroxine) and thyrotropin concentrations were measured by use of radioimmunoassay and serum catecholamines (epinephrine, norepinephrine, and dopamine) were measured by use of HPLC and electrochemical detection (21).

Statistical analyses

The effect of refeeding was tested by comparing the values obtained before with those obtained after refeeding with use of the nonparametric Mann-Whitney U test and analysis of variance (ANOVA). These tests were also used to compare values between the 3 groups. Statistical differences were weighted with the Bonferroni adjustment. Results were considered to be significant if \(P\) values were <0.05. All analyses were made with SYSTAT for WINDOWS 95 (1996; Systat Inc, Chicago). Results are reported as means ± SDs.
RESULTS

The dying patients had a body weight that was very low at the start of refeeding (Table 1), from 22.9 to 26.2 kg at a mean height of 1.61 m; a preillness weight of 51.0 ± 5.4 kg (BMI: 19.7 ± 1.3), and a BMI between 9.53 and 9.95 at the time of the study. Four of the 5 patients had minimal edema of the legs. The FFM and FM values of the dying patients were 40% and 98% lower, respectively, than those of the healthy subjects (Table 1).

Resting energy expenditure

At the start of refeeding, REE was high in each of the 5 dying patients: 5174 ± 391 kJ (1194 ± 170 kcal)/d (Figure 1). Each REE value in the 5 dying patients was higher than those of the 16 AN patients (P < 0.05); subsequently, values fell to or below the values of the AN patients.

Body weight and body composition

Brachial, calf, and thigh muscle circumferences in the dying patients were 42%, 48%, and 39% lower and mean urinary creatinine output was 42 ± 9% lower than values in the healthy subjects (Table 1). FFM represented ≈100% of body weight in the dying patients compared with 88–92% in the AN patients. Total body water was overestimated by BIA in the 4 dying patients: FFM exceeded body weight in 2 patients and represented >90% of body weight in the other 2 patients. By week 8, body composition improved: body weight increased from 24.5 ± 1.4 to 32.6 ± 1.7 kg, FFM increased from 24.6 ± 2.1 to 29.4 ± 3.7 kg, and FM increased from 0.05 ± 1.1 to 3.4 ± 1.8 kg; brachial, calf, and thigh muscle circumferences improved but remained 37%, 35%, and 42% lower (P < 0.01), respectively, than normal. Mean urinary creatinine output by week 8 was 60 ± 69 mg/d, 34% below values in the healthy subjects.

Energy intake

The mean 7-d energy intake in the dying patients before hospital admission was near zero: 962 ± 239 kJ/d (230 ± 57 kcal/d). This value was lower than that of the 16 AN patients: 3511 ± 656 kJ/d (840 ± 157 kcal/d). Food intake increased in the 4 dying patients: 4012 ± 787, 6258 ± 1247, 8642 ± 1186, 10308 ± 947, and 11251 ± 1471 kJ/d, respectively, after 1, 2, 3, 4, and 8 wk of refeeding. It also increased, by 100%, in the AN patients.

Urinary nitrogen loss

Urinary nitrogen output was initially high (16.4 ± 2.9 g/d) in the dying patients and decreased during refeeding (Figure 2). This contrasted with the low initial value and with its increase after enteral feeding in the 16 AN patients.

Serum fatty acid concentrations

Serum fatty acid concentrations were significantly lower in the dying patients than in the AN patients at the start of refeeding (Table 2). Refeeding was associated with an increase in fasting
fatty acid concentrations in the dying patients (from 0.36 ± 0.23 to 0.76 ± 0.31 mmol/L), whereas it decreased in the AN patients (from 1.03 ± 0.32 to 0.85 ± 0.29 mmol/L) at week 4.

**Nutritional markers**

Serum albumin, transthyretin, transferrin, haptoglobin, sodium, potassium, calcium, phosphorus, magnesium, and zinc values were significantly lower at the start of refeeding in the 4 surviving dying patients than in the 2 control groups (Table 3). All values in the 4 dying patients returned to normal after 8 wk of refeeding (data not shown). All markers in AN patients were within reference ranges at baseline.

**Hormone concentrations**

Serum insulin, glucose, and catecholamine (epinephrine, norepinephrine, and dopamine) concentrations were significantly lower at the start of refeeding in the dying patients than in the AN patients or healthy subjects (Table 2) and were at normal concentrations after 4 wk of refeeding. Serum free thyroxine, free triiodothyronine, and thyrotropin concentrations were within the normal range in the dying patients at the start of refeeding.

**Other results**

No inflammatory process was found in our patients, there was no bacteria in the urine or blood, thoracic X-ray results were normal, and serum acute phase reactive protein concentrations were low. In addition, none of the patients was taking any medication known to increase REE (namely thyroid hormones).

**DISCUSSION**

The present study showed that severe malnutrition may be associated with a paradoxical increase in REE in starved patients at the limit of life. This increase was associated with high urinary nitrogen losses, low serum fatty acid concentrations, and near-zero FM. This profile has never been described in humans and contrasts with that

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### Table 2

Baseline serum hormone concentrations in 3 extremely malnourished dying patients compared with those of 14 malnourished anorexia nervosa (AN) patients before refeeding and of 16 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Dying patients (n = 3)</th>
<th>AN patients (n = 14)</th>
<th>Healthy subjects (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (pmol/L)</td>
<td>12 ± 6^2</td>
<td>26 ± 3</td>
<td>29 ± 2 (15–100)</td>
</tr>
<tr>
<td>Serum glucose (mmol/L)</td>
<td>3.1 ± 0.3^2</td>
<td>4.3 ± 0.5</td>
<td>4.8 ± 0.2 (3.8–6.6)</td>
</tr>
<tr>
<td>Free triiodothyronine (pmol/L)</td>
<td>4.2 ± 0.3</td>
<td>3.5 ± 1.9</td>
<td>4.8 ± 0.3 (4–8)</td>
</tr>
<tr>
<td>Free thyroxine (pmol/L)</td>
<td>10.9 ± 3.2</td>
<td>7.2 ± 2.4</td>
<td>10.6 ± 0.4 (7.5–14)</td>
</tr>
<tr>
<td>Thyrotropin (mU/L)</td>
<td>2.1 ± 0.9</td>
<td>1.8 ± 1.2</td>
<td>2.3 ± 0.5 (1–3.5)</td>
</tr>
<tr>
<td>Epinephrine (pmol/L)</td>
<td>126 ± 50^2</td>
<td>292 ± 76</td>
<td>513 ± 152 (340–726)</td>
</tr>
<tr>
<td>Norepinephrine (ng/L)</td>
<td>786 ± 77^2</td>
<td>1022 ± 142</td>
<td>1436 ± 289 (1240–2070)</td>
</tr>
<tr>
<td>Dopamine (pmol)</td>
<td>208 ± 78^2</td>
<td>300 ± 169</td>
<td>418 ± 58 (326–457)</td>
</tr>
<tr>
<td>Fatty acids (mmol/L)</td>
<td>0.36 ± 0.23</td>
<td>1.03 ± 0.32^2</td>
<td>0.64 ± 0.18</td>
</tr>
</tbody>
</table>

^2 x ± SD; range in parentheses.

^2 Significantly different from the 2 other groups, P < 0.05.
observed in starved patients who were less extremely malnourished than the patients in the present study (3–7) but is similar to that described in the king penguin during the terminal phase of life (8).

The fact that only one of our extremely malnourished dying patients died during the study was surprising. On the basis of personal results and 11 reports from the literature, Henry (22) concluded in 1990 that survival is not possible in humans with a BMI < 10 (22). The very low body weight in our patients was concluded in 1990 that survival is not possible in humans with a BMI < 10 (22). The very low body weight in our patients was considered a very low nitrogen intake and thus a low protein oxidation. This condition was surprising because malnourished patients have a very low nitrogen intake and thus a low protein oxidation. This phenomenon appears to be similar to what has been observed in the king penguin Aptenodytes patagonicus (8). This king penguin syndrome is partly attributable to oxidation of the last available energy, ie, the FFM protein stores. The survival of such patients is possible if refeeding is initiated as soon as possible: intravenous water, potassium, phosphorus, and the REE were affected by energy input (even minimal) the day before. During refeeding, REE decreased, as did nitrogen losses, which may have been related to the sparing effect of non-protein energy input on protein catabolism (24).

The initial increase in REE in the dying patients was also associated with an increase in the permeability of the mitochondrial membrane. In healthy subjects the permeability of the mitochondrial membrane is relatively low; in the dying patients in the present study, the permeability to the protons may have increased. Such an increase would enhance leakage through the membrane and subsequently decrease the oxidative phosphorylation efficacy (25, 26) and increase oxygen consumption. A deep deficiency in essential fatty acids was also associated in vitro with an increase in mitochondrial membrane permeability (26). Such a deficiency, which is likely during severe starvation, was shown in rats to be responsible for an increase in cell respiration, a depletion of energy stores, and an increase in REE (27). The increased REE in such patients may also have been due to diseased cellular membranes throughout the body, a condition that induces dysfunction of all cellular components. Indeed, much of the oxygen needed was used to generate ATP to maintain cellular membrane potentials and to pump and channel energy requirements.

An increase in thyroid hormone or catecholamine secretion might be another explanation for an elevated REE (28, 29). In our dying patients, however, no such increase was noted. A role for thyroid hormones could not be excluded because free triiodothyronine concentrations were within reference ranges in these patients but were low in 91% of the 280 malnourished AN patients admitted to our Unit over 10 y. Serum catecholamine concentrations did not increase in the dying patients after refeeding.

In conclusion, in the dying patients there was a paradoxical increase in REE above values usually observed in other states of food deprivation. This phenomenon appears to be similar to what has been observed in the king penguin Aptenodytes patagonicus (8). This king penguin syndrome is partly attributable to oxidation of the last available energy, ie, the FFM protein stores. The survival of such patients is possible if refeeding is initiated as soon as possible: intravenous water, potassium, phosphorus, vitamins, low saline, and low glucose input (75–100 g/d) on the first day and CEN (providing an energy input of 0.5 × REE and a low protein input of 0.75 g·kg⁻¹·d⁻¹) on the second day. On the third day, the energy input should be increased to equal the REE and the protein input should increase to 1.5 g·kg⁻¹·d⁻¹. Over the subsequent 2 wk, energy input should be maintained at 1.5 × REE (providing ≈1500 kcal/d).

REFERENCES


