Resting energy expenditure in patients with newly detected gastric and colorectal cancers

Elisabeth W HM Fredrix, Peter B Soeters, Margriet J J Rouflart, Maarten F von Meyenfeldt, and Wim HM Saris

ABSTRACT Resting energy expenditure (REE) was measured in 104 patients with newly detected gastric or colorectal (GCR) cancer and was compared with two groups of control subjects without cancer: healthy subjects (H control subjects) and patients with nonmalignant diseases of the gastrointestinal tract (GI patients). REE in GCR-cancer patients was not significantly different from REE in GI patients or H control subjects. Comparison of measured REE with predicted REE obtained from prediction equations may erroneously suggest that increased REE is a contributing factor in the development of cancer cachexia. No significant differences in REE were found when patients with liver metastases were compared with patients without metastases. There were no differences in REE between gastric and colorectal cancer patients. The decrease in energy expenditure, which normally occurs during starvation and weight loss in healthy men and women, could not be demonstrated in weight-losing, GCR-cancer patients. In conclusion, elevation of REE contributes little to the pathogenesis of cancer cachexia in GCR-cancer patients. Am J Clin Nutr 1991;53:1318-22.

KEY WORDS Energy expenditure, indirect calorimetry, weight loss, cancer, patients

Introduction Cachexia is a common feature in patients with cancer. Moreover, abnormal indices of nutritional status are also frequently observed in cancer patients. Both increased energy expenditure (EE) and decreased dietary intake have been implicated as causative factors for the observed weight loss and poor nutritional status. Several authors demonstrated that patients with malignant disease have an elevated resting energy expenditure (REE) (1-5). Others (6-10), however, found no change. According to Dempsey et al (11), 22% of patients with gastrointestinal (GI) cancer have a measured REE that is higher than that predicted, whereas 36% have an abnormally low REE. In most studies the finding of an elevated REE was based on a comparison with the Harris-Benedict (HB) formula (12). This formula is universally used in hospitals to predict REE. However, studies have demonstrated that the HB equation may not be the best reference in healthy men and women (13-15) or in patients (16).

The aim of the current study was to investigate the presence of aberrations in REE in patients with newly detected gastric or colorectal (GCR) cancer. These patients were compared with two groups of control subjects without cancer: apparently healthy subjects (H control subjects) and patients with nonmalignant diseases of the gastrointestinal tract (GI patients).

Methods One-hundred four cancer patients and 72 control subjects without cancer were studied over a period of 2 y. One-hundred four patients with histologically proven GCR cancer were included in the study. All patients were ambulatory and recently admitted to the Department of Surgery or Internal Medicine of the University Hospital of Limburg, Maastricht. All patients had newly detected cancer; thus, no patient had received chemotherapy or radiation therapy previously. Ninety-six patients underwent gastrointestinal surgery. Almost 25% (25 of 104) had liver metastases at the time of diagnosis. Forty-one patients were in a relatively early phase of the disease (stages 1 and 2) whereas the remainder (n = 63) were in the later stages of the disease (stages 3 and 4).

Control subjects were patients with nonmalignant GI diseases and healthy normal subjects. Thirty-two GI patients were included in the study (Table 1). The REE of some of these patients was measured on an outpatient basis; other patients were admitted to the Department of Surgery or Internal Medicine. Forty apparently healthy men and women (H control subjects) also participated in the study. Their REEs were measured on an outpatient basis. These H control subjects underwent a medical examination to exclude disorders that might affect their metabolic rate, such as anemia, high blood pressure, thyroid dysfunction, heart failure, infectious disease, and chronic obstructive pulmonary disease (COPD). The GCR-cancer patients were retrospectively examined for the same disorders by use of the medical reports. Twenty-nine GCR-cancer patients had to be excluded because they had at least one of the above-mentioned diseases. Because limited medical information was available for some of the GI patients, it was impossible to completely rule out the possibility that they might have suffered from disorders that may have influenced energy metabolism.

1 From the Department of Human Biology and Surgery, University of Limburg, Maastricht, The Netherlands.
2 Reprints not available.
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The procedures followed were in accordance with the Helsinki Declaration and the study was approved by the Human Studies Committee of our university. REE was calculated from measurements of oxygen intake and carbon dioxide production. Gas exchange was measured by means of a ventilated hood system, which consisted of a dry gas meter, a blower, a paramagnetic oxygen analyzer (Mijnhardt Servoxem, Bunnik, The Netherlands), and an infrared carbon dioxide analyzer (modified Mijnhardt UG51). Dry gases were measured and the results converted to standard temperature and pressure. Flow through the canopy was kept constant during measurements and was adjusted to the body weight of the subject (25–30 L/min). System control and calculations were performed on a microcomputer. The hood consisted of clear plexiglass and had a volume of 30 L. REE was calculated by using the abbreviated Weir formula (17). REEs of the GCR-cancer patients and some of the GI patients were measured during their hospital stay between 0700 and 1000 after an overnight fast. REEs in the other GI patients and in the H control subjects were measured on an outpatient basis; they came to the hospital in the morning after a 10-h overnight fast; they travelled by car, bus, or train to reduce their physical activity. REE was measured after a period of ≥ 30 min of bed rest. Measurements were performed while at complete rest in the supine position, for 30 min. In a recent study (18) we showed that REE in 30 healthy volunteers measured after they had spent the night in the hospital was not significantly different from REE measured after they had come from home as in this study.

Measured REE was compared with predicted REE calculated by the HB formula. Patients and subjects with a measured REE ≥ 115% of that predicted by the HB formula were considered hypermetabolic. This definition of hypermetabolism was based on Boothby et al's (19) finding that 95% of normal individuals exhibit measured REE within 10% of that predicted and with a measurement error ≤ 5%.

Fat-free mass (FFM) was estimated with the bioelectrical-impedance (BI) method and was calculated by using the formula of Segal et al (20). BI was measured in only half of the GCR-cancer patients because at the start of the study no device was available to measure body composition. Patients were asked whether they had lost weight in the previous year. Weight loss was calculated as the difference between reported preillness body weight minus actual body weight. It is well established that people can report their stable weight accurately (21). The percentage weight loss was used to divide patients into weight-stable (< 5% weight loss) or weight-losing groups (≥ 5% weight loss). Body weight was measured with a beam scale to the nearest 0.1 kg while subjects wore light clothing and no shoes. Body height was measured to the nearest 0.1 cm while subjects were standing barefoot. Assessment of nutritional status also included measurements of serum albumin, total iron-binding capacity (TIBC), and percent ideal body weight (%IBW). Albumin was measured according to the bromocresol purple method. TIBC was measured in the supernate after transferrin was saturated and excess free iron was removed. Ideal body weight was determined from the Metropolitan Life Insurance Tables (22). Tumor staging was performed after review of medical reports, operative reports, and pathology and radiology reports. Tumor stage was assessed according to the guidelines of the American Joint Committee on Cancer (23).

REE was expressed in absolute terms (REE), per kg body wt (REE/IBW), per kg FFM (REE/FFM), or as a percentage of the HB equation (REE/IB). Statistical analysis was performed by using one-way analysis of variance followed by the Tukey pairwise multiple-comparison procedure. The Mann-Whitney U test was used where appropriate. Frequency data were compared by using the chi-square test. The slopes of the linear-regression lines were compared with t statistics by using the technique described by Kleinbaum and Kupper (24). Results are presented as mean ± SD and P values < 0.05 were regarded as statistically significant.

Results

GCR-cancer patients were older than were H control subjects and GI patients (Table 2). There was no significant difference in sex between the groups. Body weight and %IBW were lower in the GCR-cancer patients than in H control subjects. Albumin and TIBC were also significantly lower in GCR-cancer patients and in GI patients. GCR-cancer patients showed more weight loss than did GI patients (7.1% vs. 4.0%, respectively, P < 0.01). REE in absolute terms was significantly higher in the H control subjects than in the GCR-cancer patients (Table 3). However,
TABLE 3
Resting energy expenditure (REE) in GCR-cancer patients compared with patients with benign gastrointestinal (GI) diseases and healthy (H) control subjects

<table>
<thead>
<tr>
<th></th>
<th>GCR-cancer patients (n = 104)</th>
<th>GCR-cancer patients (n = 75)†</th>
<th>GI patients (n = 32)</th>
<th>H control subjects (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kJ/d)</td>
<td>5657 ± 967‡‡</td>
<td>5707 ± 1017</td>
<td>5941 ± 812</td>
<td>6326 ± 1125</td>
</tr>
<tr>
<td>REE (kJ/kg body wt)</td>
<td>87 ± 11</td>
<td>86 ± 10</td>
<td>90 ± 13</td>
<td>88 ± 8</td>
</tr>
<tr>
<td>REE (kJ/kg FFM)</td>
<td>123 ± 18†</td>
<td>119 ± 11††</td>
<td>121 ± 12</td>
<td>122 ± 10</td>
</tr>
<tr>
<td>REE (% HB)**</td>
<td>103.9 ± 9.8</td>
<td>102.6 ± 9.4</td>
<td>103.2 ± 9.4</td>
<td>106.7 ± 8</td>
</tr>
<tr>
<td>Hypermetabolic (%)</td>
<td>13</td>
<td>9</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>RQ</td>
<td>0.78 ± 0.05</td>
<td>0.79 ± 0.04</td>
<td>0.78 ± 0.04</td>
<td>0.76 ± 0.05</td>
</tr>
</tbody>
</table>

* FFM, fat-free mass; HB, Harris-Benedict; RQ, respiratory quotient.
† Excluded those patients with disorders that might affect REE.
‡‡ Significantly different from H control subjects, P < 0.01.
† n = 49.
‡ n = 36.
** By the Harris-Benedict equation.

no significant differences existed among the three groups for REE/BW, REE/FFM, and REE/HB. Thirteen percent (13 of 104) of the GCR-cancer patients were hypermetabolic compared with 13% (4 of 32) and 20% (8 of 40) of GI patients and H control subjects, respectively. This prevalence of hypermetabolism was not significantly different among the groups.

A comparison between the 29 GCR-cancer patients that were excluded from the initial sample and the 75 remaining patients revealed that the excluded patients were older, had lower %BW and lower serum albumin, and had more weight loss. Tumor stage or the presence of distant metastases were not significantly different between the two groups. REE tended to be higher in the excluded patients (REE/HB: P = 0.05; REE/BW: P = 0.07 and REE/FFM: P = 0.10). Nine percent (7 of 75) of the remaining patients were hypermetabolic (Table 3). A comparison between the remaining GCR-cancer patients and the GI patients or the H control subjects revealed no significant differences for REE/BW, REE/FFM, and REE/HB.

There were no significant differences between patients with gastric and colorectal cancer, except that significantly more gastric-cancer patients were smokers. No significant differences in REE were found when patients with liver metastases were compared with patients without metastases. Twenty percent (11 of 54) of the male GCR-cancer patients were hypermetabolic compared with only 4% (2 of 50) of female GCR-cancer patients. This difference was significant (P < 0.05).

The correlation between REE/BW or REE/FFM and percent weight loss was significant for the GCR-cancer patients (r = 0.40, P < 0.001; r = 0.30, P < 0.05, respectively) but not for the GI patients. No significant differences in REE were found when weight-losing, GCR-cancer patients were compared with weight-losing GI patients (Table 4). REE/BW, REE/FFM, and REE/HB of weight-losing, GCR-cancer patients were not different from those of weight-stable, GCR-cancer patients or H control subjects. There was no difference in the respiratory quotient (RQ) between the weight-losing and weight-stable patients.

To investigate the association between REE and the cancer-bearing state and weight-losing state, respectively, regression lines relating REE to FFM were drawn. There was no significant difference between the slopes of the regression lines for GCR-cancer

TABLE 4
REE in weight-losing and weight-stable patients

<table>
<thead>
<tr>
<th></th>
<th>GCR-cancer patients</th>
<th>GI patients</th>
<th>H control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight-losing (n = 58)</td>
<td>Weight-stable (n = 46)</td>
<td>Weight-losing (n = 12)</td>
</tr>
<tr>
<td>REE (kJ)</td>
<td>5448 ± 879*</td>
<td>5925 ± 1013</td>
<td>5763 ± 987</td>
</tr>
<tr>
<td>REE (kJ/kg body wt)</td>
<td>90 ± 13</td>
<td>85 ± 8</td>
<td>90 ± 16</td>
</tr>
<tr>
<td>REE (kJ/kg FFM)</td>
<td>123 ± 21†</td>
<td>122 ± 11‡</td>
<td>124 ± 13</td>
</tr>
<tr>
<td>REE (% HB)††</td>
<td>105.4 ± 1.0</td>
<td>102.1 ± 7.7</td>
<td>105.8 ± 9.1</td>
</tr>
<tr>
<td>Hypermetabolic (%)</td>
<td>17</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>RQ</td>
<td>0.78 ± 0.05</td>
<td>0.79 ± 0.04</td>
<td>0.79 ± 0.04</td>
</tr>
</tbody>
</table>

* ± SD.
†† Significantly different from weight-losing GCR-cancer patients, P < 0.001.
‡ n = 32.
§ n = 17.
‖ By the Harris-Benedict equation.
patients and GI patients. Also, when weight-losing patients were compared with weight-stable patients, irrespective of the primary diagnosis, the slopes of the regression lines were not significantly different (Fig 1).

**Discussion**

Increased REE may contribute to the development of cancer cachexia. In most studies aberrations in REE in patients with cancer were established by using the HB formula as a reference. This formula is a multiple-linear-regression equation derived from indirect calorimetry data, on 239 healthy volunteers, measured after an overnight fast and after resting 30 min in bed after arrival at the study center. Boothby et al (19) demonstrated that 95% of normal individuals exhibit measured REE within 10% of the predicted value, whereas Dempsey et al (11) reported that 95% of normal volunteers exhibit measured REE within 15% of that predicted. In the current study 13% of GCR-cancer patients proved to be hypermetabolic, defined as a measured REE ≥ 115% of that predicted by the HB formula. Twenty-six percent of patients had a measured REE ≥ 110% of that predicted by the HB formula. These percentages are higher than expected. Thus, a considerable number of GCR-cancer patients is found to be hypermetabolic when measured REE is compared with the HB equation. Because it would be of interest to calculate the REE by means of another reference standard, the new FAO/WHO/UNU equations were also used to estimate the degree of hypermetabolism in these cancer patients (25). When this new formula was used as a reference standard, only 6% of the GCR-cancer patients became hypermetabolic. This percentage was the same as expected in a group of healthy volunteers.

The validity of the HB formula as a reference to establish hypermetabolism in cancer patients may be questionable. Rozza and Shizgal (16) suggested that this formula fails to predict REE accurately in many patients, particularly those with weight loss. As a consequence, the number of hypermetabolic patients is probably overestimated. In contrast, Daly et al (15) found that the HB equation overestimates REE in healthy men and women. Feurer et al (26) found that in 20% of healthy control subjects, measured REE is over- or underestimated by the HB prediction. Owen et al (13, 14) concluded that the HB equation overestimates REE in healthy men and women aged < 64 y. It seems more appropriate to compare REE with measured values in healthy control subjects of the same age. The current study revealed that 20% of the H control subjects were hypermetabolic (≥ 115% HB), which was not significantly different from the prevalence of hypermetabolism in GCR-cancer patients. Only 7.5% of the H control subjects were hypermetabolic when the FAO/WHO/UNU prediction equations were used. Comparison of GCR-cancer patients with GI patients (weight-stable and weight-losing) also revealed no significant difference in the prevalence of hypermetabolism. Therefore, the suggestion in many studies that an increased REE is an important contributing factor in the development of cancer cachexia may be false because the current study suggests that this is the result of selection of inappropriate control subjects.

Hypermetabolism (≥ 115% HB) coincides to a considerable extent with disorders potentially influencing energy metabolism. Six of 13 hypermetabolic patients had to be excluded because of diseases like hypertension, anemia, COPD, thyroid dysfunction, and severe heart failure.

GCR-cancer patients had a weight loss of ~ 5 kg (7.1%). REE of the weight-losing, GCR-cancer patients was not significantly different than the REE of the nonweight-losing, GCR-cancer patients. This finding is in contrast with the decrease in EE, which normally occurs during starvation and weight loss in healthy men and women (27). In these weight-losing patients normal adiabatical mechanisms to a negative energy balance, therefore, appear to be disturbed. The fact that both GCR-cancer and GI patients fail to adapt to starvation implies that this is not a cancer-specific phenomenon. In contrast to Hansell et al (7) the slope of the regression line expressing the relationship of REE with FFM in weight-losing patients in the current study was not different from the one in weight-stable patients. Hansell et al (7) measured REE in GCR-cancer patients and lung-cancer patients whereas the current study included measurements of REE in only GCR-cancer patients. The same investigators found in another study that lung-cancer patients have a different association between REE and body weight or FFM when compared with GCR-cancer patients (8). This may be an explanation for the different results of both studies. The influence of the weight-loss state on energy metabolism in cancer patients needs to be studied in more detail. Nixon et al (9) measured REE several times in 10 cancer patients who lost weight during the study and concluded that the change in REE with weight loss varied unpredictably from patient to patient. Nevertheless, 7 of 10 patients in their study who had a mean weight loss of 10% showed an increase in REE. In the current study there was no difference in RQ between the weight-losing and weight-stable patients. However, in another study (28) on EE and energy intake in GCR-cancer patients, we demonstrated that patients who reported a reduced food intake tended to have a lower RQ than did patients who maintained their food intake on predisease levels of food intake.

Some of the previous studies suggested that advanced disease was associated with an increased REE (1, 4), but this observation was not confirmed in the present study. Patients with metastatic
disease did not have a higher REE compared with patients who had a localized malignancy. These results are in agreement with those of Hansell et al (7) that there is no evidence that the presence of liver metastases alters REE significantly.

FFM was not measured in all GCR-cancer patients. However, no significant differences were observed with regard to REE/BW, REE/HB, and weight loss in patients who did or did not undergo a measurement of FFM.

We conclude that this study demonstrates that REE is not elevated in patients with newly detected GCR cancer. There is no evidence that tumor type (gastric or colorectal) or tumor stage is important in relation to an increase in REE in cancer patients. Therefore, the suggestion that anorexia could account for the observed weight loss needs to be examined in more detail.

References