Total Energy Expenditure in Patients With Small-Cell Lung Cancer: Results of a Validated Study Using the Bicarbonate-Urea Method

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The bicarbonate-urea method for measuring CO_2 production was applied to eight free-living patients (mean age, 68 ± 10 years; mean weight, 69 ± 10 kg; mean height, 1.65 ± 0.10 m) with unresectable small-cell lung cancer for a period of 1 day (n = 5) or 2 days (n = 3). The basal metabolic rate (BMR) was measured in all subjects. The technique was first validated against whole-body indirect calorimetry over an additional 24-hour period in five of these subjects. The bicarbonate-urea method predicted net CO_2 production to be 102.1% ± 3.4% of that measured by whole-body indirect calorimetry, and energy expenditure, 101.5% ± 3.8% of the measured calorimeter value (8.1 ± 1.6 MJ/d). The 24-hour recovery of label in CO_2 excreted by the body was 95.6% ± 0.5%. In free-living conditions, the bicarbonate-urea method predicted energy expenditure to be 9.0 ± 2.6 MJ/d. BMR was elevated by a mean of 6% ($P < .05$) compared with the Schofield standards. The physical activity level ([PAL] the ratio of total energy expenditure [TEE] to BMR) was variable (1.15 to 1.87), but the mean value was only 1.36 ± 0.22, considerably less than that of moderately active healthy subjects with estimated PAL values of 1.55 ($P < .05$) to 1.65 ($P < .01$) and the mean results obtained by doubly labeled water (previous studies) in healthy age- and sex-matched subjects. This is the first time a tracer method for measuring CO_2 production and energy expenditure has been validated against whole-body 24-hour indirect calorimetry in patients with lung cancer or a systemic inflammatory reaction. The agreement between the two methods is similar to that observed in normal subjects. This is also the first time a tracer method has been used to measure energy expenditure in free-living patients with lung cancer. The results suggest that TEE and the energy requirements necessary to maintain energy balance were not increased despite basal hypermetabolism, because of the associated decrease in physical activity.

RECOMMENDATIONS about the energy requirements of patients with cancer are ill defined. This is because the recommendations are influenced by the type of cancer, the activity or stage of the disease, and the presence of infective and other complications.[1] The patients may also have symptoms such as nausea, vomiting, pain, and shortness of breath that produce changes in energy intake and/or expenditure, which may be affected by treatment that aims to reduce or eradicate the tumor, control disease activity, and prevent weight loss. For example, a recent study undertaken by our group in patients with small-cell lung cancer[2] reported no overall change in body weight between diagnosis and approximately 1 month after treatment, but about one third of the patients did not respond to treatment and lost weight and the other two thirds responded to treatment and did not lose weight (some actually had an increased body weight).

Recommendations about the energy requirements of patients with cancer are hampered by the lack of information about total energy expenditure (TEE). Measurements of the basal metabolic rate (BMR) have frequently been made (see Bozzetti[3] for a summary of the literature and Feurer et al[4] for the variability in BMR among hospitalized patients with cancer), but may be poor predictors of TEE because disease may influence physical activity, which is the most variable component of TEE. The combined use of indirect calorimetry to measure BMR, and a tracer method to measure free-living TEE is a potentially powerful investigative tool for simultaneous assessment of energy requirements and the components of TEE. For example, the difference between TEE and BMR can be used to indicate the energy cost of physical activity, and the ratio TEE/BMR can be used to compare results for subjects of different size. However, this tool has not been applied in patients with cancer.

At least two tracer methods have been used to assess energy expenditure in free-living individuals: the doubly labeled water method[5] and the bicarbonate-urea method.[6] Both methods measure CO_2 production, but the doubly labeled water method measures it over prolonged periods (typically 2 weeks in adults) and the bicarbonate-urea method measures it over considerably shorter periods (1 day or multiples of 1-day periods). However, neither method has been validated against whole-body 24-hour indirect calorimetry in patients with lung cancer or patients with a systemic inflammatory disease. The bicarbonate-urea method is based on the principle of isotopic dilution of infused labeled bicarbonate and the assumption that the specific activity of urinary urea (which is formed from CO_2 in the liver) accurately predicts the composite mean specific activity of exhaled CO_2. This seems to be a reasonable assumption in normal subjects, but it may not apply equally well to patients with disease, especially if there are major changes in the circulating bicarbonate concentration, hepatic blood flow, splanchnic CO_2 production, or formation of unlabeled urea from unlabeled arginine.[6]

The first aim of the study was to validate the bicarbonate-urea method in a whole-body indirect calorimeter in a small group of patients with lung cancer. Thereby, it would also be possible to assess whether the recovery of infused label in gaseous CO_2 is the same as in normal subjects (~95% to 96% over a 24-hour period[6]). The second aim was to assess the practicality of using the method in free-living circumstances in patients with lung cancer. The final aim was to test the hypothesis that many patients with lung cancer do not expend more total energy than normal subjects (although they may have an increase in BMR[2]), because of the associated decrease in physical activity.[7]

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SUBJECTS AND METHODS

Subject characteristics are listed in Table 1. They were recruited from the oncology outpatient clinics at Addenbrooke's Hospital, Cambridge, UK. All had histologically diagnosed small-cell lung cancer, and all had courses of chemotherapy and/or radiotherapy that were finished at least 1 month before beginning the study. All had stopped smoking prior to the study. Their body weight varied little in the 4 weeks preceding the study (0 ± 2 kg). There was no clinical evidence of hepatomegaly or hepatic metastases, although one subject had a mildly elevated plasma bilirubin and an increase in alkaline phosphatase (Table 2, subject no. 3). The results shown in Table 2 indicate that there was an acute-phase protein response (systemic inflammatory reaction) and little or no abnormality in liver function (major disturbances in liver function may affect urea formation and its isotopic dilution within the liver[6]).

The general study design involved administering a subcutaneous infusion of ^{14}C-bicarbonate and a ^{14}C-urea prime for up to 1 day before starting the comparative or validative measurements in the whole-body calorimeter at 9:00 AM. This period allowed a near-equilibrium state to be established. After the 24-hour period of whole-body calorimetry (9:00 AM the following day), the subjects were studied for another 24 hours in free-living conditions while continuing to be infused with ^{14}C-bicarbonate. A subset of patients who were not studied in a whole-body calorimeter spent the additional time in free-living conditions while being infused with ^{14}C-bicarbonate.

The subjects were administered an unprimed ^{14}C-bicarbonate infusion (24×10^6 dpm/d) using the Graseby minipump (Graseby variable-speed driver MS26; Graseby Medical, Watford, UK) and a bolus urea prime[6] (for calculation of dose). Details of procedures for inserting the subcutaneous catheter are presented elsewhere.[6]

The unprimed ^{14}C-bicarbonate infusion began 15 to 20 hours before the start of the validation study at 9:00 AM on day 1. At 8:00 PM the day before the study, the subjects entered the whole-body calorimeter (23 m^2 ventilated at a rate of 200 L/min; ambient temperature, 26° ± 1°C). The diet (47% energy from carbohydrate, 40% from fat, and 13% from protein) was provided in three approximately isoenergetic meals at breakfast (9:00 AM), lunch (1:00 PM), and the evening meal (6:30 PM), and had a total daily energy content of 1.35 times the predicted BMR.[9] A PAL value of 1.35 was chosen in an attempt to establish near energy balance in subjects undertaking light physical activity (subjects were weight-stable before the study). All of the food was weighed, and the weight of food not eaten was also recorded so that actual nutrient intake could be calculated from food tables.[10,11] BMR was measured between 8:00 and 9:00 AM on 2 consecutive days, and the mean value was calculated. The protocol within the calorimeter also included two forms of exercise: cycling for 1 half-hour (11:00 to 11:30 AM) at 25 W at a cycling rate of 50 rpm, and stepping onto a block of wood (25 cm) 10 times/min for 30 minutes (4:00 to 4:30 PM). Due to physical disabilities (shortness of breath or arthritis), one subject (subject no. 5) was only able to complete 20 minutes of exercise, and another two subjects (subjects no. 6 and 7) did not perform the formal cycling exercise, but either stood or walked in the calorimeter chamber for a similar period.

The following samples were obtained while the subjects were in the calorimeter.[6] (1) A spot breath sample for assessing the specific activity of CO_2 was taken at 9:00 AM (by trapping CO_2 in a vial containing an accurately measured amount of hyamine hydroxide (~3.00 mmol/vial). (2) Blood samples were taken through an airtight "arm hatch" in the calorimeter between 9:00 and 9:05 AM on day 1 and day 2 (for measurement of blood urea, bicarbonate, C-reactive protein, and albumin levels and liver function). (3) Spot calorimeter samples were obtained for assessing specific activity of CO_2 in calorimeter air by

Table 2. Circulating Concentrations of C-Reactive Protein, Albumin, Bilirubin, Alkaline Phosphatase, and Alanine Aminotransferase

Subject No.	CRP (mg/L), 0-6*	Albumin (g/L), 30-51*	Bilirubin (μmol/L), 1-17*	Alk Ph (U/L), 30-135*	ALT (U/L), 5-50*
1	10	32	7	94	33
2	113	34	10	98	25
3	5	43	22	252	22
4	15	32	6	115	24
5	76	29	8	142	32
6	9	31	6	76	28
7	4	42	8	141	52
8	66	24	14	150	31
Mean ± SD	37 ± 42	33 ± 6	10 [6dd] @ 5	131 ± 58	31 ± 9

Abbreviations: CRP, C-reactive protein; Alk Ph, alkaline phosphatase; ACT, alanine aminotransferase.

*Normal laboratory range.

Table 1. Subject Characteristics

Subject No.	Sex	Age (yr)	Weight (kg)	Height (m)	Body Mass Index (kg/m^2)	Fat (%)*	Clinical Details†
1	M	71	72.3	1.79	22.6	13.3	Good response to treatment, feels normal
2	M	69	74.0	1.79	23.0	25.5	Partial response to treatment, some lethargy
3	F	65	52.6	1.53	22.5	33.0	Partial response to treatment, some lethargy
4	M	43	64.5	1.69	22.6	18.5	Improvement following treatment
5	M	82	66.7	1.67	23.9	25.4	Exertional dyspnea, moderately active rheumatoid arthritis
6	F	61	77.4	1.53	33.1	45.9	Treated for cerebral metastasis, several courses of radiotherapy, shortness of breath partly due to obesity
7	M	74	83.6	1.63	31.5	33.6	Mild hyperglycemia, symptoms responded to treatment but energy level had not returned to normal
8	F	77	57.1	1.59	22.6	33.3	Chronic bronchitis, disabled by exertional dyspnea, (large p waves on ECG), possible angina, and lethargy
Mean ± SD		67.8 ± 11.9	68.5 ± 10.4	1.65 ± 0.10	25.2 ± 4.4	28.5 ± 10.2	

*Calculated from skinfold thickness using the method of Durnin and Womersley.[8]

†Treatment refers to courses of chemotherapy and/or radiotherapy that had finished at least 1 month before the start of the present study.

trapping it in a vial containing hyamine (~1.5 mmol/vial); together with the CO_2 concentration in the calorimeter, it was possible to calculate the total amount of CO_2 in the calorimeter. (4) Continuous trapping of CO_2 and $^{14}CO_2$ leaving the calorimeter was achieved by bubbling an accurately measured volume of calorimeter air (known temperature and barometric pressure) through a hyamine/methanol/phenolphthalein mixture over the entire 24-hour period.[6] (5) Urine collections were obtained (described later).

Details of these procedures, including the titration of hyamine hydroxide and scintillation counting of ^{14}C-bicarbonate, are given elsewhere.[6] The CO_2 analyzers were checked for linearity. Infusion tests with 80% N_2 and 20% CO_2 at a rate of 1.25 L/min confirmed the accuracy of the calorimetric gas-exchange measurements (±1%). After completion of the calorimeter protocol (subjects no. 1 to 5) or after insertion of the subcutaneous cannula (subjects no. 6 to 8), the subjects went home and were asked to maintain their normal daily activities. Urine collections were obtained from all subjects on 2 consecutive days from 9:00 PM to 7:00 AM and 7:00 AM to 9:00 PM,[6] irrespective of whether the first day was spent in the calorimeter or at home.

Following the free-living measurements, the subjects were interviewed to ascertain habitual activity patterns (type of activity and length of time involved in each activity). TEE was then calculated by reference to the energy cost of individual activities, which have PAL values ascribed to them[10,11]: TEE = BMR (measured) [time in bed + (time at work × PAL + nonoccupational time × PAL)].

A semiquantitative assessment of energy intake was made on the basis of 24-hour recall of food intake and standard food tables.[12]

The study was approved by the Medical Research Council Dunn Nutrition Unit and Addenbrooke's Hospital Ethics Committees and the consultants in charge of each patient. Informed written consent was obtained from the patients before beginning the study.

Calculations

Energy expenditure was calculated from O_2 consumption and CO_2 production (indirect calorimetry) using the equation of Elia and Livesey.[13] Energy expenditure = $15.818O_2 + 5.176CO_2$, where O_2 and CO_2 are in liters and energy expenditure is in kilojoules.

Calculation of CO_2 production from the bicarbonate-urea method was made using the equation from Elia et al[6]: net CO_2 production (mol/d) = 0.95 × 0.85 dpm infused per day/24-hour specific activity of urea (dpm/mol). The energy equivalent of CO_2 was assumed to be 535 kJ/mol (which approximates the value obtained in subjects close to nutrient balance while ingesting a typical Western diet,[14] who have a respiratory quotient [RQ] of ~0.85). However, one subject (subject no. 6) had recently become anorectic and had a large negative energy balance. It was estimated[9,10] that the 24-hour RQ would be approximately 0.75 and the energy equivalent of CO_2 581 kJ/mol (both in the calorimeter and at home). Small correction factors to take into account changes in the amount of label in calorimeter air (between 9:00 AM on day 1 and 9:00 AM on day 2) and changes in the size and specific activity of the urea pool were also used as described previously.[6] The energy expended in physical activity plus thermogenesis was calculated as the difference between TEE and BMR. PAL was calculated as the ratio TEE/BMR.

Statistical Methods

Results are expressed as the mean ± SD. Comparisons between results were made by correlation analysis, Student's *t* test, which was applied to paired data when possible, and the procedures described by Bland and Altman.[15]

RESULTS

Practicalities

The subjects tolerated the infusion well, and the minipump apparently did not interfere with normal daily activities, which included brisk walking and jogging (subject no. 1) and routine household activities. The subcutaneous infusion did not cause a local inflammatory reaction.

Measurements During Whole-Body Calorimetry

Twenty-four-hour energy expenditure measured by whole-body indirect calorimetry (Table 2) was found to be 7.96 ± 1.56 MJ/d, and the mean PAL (TEE/BMR) was only 1.23 ± 0.07. Subject no. 6, who consumed only a portion of the food provided, had a considerable negative energy balance of −2.22 MJ/d relative to her TEE (~5.7 MJ/d). The remaining group consumed most of the food provided and had a mean negative energy balance of only −0.66 ± 1.05 MJ/d and a TEE of 8.85 ± 1.09 MJ/d. The BMR of the latter group was 108% ± 13% (NS) of the predicted BMR,[9] and of the group as a whole, 106% ± 11% of the predicted BMR ($P < .05$; Table 3).

Table 3. Gas Exchange, RQ, BMR, and Energy Balance During 24-Hour Whole-Body Calorimetry

	Basal State (BMR)						24-Hour Calorimetry						
Subject No.	O_2 (L/24 h)	CO_2 (L/24 h)	RQ	BMR (kJ/min)	BMR (MJ/24 h)	Predicted BMR (MJ/d)	O_2 (L/24 h)	CO_2 (L/24 h)	RQ	Energy Expenditure (MJ/24 h)	PAL*	Energy Intake MJ/24 h)	Energy Balance (MJ/24 h)
1	358.6	286.6	0.79	4.97	7.16	6.54							
2	332.6	257.8	0.78	4.56	6.57	6.41							
3	361.4	205.9	0.79	3.56	5.13	5.15							
4	257.8	286.6	0.79	4.87	7.01	6.78	427.68	380.16	0.89	8.87	1.26	10.00	+1.13
5†	288.0	246.2	0.85	4.05	5.83	5.87	383.04	328.32	0.85	7.75	1.33	6.46	−1.29
6	253.4	194.4	0.76	3.48	5.01	5.56	292.32	220.32	0.75	5.75	1.15	3.53	−2.22
7‡	419.0	325.4	0.78	5.58	8.04	6.31	495.36	398.88	0.81	9.89	1.23	9.00	−0.89
8	319.7	247.7	0.77	4.40	6.34	5.01	374.4	308.16	0.82	7.52	1.19	5.98	−1.57
Mean	323.82	256.32	0.789	4.43	6.39	5.95	394.56	327.17	0.824	7.96	1.232	6.994	−0.968
SD	56.55	43.35	0.027	0.72	1.04	0.66	74.58	70.23	0.052	1.56	0.069	2.568	1.269

NOTE. Measurement of BMR in the first 3 subjects was made using the ventilated-hood system. All other measurements were made in the whole-body calorimeter.

*Ratio of 24-hour energy expenditure to BMR.

†Subject completed 2 × 20 minutes of exercise only.

‡Subject was unable to undertake exercise, and either stood or walked around the chamber.

Mean CO_2 production obtained by the tracer and calorimetry methods during the whole-body calorimetry study was 14.90 ± 3.25 and 14.58 ± 3.14 mol/d, respectively (100 tracer/calorimetry = 102.1% ± 3.4%; mean difference, −0.32 ± 0.43 mol/d). Twenty-four-hour energy expenditure was found to be 8.07 ± 1.53 MJ/d using the tracer method and 7.96 ± 1.55 MJ/d using indirect calorimetry (100 tracer/calorimetry = 101.5% ± 3.9%; mean difference, −0.11 ± 0.31 MJ/d) (Table 4). The recovery of label as CO_2 leaving the calorimeter was found to be 95.6% ± 0.5% (Table 4). The amount of CO_2 leaving the calorimeter as calculated by the hyamine trapping and titration procedure (426 ± 76 L/d) was found to be 99.0% ± 1.6% of that obtained by indirect calorimetry (mean ± SD, 3.8 ± 7.7 L/24 h).

The mean specific activity of breath CO_2 at 9:00 AM on day 1 and 9:00 AM on day 2 was similar (1,672 ± 271 *v* 1,724 ± 535 dpm/mmol). The specific activities of calorimeter CO_2 were also similar (1,616 ± 204 *v* 1,631 ± 225 dpm/mmol), as were the plasma bicarbonate (25.5 ± 1.0 *v* 25.2 ± 2.3 mmol/L) and urea concentrations (4.5 ± 1.0 *v* 4.8 ± 1.0 mmol/L). The hemoglobin concentration was 127.4 ± 21 g/L, and the hematocrit was 38% ± 2%.

Free-Living Measurements

Free-living measurements of TEE (tracer method) were found to be 8.73 ± 2.36 MJ/d and PAL was 1.36 ± 0.22 (Table 5), with seven of eight subjects having a PAL value of 1.4 or less (tracer method in conjunction with measurement of BMR). The mean PAL value was significantly less than the PAL values considered to apply to moderately active subjects with light to moderate occupational activity (ie, individuals with a PAL[10] value of 1.55 ($P < .05$) to 1.65 ($P < .01$, Student's paired *t* test). It was also significantly lower than the results obtained by the doubly labeled water method[16] (1.59 ± 0.07 for healthy age- and sex-matched subjects, using mean values from each age category). Similarly, activity plus thermogenesis (TEE [bicarbonate-urea method] − BMR, 0.034 MJ/kg/d) was significantly lower ($P < .05$) than the reference values (0.049 to 0.057 MJ/kg/d, corresponding to PAL values of 1.55 to 1.65[10]). It was also significantly lower than the values obtained from doubly labeled water studies, 0.059 ± 0.07 MJ/kg/d ($P < .01$).[16] Energy balance calculated from TEE (bicarbonate-urea method) and dietary recall (Table 5) suggested that the subjects were close to energy balance (−0.70 ± 1.18 MJ/d, not significantly different from zero). There was a good relationship between PAL values calculated from measurement of TEE (bicarbonate-urea method) and measured BMR, on one hand, and those calculated by recall of daily activities, on the other ($R^2 = .90$, $y = 0.353 + 0.717x$, $P < .001$; mean difference, 0.04 ± 0.09).

DISCUSSION

Three conclusions emerge from this investigation. First, the study demonstrates the practicality of infusing subcutaneous bicarbonate for up to 3 days in free-living conditions in patients with lung cancer. The minipump was well tolerated, and the infusion did not cause a local inflammatory reaction. The procedures apparently did not limit, prevent, or alter normal daily activities in the subjects studied.

Second, the study provides the first validation of the bicarbonate-urea method in a whole-body calorimeter in patients with lung cancer, and indeed the first validation in patients with a systemic inflammatory reaction. Furthermore, no whole-body calorimetric validations have been made with the doubly labeled water method in such groups of patients. The results in this small group of patients, which included subjects with low activity and subject no. 6, who was in substantial negative energy balance, provide as good an estimate of CO_2 production (102.1% ± 3.4% of the calorimetry results) as in normal subjects.[4] For comparison, the doubly labeled water method yielded the following results relative to CO_2 production measured by indirect calorimetry in adult subjects without inflammatory disease who were close to energy balance: −5.9% ± 7.6%, 5-day study, n = 5[17], 1.4% ± 3.9%, 6-day study, low activity, n = 5[18]; −1.0% ± 7.0%, 4-day study, high activity, n = 8[18]; −1.9% ± 1.8%, 12-day study, n = 4[19], 5% ± 9%, 4-day study, low-dose tracers, n = 6[20]; 2% ± 5%, 4-day study, high-dose tracers, n = 3[20]; and −2.5% ± 5.8%, 7-day study, n = 12.[21] In a 12-day validation study in a whole-body calorimeter[22] in which healthy men were specifically underfed to lose weight (n = 3, negative energy balance of ~6 MJ/d) or overfed to gain weight

Table 4. Comparison of 24-Hour Net CO_2 Production and Energy Expenditure by Indirect Calorimetry and the Tracer Method

Subject No.	Indirect Calorimetry			Tracer Method		$\frac{\text{Tracer Method}}{\text{Indirect Calorimetry}} \times 100$	
	CO_2 Production (mol/24 h)	EE (MJ/24 h)*	24-Hour Recovery of Label (%)	CO_2 Production (mol/24 h)	EE (MJ/24 h)	CO_2 Production (%)	24-Hour EE (%)
4	16.95	8.87	96	17.18	9.19†	101.4	103.6
5	14.62	7.75	96	15.14	8.10†	103.6	104.5
6	9.80	5.76	95	9.60	5.65‡	98.0	98.2
7	17.80	9.89	95	17.87	9.56†	100.4	96.6
8	13.75	7.52	96	14.70	7.86†	106.9	104.5
Mean	14.58	7.96	95.6	14.90	8.07	102.1	101.5
SD	3.14	1.56	0.5	3.25	1.53	3.4	3.8

Abbreviation: EE, energy expenditure.

*Calculated using measured 24-hour O_2- and CO_2-exchange rates.

†Calculated assuming a value for the energy equivalent of CO_2 of 535 kJ/mol CO_2, which closely applies when RQ = 0.85.

‡Calculated using an energy equivalent of 580.7 kJ/mol CO_2, which closely applies when RQ = 0.75 (see Table 3 for actual 24-hour gas exchange and RQ).

Table 5. CO_2 Production and Components of Energy Balance in Free-Living Conditions

Subject No.	Day	CO_2 Production (mol/d)	24-Hour EE (MJ/d)	BMR (MJ/d)	PAL	Activity EE +Thermogenesis (MJ/d)	Energy Intake (MJ/d)	PAL by Recall	Energy Balance (MJ/d)
1	1	26.10	13.96	7.16	1.95	6.80		1.75	
	2	24.00	12.83		1.79	5.67		1.63	
2	1	15.90	8.52	6.56	1.30	1.96		1.40	
	2	17.00	9.11		1.39	2.55		1.35	
3	1	12.80	6.85	5.13	1.33	1.72	5.86	1.33	−0.99
	2	12.34	6.60		1.29	1.47	5.86	1.33	−0.74
4	2	17.18	9.19	7.08	1.30	2.11	6.94	1.35	+0.81
5	2	15.22	8.14	5.82	1.40	2.32	9.00	1.28	+0.86
6	2	10.80	5.78	5.01	1.15	0.77	3.89	1.14	−2.40
7	2	19.41	10.38	8.04	1.29	2.34	9.05	1.19	−1.33
8	2	13.84	7.40	6.34	1.17	1.06	6.24	1.15	−1.16
Mean		16.78	8.98	6.39	1.39	2.62	6.69	1.35	−0.704
SD	(all values)	4.78	2.56	1.04	0.25	1.89	1.84	0.18	1.176
Mean	(1 value per	16.07	8.73	6.39	1.36	2.34	6.69	1.31	−0.704
SD	subject)*	3.91	2.38	1.04	0.22	1.69	1.84	0.18	1.176

Abbreviation: EE, energy expenditure.

*The mean of the 2 daily values for each of the first 3 subjects is used in the calculations.

(n = 3, positive energy balance of ~7 MJ/d), the results were not as good (−17% ± 16% in the underfeeding study and −8% ± 7% in the overfeeding study). The bicarbonate method has yet to be tested in patients with gross energy imbalance.

There are two basic assumptions associated with the bicarbonate-urea method.[6] The first is that the recovery of labeled CO_2 is 95%. This study confirms that a similar recovery occurs in patients with lung cancer (95.6% ± 0.5%). The second assumption is that the specific activity of urinary urea accurately predicts the composite mean specific activity of CO_2 excreted by the body. This study suggests that a similar relationship exists in patients with lung cancer (those studied in the whole-body calorimeter) as in normal subjects.[6] As a result, the estimates of CO_2 production in our patients with lung cancer were as good as in normal subjects.

Finally, this study provides information about TEE and its components in free-living conditions in patients with malignancy. As in healthy subjects, the physical activity component of TEE was variable (Table 5: PAL ratio of 1.15 in subject no. 6 to 1.87 [mean of consecutive daily values] in subject no. 1), but the results correlated well with estimates of physical activity obtained using the activity questionnaire. However, in most subjects physical activity was reduced. Seven of eight subjects had a PAL ratio of 1.4 or less. This contrasts with values of 1.5 to 1.7 in moderately active healthy individuals undertaking light to moderate occupational activity as suggested in a recent government report,[10] and with a meta-analysis of doubly labeled water studies[15] used to establish an age- and sex-matched control group. However, values as low as 1.4 are thought to be typical of nonactive healthy individuals with a sedentary life-style.[10] The decrease in physical activity is almost certainly due to the effect of inflammatory disease (confirmed by the presence of an acute-phase protein response and/or hypoalbuminemia in most of the subjects), coupled with the additional presence of arthritis and exertional dyspnea in some of the subjects (Table 1). This study also confirms the significant increase in BMR, which we have reported previously in a similar but larger group of patients with small-cell lung cancer.[2] The increase is probably partly due to heat production by the tumor itself and mostly due to increased heat production by the remaining tissues of the body, which are likely to respond to circulating humoral mediators such as cytokines. However, the extent to which BMR was increased in our subjects was small (6%) and generally counterbalanced by a reduction in physical activity, such that TEE is likely to be unchanged or decreased. We have recently reported a similar situation in patients with AIDS.[23,24] Therefore, in this group of patients with cancer of the lung, it appears that disease had little effect on body weight, but it reduced total energy turnover by altering the components of energy expenditure in different ways (increased BMR and reduced physical activity). It is likely that decreases in energy intake (Table 5) rather than increases in TEE are the major cause of the negative energy balance that leads to weight loss. This implies that in attempting to reverse this weight loss, it is probably clinically more relevant to focus on improving food intake rather than attempting to modulate BMR or TEE. Although controlling disease and its complications may improve energy balance by influencing both intake and expenditure, alternative strategies exist that focus primarily on intake or expenditure. The second clinically relevant implication emerging from this study is that the energy requirements (for maintaining energy balance) of patients similar to those studied here are not increased and may even be decreased. However, these conclusions would be strengthened by studies of larger groups of subjects that also take into account the stage of disease, infective and other complications, and the presence of intercurrent nonneoplastic disease.

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