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Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass

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¹*Obesity Research Center and* ³*Department of Cardiology, St. Luke's-Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, New York 10025; and* ²*Department of Human Nutrition, Wageningen Agricultural University, 6703 HD Wageningen, The Netherlands*

Gallagher, Dympna, Daniel Belmonte, Paul Deurenberg, Zimian Wang, Norman Krasnow, F. Xavier Pi-Sunyer, and Steven B. Heymsfield. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. *Am. J. Physiol.* 275 (*Endocrinol. Metab.* 38): E249–E258, 1998.—Investigators have expressed interest in the associations between resting energy expenditure (REE) and body mass for over a century. Traditionally, descriptive models using regression analysis are applied, linking REE with metabolically active compartments such as body cell mass (BCM) and fat-free body mass (FFM). Recently developed whole body magnetic resonance imaging (MRI) and echocardiography methods now allow estimation of all major organs and tissue volumes in vivo. Because measured values are available for REE, BCM, and FFM content of individual organs and tissues, it should now be possible to develop energy expenditure-body composition estimation models based on MRI-measured organ-tissue volumes. Specifically, the present investigation tested the hypothesis that in vivo estimation of whole body REE, BCM, and FFM is possible using MRI- and echocardiography-derived organ volumes combined with previously reported organ-tissue metabolic rates and chemical composition. Thirteen subjects (5 females, 8 males) had REE, BCM, and FFM measured by indirect calorimetry, whole body ⁴⁰K counting, and dual-energy X-ray absorptiometry, respectively. Models developed from estimated and measured variables were highly correlated, with no significant differences between those estimated and measured [e.g., calculated vs. measured REE: $r = 0.92$, $P < 0.001$; (mean \pm SD) $6,962 \pm 1,455$ and $7,045 \pm 1,450$ kJ/day, respectively ($P =$ not significant)]. Strong associations were observed between REE, individual or combined organ weights, BCM, and FFM that provide new insights into earlier observed metabolic phenomena. The present approach, the first to establish an energy expenditure-body composition link with a mechanistic model in vivo, has the potential to greatly expand our knowledge of energy expenditure-body size relationships in humans.

organ mass; fat-free mass; body cell mass; magnetic resonance imaging; resting energy expenditure

LAVOISIER AND LaPlace (26) were the first investigators to elucidate the nature of animal heat production as combustion in 1780. Over the past century, these oxidative processes have been localized to the intracellular or protoplasmic compartment, mainly within mitochondria and to a lesser extent the endoplasmic reticulum (27).

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Nevertheless, relating heat production to body mass poses a challenge to modern investigators who, as yet, lack the ability to quantify heat-producing organs in living humans. The expression of heat production relative to body mass is essential when thermal or energy flux rates are compared between individuals that differ in size or, more specifically, in heat-producing tissue.

The surface law first formulated by Rubner in 1883 [cited by Krogh (24)] and Richet in 1889 (42) suggests that animals produce heat in proportion to body surface area. Investigators in the first several decades of this century developed age- and gender-specific resting energy expenditure (REE) norms based on body weight and stature (4). Kleiber (23) added yet another dimension to this notion by demonstrating that adult animals differing widely in body size had similar metabolic rates relative to body weight raised to the 0.75 power (23).

Another approach, first suggested by Rubner (46) in 1902, is to express REE relative to heat-producing "active tissue mass." Two components are usually considered as representative of whole body metabolically active tissue, body cell mass (BCM) and fat-free body mass (FFM). BCM is typically estimated as the exchangeable potassium space that can be measured by total body potassium (TBK) (31). The fat and fat-free components of body weight can be measured with the use of a number of two-component methods, such as underwater weighing or dilution techniques (11). Almost all human research over the past three decades has explored thermal processes and energy flux with the use of either BCM (22) or as measures of metabolically active tissue mass.

An important problem arising from the use of BCM and FFM as metabolically active tissue surrogates is that the ratio of REE to BCM or to FFM is not constant among individuals but varies systematically with body weight (3, 22, 37–39, 49, 51). Individuals with lower body weights tend to have higher REEs per kilogram of BCM and FFM. That is, heat production rates per unit of BCM and FFM at rest are not the same between individuals who differ in body size. Although this phenomenon can be attributed to a nonzero intercept when REE is regressed on either BCM or FFM (38), the finding remains that energy production rates per unit of metabolically active tissue are not constant but vary systematically as a function of body size. Therefore, attempts to explore between-individual differences in thermal flux have appropriately moved away from REE/BCM and REE/FFM ratios and instead are now largely based on statistical modeling using linear regression analysis methods (3, 22, 28, 37–39, 51).

The lack of homogeneity in heat-producing tissues that constitute BCM and FFM has long been recognized by investigators. Grande (15) and later Holliday and co-workers (19, 20) published reviews summarizing animal and human studies that illustrated between-organ differences in REE. More recently, Elia (8, 9) has expanded on these reviews highlighting the existence of large between-organ differences in the rates of energy flux. Brain, liver, and other visceral organs have high rates of heat production in the postabsorptive state, whereas organs such as adipose tissue and skeletal muscle have relatively low rates of heat production. Garby and Lammert (14) suggested that a large part of between-subject variation in REE can be explained by variation in organ-tissue proportions. Owen et al. (33) hypothesized a higher proportion of metabolically active tissues as an explanation for the increased REE observed after controlling for FFM in achondroplastic dwarfs. Thus it would appear that heterogeneity in the proportion of body weight as various tissues and organs is a likely explanation for the large observed between-individual differences in REE, even after adjustment for body surface area, BCM, or FFM.

Although it has been evident for some time that quantification of organ-tissue compartment size in body composition studies might provide insight into individual variations in energy expenditure, advances in this area were limited until the recent introduction of whole body magnetic resonance imaging (MRI). Although computerized axial tomography afforded an earlier opportunity to quantify organ and tissue volumes (18), MRI is capable of *in vivo* body composition analysis without the risks associated with ionizing radiation (44). Complete organ-tissue volume reconstruction of some compartments is now possible in females and males of all ages, with MRI alone or in combination with echocardiography for estimating left ventricular volume, when gated cardiac MRI is unavailable.

With these advances in imaging methodology, it should now be possible to develop models that derive an individual's REE, BCM, and FFM from mass measurements of specific organs and tissues. That is, because estimates are available for specific organ-tissue oxygen consumption or energy flux rates, and the proportion of tissues as FFM and potassium is known, it should be feasible, given the mass of an individual's organs and tissues, to estimate total REE, BCM, and FFM.

The study of associations between REE, BCM, and FFM could provide new insights into many inadequately explained metabolic phenomena and help to establish the basis of observed differences in energy requirements between individuals and between groups such as young, old, lean, and obese. Accordingly, the present investigation was designed to test the hypothesis that the *in vivo* estimation of whole body REE, BCM, and FFM is possible using MRI- and echocardiography-derived organ volumes combined with previously reported organ-tissue metabolic rates and chemical composition.

METHODS

Protocol

Three models were evaluated by comparing respective estimated values with available reference methods. Accordingly, REE calculated from organ-tissue mass (REE_c) was compared with REE measured with a ventilated hood inside the Columbia respiratory chamber indirect calorimeter (REE_m). BCM and FFM estimated on the basis of organ-tissue mass (BCM_c and FFM_c) were compared with TBK-derived whole body fat-free cell mass (BCM_m) and FFM (FFM_m) estimated with whole body dual-energy X-ray absorptiometry (DXA), respectively.

Subjects required three closely spaced evaluations for all metabolic and body composition studies. On the first evaluation day, each subject completed a medical evaluation that included a physical examination and screening blood tests after an overnight fast. Healthy subjects without any diagnosed medical conditions and with normal thyroid hormone values were enrolled in the study. On the second day, whole body MRI was carried out for the determination of total body skeletal muscle, adipose tissue, brain, liver, and kidney mass, and left ventricular heart mass was quantified by echocardiography. REE was measured on the third evaluation day after an overnight fast.

Models

In the current study, total body mass is considered a seven-component system, with body mass (BM) expressed as

$$BM = \sum_{i=1}^7 (M_i) \quad (1)$$

where M_i is the mass of individual organs and tissues. Specifically

$$BM = M_{\text{brain}} + M_{\text{liver}} + M_{\text{heart}} + M_{\text{kidneys}} + M_{\text{SM}} + M_{\text{AT}} + M_{\text{residual}} \quad (2)$$

Residual mass was calculated as body mass minus the sum of brain, liver, heart, kidneys, skeletal muscle (SM), and adipose tissue (AT) mass. Residual mass in Reference Man (48) accounts for 33% of body weight and consists of skeleton (8.5 kg or 12.1%), blood (5.5 kg or 7.9%), skin (2.6 kg or 3.7%), connective tissue (1.6 kg or 2.3%), gastrointestinal tract (1.2 kg or 1.7%), and lung (1.0 kg or 1.4%).

Whole body REE (in kJ/day) was calculated as the sum of REE for six individual (subscript i) organs/tissues plus residual mass

$$REE_c = \sum_{i=1}^7 (REE_i) = \sum_{i=1}^7 (OMR_i \times M_i) \quad (3)$$

where OMR is organ metabolic rate (in $\text{kJ} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and M_i is organ mass in kilograms. Energy flux rates were assigned for each of the seven components as indicated in Table 1 on the basis of a summary of earlier literature reported by Elia (8). Residual mass was assigned an energy expenditure of $50 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ as reported by Elia (9). The composite REE equation is

$$REE_c = 1,008 \cdot M_{\text{brain}} + 840 \cdot M_{\text{liver}} + 1,848 \cdot M_{\text{heart}} + 1,848 \cdot M_{\text{kidneys}} + 55 \cdot M_{\text{SM}} + 19 \cdot M_{\text{AT}} + 50 \cdot M_{\text{residual}} \quad (4)$$

Table 1. *Organ and tissue coefficients used in developing models*

	Weight, kg	Density, kg/l	Potassium, mmol/kg	Metabolic Rate, kJ·kg ⁻¹ ·day ⁻¹
Skeletal muscle	28.0	1.04	76.7	55.0
Adipose tissue	15.0	0.92	8.2	19
Liver	1.8	1.050	63.9	840
Brain	1.4	1.03	76.4	1,008
Heart	0.33	1.03	54.5	1,848
Kidneys	0.31	1.05	48.4	1,848
Residual*	23.16		45.6	50

Weight, density, and potassium were derived from 70-kg Reference Man (48); metabolic rate was derived from Elia (8). *Residual mass was not assigned a density but was calculated as body mass minus sum of other measured mass components.

Organ and tissue mass in kilograms was reconstructed from MRI-derived cross-sectional images

$$M_i = V_i \times d_i \quad (5)$$

where V is volume (in l) and d is organ-tissue density (in kg/l) (Table 1) (48). BCM (in kg) was calculated as a function of potassium contents for the seven organs and tissues

$$\text{BCM} = 0.00833 \times \sum_{i=1}^7 (K_i \times M_i) \quad (6)$$

where K_i is organ potassium content (in mmol/kg) as summarized in Table 1, and 0.00833 is the conversion factor of potassium to BCM reported by Moore et al. (31). Specifically

$$\text{BCM} = 0.00833 \times (76.4 \cdot M_{\text{brain}} + 63.9 \cdot M_{\text{liver}} + 54.5 \cdot M_{\text{heart}} + 48.4 \cdot M_{\text{kidneys}} + 76.7 \cdot M_{\text{SM}} + 8.2 \cdot M_{\text{AT}} + 45.6 \cdot M_{\text{residual}}) \quad (7)$$

Potassium content of the residual mass was assumed a constant 45.6 mmol/kg on the basis of Reference Man (48). FFM (in kg) was calculated as

$$\text{FFM} = \text{BW} - 0.80 \times M_{\text{AT}} \quad (8)$$

where BW is body weight, and 0.80 is the fraction of adipose tissue as ether-extractable fat. We assume a negligible fat content of other organs and tissues.

Subjects

The subjects were a convenience sample of healthy women and men recruited from among hospital center employees and participants in an ongoing longitudinal aging study (13). Age (18–50 yr) and body mass index (18–27 kg/m²) limits were set to avoid the influence of aging and excess weight on the main study hypothesis. Inclusion criteria required that subjects be ambulatory, nonvigorously exercising, and with no orthopedic problems that could potentially affect body composition. The study was approved by the Institutional Review Board of St. Luke's-Roosevelt Hospital, and all subjects gave written consent to participate.

Body Composition

Body weight was measured to the nearest 0.1 kg (Weight Tronix, New York, NY) and height to the nearest 0.5 cm with the use of a stadiometer (Holtain, Crosswell, UK).

MRI

Adipose tissue and skeletal muscle mass were measured using MRI cross-sectional images of the total body (18, 45).

Subjects were placed on the 1.5-T scanner (General Electric, 6X Horizon, Milwaukee, WI) platform with their arms extended above their heads. The protocol involved the acquisition of ~40 axial images at 10-mm thickness and at 40-mm intervals across the whole body (44). The technical error for measurements of the same scan on two separate days by the same observer of MRI-derived skeletal muscle and adipose tissue volumes in our laboratory is $0.7 \pm 0.1\%$ and $1.1 \pm 1.2\%$ in four subjects, respectively.

Liver and kidney images were produced using an axial T1-weighted spin echo sequence with 5-mm slice thickness, no interslice gap, and a field of view equal to $40 \times 40 \text{ cm}^2$ [$256 \times 192/2$ number of excitations (NEX)]. Approximately 40 slices were acquired from the diaphragm to the base of the kidneys. Brain images (~29) were produced using a body coil with a fast spin echo T2-weighted sequence with 5-mm contiguous axial images and a $40 \times 40 \text{ cm}^2$ ($256 \times 256/1$ NEX) field of view.

All MRI scans for adipose tissue and skeletal muscle were read by the same trained observer, and the remaining organ volumes were all read by a second trained observer. Images were analyzed using VECT image analysis software (Martel, Montreal, CA) on a Sun Workstation (Silicon Graphics, Mountain View, CA). Organ and tissue cross-sectional areas on each axial image were integrated to mass estimates for the whole body (18) as

$$\text{organ or tissue mass (kg)} = 0.001 \times \{d_i \times \sum [A \times (B_1 + B_2)/2]\} \quad (9)$$

where d_i (in kg/l) is the density for each organ and tissue (Table 1), A is the distance (in cm) between scans, and B_1 and B_2 are the organ-tissue areas (in cm²) in adjacent scans.

Echocardiography

Left ventricular mass was evaluated with a two-dimensionally guided M-mode echocardiogram (Hewlett-Packard 1500, Boise, Idaho) interfaced with strip chart recorder, two-dimensional video recorder, and either a 2.5- or a 3.5-MHz probe. Subjects were studied in the partial left decubitus position. Left ventricular dimensions were recorded from the parasternal long axis view at or below the tips of the mitral valve leaflets. The hard-copy strip chart recording was used for all measurements. End-diastolic and end-systolic dimensions were measured at the peak of the R wave and peak of the posterior wall motion, respectively, according to the American Society of Echocardiography convention (21). Wall thickness was measured using the Penn convention, and left ventricular mass was calculated according to the formula of Devereux and Reichek (7). A minimum of five cardiac cycles were used for all measurements. All echocardiographic tracings were read by a single investigator (Krasnow). The technical error for repeated echo measurements of the same scan by the same observer for left ventricular mass was 1.1%. Left ventricular mass was used as a surrogate for total heart weight in the present study.

Whole Body ⁴⁰K Counting

TBK was measured using the St. Luke's four-pi whole ⁴⁰K body counter (35). The ⁴⁰K raw counts accumulated over 9 min were adjusted for body size on the basis of a ⁴²K calibration equation (35). The current technical error in our laboratory for repeated phantom ⁴⁰K counting is 2.4%. TBK was calculated as ⁴⁰K/0.000118 (11).

DXA

Total body fat and FFM [body wt - (body wt × percent fat)] were measured with a whole body DXA scanner (DPX, Lunar Radiation, Madison, WI; version 3.6 software) (30). The between-measurement technical error for DXA-measured FFM in the same subject is 1.2%.

Energy Expenditure

Whole body REE was measured with the use of a ventilated hood inside the Columbia respiratory chamber indirect calorimeter (17). The subject reported in the morning in a postabsorptive state. After entering the chamber, subjects rested comfortably in the thermoneutral environment on a bed, and a plastic transparent ventilated hood was placed over the head for 40–60 min. Rates of oxygen consumption and carbon dioxide production were analyzed using magneto-pneumatic oxygen (Magnos 4G) and carbon dioxide (Magnos 3G) analyzers (Hartmann & Braun, Frankfurt, Germany), and the data were displayed and stored by the on-line computer system. Gas exchange results were evaluated during the stable measurement phase and converted to REE (in kJ/day) with the use of the formula reported by Weir (52). Gas concentration measurements are reproducible to within 0.8% for a standard alcohol phantom.

Statistical Analysis

Three statistical methods were used to examine agreement between calculated and measured REE, BCM, and FFM. First, calculated and measured means ± SD were compared using the Student's *t*-test. In the second stage of analysis, correlations between calculated and measured variables were compared by simple linear regression analysis. The third and final analysis was an exploration of agreement between calculated and measured variables as described by Bland and Altman (2). Statistical significance was set at $P < 0.05$.

Exploratory correlations between REE and body composition were examined using simple and multiple linear regression analyses. Data were analyzed using Microsoft Excel (version 5.0). Descriptive subject data are expressed as means ± SD.

RESULTS

Baseline Characteristics

The baseline subject characteristics are shown in Table 2. The subject pool consisted of five women and eight men who ranged in age from 25 to 48 yr. The mean ages of women and men were similar and not significantly different. Men as a group were heavier, taller, and had a greater body mass index compared with the women (all between-gender comparisons, $P < 0.001$).

Table 2. Subject baseline characteristics

	Women (<i>n</i> = 5)	Men (<i>n</i> = 8)	Combined (<i>n</i> = 13)
Age, yr	31.6 ± 7.4	30.9 ± 7.6	31.2 ± 7.2
Body wt, kg	51.6 ± 6.5	78.6 ± 7.4*	68.2 ± 15.3
Height, cm	159.3 ± 9.1	179.2 ± 7.0*	171.6 ± 12.6
Body mass index, kg/m ²	20.3 ± 1.5	24.4 ± 1.4*	22.9 ± 2.5
Body fat, %	21.8 ± 5.6	14.8 ± 4.8*	17.1 ± 6.0

Values are means ± SD; *n* = no. of subjects. * $P < 0.001$ for women vs. men.

Table 3. Subject resting energy expenditure

	Women	Men	Combined
Resting energy expenditure, kJ/day			
Measured	5,558 ± 296	7,975 ± 995*	7,045 ± 1,450
Calculated	5,430 ± 459	7,920 ± 888*	6,962 ± 1,455
Difference	128 ± 285	55 ± 650	83.3 ± 525

Values are means ± SD. Difference is calculated resting energy expenditure (see Eq. 4) minus measured resting energy expenditure. * $P < 0.001$ for women vs. men.

Men had a significantly ($P < 0.001$) lower percentage of body weight as fat by DXA compared with the women.

Men had greater REE (Table 3), TBK, BCM, FFM, five organ-tissue weights (brain, liver, heart, kidneys, and skeletal muscle), and residual mass (Table 4) than women (all between-gender differences, $P < 0.001$). The difference between women and men in total body adipose tissue (13.9 ± 3.8 vs. 13.7 ± 3.8 kg) was not statistically significant.

Energy Expenditure-Body Composition Correlations

REE_m, FFM_m, and BCM_m were all highly correlated with each other (REE_m vs. FFM_m: $r = 0.92$, $P = 0.0001$; REE_m vs. BCM_m: $r = 0.92$, $P = 0.0001$; and BCM_m vs. FFM_m: $r = 0.99$, $P = 0.0001$) and with body weight (Table 5; all r values in Table 5 ≥ 0.53 are $P < 0.05$).

Visceral organs (i.e., liver and kidneys) and heart were all highly intercorrelated with each other (r values = 0.89–0.95), with skeletal muscle (r values = 0.75–0.85), and with total adipose tissue free mass (ATFM = body wt - adipose tissue; r values = 0.79–0.85). Note that ATFM is similar to the FFM component (i.e., ATFM = FFM - fat-free adipocyte mass). Brain mass was also significantly correlated with other components within ATFM, but the magnitudes of these correlations (r values = 0.51–0.58) were smaller compared with those for the visceral organs and heart. For example, there was a strong correlation between liver

Table 4. Subject body composition results

	Women	Men	Total
TBK, mmol			
Measured	2,273 ± 327	4,315 ± 373*	3,530 ± 1,089
Calculated	2,495 ± 315	4,280 ± 396*	3,594 ± 971
BCM, kg			
Measured	18.5 ± 2.7	35.1 ± 3.0*	28.7 ± 8.9
Calculated	20.3 ± 2.6	34.8 ± 3.2*	29.2 ± 7.9
FFM, kg			
Measured	40.4 ± 4.6	66.2 ± 8.0*	56.7 ± 14.7
Calculated	40.4 ± 4.8	67.7 ± 6.2*	57.2 ± 14.8
Organ/tissue wt, kg			
Brain	1.47 ± 0.14	1.65 ± 0.15‡	1.58 ± 0.17
Liver	1.33 ± 0.26	1.93 ± 0.36†	1.70 ± 0.44
Heart	0.12 ± 0.04	0.21 ± 0.05†	0.17 ± 0.06
Kidneys	0.29 ± 0.03	0.42 ± 0.10†	0.37 ± 0.10
Skeletal muscle	18.9 ± 3.2	35.7 ± 3.8*	29.2 ± 9.2
Adipose tissue	13.9 ± 3.8	13.7 ± 3.8	13.8 ± 3.7
Residual	15.5 ± 1.9	25.0 ± 2.9†	21.4 ± 5.4

Values are means ± SD. TBK, total body potassium; BCM, body cell mass; FFM, fat-free body mass. * $P < 0.001$, † $P < 0.01$, and ‡ $P < 0.05$ for women vs. men.

Table 5. *Metabolism-body composition correlation matrix*

	REE _m	BCM _m	FFM _m	BW	Organs	Organs + SM	ATFM	Brain	Liver	Heart	Kidneys	SM	AT	Residual
REE _m														
BCM _m	0.92													
FFM _m	0.92	0.991												
BW	0.87	0.96	0.97											
Organs	0.90	0.83	0.87	0.84										
Organs+SM	0.92	0.99	0.98	0.96	0.87									
ATFM	0.91	0.99	0.997	0.97	0.86	0.99								
Brain	0.73	0.56	0.56	0.47	0.70	0.56	0.56							
Liver	0.84	0.82	0.86	0.85	0.97	0.87	0.85	0.51						
Heart	0.84	0.82	0.85	0.83	0.96	0.86	0.84	0.59	0.95					
Kidneys	0.83	0.75	0.82	0.79	0.93	0.77	0.79	0.58	0.90	0.89				
SM	0.91	0.99	0.98	0.96	0.85	1.00	0.99	0.54	0.85	0.84	0.75			
AT	-0.09	-0.01	0.01	0.24	-0.00	0.02	-0.00	-0.33	0.09	0.05	0.09	0.02		
Residual	0.85	0.94	0.96	0.92	0.79	0.90	0.96	0.53	0.76	0.76	0.78	0.90	-0.04	

REE_m, measured resting energy expenditure; BCM_m, measured BCM; FFM_m, measured FFM; BW, body wt; SM, skeletal muscle; AT, adipose tissue; ATFM, AT free mass; organs, brain+liver+heart+kidneys; residual, BW minus sum of brain+liver+heart+kidneys+SM+AT.

mass and ATFM ($r = 0.85$, $P = 0.0002$), whereas there was a weaker correlation between brain mass and ATFM ($r = 0.56$, $P = 0.047$).

An expanded exploratory analysis of associations between REE and organ-tissue components was carried out using multiple regression analysis. Measured REE (kJ/day) was set as the dependent variable, and the seven organ-tissue system components (in kg) were set as independent variables in the regression model. Of the seven components, brain and skeletal muscle were significant independent variables, as indicated in the following model

$$\text{REE}_m = -881 + 2,883 \cdot \text{brain} + 115 \cdot \text{SM}$$

with $r = 0.95$, standard error of estimate (SEE) = 450 kJ/day, and $P < 0.001$.

REE

The mean values for REE_c (Eq. 4) and REE_m were $6,962 \pm 1,455$ and $7,045 \pm 1,450$ kJ/day, respectively [$P = \text{not significant (NS)}$]. REE_c was highly correlated with REE_m ($\text{REE}_c = 352.4 + 0.94 \times \text{REE}_m$; $r = 0.94$, $\text{SEE} = 540$ kJ/day, $P = 0.0001$; Fig. 1). A Bland Altman plot showed no significant trend ($r = -0.01$, $P = \text{NS}$) between calculated and measured REE difference (i.e., $\text{REE}_m - \text{REE}_c$; 83 ± 525 kJ/day) vs. the average of REE_c and REE_m.

BCM

The mean values for calculated TBK and measured TBK were $3,512 \pm 999$ mmol and $3,530 \pm 1,089$ mmol, respectively ($P = \text{NS}$). A similar good agreement was observed between BCM_c (Eq. 7) and BCM_m (Table 4). BCM_c was highly correlated with BCM_m ($\text{BCM}_c = 3.8 + 0.89 \times \text{BCM}_m$; $r = 0.99$, $\text{SEE} = 0.87$ kg, $P = 0.0001$; Fig. 2). A Bland Altman plot showed a small but statistically significant trend ($r = 0.69$, $P < 0.01$) between calculated and measured BCM difference (i.e., $\text{BCM}_m - \text{BCM}_c$; -0.5 ± 1.3 kg) vs. the average of BCM_c and BCM_m. The deviation from the line of identity can

be seen in the BCM_c vs. BCM_m scatter plot presented in Fig. 2.

FFM

The mean values for FFM_c (Eq. 8) and FFM_m were 57.2 ± 14.8 and 56.7 ± 14.7 kg, respectively ($P = \text{NS}$). FFM_c was highly correlated with FFM_m in the pooled group ($\text{FFM}_c = 0.07 + 1.01 \times \text{FFM}_m$; $r = 0.996$, $\text{SEE} = 1.37$ kg, $P = 0.0001$; Fig. 3). A Bland Altman plot showed no significant trend ($r = 0.13$, $P = \text{NS}$) between calculated and measured FFM difference (i.e., $\text{FFM}_m - \text{FFM}_c$; -0.5 ± 1.3 kg) vs. the average of FFM_c and FFM_m, with one data point below the 2 SD limits of agreement.

Metabolism-Body Composition Interrelations

The estimated proportional contributions of organs and tissues to REE, BCM, and FFM are presented in Fig. 4. The proportional contribution of each organ and

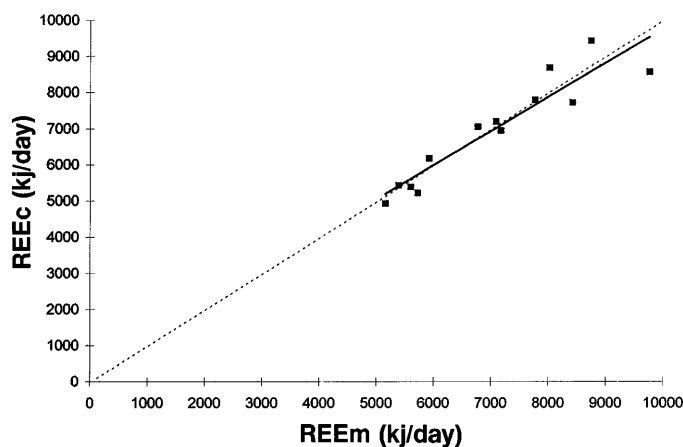


Fig. 1. Calculated resting energy expenditure (REE_c) plotted against measured resting energy expenditure (REE_m), both expressed in kJ/day, for 13 women and men [$\text{REE}_c = 352.4 + 0.94 \times \text{REE}_m$; $r = 0.94$, standard error of estimate (SEE) = 540 kJ/day, $P = 0.0001$]. Dashed line is line of identity, and solid line is regression line. REE_c and REE_m were not significantly different.

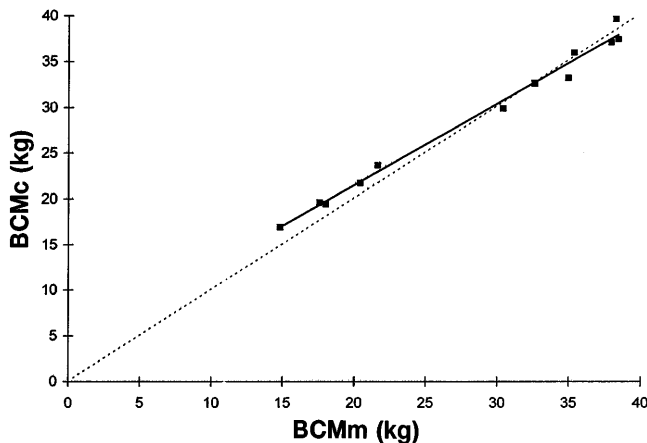


Fig. 2. Calculated body cell mass (BCM_c) plotted against measured body cell mass (BCM_m), both expressed in kg, for 13 women and men ($BCM_c = 3.8 + 0.89 \times BCM_m$; $r = 0.99$, $SEE = 0.87$ kg, $P = 0.0001$). Dashed line is line of identity, and solid line is regression line.

tissue to the total estimated variable was calculated using the respective REE and body composition formulas along with measured organ and tissue masses. As shown in Fig. 4, organs were major contributors to total calculated REE. Specifically, brain, liver, heart, and kidneys accounted for $58.0 \pm 4.8\%$ of total calculated REE. These four organs, which comprise 5.7% of mean body weight, are smaller contributors to both total calculated FFM ($6.9 \pm 1.1\%$) and BCM ($7.5 \pm 1.3\%$). In contrast to organs, skeletal muscle was a smaller REE determinant in the 13 subjects ($22.5 \pm 3.4\%$) but accounted for a large proportion of both FFM ($50.4 \pm 4.1\%$) and BCM ($62.1 \pm 3.9\%$). Adipose tissue, which accounted for $13.8 \pm 3.7\%$ of body weight, was a minor contributor to total calculated REE ($3.9 \pm 1.3\%$), BCM ($3.4 \pm 1.3\%$), and FFM ($5.2 \pm 2.0\%$).

DISCUSSION

Investigators over the past several decades have expressed interest in the associations between REE, BCM (15, 22), and FFM (3, 37–39, 49, 51). The present

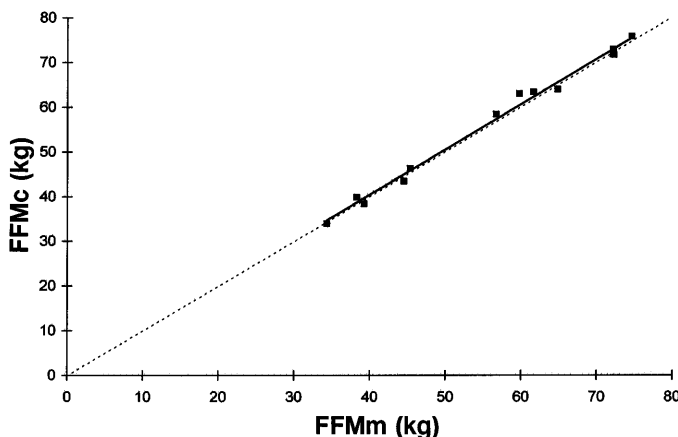


Fig. 3. Calculated fat-free body mass (FFM_c) plotted against measured fat-free mass (FFM_m), both expressed in kg, for 13 women and men ($FFM_c = 0.07 + 1.01 \times FFM_m$; $r = 0.996$, $SEE = 1.37$ kg, $P = 0.0001$). Dashed line is line of identity, and solid line is regression line.

in vivo study is the first to our knowledge that demonstrates the common link between oxidative metabolism and body composition variables within the tissue system level of body composition. That is, total body REE, BCM, and FFM were accurately reconstructed (with the exception of a small systematic bias for BCM) and related to each other in our subjects with the use of seven tissue system level components, namely, brain, liver, heart, kidneys, skeletal muscle, adipose tissue, and residual mass. These observations suggest that at the group level in normal-weight young adults, both oxidative metabolism and body composition follow definable relations.

Linkage With Earlier Studies

Investigators, beginning in the nineteenth century, attempted to comprehend the associations between energy expenditure and body mass in almost every species of animal, including humans (23). Two broad approaches have been applied in humans over the past several decades. The first is to formulate descriptive models (5), as in the early work reported by Harris and Benedict (16), linking REE with body mass, in which REE gender-specific regression models were developed based on subject body weight, stature, and age. Because body weight, per se, includes the large oxidatively inert fraction triglycerides (i.e., fat), recent investigators improved REE regression models by replacing body weight and stature with either BCM (22) or FFM (3, 28, 37–39, 51). The alternative approach is based on theoretical or experimentally derived “mechanistic models” (5) such as those reported by Grande (15), Holliday and co-workers (19, 20), and Elia (8, 9) and as expanded on in the present study.

An important question arose from earlier energy expenditure-body composition studies, a finding fully supported in the present study: why are correlations developed from regression models between REE and either BCM or FFM so strong? Strong associations are observed in our subjects (r values = 0.75–0.86) between liver, heart, and kidneys with both BCM and FFM (Table 5). Moreover, these organs with the addition of brain mass provided correlation coefficients with REE approaching those observed for the substantially larger ATFM and the closely related FFM component. The results of the present study, therefore, support the hypothesis that BCM and FFM are good surrogate body composition markers for oxidatively active tissues. This observation may also explain the good correlations observed by many investigators over the past few decades between REE and either BCM or FFM.

The one exception to these strong organ-BCM/FFM associations was brain (r values = ~ 0.56). Unlike the other organs and tissues, which scale closely to body weight or body weight to the 0.75 power in most mammals and humans (1, 6, 25), brain mass is only weakly associated with body weight and its BCM and FFM components or it may scale to powers of body weight that are different from those of other metabolically active components (e.g., 0.66) (47). This observation is supported by earlier studies, including the

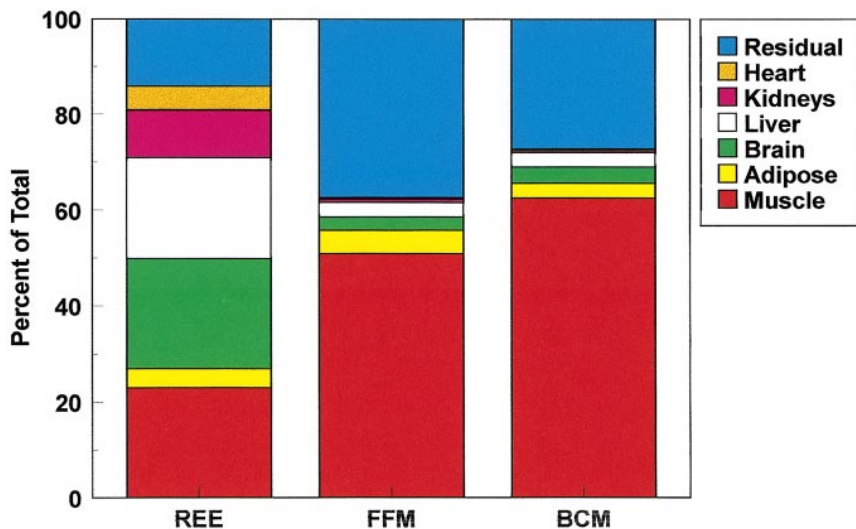


Fig. 4. Proportional contribution of organs and tissues to calculated REE, FFM, and BCM. Proportional contribution of each organ and tissue to total estimated variable was calculated using respective REE and body composition formulas presented in METHODS section.

postmortem internal organ investigation of 4,667 Japanese subjects (32) in which there was no apparent within-gender association between body weight and brain mass in adults.

The weak association between body size and brain mass compared with other organs and tissues may also explain why, in the current study, brain entered into the exploratory REE multiple regression model along with skeletal muscle mass. Skeletal muscle, a large ATFM component, was highly correlated with heart and visceral organs and likely represents a surrogate for body weight-sensitive, metabolically active organs and tissues. On the other hand, brain is highly metabolically active and yet shows only limited associations with body size or scales differently with respect to body weight than other organs and tissues. Hence, a reasonable hypothesis is that the high correlation observed between REE and brain along with skeletal muscle is due to inclusion of weight-sensitive and weight-insensitive metabolically active components. Alternatively, skeletal muscle may scale in relation to body weight similar to heart, liver, and kidneys, whereas a different scaling relation to body weight exists for brain (47).

Applications

Investigators have studied the body mass determinants of energy expenditure for over a century, and interest in this topic continues in relation to body weight regulation (43) and estimation of energy requirements (9). Growth and development, pregnancy and lactation, and aging are only a few of the topics for which limited information is available on REE in relation to body mass and composition, beyond the associations developed in descriptive regression models.

An example of how the present approach provides illuminating information on energy expenditure-body composition relations is the long-standing observation that the association between REE and FFM has a nonzero positive intercept (38). One consequence of this

phenomenon is that the ratio of REE to FFM is not the same between individuals but varies systematically with body mass. Specifically, individuals with small body mass and FFM have REE/FFM ratios that are larger in magnitude than those observed in heavier subjects (9, 38). A similar phenomenon is observed across mammals as a whole, and one hypothesis is that small animals (e.g., shrew, rat, etc.) have a greater proportion of body mass and FFM as high-metabolic-rate components such as brain (6) and liver and correspondingly reduced proportions of low-metabolic-rate organs and tissues such as adipose tissue and skeleton (8, 23).

Hypotheses such as this one can be explored using the present study methods as shown in Fig. 5 for the 13 study subjects. Regression lines are not included in this example, as the subject pool is small and includes both women and men. REE and organ weights are expressed relative to ATFM and plotted against body weight. There is a progressive lowering with increasing body weight in the REE/ATFM ratio and in the proportion of ATFM as brain and three organs (heart, liver, and kidney) and a reverse trend with increasing body weight in the proportion of ATFM as skeletal muscle. Subjects with a lower body mass, primarily women in the current study, have a larger fraction of their ATFM as high-metabolic-rate organs and tissues and, as would be expected, based on these findings, women also have a higher REE/ATFM ratio. Hence, ATFM and related FFM are clearly not homogeneous across all subjects with respect to organ-tissue proportions, and these proportions may vary systematically with body mass. Observations such as these may explain why, for example, women have a larger ratio of REE to FFM than men and, similarly, why lean subjects have a larger ratio of REE to FFM than their obese counterparts. Obviously, a much larger and diverse subject pool is required to appropriately explore these issues, but this demonstration clearly shows that such analyses are now possible.

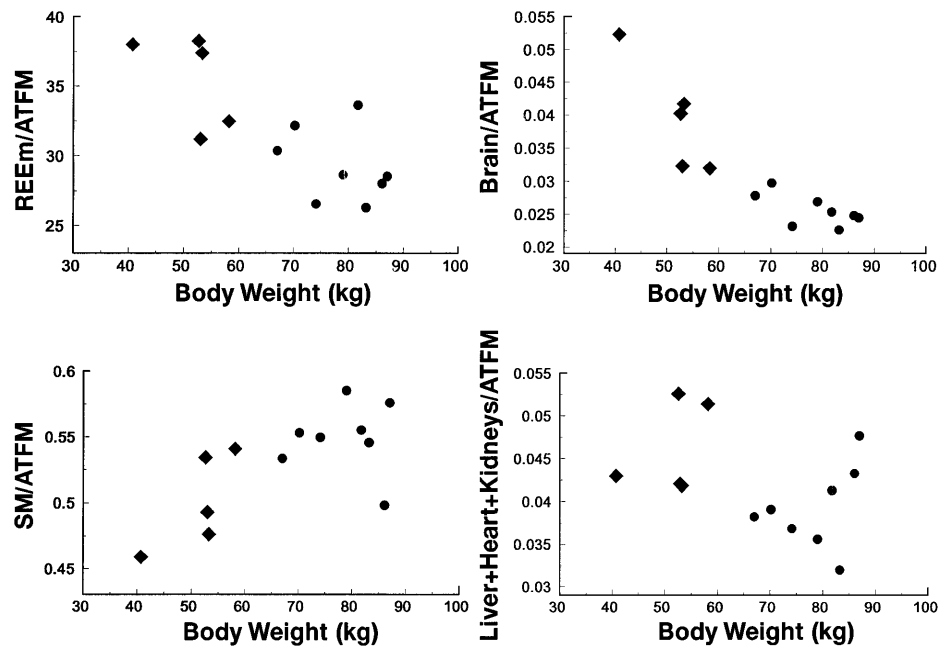


Fig. 5. Ratio of REE_m, brain mass, skeletal muscle (SM), and sum of heart+liver+kidney mass to adipose tissue free mass (ATFM) vs. body wt for 13 women (◆) and men (●).

Another potential application of the findings of the present study are improved REE-body composition regression models. With multiple regression analysis, the measured organ volumes, namely brain and skeletal muscle, provided a higher correlation with REE compared with all of the other evaluated body composition components. This exploratory analysis can be expanded on in future studies.

Study Limitations

Assumed constants. The main disadvantage of model-based prediction methods such as those advanced in the present report are the required assumed constants. Twenty-two separate assumed constants were needed in developing the three energy expenditure-body composition estimation models, and the potential for model error is sizable. Our models make no provision for individual variation in organ energy expenditure, as might be the case with aging and obesity (39), during various stages of the menstrual cycle, and with disease states such as thyroid disturbances. Additionally, factors extrinsic to mass-related organ heat production, such as brown fat in animals and sympathetic nervous system activity in humans and animals (29, 36, 40, 50), may also influence measured whole body REE. A final concern is that the assumed tissue potassium concentrations were developed from Reference Man data (48), and it is unclear whether the assumed constants are equally accurate in women. Subtle model errors may explain, for example, the bias observed between estimated and measured BCM.

This important limitation of the present approach suggests the need for new and improved modeling and physiological measurement methods. The energy expenditure-body composition modeling strategy reported in the present investigation represents a transition from earlier cadaver studies to now-measurable organ-tissue components in vivo. This approach hopefully

represents an intermediate development stage on the eventual pathway to the measurement of organ-tissue oxygen consumption or related metabolic rates, in addition to chemical composition, in vivo. Methods based on magnetic resonance spectroscopy and positron emission tomography are becoming available that will allow in vivo quantification of oxygen uptake of defined regions within an organ or tissue of interest (10, 41). Similarly, the possibility now exists to quantify organ water content and cell mass using various MRI and magnetic resonance spectroscopy methods (12). Assumed physiological values such as those summarized in Table 1 and employed in the current models may no longer be needed if the anticipated advances are made in noninvasive monitoring over the coming years.

Organ-tissue homogeneity. In addition to the many constants required for model development that are listed in Table 1, the approach employed in the current study assumes that organs and tissues are homogeneous in composition. Notably, the developed models and MRI measurement protocol assume negligible amounts of infiltrated organ and tissue fat, edema, cystic structures, and inclusion of any other substance that would render inaccurate the assumed organ and tissue properties summarized in Table 1. Our models therefore may not prove equally accurate in subjects with diseases such as muscular dystrophy (i.e., lipid replacement of skeletal muscle fibers) or alcoholic hepatitis (i.e., fatty infiltration of liver). Additional validation studies are required in groups such as the obese and elderly in whom the developed models may prove less accurate. A related concern is that we used left ventricular mass as a surrogate for total heart weight. Left ventricular mass accounts for approximately two-thirds of heart weight in the healthy adult, and the errors introduced by our assumption are likely small.

Residual mass heterogeneity. Another less significant problem is that residual mass does not represent one histologically distinct component, but, by necessity, smaller organs and tissues were grouped into this single unmeasured component, which on average accounted for 31.4% of body weight in the pooled women and men. MRI measurement methods as employed in the current study are capable of quantifying smaller organs (e.g., pancreas, spleen, thyroid gland, etc.) and tissues (e.g., skin, etc.); however, limited data are available on respective densities, oxygen consumptions, and potassium concentrations per cell mass content. The potential exists for future studies to provide answers to this missing information by additional experimentation. Nevertheless, our three energy expenditure-body composition models provided excellent predictions of respective measured components.

Conclusions

The present study validated in a young and normal-weight cohort of women and men three metabolism-body composition formulas, all based on organ and tissue volumes derived by whole body MRI. These formulas offer the potential to explore oxidative metabolic processes in relation to body mass in both health and disease. The formulas also offer a bridge to future studies designed to quantify directly in vivo organ-tissue energy flux and chemical composition.

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