Relationship Between Resting Metabolic Rate and the Composition of the Fat-Free Mass

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Although a low resting metabolic rate (RMR) has been shown to be a risk factor for future weight gain, little is known about the mechanisms determining its level. We tested the hypothesis that the composition of the fat-free mass (FFM) is a main determinant of RMR. If this hypothesis is true, a regression model including internal organ masses as independent variables should explain a larger fraction of the variance in RMR than is explained using only FFM as a predictor. We measured fat mass by hydrodensitometry, liver and kidney volumes by computed tomography (CT), heart mass by echocardiography, muscle mass by dual-energy x-ray absorptiometry (DEXA), and RMR by calorimetry in 40 subjects. FFM and fat mass explained 83% of the variability in RMR (standard error of the estimate [SEE], 420 kJ/d) in a multiple regression analysis. Combinations of organ and muscle masses performed as well as but not better than stepwise multiple regression models. The fact that the composition of the lean mass could not improve the prediction of RMR in comparison to the traditional FFM–fat mass model suggests that the weight of internal organs is not a main determinant of RMR. This may indicate that the variability in RMR is associated with variation in energy expenditure per kilogram of tissue of the individual organs.

RESTING METABOLIC RATE (RMR), defined as the rate of energy expenditure measured at rest after an overnight fast, is mainly determined by fat-free mass (FFM). Several studies have been published on the relationship between RMR and FFM.[1] All have shown that RMR is strongly associated with FFM. However, FFM consistently explains only 70% to 80% of the variability in RMR. Thus, 20% to 30% of the variability remains unaccounted for. The study of factors associated with this residual variation in RMR has received much attention, since RMR is the main determinant of total daily energy expenditure[2] and a low RMR is a risk factor for future weight gain.[3] The residual variability has been shown to be associated with age,[4] body fatness,[5,6] body temperature,[7] and activity of the sympathetic nervous system.[8] Any one of these factors explains only a small fraction of the residual variability, so a large proportion of it remains unexplained.

A factor that could potentially explain a large fraction of the residual variability in RMR is the composition of the FFM. Indeed, FFM itself is composed of tissues characterized by different levels of energy expenditure per unit of mass.[9] In particular, the energy expenditure of the visceral organs and the brain is roughly 1 MJ/kg/d, whereas for skeletal muscle (at rest) it is about 20 times lower.[9,10] This has led several groups to hypothesize that variation in organ weight beyond that associated with FFM may be the main source of residual variability in RMR.[11-13] However, little information exists in the literature on variability of the composition of the lean mass. Garby et al,[14] who analyzed cadaver data, showed that in their sample population considerable variability existed in organ weights, even after the effect of body weight or FFM had been removed by regression.

The specific aim of this study was to test this hypothesis by measuring RMR and the size of the main body compartments in human volunteers.

SUBJECTS AND METHODS

Forty subjects (20 males and 20 females, all white) participated in the study. All were healthy as determined by a physical examination and by routine blood and urine chemistry. In particular, all subjects had a normal thyroid status as determined by the free thyroxine index, which ranged from 6.4 to 9.7 μg/dL, and by serum thyrotropin, which was 0.57 to 3.07 μU/mL. Subject characteristics are presented in Table 1. All subjects provided written consent before participating in the study. The protocol of the study was approved by the Institutional Review Boards of Louisiana State University and the Baton Rouge General Medical Center (BRGMC).

To assess the relationship between RMR and composition of the FFM, we first divided total body weight into fat mass and FFM. Then, FFM was further subdivided into bone mineral content (BMC), liver, kidney, and heart masses, skeletal muscle mass, and total body water (TBW). Body composition and RMR measurements were made during two visits to the Pennington Biomedical Research Center and one to the Radiology Department of the BRGMC, where computed tomographic (CT) scans were made. In 34 cases, all measurements were taken within 1 week; in five cases, 10 days separated the first from the last visit; and in one case, the last visit had to be scheduled 19 days after the first. All measurements except CT scans were performed in the morning after an overnight fast. No attempt was made to control for the effect of the menstrual cycle in female subjects.

Height was measured to the nearest 5 mm with a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using an electronic scale (model 3003; National Controls, Santa Rosa, CA). Subjects were weighed after voiding and while wearing a hospital gown. Body surface area was estimated from weight and height using the DuBois formula.[15]

The proportion of fat mass and FFM in the body was determined by a densitometric four-compartment model as described by Heymsfield et al.[16] This method relies on fewer assumptions than the traditional equation of Siri,[17] and has been shown to yield reliable results as compared with more direct measurement by neutron activation.[16] The same formulae and constants reported in the original description of the method[16] were used here, except that body mineral content was estimated from BMC measured by dual-energy x-ray absorptiometry (DEXA). This resulted in the following equation: $F = 2.05(1.34/D_b - 0.348TBW/WT + 0.685BMC/WT - 1)$, where F is the fat fraction of the body, D_b is body density, and WT is body weight.

TBW was measured by the deuterium dilution technique.[18,19] Sub-

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Table 1. Characteristics of 40 Subjects Who Participated in the Study

Characteristic	Females (n = 20) Mean ± SD	Males (n = 20) Mean ± SD
Age (yr)	24.4 ± 6.2	27.4 ± 7.0
Weight (kg)	64.7 ± 11.9	75.6 ± 10.9
Height (cm)	165.1 ± 6.0	177.5 ± 8.4
BMI (kg/m²)	23.7 ± 3.6	23.9 ± 2.2

Abbreviation: BMI, body mass index.

jects collected a predose urine sample used to estimate background isotope composition. Then, they received a precisely weighed 100-g dose of water containing 0.08 g D_2O/kg estimated TBW. The container was then washed with an additional 50 mL tap water and also given to the subject. Saliva samples were collected 3 and 4 hours postdose for deuterium enrichment determination.

BMC and skeletal muscle mass were measured by DEXA (QDR2000; Hologic, Waltham, MA). No good method exists for in vivo measurement of skeletal muscle mass. However, for this study, it was important to have at least an estimate of muscle mass, since given its size this tissue was likely to be an important determinant of RMR. We decided to use the lean mass of the limbs measured by DEXA as an index of total muscle mass, as suggested by Heymsfield et al.[20] In this report, we will refer to this variable as muscle mass, with it being understood that it is actually only an index of the true skeletal muscle mass. DEXA whole-body scans were conducted in array mode and analyzed with enhanced whole-body version 5.54 (Hologic).

Left ventricular mass (LVM) by M-mode echocardiography (Aloka 650; Corometrics Medical Systems, Milwaukee, WI) was measured as an estimate of heart size. LVM was computed following the Penn convention.[21] This method has been shown to yield reproducible results with a standard error of less than 30 g.[22] For simplicity in this report, we will refer to this variable as heart mass.

Liver and kidney volumes were measured from serial CT images as described by Heymsfield et al.[23] Unfortunately, we did not have access to the scanner in the morning, so subjects were scheduled for scans between 7 and 8 PM, and were not allowed to eat after lunch. In this way, at the moment of the scan they had been fasting for at least 6 hours. This was an attempt to standardize the size of hepatic glycogen stores, since variability in this parameter would confound our measurement. All scans were made on a General Electric scanner (9800 Quick CT Scanner; GE, Milwaukee, WI) at BRGMC. Serial images of the abdomen were taken at 1-cm intervals to include the liver and the kidney. The volume of each organ was then determined as the sum of the cross-sectional area in all images multiplied by the distance between scans. The cross-sectional areas were measured "by hand" on the images by drawing with the cursor a line surrounding the area occupied by the tissue. The program could then compute the area enclosed within the line. On each image, the areas of the tissues were computed three times and the average of the measurements was taken. Liver and kidney volumes were then transformed into organ weight using organ densities from Heymsfield et al.[23]

RMR was measured twice in each subject: once on the first visit and once on the last. The first measurement was made to familiarize the subjects with the procedure. However, the two measurements produced similar results: the overall standard deviation of the repeated measurements was 272 kJ/d, for a coefficient of variation of 4% and an intraclass correlation coefficient of .98. As a consequence, the average value of the two measurements was taken here as an estimate of the individual RMR. Measurements were made with a Sensormedics 2900z metabolic cart (Sensormedics, Anaheim, CA) with a transparent hood. Before RMR measurement, subjects were allowed to rest on a bed in a quiet room for 30 minutes. Then, they were placed under the hood for an additional 30 minutes, during which time respiratory gas exchange was measured. The cart analyzers were calibrated each morning using standard span gases and fresh air. The cart flowmeter was also calibrated daily using a 3.00-L syringe. During the measurement, air flow through the hood was adjusted to maintain CO_2 concentration in the outgoing air in the optimal range of 0.65% to 0.95%. Metabolic rate was calculated from oxygen production and carbon dioxide production according to the method of Simonson and DeFronzo.[24]

Table 2. Average Size of the Body Compartments Measured in 40 Subjects

Compartment	Females (n = 20) Mean ± SD	Males (n = 20) Mean ± SD
Fat mass (kg)	20.4 ± 7.4	15.3 ± 5.9
FFM (kg)	44.4 ± 6.0	60.4 ± 7.9
TBW (kg)	31.6 ± 4.3	42.8 ± 5.4
BMC (kg)	2.2 ± 0.3	2.9 ± 0.5
Limb muscle mass (kg)	16.1 ± 2.5	26.2 ± 3.5
LVM (g)	139 ± 44	185 ± 53
Liver mass (g)	1,410 ± 241	1,598 ± 246
Kidney mass (g)	262 ± 47	318 ± 46

A model inspired by the one presented by Garby et al[25] was used to represent the contribution of organs and tissues to total energy expenditure. This model assumes that whole-body RMR is the sum of the energy expenditure of several tissues. Each tissue has a mass, M_i, and a specific energy expenditure, k_i (in joules per unit weight), so that for n tissues RMR is

$$\mathrm{RMR} = \sum_{1}^{n} k_i \cdot M_i.$$

Since k_i values for visceral organs are very high,[10] their contribution to RMR should be easily demonstrated by multiple regression analysis. Our hypothesis was that a regression model including the individual organ contribution would explain a larger proportion of the total variance in RMR than the traditional model including only FFM and fat mass.

Statistical analyses were made using SAS version 6.09 (SAS Institute, Cary, NC). The variables used were tested for normality with the SAS univariate procedure. The simple association between variables was measured with the Pearson correlation coefficient. Stepwise multiple regression analyses were performed to investigate the relationship between RMR and body composition. In all tests, the probability value of .05 was accepted as the limit for significance.

RESULTS

The average size of body compartments that were measured is shown in Table 2. All body compartments except fat mass were significantly associated with FFM according to simple correlation analysis (Table 3). Relationships between tissue mass and FFM are shown in Figs 1 to 4. Tissue masses were

Table 3. Pearson Correlation Coefficients Among Body Compartment Sizes in 40 Subjects

	FFM	FM	Muscle	Heart	Kidney	Liver	BMC
FM	−.05						
Muscle	.95*	−.21					
Heart	.77*	.01	.70*				
Kidney	.78*	.15	.69*	.60*			
Liver	.76*	.30	.67*	.75*	.70*		
BMC	.94*	.03	.88*	.76*	.76*	.74*	
TBW	.99*	−.04	.94*	.75*	.79*	.73*	.94*

Abbreviations: FM, fat mass; muscle, limb muscle mass; heart, LVM.
*$P < .001$.

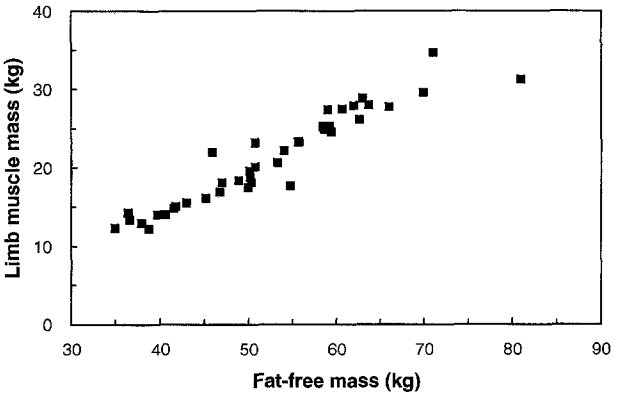

Fig 1. Relationship between limb muscle mass, estimated as the lean soft tissue of the limbs measured by DEXA, and FFM (R^2 = .90, SEE = 1.9 kg, N = 40).

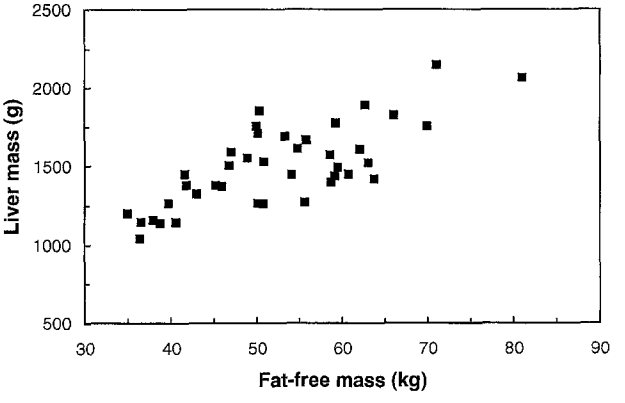

Fig 3. Relationship between liver mass, estimated from the liver volume by CT, and FFM (R^2 = .57, SEE = 171 g, N = 40).

also significantly associated with body weight and height, but the coefficients were smaller. None of the tissue masses were significantly associated with fat mass.

Simple correlation analyses between RMR and tissue masses are shown in Table 4. RMR was significantly associated with all tissue masses except fat mass (r = .09, P = .58). The highest correlation coefficient was observed with FFM (r = .90, $P < .0001$), whereas the weaker association was seen with kidney mass (r = .67, $P < .0001$). Correlation coefficients for body weight and body surface area were .82 ($P < .0001$) and .86 ($P < .0001$), respectively. The same analysis performed in each gender group separately yielded qualitatively similar results (Table 4).

The relationship between RMR and body composition was further explored by multiple regression analysis. When FFM and fat mass were presented as independent variables, the analysis produced the following model: RMR (kJ/d) = 1,827 + 84 FFM + 18 fat mass. For this model, the coefficient of determination (R^2) was .83 and the standard error of the estimate (SEE) of the regression was 420 kJ/d. This represents the "traditional" model between RMR and body composition. For this and all of the following regression models, the analysis was performed also for each gender group separately. However, since the gender-specific results were qualitatively similar to the results obtained for the whole group, we report only results obtained on the two gender groups combined.

To test if a larger proportion of total variability in RMR could be explained by a different set of independent variables, we conducted a series of stepwise regression analyses. In the first analysis, we included muscle, fat, heart, liver, and kidney masses as possible independent variables. Only muscle, fat, and heart masses contributed significantly to the model, as follows: RMR (kJ/d) = 2,708 + 117 muscle mass + 32 fat mass + 4,774 heart mass. The coefficient of determination for the model was .81 (the contributions of each variable were 0.70 for muscle mass, 0.07 for fat mass, and 0.03 for heart mass), and the SEE of the regression was 451 kJ/d.

Next, we tried to combine the liver, heart, and kidney in a single "organ" variable, since together the three organs should contribute close to 40% of total RMR.[10] In this case, muscle and organ masses but not fat mass contributed significantly to the model as follows: RMR (kJ/d) = 2,378 + 92 muscle mass + 1,129 organ mass. R^2 for this model was .77 (partial R^2 was .70 and .07 for muscle and organ masses, respectively), and SEE was 481 kJ/d. The next attempt to improve the prediction of RMR with information on individual organ sizes was to use the ratio of muscle mass to organ mass. However, in a multiple regression model with FFM and fat mass as other variables, this ratio was not significantly associated with RMR.

Finally, we calculated partial correlation coefficients between

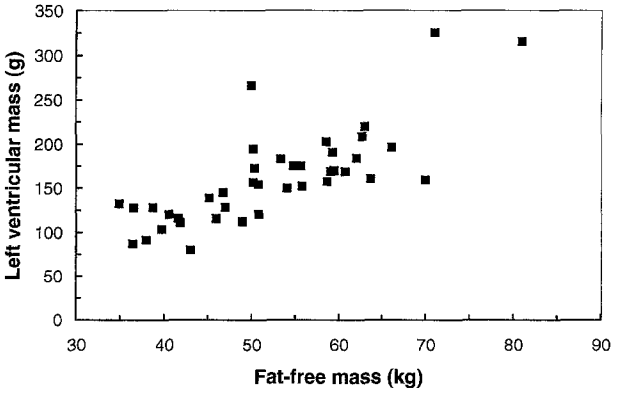

Fig 2. Relationship between heart mass, estimated from the LVM by echocardiography, and FFM (R^2 = .60, SEE = 34 g, N = 40).

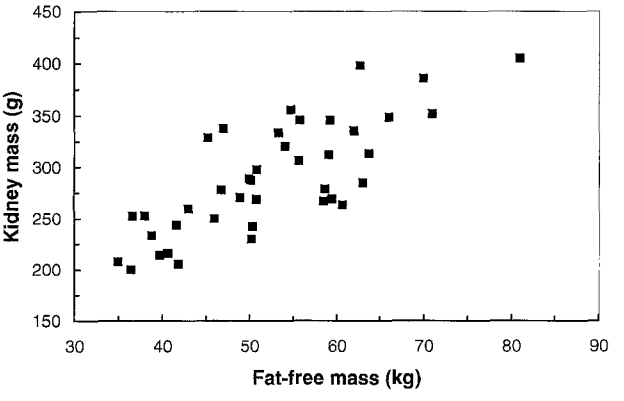

Fig 4. Relationship between kidney mass, estimated from the kidney volume by CT, and FFM (R^2 = .61, SEE = 34 g, N = 40).

Table 4. Pearson Simple and Partial (controlling for FFM) Correlation Coefficients Between RMR and Tissue Masses for All Subjects and for Females and Males Separately

	Simple Correlation			Partial Correlation (controlling for FFM)		
	All (n = 40)	Female (n = 20)	Males (n = 20)	All (n = 40)	Female (n = 20)	Males (n = 20)
Body surface area	.86*	.79*	.81*	.29	.23	.26
Height	.80*	.50†	.73*	.05	−.15	.19
Weight	.82*	.79*	.78*	.30	.32	.23
FFM	.90*	.82*	.84*	—	—	—
Limb muscle mass	.84*	.71*	.76*	−.13	−.25	.10
Fat mass	.09	.61*	.31	.30	.31	.23
LVM	.75*	.76*	.64*	.21	.51†	−.13
Kidney mass	.67*	.42	.60*	−.11	−.36	.04
Liver mass	.75*	.75*	.70*	.24	.21	.17

*$P < .001$.
†$P < .05$.

RMR and organ masses controlling for FFM (Table 4). A significant positive correlation would indicate that subjects with a higher RMR than expected also have organs that are larger than expected for their level of FFM. However, none of the coefficients were significantly different from zero, with P values of .14 to .52.

To assess the total variability in RMR that could be attributed to the composition of FFM, we obtained for each subject a calculated RMR (RMR_C) computed by multiplying the tissue masses with published values for their specific energy expenditure.[11] Then, we regressed RMR_C on the FFM measured for each subject and calculated the SEE of the regression. This should yield an estimate of the variability in RMR that is attributable to the variability in organ weight, under the assumption that all subjects have the same organ energy expenditure per kilogram of tissue. The R^2 of this regression was .91 and the SEE was 195 kJ/d. As a comparison, the R^2 for the regression between measured RMR and FFM was .80, and the SEE of the regression was 435 kJ/d. Thus, the variability in organ weight as measured in our sample could generate a variance in RMR that corresponded to approximately 20% of the variance unexplained by FFM. This approach is shown in Fig 5.

DISCUSSION

Our data do not support the hypothesis that most of the residual variability in RMR, once the effect of FFM has been accounted for, is associated with the composition of the FFM. Indeed, none of the regression models tested was superior, in terms of explained variance, to the traditional FFM–fat mass model. The SEE and fraction of explained variance were similar in all models, which always left unexplained about 20% of the total variance in RMR. In addition, partial correlation coefficients between RMR and organ sizes controlling for FFM were all nonsignificant. Finally, the estimated variability in RMR that could be generated from our tissue-size data (195 kJ/d) was much smaller than the observed value (435 kJ/d). However, it is important to point out that all the regression models that included tissue masses explained a larger proportion of the variance than either body weight or body surface area. Thus, composition of the lean mass is a significant determinant of RMR; however, it does not explain a larger proportion of the variance than that already explained by FFM.

Most of the evidence on a relationship between RMR and the composition of the lean mass is only theoretical, and stems from the recognition of the high energy expenditure of internal organs. According to the values measured by arteriovenous difference, variability in the size of internal organs could explain a large fraction of the variability in RMR observed both longitudinally and cross-sectionally.[6,9,10,12,13,26] Garby and Lammert[12] performed a formal analysis of the sources of variation of energy expenditure, based on a two-compartment model of the lean mass (ie, organ mass and nonorgan lean mass). They showed that under the assumptions of their model, the variance in energy expenditure is dominated by the variance in the internal organ mass and by their energy expenditure. According to their computation, a standard deviation of up to 300 kJ/d in energy expenditure can be attributable to variations in the composition of the lean mass. This would represent about 50% of the residual variance measured in our study.

To our knowledge, there is only one published study that addressed this problem in humans by making direct measurements of body compartment sizes.[27] The investigators estimated adipose tissue mass, skeletal muscle mass, and nonmuscular lean mass by CT in 22 subjects. Then, they analyzed the association between lean mass composition and RMR by stepwise multiple regression. As in our study, the association between RMR and the constituents of the lean mass was weak. In particular, nonmuscular lean mass (constituted mainly by the internal organs of the body) was not significantly associated with RMR once the effect of skeletal muscle was accounted for. In addition, the use of lean mass constituents did not improve the predictive power of the regression over the simpler equation with FFM.

Svendsen et al[28] compared the correlation coefficients between RMR and regional lean tissue masses obtained by DEXA. They showed that the association between RMR and trunk lean mass was significantly higher than with peripheral or total-body lean mass. They interpreted this as evidence that the

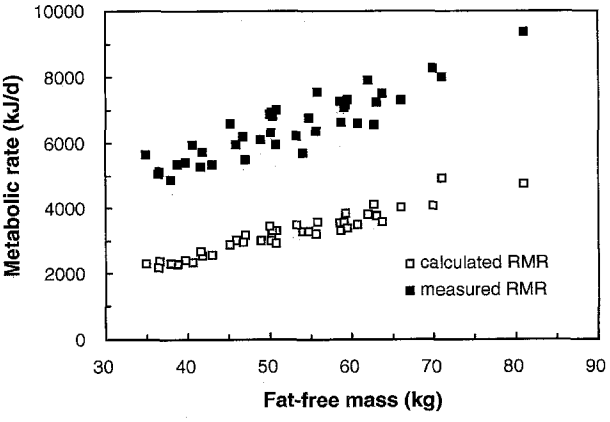

Fig 5. Measured RMR and RMR computed as the sum of tissue masses multiplied by their energy expenditure. Measured RMR: R^2 = .80, SEE = 435 kJ/d. Calculated RMR: R^2 = .91, SEE = 195 kJ/d.

visceral organs (represented by the trunk lean mass) contribute more to RMR than muscle mass. However, this is again an indirect approach. Our DEXA measurements allowed us to perform the analysis suggested by Svendsen et al[28] on our data set. The results showed strong and highly significant correlations between both peripheral and trunk lean tissue and RMR ($r = .82$ and $r = .86$ for peripheral and trunk lean tissue, respectively). However, the coefficients were not significantly different from each other ($P > .5$). As a comparison, Svendsen et al[28] reported a correlation coefficient of .61 for trunk lean mass and RMR and .30 for peripheral lean mass and RMR. The reasons for these differences are not clear; however, again, our data do not support a main influence of visceral organs on RMR.

However, there is animal data supporting this hypothesis. Ferrell and Koong[29,30] altered the body composition of rats, pigs, and sheep by nutritional manipulation. They did not directly measure the association between internal organ size and heat production; instead, they observed that among treatment groups fasting heat production and the weight of internal organs were affected in a parallel direction by their manipulations.

Measurement errors in RMR and body organs will reduce the strength of the association estimated between these variables, so our finding may simply be explained by a lack of statistical power. The experimental errors associated with measurements of organ volumes by CT were estimated by Heymsfield et al[23] at about 5%. The coefficient of variation obtained by twice analyzing the images in four of our subjects was 8%. The error in the echocardiographic measurement of LVM was estimated at about 30 g by Devereux,[22] representing a relative error of approximately 20%. The effect of these errors on the multiple regression analysis will be to increase the SEE of the slopes relating the body organs to RMR, making it more likely for the estimated slopes not to be significantly different from zero. However, the mean ± SD values of the internal organ masses estimated in our study were not very different from the ones reported by Garby and Lammert,[12] which were obtained by direct weighing. Thus, errors in the measurement of the size of body compartments might not have been too important. It is also possible that subjects differed widely in the size of hepatic glycogen stores. This would affect the liver volume in a way that is unrelated to its energy expenditure. We tried to control for this effect by performing the CT scans after a period of fasting of at least 6 hours. However, it is obvious that this will only reduce the acute effect of a meal on glycogen stores, while chronic differences among subjects will remain unaffected.

What is the expected contribution of the individual differences in internal organ size to the variability in RMR? Garby and Lammert[12] estimated that the variability in internal organ mass could generate a SD in energy expenditure of about 300 kJ/d. However, in our opinion, this figure overestimates the effect of organ size, since in their computation Garby and Lammert[12] used the total organ mass variance, and the component associated with differences in FFM should not be included in the calculation. In our data set, the total organ mass SD was 341 g, a value close to the one reported by Garby and Lammert.[12] When the FFM effect is removed, the remaining SD is only 199 g. If we use our data to calculate the expected contribution of organ size to RMR, after the effect of FFM has been removed, we obtain a SD of 198 kJ/d, a value close to the one estimated from the data presented in Fig 5. This value represents approximately 20% of the residual variation. The different variance components of RMR are presented in Fig 6. The figure includes variance estimated from repeated measurements of RMR, referred to as within-individual variance, which represents the sum of the measurement error and daily variation in RMR. This component is significantly smaller (F test, $P < .01$) than the variability in RMR adjusted for FFM but higher (F test, $P < .05$) than the variability associated with organ size as already estimated.

From Figs 5 and 6, it is obvious that the variability in RMR that can be attributed to variation in organ mass is small. Thus, our data suggest that organ mass does not represent a main determinant of RMR variability. In addition, since the day-to-day variability in RMR is about twice that attributable to organ mass, a very large sample size may be needed to show a significant effect of this latter factor.

The model we used to represent RMR assumed that the energy expenditure per kilogram of tissue, k_i in our equation, was fixed for each organ. When this is true, the mass of a tissue is directly proportional to its energy expenditure. Conversely, if k_i values are not constant, the relationship between an organ's energy expenditure and its mass will be loose. As a consequence, the association between organ masses and RMR might also be weak or even nonexistent. Individual differences in the energy expenditure of body tissues per kilogram may be reflection of differences in protein turnover[31] or in Na/K-ATPase activity.[32] Not many studies have assessed the individual variability in organ energy expenditure. Zurlo et al[33] showed that the coefficient of variation for oxygen uptake in forearm skeletal muscle was 27% and, more importantly, that this variability was strongly associated with the residual variation in RMR. If this kind of variability existed in other tissues, tissue sizes would not be expected to be associated with RMR.

In conclusion, our data failed to show a relationship between

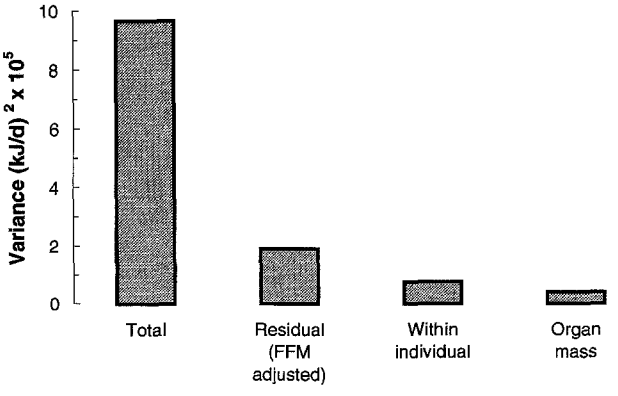

Fig 6. Variance components for RMR. Total is the variance among 40 individuals; residual is the remaining variance once the effect of FFM has been accounted for; within is the day-to-day variation from repeated measurements; organ mass is the variance component that we estimated can be attributed to the variation in organ mass.

internal organ masses and the residual variability in RMR. Thus, in healthy people, FFM-independent differences in RMR seem not to be related to anatomical differences among subjects. As a consequence, the observed between-subject differences in RMR might be associated with differences in energy expenditure per kilogram at the tissue level.

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