Association Between Blood Pressure and Resting Energy Expenditure Independent of Body Size

Amy Luke, Adebowale Adeyemo, Holly Kramer, Terrence Forrester, Richard S. Cooper

Abstract—Obesity is an important risk factor for hypertension; however, the pathway through which it raises blood pressure (BP) is poorly understood. Body size is also the primary determinant of energy expenditure, and we therefore examined the joint relationship of energy expenditure and body size to blood pressure. Resting energy expenditure (REE) was measured using respiratory gas exchange in population-based samples of 997 Nigerians and 452 African Americans. In a third sample of 118 individuals, nonresting energy expenditure (ie, physical activity) was measured in addition to REE. The univariate correlation between REE and BP ranged from 0.10 to 0.22 in the 3 samples ($P<0.001$). In multivariate models, adiposity, whether defined by body mass, fat mass, or leptin, was no longer associated with BP, while REE remained highly significant ($P<0.001$). The REE–BP association also persisted after adjustment for physical activity measured with doubly labeled water. The odds ratio for hypertension among persons in the highest quartile versus the lowest quartile of REE, after adjustment for body size, was 1.7. This relationship was not the result of hypertension among the obese, because it did not vary across the range of BMI and was the same in lean Nigerians as in obese Americans. These data suggest that metabolic processes represented by REE may mediate the effect of body size on BP. The interrelationship of REE with sympathetic tone, transmembrane ion exchange, or other metabolic processes that determine energy costs at rest could provide physiological explanations for this observation. **(*Hypertension*. 2004;43:555-560.)**

Key Words: hypertension ■ obesity ■ metabolism ■ body mass index ■ body weight

Body size measures have been widely studied as determinants of inter-individual variation in blood pressure (BP). Although height appears to have little or no influence on BP among humans, adiposity has been universally identified as a predictor of increased risk of hypertension.[1,2] Despite substantial efforts, the underlying physiological mechanisms linking excess body fat stores to BP are poorly understood. Obesity is a complex syndrome, representing the joint effect of metabolic alterations as well as lifestyle patterns that involve, among others, a high-calorie/high-sodium intake and reduced physical activity.[3] Various regulatory hormones, including insulin and leptin, are increased among the obese, and abnormalities in the renin–angiotensin system have been described.[4–6] At the same time, a wide range of other metabolic abnormalities, including rates of ion transport and resting sympathetic tone, have been reported in obese hypertensives compared with the non-obese, although these associations are inconsistent.[7]

An important challenge faced by studies that attempt to isolate the role of individual components of body composition and energy metabolism is the need to account for their intercorrelation. Although it is often assumed that the size of body fat stores is a primary determinant of hypertension risk, lean body mass increases in parallel with total body weight and is highly correlated with fat mass.[8] In addition, in societies where virtually the entire population experiences some degree of overweight, it may be difficult to identify cause and effect relationships given the absence of an appropriate control group.

As part of an international comparative study of hypertension, we have been investigating the effects of energy expenditure and obesity on BP in populations of the African diaspora. Using community-based samples in Nigeria, Jamaica, and the United States, we tested the hypothesis that metabolic processes represented by resting energy expenditure (REE) mediate the effect of body size on BP. We report here a new observation of an association between REE and BP that is consistently observed in these widely contrasting social environments.

Methods

Subject Recruitment

The sampling frame for this study was provided by the International Collaborative Study on Hypertension in Blacks, as described in

Received November 18, 2003; first decision December 9, 2003; revision accepted January 6, 2004.

From Department of Preventive Medicine and Epidemiology (A.L., H.K., R.S.C.), Loyola University Medical Center, Maywood, Ill; Department of Pediatrics (A.A.), University College Hospital, University of Ibadan, Ibadan, Nigeria; and Tropical Medicine Research Institute (T.F.), University of the West Indies, Kingston, Jamaica.

Correspondence to Dr Amy Luke, Department of Preventive Medicine and Epidemiology, Loyola University Medical Center, Maywood, IL 60153. E-mail aluke@lumc.edu

Hypertension **is available at http://www.hypertensionaha.org** **DOI: 10.1161/01.HYP.0000118020.44335.20**

TABLE 1. Characteristics of Study Participants: Mean (SD)

	Nigeria		United States	
	Men (n=475)	Women (n=521)	Men (n=172)	Women (n=280)
Age (y)	44.4 (18.9)	45.4 (17.4)	34.5 (10.7)	36.9 (11.1)
Height (cm)	169.6 (7.0)	158.8 (6.7)	176.5 (6.7)	163.8 (6.6)
Weight (kg)	61.8 (10.9)	59.2 (12.6)	84.0 (20.4)	81.3 (21.4)
Body mass index	21.4 (3.3)	23.5 (4.8)	26.9 (6.1)	30.3 (7.8)
Fat-free mass (kg)*	48.6 (6.7)	39.4 (5.7)	61.1 (8.6)	46.5 (6.8)
Fat mass (kg)	13.3 (6.9)	19.8 (8.7)	23.1 (13.0)	35.2 (15.2)
% Body fat	20.7 (7.5)	32.2 (8.2)	25.8 (8.1)	41.3 (8.2)
Plasma leptin (ng/mL)†	2.9 (4.8)	12.6 (13.6)	5.7 (6.5)	22.9 (15.6)
Mean SBP (mm Hg)	117.9 (20.7)	114.4 (23.3)	116.8 (15.2)	114.6 (17.1)
Mean DBP (mm Hg)	71.5 (12.8)	70.5 (13.1)	72.8 (12.0)	72.1 (12.3)
Mean heart rate (beat/min)	59.0 (23.3)	59.7 (24.1)	70.0 (10.1)	71.9 (11.0)
Resting energy expenditure (kcal/d)	1472 (197)	1284 (179)	1707 (290)	1420 (244)

*Body composition measures, ie, fat-free mass, fat mass and % body fat, were missing for 4 Nigerian men, 12 US men, and 25 US women.

†Plasma leptin was measured on a subset of participants: Nigerian men, n=309; Nigerian women, n=312; US men, n=148; US women, n=244.

detail elsewhere.[9] In the second phase, nuclear families were identified through middle-aged probands, and all available first-degree relatives were enrolled in Ibadan, Nigeria and metropolitan Chicago, Illinois. In this analysis, we used data from participants older than 18 years who were not using hypertension medications. Exclusion criteria also included diagnosed major medical conditions such as coronary heart disease, diabetes mellitus, kidney disease, and severe arthritis. There were 997 participants from Nigeria belonging to 255 families and 452 participants from the United States from 152 African-American families.

Because the primary sample consisted of families, and because familial aggregation exists for all the traits that were examined, we included an additional independent sample of unrelated individuals recruited in a separate study of physical activity and BP. We enrolled 57 Nigerians, 35 Jamaicans, and 26 African Americans in this smaller independent study. These individuals were recruited from the same communities in Nigeria and the United States, and from suburban Kingston, Jamaica. Study protocols were reviewed and approved by the review boards of the University of Ibadan, the University of the West Indies, and Loyola University. Written informed consent was obtained in Yoruba for the Nigerian participants and in English for the Jamaican and US participants.

Survey Methods

A screening examination was completed by trained research staff using a standardized protocol.[8] Local interviewers obtained a medical history and a family pedigree in the participant's native language. BP observers were trained and certified by a previously described procedure.[8,10] Measurements were made in the sitting position, with the arm at heart level after a 5-minute rest. An oscillometric device, previously evaluated in our field settings, was used for all BP measurements (Omron HEM-412).[10] Three measurements were taken 3 minutes apart and the average of the final 2 was used in the analysis. Height was measured to the nearest 0.1 cm using a stadiometer consisting of a steel tape attached to a straight wall and a wooden headboard. The headboard was positioned with the participant shoeless, with feet and back against the wall, and head held in the Frankfort horizontal plane. Body weight was measured to the nearest 0.2 kg using calibrated electronic scales uniform to all sites. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Body composition was estimated using bioelectrical impedance analysis using a single-frequency (50-kHz) impedance analyzer (model BIA 101Q; RJL Systems, Clinton Township, Mich).[11] A tetrapolar placement of electrodes was used on the right hand and foot.[12] Fat-free mass (FFM) and fat mass (FM) were estimated from measured resistance using equations validated in our populations.[11] Leptin was measured in a subset of participants, as previously described,[11] using a radioimmunoassay kit (Linco, St. Charles, Mo).

Measurement of Resting Energy Expenditure

REE was measured using respiratory gas exchange. Under supervision by one of the investigators (A.L.), certified staff made all measurements in a clinic setting in Nigeria, Jamaica, and the United States using the same indirect calorimeter (DeltaTrac II Metabolic Monitor; SensorMedics, Anaheim, Calif). To control for the thermic effect of food during the REE measurement, the participants fasted from 10:00 PM the previous evening. Compliance with the request for fasting was assessed by monitoring respiratory quotient; any participant with respiratory quotient greater than 1.00, suggesting recent food consumption, was asked to return for a second visit. Mean (±SD) respiratory quotient was 0.85±0.05 in Nigeria, 0.82±0.04 in Jamaica, and 0.84±0.05 in the United States.

After arriving at the clinic, the participant rested in a supine position for at least 15 minutes. A clear Lucite hood was placed over the participant's head and respiratory gases were collected for 30 to 45 minutes. Using the modified Weir equation,[13] energy expenditure was calculated from oxygen consumption and carbon dioxide production values. Alcohol burn tests indicated that the instrument was accurate to within 2% at all times; replicate measurements (n=35, up to 1.5 years apart) indicate the intra-individual coefficient of variation of REE to be ≈3.5%.[14]

Total energy expenditure was measured using the doubly labeled water method in the smaller sample from the 3 sites.[15] Standardized doses of O^{18} and deuterium were given at baseline and samples of body fluids were obtained at baseline, at equilibration with total body water and after 10 to 14 days, as previously described.[15,16] Physical activity was calculated as the difference between total energy expenditure and REE and was normalized to body weight and expressed as kcal/kg per day.[17] Body composition in this sample was determined by deuterium dilution, as described in detail elsewhere.[18]

Statistical Analysis

Descriptive characteristics were calculated as means and frequencies. During the first step in the analysis, correlation was used to

TABLE 2. Characteristics of Participants in the Physical Activity Study in Mean SD*

	Nigeria (n=57)	Jamaica (n=35)	United States (n=26)
% Female	47.4	51.4	38.5
Age (y)	41.0 (8.8)	37.9 (6.8)	33.8 (13.8)
Body mass index	21.0 (3.1)	28.0 (7.1)	29.0 (6.6)
Fat-free mass (kg)	44.4 (9.7)	53.2 (12.3)	60.3 (10.9)
Fat mass (kg)	12.5 (6.8)	26.2 (13.5)	26.2 (14.1)
Mean systolic BP (mm Hg)	124.6 (28.5)	114.2 (21.1)	114.5 (16.6)
Mean diastolic BP (mm Hg)	78.4 (16.4)	66.5 (15.4)	72.8 (11.9)
Resting energy expenditure (kcal/d)	1333 (227)	1455 (313)	1604 (296)
Activity energy expenditure (kcal/kg · d)†	13.6 (6.5)	13.4 (6.4)	14.6 (5.0)

*These are unrelated persons enrolled in a small study on energy expenditure and blood pressure.
†Activity energy expenditure measured using doubly labeled water method.

assess interrelationships. Linear regression was subsequently used to conduct the multivariate analyses. All analyses were repeated using the following adjustments: height and weight; BMI; and FFM and FM. To verify the consistency of the analyses, they were conducted separately on the entire Nigerian and United States samples, with the unrelated persons in those samples and finally on the smaller independent sample used to study physical activity. Statistical significance was assessed if the associated *P* values were ≤0.05. Logistic regression was used to calculate the odds ratio for hypertension in the highest versus lowest quartile of REE adjusted for body size and age.

The precision of the measurements was estimated through within-person correlations in a random sample over a short time interval. For BMI and REE, the correlation was 0.97, indicating stability and accuracy of the measurement (N=58 and 25, respectively). The corresponding correlations were 0.70 for systolic BP (SBP) and 0.75 for diastolic BP (DBP) (N=58).

Results

Descriptive characteristics of the participants from the community samples in Nigeria and the United States are presented in Table 1. The mean age of the participants in the 2 sites was similar. The parent study was designed to recruit persons from the upper and lower tails of the BP distributions; because the Nigerians were not treated for hypertension at the time of enrollment, and because many hypertensive US participants were excluded from these analyses due to medication use, mean BPs were higher in Nigerians. As anticipated, the African American sample was substantially more obese and had higher levels of plasma leptin. Body composition, ie, FFM, FM, and percent body fat, were missing for 4 Nigerians and 37 African Americans. The secondary sample underwent measurement of energy expended in physical activity using stable isotopes and included Jamaicans (Table 2). Similar patterns were present across the study sites, with increases in body size and energy expenditure in a stepwise fashion from Nigeria to the United States.

Correlation analysis was conducted within each of the 2 larger population samples (Table 3 and Table 4). In both groups of participants, SBP and DBP were significantly associated with absolute levels of REE (ie, unadjusted for body size). All measures of body size and composition were also significantly associated with SBP and DBP. As anticipated, REE was related most strongly to FFM (r=0.72 to 0.77). In these unadjusted analyses, plasma leptin was significantly correlated with BP in the Nigerians but not in the African Americans.

TABLE 3. Correlations Between Resting Energy Expenditure, Body Composition Measures, and Blood Pressure for 996 Nigerian Men and Women (*P* Values)

	REE (kcal/d)	Age (y)	Weight (kg)	Body Mass Index	Fat-Free Mass (kg)	Fat Mass (kg)	Leptin (ng/mL)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart Rate (bpm)
REE	—									
Age	−0.32 (0.001)	—								
Weight	0.58 (0.001)	0.07 (0.001)	—							
Body mass index	0.29 (0.001)	0.14 (0.001)	0.85 (0.001)	—						
Fat-free mass	0.72 (0.001)	−0.07 (0.05)	0.71 (0.001)	0.33 (0.001)	—					
Fat mass	0.17 (0.001)	0.16 (0.001)	0.77 (0.001)	0.89 (0.001)	0.09 (0.01)	—				
Leptin	−0.03 (0.45)	0.03 (0.45)	0.35 (0.001)	0.53 (0.001)	−0.07 (0.05)	0.57 (0.001)	—			
Systolic BP	0.10 (0.001)	0.42 (0.001)	0.18 (0.001)	0.18 (0.001)	0.10 (0.001)	0.17 (0.001)	0.08 (0.05)	—		
Diastolic BP	0.12 (0.001)	0.41 (0.001)	0.32 (0.001)	0.30 (0.001)	0.16 (0.001)	0.30 (0.001)	0.17 (0.001)	0.83 (0.001)	—	
Heart rate	−0.05 (0.14)	0.20 (0.001)	0.03 (0.30)	0.04 (0.16)	−0.03 (0.27)	0.07 (0.05)	−0.04 (0.39)	0.24 (0.001)	0.24 (0.001)	—

REE indicates resting energy expenditure.

TABLE 4. Correlations Between Resting Energy Expenditure, Body Composition Measures, and Blood Pressure for 454 US Men and Women (*P* Values)

	REE (kcal/d)	Age (y)	Weight (kg)	Body Mass Index	Fat-Free Mass (kg)	Fat Mass (kg)	Leptin (ng/mL)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart Rate (bpm)
REE	—									
Age	−0.19 (0.001)	—								
Weight	0.67 (0.001)	0.01 (0.90)	—							
Body mass index	0.44 (0.001)	0.05 (0.27)	0.90 (0.001)	—						
Fat-free mass	0.77 (0.001)	−0.01 (0.82)	0.69 (0.001)	0.39 (0.001)	—					
Fat mass	0.37 (0.001)	0.03 (0.53)	0.88 (0.001)	0.95 (0.001)	0.26 (0.01)	—				
Leptin	0.02 (0.67)	0.06 (0.20)	0.54 (0.001)	0.70 (0.001)	−0.08 (0.11)	0.76 (0.001)	—			
Systolic BP	0.22 (0.001)	0.44 (0.001)	0.21 (0.001)	0.16 (0.001)	0.22 (0.001)	0.12 (0.05)	−0.01 (0.90)	—		
Diastolic BP	0.14 (0.001)	0.38 (0.001)	0.16 (0.001)	0.12 (0.05)	0.14 (0.001)	0.10 (0.05)	0.01 (0.83)	0.70 (0.001)	—	
Heart rate	0.11 (0.05)	−0.03 (0.60)	0.08 (0.08)	0.09 (0.06)	−0.02 (0.63)	0.12 (0.05)	0.10 (0.05)	0.06 (0.17)	0.05 (0.27)	—

REE indicates resting energy expenditure.

After adjustment for body composition (FFM and FM) or body size (height+weight or BMI), REE was found to be consistently associated with SBP and DBP in the Nigerians and African Americans separately and in the combined sample (Table 5). Conversely, no association with BP persisted for the body size measures after accounting for the effect of REE. We noted no association between leptin and BP in the multivariate regression models and deleted it from the models. Gender and population origin also had no effect. To account for potential familial aggregation, we repeated the regression analyses in a subset of unrelated participants from Nigeria and the United States (N=354) and in the physical activity sample (N=118). The association between BP and REE remained unchanged.

To assess the relative contribution of REE and body size, we calculated the percent of variance in BP (ie, R^2) accounted for in multivariate models with each of these predictors. A model including BMI, age, gender, and population group explained 19% of the variance in SBP. The same model with REE instead of BMI explained 23% of the variance; adding BMI to the model with REE resulted in no change in R^2. This result was to be anticipated because BMI was rendered uninformative in the multivariate regression model by addition of REE.

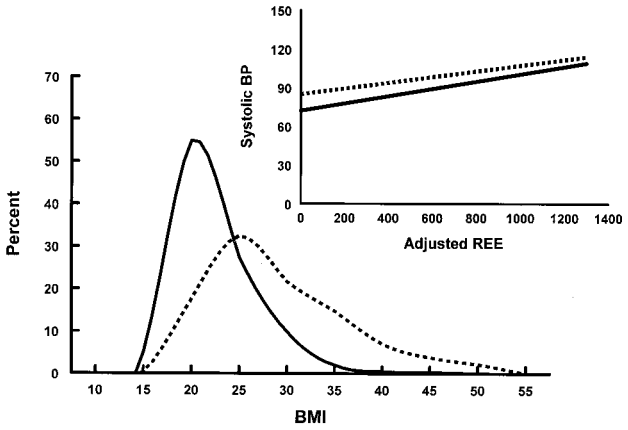
We quantified the effect of REE in terms that make it comparable to other widely known factors that influence BP. Adjusted for body size and age, SBP and DBP were substantially higher among participants in the highest versus lowest quartile of REE (SBP 120.9 versus 112.2 mm Hg, $P<0.001$; DBP 74.1 versus 69.8 mm Hg, $P<0.001$). The odds ratio for hypertension among participants in the highest versus lowest quartile of REE adjusted for body size and age was 1.7 (95% confidence interval, 1.1 to 2.7).

To determine whether the association between BP and REE was restricted to the frankly obese, we repeated all analyses among persons with BMI <30 and found no change in the associations. Taking advantage of the contrasting levels of obesity in the 2 population samples, we tested for a difference in the slope of the multivariate association between REE and BP in Nigeria versus the United States. Similar relationships were observed in both populations, with a nominally steeper slope in Nigeria compared with the United States (ie, $\beta=0.28$ versus 0.20, respectively) (Figure).

The same regression models were applied to the independent set of 118 individuals with direct measurement of energy expended in physical activity. The association between REE and BP was statistically significant in all the models, while a borderline significant negative association with physical activity was observed (Table 6).

Discussion

The physiological mechanisms that underlie the causal processes in hypertension are inherently difficult to study because of their nonindependence. Adiposity and excess sodium intake are the best described exposures thought to play a causal role. While the BP-elevating role of sodium is no longer in doubt, the causal process linking obesity to hypertension is still poorly understood. Moreover, obesity is a complex syndrome, representing a nexus of lifestyle and hormonal factors, including low physical activity, high-



Distribution of BMI in Nigerians (—) and African Americans (- - -). In the small graph, the relation between SBP and REE adjusted for body composition, age, and sex are depicted for Nigerians (—) and African Americans (- - -). The association between SBP and REE is similar in the 2 populations regardless of mean BMI.

TABLE 5. Regression Coefficients for the Relation Between Blood Pressure and Resting Energy Expenditure, Adjusted for Body Size or Composition, Age, Sex, and Site (*P* Values)

Site	n	Intercept	β_1 (REE)	β_1 (BMI)	β_3 (FFM)	β_4 (FM)	β_5 (Age)	β_6 (Sex)	β_7 (Site)	SEE (mm Hg)	R^2
Systolic Blood Pressure											
Nigeria	996	47.3 (0.001)	0.028 (0.001)	0.16 (ns)	—	—	0.58 (0.001)	0.89 (ns)	—	19.6	0.22
US	452	59.6 (0.001)	0.020 (0.001)	−0.09 (ns)	—	—	0.75 (0.001)	1.97 (ns)	—	13.9	0.29
Combined	1448	55.9 (0.001)	0.024 (0.001)	0.02 (ns)	—	—	0.60 (0.001)	1.15 (ns)	0.90 (ns)	18.0	0.23
Diastolic Blood Pressure											
Nigeria	996	25.0 (0.001)	0.015 (0.001)	0.50 (0.001)	—	—	0.30 (0.001)	0.60 (ns)	—	11.4	0.23
US	452	39.8 (0.001)	0.011 (0.001)	−0.05 (ns)	—	—	0.47 (0.001)	1.42 (ns)	—	11.0	0.19
Combined	1448	34.4 (0.001)	0.013 (0.001)	0.17 (0.01)	—	—	0.32 (0.001)	1.04 (ns)	0.97 (ns)	11.5	0.19
Systolic Blood Pressure											
Nigeria	992	55.5 (0.001)	0.034 (0.001)	—	−0.31 (0.05)	0.15 (ns)	0.59 (0.001)	−1.57 (ns)	—	19.6	0.23
US	415	51.9 (0.001)	0.019 (0.001)	—	0.16 (ns)	−0.10 (ns)	0.76 (0.001)	4.90 (ns)	—	14.1	0.30
Combined	1407	58.9 (0.001)	0.027 (0.001)	—	−0.17 (ns)	0.04 (ns)	0.60 (0.001)	−0.28 (ns)	1.71 (ns)	18.2	0.23
Diastolic Blood Pressure											
Nigeria	992	32.0 (0.001)	0.015 (0.001)	—	0.02 (ns)	0.28 (0.001)	0.29 (0.001)	−0.14 (ns)	—	11.4	0.23
US	415	37.1 (0.001)	0.008 (0.01)	—-	0.11 (ns)	−0.04 (ns)	0.47 (0.001)	2.8 (ns)	—	10.9	0.21
Combined	1407	36.3 (0.001)	0.012 (0.001)	—	0.05 (ns)	0.09 (0.01)	0.32 (0.001)	1.04 (ns)	0.54 (ns)	11.5	0.19

Site covariate: Nigeria=0, US=1.

REE indicates resting energy expenditure; BMI, body mass index; FFM, fat-free mass; FM, fat mass.

calorie and high-sodium intake, increased cardiac output, sympathetic tone, and hormone levels.[5]

Energy expenditure for all organisms is determined primarily by body size. Variation in REE among humans reflects differences in the mass of lean body tissue, primarily muscle.[8,19] REE is also linked in an obligatory fashion to fat mass, because changes in fat mass are accompanied by parallel changes in lean mass.[8] All associations between body size and other traits, like cardiovascular risk factors, are therefore potentially confounded by the association with REE. In this setting, 2 competing hypotheses must be entertained. Epidemiologic analyses have traditionally been based on the assumption that accumulation of body fat stores is the primary abnormality that in turn causes a series of downstream pathologic consequences. We have demonstrated in these 3 independent samples that the effect of BMI can be entirely explained by REE. These data provide the basis for a new hypothesis linking obesity to hypertension. In this construct, REE increases in parallel with body size, and in turn either serves as a proxy for other correlated metabolic processes or leads directly to increases in BP. We acknowledge that on the surface, this effect seems counterintuitive, because increases in habitual levels of voluntary energy expenditure, ie, through exercise, reduce BP. As we have shown here using the precision of stable isotopes, habitual physical activity is indeed associated with lower adiposity and lower BP. However, after accounting for physical activity the residual positive correlation of increased REE with BP remained highly significant and was much stronger than the effect of energy expended in physical activity.

Because all 3 of the major variables in this analysis, ie, BP, REE, and BMI, are intercorrelated, the judgment about the causal arrangement depends on the results of the multivariate models. The obvious rejoinder to the interpretation that REE accounts for the variation in BP with body size would be residual confounding by the relationship between REE and obesity. However, that hypothesis is not consistent with the statistical analysis. In all 3 independent samples, the measures of body size, including weight, height, FFM, FM, and BMI are all unrelated to BP once REE has been entered into the model. Measurement error can potentially distort multivariate models. If 1 of 2 correlated traits is measured with greater precision, it may absorb a disproportionate share of the common variance. In this instance, however, the 2 classes

TABLE 6. Regression Coefficients for the Relation Between Systolic Blood Pressure and Resting Energy Expenditure and Activity,* Adjusted for Body Size or Composition and Age† (*P* Values)

Intercept	β_1 (REE)	β_1 (Activity)	β_3 (BMI)	β_4 (FFM)	β_5 (FM)	β_6 (Age)	SEE (mm Hg)	R^2
70.8 (0.001)	0.025 (0.01)	−0.642 (0.06)	−0.55 (0.21)	—	—	0.94 (0.001)	22.1	0.22
62.3 (0.001)	0.041 (0.02)	−0.63 (0.09)	—	−0.46 (0.25)	−0.31 (0.11)	0.95 (0.001)	21.9	0.24

N=118.

*Activity measured using doubly labeled water method.

†Sex and site were consistently not statistically significant and were omitted from the models.

REE indicates resting energy expenditure; BMI, body mass index; FFM, fat-free mass; FM, fat mass.

of exposure variables, eg, REE and body size, are measured with a similar high degree of precision (intra-individual $r>0.97$). Furthermore, the inter-individual variation in REE is comparable to a range of other anthropometric and physiological traits (ie, coefficient of variation 10% to 15%) and of sufficient magnitude to have an important influence on the level of a correlated CV risk factor.

Despite the strong association that has been demonstrated, the causal sequence at the physiological level should not be confused with the overall causal process at the level of the whole organism. Approximately half of the inter-individual variation in REE is attributable to body size while a residual effect of approximately similar magnitude remains for inherent variation in the level of REE and random processes. If in fact REE captures information that summarizes one of the pathways to hypertension, adiposity would be an additional contributor, but a substantial effect exists independent of BMI. Thus, persons at similar levels of BMI or body size with REE in the highest quartile compared with those in the lowest quartile have a 1.7-fold higher risk for hypertension.

To our knowledge, the only previous direct examination of this question was undertaken by Kunz et al.[20] In their clinical study, REE was significantly higher by 9% in 43 obese hypertensive patients when compared with 27 obese normotensives, as were plasma catecholamines and leptin.[20] Substantial alterations in REE occur in hypothyroidism and hyperthyroidism, and in both instances elevated BP is commonly observed.[21,22] The implications of thyroid disease, with a variety of other associated effects, for normal variation in REE is difficult to judge, however. REE may reflect sympathetic tone, although measurement of various compartment effects is challenging.[23] A large proportion of resting energy is expended to maintain ion gradients across cell membranes.[20] A large, generally inconsistent body of research exists on the potential relationship between ion exchange and BP.[24] Studies of ion exchange are plagued by the imprecision of measuring activity in cell suspensions.[24] The possibility remains that the precision provided by total body measurement of REE has illuminated evidence of the role for a metabolic set-point that previously escaped notice.

Perspectives

In summary, the data presented here demonstrate that the relationship between adiposity and BP is confounded by the joint association with REE. Body fat stores, per se, appear to have no impact on BP or risk of hypertension after adjustment for the associated increases in REE. If confirmed, this causal model modifies the conceptual framework within which we understand the link between obesity and hypertension and suggests a new direction for pathophysiologic research.

Acknowledgments

This work was conducted with support from the National Institutes of Diabetes, Digestive, and Kidney Diseases and Heart Lung and Blood Diseases (DK 56781, HL 45508 and HL 53353).

References

1. Dyer AR, Elliott P. The INTERSALT study: relations of body mass index to blood pressure. INTERSALT Cooperative Research Group. *J Human Hypertens.* 1989;3:299–308.
2. Stamler J. Epidemiologic findings on body mass and blood pressure in adults. *Ann Epidemiol.* 1991;1:347–362.
3. Weinsier RL, Hunter GR, Heini AF, Goran MI, Sell SM. The etiology of obesity: relative contribution of metabolic factors, diet, and physical activity. *Am J Med.* 1998;105:145–150.
4. Imazu M. Hypertension and insulin disorders. *Curr Hypertens Rep.* 2002; 4:477–482.
5. Masuo K. Obesity-related hypertension: role of the sympathetic nervous system, insulin, and leptin. *Curr Hypertens Rep.* 2002;4:112–118.
6. Hall JE. The kidney, hypertension and obesity. *Hypertension.* 2003;41: 625–633.
7. Hall JE, Brands MW, Jones DW, Shek EW, Henegar J. Mechanisms of obesity hypertension and relevance to essential hypertension. In: Fletcher GF, Gundy SM, Hayman L, eds. *Obesity: Impact on Cardiovascular Disease*. Armonk, NY: Futura Publishing; 1999:133–153.
8. Nelson KM, Weinsier RL, Long CL, Schutz Y. Prediction of resting energy expenditure from fat-free mass and fat mass. *Am J Clin Nutr.* 992;56:848–856.
9. Cooper RS, Rotimi CN, Ataman SL, McGee D, Osotimehin B, Kadiri S, Muna W, Kingue S, Fraser H, Forrester T, Bennett F, Wilks R. The prevalence of hypertension in seven populations of West African origin. *Am J Public Health.* 1997;87:160–168.
10. Cooper RS, Puras A, Tracy J, Kaufman J, Asuzu M, Ordunez P, Mufunda J, Sparks H. Evaluation of an electronic blood pressure device for epidemiologic studies. *Blood Pressure Monitoring.* 1997;2:35–40.
11. Luke A, Rotimi CN, Cooper RS, Long AE, Forrester TE, Wilks R, Bennett FI, Ogunbiyi O, Compton JA, Bowsher RR. Leptin and body composition of Nigerians, Jamaicans and US blacks. *Am J Clin Nutr.* 1998;67:391–396.
12. Lukaski HC, Bolonchuk WW, Hall CB, Ciders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. *J Appl Physiol.* 1986;60:1327–1332.
13. Weir JBV. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol.* 1949;109:1–9.
14. Luke A, Rotimi CN, Adeyemo AA, Durazo-Arvizu RA, Prewitt TE, Moragne-Kayser L, Harders R, Coooper RS. Comparability of resting energy expenditure in Nigerians and U.S. blacks. *Obesity Res.* 2000;8: 351–359.
15. Luke A, Durazo-Arvizu RA, Rotimi CN, Iams H, Schoeller DA, Adeyemo AA, Forrester TE, Wilks R, Cooper RS. Activity energy expenditure and adiposity among black adults in Nigeria and the United States. *Am J Clin Nutr.* 2002;75:1045–1050.
16. Schoeller DA, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, Jequier E. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. *Am J Physiol.* 1986;250:R823–R830.
17. Schoeller DA, Jeffords G. Determinants of the energy costs of light activities: inferences for interpreting doubly labeled water data. *Int J Obes Relat Metab Disord.* 2002;26:97–101.
18. Schoeller DA, Kushner RF, Taylor PB, Dietz WH, Bandini LG. Measurement of total body water: isotope dilution techniques. In: Roche AF, ed. *Body composition in youths and adults. Report of the Sixth Ross Conference on Medical Research.* Columbus, OH: Ross Laboratories; 1985:24–39.
19. Summers M, McBride BW, Milligan LP. Components of basal energy expenditure. In: Dobson A, Dobson MJ, eds. *Aspects of Digestive Physiology in Ruminants. Proc. of Satellite Symposium of 30th International Congress of International Union of Physiological Sciences.* Ithaca, NY: Comstock Pub Assoc; 1988:257–285.
20. Kunz I, Schorr U, Klaus S, Sharma AM. Resting metabolic rate and substrate use in obesity hypertension. *Hypertension.* 2000;36:26–32.
21. Marcisz C, Jonderko G, Kucharz EJ. Influence of short-time application of a low sodium diet on blood pressure in patients with hyperthyroidism or hypothyroidism during therapy. *Am J Hypertens.* 2001;14:995–1002.
22. Fommei E, Iervase G. The role of thyroid hormone in blood pressure homeostasis: Evidence from short-term hypothyroidism in humans. *J Clin Endocrinol Metab.* 2002;87:1996–2000.
23. Amerena J, Julius S. Role of the Nervous System in Human Hypertension. In: Braunwald E, ed. *Atlas of Heart Diseases.* Philadelphia: Current Medicine; 1995:2.2–2.18.
24. Cooper RS, Borke JL. Intracellular Ions and Hypertension in Blacks. In: Fray JCS, Douglas J, eds. *Pathophysiology of Hypertension in Blacks.* Oxford, New York; 1993:181–213.

Hypertension
Journal of the American Heart Association

Association Between Blood Pressure and Resting Energy Expenditure Independent of Body Size

Amy Luke, Adebowale Adeyemo, Holly Kramer, Terrence Forrester and Richard S. Cooper

Hypertension. 2004;43:555-560; originally published online February 2, 2004;
doi: 10.1161/01.HYP.0000118020.44335.20
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563