Body composition and fat distribution influence systemic hemodynamics in the absence of obesity: the HyperGEN Study

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ABSTRACT
Background: We have shown that increased cardiac output is related to both fat-free mass and fat mass in obesity.
Objective: We studied the association of body fat distribution and body composition with flow-resistance relations in overweight.
Design: We studied 521 overweight, nonobese participants in the Hypertension Genetic Epidemiology Network (HyperGEN) Study— a component of the National Heart, Lung, and Blood Institute Family Blood Pressure Program, designed to assess the genetic basis of hypertension. Participants had normal ventricular function and no cardiovascular disease: 261 with central fat distribution (CFD) (waist girth > 88 cm in women and > 102 cm in men) and 260 with peripheral fat distribution (PFD). Fat-free mass (FFM) and fat mass (FM) were measured by bioelectric impedance. Body composition was estimated as FM/FFM. Echocardiographic stroke volume (SV) and cardiac output (CO) were measured.
Results: Hypertension was present in 73% of the subjects with PFD and in 78% with CFD. Overweight with CFD was associated with greater FM/FFM in both normotensive and hypertensive participants. After FFM, age, sex, and race were controlled for, SV and CO were higher in subjects overweight with CFD than in those with PFD, whereas peripheral resistance was not significantly different. Differences in CO between CFD and PFD were reduced after further adjustment for FM. After the covariates were controlled for, hypertensive subjects had higher peripheral resistance and lower arterial compliance than did normotensive participants, but cardiac output was not significantly different.

KEY WORDS Body composition, obesity, cardiac output, blood pressure, fat-free mass, waist circumference

INTRODUCTION
A strong link exists between obesity and hypertension, which may be attributed to several genetic, environmental, and hemodynamic factors (1–4). Arterial hypertension in obesity is thought to be related to high circulating volume. In fact, compared with lean hypertensive patients, obese hypertensive patients tend to have lower peripheral resistance with a slightly higher cardiac output (2). Because cardiac output is closely related to body size, mostly as a result of metabolic requirements of fat-free body mass (5, 6), the increased cardiac output seen in obese individuals is substantially attributable to the relative increase in metabolically active fat-free body mass that accompanies the increased body weight (7, 8), and this relation also affects the development of left ventricular (LV) mass (9).
Together with the evidence of the strong association between increased fat-free mass and enhanced flow output, there is reason to suspect that the excess of fat mass might also contribute to the hemodynamic changes underlying both the development of arterial hypertension and the magnitude of LV mass (10), at least in the context of overt obesity. Little information exists on how much fat mass and body fat distribution influence flow and resistance relations in the absence of clear-cut obesity but when overweight is present, a condition quite frequent in arterial hypertension. Accordingly, this study was designed to explore whether body fat distribution and abnormal body composition because of an excess of fat mass are associated with abnormal flow and resistance relations in normotensive and hypertensive overweight, nonobese participants in the Hypertension Genetic Epidemiology Network (HyperGEN) Study.

SUBJECTS AND METHODS
Study population
We examined data from 2466 individuals (1474 women), of whom 2103 were hypertensive, with available Doppler scanning...
Definition and measurements of variables of interest

Centrally trained and certified technicians used a standardized protocol to measure blood pressure at rest (11); the average of 6 resting, seated measures was used in the present report for descriptive statistics. Patients were classified as hypertensive when taking antihypertensive medications or when the average of 3 measurements was $\geq 140$ mm Hg for systolic or $\geq 90$ mm Hg for diastolic blood pressures on $\geq 2$ separate clinic visits. A large proportion (83%) of hypertensive individuals was treated with $\geq 1$ medication in different combinations, most commonly thiazides, $\beta$-blockers, angiotensin-converting enzyme inhibitors, Ca$^{++}$-blockers, or angiotensin type 1–receptor antagonists.

Standardized measurements of BMI and laboratory blood tests were also obtained. Fat distribution was assessed by measuring waist circumference with the use of sex–specific partition values for definition of central body fat distribution ($\geq 88$ cm in women or $\geq 102$ cm in men (13)). Waist circumference was measured in the morning while the participants were standing and wearing loose-fitting clothing.

Fat-free mass was estimated by bioelectric impedance measurements with the use of the Lukaski equation (17), which is based on body height and body conductance. Fat mass was obtained by subtraction of fat-free mass from body weight.

Echocardiographic methods

We used standardized acquisition methods for imaging and Doppler scan echocardiograms that were performed locally (18, 19). Studies were performed with the use of phased-array echocardiographs, as previously reported (12, 20–22). Briefly, echocardiographic measurements were taken during up to 3 cardiac cycles with the use of a computerized review station, according to the recommendations of the American Society of Echocardiography (23, 24).

Stroke volume was obtained from linear measurements of diastolic and systolic diameter with the use of the z-derived method for computation of volumes (25). Cardiac output was obtained by multiplying stroke volume by heart rate. Total peripheral resistance was thereafter estimated in dynes·s·cm$^{-2}$ as $80 \times$ mean blood pressure/cardiac output (26).

Statistical analysis

Data were analyzed with the use of SPSS 12.0 software (SPSS, Chicago, IL). Descriptive statistics were displayed as mean ± SD or as proportions examined by the chi-square test. All variables of interest were examined in relation to the presence or the absence of arterial hypertension and body fat distribution (ie, peripheral or central) by using a full-factorial two-factor analysis of covariance with a hierarchical model and priority entrance for covariates. Thus, the effects of hypertension and fat distribution were adjusted for age, sex, race, fat-free mass, and fat mass in additional models. The estimated marginal means (ie, adjusted for covariates) are reported in the tables. In the hypertensive subgroup, the analysis could also be repeated with the use of a “sandwich estimator,” to account for nonindependence among family members and, therefore, to adjust the hypothesis tests for dependencies (27, 28), under the assumption of same degree of dependency among all members within a family. The null hypothesis was rejected at a two-tailed $\alpha \leq 0.05$.

RESULTS

Fifty-six percent of the examined population was women. Hypertension was present in 394 subjects (76%), 61% of whom were women. Central fat distribution was detected in 261 participants (50%); it was more common in women (81%) than in men (51%; $P < 0.0001$). Central fat distribution was more common in whites (60%) than in African Americans (43%; $P < 0.0001$) and in hypertensive subjects (52%) than in normotensive subjects (44%; $P = 0.127$).

Body composition and blood pressure of overweight individuals

After sex, race, and age were controlled for, central fat distribution was associated with significantly higher BMI ($P < 0.0001$) in the absence or in the presence of arterial hypertension (Table 1). Consistently, both fat-free body mass and fat mass were significantly higher in the group with central fat distribution than in the group with peripheral fat distribution ($P < 0.001$); the ratio between fat mass and fat-free body mass was higher in the presence of central fat distribution ($P < 0.0001$). Systolic, diastolic, and mean blood pressures were not influenced by body fat distribution but, by definition, were higher in hypertensive subjects (all $P < 0.0001$). No differences were found in heart rate.

Fat distribution and hemodynamic characteristics

The relation between flow and resistance was examined also after adjustment for fat-free mass in addition to age, sex, and race. After the covariates were controlled for, stroke volume was unaffected by hypertension, but it was significantly greater when fat distribution was central, resulting in a substantially greater cardiac output (Table 2). The greater cardiac output in the central fat distribution phenotype was mostly attributable to the greater fat mass, because this difference became appreciable when fat mass was also added as a covariate into the model ($P > 0.3$ for fat distribution effect). No interactions were detected between hypertension and fat distribution. Total peripheral resistance and the ratio of stroke volume to pulse pressure were not influenced by fat distribution, whereas they were abnormal in hypertensive subjects, as expected (Table 2). Consideration of family relatedness, by using the sandwich estimator, did not change the results in the hypertensive population.
DISCUSSION

This study provides the first evidence that body composition and fat distribution may influence systemic hemodynamic in normotensive and hypertensive adults from a population-based sample, even in the absence of obesity. Eighty-five percent of hypertensive individuals from this study population were taking antihypertension medications and, therefore, in a condition in which the native hemodynamic pattern could be altered. In an attempt to isolate the effect of the biological factors that were under study, we adjusted for several covariates.

The relation between flow and resistance in obesity is frequently characterized by a blunted decrease in peripheral resistance in the presence of increased cardiac output (1). This abnormality leads either to an increase in blood pressure within the normal range or even to overt hypertension. This abnormality is frequently characterized by a blunted decrease in peripheral resistance, as manifested by an increase in the ratio of fat mass to fat-free mass. Because central (abdominal) fat is metabolically active (31), it also contributes to body requirements for blood flow supply (32) and, therefore, should affect the magnitude of cardiac output. This study, in fact, demonstrates an independent association of central adiposity with cardiac output, even in the absence of clear-cut obesity, an observation that has not been reported before. This association is especially evident when hypertensive subjects are considered separately and remains also independent of fat mass and family relatedness. In the HyperGEN Study normotensive subjects were not recruited as sibships (28).

TABLE 1

General characteristics of normotensive and hypertensive overweight participants in the Hypertension Genetic Epidemiology Network Study with either peripheral or central fat distribution.

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 127)</th>
<th>Hypertensive (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peripheral fat distribution (n = 71)</td>
<td>Central fat distribution (n = 56)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.34 ± 1.72</td>
<td>27.95 ± 1.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7 ± 2.3</td>
<td>29.9 ± 2.1</td>
</tr>
<tr>
<td>Waist girth (cm)</td>
<td>100.6 ± 6.3</td>
<td>101.1 ± 6.1</td>
</tr>
<tr>
<td>Fat-free mass (%)</td>
<td>50.2 ± 1.4</td>
<td>50.4 ± 1.6</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>49.8 ± 1.2</td>
<td>49.6 ± 1.1</td>
</tr>
<tr>
<td>Fat mass/fat-free mass</td>
<td>0.09 ± 0.2</td>
<td>0.08 ± 0.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>126.8 ± 2.4</td>
<td>127.4 ± 2.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>79.5 ± 2.3</td>
<td>80.1 ± 2.5</td>
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</table>

1 All values are x ± SD. Two-factor analysis of covariance was used to adjust for age, sex, race, and fat-free mass. No interaction was found between hypertension status and central fat distribution.

2 Significant differences by type of fat distribution: 2P < 0.0001, 2P < 0.001.

3 Significant differences between normotensive and hypertensive subjects, P < 0.0001.

TABLE 2

Flow and resistance relations in normotensive and hypertensive overweight participants in the Hypertension Genetic Epidemiology Network Study with either peripheral or central fat distribution.

<table>
<thead>
<tr>
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<th>Normotensive (n = 127)</th>
<th>Hypertensive (n = 394)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Peripheral fat distribution (n = 71)</td>
<td>Central fat distribution (n = 56)</td>
</tr>
<tr>
<td>Stroke volume (mL/beat)</td>
<td>72.20 ± 12.60</td>
<td>75.91 ± 15.08</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.73 ± 0.90</td>
<td>4.95 ± 1.03</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes · s · cm⁻²)</td>
<td>1636.74 ± 336.48</td>
<td>1644.41 ± 324.81</td>
</tr>
<tr>
<td>Stroke volume/pulse pressure (mL/mm Hg)</td>
<td>1.62 ± 0.38</td>
<td>1.61 ± 0.45</td>
</tr>
</tbody>
</table>

1 All values are x ± 1 SD. Two-factor analysis of covariance was used to adjust for age, sex, race, and fat-free mass. No interaction was found between hypertension status and central fat distribution.

2 Significant differences by type of fat distribution, P < 0.03.

3 Significant differences between normotensive and hypertensive subjects: 3P < 0.01, 4P < 0.0001.
After demographic variables, body composition, and fat distribution were accounted for, the only hemodynamic abnormality associated with arterial hypertension was increased afterload (high peripheral resistance and arterial stiffness). In contrast, the volume component (namely stroke volume), which has been traditionally considered an important hemodynamic characteristic of overweight-associated arterial hypertension (33, 34), was not significantly different between hypertensive and normotensive participants once the effect of fat distribution was taken into account. Thus, because in the general population the prevalence of overweight is much higher in the presence of arterial hypertension, the traditional interpretation of relations between hypertension and volume overload need to be revisited in view of the evidence that abnormal body composition and fat distribution influence the flow and resistance relation even in the absence of overt obesity, as defined by current guidelines (13). Rather, this finding indicates that clear-cut separation of categories of BMI does not have a strong physiologic rationale. Similarly, use of dichotomization of waist circumference might be misleading also, because it does not highlight the real effect of this measure on human health, as previously highlighted (35).

Whether abdominal fat represents a source of potential health problems also in nonobese subjects is still to be clarified (36). The evidence that fat accumulated in the trunk should be considered harmful is becoming stronger (29, 37–39), even independent of the traditional measure of general adiposity, BMI (13, 40, 41). Recently, in a young cohort with low prevalence of obesity, McCarthy et al (42) observed that the increase over time in waist circumference [the measure of central fat distribution used in the present study and one which is suggested as a reliable measure of body fatness in the most recent guidelines (13, 40)] exceeded the increase in BMI, particularly in girls. Those investigators suggested that BMI might underestimate the rising prevalence of obesity in young people. This observation is consistent with the evidence that even in nonobese subjects (based on the measurement of BMI), abdominal fat accumulation is correlated with glucose intolerance, hyperlipidemia, and hypertension (43).

In addition to the limitation of BMI, we should also highlight that waist circumference and bioelectrical impedance analysis are imprecise measures of body composition. However, in a study on epidemiologic scale, these measures cannot be easily replaced, and the potential error they might introduce is at least minimized in the large number of observations.

Most recently, Ferreira et al (44) reported that measures of central fat distribution during puberty and adolescence, but not overall adiposity, were predictors of future carotid intima-media thickness and arterial stiffness during adulthood (at age 36 y) in a group of individuals with low prevalence of obesity or even overweight as assessed by BMI. They also found that, in a cross-sectional analyses, abdominal fat at age 36 y was positively associated with measures of arterial stiffness.

If body composition and abdominal fat are important for volume homeostasis, because both subcutaneous and visceral fat are metabolically active (45, 46), it is reasonable to think that in some circumstances abdominal fat might promote pathophysiological changes that blunt the physiologic reduction of peripheral resistance in response to increased cardiac output, eventually yielding increased blood pressure. This hypothesis is consistent with the evidence that android fat distribution is correlated with decreased arterial compliance and endothelial dysfunction even at a young age (47). Candidate mechanisms responsible for the alteration of flow and resistance relations caused by abdominal fat are insulin resistance, alterations in the angiotensin pathway, and production of chronic inflammation-related substances that can be responsible for direct vascular insult (41, 48–55). The fact that the greater cardiac output found in overweight subjects with central fat distribution was not fully explained by fat-free mass, but was also attributable to the greater fat mass demonstrates that abdominal fat independently contributes to the blood requirements of the body, indirectly confirming its energetic activity. Future research should be addressed to identify promoters of vascular changes in abdominal adipose tissue that might explain the inadequacy of peripheral resistance to decrease when cardiac output is increased for metabolic requests.

The HyperGEN Participating Institutions and Principal Staff are listed below. Network Center, University of Utah Field Center: Steven C Hunt, Roger R Williams (deceased), Hilaire Coon, Paul N Hopkins, Janet Hood, Nona Gallacher, Michael McGinty, Karen Nielsen, Lily Wu, and Jan Skuppin; University of Alabama at Birmingham Field Center: Albert Oberman, Cora E Lewis, Michael T Weaver, Philip Johnson, Randi Gilinson, and Christie Oden; Boston University, Framingham Field Center: R Curtis Ellisson, Richard H Myers, Yuqiang Zhang, Luc Djoussé, Jemma B Wilk, and Greta Lee Splansky; University of Minnesota Field Center: Donna Arnett, Aaron R Folsom, Larry D Atwood, Gregory Feitl, Jim Pankow, and Barb Lux; University of North Carolina Field Center: Gerardo Heiss, Barry Freedman, Dee Posey, Kathryn Rose, and Amy Haire; Data Coordinating Center, Washington University: DC Rao, Michael A Province, Ingrid B Borecki, Yuling Hong, Avril Adelman, Derek Morgan, Karen Schwander, David Lehrer, Aldi Kraja, and Stephen Mandel; Central Biochemistry Laboratory, University of Minnesota: John H Eckfeldt, Ronald C McGlennen, Michael Y Tsai, Catherine Leiderlecker-Foster, and Greg Rynders; Molecular Genetics Laboratory, University of Utah: Mark Leppert, Steven C Hunt, Jean-Marc Lalouel, and Robert Weiss; National Heart, Lung, and Blood Institute: Stephen Mockrin, Susan E Old, Millicent Higgins (retired), Peter Savage, and Cashell Jaquish.

GdS, RBD, and DKA designed the study. GdS, JRK, and MC conducted the analysis. INB, AO, DCR, DWK, and PNH made substantial conceptual contributions and revisions. GdS and RBD wrote this draft. None of the authors had a conflict of interest to report.

REFERENCES