Increased abdominal-to-peripheral fat distribution contributes to altered autonomic-circulatory control with human aging

Demetra D. Christou, Pamela Parker Jones, Annemarie E. Pimentel, and Douglas R. Seals. Increased abdominal-to-peripheral fat distribution contributes to altered autonomic-circulatory control with human aging. Am J Physiol Heart Circ Physiol 287: H1530–H1537, 2004. First published June 3, 2004; 10.1152/ajpheart.00322.2004.—Autonomic nervous system (ANS) control of the circulation is altered with aging in adult humans. Similar changes are observed in obesity, particularly abdominal obesity. To determine whether age-associated differences in ANS-circulatory function can be partially explained by increased body fatness, we examined ANS functions and three expressions of adiposity (total body fat, abdominal body fat, and abdominal-to-peripheral body fat distribution; dual-energy X-ray absorptiometry) in 43 healthy men: 27 young (25 ± 1 yr) and 16 older (65 ± 1) yr. ANS functions assessed included 1) a) baroreflex sensitivity (Oxford technique); and 2) baroreflex buffering, i.e., the increase in systolic BP with continuous incremental and bolus infusions of phenylephrine during versus before GB; 3) baroreflex buffering, i.e., the increase in systolic BP with continuous incremental and bolus infusions of phenylephrine during versus before GB; 3) baroreflex buffering, i.e., the increase in systolic BP with continuous incremental and bolus infusions of phenylephrine during versus before GB; 4) heart rate variability (time- and frequency-domain analyses). Covarying for abdominal-to-peripheral fat distribution explains a significant portion of the variance in a number of autonomic-circulatory functions attributable to aging. Therefore, the development of this fat pattern may contribute to several changes in ANS-cardiovascular function observed with aging. These results may help explain how changes in body fat distribution with advancing age are linked to impairments in circulatory control.

METHODS

Subjects

Data from 43 men, 27 young (25 ± 1 yr) and 16 older (65 ± 1 yr), were used for the analysis. Subjects were normotensive (BP < 140/90 mmHg) nonsmokers who were not taking any medications. All were healthy as assessed by medical history, physical examination, urinalysis, blood chemistries, and resting and maximal exercise electrocardiograms (older men only). All procedures were approved by the Colorado Multiple Institutional Review Board and the University of Colorado at Boulder Human Research Committee. The nature, benefits, and risks of the study were explained to the volunteers, and their written informed consent was obtained before the study.

Autonomic-Car Cardiovascular Function

Subjects were studied during supine rest beginning at 0800 according to procedures previously described (21, 24). They were instrumented with a radial artery catheter in the nondominant arm and two intravenous catheters in the contralateral arm. BP (in mmHg) was continually monitored by a pressure transducer connected to the arterial catheter, and heart rate was measured via electrocardiograms. Cardiac vagal modulation of heart rate was assessed from heart rate variability (HRV) (11, 24). Both the standard deviation of the R–R intervals (time-domain measure of HRV) and the high-frequency

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power of the HRV (frequency-domain measure of HRV) were determined. Breathing frequency was not regulated, but it did not differ between young and older groups (18 ± 2 vs. 16 ± 2 breaths/min, respectively; P = 0.5).

Cardiovascular BRS was determined from incremental bolus doses of phenylephrine (25, 50, 100, and 200 µg) administered at 3-min intervals (21). R-R intervals were regressed against the corresponding systolic blood pressures (SBP) during increases in BP induced by the phenylephrine bolus.

ANS support of BP was determined by blockade of NANC-cholinergic receptors via continuous intravenous infusion of trimetaphan (24). Complete cardiovascular-autonomic blockade was documented by the absence of a change in heart rate in response to bolus injection of phenylephrine (25, 50, and/or 100 µg). The reduction in BP during ganglionic blockade from pre-trimethaphan baseline levels was used as a measure of ANS support of BP.

BRB was measured 1) as the potentiation of the SBP responses to a standard 25-µg bolus dose of phenylephrine (BRBbase) during compared with before ganglionic blockade and 2) as the change in the slope of the increase in SBP in response to incremental dose infusions of phenylephrine (BRBslope) from baseline during ganglionic blockade (21, 25). These approaches are based on the fact that before ganglionic blockade (i.e., under normal conditions with intact cardioadrenergic (21, 25). These approaches are based on the fact that before ganglionic blockade (i.e., under normal conditions with intact cardioadrenergic

The former presents a relatively brief hypertensive stimulus to the baroreceptors, likely eliciting little or no central nervous system BP resetting, whereas the latter, more sustained stimulus evokes an integrative ANS response that likely reflects the effects of at least some central baroreflex resetting.

Cardiac output was measured by two-dimensional echocardiography (Hewlett-Packard ultrasonography 2500) with a 3.5-MHz phased-array transducer using the parasternal short-axis view as previously described (10, 20). All measurements were made by a certified echocardiologist according to the guidelines of the American Association of Echocardiography. Systemic vascular resistance was calculated as mean BP divided by cardiac output. Plasma samples were analyzed for vasopressin (37) and catecholamine (35) concentrations. Vasopressin was measured because it could partially counteract the fall in BP in response to ganglionic blockade and lead to an underestimation of ANS support of BP (2, 26–28).

Body Composition

Body weight was measured to the nearest 0.1 kg with a physician’s balance scale. Whole body composition was determined by dual-energy X-ray absorptiometry (DXA; DPX-IQ, software version 4.1, Lunar Radiation; Ref. 44). With the standard soft tissue analysis, fat, lean, bone, and total mass were measured with standard cut lines. Because this mode of analysis does not provide body composition information for specific areas of interest such as the abdomen and thigh, we also manually defined specific regions of interest as recently described by our laboratory (14). Briefly, we defined the abdominal and thigh areas as the region from the upper edge of the first lumbar vertebra to the anterior superior iliac spine and the region from (but not including) the ischial tuberosities to the midpoint between the greater trochanter and the knee joint line, respectively. Both regions extended laterally to include any trunk soft tissue. Total adiposity (in kg) was determined from the standard analysis by summing the amount of fat that lies in the whole body. Abdominal adiposity (kg) was determined by calculating the fat content in the manually defined abdominal region. Although DXA is unable to distinguish between intra-abdominal and subcutaneous fat depots, recent studies indicate that there is a strong correlation between abdominal fat estimated from regional analysis of DXA scans and visceral fat directly measured by magnetic resonance imaging (29, 34) and computed tomography (3, 42). To determine abdominal-to-peripheral body fat distribution, i.e., central versus peripheral fat storage, we used the analysis from the manually defined regions and divided the fat (in kg) content in the abdominal region by the fat (in kg) content in the thigh region (abdominal-to-thigh fat ratio). In men, this DXA-derived abdominal-to-thigh fat ratio is positively associated with visceral fat and not associated with subcutaneous fat determined by computed tomography (3). All DXA scans were analyzed by the same investigator (A. E. Pimentel). To assess intraobserver reliability, the scans of 10 representative subjects were analyzed three times for total and abdominal fat content and abdominal-to-peripheral body fat distribution. For each adiposity measure we calculated the coefficient of variation and performed an intraclass reliability analysis. Intraobserver reliability was very high, with coefficients of variation ranging from 0.4 to 1.9% and intraclass reliability from 0.9941 to 1.

Data Analysis

Statistical analyses were performed with the SPSS statistical package (version 11.0; SPSS, Chicago, IL). The distribution of each variable was examined with the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Age-group comparisons were made with t-tests for independent groups. The bivariate relation of adiposity with measures of ANS function was examined with Pearson product-moment correlation coefficients. A preliminary analysis was conducted to evaluate the homogeneity-of-slopes assumption. The homogeneity of variance assumption was examined with Levene’s test. One-way analysis of covariance (ANCOVA) was conducted to determine the contribution of adiposity to the age-related differences in autonomic-circulatory function. Each of the three expressions of adiposity, respectively, was used as the covariate in the model. To determine the proportion of variance in the dependent variable explained uniquely by adiposity while partiailling out the effect of age, partial η² was obtained for adiposity from the ANCOVA models. In addition, to determine the proportion of variance of the dependent variable explained uniquely by age while partiailling out adiposity, partial η² was also obtained for age from the same ANCOVA models. The α was set at 0.05. All data are reported as means ± SE.

RESULTS

Body Mass and Composition

Body mass and body mass index (BMI) were not different in the young and older men (P > 0.05; Table 1). Total and abdominal body fat and the abdominal-to-thigh fat ratio were greater in the older men (P < 0.01).

Contribution of Abdominal-to-Peripheral Body Fat Distribution to Age-Related Differences in ANS-Circulatory Function

ANS support of BP. Greater abdominal-to-peripheral body fat distribution was associated with correspondingly greater ANS support of SBP (Fig. 1A). Independent of age, abdominal-to-peripheral body fat distribution accounted for 12% of the variance in ANS support of SBP (P < 0.05). Age explained 39% of the variance in ANS support of SBP (P < 0.001). After partialing out the effect of abdominal-to-peripheral body fat distribution, the amount of variance explained by age was
reduced to 13% and the age-related difference in the group means was reduced by 40%, although still significant ($P < 0.05$; Fig. 2A). Abdominal-to-peripheral body fat distribution did not contribute significantly to the age-related differences in the change in cardiac output, systemic vascular resistance, and vasopressin in response to ganglionic blockade ($P > 0.05$).

**BRS.** Greater abdominal-to-peripheral body fat distribution was associated with lower BRS (Fig. 1B). Independent of age, abdominal-to-peripheral body fat distribution explained 13% of the variance in cardiovagal BRS ($P < 0.05$). Age explained 28% of the variance in cardiovagal BRS ($P < 0.01$). Removing the effect of abdominal-to-peripheral body fat distribution reduced the age-related difference in the group means by 52%, abolishing the significance of the age effect ($P = 0.1$; Fig. 2B).

**HRV.** Greater abdominal-to-peripheral body fat distribution was associated with lower expressions of HRV (Fig. 1, C and D).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young</th>
<th>Range</th>
<th>Older</th>
<th>Range</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass, kg</td>
<td>76.9±1.4</td>
<td>63.8–93.0</td>
<td>79.7±2.7</td>
<td>63.0–104.5</td>
<td>0.15</td>
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<td>Body mass index, kg/m²</td>
<td>24.4±0.5</td>
<td>20.9–31.7</td>
<td>25.6±0.7</td>
<td>21.8–33.0</td>
<td>0.07</td>
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<tr>
<td>Body fat, %</td>
<td>16.0±1.3</td>
<td>5.6–27.6</td>
<td>21.9±1.6*</td>
<td>11.8–35.5</td>
<td>0.04</td>
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<tr>
<td>Total body fat, kg</td>
<td>12.3±1.1</td>
<td>4.0–24.8</td>
<td>17.4±1.8*</td>
<td>7.8–37.3</td>
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<tr>
<td>Abdominal fat, kg</td>
<td>1.7±0.2</td>
<td>0.7–4.0</td>
<td>3.1±0.4*</td>
<td>1.2–8.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Abdominal-to-thigh fat ratio</td>
<td>1.1±0.1</td>
<td>0.5–2.1</td>
<td>1.7±0.1*</td>
<td>1.3–2.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different vs. young subjects.

Fig. 1. Relation of abdominal-to-peripheral fat distribution (abdominal-to-thigh fat ratio) with change ($\Delta$) in systolic blood pressure (SBP) in response to ganglionic blockade (A), with cardiovagal baroreflex sensitivity (BRS; B), with time-domain [standard deviation of R-R interval (SDR,R)] measure of heart rate variability (HRV) (C), and with high-frequency power (HFP) measure of HRV (D). □, Young men; ■, older men.
Independent of age, abdominal-to-peripheral body fat distribution explained 10% of the variance in these measures of HRV ($P < 0.05$). Age explained 7% of the variance for both the time- and frequency-domain measures of HRV ($P < 0.05$). Removing the effect of abdominal-to-peripheral body fat distribution completely abolished the age-related differences in both measures of HRV ($P = 0.5$; Fig. 2, C and D).

**BRB.** Age explained 20% of the variance in BRB$_{bus}$ and 35% of the variance in BRB$_{tapp}$ ($P < 0.05$). Abdominal-to-peripheral body fat distribution did not contribute significantly to the age-related differences in BRB ($P > 0.05$).

**Contribution of Abdominal Adiposity to Age-Related Differences in Autonomic-Cardiovascular Function**

**ANS support of BP.** Greater abdominal adiposity was associated with greater ANS support of SBP (Fig. 3A). Independent of age, abdominal body fat explained 7% of the variance in autonomic support of SBP ($P < 0.05$). Removing the effects of abdominal adiposity reduced the amount of variance in ANS support of SBP explained by age from 39% to 27% and reduced the age-related difference in the group means by 15%, although still highly significant ($P < 0.001$; Fig. 4A). Abdominal adiposity did not significantly contribute to the age-related differences in the change in cardiac output, systemic vascular resistance, and vasopressin in response to ganglionic blockade ($P > 0.05$).

**Other ANS-cardiovascular functions.** Greater abdominal adiposity was associated with lower expressions of HRV (Fig. 3, B and C). Independent of age, abdominal body fat accounted for 22% and 8%, respectively, of the variance in the time- and frequency-domain measures of HRV ($P < 0.05$). After partialling out the effect of abdominal adiposity, the age-related differences in the time- and frequency-domain measures of HRV were reduced by 88% and 54%, respectively, abolishing the age effects ($P > 0.3$; Fig. 4, B and C). Abdominal fat did not contribute significantly to the age-related differences in BRB or cardiovagal BRS ($P > 0.05$).

**Contribution of Total Adiposity to Age-Related Differences in Autonomic-Cardiovascular Function**

**HRV.** Greater total adiposity was associated with lower expressions of HRV (Fig. 5). Independent of age, total body fat accounted for 18% of the variance in the time-domain measure of HRV ($P < 0.01$) but did not explain a significant portion of the variance for the frequency-domain measure of HRV (5%; $P = 0.07$). After partialling out the effect of total body fat, the...
age-related differences in the time- and frequency-domain measures of HRV were reduced by 59% and 35%, abolishing the significance of the age effects ($P > 0.15$; Fig. 6).

**Other ANS-cardiovascular functions.** Total adiposity did not contribute significantly to the age-related differences in the other ANS-cardiovascular functions ($P > 0.05$).

**Fig. 3.** Relation of abdominal adiposity with $\Delta$SBP in response to ganglionic blockade (A), with time-domain (SDR-R) measure of HRV (B), and with HFP measure of HRV (C). □, young men; ■, older men.

**Fig. 4.** Mean difference in autonomic-cardiovascular function between young and older adult males before and after adjusting for abdominal adiposity. A: autonomic nervous system support of SBP. B: time-domain measure (SDR-R) of HRV. C: HFP measure of HRV.
DISCUSSION

The novel finding of this study is that increased abdominal-to-peripheral fat distribution explains a significant portion of the variance attributable to aging for several key ANS-circulatory functions in healthy normotensive men varying widely in age. Indeed, correcting for abdominal-to-peripheral fat distribution reduces, and, in some cases, completely abolishes age-associated differences in these ANS-cardiovascular functions, whereas abdominal adiposity and total body fat contribute progressively less, respectively, to these differences with age. Overall, our findings provide the first systematic experimental evidence that abdominal-to-peripheral fat distribution may influence a number of physiologically important ANS-cardiovascular functions in humans and may play a major role in mediating potentially adverse changes in autonomic-circulatory control with aging.

ANS-Circulatory Function, Adiposity, and Aging

The present results supporting a significant role of adiposity in the age-related differences in ANS-circulatory function are consistent with observations of differences in autonomic-cardiovascular function in obese compared with lean young adults (4, 47, 48), as well as with previous reports linking elevated adiposity to increases in sympathetic nervous system activity (1, 16).

A key question stemming from our findings is why the influence of abdominal-to-peripheral fat distribution in the age-related differences in ANS-circulatory function was more robust compared with abdominal or total body fat. Our results provide no direct insight regarding this issue. However, we speculate that 1) autonomic-cardiovascular function is most greatly influenced by abdominal visceral adiposity and 2) our measure of abdominal-to-peripheral fat distribution is more closely related to abdominal visceral fat storage than the other two expressions of adiposity, as suggested by previous findings (3). Support for the idea of a strong ANS-visceral fat connection comes from recent findings that muscle sympathetic nerve activity is more strongly related to abdominal visceral adiposity than to either subcutaneous abdominal fat or total body fat (1). These associations between a visceral fat distribution phenotype and peripheral ANS activity are physiologically consistent with previous observations showing a strong coupling between visceral adiposity and a variety of metabolic functions, including fat metabolism (8, 45).
The specific physiological signals that link visceral fat to autonomic-cardiovascular function are incompletely understood, but they could involve adipocyte-released endocrine modulating factors such as circulating adipokines, free fatty acids, angiotensin II, insulin, leptin, and/or cortisol. These putative factors circulate at levels proportional to peripheral fat stores and the distribution of those fat stores, cross the blood-brain barrier, and access nuclei in the hypothalamus and perhaps other areas of the brain involved in the regulation of autonomic outflow to the heart and vasculature. Future studies must identify the exact nature of the physiological signals linking adiposity with ANS activity.

Although the adiposity-sympathetic nervous system relation has been widely discussed (15, 30, 39), potential associations with other autonomic-cardiovascular functions including those associated with cardiovascular control have received much less attention (4). Our findings support the concept of a physiological interaction between a number of different ANS-circulatory functions and adiposity, particularly abdominal-to-peripheral fat distribution, in healthy young and older men.

If true, these physiological interactions may explain the present findings related to aging. Specifically, advancing age in adult humans is associated with increases in total body fat and abdominal adiposity, as well as a progressive shift from a peripheral to a central/abdominal fat pattern (6, 7). Consistent with this, many if not all of the putative adiposity-sensitive physiological signals described above increase with age (32, 33). Thus changes in one or more of these signals could account for the apparent important contribution of increased abdominal-to-peripheral fat distribution to age-associated changes in autonomic-circulatory function.

Statistically partialling out the effect of abdominal-to-peripheral fat distribution did not affect age-associated differences in BRB. This suggests that increases in abdominal-to-peripheral fat distribution with age do not contribute to changes in this function. We can advance no obvious explanation for this apparent distinction within our overall results. It is possible that BRB may not be as directly influenced by adiposity-evoked changes in central ANS activity as other functions such as cardiovascular BRS and cardiac vagal modulation of heart rate (i.e., HRV).

Limitations

We emphasize that the men in the present study represented a relatively modest range of BMI. The inclusion of subjects with higher BMI might have resulted in even stronger associations between ANS-circulatory function and adiposity. Similarly, inclusion of older men with higher BMI might have increased the portion of the age-attributable variance in autonomic-cardiovascular function explained by adiposity. Therefore, the absence of subjects with greater obesity than those studied here could have resulted in underestimation of the role of body fatness in the age-related differences in ANS-circulatory function.

DXA, the method we used to measure adiposity, is unable to determine visceral fat independently from subcutaneous fat. However, recent studies indicate that there is a strong correlation between abdominal fat estimated from regional analysis of DXA scans and visceral fat measured directly by magnetic resonance imaging (29, 34) and computed tomography (3, 42).

These three methods differ in cost, technical difficulty, accuracy, reproducibility of results, and, perhaps, subject safety. DXA offers a simple, accurate, and reliable method to obtain total and regional body composition analysis while exposing subjects to low amounts of radiation.

Finally, a causal relation between adiposity and age-associated changes in ANS-circulatory function cannot be established from the present results. Our results represent, however, an appropriate initial step to establish the role of adiposity in the changes in autonomic-cardiovascular function with aging. More definitive approaches that involve significant investigative and human subject burden such as weight loss in older adults and overfeeding studies in young adults can be justified based on the results of the present study.

Physiological and Clinical Significance

ANS-circulatory abnormalities with the development of age-associated obesity may negatively impact physiological function, including the ability to maintain homeostasis during acute stress, and may increase the risk of clinical cardiovascular and metabolic diseases. For example, reduced cardiac vagal modulation of heart rate with age is associated with impaired BP control (e.g., increased BP variability) (46) and a reduced ability to augment heart rate during exercise (43). Decreased cardiac vagal modulation of heart rate and reduced cardiovascular BRS are associated with cardiac electrical instability, increased susceptibility to ventricular tachyarrhythmias, and an increased incidence of cardiac sudden death in the presence of myocardial ischemia (5, 9, 38). Importantly, these autonomic-cardiovascular changes are a fundamental feature of age-associated clinical disorders including Type 2 diabetes, essential hypertension, coronary artery disease, and congestive heart failure. In the present study we have identified a key modulatory factor associated with a number of ANS-circulatory functions in healthy adult men and have provided new insight as to why some of these functions may become altered with advancing age. Our findings also provide another compelling argument for properly controlling body weight during adult aging.

In conclusion, our findings indicate that abdominal-to-peripheral fat distribution plays a significant role in a number of autonomic-circulatory functions in healthy men. Moreover, the development of this fat pattern may contribute to several changes in ANS-cardiovascular function observed with aging.

ACKNOWLEDGMENTS

The authors thank Christopher Gentile for technical assistance.

GRANT

This work was supported by National Institutes of Health Grants AG-06537, AG-15897, HL-07822, AG-00828, and RR-00051.

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