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Weight loss increases cardiovagal baroreflex function in obese young and older men

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Alvarez, Guy E., Brenda M. Davy, Tasha P. Ballard, Stacy D. Beske, and Kevin P. Davy. Weight loss increases cardiovagal baroreflex function in obese young and older men. *Am J Physiol Endocrinol Metab* 289: E665–E669, 2005. First published June 7, 2005; doi:10.1152/ajpendo.00487.2004.—We tested the hypothesis that reductions in total body and abdominal visceral fat with energy restriction would be associated with increases in cardiovagal baroreflex sensitivity (BRS) in overweight/obese older men. To address this, overweight/obese ($25 \leq$ body mass index ≤ 35 kg/m²) young (OB-Y, $n = 10$, age = 32.9 ± 2.3 yr) and older (OB-O, $n = 6$, age = 60 ± 2.7 yr) men underwent 3 mo of energy restriction at a level designed to reduce body weight by 5–10%. Cardiovascular BRS (modified Oxford technique), body composition (dual-energy X-ray absorptiometry), and abdominal fat distribution (computed tomography) were measured in the overweight/obese men before weight loss and after 4 wk of weight stability at their reduced weight and compared with a group of nonobese young men (NO-Y, $n = 13$, age = 21.1 ± 1.0 yr). Before weight loss, cardiovagal BRS was ~35% and ~60% lower ($P < 0.05$) in the OB-Y and OB-O compared with NO-Y. Body weight (-7.8 ± 1.1 vs. -7.3 ± 0.7 kg), total fat mass (-4.1 ± 1.0 vs. -4.4 ± 0.8 kg), and abdominal visceral fat (-27.6 ± 6.9 vs. -43.5 ± 10.1 cm²) were reduced (all $P < 0.05$) after weight loss, but the magnitude of reduction did not differ (all $P > 0.05$) between OB-Y and OB-O, respectively. Cardiovascular BRS increased (11.5 ± 1.9 vs. 18.5 ± 2.6 ms/mmHg and 6.7 ± 1.2 vs. 12.8 ± 4.2 ms/mmHg) after weight loss (both $P < 0.05$) in OB-Y and OB-O, respectively. After weight loss, cardiovagal BRS in the obese/overweight young and older men was ~105% and ~73% ($P > 0.05$) of NO-Y (17.5 ± 2.2 ms/mmHg). Therefore, the results of this study indicate that weight loss increases the sensitivity of the cardiovagal baroreflex in overweight/obese young and older men.

aging; obesity; baroreflex

ABRUPT DECREASES AND INCREASES in systolic arterial blood pressure produce baroreflex-mediated shortening and lengthening, respectively, of the R-R interval (7). This phenomenon is best described by the sigmoidal relationship between R-R interval length and systolic blood pressure and is otherwise known as the cardiovagal baroreflex. The linear portion of this relation is used to derive the gain or sensitivity of the cardiovagal baroreflex.

Cardiovascular baroreflex sensitivity (BRS) declines (6, 12, 13) and total and abdominal adiposity increases (8, 19, 24) with advancing age. Importantly, reduced cardiovascular BRS has been associated with poor orthostatic tolerance in older adults (23) and an increased risk of cardiac sudden death in postmyocardial infarction patients (16, 17).

We (1, 3) and others (9, 11) have observed reduced cardiovagal BRS in overweight and obese humans, particularly in those with elevated abdominal visceral fat (1, 3). In addition, total body and abdominal adiposity are important physiological correlates of reduced cardiovagal BRS in older adults (20). However, whether weight loss, and the accompanying reductions in total body and abdominal visceral fat, is associated with increases in cardiovagal BRS in older men is unknown. Therefore, we tested the hypothesis that reductions in total body and abdominal visceral fat with weight loss would be associated with increases in cardiovagal BRS in overweight/obese older men.

METHODS

Subjects. Six overweight/obese [$25 \leq$ body mass index (BMI) ≤ 35 kg/m²] older (OB-O, age = 51–70 yr), 10 overweight/obese young (OB-Y, age = 32.9 ± 2.3 yr), and 13 nonobese (BMI < 25 kg/m²) young (NO-Y, age = 21.1 ± 1.0 yr) men were studied in the present investigation. All subjects were normotensive (arterial blood pressure $< 140/90$ mmHg) and free from overt cardiovascular diseases as determined from individual health histories. Subjects were further evaluated for the presence of overt cardiopulmonary disease by resting and maximal exercise electrocardiograms. These individuals were nonsmokers, nondiabetic (2-h postglucose load < 200 mg/dl) and not taking any medications that could influence autonomic-circulatory function. All subjects were sedentary and not participating in any program of regular physical activity (defined as > 20 min on > 2 days/wk). The University Institutional Review Board approved all experimental protocols. The nature, purpose, risks, and benefits were explained to the subject before obtaining informed consent.

Experimental procedures. Body mass was measured on a physician's balance to the nearest 0.1 kg. Height was measured using a stadiometer. Waist and hip circumference were measured using procedures recommended by the Arlie Conference (18); the waist-to-hip ratio was calculated. Body composition was measured using dual-energy X-ray absorptiometry (DPX-IQ; Lunar Radiation) using software version 4.5c. Computed tomography scans (HiSpeed CTi; GE Medical) were performed to quantify abdominal visceral and subcutaneous fat levels as previously described (1, 3). Maximal oxygen consumption was measured during graded treadmill exercise to exhaustion using open-circuit spirometry (TrueMax 2400; ParvoMedics). Heart rate was measured from lead II of an electrocardiogram. Respiration was monitored by placing a pneumobelt around the upper abdomen. Beat-to-beat arterial blood pressure was measured using finger photoplethysmography (Finometer; Finapres Medical Systems). Resting finger arterial blood pressures were "adjusted" to brachial arterial blood pressures with an automated device (Dinamap; Critikon) before the injection of vasoactive drugs (see below). Cardiovascular BRS was measured using the modified Oxford technique (5).

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Experimental protocol. All subjects were studied after a 12-h overnight fast between 7:00 AM and 11:00 AM. Subjects were instructed to refrain from consuming alcohol and foods and beverages containing caffeine for 24 h before all testing sessions. Subjects were also asked to not participate in any vigorous activity for 24 h before testing.

An antecubital venous catheter was placed for the injection of vasoactive drugs. After a 20-min rest period and stabilization of baseline arterial blood pressure, heart rate, and respiration, a bolus injection of sodium nitroprusside (75–100 μg) was given intravenously followed 60 s later by a bolus injection of phenylephrine hydrochloride (100–150 μg). These pharmacological perturbations decreased and increased arterial blood pressure ~ 15 mmHg from baseline levels during a 3-min period. We used lower doses of sodium nitroprusside (75–80 μg) in the older subjects, but the same dose was used before and after weight loss. Three trials were completed, and each was separated by a minimum of 15 min quiet rest.

Data analysis. Abdominal fat regions (L4–L5 interspace) were determined using commercially available medical imaging software (SliceOmatic version 4.2; Tomovision). Total abdominal fat (i.e., adipose tissue) area was identified by selecting those pixels having an attenuation range of -30 to -190 Hounsfield Units (HU). Abdominal visceral fat was calculated as the pixel area in the appropriate HU range within the abdominal wall. Abdominal subcutaneous fat was calculated as the pixel area in the appropriate HU range outside the abdominal wall. Computed tomography scans were not performed after weight loss in one older subject. Therefore, these data are presented for only five of these individuals.

Heart rate, blood pressure, and respiration were recorded continuously and digitized at 500 Hz to a laboratory computer for later analysis using signal processing software (Windaq; Dataq Instruments). The sensitivity and operating range of the cardiovagal baroreflex was calculated using procedures previously described (2). We could not calculate the operating range for two of the overweight/obese young men because the saturation and threshold regions were not clearly identifiable. R-R intervals were used for the slope calculation because they are more closely related to vagal outflow than heart rate (7). We accepted only regressions with correlation coefficients (r) ≥ 0.70 . The average of at least two of the three trials performed was used to determine the average parameters of cardiovagal baroreflex function for each individual.

Weight loss intervention. The intervention was devised to produce a 5–10% reduction in body mass over a 3-mo period. Subjects were

individually counseled to reduce their energy intake by ~ 500 – 800 kcal/day until the desired 5–10% reduction in body weight was observed. The diet was prescribed with the assistance of sample menus and meal replacement supplements (SLIMFAST Foods). The macronutrient content of the habitual diet (primarily the dinner meal) was 55–60% carbohydrate, 20–25% fat, and 15–20% protein. Subjects met with a research dietitian (B. M. Davy) weekly for the first 4–6 wk and every other week thereafter. During these visits, body weight was measured and any difficulties adhering to the weight loss intervention were discussed. The subjects were instructed to maintain their current level of habitual physical activity and to not begin a program of regular physical activity. Maximal oxygen consumption was measured to ensure that changes in aerobic fitness did not confound the interpretation of our findings.

Statistical analysis. Differences in subject characteristics and dependent variables between groups were assessed with one-way ANOVA. Differences in subject characteristics and dependent variables in the young and older men after weight loss were assessed with repeated-measures ANOVA. There were no significant interaction effects observed for any of the variables, and, as such, there were no post hoc tests performed. Relations among variables were assessed using bivariate correlation analysis. Data are expressed as means \pm SE. The significance level was set a priori at $P < 0.05$.

RESULTS

Subjects' characteristics. The characteristics of the subjects are displayed in Table 1. There was an approximate 12- and 36-yr age difference between the NO-Y and the OB-Y and OB-O, respectively. Body mass, BMI, percent body fat, fat mass, fat-free mass, total abdominal fat, subcutaneous fat, visceral fat, systolic blood pressure, and diastolic blood pressure were all similar in the OB-Y and OB-O but were higher in these groups compared with the NO-Y (all $P < 0.05$). Maximal oxygen consumption was ~ 26 – 35% lower ($P < 0.05$) in the OB-O compared with both OB-Y and NO-Y (both expressions). In addition, maximal oxygen consumption was lower ($P < 0.05$) in OB-O compared with NO-Y, regardless of expression. R-R interval (and heart rate) at rest was similar among the groups (all $P > 0.05$).

Table 1. Subject characteristics at baseline and after weight loss

Variable	Nonobese Young (n = 13)	Obese Young Baseline (n = 10)	Obese Young Weight Loss (n = 10)	Obese Older Baseline (n = 6)	Obese Older Weight Loss (n = 6)
Age, yr	21.1 \pm 1.0	32.9 \pm 2.3*		60 \pm 2.7*	
Height, cm	182.9 \pm 2.6	179.3 \pm 2.3		177.6 \pm 3.2	
Body mass, kg	71.6 \pm 2.4	97.9 \pm 4.3*	90.2 \pm 3.8	91.2 \pm 4.1*	83.9 \pm 4.0 \ddagger
Body mass index, kg/m ²	21.5 \pm 0.5	30.4 \pm 1.0*	28.0 \pm 1.0	28.9 \pm 1.1*	28.1 \pm 1.4
Body fat, %	16.4 \pm 1.3	28.0 \pm 1.5*	25.9 \pm 1.4	27.9 \pm 2.0*	24.9 \pm 2.8 \ddagger
Fat mass, kg	11.8 \pm 1.1	27.6 \pm 2.4*	23.5 \pm 1.9	25.7 \pm 2.7*	21.2 \pm 3.1 \ddagger
FFM, kg	56.5 \pm 0.8	67.0 \pm 2.4*	63.4 \pm 2.3	62.7 \pm 2.5*	59.2 \pm 2.3 \ddagger
Total abdominal fat, cm ²	184 \pm 16	471 \pm 37*	393 \pm 32	516 \pm 56*	414 \pm 63 \ddagger
Subcutaneous fat, cm ²	131 \pm 13	337 \pm 31*	286 \pm 25	333 \pm 58*	274 \pm 47 \ddagger
Visceral fat, cm ²	53 \pm 4	135 \pm 17*	107 \pm 14	184 \pm 27*	140 \pm 31 \ddagger
$\dot{V}O_{2 \text{ max}}$, ml·kg ⁻¹ ·min ⁻¹	52.4 \pm 1.8	40.3 \pm 2.6*	44.4 \pm 2.3	32.6 \pm 1.0*	35.0 \pm 1.7 \ddagger
$\dot{V}O_{2 \text{ max}}$, ml·kg FFM ⁻¹ ·min ⁻¹	66.3 \pm 2.0	58.3 \pm 2.8*	62.4 \pm 2.2	47.6 \pm 2.3*	49.2 \pm 2.5 \ddagger
SBP, mmHg	116 \pm 2	124 \pm 2*	121 \pm 3	121 \pm 2*	111 \pm 5 \ddagger
DBP, mmHg	64 \pm 1	72 \pm 3*	70 \pm 3	76 \pm 2*	70 \pm 2 \ddagger
R-R interval, ms	1,047 \pm 50	1,071 \pm 26	1,002 \pm 55	950 \pm 12	1,062 \pm 41
Heart rate, beats/min	57 \pm 2	64 \pm 3	61 \pm 3	57 \pm 2	57 \pm 2

Values are means \pm SE; n, no. of subjects. FFM, fat-free mass; SBP, systolic blood pressure; DBP, diastolic blood pressure. * $P < 0.05$ vs. nonobese young men; significant group (\ddagger) and time effect (\ddagger).

Effects of weight loss on selected subject characteristics.

The changes in selected subject characteristics with weight loss are shown in Table 1. Body mass, body fat percentage, fat mass, fat-free mass, and total abdominal, visceral, and subcutaneous fat were reduced after weight loss in the OB-Y and OB-O (all $P < 0.05$). Maximal oxygen consumption, expressed relative to body weight, increased ($P < 0.05$) after weight loss in OB-Y and OB-O. However, there was no significant change in maximal oxygen consumption when expressed relative to fat-free mass. Maximal oxygen consumption adjusted for the level of fat-free mass (analysis of covariance) also did not change with weight loss in the two groups ($P > 0.05$). Both systolic and diastolic blood pressure decreased ($P < 0.05$) after weight loss in these men; the decrease in systolic and diastolic blood pressure tended (both $P = 0.11$) to be larger in the older men. However, there was no change in resting R-R interval (or heart rate; $P > 0.05$) after weight loss.

Effect of weight loss on the cardiovagal baroreflex. Before weight loss, cardiovagal BRS was ~ 35 and $\sim 60\%$ lower (both $P < 0.05$) in OB-Y and OB-O compared with NO-Y (11.5 ± 1.9 vs. 6.7 ± 1.2 vs. 17.5 ± 2.2 ms/mmHg; Fig. 1). Cardiovascular BRS was lower ($P < 0.05$) in OB-Y compared with OB-O (Fig. 1). The operating range was $\sim 50\%$ smaller (172 ± 28 vs. 370 ± 90 ms, $P = 0.054$; Fig. 2) in the OB-O compared with young men (Fig. 2), but did not differ significantly between OB-Y and OB-O ($P = 0.14$). Cardiovascular BRS increased to 18.5 ± 2.6 and to 12.8 ± 4.2 ms/mmHg in the OB-Y and OB-O (both $P < 0.05$), respectively, because of changes in both the saturation and threshold regions (data not shown). After weight loss, cardiovagal BRS in the obese/overweight young and older men was $\sim 105\%$ and $\sim 75\%$ ($P > 0.05$) of that observed in NO-Y (Fig. 1). The operating range increased to 356 ± 57 and 356 ± 78 ms in the OB-Y and OB-O ($P < 0.05$), respectively. After weight loss, the operating range of both the OB-Y and OB-O men was $\sim 95\%$ ($P > 0.05$) of the levels observed in the young men (Fig. 2). The operating point was similar in the three groups, but was shifted significantly toward higher systolic blood pressures in the OB-Y and OB-O compared with NO-Y, i.e., to a lower level of systolic BP after weight loss. The results were identical when

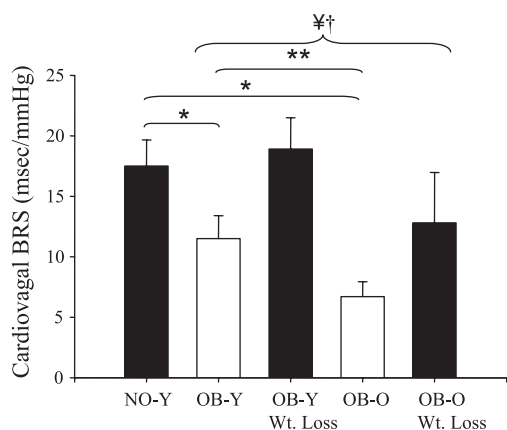


Fig. 1. Cardiovascular baroreflex sensitivity (BRS) in young nonobese (NO-Y, $n = 13$) men and the young (OB-Y, $n = 10$) and older obese (OB-O, $n = 6$) men at baseline and after weight (Wt) loss. Values are means \pm SE. * $P < 0.05$ vs. NO-Y; ** $P < 0.05$ vs. OB-Y; $P < 0.05$ for group effect (¥) and time effect (†).

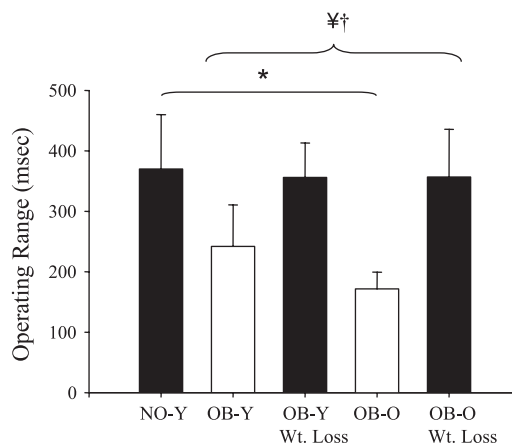


Fig. 2. Operating range in NO-Y ($n = 13$), OB-Y ($n = 8$), and OB-O ($n = 6$) men at baseline and after weight loss. Values are means \pm SE. * $P = 0.05$ vs. NO-Y men. $P < 0.05$ for group effect (¥) and time effect (†).

heart rate was used as the efferent response variable instead of R-R interval (data not shown).

Correlates of the increase in cardiovagal BRS and operating range with weight loss. There were no significant correlates of the improvements in cardiovagal BRS or operating range with weight loss.

DISCUSSION

The new and important finding of this investigation was that the sensitivity and operating range of the cardiovagal baroreflex increased dramatically after modest weight loss in overweight/obese young and older adults. In addition, the operating point of the cardiovagal baroreflex was shifted toward lower blood pressures in both groups. Interestingly, the sensitivity and operation range of the cardiovagal baroreflex in overweight/obese young men after weight loss was similar to that observed in nonobese young men. However, cardiovagal baroreflex BRS and operating range remained lower in overweight/obese older men after weight loss compared with the nonobese young men.

The increase in cardiovagal BRS with weight loss in the young and older men from the present study is consistent with that reported by Grassi et al. (10) in young severely obese men and women. Our findings extend these previous observations in a number of important aspects. First, the results of the present study suggest that weight loss also increases cardiovagal BRS in older adults, a population with particularly low cardiovagal BRS (6, 12, 13). Importantly, the increase in cardiovagal BRS can be achieved in these individuals with mild to moderately obese individuals who undergo only modest weight loss.

Second, the results of the present study suggest that the operating range of the cardiovagal baroreflex is also increased after weight loss in both young and older men. To our knowledge, we are the first to report an increased operating range of the cardiovagal baroreflex with a nonpharmacological intervention in adults of any age. This is an important observation because the operating range of the cardiovagal baroreflex is reduced with advancing age (22). Taken together with the increase in cardiovagal BRS with weight loss, these observations may have important implications for arterial blood pressure regulation in older adults. Whether weight loss is associ-

ated with improved orthostatic tolerance in older adults is unknown.

The mechanism(s) responsible for the increase in cardiovagal BRS remains unclear. However, there are several possibilities. First, arterial stiffness is an important determinant of cardiovagal BRS (14). Thus it is possible that improvements in cardiovagal BRS with weight loss may be due, at least in part, to corresponding reductions in arterial stiffness.

Second, it is possible that changes in one or more factors that determine the transduction of barosensory stretch into cardiac vagal outflow (e.g., sensitization of vagal afferents, alterations in central integration, and/or increases in the number or sensitivity of muscarinic receptors) may contribute to increases in cardiovagal BRS with weight loss.

Finally, oxidative stress is elevated in obese older adults (15), and weight loss reduces oxidative stress (4). The results of a recent study suggests that ascorbic acid infusion improves cardiovagal BRS in older adults (21). Thus it is possible that the increase in cardiovagal BRS with weight loss may be due, at least in part, to a reduction in oxidative stress. Future studies will be necessary to explore these possibilities.

After weight loss, cardiovagal BRS remained lower in the overweight/obese older compared with nonobese young men. In contrast, cardiovagal BRS was similar after weight loss in the overweight/obese compared with nonobese young men. The lack of correlation between increases in cardiovagal BRS and changes in total body and abdominal fat in overweight/obese young or older men (or in the pooled sample of overweight/obese men) suggests that factor(s) other than loss of body fat is(are) important in contributing to increases in cardiovagal BRS. The increase in cardiovagal BRS and operating range observed with weight loss may be an acute aftereffect of the negative energy balance imposed by caloric restriction. We believe this is unlikely because our subjects were studied after their reduced body weight had been maintained for a 1-mo period. However, it is possible that the magnitude of increase in cardiovagal BRS may have been smaller or altogether absent with a longer period of weight stability. This is an interesting possibility needing further exploration.

There are at least two other possibilities that could account for the remaining difference in cardiovagal BRS after weight loss between the overweight/obese older and nonobese young men for this observation. First, the difference may be attributed to the fact that body fat and regional fat distribution were not "normalized" with caloric restriction in the older men. Thus larger increases in cardiovagal BRS may be observed with a more substantial weight loss in the older men. Second, the difference in cardiovagal BRS after weight loss in the overweight/obese older men and nonobese young men may be due, at least in part, to biological aging per se. Future studies will be necessary to clarify this issue.

The increase in cardiovagal BRS weight loss in the present study was quite large (~60–90%) compared with that achieved by regular aerobic exercise training in older men (~25%; see Ref. 20). We recognize that it is difficult to make direct comparisons across different studies. However, taken together, our findings suggest that weight loss is a highly effective strategy to increase cardiovagal BRS in (young and) older men. Whether the combination of weight loss with regular aerobic exercise provides an additional benefit is unknown, but future studies should be designed to address this issue.

The major limitation of the present study is the small sample size and lack of a control group. Future studies with larger sample sizes and a control group will be necessary to confirm or refute our findings and determine the mechanism(s) responsible for the increase in cardiovagal BRS.

In summary, the results of the present study suggest that weight loss improves cardiovagal baroreflex function in young and older overweight/obese men. Importantly, the increase in cardiovagal baroreflex function was observed in overweight/obese men exhibiting only moderate levels of weight loss. These findings may have important implications for understanding the potential of weight loss to reduced cardiovascular disease risk in overweight/obese adults. Furthermore, these findings lend further support to the idea that weight loss may be an important therapeutic strategy for preserving or restoring cardiovascular health in older adults.

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