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Impact of Six-Month Caloric Restriction on Autonomic Nervous System Activity in Healthy, Overweight, Individuals

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Abstract

Caloric restriction (CR) increases maximum lifespan but the mechanisms are unclear. Dominance of the sympathetic nervous System (SNS) over the Parasympathetic Nervous System (PNS) has been shown to be a strong risk factor for cardiovascular disease. Obesity and aging are associated with increased SNS activity and weight loss and/or exercise seem to have positive effects on this balance. We therefore evaluated the effect of different approaches of CR on autonomic function in 48 overweight individuals participating in the CALERIE Trial. Participants were randomized to either Control; CR: 25% decrease in energy intake; CREX: 12.5% CR +12.5% increase in energy expenditure, or LCD: low calorie diet until 15% weight reduction followed by weight maintenance. Autonomic function was assessed by spectral analysis of heart rate variability while fasting and after a meal. Measurements were performed at baseline and Month 6. Heart rate (HR) and SNS index decreased and PNS index increased in all intervention groups but reached significance only in CREX. Heart rate and SNS index increased and PNS index decreased in response to the meal in all intervention groups. The results therefore suggest that weight loss improved SNS/PNS balance especially when CR is combined with exercise.

Introduction

It has been shown that caloric restriction (CR) increases average and maximum lifespan but the mechanisms are unclear. CR reduces metabolic rate and oxidative stress, improves insulin sensitivity, cardiac function, and alters the neuroendocrine axes in animals (1). The Autonomic Nervous System (ANS) is an important regulator of both the cardiovascular system and energy balance, and is assumed to play a role in the pathophysiology of obesity. Furthermore, an increase in the ratio between the two components of the ANS, the SNS and the Parasympathetic Nervous System (PNS) is an independent risk factor of cardiovascular disease (2). Both obesity and aging are associated with this kind of imbalance (3) but weight loss (4) and regular exercise seems to have a normalizing effect (5). Increased PNS has been implicated as a driving force for obesity in rodents (6). Although a relationship has been found between PNS activity and fat mass in humans, the specific involvement of PNS in human energy metabolism is still unclear. Evaluation of PNS activity in humans is difficult since no direct measurement is available at the present time and invasive techniques cannot be used in human research.

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CALERIE - Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy

Beat-to-beat variation in heart rate (heart-rate variability [HRV]) has been a safe tool to measure ANS balance providing a quantitative and qualitative evaluation of neuroautonomic function (7). Power spectral analysis of HRV has shown at least two distinct regions of periodicity in electrocardiogram R-wave intervals. The high frequencies (HI) of HRV are associated with PNS activity, and the low frequencies (LO) are associated with both SNS and PNS activities (8). HRV power spectral analysis therefore represents a method to quantify the SNS/PNS balance of the neuroautonomic regulatory system. Meal ingestion has been shown to cause a thermogenic response in normal weight subjects, but less in obese individuals and to influence both SNS and PNS activities (9). The objective of this study was therefore to examine the effect of different approaches of caloric restriction on autonomic function before and after a meal stimulus in participants in the CALERIE trial.

Methods and Experimental Procedures

Twenty-eight healthy men and women (16F/12M; age: 37.1 ± 0.9 y; BMI: 27.9 ± 0.2 kg/m²) participated in this study which was part of the Comprehensive Assessment of Long Term Effects of Reducing Intake of Energy (CALERIE) trial. Details of this trial have been described previously (1). None of the subjects were receiving drugs known to affect ANS activity. The IRB of the Pennington Biomedical Research Center and the data safety monitoring board of CALERIE approved the study protocol. Written consent was obtained from all subjects.

Body composition was measured by DXA (Hologics, QDA 4500A Bedford, MA). The participants were admitted on our inpatient unit at 3 time points; at baseline (M0), three months (M3), and six months (M6) into the trial. Only the results for baseline and M6 are reported in this paper. After completion of baseline testing, participants were randomized into one of four groups: C = control (weight maintenance); CR = 25% caloric restriction by diet, CREX = 25% energy deficit by diet (12.5%) and increased aerobic activity (12.5%), LCD = very low calorie diet until 15% weight reduction, followed by weight maintenance for the remaining of the study. Increased energy expenditure in CREX was achieved by structured exercise 5 days/week. Target energy cost was 403 ± 63 kcal/session for women and 569 ± 118 kcal/session for men.

Autonomic function was assessed by spectral analysis of HRV for 15 minutes after a 12 hour fast and 30 minutes after ingestion of a 500 kcal standardized meal (Ensure; Abbott Laboratories, Abbott Park, IL; 20% energy as Fat, 64% as Carbohydrate, 16% as Protein). A liquid meal was chosen to participants did not have to sit up during the procedure, and to limit the time of the meal. All experiments were performed between 7.30 and 8.30am in a temperature-controlled (23–24°C) room with minimal arousal. ECG electrodes were placed on the subjects, who then rested for 30 minutes before the start of the experiment. Heart rate was continuously recorded while the subjects remained in supine position and breathing at a controlled rate of 15 breaths/min. Signals were acquired continuously for 5 min. using an ECG lead II, Lifepack 9P (Physio-Control, Redmond, VA), interfaced to an analogue/digital converter (PCL-812 PC-LabCard, Omega Scientific Company, Stamford, CT) at a sampling rate of 500Hz. Before R-R spectral analysis was performed, the stored R-R interval data were displayed and aligned sequentially to obtain equally spaced samples with an effective sampling frequency of 2 Hz and displayed on a computer screen for visual inspection. The root mean value of R-R interval was calculated as representing the average amplitude. Power spectrum was analyzed using a discrete Fourier transformation (DFT) algorithm. Based on previous investigations (8), the spectral power in frequency domain was quantified by integrating the areas under the curves for the following bands: very low frequency (VLO; 0.007 to 0.035 Hz), low frequency (LO; 0.035 to 0.15 Hz), high vagal component (HI; 0.15 to 0.5 Hz), and total power (0.007 to 0.5 Hz). In addition, indices of the SNS and PNS activities were calculated as

the ratio of (VLO+ LO)/HI and HI/TOTAL, respectively. The mean heart rate and standard deviation of each 300-second segment was also calculated.

All data are expressed as mean $\pm$ SEM. The change in variables from baseline to M6 were calculated and analyzed by repeated measures analysis of variance with treatment and time as main effects in the models and time-by treatment interaction. Baseline values were used as covariates in the models to adjust for baseline variability. Analysis of variance (ANOVA) using the SAS General Liner Models Procedure was applied to evaluate differences between groups in overall autonomic function, sympathetic and parasympathetic activity and heart rate variability. Post-hoc multiple comparisons testing by the Least Significant Means (LSM) method was performed to assess differences among groups. An $\alpha < 0.05$ was considered significant.

Results

Baseline characteristics and changes in weight and body composition for those with complete HRV measurements at both time points ($n=28$) are described in Table 1. There was no significant difference in any of the variables between the entire group and the subgroup.

The results of the effects of the 6-month intervention on HR, SNS and PNS index are shown in table 1. Baseline HR was significantly higher in the control group compared to the intervention groups and tended to increase over the course of the study. There was however a significant decrease in the combined intervention groups ($p < 0.01$), only reaching significance in CREX ($p < 0.05$). Baseline SNS-index was not different between groups and there was no significant change in SNS index in either the control or the combined intervention groups. However, there was a significant decrease from baseline to M6 in CREX ($p < 0.05$). Similarly, there was no change over time in PNS index in either the control or the combined intervention groups. However, there was a significant increase in CREX at M6.

The results of the response to a meal are shown in table 1. Heart rate increased in all groups. Baseline response was not significantly different between groups. At M6, the change in response of heart rate to the meal from baseline was significantly higher in the combined intervention groups compared to the control group mostly due to a larger response in the in CREX group. Within groups, heart rate response to the meal increased significantly from baseline to M6 in CR and the CREX group ($p < 0.05$). The effects of the meal on SNS decreased over the 6 month period in all but the CREX group that showed a significant increase ($p < 0.01$).

Discussion

The objective of this study was to examine the effect of different approaches of caloric restriction on ANS function in overweight subjects. The ANS is an important contributor to the regulation of both the cardiovascular system and energy expenditure, and it is assumed to play a role in the pathophysiology of obesity and related complications. An impaired activity of SNS is accepted to promote the onset and development of obesity (10). However, disagreement still exists over the nature of the sympathetic abnormality within the adult obese population (11). In addition in some but not all studies weight loss increased parasympathetic control of HRV (12)

Our study shows a general decrease of the SNS component in all groups while the PNS component increased, indicating an improvement of the SNS/PNS balance. This is consistent with the results from other studies. Several studies observed a decrease in the SNS component and an increase in the PNS component of ANS after a CR program in obese individuals (13) while Pigozzi et al (5) saw improvements after a 2 month weight reduction plan involving both CR and an increase in physical activity. However, all the above mentioned studies were

performed in obese individuals, in contrast to our participants who were overweight but not obese. A larger improvement could have been expected in the exercise group, but we did not find a significant difference in the change between groups. However, there are no studies that compared the effect of different weight loss treatments on HRV. The results of our study are therefore the first to show the independent effects of different weight loss approaches on HRV. However, one has to take into account that the number of subjects per group in our study was a limiting factor as well as that both genders were included in all groups. There is little information on gender effects on HRV but one study in aging individuals shows a lower SNS/PNS ratio in women compared to men independent of BMI, blood pressure and level of physical activity (14). In summary the results of this study suggest a decrease in SNS and increase in PNS function occurs with weight loss but that this is more pronounced when CR is combined with exercise.

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Table 1

Changes from baseline in weight and fasting and postprandial autonomic activity after 6 months of intervention.

	Control N=7	Intervention N=21	CR+LCD N=13	CREX N=8
Δ Weight (kg)	-0.12±0.34	-7.10±0.49**	-8.27±0.79**	-8.08±0.81**
Δ BMI (kg/m ²)	-1.01±0.12	-3.03±0.24**	-3.1±0.34**	-3.7±0.56**
Δ Fat Mass (kg)	-1.26±1.33	-8.25±1.16**	-9.04±1.32**	-9.66±0.67**
Δ Fat Free Mass (kg)	0.98±0.34	2.46±2.10	2.62±1.86	2.16±1.52
HR _{fast} (BPM)	2.85±3.52	-2.74±3.45	-1.59±1.24	-3.02±2.84*
Δ SNS _{fast}	1.90±1.60	-0.72±1.43	-0.33±1.11	-1.98±2.59*
Δ PNS _{fast}	-0.08±0.06	0.02±0.03	0.01±0.06	0.07±0.06
Δ SNS/PNS _{fast}	4.79±1.45**	-1.65±0.54	-1.59±2.01	-2.24±0.18*
Δ HR _{meal} (BPM)	1.51±2.13	1.76±2.34	0.28±2.20	2.23±1.37*
Δ SNS _{meal}	-1.43±0.90	-1.63±1.89	-3.70±2.35*	1.52±0.71**
Δ PNS _{meal}	0.05±0.04	0.04±0.03	0.04±0.05	0.03±0.03
Δ SNS/PNS _{meal}	3.45±0.67**	-1.45±0.34	-1.11±2.78	-2.03±1.23

Values are given as Mean SEM;

* P<0.05,

** p<0.01