Metabolic and endocrine adaptations to fasting in lean and obese individuals

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Chapter 3

Obesity is associated with an altered autonomic nervous system response to nutrient restriction

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Abstract

Objective

Heart rate variability (HRV) reflects the balance of activities of sympathetic and parasympathetic components of the autonomic nervous system. We compared HRV parameters in response to a prolonged fast in obese versus normal weight humans. In addition, the effect of weight-loss was evaluated in obese individuals.

Design

Intervention study

Patients

14 non-diabetic obese (12 females/2 males, aged 30 ± 3 years, Body Mass Index (BMI) 35.2 ± 1.2 kg/m^2) and 12 lean subjects(10 females/2 males, aged 27 ± 3 years, BMI of 23.3 ± 0.5 kg/m^2)

Measurements

HRV was examined 75 minutes after standardized breakfast and after a 48h fast in 14 non-diabetic obese and 12 lean subjects. The postprandial measurement was repeated in 12 obese subjects after weight-loss.

Results

In lean subjects, fasting decreased high frequency (HF) power by 43 % ($p<0.05$) and decreased low frequency (LF) power by 37% ($p=0.1$), leaving the LF/HF ratio unchanged ($p=0.7$). In the obese group, autonomic nervous system tone shifted to sympathetic dominance as the LF/HF increased from 0.61 to 1.14 ($p=0.03$). After an average weight-loss of 13.8 kg in obese subjects, a trend for sympathetic dominance was found; the LF/HF ratio increased by 56% ($p=0.06$).

Conclusion

Our data show that a 48h fast leaves autonomic nervous system balance unaltered in lean subjects. In contrast, a 48h fast as well as weight-loss induce sympathetic dominance in obese humans.

Introduction

Diabetes and obesity have been associated with an altered autonomic nervous system tone, marked by increased orthosympathetic nervous system activity and decreased parasympathetic/ vagal nervous system (PSN) tone. In the framework of energy balance, activation of the orthosympathetic nervous system generally mobilizes energy while the parasympathetic nervous system promotes digestion and energy storage. The dynamic balance between the orthosympathetic nervous system and the parasympathetic nervous system quickly responds to environmental cues, such as fasting, to appropriately adapt energy metabolism. Heart rate variability (HRV) can be used as a measure of activity of both components of the autonomic nervous system.[1] It has been shown that overall HRV, after an overnight fast, is decreased in obesity[2] and that fasting increases orthosympathetic nervous system activity in lean individuals.[3;4] Importantly, a 48h fast has different effects than prolonged fasting (starvation). Truly starved humans show symptoms of profoundly decreased orthosympathetic nervous system activity such as hypotension, bradycardia and hypothermia.[5;6]

We hypothesized that the autonomic nervous system response to a 48h fast would be different in obese compared to lean individuals, reflecting a disturbed handling of energy balance disturbances. We compared postprandial values with post-48-hours of fasting to determine the real impact of food deprivation (comparison with values after an overnight fast at baseline obviously entails 10 hours of fasting prior to the baseline measurement). We also wondered whether weight loss would reduce any potential difference in postprandial HRV between lean and obese subjects.

Material & Methods

We included 12 obese (BMI >30 kg/m^2) and 12 lean volunteers (19-25 kg/m^2), matched for gender and age. All participants were healthy, without medication, non-smoking, weight-stable (<3kg weight change in the preceding 3 months), with a negative family history for type 2 diabetes and a fasting plasma glucose ≤5.6 mmol/l. The study was approved by the medical ethics committee of the Leiden University Medical Center and executed in accordance with the Declaration of Helsinki (as amended in Seoul (2008), including the clarifications added in Washington (2002) and Tokyo (2004)). The study was registered in The Netherlands Trial Register (NTR2401). All volunteers gave written informed consent.

This study consisted of 2 interventions: a 48h fast for all participants and a weight-loss program for the obese participants. During fasting, overnight-fasted participants were admitted to our research center. Upon arrival subjects consumed a standardized breakfast (2 slices of brown bread with cheese; 300 calories, 27g carbohydrates, 18g protein and 11g fat). At 75 minutes after breakfast, a five-minute ECG-recording was made while subjects were supine, lying still and awake in a quiet environment. The second ECG was made after 48h fasting. The ECG-recordings were made with a CardioPerfect ECG recording system (Cardiocontrol, Rijswijk, The Netherlands) using a sampling rate of 500 Hz. After recording the ECG signals were scrutinized for artefacts and subsequently analyzed for the duration of the RR-intervals using the software supplied with the device. The RR-interval time series were subjected to HRV analysis according to international guidelines [7] for the frequency-domain HRV parameters. These consist of the mean RR-interval (RR-int), the power of the high-frequency (HF; vagal activity), and low-frequency (LF; sympathetic activity) band and their ratio (LF/HF; sympathovagal balance) with Kubios HRV software version 2 (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland).

Subsequently, 12 of the 14 obese subjects participated in an 8 week dietary weight-loss program. This consisted of a high protein low calorie diet (HPLC; Prodimed®, Valkenswaard, The Netherlands), with an average intake of 600 kcal/day taken as 4-5 (females) or 5-6 (males) sachets daily with a tablespoon of vegetable oil and selected vegetables. Each sachet contained approximately 90 kcal (about 18 g protein, 2.5-5 g carbohydrates, 0.5-2 g fat). After dieting, the obese subjects underwent HRV measurements, again 75 minutes after standardized breakfast. We also collected plasma samples and muscle biopsies; these results will be presented elsewhere.

All values are expressed as median and range and variables were log-transformed prior to analysis to correct for the log-normal distribution of the data. For both groups, baseline data was compared to the 48h data using a mixed model analysis of variance with fixed factors time, group and time by group, and random factor subject. The postprandial data before and after weight-loss was compared with a mixed model analysis of variance with fixed factor time and random factor subject. The analysis is summarized as the back-transformed geometric means of the percentage difference along with the corresponding 95% confidence intervals, and the p-value of the contrasts. Analyses were performed using SAS for Windows V9.1.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Lean subjects (10F/2M) were on average (±SEM) aged 27 ± 3 years with a BMI of 23.3 ± 0.5 kg/m^2. We planned to include 12 obese participants, but 2 patients who discontinued the diet were replaced. Hence, 14 obese subjects (12F/2M, aged 30 ± 3 years, BMI 35.2 ± 1.2 kg/m^2) were studied at baseline.

The HPLC program in the 12 obese subjects (10F/2M, aged 29 ± 2 years, BMI: 35.9 ± 1.3 kg/m^2) reduced weight by 13.8 ± 1.2 kg and decreased BMI by 4.4 ± 0.4 kg/m^2.

For one lean and one obese subject the postprandial measurements were not performed on time, these subjects were excluded from analysis.

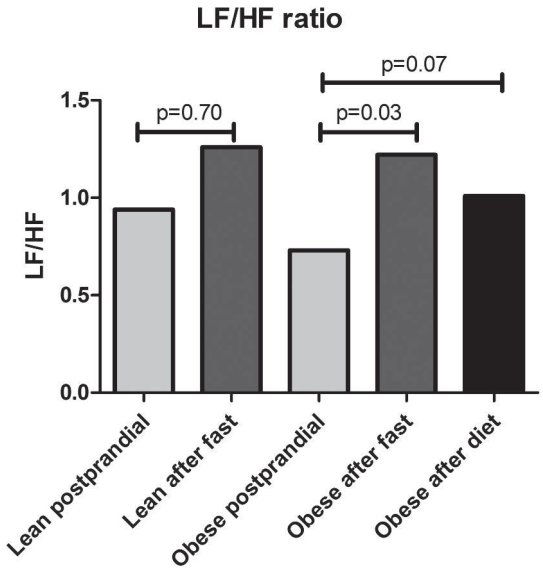

Figure 1: LF/HF ratio after a standardized breakfast and after a 48 hour fast in lean and obese subjects.
Data are shown as median. We show the LF/HF ratio after a standardized breakfast in lean and obese subjects as well as after a 48 hour fast. The ratio after weight loss in the obese subjects was also measured after a standardized breakfast.

At baseline, the LF power and LF/HF ratio were lower in obese compared to lean subjects, but not significantly (p= 0.17 and p= 0.49, Tables 1 and 2).

In lean subjects, the 48h fast de-

Table 1 HRV parameters in the frequency domain for lean and obese subjects after a standardized breakfast (post-prandial) and after a 48h fast.

		N	RR-interval (ms)	CV (%)	HF power (ms^2)	LF power (ms^2)	LF/HF
Lean	Postprandial	11	941 (711 – 1307)	6.8 (3.9 – 14.4)	795 (317 - 14919)	1348 (158 - 5187)	0.94 (0.06 - 4.59)
	48h fast	12	829 (701 – 1106)	6.2 (3.1 – 13.6)	418 (224 – 15122)	780 (87 – 4253)	1.26 (0.07 - 4.80)
Obese	Postprandial	13	915 (644 – 1101)	6.4 (1.8 – 23.0)	955 (33 – 27794)	755 (22 – 2846)	0.73 (0.10 - 2.11)
	48h fast	14	922 (640 – 1165)	5.5 (2.8 – 22.6)	375 (49 – 29695)	635 (100 - 9083)	1.22 (0.31 - 6.61)
	Postprandial after weight loss	12	917 (805 – 1212)	5.7 (3.7 – 25.2)	640 (222 – 37661)	1002 (168 – 4472)	1.01 (0.12 - 2.71)

Data are depicted as median (range). Abbreviations: ms; millisecons, h; hours, RR-int; RR-interval, CV; coefficient of variation, LF; power of the low frequency band in the power spectrum, HF; power of the high frequency band in the power spectrum, LF/HF; ratio of low over high frequency power.

creased the RR-interval by 8.6% (p=0.02), decreased HF-power by 43% (p<0.05) and decreased LF-power by 37% (p=0.1) leaving the LF/HF ratio unchanged (p=0.7) (Tables 1 and 2).
In the obese subjects, the 48h fast decreased the RR-interval with 1.5% (p=0.7), decreased HF-power by 40% (p=0.06), increased LF-power by 20% (p=0.5) and therefore increased the LF/HF ratio by 90% (p=0.03, Tables 1 and 2).

Repeating the postprandial measurements after weight-loss in the obese subjects showed that the RR-interval and HF-power remained similar, LF power increased by 52% (p=0.12). This resulted in a 56% increase (p=0.07) in the LF/HF ratio (Figure 1, Tables 1 and 2).

Table 2 Frequency domain heart rate variability parameters for lean and obese subjects at postprandial baseline compared to the 48h fast and in obese subjects at postprandial baseline compared to after the High Protein Low Calorie diet.

	Point estimate (95%CI) of change		p-value
RR-int (ms)			
Lean fast	-8.6%	(-15; -2%)	0.02
Obese fast	-1.5%	(-8; +6%)	0.66
Obese diet	4.3%	(-3; +12%)	0.23
HF (ms^2)			
Lean fast	-43.1%	(-67; -1%)	<0.05
Obese fast	-39.6%	(-64; +2%)	0.06
Obese diet	-4.9%	(-46; +68%)	0.86
LF (ms^2)			
Lean fast	-36.7%	(-66; +19%)	0.14
Obese fast	21.0%	(-33; +120%)	0.52
Obese diet	51.5%	(-11; +158%)	0.12
LF/HF			
Lean fast	11.8%	(-39; +105%)	0.70
Obese fast	87.8%	(9; +244%)	0.03
Obese diet	55.6%	(-3; +150%)	0.07

Data are depicted as point estimates of the percentage difference (95% confidence interval). Abbreviations: ms; milliseconds, CI; confidence interval, RR-int; RR-interval, LF; power of the low frequency band in the power spectrum, HF; power of the high frequency band in the power spectrum, LF/HF; ratio of low over high frequency power.

Discussion

We investigated the effect of 48h of fasting on HRV parameters in lean and obese subjects. First, we studied differences in HRV measurements between groups at baseline since obese humans were shown to have lower HRV. However we did not find significant differences in HRV parameters between groups at baseline, although autonomic nervous system tone in obese subjects seemed to be characterized by parasympathetic nervous system predominance. This appears to contradict earlier studies showing orthosympathetic nervous system overactivity in obese subjects after an overnight fast.[2] However, our baseline values were determined postprandially, and obesity is marked by a blunted postprandial increase in orthosympathetic nervous system tone.[8;9] Thus, the apparent discrepancy with previous findings may be explained by differences in the timing of measurements.

In lean subjects, 48 hours of subsequent fasting decreased both vagal and sympathetic tone, leaving the sympathovagal balance unaltered compared to postprandially. Accordingly, a previous study showed that 72h of fasting in lean subjects blunts both LF and HF power, leaving the LF/HF ratio unchanged.[3] In contrast, 48h of fasting decreased parasympathetic nervous system activity and increased orthosympathetic nervous system activity in the obese subjects. This shifted overall autonomic nervous system tone towards a more sympathetic state. One previous study also documents an increased orthosympathetic nervous system activity in skeletal muscle after a 48h fast in obese women.[10] Taken together, our results suggest that obese subjects cannot maintain the overall autonomic nervous system tone balanced during a 48h fast, which might reflect a disturbed response to alterations in energy balance.

The causes of autonomic nervous system tone alterations upon a prolonged fast are multifactorial. There may be effects of catecholamines; norepinephrine and dopamine levels increase during fasting.[3] Thyroid hormones might also be involved, since both hyperthyroidism and hypothyroidism are characterized by an altered sympathovagal balance.[11;12] However, it is unlikely that changes in thyroid hormones play a major role in the altered autonomic nervous system tone we observed, because fasting reduces plasma triiodothyronine levels, which is expected to reduce the LF/HF ratio.[4;12;13] Fasting enhances lipolysis and elevates FFA levels. Infusion of lipids has been shown to increase orthosympathetic nervous system activity.[14] Although the

rate of appearance of FFAs per unit of adipose mass is attenuated during fasting in obese subjects[15], plasma FFA levels are higher, which could underlie their increased orthosympathetic nervous system response.

Finally we studied the effect of weight-loss on HRV parameters in obese subjects. Weight-loss, 13.8kg on average, was characterized by an increased in orthosympathetic nervous system and thus overall autonomic nervous system tone. In fact, the LF/HF ratio increased to a level similar to that observed in lean subjects at baseline, suggesting that the (not significantly) altered postprandial autonomic nervous system tone in obese subjects is reversible upon weight loss.

What do these findings mean? The fact that fasting alters autonomic nervous balance in obese subjects but not in lean suggests that obese individuals distinctly process the challenge of food (energy) deprivation (at least in terms of autonomic nervous system response). The physiological meaning of that finding is unclear, but it may have endocrine and/or metabolic corollaries that hamper weight loss. The fact that weight loss tends to normalize (postprandial) autonomic balance in obese individuals suggests that autonomic balance is not critically involved in the pathogenesis of weight gain (in view of the fact that the vast majority of post-obese subjects tends to regain their weight).

Future studies should address changes in the time course of autonomic nervous system activity after food intake between lean and obese subjects. It would also be interesting to study autonomic nervous system modulation by FFAs. Limitations of the current study include that the influence of the menstrual cycle on HRV was not taken into account.[16;17]

In summary, we compared HRV parameters in the fed and fasted state between lean and obese individuals. Importantly, 48h of fasting in lean individuals similarly reduced vagal and sympathetic tone, whereas it reduced vagal and increased sympathetic tone in obese individuals. This suggests that obese subjects cannot maintain autonomic nervous system balance upon fasting. We also show that weight-loss diminishes the (non significant) difference in postprandial autonomic nervous system tone between lean and obese subjects, suggesting that the effects of obesity on postprandial HRV are reversible.

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