# Alterations in the autonomic control of heart rate variability in patients with anorexia or bulimia nervosa: Correlations between sympathovagal activity, clinical features, and leptin levels

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**ABSTRACT. Changes in body composition, hormone secretions, and heart function with increased risk of sudden death occur in eating disorders. In this observational clinical study, we evaluated sympathovagal modulation of heart rate variability (HRV) and cardiovascular changes in response to lying-to-standing in patients with anorexia (AN) or bulimia nervosa (BN) to analyze: a) differences in autonomic activity between AN, BN, and healthy subjects; b) relationships between autonomic and cardiovascular parameters, clinical data and leptin levels in patients with eating disorders. HRV, assessed by power spectral analysis of R-R intervals, blood pressure (BP) and heart rate (HR) were studied by tilt-table test in 34 patients with AN, 16 with BN and 30 healthy controls. Autonomic and cardiovascular findings were correlated with clinical data, and serum leptin levels. Leptin levels were lowered in AN *vs* BN and healthy subjects ($p<0.0001$), but both AN and BN patients showed unbalanced sympathovagal control of HRV due to relative sympathetic failure, prevalent vagal activity, impaired sympathetic activation after tilting, independently from their actual body weight and leptin levels. No significant correlations were obtained between HRV data *vs* clinical data, BP and HR findings, and leptin levels in eating disorders. Body mass indices (BMI) ($p<0.02$), and leptin levels ($p<0.04$) correlated directly with BP values. Our data showed alterations of sympathovagal control of HRV in eating disorders. These changes were unrelated to body weight and BMI, diagnosis of AN or BN, and leptin levels despite the reported effects of leptin on the sympathetic activity.**

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## INTRODUCTION

Eating disorders, including both anorexia nervosa (AN) and bulimia nervosa (BN), are characterized by relevant modifications in body composition, hormone secretions (1, 2), blood pressure, heart mass and function (3-8), the latter ascribed to cardiac adaptation to starvation, to changes in sympathovagal activity and to electrolyte abnormalities (5, 7, 9-14), which may justify the higher incidence of cardiovascular mortality and sudden death in these patients (7, 15, 16).

Both increased body fat mass and weight loss or starvation modify blood levels of leptin (17, 18), which result markedly lowered in AN (1, 2). Leptin is involved in the regulation of food intake and energy expenditure by acting on specific receptors in the hypothalamus (17), but it also exerts a dose-dependent modulation of the autonomic nervous system activity by stimulating sympathetic outflow (19-22). In addition, leptin increases blood pressure (BP) and heart rate (HR) after intracerebroventricular infusion in experimental animals (22, 23), and it has been suggested that it influences the very low frequency (VLF) component of heart rate variability (HRV) in ill hu-

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mans (24). However, no evidence is as yet available on the effects exerted on heart function and arterial pressure by leptin levels in eating disorders.
The study of HRV by power spectral analysis (PSA) of electrocardiographic (ECG) R-R intervals is a simple, non-invasive tool suitable for investigating autonomic regulation of the sinus atrial activity pacing cardiac frequency (25, 26).
In this observational study, baseline autonomic control of HRV in supine patients and its changes during tilt-table test were assessed by PSA in AN or BN women. The study was aimed at investigating reciprocal differences in the autonomic control of HRV either between patients with AN and BN, or *vs* healthy subjects with normal weight. In addition, autonomic and cardiovascular data were correlated with serum leptin levels, and with other clinical parameters to discriminate the roles of some of the factors which possibly influence cardiovascular function and autonomic activity in eating disorders.

## MATERIALS AND METHODS

### *Study population*

Fifty women with primary eating disorders, inpatients at the "Centre for Eating Disorders and Psychological Disturbances of Adolescence", Azienda Sanitaria Locale 2 - Savona (Italy), participated in this study. AN was diagnosed in 34, and BN in 16 cases according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IVR (27) (Table 1). Patients were studied after correction of possible serum $K^+$ and other electrolyte abnormalities presented at hospital admittance. In 4 patients, a body weight gain below 6 kg was observed during the first 2 weeks of hospital stay. No drugs known to interfere with the autonomic nervous system were administered before or during the study. Patients were compared with 30 healthy women with normal menstrual cycle, body weight and body mass index (BMI) (Table 1). Informed and written consent was obtained from all subjects according to the Helsinki declaration and the study was approved by the local Ethics Committee.

### *Leptin assays*

Blood samples for hormone assays were obtained between 08:00 and 09:30 h after a 12-h fasting and sera maintained at –20 C until processed. Leptin was assayed by radio-immuno assay (RIA) (DRG Diagnostics GmbH, Germany). Sensitivity of the method was 0.5 µg/l. Intra-assay and inter-assay percent coefficients of variation were lower than 3.9% and 4.7%, respectively.

### *Study protocol*

ECG recordings lasting 330 seconds for both postures, and BP measurements in all subjects were made during clino- and orthostatism between 10:00 and 11:00 h, as previously described (28). ECG records were analyzed by a personal computer equipped with software which sampled the analogical signal of about 200 Hz using an analogic/digital converter. Two series of data corresponding to clino- and orthostatic R-R intervals were analyzed by a parametric method, based on the autoregressive algorithm for the quantification of HRV signal (26, 28). Total powers (TP) (0-0.5 Hz) and three basic spectral measures were defined as spectral power in VLF (0-0.04 Hz), low frequency (LF) (0.04-0.15 Hz), and high frequency (HF) (0.15-0.50 Hz) regions. HF corresponds to vagal activity connected with respiration (29, 30), while LF is thought to express a baroreflex-mediated modulation of vagal and sympathetic tone (30-32). VLF has been related to various mechanisms such as vagal activity, renin-angiotensin system, plasma leptin concentrations and thermoregulation (24, 25, 33). LF/(LF+HF) ratios were also calculated, as indices of sympathovagal balance in the frequency domain (25, 26, 30).

Table 1 - *Clinical findings and serum leptin levels in women with anorexia (AN) or bulimia nervosa (BN), and in healthy controls. Values are given as means (M), their 95% confidence limits (CI), and range intervals.*

| Characteristic | | AN | BN | Healthy controls | *p* AN *vs* BN | *p* All groups |
|---|---|---|---|---|---|---|
| no. | | 34 | 16 | 30 | – | – |
| Age (yr) | M | 24.2 | 24.2 | 25.9 | 0.9950 | 0.6595 |
| | CI | (21.4-27.1) | (21.6-26.9) | (23.3-28.5) | | |
| | Range | 14-45 | 18-34 | 16-44 | | |
| Body weight (kg) | M | 42.4 | 57.9 | 60.5 | <0.0001 | <0.0001 |
| | CI | (40.5-44.3) | (52.7-63.1) | (58.4-62.6) | | |
| | Range | 31-52 | 47-84 | 52-72 | | |
| BMI (kg/m$^2$) | M | 15.7 | 21.5 | 22.9 | <0.0001 | <0.0001 |
| | CI | (15.1-16.4) | (19.6-23.4) | (22.3-23.6) | | |
| | Range | 11.4-18.1 | 18.2-30.3 | 19.7-26.1 | | |
| Disease duration (month) | M | 55.4 | 84.7 | – | 0.0529 | – |
| | CI | (38.6-72.1) | (52.4-117.1) | | | |
| | Range | 6-204 | 24-216 | | | |
| Leptin (µg/l) | M | 4.7 | 15.8 | 11.8 | <0.0001 | <0.0001 |
| | CI | (3.6-5.7) | (10.2-21.4 ) | (10.2-13.4) | | |
| | Range | 0.7-10.7 | 3.9-23.7 | 7.2-21.3 | | |

BMI: body mass index.

HR (beats/min) was calculated from mean R-R intervals on the 330 s tachogram series achieved in clino- and orthostatism. Systolic (SBP) and diastolic blood pressure (DBP) were measured by an automatic pressurometer (AMI System 7100). Mean values of three consecutive BP measures in clinostatism and those obtained after 1, 3, and 5 min of orthostatism were considered.

### *Statistical analysis*

Results were given as mean values and their lower and upper 95% confidence limits (95% CI). Data were processed by the SAS 8.2 Statistical package (Carey, NC). Statistical differences between AN, BN, and healthy control groups were analyzed by the SAS GLM procedure and the differences between two groups by the non-parametric Mann-Whitney U test for unpaired data.

The Wilcoxon test was used to analyze differences between clino- and orthostatic data in each group. BP and HR values during clinostatism and at different times after orthostatism were processed by the analysis of variance (ANOVA) option for repeated measures of the one-way procedure (PROC NPAR1WAY) of SAS package, suitable to analyze sequences of non parametric data.

The Pearson correlation coefficient (CORR Procedure of SAS Principal Component Analysis Correlations) was adopted to assess correlations between clinical and biometric data, leptin levels, autonomic data, and the mean values of BP and HR measured during clino- and orthostatism.

The level of significance was assumed at $p<0.05$.

## RESULTS

### *Clinical, biometric and leptin data*

Body weight, BMI, and serum leptin levels in patients with AN were significantly lower than in BN and in healthy subjects, while no significant difference was found between the latter two groups for the same parameters (Table 1). Leptin values correlated directly with body weight and BMI (r=0.8825 and r=0.8794, respectively; $p<0.0001$), but not with age (r=–0.0990; $p=0.4941$) or disease duration (r=0.1255; $p=0.4661$).

### *Blood pressure and heart rate data*

BP and HR values, and their changes during the tilt-table test are shown in Table 2. SBP and DBP were significantly lower in women with AN or BN than in controls ($p<0.0001$). Clinostatic HR was slower in women with AN or BN *vs* healthy subjects, but not significantly different ($p=0.0855$). Lying to standing significantly increased heart rate in all studied groups (Table 2).

### *Autonomic control of HRV*

No significant difference was found in absolute values of TP, VLF, LF, HF powers between patients with AN or BN and healthy subjects during clinostatism (Table 3). However, sympathetic failure in both groups of patients was emphasized by clinostatic LF/(LF+HF) ratios, which were significantly lower in patients than in controls because of relatively decreased LF and increased HF components.

Lying-to-standing highlighted some differences between patients and healthy controls (Table 3). LF power increased in response to postural change in controls but it decreased both in women with AN or BN. No significant differences were observed in orthostatic HF powers between patients and controls, all these data showing a marked drop in vagal activity after lying to standing. Thus, orthostatic LF/(LF+HF) ratios remained significantly lower in patients in comparison with those found in controls, confirming a relative sympathetic failure after standing.

No significant correlations were found between autonomic data, and BP or HR values ($p>0.05$).

### *Correlations between clinical, leptin and cardiovascular findings*

Age, disease duration, BMI or leptin levels in patients did not significantly correlate with any PSA data ($p>0.05$). BMI directly correlated with SBP (clino: r=0.450, $p=0.001$; ortho: r=0.493, $p=0.017$) and DBP (clino: r=0.335, $p=0.017$; ortho: r=0.310, $p=0.028$), while leptin levels were directly correlated with clinostatic SBP (r=0.338, $p=0.016$) and DBP (r=0.292, $p=0.040$) values and with SBP after orthostatism (r=0.451, $p=0.001$).

## DISCUSSION

This study was primarily aimed at investigating possible differences in sympathovagal control of HRV in patients with AN or BN, as well as possible relationships between the autonomic parameters and leptin levels, which are known to be strictly related to body fat mass (17) and to modulate autonomic function by acting on the central nervous system (19-22), thereby influencing arterial pressure (23). In this perspective, we attempted to correlate cardiac autonomic parameters obtained by PSA of HRV and BP values with some biometric findings, clinical data, and serum leptin concentrations.

In women with primary eating disorders we found a relative sympathetic failure and the prevalence of vagal activity in both groups of patients during clinostatism, but chiefly in response to passage to orthostatism. In fact, sympathetic activity does not increase in patients after lying to standing as occurred in healthy controls, while a drop in orthostatic vagal activity was found both in patients and in healthy volunteers. However, changes in autonomic control of HRV was similar in patients with AN and BN, although body weight, BMI, and leptin levels were markedly decreased in AN, but normal in patients with BN. Either normal or decreased leptin levels, inversely correlated with illness duration and frequency of bingeing and vomiting, have been reported in patients with

Table 2 - *Systolic (SBP) and diastolic blood pressure (DBP), and heart rate (HR) during clinostatism and after 1, 3, 5 min of orthostatism in women with anorexia or bulimia nervosa, and in healthy controls. Values are given as means and 95% confidence limits. Statistical analysis by the analysis of variance (ANOVA) for repeated measures of the one-way procedure (PROC NPAR1WAY) of SAS package.*

| | SBP (mmHg) | DBP (mmHg) | HR (b/min) |
|---|---|---|---|
| Anorexia nervosa (no.=34) | | | |
| Clinostatism | 99.5 (95.2-103.8) | 59.9 (56.7-63.1) | 66.7 (62.4-70.9) |
| Orthostatism 1 min | 96.7 (93.2-100.2) | 61.0 (57.4-64.6) | 78.6 (73.1-84.0) |
| Orthostatism 3 min | 98.7 (93.8-103.5) | 62.3 (58.8-65.7) | 79.6 (73.8-85.5) |
| Orthostatism 5 min | 98.3 (94.1-102.6) | 61.4 (58.2-64.7) | 79.6 (74.2-84.9) |
| *p*= | 0.8110 | 0.7911 | 0.0008 |
| Bulimia nervosa (no.=16) | | | |
| Clinostatism | 110.9 (102.3-119.5) | 66.9 (61.9-72.0) | 62.1 (55.5-68.7) |
| Orthostatism 1 min | 105.6 (96.6-114.5) | 69.1 (63.5-74.7) | 73.7 (67.3-80.1) |
| Orthostatism 3 min | 109.4 (100.4-118.4) | 70.6 (63.4-77.7) | 76.4 (69.9-82.9) |
| Orthostatism 5 min | 108.3 (99.3-117.2) | 69.1 (62.8-75.4) | 78.3 (85.1) |
| *p*= | 0.8310 | 0.8428 | 0.0021 |
| Healthy controls (no.=30) | | | |
| Clinostatism | 122.3 (119.6-125.0) | 72.4 (69.1-75.7) | 69.9 (66.5-73.2) |
| Orthostatism 1 min | 119.1 (114.7-123.4) | 76.4 (73.3-79.5) | 80.9 (76.6-85.2) |
| Orthostatism 3 min | 122.2 (117.3-127.1) | 80.2 (77.3-83.0) | 87.2 (82.1-92.2) |
| Orthostatism 5 min | 118.3 (114.5-122.1) | 79.9 (76.7-83.1) | 86.3 (81.3-91.4) |
| *p*= | 0.3322 | 0.0012 | <0.0001 |

BN (34-35). In our patients, leptin levels were directly correlated with body weight and BMI, as well as with BP values, but no significant correlation was observed between hormone levels and PSA parameters.

Besides hypovolemia due to starvation and bulimic behavior, abnormalities in the mitral valve motion, slower velocity in transmitral flow in late diastole and reduced left ventricular mass and filling (3-5) and changes in electrolyte balance, mainly involving decreased $K^+$ levels (6, 7), contribute to systolic dysfunction, cardiac output reduction, QT prolongation and arrhythmias in patients with AN, thus in part explaining the decrease in BP levels and heart abnormalities. In the women with AN or BN we studied, DBP values were not significantly enhanced in response to lying-to-standing as physiologically occurred in healthy controls. Moreover, cardiovascular parameters such as BP and HR were independent from the sympathetic and vagal control of HRV, as well as from VLF power, which has been reported to be influenced by vagal activity and the renin-angiotensin system, besides leptin concentrations and thermoregulatory mechanisms (14, 24, 33).

Despite some discrepancies due to different investigational procedures and possibly to the study of anorectic patients during the acute or chronic phase of the disease (14), our data agree with previous reports in the literature (5, 7, 9-14, 16), which indicate

Table 3 - *Clino- and orthostatic power spectral analysis data of heart rate variability (msec$^2$) in women with anorexia (AN) or bulimia nervosa (BN), and in healthy controls. Values are given as means and 95% confidence limits.*

| Characteristic | AN | BN | Healthy controls | *p* AN *vs* BN | *p* All groups |
|---|---|---|---|---|---|
| Clinostatic values | | | | | |
| VLF (msec$^2$) | 1114.7 (880.3-1349.0) | 924.4 (670.1-1179.0) | 913.2 (759.3-1067.0) | 0.539 | 0.4278 |
| LF (msec$^2$) | 289.1 (224.4-353.9) | 301.9 (185.9-417.9) | 355.7 (285.5-425.8) | 0.907 | 0.1486 |
| HF (msec$^2$) | 465.0 (377.0-553.0) | 470.0 (343.0-597.0) | 345.3 (252.5-437.5) | 0.967 | 0.1236 |
| Total (msec$^2$) | 1868.8 (1583.0-2155.0) | 1696.2 (1343.0-2050.0) | 1614.0 (1371.0-1857.0) | 0.426 | 0.6053 |
| LF/(LF+HF) | 0.38 (0.34-0.42) | 0.40 (0.32-0.48) | 0.52 (0.46-0.59) | 0.472 | 0.0004 |
| Orthostatic values | | | | | |
| VLF (msec$^2$) | 1202.3 (1059.0-1345.0) | 1377.5 (873.6-1881.0) | 1269.1 (1110.0-1429.0) | 0.917 | 0.5962 |
| LF (msec$^2$) | 245.6 (177.3-313.9) | 255.6 (102.6-408.7) | 425.0 (333.3-516.7) | 0.647 | 0.0014 |
| HF (msec$^2$) | 240.6 (171.9-309.2) | 200.6 (89.7-311.6) | 186.7 (139.3-234.1) | 0.460 | 0.5422 |
| Total (msec$^2$) | 1688.5 (1514.0-1863.0) | 1833.7 (1302.0-2365.0) | 1881.1 (1702.0-2060.0) | 0.625 | 0.2629 |
| LF/(LF+HF) | 0.50 (0.42-0.57) | 0.53 (0.40-0.66) | 0.69 (0.63-0.75) | 0.522 | 0.0008 |

VLF: very low frequency; LF: low frequency; HF: high frequency.

the predominance of vagal activity in patients with eating disorders studied either by analyzing HRV on short ECG records, or by 24-h Holter monitoring of R-R intervals.

We studied our inpatients with eating disorders after normalization of electrolyte changes due to restrictive or purging behaviors observed at hospital admission, as confirmed by ECG recordings and serum electrolyte determinations, so that, as recently suggested (7), a role of low $K^+$ concentrations on autonomic and cardiac dysfunction might be ruled out.

Opposite changes in autonomic heart control, with decreased HR and increased HRV in acute AN due to vagal prevalence and increased HR in chronic patients because of sympathetic activation, have been found by studying HRV by linear and non-linear methods on 24-h ECG R-R series during usual physical activity (14). However, we were unable to confirm this finding by correlating disease durations and HRV parameters in our patients with eating disorders.

In conclusion, in patients with eating disorders but normal electrolyte balance, leptin levels directly correlated with BP values, but PSA autonomic parameters were independent from the main clinical indices, body weight, BMI, as well as from serum leptin levels. Recently, a significant association between alterations in autonomic control of HRV and two measures of sustained extreme loss of body weight, such as illness duration and BMI, were reported in women with AN by PSA study of beat to beat HRV. Besides, anxiety, assessed by the State and Trait Anxiety Inventory, had a significant negative correlation with heart autonomic parameters (36). Thus, the pathogenesis of autonomic dysfunction in frequency domain in eating disorders might possibly be sought in other factors directly affecting the central regulation of the autonomic nervous system rather than in changes of body weight and peripheral leptin levels.

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