Cardiopulmonary exercise test in young women affected by anorexia nervosa

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Key words:
Exercise test; Exercise tolerance; Oxygen consumption.

Background. **The aim of this study was to evaluate exercise performance in patients affected by anorexia nervosa.**

Methods. **We studied 19 patients (all females, mean age 23.1 ± 5.2 years) affected by anorexia nervosa (mean weight 37.3 kg, body mass index 14.04 ± 1.4 kg/m^2) and 20 constitutionally thin women, matched for age, height and physical activity, with a body mass index < 19 kg/m^2. All these women underwent clinical examination, standard ECG and a cardiopulmonary stress test.**

Results. **Patients affected by anorexia nervosa showed a lower heart rate and systolic blood pressure at peak exercise (148.8 ± 13.8 vs 171 ± 9.2 b/min, p < 0.001, and 130 ± 9.5 vs 152 ± 11.2 mmHg, p < 0.001), work load (85.5 ± 15.1 vs 117.2 ± 20.3 W, p < 0.001), rate-pressure product (19 371 ± 2391 vs 25 986 ± 2218 b/min/mmHg, p < 0.001), oxygen uptake (VO_2) at rest and maximum VO_2 (5.4 ± 1.7 vs 7.1 ± 1.1 ml/kg/min, p < 0.001, and 28.08 ± 6.3 vs 40.2 ± 7.1 ml/kg/min, p < 0.001), anaerobic threshold (15.7 ± 1.9 vs 20.4 ± 2.1 ml/kg/min, p < 0.001), VO_2 during exercise (9.5 ± 1.2 vs 12.8 ± 1.3 ml/min/W, p < 0.001), maximum minute ventilation (34.5 ± 9.9 vs 48.4 ± 10.3 l/min, p < 0.001), and oxygen pulse (7.2 ± 2 vs 10.9 ± 2.4 ml/b, p < 0.001).**

Conclusions. **These data show an abnormal working capacity and cardiovascular responses to exercise in patients affected by anorexia nervosa. The low VO_2, both at rest and during exercise, allows them to maintain a relatively high level of physical activity, which contributes to increase the energy expenditure needed for weight loss.**

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Introduction

Anorexia nervosa is the most frequent nutrition disorder in industrialized countries[1] and affects about 1% of all women between 15 and 25 years of age[2], with a mortality of 10-30%[3]. The high mortality is often due to suicide, but sudden death is not infrequent[4]. Anorectic patients present a severe physical emaciation, directly attributable to loss of both fat and muscle. Medical complications of anorexia nervosa may include metabolic, renal, gastrointestinal, endocrine, neurological, hematological and dermatological effects[5]. Most of these complications are the results of starvation and can be reversed with a well planned refeeding program[6]. As in other forms of malnutrition, even the cardiovascular system can be involved. Sudden deaths in young patients affected by anorexia nervosa suggest that cardiac involvement may contribute to the high mortality[7]. The role of the nutritional status as an important determinant of myocardial function is known and a variety of cardiovascular complications in anorexia nervosa are described, such as thinning of the left ventricle, reduction of left ventricular mass, abnormalities of the mitral valve, systolic and diastolic dysfunction, and lengthening of the QT interval[8-10]. Several studies have shown a reduction in oxygen consumption (VO_2) in several forms of starvation, including anorexia nervosa[11,12].

The self-induced starvation typical of anorexia nervosa patients, however, differs in many important aspects from other forms of malnutrition. In anorexia nervosa patients an inflammatory process is not present and there are seldom any signs of electrolyte disorders, protein and vitamin deficiency and anemia[13,14]. Anorexia nervosa represents a pertinent model for the study of the effects of chronic starvation and malnutrition since it can cause malnutrition by semistarvation alone, without any inflammatory process or digestive loss of proteins or trace

elements[15]. Anorexia nervosa is characterized by voluntary caloric restriction, often associated with a high level of physical activity[16]. Anorectic patients are able to maintain a relatively high level of physical activity, even during the starving phase[17], in spite of a significant reduction in total body weight, percent fat and fat-free body mass (muscular mass).

The aim of this study was to evaluate the physical performance and cardiovascular response to exercise in young women affected by anorexia nervosa.

Methods

Population. The study population consisted of individuals consecutively referred to the Eating Disorder Unit of the Psychiatric Department, University of Pisa, between January and October 1999, with a diagnosis of anorexia nervosa. The patients selected for the investigation all conformed to the following criteria: a diagnosis of anorexia nervosa based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria, a body mass index (BMI) < 17.5 kg/m^2 associated with a body weight that, according to clinical reports, had been stable (± 1 kg) for at least 3 months before enrollment. In all cases, medications were suspended 24 or 48 hours before the exercise test, depending on the type of medication. All the patients were treated in hospital for some time and were regularly seen by a psychiatrist. None of them had been restricted to home or to bed or had started a refeeding program.

Nineteen female patients entered the study: 6 were inpatients (4 in the psychiatric ward and 2 in the pediatric ward because of young age) and the remainder were outpatients. The mean age was 23.1 ± 5.2 years (range 12-37 years). Their mean weight was 37.3 kg, with a BMI of 14.04 ± 1.4 kg/m^2. Ten subjects satisfied the criteria for restricting type anorexia nervosa whereas 8 were regularly engaged in binge-eating or other compensatory measures. In 1 patient, the diagnosis was changed from a restricting to a binge-eating/purging type. The average duration of illness was 105.8 ± 86.1 months (range 8-288 months). Amenorrhea was present in all patients.

We also studied 20 constitutionally thin women, matched for age, height and physical activity, with a BMI < 19 kg/m^2 (mean 17.7 ± 0.9 kg/m^2).

Exclusion criteria for both patients and controls were the following: a known cardiovascular, lung, osteoarticular or inflammatory disease, diabetes or anemia, a family history of deafness or sudden death, a history of overweight and tobacco smoking, and a low motivation to perform the exercise test. None of the subjects had been a trained athlete.

The research protocol and all the details about the exams were fully explained to the patients and to the controls in order to obtain homogeneous results and to reduce anxiety. All subjects or their families (for subjects < 18 years old) gave informed consent for the study.

Both patients and controls underwent clinical examination, standard ECG and a cardiopulmonary stress test "breath by breath" at the Cardio Thoracic Department of the University of Pisa. Serum electrolytes, blood count, hemoglobin, total proteins, liver function tests, serum cholesterol and triglyceride concentrations and thyroid hormones were measured on the day the exam was performed.

Standard ECG. A basal ECG was also performed in our patients and the QT interval was measured in order to confirm or exclude electrocardiographic abnormalities, in particular a longer QT interval, as reported in previous studies[8-10]. Other authors, in fact, suggested that sudden death in these patients could be caused by fatal arrhythmias correlated with a long QT interval. The QT interval was measured from the initial downward deflection of the QRS complex to the end of the T wave determined according to the criteria described by Lepeshkin and Surawicz[18]. It was measured in every lead in which the T wave was visible. The RR interval was calculated from the cycle preceding the one in which the maximum QT interval was measured. The Bazett rate corrected for the QT interval (QTc) was calculated using the formula $QTc = QT/\Delta RR$, where the QT interval is measured in milliseconds and the RR interval in seconds[19].

Cardiopulmonary exercise testing. All patients and controls, after clinical examination and standard ECG, were seated on a magnetic brake cycloergometer (STS 3 NT Cardioline) and monitored with a 12-lead ECG tracing (ECT WS 2000, REMCO Italia, Milan, Italy). The patients and controls were then told to wear nose-clips and a mouth-piece with a two-way valve connected to a computerized gas analyzer (Partn'air 5400 Ergospirometry, Medisoft, Dinant, Belgium) which every 10 s calculates the minute ventilation (V_E, ml/min), the weight-normalized VO_2 (ml/kg/min) and the weight-normalized carbon dioxide production (VCO_2, ml/kg/min). The instrument was calibrated before each test, taking into consideration room humidity, temperature and barometric pressure. After a 5-min period of adaptation to the mouth-piece, resting data were registered; then following 2 min of unloaded pedaling, an incremental exercise test to exhaustion (intolerable dyspnea and/or fatigue and/or 90% of the predicted maximal heart rate) was performed. The work rate was increased by 25 W every 3 min.

We evaluated the basal and maximal values of: systolic blood pressure, heart rate and VE, maximal work performed and work standardized to body weight (W/kg); we also evaluated the rate-pressure product, the weight-normalized VO_2 at rest, the weight-normalized maximum VO_2 (VO_2 max), the anaerobic threshold (ml/kg/min) by the modified V-slope method[20], the oxygen pulse as VO_2 /heart rate and VO_2 during exercise

($\Delta VO_2/\Delta W$, ml/min/W), where ΔVO_2 is the overall increase in VO_2 from unloaded pedaling to peak exercise and ΔW is the increase in work load. In accordance with Weber et al.[21] we defined the VO_2 max a charge in VO_2 < 1 ml/kg/min that is sustained for a minimum of 30 s into the next step of incremental bicycle work.

Linear regression analysis was performed to identify the relationship between VO_2 max, anaerobic threshold, VE max, oxygen pulse, $\Delta VO_2/\Delta W$ and clinical variables.

The basal ECG and cardiopulmonary stress test results were interpreted by two experienced cardiologists blinded to each other's interpretation and to the clinical picture. In the absence of consensus a third independent cardiologist made the decisions.

Statistical analysis. Data are reported as mean values ± SD. The Mann-Whitney test was used to analyze differences among continuous variables. Linear regression analysis was performed to identify the correlation between continuous variables. A p value < 0.05 was considered statistically significant. Statistical tests were performed using NCSS 2000 Software (Statistical Solutions Ltd., Cork, Ireland).

Results

Physical examination both in patients and in controls did not reveal heart murmurs or signs of heart disease. Anorexia nervosa patients in the present study had a subnormal blood pressure at rest (mean blood pressure 93/60 mmHg), which is characteristic of long standing starvation. In the patients, routine biochemical and hematological tests, blood count, hemoglobin (mean 13 ± 4.1 g/dl), serum electrolytes, proteins, albumin, liver function tests and serum cholesterol and triglyceride concentrations were normal (Table I). Thyroid function tests were normal: the mean serum level of thyroid stimulating hormone was 2.2 mU/l (normal range 0.05-4.2 mU/l), the mean level of free thyroxine was 16.2 pmol/l (normal range 12-28 pmol/l) and the mean level of free triiodothyronine was 6.6 pmol/l (normal range 3.0-9.0 pmol/l). Only in 1 patient did we find a reduction in the levels of thyroid stimulating hormone (0.03 mU/l).

The standard ECG was normal both in patients and in controls. None of ECG showed long PR, QRS, QT or QTc intervals. The two groups did not show a significantly different QTc interval (0.38 ± 0.02 vs 0.37 ± 0.03 s, p = 0.32).

Circulatory response. All patients and controls exercised to exhaustion and remained asymptomatic throughout the exercise test and the recovery period. All subjects reached the anaerobic threshold and VO_2 max.

The maximal heart rate and peak systolic blood pressure were significantly lower in patients (148.8 ± 13.8 vs 171 ± 9.2 b/min, p < 0.001, and 130 ± 9.5 vs 152 ± 11.2 mmHg, p < 0.001 vs controls; Fig. 1). The ECG results remained normal in both patients and controls and none of them presented arrhythmias either at rest or during exercise (Table II).

Working capacity. The maximal work performed was significantly different between patients and controls, being respectively 85.5 ± 15.1 and 117.2 ± 20.3 W (p < 0.001). When work was standardized to body weight and expressed as watts per kilogram, the difference did

Table I. Baseline clinical characteristics of the study population.

	AN patients (n=19)	Controls (n=20)	p
Age (years)	23.1 ± 5.2	22.05 ± 2.1	0.26
Body weight (kg)	37.3 ± 3.5	46.05 ± 4.1	< 0.001
Height (cm)	1.57 ± 0.3	1.57 ± 0.4	0.64
BMI (kg/m^2)	14.04 ± 1.4	17.7 ± 0.9	< 0.001
Hemoglobin (g/dl)	13 ± 4.1	13 ± 4.8	0.63
White blood cell (U/l)	6277 ± 883	6137 ± 829	0.68
Triglyceride (mg/dl)	89 ± 16	90 ± 12	0.86
Cholesterol (mg/dl)	146 ± 26	160 ± 23	0.09
Total protein (g/dl)	7.4 ± 0.4	7.5 ± 0.3	0.53
Albumin (g/dl)	4.5 ± 0.3	4.6 ± 0.4	0.72
Creatinine (mg/dl)	0.85 ± 0.4	0.9 ± 0.4	0.52
K^+ (mmol/l)	4.2 ± 0.5	4.2 ± 0.2	0.38
Na^+ (mmol/l)	141.7 ± 3.5	142 ± 4.4	0.73
Cl^- (mmol/l)	102.2 ± 5	102.8 ± 4	0.63
Ca^{++} (mg/dl)	9.1 ± 0.3	9.2 ± 0.6	0.31
TSH (mU/l)	2.2 ± 0.5	2.1 ± 0.6	0.61
FT3 (pmol/l)	6.6 ± 1.2	6.3 ± 1.4	0.56
FT4 (pmol/l)	16.2 ± 2.7	16 ± 2.2	0.96

AN = anorexia nervosa; BMI = body mass index; FT3 = free triiodothyronine; FT4 = free thyroxine; TSH = thyroid stimulating hormone.

Table II. Circulatory response.

	AN patients (n=19)	Controls (n=20)	p
Resting HR (b/min)	79.9 ± 17.7	83.3 ± 13.5	0.53
Peak HR (b/min)	148.8 ± 13.8	171 ± 9.2	< 0.001
QTc interval (s)	0.38 ± 0.02	0.37 ± 0.03	0.32
SBP at rest (mmHg)	93.1 ± 8.2	97.2 ± 7.9	0.079
DBP at rest (mmHg)	58.6 ± 7.5	59.2 ± 7.6	0.86
SBP max (mmHg)	130 ± 9.5	152 ± 11.2	< 0.001
DBP max (mmHg)	93.4 ± 9.9	95.7 ± 10	0.67
Work load (W)	85.5 ± 15.1	117.2 ± 20.3	< 0.001
Work load/kg (W/kg)	2.3 ± 0.4	2.5 ± 0.6	0.18
RPP (b/min/mmHg)	19 371 ± 2391	25 986 ± 2218	< 0.001
VO_2 max (ml/kg/min)	28.08 ± 6.3	40.2 ± 7.1	< 0.001
VO_2 max (ml/min)	1058.4 ± 291.1	1852.2 ± 374.3	< 0.001
AT VO_2 (ml/kg/min)	15.7 ± 1.9	20.4 ± 2.1	< 0.001
$\Delta VO_2/\Delta W$ (ml/min/W)	9.5 ± 1.2	12.8 ± 1.3	< 0.001
Oxygen pulse (ml/b)	7.2 ± 2	10.9 ± 2.4	< 0.001
Peak ventilation (l/min)	34.5 ± 9.9	48.4 ± 10.3	< 0.001

AN = anorexia nervosa; AT = anaerobic threshold; DBP = diastolic blood pressure; HR = heart rate; RPP = rate-pressure product; SBP = systolic blood pressure; VO_2 = oxygen consumption; $\Delta VO_2/\Delta W$ = oxygen consumption during exercise.

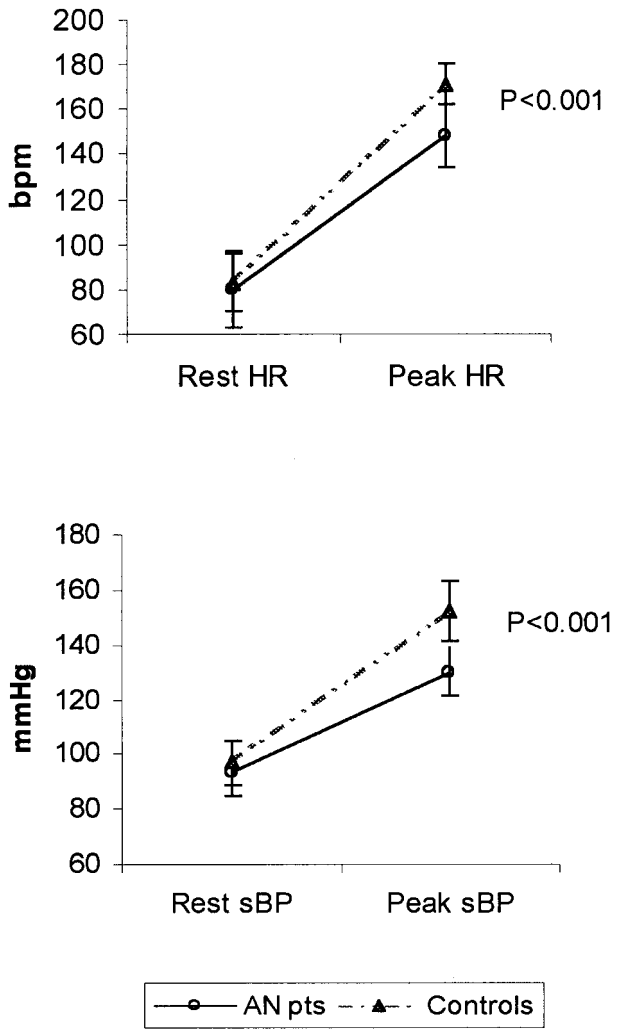

Figure 1. *Heart rate (HR) and systolic blood pressure (sBP) at rest and at peak exercise in anorexia nervosa (AN) patients and in constitutionally thin women.*

not remain statistically significant (2.3 ± 0.4 vs 2.5 ± 0.6 W/kg, p = 0.18). The rate-pressure product was significantly higher in controls than in patients (19 371 ± 2391 vs 25 986 ± 2218 b/min/mmHg, p < 0.001).

Similarly, also the VO_2 parameters differed significantly. VO_2 at rest was 5.4 ± 1.7 vs 7.1 ± 1.1 ml/kg/min in patients and controls respectively (p < 0.001). The VO_2 max was significantly lower in patients than in controls (1058.4 ± 291.1 vs 1852.2 ± 374.3 ml/kg/min, p < 0.001), and the difference remained significant after correction for body weight (28.08 ± 6.3 vs 40.2 ± 7.1 ml/kg/min, p < 0.001; Fig. 2).

The VO_2 during exercise and oxygen pulse were significantly higher in controls than in patients (9.5 ± 1.2 vs 12.8 ± 1.3 ml/min/W, p < 0.001, and 7.2 ± 2 vs 10.9 ± 2.4 ml/b, p < 0.001) respectively.

The anaerobic threshold was significantly lower in patients than in controls (15.7 ± 1.9 vs 20.4 ± 2.1 ml/kg/min, p < 0.001). The VE max was also lower in patients than

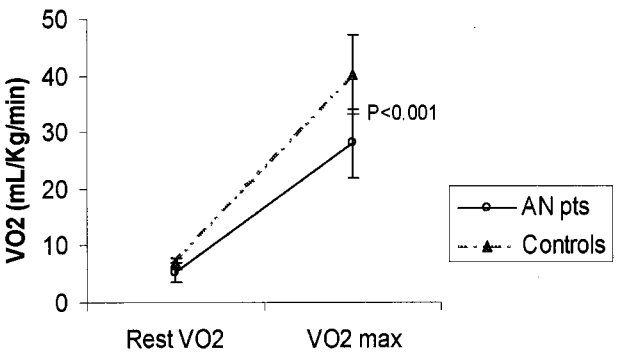

Figure 2. *Oxygen uptake (VO_2) at rest and maximal oxygen uptake (VO_2 max) in anorexia nervosa (AN) patients and in constitutionally thin women.*

in controls (34.5 ± 9.9 vs 48.4 ± 10.3 l/min, $p < 0.001$). We did not find any significant differences in the other parameters (Table II).

The results of canonical correlation analysis showed that the VO_2 max was significantly correlated with BMI ($r = 0.93$, $p < 0.0001$; Fig. 3), while no correlation was found between the VO_2 max and the duration of illness ($r = -0.41$) and between VO_2 max and age ($r = -0.35$).

Also the oxygen pulse was significantly correlated with BMI ($r = 0.89$, $p < 0.001$) but it did not show any correlation with the duration of illness ($r = -0.21$) and age ($r = -0.12$). A significant correlation was found between the VE max and BMI ($r = 0.76$, $p < 0.01$) and between the VE max and the duration of illness ($r = -0.70$, $p < 0.001$). The BMI was also significantly correlated with the VO_2 during exercise ($r = 0.80$, $p < 0.001$) and with the VO_2 max ($r = 0.94$, $p < 0.001$).

No significant correlation was found between all the other parameters and BMI and age.

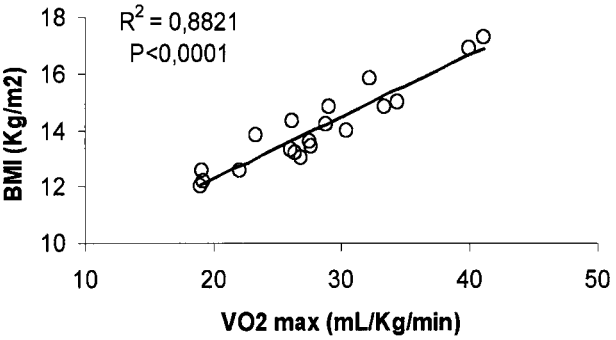

Figure 3. *Maximal oxygen uptake (VO_2 max) in relation to body mass index (BMI) in anorexia nervosa patients.*

Discussion

The present study was designed to evaluate the cardiovascular response to exercise during the starvation phase of anorexia nervosa. Results showed the presence of an impaired response to exercise in the absence of ECG abnormalities. None of the patients presented arrhythmias, an ST segment depression and a longer QT interval. Anorexia nervosa patients presented a lower rate-pressure product and exercise-related VO_2 compared to healthy control subjects. Besides, the maximal work performed was significantly lower in the patient group, but the difference did not remain statistically significant when work was standardized to body weight. The data of our study show a VO_2 during work which was significantly lower for patients than for controls: at each level of exercise the increase in VO_2 was significantly lower in anorexia nervosa patients than in the controls. These results suggest that the anorexia nervosa subjects could pedal with greater mechanical efficiency and consumed less energy than normal weight subjects to perform a similar exercise test. In our study, a significant correlation was also found between BMI and VO_2 max, VO_2 during exercise and oxygen pulse.

The finding that VO_2 both at rest and during exercise is lower in anorexia nervosa patients than in controls is consistent with reports of an abnormal response to exercise in malnourished subjects. In previous studies, some authors evaluated the cardiovascular response to exercise in patients with anorexia nervosa and demonstrated a VO_2 max which was lower in the patients than in the controls, and the difference remained significant after correction for body weight[11]. During exercise, in patients suffering from anorexia nervosa VO_2 for a given work load was lower than expected[12] and the reduction in VO_2 max in case of maximal exercise performed during starvation was reversible[16].

Although some authors attributed the decreased energy expenditure associated with malnutrition to decreased oxygen transport and altered hemoglobin, the malnourished subjects of this study did not have reduced hemoglobin levels.

A lower VO_2 is probably a phenomenon of the process of adaptation to a low metabolic rate. The consequence of a decrease in food intake is a decrease in energy intake, which must result in weight loss and/or decreased energy utilization[22,23]. It could also be correlated with a change in circulatory dimensions in anorexia nervosa, proportional to the reduction in weight. This could explain the significant correlation between BMI and VO_2 max, VO_2 during exercise and oxygen pulse found in our study. Cardiac changes such as a reduction in heart and blood volumes and in left ventricular mass, thinning of the left ventricle, abnormalities of mitral valve function and systolic and diastolic dysfunction have been described during the starvation phase[8,16,24-26]. The blood and heart volumes increased significantly in all patients following weight gain[16]. Previous studies also showed an altered association between VO_2 max and heart volume, which could indicate that the working capacity measured as aerobic power decreases independently and out of proportion to the circulatory dimensions[12]. Hemodynamic studies confirmed a lowered cardiac index, most likely secondary to the small size of the heart and to the reduction in stroke volume[27].

On the other hand, the maintenance of a relatively intense physical activity even during the starvation phase of anorexia nervosa remains completely unexplained. Two factors could play a role: restoration of type II muscle fibers which can improve force without increasing VO_2 and a low catecholamine secretion, since, as shown by previous studies[15], plasma norepinephrine stimulates futile energy cycles. But even the elevated plasma levels of immunoreactive beta-endorphin may be relevant not only to the hypothalamic hypogonadism and to the suppression of appetite, but also to the tolerance of fasting in anorexia nervosa[28]. Plasma levels of beta-endorphin are, in fact, significantly higher in anorexia nervosa patients when compared with control subjects and self-starvation, exacerbated by excessive ex-

ercise, might itself be a state of addiction to the body's endogenous opioids[29].

Some authors reported that in anorexia nervosa patients, besides a cardiovascular involvement, there is also an impaired muscle performance[15] which could be related to alterations in the intracellular concentrations of micronutrients, to a decrease in the muscle relaxation rate and to a reduction in muscle mass. In contrast, in this study the maximal work performed was significantly lower in the patient group compared with controls, but the difference did not remain statistically significant when work was standardized to body weight. These results clearly show that our patients did not present with muscle impairment: muscle function could be altered in other types of malnutrition and related to the associated inflammatory process, but probably not in anorexia nervosa, where an inflammatory process is not present.

We were able to identify an impaired response to exercise in patients affected by anorexia nervosa. This indicates a cardiovascular involvement during the starvation phase of anorexia nervosa. Thus, in such patients accurate cardiovascular assessment is of paramount importance. The identification of these abnormalities in the starvation phase may help us to devise refeeding programs to prevent heart failure, a complication which, possibly due to the abrupt increase in preload, often develops during clinical refeeding.

We are aware that further studies with a larger patient population need to be carried out. Controlled studies should also be performed to show the effect of refeeding on each abnormality, to evaluate its reversibility and to assess the extent of the recovery. Long-term follow-up studies with repeated exercise tests during recovery from anorexia nervosa may contribute to the understanding of the cause of this disease and may also provide important prognostic clues.

Cardiopulmonary exercise test is an economic, reproducible test which can be easily used to assess the presence of cardiovascular abnormalities in patients affected by anorexia nervosa and to evaluate their reversibility during refeeding.

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