Reduced hemodynamic load and cardiac hypotrophy in patients with anorexia nervosa¹,²

Carmela Romano, Marcello Chinali, Fabrizio Pasanisi, Rosanna Greco, Aldo Celentano, Alessandra Rocco, Vittorio Palmieri, Ada Signorini, Franco Contaldo, and Giovanni de Simone

ABSTRACT

Background: Anorexia nervosa is associated with lower left ventricular mass (LVM) and systolic dysfunction. Whether these abnormalities reflect chronic protein-energy malnutrition or are primarily related to lower cardiac workload is unclear.

Objective: The objective of the study was to verify whether low LVM in anorexia nervosa is explained by low hemodynamic load.

Design: Ninety-one women with anorexia nervosa [mean ± SD age: 20.5 ± 6.1 y; body mass index (in kg/m²): 15.6 ± 1.9; group 1] and 62 normal-weight female control subjects [age: 22.5 ± 5.5 y; body mass index: 20.9 ± 1.2; group 2] underwent Doppler echocardiography. LVM was evaluated as the percentage predicted by body height, sex, and stroke work (systolic blood pressure × stroke volume).

Results: The left ventricular chamber dimension was smaller and the chamber walls were thinner in group 1 than in group 2, which resulted in significantly lower LVM and LVM indexes (P < 0.0001). Ejection fraction, heart rate, stroke volume, and cardiac output were significantly (P < 0.007) lower in group 1, but peripheral resistance was substantially higher (P < 0.0001). The deviation of LVM from predicted values was lower and the proportion of subjects with inadequate LVM was significantly higher in group 1 than in group 2 (P < 0.0001). This difference was attenuated after adjustment for body height and heart rate. There were no relations between LVM and laboratory tests in group 1.

Conclusions: Anorexia nervosa is a condition of low hemodynamic load that leads to low LVM. Even with adjustment for stroke work, however, LVM is lower than would be predicted by height, because of the effect of body weight reduction (ie, wasting of lean body mass).


KEY WORDS Anorexia nervosa, echocardiography, left ventricular hypotrophy, cardiac load, systolic dysfunction, inadequate left ventricular mass

INTRODUCTION

Anorexia nervosa is a major psychiatric disease, characterized by severe eating disorders that lead to chronic protein-energy malnutrition and, consequently, severe morbidity and a high mortality rate (1). Patients with anorexia nervosa lose weight as a consequence of extreme energy and water restriction and their willingness to dissipate energy and fluids. Persons with anorexia nervosa show metabolic and endocrine alterations similar to those in persons with secondary protein-energy malnutrition (2). Clinical and prognostic characteristics of anorexia nervosa (refeeding edema and sudden death) might be attributed to cardiovascular failure (3). Electrocardiographic abnormalities (4) have been reported in anorectic patients with severe malnutrition, including extreme bradycardia, reduction in QRS amplitude, increased QT interval, nonspecific alterations in ST segment, and cardiac arrhythmias, possibly resulting in sudden death.

Left ventricular (LV) modifications have been reported as well (5–7) and are mainly characterized by reduced LV mass (LVM) and some degree of systolic dysfunction, which are possible consequences of nutritional status. It is still unclear whether the observed low LV weight directly reflects protein-energy malnutrition or is a consequence of reduced pressure and volume load. Although it has never been directly measured in patients with anorexia nervosa, cardiac workload most probably is less, paralleling the reductions in blood pressure and volume load (7, 8).

We showed that, when body size and composition are normal, ≤ 82% of normal variability in LVM can be explained by phenotypic variations in body size and cardiac workload (8). This approach allows distinguishing dimensions of LVM that fully compensate individual cardiac workload at a given body size. Among the measures that can be used to represent body size, including body weight (ie, body mass index or body surface area), height is the only one that cannot be phenotypically influenced by “lifestyle” once the body growth is completed (9, 10). In fact, as shown in studies in mammals (11), body length (or height in primates) is determined by skeletal size, which is in turn physiologically (and genetically) linked to muscle mass (12). Height is, therefore, a potent correlate of “ideal” (ie, genetically programmed) lean body mass (13). The heart can tolerate deviations from this pattern in relation to the phenotypic variation in loading conditions, as a result of individual regulation of blood pressure and volume load (8). There are, however, situations in which LVM deviates in excess from this physiologic amount, and we...
know that a condition of inappropriately large LVM is associated with a high-risk cardiovascular phenotype (14–17) and that it predicts an adverse outcome in arterial hypertension (17). We know also from these studies that LVM can be lower than would be expected (17) and that this condition might be associated with adverse hemodynamic features (17). An abnormally low LVM is rare in arterial hypertension (14–17), but it is more frequent in the context of anorexia nervosa. However, there is no information on the physiology of reduced LVM in anorexia. Accordingly, this study was designed to verify whether low LVM reported in patients with anorexia nervosa is explained by a low hemodynamic load and a loss of body mass that is a consequence of protein-energy malnutrition.

SUBJECTS AND METHODS

Subjects

Ninety-one young women with either restrictive or bulimic anorexia nervosa (± SD age: 20.5 ± 6.1 y; body mass index (BMI; in kg/m²): 15.6 ± 1.9) were consecutively referred from the outpatient clinic of the Clinical Nutrition Unit, Federico II University Hospital, to the Echocardiography Laboratory of the Department of Clinical and Experimental Medicine. Two consultant psychiatrists based the diagnosis of anorexia nervosa on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV; 18). BMI < 18.5 associated with a stable body weight (± 1 kg) for ≥ 3 mo before the study and primary amenorrhea were considered essential diagnostic criteria. None of the patients had clinical symptoms or signs of cardiovascular disease; all of them were in a starvation phase. Patients and their families gave informed consent for the study. All anorexic women underwent a complete clinical examination and filled out a food-frequency questionnaire. Blood samples were taken in the morning after an overnight fast (≥ 14 h) for standard laboratory tests, and the echocardiogram was performed on the same day. Recently, evaluation of triiodothyronine, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone was also introduced into the study. Recently, evaluation of triiodothyronine, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone was also introduced into the clinical protocol, and values are reported for a subgroup of the patients.

Blood pressure measurements

Blood pressure was measured twice with the patient in a supine position, immediately after the echocardiogram was performed. Phase 1 and phase 5 Korotkoff sounds were taken to define systolic and diastolic blood pressure, respectively. Blood pressure was measured with a normal adult or pediatric arm-cuff, according to subjects’ arm circumference, and by using a standard mercury sphygmomanometer.

Echocardiography

The echocardiographic examination was performed by expert sonographers, with the subjects in a partial left decubitus position, according to our standard procedures (7, 8, 15, 16), and with the use of commercially available machines equipped with 2.5–5-MHz annular-array or phased-array transducers. Under a 2-dimensional guide, time-motion tracings (M-mode) were recorded on strip-chart paper at 50 mm/s and then coded and read by 2 investigators blinded to clinical data. Primary measurements of M-mode tracings were done according to the recommendations of the American Society of Echocardiography (19, 20).

LVM was calculated by using a necropsy-validated formula (20) and was normalized by body surface area or height in meters to the power of 2.7. This power is the allometric signal that has been shown to linearize the relation between the one-dimensional variable, height, and the 3-dimensional variable, LVM (21).

LV end-systolic and end-diastolic volumes were estimated from M-mode measures by use of the formula of Teichholz et al (22). Stroke volume was the difference between end-diastolic and end-systolic volumes and was used as a direct indicator of LV volume load; cardiac output was calculated as stroke volume × heart rate and was used as a measure of LV pump function (ie, the ability to provide a given amount of blood in a unit of time to meet body needs). Ejection fraction represents the amount of blood ejected per each milliliter of LV diastolic volume, and it was computed as stroke volume divided by end-diastolic volume, as a raw measure of LV chamber performance. Stroke work, a measure of cardiac workload, was calculated as systolic blood pressure in mm Hg (pressure load) × stroke volume in milliliters per beat (volume load) and converted into gram-meters per beat by multiplying by the conversion factor 0.0014.

LVM was also evaluated as the percentage of deviation from the ideal individual value predicted from stroke work and body size by using an equation obtained in a reference nonoverlapping population of 766 normotensive, normal-weight subjects with a broad age range (8). Two age-specific equations were used to predict LVM in our population. LVM in adolescents ≤ 17 y old was calculated with the equation

\[
LVM_{pr} = 1.58 + 17.8 \times \text{height}^{2.7} + 0.36 \times \text{stroke work} - 7.76
\]

where LVM_{pr} is predicted LVM, 1.78 is the constant, and 7.76 is the coefficient after adjustment for female sex. In adults (> 17 y old), the following equation was used:

\[
LVM_{pr} = 55.375 + 6.635 \times \text{height}^{2.7} + 0.641 \times \text{stroke work} - 36.15
\]

Thus, the value of LVM predicted by these equations is the ideal value that would be compensatory in girls and women for a given body height and cardiac load. Eventually, the echocardiographically observed individual value of LVM (LVM_{o}) could be compared with the predicted value (LVM_{pr}/LVM_{pr} × 100) to provide the percentage of deviation of the observed value from that predicted as the ideal. Thus, the effect of body weight could be measured. For convenience, LVM was defined as “inadequate” when it was lower than the 5th normal percentile obtained in our reference population (8); an LVM_{o}/LVM_{pr} above the 95th normal percentile was previously defined as an “inappropriately high LVM” (14–17). In our reference population (8), the condition of an appropriate LVM in children and adolescents ranged between 61% and 140% of LVM_{pr}, whereas in adults it ranged between 73% and 128%.

Statistical analysis

Data were expressed as means ± SDs. Analysis of variance was used to compare groups, and covariance was used to adjust for confounders. Least-squares linear regression analysis was
used to study univariate relations between 2 variables. Multiple linear regression analysis was used to highlight the independence of observed univariate relations, on the condition that tolerance (as a measure of multicollinearity) was > 0.7 in the final model. A two-tailed α value ≤ 0.05 was generally used to reject the null hypothesis, although a different value might occasionally be reported.

RESULTS

The general characteristics of the study population are shown in Table 1. The mean age of patients with anorexia did not differ significantly from that of healthy control subjects, whereas BMI was lower in patients with anorexia by design. Systolic, diastolic, and mean arterial blood pressures were significantly lower in patients with anorexia than in control subjects (P < 0.0001).

The metabolic and nutritional status of patients with anorexia nervosa is shown in Table 2. Average values were not evidently abnormal in patients with anorexia nervosa, but the variability was great, ranging from normality to severe dysfunction. In particular, 37 patients (41%) had a high plasma albumin concentration (> 78 g/L); 18 had a low cholesterol concentration (< 2.7 mmol/L; 20%), and 34 had a high cholesterol concentration (> 8.66 mmol/L; 35%) cholesterol; fasting plasma glucose concentrations were < 2.39 mmol/L in 13% of patients. A relatively small proportion of patients had severe electrolyte abnormalities. A calcium concentration > 2.7 mmol/L was detected in 13% of patients. In the subgroup of 20 patients who underwent hormonal evaluation, luteinizing hormone was low in 95% and follicle-stimulating hormone was low in 50%, but thyroid-stimulating hormone was substantially increased in 26%.

Left ventricular (LV) geometry and function in patients with anorexia nervosa and in control subjects

The LV chamber dimension was smaller and the wall thinner (not shown) in anorexic patients than in the control subjects, which resulted in lower LVM and LVM indexes (Table 3; P < 0.0001). Ejection fraction, stroke volume, cardiac output, and heart rate were also lower in patients with anorexia (all P < 0.007). Whereas blood pressure was lower in anorexic patients than in control subjects, the peripheral resistance in anorexic patients was significantly higher (P < 0.0001), because of their low cardiac output.

Matching cardiac workload with left ventricular mass

The reason for the reduced LVM in anorexia nervosa patients, even after normalization for different measures of body size (ie, height and body surface area), could be attributed to the reduced hemodynamic load, as suggested by values of systolic blood pressure and stroke volume presented in Tables 1 and 3. In fact, Table 4 shows that stroke work was ~30% less in anorexic patients (P < 0.0001) than in control subjects. However, LVMpr/LVMpr (ie, the deviation of observed LVM from the theoretical value

### Table 1

Clinical characteristics of the population

<table>
<thead>
<tr>
<th></th>
<th>Patients with anorexia nervosa (n = 91)</th>
<th>Control subjects (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>20.5 ± 6.1</td>
<td>22.2 ± 5.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.6 ± 1.9²</td>
<td>20.9 ± 1.2</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>90.8 ± 9.9²</td>
<td>110.9 ± 10.8</td>
</tr>
<tr>
<td>Diastolic</td>
<td>62.1 ± 7.6²</td>
<td>70.3 ± 8.9</td>
</tr>
<tr>
<td>Mean</td>
<td>71.7 ± 7.7²</td>
<td>83.8 ± 8.2</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.7 ± 7.3²</td>
<td>40.5 ± 10.4</td>
</tr>
</tbody>
</table>

1 ± SD. 2 Significantly different from control subjects, P ≤ 0.0001.

### Table 2

Standard laboratory tests and markers of nutritional status in patients with anorexia nervosa (n = 91)

<table>
<thead>
<tr>
<th>Markers of nutritional status</th>
<th>Minimum²</th>
<th>Maximum²</th>
<th>x ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>37 [0]</td>
<td>78 [41]</td>
<td>49.8 ± 6.6</td>
</tr>
<tr>
<td>Urea (g/L)</td>
<td>0.07</td>
<td>0.82</td>
<td>0.31 ± 0.15</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>2.7 [20]</td>
<td>8.66 [35]</td>
<td>4.87 ± 1.21</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.42 [9]</td>
<td>2.47 [3]</td>
<td>0.94 ± 0.35</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.39 [13]</td>
<td>5.99 [0]</td>
<td>4.23 ± 0.60</td>
</tr>
<tr>
<td>WBCs (mm⁻³)</td>
<td>2030</td>
<td>9100</td>
<td>4950 ± 1560</td>
</tr>
<tr>
<td>Lymphocytes (mm⁻³)</td>
<td>500</td>
<td>3210</td>
<td>1860 ± 510</td>
</tr>
<tr>
<td>Circulating electrolytes (mmol/L)</td>
<td>18.17</td>
<td>75.60</td>
<td>39.35 ± 10.87</td>
</tr>
</tbody>
</table>

1 ± SD. 2 Significantly different from control subjects: ² P ≤ 0.0001, ³ P ≤ 0.007.

### Table 3

Left ventricular (LV) geometry and function in patients with anorexia nervosa and in control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients with anorexia nervosa (n = 91)</th>
<th>Control subjects (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Diastolic diameter (cm)</td>
<td>4.26 ± 0.39²</td>
<td>4.57 ± 0.35</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>71.2 ± 17.6²</td>
<td>96.9 ± 21.2</td>
</tr>
<tr>
<td>Mass/height (g/m².7)</td>
<td>20 ± 4²</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62.7 ± 5.8³</td>
<td>65.03 ± 4.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>55.6 ± 11.4²</td>
<td>72.4 ± 12.3</td>
</tr>
<tr>
<td>Stroke volume (mL/beat)</td>
<td>50.7 ± 13.3²</td>
<td>62.1 ± 13.3</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.8 ± 1.1²</td>
<td>4.5 ± 1.1</td>
</tr>
<tr>
<td>Peripheral resistance (dyne · s⁻¹ · cm⁻³)</td>
<td>2191 ± 757²</td>
<td>1590 ± 381</td>
</tr>
</tbody>
</table>

1 ± SD. 2 Significantly different from control subjects: ² P ≤ 0.0001, ³ P ≤ 0.007.

³ Obtained in 20 patients.
CARDIAC HYPOTROPHY IN ANOREXIA NERVOSA

TABLE 4
Deviation of observed left ventricular mass (LVM) from predicted ideal values, compensatory for body height and cardiac workload

<table>
<thead>
<tr>
<th></th>
<th>Patients with anorexia nervosa</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 91)</td>
<td>(n = 62)</td>
</tr>
<tr>
<td>Stroke work (g-m/beat)</td>
<td>66.45 ± 19.44</td>
<td>99.16 ± 23.4</td>
</tr>
<tr>
<td>LVM (% of the predicted value)</td>
<td>84.5 ± 13.33</td>
<td>104.4 ± 15.7</td>
</tr>
<tr>
<td>Patients with inadequate LVM (%)</td>
<td>19.4</td>
<td>5.7</td>
</tr>
</tbody>
</table>

1,2 ± SD.
1,3 Significantly different from control subjects: 1P ≤ 0.001, 2P ≤ 0.01.

compensating cardiac load at a given body size) was markedly lower in anorexic patients than in normal controls. In addition, the proportion of subjects with clearly inadequate LVM was substantially higher in anorexic patients than in control subjects (both P < 0.0001). The reason for this difference is clarified in Figure 1. There was a positive relation between LVMob/LVMpr and body weight (r = 0.28, P < 0.0001) but not between LVMob/LVMpr and height (Figure 1).

In patients with anorexia, LVMob/LVMpr was also negatively related to heart rate (r = −0.25, P < 0.02), which was in turn directly related to body weight (r = 0.34, P < 0.001), which raises the question of how much the relation with body weight could be affected by the relation with heart rate. Multiple regression analysis revealed that both body weight (slope = 0.70, P < 0.0001) and heart rate (slope = −0.29; P < 0.01) were independent correlates of LVMob/LVMpr (constant = 65%) either in pooled groups (multiple R = 0.34, SEE = 17%; P < 0.0001) or in patients with anorexia, at a low degree of collinearity (tolerance = 0.73).

Thus, the LVMob/LVMpr was compared between anorexia and controls, by adjustment for body weight and heart rate in a model of one-factor analysis of covariance. The between-group comparison was markedly reduced, but some difference remained (P = 0.07). The adjusted mean values were 86% in anorexia and 93% in controls. There was no significant relation between LVMob/LVMpr and the variables shown in Table 2.

DISCUSSION

In this study, we investigated geometric abnormalities of the left ventricle in women with anorexia nervosa in relation to body size and cardiac workload. Anorexia nervosa is a chronic type of severe marasma, such as protein-energy malnutrition, which is characterized by a high incidence of sudden cardiac death (3). Patients with anorexia nervosa in the present study were confirmed to have low LVM, depressed pump function, and increased peripheral resistance (5–7).

A relatively low cardiac output status was associated with both reduced stroke volume and low heart rate, the latter of which we suggested (23) might be related to increased vagal tone, as additional mechanisms for preserving energy. By matching low blood pressure with low stroke volume, we also showed that anorexia is a low-cardiac-workload status; this finding may explain why LVM is persistently lower even with normalization for different measures of body size (as seen in Table 3), but it also raises the question of whether reduced hemodynamic load could fully explain the difference from a normal condition.

The approach used in this study was generated in normal-weight conditions. It has never been tested in conditions of undernutrition, but it has been shown to be useful in discriminating pathologic from compensatory LV hypertrophy in the presence of another deviation from normal body size and composition, specifically obesity (14–17). We found that in patients with anorexia nervosa and low stroke volume, LVM was lower than predicted. This result was mostly due to the use of height in the predicting equation, and it disappeared when height was replaced with body weight in the equation derived from the reference population (data not shown) or was substantially attenuated when anorexic patients and control subjects were compared after adjustment for body weight.

In anorexia nervosa, body composition is abnormal because virtually the entire body weight is fat-free mass. Thus, as opposed to height, which represents the programmed lean body mass (9, 10), body weight in this context represents fat-free body mass and in particular bone mass (the actual muscle mass), which has lower metabolic needs and requirements for blood flow. In this context, the deviation of LVM from the predicted value can be considered a marker of the extent of muscle waste, and, ultimately, it might be a measurable bioassay of the protein malnutrition in these patients. The catastrophic muscular status of these patients is indirectly shown by the extremely high concentration of circulating albumin (24). When the value of LVMob/LVMpr was adjusted for body weight (ie, a surrogate of lean body mass), the physiologic adaptation of LV mass appeared to be mostly consistent with both the reduced hemodynamic load and the decreased body weight (fat-free mass). The difference that remained, nearly reaching statistical significance, might be attributed to the fact that the heart cannot preserve energy as well as peripheral muscles can, because cardiomyocytes produce and dissipate large amounts of energy without any interruption and because pump function cannot decrease under life-compatible concentrations.

In conclusion, anorexia nervosa is a condition of low hemodynamic load that leads to low values of LVM. Even after adjustment for stroke work, however, LVM is lower than would be predicted by height, as a result of the effect of body weight reduction (ie, wasting of lean body mass). There is no evidence that this condition of LV hypotrophy is related to a greater risk of cardiovascular disease, but in anorexia nervosa LV hypotrophy is probably a marker of nutritional status and is more informative than most laboratory tests. Longitudinal ad hoc studies should be implemented to measure the extent to which the appropriateness of LVM might be used as an objective bioassay of change in nutritional conditions.
We are indebted to Emilia De Filippo and Renata Bracale for their extraordinary work in managing patients with anorexia nervosa.

REFERENCES


