Effects of Self-Induced Starvation on Cardiac Size and Function in Anorexia Nervosa

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SUMMARY Cardiac size, function and rhythm were examined in 11 patients with anorexia nervosa. Mean left ventricular, left atrial and aortic dimensions on echocardiogram were below normal adult values at baseline. In addition to decreased cardiac dimensions — ventricular ectopy, relative hypotension, bradycardia and blunted heart rate — response to exercise were noted. Left ventricular systolic function, however, was unimpaired as indicated by normal echocardiographic fractional shortening, and by normal exercise augmentation of ejection fraction determined by radionuclide cineangiography. Eight of the patients responded to treatment with a mean weight gain of 32%. In these eight, cardiac dimensions increased toward normal: left ventricular dimension increased by 13%; left atrial dimension by 20%; aortic dimension by 15% and estimated left ventricular mass by 20%. We conclude that abnormalities of heart size and rhythm occur in patients with anorexia nervosa. However, cardiac dimensions, including left ventricular mass, may increase following nutritional rehabilitation, accompanied by an increase in heart rate and blood pressure.

DEATH IN ANOREXIA NERVOSA may be sudden, and the mortality rate is the highest of any psychiatric disease.1 Self-enforced starvation in this condition results in severe reduction of body mass, comparable to that of famine victims.2 Despite intensive investigation of its psychiatric3 and endocrine4,5 manifestations, little has been written about the cardiovascular system in this disease, which offers a clinical model for the study of protein-calorie deprivation.

The recent development of noninvasive diagnostic techniques such as echocardiography, radionuclide cineangiography and Holter ambulatory electrocardiographic monitoring, permit more accurate estimation of cardiac size, and cardiac mechanical and electrical function, than previously possible. We have used these techniques to study patients with anorexia nervosa before and after weight gain. The data from these patients may be pertinent to the potential reversibility of the effects of starvation on cardiac size and function in the victims of famine and other causes of nutritional deprivation.

Methods

Patient Population

Eleven patients admitted to the Clinical Center of the National Institutes of Health with the diagnosis of anorexia nervosa as defined by the criteria of Feighner et al.6 were studied. Informed consent was obtained from each patient before the study. Each was admitted for evaluation and treatment of anorexia nervosa; none had cardiovascular symptoms or previously identified cardiovascular abnormalities. All had normal serum electrolytes. All were white females varying in

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age from 12–32 years (mean 21.7 years, median 22 years), who because of active refusal to eat had suffered a weight loss of greater than 25% of original body weight, or 15% of the ideal body weight determined from Metropolitan Life tables. All were amenorrheic following the onset of their illness for at least three months and had no evidence of organic psychiatric disease, schizophrenia or severe depression.

An echocardiogram and electrocardiogram (11 patients), 24-hour ambulatory taped electrocardiogram (10 patients), and maximum exercise treadmill stress test (nine patients) were performed on entry to the study. Three patients had radionuclide cineangiograms at rest and with supine bicycle exercise. Blood pressure and heart rate were monitored in nine patients during 80° passive tilt. Following a program of psychiatric counseling and behavioral modification treatment, eight patients had a mean weight gain (fig. 1) of 32% (range 20%–77%). Repeat echocardiograms were obtained after weight gain in these eight; three individuals who refused continued participation in the program were not available for further study.

**Echocardiographic Techniques**

Echocardiograms were performed with a 2.25 MHz, 1.25 cm diameter unfocused Aerotech transducer, connected to a modified Echoline 20A or to an Hoffrel 201 ultrasound unit. The ultrasound signal was recorded continuously on light sensitive paper using a Honeywell 1856 Visicorder. Each patient was studied in the basal state in a supine position.

End-diastolic and end-systolic dimensions of the left ventricle were measured as the maximal and minimal distances, respectively, between the left side of the interventricular septum and the endocardium of the posterior free-wall. Measurements were made with the ultrasound beam passing through the left ventricle at or slightly caudal to the tips of the mitral leaflets. Ventricular septal and posterior left ventricular free wall thicknesses were measured both at and slightly below the level of the distal margins of the mitral valve leaflets before atrial systole (fig. 2). A switched-gain circuit was used to improve definition of the posterior wall thickness. The left atrial dimension was taken from a damped portion of the record as the maximum distance between the posterior left atrial wall and center of the posterior aortic wall (fig. 3) where the ultrasound beam traversed the aortic leaflets. The aortic root dimension was measured in the same portion of the record, taking the distance between the center of the anterior and posterior aortic walls at end-diastole (fig. 3). Percent fractional shortening of the echocardiographic minor axis and the left ventricular mass were calculated. Echocardiographic values were corrected for body surface area, calculated from body weight and height, using the Boothby and Sandiford modification of the Dubois nomogram. These corrected values were determined to be normal or abnormal using regression equations derived from a population of young, normal subjects without cardiovascular disease. Although a few patients exceeded the age range in that study, data obtained from an older normal population indicate that the regression equations used are applicable in these slightly older individuals as well.

Changes in echocardiographic measurements and derived data after weight gain were analyzed using the t test for paired values.

**Multistage Treadmill Exercise Testing**

Exercise testing was performed with continuous electrocardiographic monitoring of modified V5 and infero-posterior leads. The initial treadmill speed of 1.9 mph and inclination of 10° were increased every 2.5 minutes by 0.4 mph and 2°, respectively; peak inclination in any test was 20°. Blood pressure was measured by cuff at each exercise stage. Exercise was terminated by physical exhaustion.

**Tilt Table Response**

Nine patients were subjected to passive tilt. Blood pressure by cuff and heart rate on a continuously recorded electrocardiogram were determined at 0 and 80° tilt. Measurements were made after two minutes of sustained tilt or until serial determinations were stable.
Figure 2. Left ventricular dimensions in patient JW before (panel A) and after (panel B) 7.5 kg (21%) weight gain in six weeks. Note increase in end-diastolic (Dd) and end-systolic (Ds) left ventricular (LV) dimensions. Posterior left ventricular wall (LVW) and interventricular septal (IVS) thicknesses remain unchanged. RV = right ventricular cavity; ECG = electrocardiogram.

Figure 3. Left atrial (LA) and aortic dimensions (Ao) before (panel A) and after (panel B) weight gain in same patient as in figure 2. Note increase in left atrial dimension and smaller increase in aortic dimension after weight gain.
Radionuclide Cineangiography

Gated cardiac scintigraphy was performed in three patients at rest and during supine bicycle exercise using human serum albumin labeled with 10 mCi of radioactive technetium (99mTc) administered intravenously. Global ejection fractions were calculated by computer from the time-activity curves.15

Electrocardiograms

Twelve lead electrocardiograms were obtained in each patient on admission. The QT interval was measured in standard lead II from the onset of the Q wave (or the onset of the R wave if the Q wave was absent) to the end of the T wave; three to six beats were averaged. Our measured values were compared to the normal standards of Ashman and Hull.16 The QRS amplitude was judged to be diminished if the total amplitude was less than 0.5 mV in all three standard leads.17 Total electrical activity of the heart, estimated by summing the amplitude of leads I, AVF, and V1, was compared in three patients in whom electrocardiograms were available after weight gain.

Holter Monitoring

Ambulatory 24-hour electrocardiographic records on magnetic tape were obtained in 10 patients during normal ward activity. The playback was displayed in real time on a large screen oscilloscope for visual identification of ectopic beats and other dysrhythmia, which were subsequently tabulated by computer.

Results

Cardiac Dimensions Before Weight Gain

Patients with anorexia nervosa had smaller end-diastolic and end-systolic left ventricular dimensions, left atrial dimension, aortic root dimension, and left ventricular wall thicknesses (table 1) than published normal adult values.18 The left ventricular end-diastolic dimension, left ventricular wall thickness and aortic root dimension were below the normal mean value in all 11 anorexia patients. The left atrial dimension was below the mean in eight individuals. However, since standard errors of these normal data were not provided,18 statistical comparison could not be made. While the normal values described above were not corrected for body size, comparison (fig. 4) of cardiac dimensions in anorexia patients with body surface area adjusted normal data19,14 nonetheless show abnormalities. In four patients, the left ventricular end-diastolic dimension and left atrial dimension were at or below 95% predictive limits of normal; three of these evidenced ventricular arrhythmia. Only one of four patients with arrhythmia had left atrial or left ventricular end-diastolic dimensions which were within normal limits. Left ventricular wall thickness was below 95% predictive limits of normal in five patients. However, patients with arrhythmia were apparently evenly distributed as to wall thickness. The number of individuals with arrhythmias was not sufficient to allow statistically meaningful comparison of their cardiac dimensions with those anorexia patients free of arrhythmia.

Table 1. Cardiac Dimensions in Anorexia Nervosa Patients

<table>
<thead>
<tr>
<th></th>
<th>Left ventricular dimension (Diastole)</th>
<th>Left atrial dimension (Systole)</th>
<th>Aortic root dimension (Diastole)</th>
<th>Left ventricular wall dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>mean 47 mm</td>
<td>29 mm</td>
<td>27 mm</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>range (35–57)</td>
<td>(19–40)</td>
<td>(20–37)</td>
<td>(6–11)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>mean 38 mm</td>
<td>26</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>range (33–44)</td>
<td>(17–34)</td>
<td>(18–26)</td>
<td>(6–9)</td>
</tr>
</tbody>
</table>

*Eleven patients on initial study; three did not respond to therapy and did not have subsequent echoangiograms.
†Measurements obtained at the peak of the R wave yield values averaging 1% less than those obtained by methods used in this study.
‡Measurements obtained from the outer aortic wall to the left atrial wall yield values averaging 6% less than those obtained by methods used in this study.
§Measurements obtained from outer wall to outer wall of an undamped record, in late diastole yield values averaging 12% greater than those obtained by methods used in this study.

Figure 4. Cardiac dimensions in anorexia nervosa patients expressed as the percent difference from the predicted normal mean value, determined from a population of young, healthy subjects. Shaded area represents 95% predictive limits. Closed circles indicate patients who evidenced ventricular arrhythmia. LVDD = left ventricular end-diastolic dimension; LVW = average of interventricular septal and posterior left ventricular free wall thicknesses; LAD = left atrial dimension; Ao = aortic dimension.
Cardiac Dimensions after Weight Gain

In eight patients who had a mean weight gain (fig. 1) of 32% (range 21–77%), left ventricular end-diastolic dimension (fig. 5A), left atrial dimension (fig. 6A) and aortic dimension (fig. 6B), increased significantly ($P < 0.005$). Following weight gain in these eight patients, left ventricular wall thickness showed a small increase (fig. 5B) which did not achieve statistical significance. Left ventricular mass (fig. 5C) showed a mean 28% increase ($P < 0.005$), with a range of 5%–87%. The effect of weight gain on cardiac dimensions and left ventricular mass divided by body weight and body surface area is shown in table 2.

Left Ventricular Function

Left ventricular systolic function as estimated from the echocardiographic percent fractional shortening (mean 35.5% ± 1.1 SEM) was within 95% predictive
limits (28–45%) of normal individuals\textsuperscript{13, 14} and showed no significant change (mean 33.5\% \pm 1.5 \text{ SEM}) after weight gain. The mean resting ejection fraction estimated from radionuclide cineangiograms was normal in three patients before weight gain (mean 52\%, normal \geq 45\%), and increased appropriately with supine bicycle exercise (mean 64\%, normal \geq 55\%).

Heart Rate and Blood Pressure Response

The response of the systolic blood pressure and heart rate to maximal exhausting exercise was subnormal,\textsuperscript{15} with a mean increase in systolic blood pressure from 94 ± 10 to 127 ± 20 mm Hg and increase in heart rate from 74 ± 15 to 168 ± 10 beats/min. Body and axillary sweating were absent in these patients, despite normal ambient temperature, and their insistence on wearing moderately heavy clothing during exercise.

There was a normal 15–20\% increase in heart rate and variable systolic blood pressure response to 80\° of tilt, as has been noted in healthy individuals.\textsuperscript{20} Supine and standing heart rates and blood pressure before and after weight gain are shown in figure 7. Significant (\(P < 0.05\)) increases in supine and standing heart rate and supine systolic blood pressure occurred after weight gain.

Electrocardiographic Abnormalities

Exercise electrocardiography (table 3) demonstrated a short run of ventricular tachycardia (three ventricular premature beats in succession) during exercise in one individual; occasional ventricular premature beats during exercise were observed in three other patients. Twenty-four-hour Holter monitoring showed rare ventricular premature beats in the individual who had ventricular tachycardia demonstrated on exercise testing, and frequent multifocal ventricular premature beats, greater than 10 per hour, were documented in a patient who had ventricular premature beats induced with exercise.

The routine 12 lead electrocardiogram (table 3) showed an ectopic atrial focus in two patients who were identical twins. Sinus bradycardia less than 60 beats/min at rest was noted in five patients. Nonspecific repolarization changes, characterized by T wave flattening, were noted in only two individuals. Low voltage was not present in any anorexia patient; however, summed QRS voltage showed a 21\%–44\% increase (mean 29\%) in the three patients in whom repeat electrocardiograms after weight gain were available. Prolongation of the QT interval beyond the upper limits of normal was not observed in any anorexia patient.

Discussion

Our study shows that cardiac chamber dimensions and left ventricular mass may be decreased in patients with anorexia nervosa compared with normal adults.\textsuperscript{16} In addition, cardiac dimensions are small in some anorexia patients even after correction of these

<table>
<thead>
<tr>
<th>TABLE 2. Effects of Weight Gain on Cardiac Dimensions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before weight gain</td>
</tr>
<tr>
<td>Body weight (kg)\textsuperscript{-}</td>
</tr>
<tr>
<td>Body surface area (m\textsuperscript{2})</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Left ventricular mass/body weight (g/kg)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension (mm)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension/ body surface area (mm/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension/ body weight (mm/kg)</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
</tr>
<tr>
<td>Left atrial dimension/ body surface area (mm/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Left atrial dimension/body weight (mm/kg)</td>
</tr>
<tr>
<td>Aortic root dimension (mm)</td>
</tr>
<tr>
<td>Aortic root dimension/ body surface area (mm/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Aortic root dimension/ body weight (mm/kg)</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM.
*Data refer to the eight patients responding to therapeutic program. All derived functions were computed individually for each patient, and the mean values tabulated above.
N.S. = not significant.
values for body surface area. In 10 of the 11 patients both exercise testing and 24-hour electrocardiographic monitoring were performed; ventricular ectopy was detected in four of these. Three of the four patients, including one with a short run of ventricular tachycardia on exercise, and another with frequent multifocal ventricular premature contractions, had left ventricular end-diastolic dimensions which were below the 95% predictive limits for body surface area adjusted normal values. Of two other patients with a left ventricular end-diastolic dimension less than 95% predictive limits, no arrhythmias were evidenced, although one did not undergo exercise testing. It is tempting to speculate that an unusually small left ventricular end-diastolic dimension in anorexia patients allows identification of risk for ventricular ectopy and possible arrhythmic death. However, analysis of arrhythmia incidence and its echocardiographic correlates in a larger population of patients with anorexia nervosa would be necessary to validate this speculation.

Although starvation may be associated with heart

![SUPINE HEART RATE](image)
![STANDING HEART RATE](image)
![SUPINE SYSTOLIC BLOOD PRESSURE](image)

**FIGURE 7.** Heart rate (panels A and B) and systolic blood pressure responses to weight gain in anorexia nervosa. Circles and brackets indicate the mean ± SEM.

### Table 3. Electrocardiogram and Arrhythmia Screen

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Average QT (seconds)</th>
<th>Average QT U.L. (Ashman &amp; Hull)</th>
<th>Average QT mean (Ashman &amp; Hull)</th>
<th>QRS A (mV)</th>
<th>ST-T Abnormality</th>
<th>Rhythm</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>0.40</td>
<td>0.42</td>
<td>0.42</td>
<td>0.38</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>0.39</td>
<td>0.40</td>
<td>0.43</td>
<td>0.39</td>
<td>None</td>
<td>Ectopic atrial rhythm, VPCs; three in succession (E)</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>0.41</td>
<td>0.40</td>
<td>0.44</td>
<td>0.40</td>
<td>T wave flattening I, AVL, AVF</td>
<td>Ectopic atrial focus, VPCs (E)</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>0.37</td>
<td>0.44</td>
<td>0.37</td>
<td>0.34</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.36§</td>
<td>0.39§</td>
<td>0.41§</td>
<td>0.37§</td>
<td>1.7§</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>0.44</td>
<td>0.42</td>
<td>0.45</td>
<td>0.41</td>
<td>None</td>
<td>SB, VPCs (E)</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>0.44</td>
<td>0.37</td>
<td>0.49</td>
<td>0.45</td>
<td>None</td>
<td>SB, Frequent VPCs, (E,H); none after weight gain</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>0.41</td>
<td>0.43</td>
<td>0.42</td>
<td>0.38</td>
<td>None</td>
<td>Normal</td>
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<tr>
<td>8</td>
<td>22</td>
<td>0.40</td>
<td>0.39</td>
<td>0.45</td>
<td>0.41</td>
<td>2.1</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td>0.46§</td>
<td>0.41§</td>
<td>0.47§</td>
<td>0.43§</td>
<td>2.6§</td>
<td>SB</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>0.40</td>
<td>0.39</td>
<td>0.44</td>
<td>0.41</td>
<td>2.7</td>
<td>Diffuse T wave flattening SB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.39§</td>
<td>0.40§</td>
<td>0.42§</td>
<td>0.39§</td>
<td>3.9§</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>0.41</td>
<td>0.41</td>
<td>0.43</td>
<td>0.40</td>
<td>None</td>
<td>SB</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>0.40</td>
<td>0.41</td>
<td>0.42</td>
<td>0.39</td>
<td>None</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*QT calculated by dividing average QT by the square root of the RR interval.*

†Upper limits of normal (90th percentile) for females with the same heart rate as the patient listed.

‡Identical twins.

§Values after weight gain.

Abbreviations: E = detected on exercise testing; SB = sinus bradyarrhythmia; VPC = ventricular premature contractions; H = detected on ambulatory (Holter) monitoring; Δ = QRS amplitude summated in leads I, AVL, and V1, expressed in mV.
failure and histological abnormalities of the myocardium,21, 22 left ventricular systolic performance determined in our patients at rest by echocardiography, and by radionuclide cineangiography at rest and during supine exercise, was unimpaired. Furthermore, despite weight gain and an increase in the left ventricular enddiastolic dimension, the proportional shortening of the left ventricular minor axis (fractional shortening) was unchanged. Percent fractional shortening and ejection fraction are independent of body weight in normal individuals as well.13, 14

Since QT interval prolongation may be associated with sudden death,23 the description of QT interval prolongation in anorexia nervosa patients24 is of interest. However, we could not confirm this observation. The QT interval did not exceed the upper limits of normal as defined by Ashman and Hull in any of our patients and the ratio of the QT interval to the square root of the RR interval (QTc) was increased in only one individual. Reasons for this discrepancy between our data and those from another study24 may include different criteria for QT prolongation and different techniques for its measurement.

While the repolarization abnormalities, diminished resting heart rate and blunted chronotropic response to exercise in some patients might be consistent with direct cardiac involvement, cardiac mechanical performance is unimpaired. Although our data do not permit us to exclude myocardial abnormality, the absence of diaphoresis with heavy exertion, and the observation of decreased plasma norepinephrine levels at supine rest, after standing, and with handgrip26 in patients with anorexia nervosa before weight gain, provide indirect evidence consistent with autonomic or neuroendocrine abnormality as sources of the electrocardiographic and heart rate findings. This speculation is somewhat strengthened by the presence of endocrine-metabolic abnormalities referable to hypothalamic dysfunction in anorexia patients.

Apart from the importance of anorexia nervosa as a physically disabling psychiatric disease with high mortality, it offers a model for studying the pathophysiologic effects of nutritional deprivation in humans. While there are differences between the induction of anorexia nervosa and that seen in famine victims, the similarities are striking.2 Bradycardia, relative hypotension, amenorrhea, decrease in basal metabolic rate, relative hypothermia, hypocholesterolemia and abnormal skin pigmentation may be observed in both conditions. Some dissimilarities, such as the decreased physical activity, muscle weakness and edema noted in involuntary starvation, but less frequently in anorexia nervosa, may be the result of the extreme differences in the social and psychological environment.

Detailed observations of the effects of starvation and subsequent nutritional rehabilitation on normal volunteers were made by Keys and coworkers.26, 27 Following starvation they noted a decrease in systolic blood pressure, pulse pressure, resting heart rate, basal oxygen consumption and QRS amplitude. Starvation was associated with an increase in the absolute QT interval, but no change in the QT interval corrected for heart rate.27 Using roentgenkymography,28 decreases in systolic heart volume, stroke volume and cardiac output were observed after starvation. Following nutritional rehabilitation, all of these abnormalities approached control values. Relative changes in cardiac volume paralleled those of body weight. Similarly, proportional decreases in heart weight and body weight have been described in autopsy studies of famine victims,29-31 as well as in individuals who perished of starvation during the Nazi siege of the Warsaw ghetto in 1942.22 These data compare with our findings in anorexia nervosa, where left ventricular mass divided by body weight did not change significantly after weight gain (table 2), despite significant increases in the absolute left ventricular mass and the left ventricular mass normalized for body surface area (left ventricular mass index).

In conclusion, the self-induced starvation of anorexia nervosa is associated with a decrease in cardiac chamber size and estimated left ventricular mass. In some patients, including several with ventricular arrhythmia, cardiac chamber size and left ventricular mass were lower than would be predicted by the even diminutive body surface areas. These parameters increased after nutritional rehabilitation. In contrast, however, left ventricular systolic function is normal and remains unchanged after weight gain. Bradycardia, relative hypotension, ventricular dysrythmia and T wave abnormalities on the electrocardiogram occur in these patients and may be related to autonomic dysfunction.

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