

## Cardiac Disorders in Young Women With Anorexia Nervosa

Margarita Vázquez,<sup>a</sup> José L. Olivares,<sup>a</sup> Jesús Fleita,<sup>a</sup> Isaac Lacambra,<sup>b</sup> and Mariano González<sup>b</sup>

<sup>a</sup>Departamento de Pediatría, Hospital Clínico Universitario Lozano Blesa, Zaragoza.

<sup>b</sup>Servicio de Cardiología, Hospital Clínico Universitario Lozano Blesa, Zaragoza. Spain.

**Introduction and objectives.** The objective of this study was to compare heart abnormalities in young women with anorexia nervosa and in a control group of the same age and sex.

**Patients and method.** We report a matched case-control study of 30 adolescents with anorexia nervosa and 30 healthy women of the same age with normal weight. An electrocardiogram and echocardiogram were done. Heart parameters were measured on the electrocardiographic tracings, and QT dispersion was defined as the difference between maximum QT and minimum QT in any of the 12 leads. Diameter, mass and left ventricular mass index were measured.

**Results.** QT and corrected QT intervals were significantly greater in patients with anorexia nervosa than in the control group. QT dispersion and corrected QT dispersion were significantly greater in anorexia nervosa than in the control group (QTd,  $59.3 \pm 23.0$  vs  $38.4 \pm 8.0$  ms;  $p = 0.000$ ; QTcd,  $56.5 \pm 24.2$  vs.  $40.3 \pm 21.8$  ms;  $p = 0.011$ ). Left ventricular mass was significantly lower in young women with anorexia nervosa. We found a significant relationship between body mass index and left ventricular mass index, and between the former and corrected QT dispersion.

**Conclusions.** Adolescents with anorexia nervosa show significant cardiac disorders in comparison to healthy women of the same age. This finding may be a useful indicator of the risk of arrhythmia and sudden death in patients with anorexia nervosa.

**Key words:** Anorexia nervosa. QT interval. QT interval dispersion. Left ventricular mass.

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SEE EDITORIAL ON PAGES 652-3

Correspondence: J.L. Olivares López.  
Departamento de Pediatría. Facultad de Medicina.  
Universidad de Zaragoza.  
Domingo Miral, s/n. 50009 Zaragoza. España.  
E-mail: [olivares@posta.unizar.es](mailto:olivares@posta.unizar.es)

Received 4 November 2002.

Accepted for publication 21 February 2003.

### Alteraciones cardiológicas en mujeres adolescentes con anorexia nerviosa

**Introducción y objetivos.** El objetivo de este estudio es comparar las alteraciones cardiológicas de mujeres adolescentes con anorexia nerviosa con un grupo control de la misma edad y sexo.

**Pacientes y método.** Se trata de un estudio de casos y controles apareado en 30 mujeres adolescentes con anorexia nerviosa y 30 controles sanas de la misma edad y peso normal. Se les realizó electrocardiograma y ecocardiograma. Los parámetros cardiológicos fueron medidos sobre la superficie de los electrocardiogramas y la dispersión de QT fue definida como la diferencia entre el máximo y el mínimo QT de las 12 derivaciones. Se cuantificó el diámetro y la masa y el índice masa del ventrículo izquierdo.

**Resultados.** Los intervalos QT y QT corregidos fueron significativamente mayores en pacientes con anorexia nerviosa que en el grupo control. Las dispersiones del intervalo QT y del intervalo QT corregido fueron significativamente mayores en la anorexia nerviosa que en el grupo control (QTd,  $59,3 \pm 23,0$  frente a  $38,4 \pm 8,0$  ms;  $p = 0,000$ ; QTcd,  $56,5 \pm 24,2$  frente a  $40,3 \pm 21,8$  ms;  $p = 0,011$ ). La masa del ventrículo izquierdo fue significativamente menor en las mujeres con anorexia nerviosa. Existe una correlación significativa entre el índice de masa corporal y el índice de masa del ventrículo izquierdo y la dispersión del intervalo QT corregido.

**Conclusiones.** Las adolescentes con anorexia nerviosa presentan alteraciones cardiológicas significativas en relación con mujeres sanas de la misma edad. Dichos parámetros pueden ser indicadores útiles de riesgo de arritmia y muerte súbita en pacientes con anorexia nerviosa.

**Palabras clave:** Anorexia nerviosa. Intervalo QT. Dispersión del intervalo QT. Masa del ventrículo izquierdo.

### INTRODUCTION

Anorexia nervosa is an eating disorder characterized by voluntary restriction of food intake, leading to marked loss of weight, and which may even result in severe malnutrition and death. It mostly affects women

## ABBREVIATIONS

QTc: corrected QT interval.

between the ages of 12-25 years, with adolescence being the period of greatest risk. Almost 80% of patients have cardiovascular abnormalities, mainly bradycardia, hypotension, arrhythmias and repolarization disorders; sudden death has been reported in 10% of patients.<sup>1-6</sup> Special attention has been given over recent years to changes in the QT interval<sup>7,8</sup> and modifications of the myocardial mass and heart function detected by echocardiography.<sup>9-12</sup> The aim of this study was to compare heart abnormalities in young women with anorexia nervosa and a control group of healthy women matched for age.

## PATIENTS AND METHODS

### Patients and controls

This case-control study included 30 patients, all women, with anorexia nervosa, who had been referred by the psychiatry outpatient service of the hospital and who were admitted between 1 January 2001 and 30 August 2002. Their ages ranged from 12.1-18.5 years (mean, 15.5±1.6 years). Anorexia nervosa was defined according to DSM-IV of the American Academy of Psychiatry.<sup>13</sup>

The control group was composed of 30 matched healthy adolescents, mean age 15.5±1.6 years, of normal weight, who had been referred to the hospital for evaluation of an innocent murmur or functional chest pain. Controls were excluded from the study if they had a chronic disease, a family history of arrhythmia<sup>14</sup> or were receiving pharmacological therapy.<sup>15</sup>

### Electrocardiographic study

Standard 12-lead ECGs were obtained at a paper speed of 25 mm/s. Heart rate was calculated from the average RR interval of the tracings. Manual measurement of the QT interval was made in all leads from the start of the QRS complex to the end of the T wave on the iso-electric line. In the presence of a U wave, the end of the QT interval was considered to be the nadir between the T and U waves. Patients with bundle branch block were excluded. The corrected QT interval (QTc) was adjusted with Bazett's formula.<sup>16</sup> QTc was considered to be increased if it was greater than 440

ms. QT dispersion was defined as the difference between the maximum QT interval and the minimum QT interval in all leads. The QTc interval dispersion was the difference between the maximum and the minimum QTc intervals measured in the 12 leads.<sup>17-20</sup> Based on previous studies<sup>21</sup> and our own control group, the cut-off value was set at a dispersion of 60 ms. Holter monitoring was carried out according to the guidelines of the Spanish Society of Cardiology.<sup>22</sup>

### Echocardiographic study

All patients and controls underwent two-dimensional M mode echocardiogram and Doppler study, with the subject at rest in the left lateral decubitus position. Quantitative evaluation was made of the left ventricular end-diastolic diameter, the left ventricular end-systolic diameter, the interventricular septum thickness, the left ventricular posterior wall, the shortening fraction, the ejection fraction, the left ventricular mass and the heart mass index. Measurements were determined with standard techniques in accordance with the recommendations of the American Society of Echocardiography.<sup>23-25</sup>

### Statistical study

Data are expressed as the mean±standard deviation. The Kolmogorov-Smirnov test, with Lilliefors modification, was used to verify normality of the variables, and Student *t* test and Mann-Whitney U to compare differences between means with independent data, together with Spearman correlation index and regression line. Categorical variables were expressed as percentages and compared by  $\chi^2$  test and odds ratios (OR) were calculated with 95% confidence intervals (95% CI). Data were analyzed with the SPSS statistical software for Windows 10.0 (SPSS Inc.) and differences were considered significant if the *P*<.05.

## RESULTS

### Patient characteristics

Table 1 shows the main clinical characteristics, age, weight, body mass index (BMI) and heart rate of the young women with anorexia nervosa and the matched controls. Though there was no difference in age, the weight, BMI and heart rate were all significantly lower in the patients with anorexia nervosa than the controls.

### Electrocardiographic and echocardiographic results

Table 2 shows the electrocardiographic (QT interval, QTc, QT dispersion, QTc dispersion) and echocardiographic measurements (left ventricular end-

**TABLE 1. Clinical characteristics of the young women with anorexia nervosa and the control group of matched healthy women**

	Anorexia nervosa (n=30)	Control group (n=30)	P
Age, years	15.5±1.6	15.1±1.6	NS
Weight, kg	39.4±6.2	53.1±4.9	.000
BMI, kg/m <sup>2</sup>	15.3±2.1	20.3±1.3	.000
Heart rate, bpm	56.9±12.0	82.9±11.9	.000

The results are expressed as the mean±standard deviation.  
n indicates number of cases; NS, not significant; BMI, body mass index; bpm, beats per minute.

**TABLE 2. Electrocardiographic and echocardiographic measurements in young women with anorexia nervosa and healthy controls matched for age and sex**

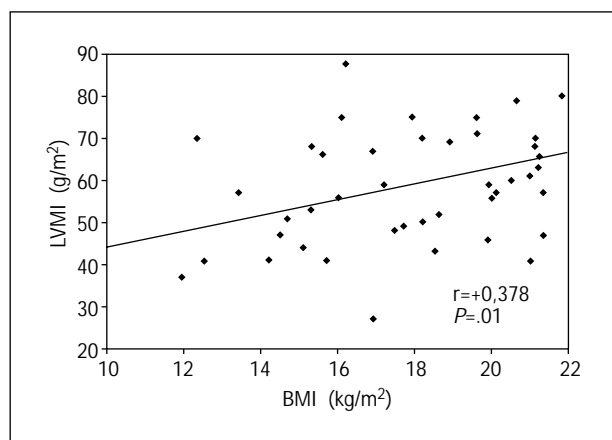
	Anorexia nervosa (n=30)	Control group (n=30)	P
QT, ms	438.6±36.2	360.0±20.0	.001
QTc, ms	436.3±35.5	391.4±24.3	.001
QTc>440 ms (N)	12/30 (40%)	0/30 (0%)	
QT dispersion, ms	59.3±23.0	38.4±8.0	.000
QTc dispersion, ms	56.5±24.2	40.3±21.8	.011
QTc dispersion>60 ms (N)	11/30 (36.7%)	2/30 (6.7%)*	
EDD, mm	41.9±4.3	44.9±3.8	.006
ESD, mm	25.3±2.8	27.8±3.5	.008
IVST, mm	6.1±1.1	6.9±1.0	.006
LVPW, mm	6.6±1.2	7.0±0.9	NS
Shortening fraction, %	39.6±4.3	38.4±5.3	NS
Ejection fraction, %	64.9±4.8	62.8±6.6	NS
Left ventricular mass, g	76.2±22.6	98.3±21.2	.001
Cardiac mass index, g/m <sup>2</sup>	53.9±14.4	64.0±12.4	.015

The results are expressed as the mean±standard deviation

\*Odds ratio=8.11; 95% confidence interval, 1.47-80.65; P=.01.

diastolic diameter, left ventricular end-systolic diameter, interventricular septum thickness, left ventricular posterior wall, shortening fraction, ejection fraction, left ventricular mass and cardiac mass index) of the patients with anorexia nervosa and the control group. The QT interval, QTc, QT interval dispersion and QTc dispersion in women with anorexia nervosa were all significantly greater than in the control group. The mean QTc in the anorexia group was 436.3±35.5 ms (range, 359-492 ms), with 12 (40%) patients having a QTc above 440 ms. The mean QTc in the control group was 391.4±24.3 ms (range, 342-426 ms) and no control had a QTc above 440 ms.

The dispersion of the QTc interval was wider in patients with eating disorders than in controls (56.5±24.2 vs 40.3±21.8 ms; P=.011). Eleven patients with anorexia had an increased QTc dispersion (above

**Fig.1.** Correlation between body mass index and left ventricular mass index.

60 ms) whereas only two of the control group had an increased QTc dispersion. There was a greater likelihood of arrhythmia in women with anorexia than in controls (36.7 vs 6.7%; OR=8.11; 95% CI, 1.47-80.65; P=.01).

The left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septum thickness, left ventricular mass and cardiac mass index were all significantly lower in patients with anorexia nervosa than controls. There were no significant differences in the left ventricular posterior wall, shortening fraction or ejection fraction.

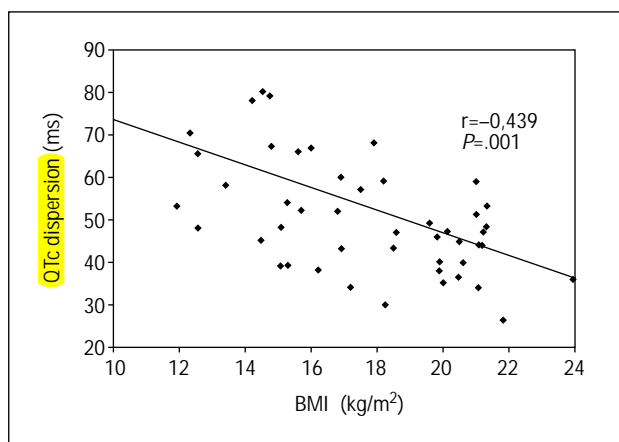
Figure 1 shows the correlation between BMI and left ventricular mass index, which was significantly positive ( $y=0.08x+13.32$ ;  $r=+0.378$ ;  $P<.01$ ).

Figure 2 shows the correlation between BMI and QTc dispersion, which was significantly negative ( $y=-0.07x+21.44$ ;  $r=-0.4396$ ;  $P<.001$ ).

## DISCUSSION

The process of slimming during anorexia nervosa leads to marked loss of muscle mass. This is further complicated by electrolyte and mineral disturbances induced by habitual use of emetics, laxatives and diuretics, and which result in loss of weight, exercise limitation, arrhythmia and possibly even sudden death.<sup>26</sup>

Arrhythmias, mainly acute bradycardia, are the best known cardiac disorders, and probably occur in response to the organism attempting to conserve energy by reducing cardiac output. Several different pathogenic mechanisms have been proposed, including electrolyte loss, drugs with adverse cardiovascular effects, reduction in the glycogen content of the heart cell, myofibrillar atrophy, interstitial edema, mitochondrial tumefaction and activation of calcium dependent proteinases.<sup>27,28</sup>



**Fig. 2.** Correlation between body mass index and heart rate corrected QT interval dispersion.

### QT interval and interval dispersion

Most of the patients with anorexia nervosa in this study had arrhythmias in the form of manifest bradycardia, frequent atrial extrasystole, occasional ventricular extrasystole and significantly **increased QT and QTc intervals** compared to healthy women of the same age. These findings are similar to those reported by others.<sup>8,29</sup>

An important finding of the study was the fact that young people with anorexia nervosa had a significant increase in QT interval dispersion and a reduction in cardiac chamber size and left ventricular mass compared to the control group, both in absolute figures and relatively after adjusting for body mass. These results are similar to those reported by Galetta et al<sup>12</sup> and Swenne and Larsson,<sup>8</sup> who showed that weight loss in adolescents with anorexia nervosa and eating disorders is a risk factor for prolongation and dispersion of the QT interval.

### Correlation between body mass index, left ventricular mass index and QT interval dispersion

A significant positive correlation was seen between BMI and left ventricular mass index, demonstrating that weight loss is accompanied by a reduction in left ventricular mass, as mentioned by Conri et al.<sup>11</sup> There was also a significant negative correlation between the QTc interval dispersion and BMI in patients with anorexia nervosa.

**An increase in QT interval dispersion on ECG represents regional differences in myocardial recovery of excitability and may give rise to a greater arrhythmogenic substrate, with the corresponding increased risk of clinically important ventricular arrhythmia and sudden death.** In fact, increases in QT

interval and QT dispersion have been related to a greater risk of ventricular arrhythmia in patients with coronary heart disease and healthy subjects. **The predictive value of increased dispersion of the QT interval as a marker of acute ventricular arrhythmia or sudden death has been demonstrated.**<sup>5,6</sup>

The relation between BMI and left ventricular mass index in anorexia nervosa suggests that the reduction in left ventricular mass may be responsible for the increase in QT interval dispersion. This increase in QT interval dispersion may also be explained by histologic changes and alterations of the cardiac muscle fibers. Indeed, changes in orientation, structure or geometry of the muscle fibers and the collagen network or variations in myocardial blood flow or water content, as described in hypotrophic hearts in states of malnutrition, may be the basis of a non-homogenous repolarization. This is also the case in hypertrophic heart disease.<sup>30</sup> An increase in workload may produce ECG changes suggestive of myocardial ischemia and increased duration and dispersion of the QT interval.<sup>31</sup>

Another possible mechanism influencing increased QT dispersion is alteration of ion channels, active in cardiac repolarization. Alterations have been seen in potassium channels of hypotrophic myocytes with prolongation of the action potential. A further explanation may be the presence of a greater amount of fibrous tissue and an alteration of homogenous ventricular recovery. Autopsy studies have shown myocardial degeneration, myocytolysis, mononuclear infiltrate, fat infiltrate and substitution of muscle tissue for collagen.<sup>32,33</sup>

### Conclusions and clinical implications

Our study suggests that patients with anorexia nervosa have important cardiologic alterations and a greater probability of arrhythmia than healthy adolescents of the same age. Systematic monitoring of the parameters mentioned above may detect the development of acute arrhythmia and the risk of sudden death in these patients.

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