The 12-Lead Electrocardiogram in Anorexia Nervosa: A Report of 2 Cases Followed by a Retrospective Study

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Abstract: Anorexia nervosa (AN) has been associated with various cardiac disorders and several electrocardiographic abnormalities, the most prominent being sudden death and prolonged QT duration and dispersion. We report 2 cases of AN with marked repolarization abnormalities, the first clearly related to electrolyte imbalance, the second without a good explanation from metabolic, electrolytic or pharmacological sources. A retrospective analysis of 47 other consecutive patients with AN showed that sinus bradycardia was the most common ECG finding, but that QT or QTc interval prolongation was not a typical feature, being present in only 1 patient. The sole variable slightly correlated with QTc duration was the serum potassium concentration. Consequently, marked repolarization changes (QT interval and/or T wave morphology) in AN should not be taken as a feature of the disease, but should call for the search of potential causes such as metabolic and electrolytic disturbances, drug effects, or a possible genetic component. **Key words:** Anorexia nervosa, electrocardiogram, QTc duration.

Anorexia nervosa (AN), the most common and serious of eating disorders, has been associated with various cardiovascular complications, including hypotension, impaired myocardial performance, mitral valve prolapse and sudden death (1). Several electrocardiographic abnormalities have been described in patients with AN, eg, bradycardia, right axis deviation of the QRS complex, low QRS, P and T wave voltages, ventricular tachyarrhythmias and lengthening of the QT interval (2,3). So far, there have been conflicting results concerning the association between AN and QT interval changes. The study of the QT interval in patients with AN was motivated by several reports of sudden death preceded by QT interval prolongation and documented as being caused by terminal ventricular tachyarrhythmias such as torsade de pointes (4).

Here we report on 2 women with AN, presenting with definite repolarization abnormalities, due in one patient to a plausible mechanism, but in the other without a clear explanation. These 2 cases prompted us to undertake a retrospective study of the ECGs of 47 other patients who had been taken care of because of AN in our department of internal medicine.

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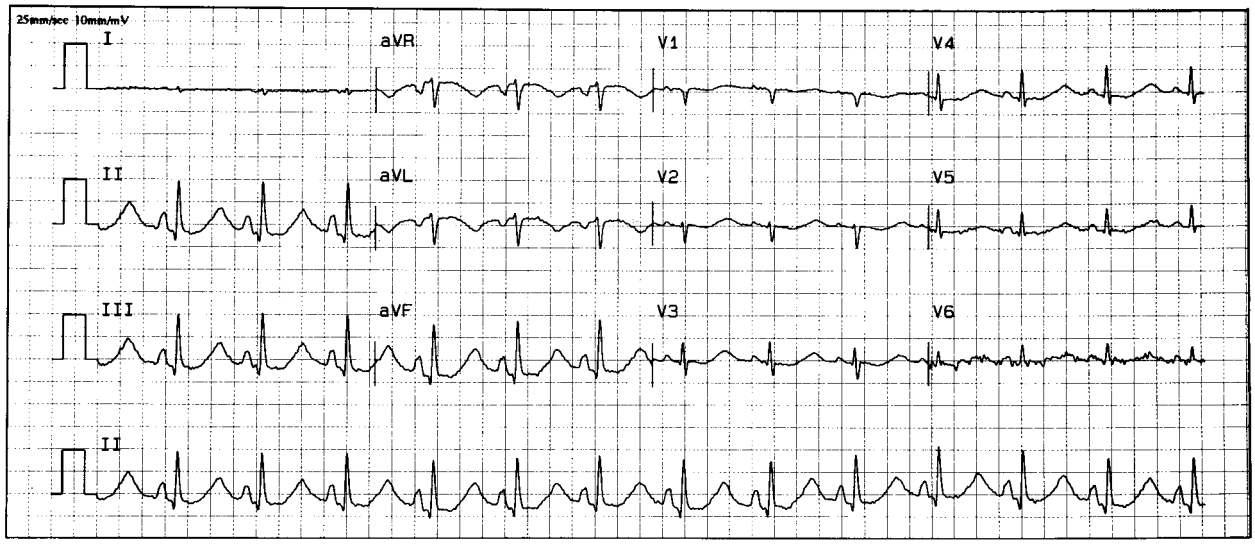

Fig. 1. Case #1. ECG at admission: the main feature is QT interval prolongation (QT = 525 ms, QTc = 594 ms).

Case Reports

The first patient was a 42-year-old woman hospitalized for malnutrition associated with a long-lasting AN. She had already been hospitalized for the same reason 3 months before. The eating disorder had been present for more than 30 years. She also had severe chronic obstructive lung disease and emphysema secondary to cigarette smoking. At the time of admission, her weight was 32.5 kg, the height was 169 cm and the body mass index (BMI) was 11.6 kg/m^2. The weight loss has been estimated as minus 9 kg over the 3 months after the preceding hospitalization. The blood pressure was low: 80 mmHg of systolic blood pressure in supine position, 60 mmHg in standing position. There were no signs of congestive heart failure. The patient was taking psychotropic drugs of the phenothiazine class but received no tricyclic antidepressants.

The admission 12-lead ECG is shown in Figure 1: there was a normal sinus rhythm of 78 bpm, a reduced R wave amplitude in leads V1 and V2, a right axis of the QRS complex in the frontal plane (+90°), peaked P waves in inferior leads suggesting right atrial overload possibly related to a status of chronic obstructive pulmonary disease and prolonged QT interval, although a superimposed U wave onto the T wave could not be ruled out. The "QT" or "QU" interval was measured at 525 ms and the QTc interval would be at 594 ms according to the Bazett's formula (5). The concomitant measurements of serum electrolytes (normal range: NR) were as follows: sodium 116 mmol/L (NR = 135-145); potassium 2.35 mmol/L (NR = 3.5-5.0); calcium 8.15 mg/dL (NR = 8.8-10.4); albumine 2.5 g/dL; phosphate 1.40 mg/dL (NR = 2.2-4.4) and magnesium 1.40 mEq/L (NR = 1.45-1.90).

An oral refeeding was undertaken resulting in a weight gain of 12.5 kg (from 32.5 to 45 kg) in 2 weeks. Figure 2 shows the 12-lead ECG after the weight gain (BMI = 13.2 kg/m^2) and after the correction of electrolyte imbalance (serum sodium raised to 136 mmol/L, potassium to 3.80 mmol/L, calcium to 8.8 mg/dL, phosphate to 3.3 mg/dL, magnesium to 1.50 mEq/L). The sinus rhythm was 63 bpm. There was still low voltage and a right QRS axis but the QT interval had returned to normal values: 416 ms for the QT and 426 ms for the corrected QT interval. So, in this patient, the electrocardiographic changes of the repolarization phase were clearly explained by the denutrition status, the serum electrolyte abnormalities, or by both mechanisms.

The second case was a 14-year-old girl hospitalized in our department with the diagnosis of AN. Her weight loss caused by a hypocaloric diet amounted to 11 kg in 2 months. The weight at admission was 39 kg, the height 156 cm and the BMI 16.2 kg/m^2. The physical examination was normal except for a low blood pressure at 90/60 mmHg in supine position. The electrocardiogram (ECG) at admission (Fig. 3) showed a marked sinus bradycardia at 41 bpm and pronounced repolarization abnormalities: biphasic T waves (negative-positive) from leads V1 to V4 with a slow return of the positive component to the baseline best seen in lead V4, apparently prolonged ST segment best seen in inferior leads II, III, aVF, and probably prolonged QT interval (QT of about 500 ms,

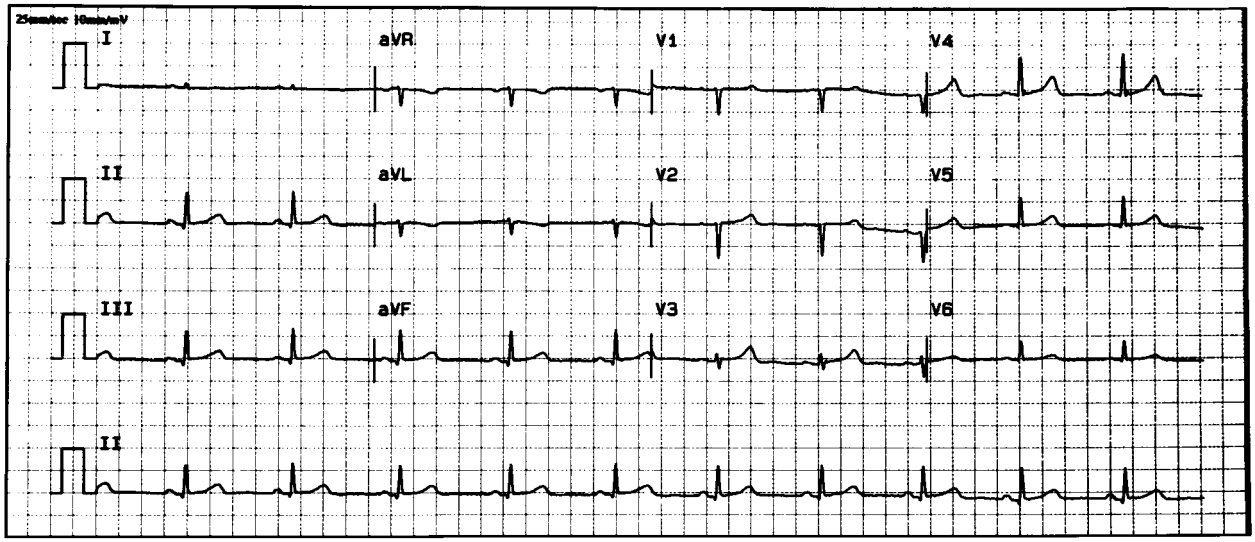

Fig. 2. Case #1. ECG recorded after correction of the electrolyte disturbances: there is complete normalization of QT interval (QT = 416 ms, QTc = 426 ms).

QTc of 410 ms) but with the difficulty of the exact location of the end of the T wave in lead V4 as compared with the other precordial leads. This pattern was different from that of the "Juvenile pattern," which consists of negative T waves in the right precordial leads V1-V4, without distortion of the shape of T waves nor QT prolongation. Two days later, the ECG (Fig. 4) showed a somewhat faster heart rate (54 bpm) with sinus arrhythmia, persistent repolarization abnormalities with biphasic T wave in leads V1 to V3 and seemingly prolonged QT interval. However, because of the inherent difficulty in precisely locating the T wave offset, the QT dispersion across the 12 leads varied from 39.5 to 146.6 ms according to the different end-points proposed for the T wave offset in the six precordial leads.

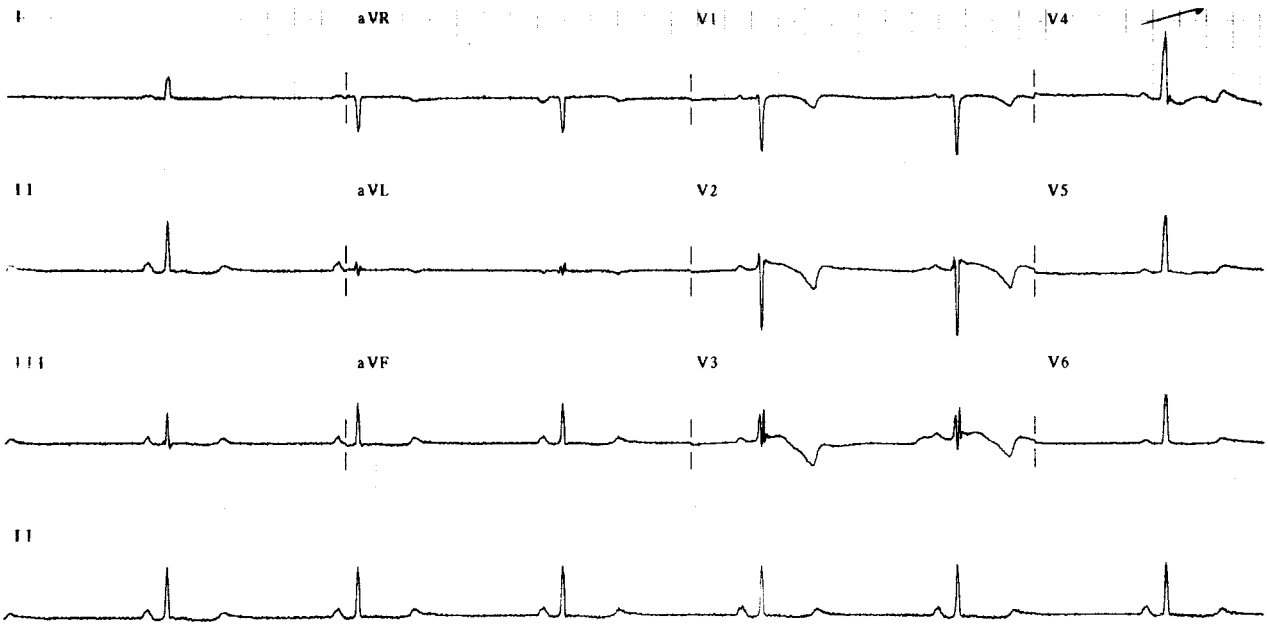

Fig. 3. Case #2. ECG at admission: there are marked repolarization abnormalities with biphasic T waves (negative → positive) in precordial leads, prolonged ST segment and prolonged QT interval (497 ms), although the QTc is normal at 410 ms.

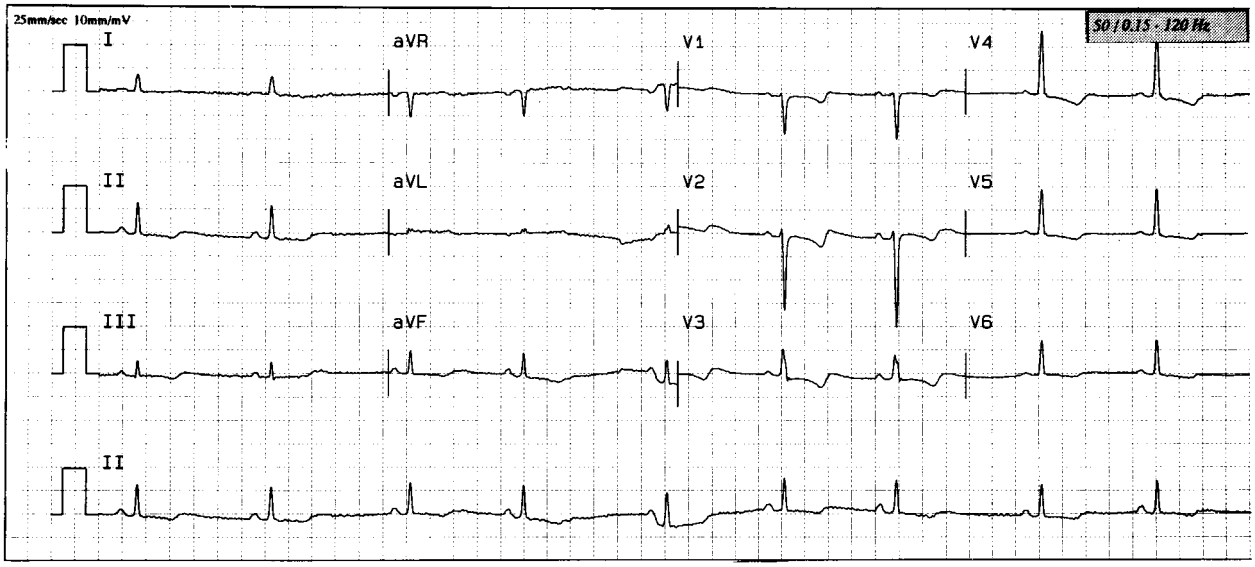

Fig. 4. Case #2. ECG recorded two days later: unchanged repolarization abnormalities. Because of the strange pattern of the T wave, it is difficult to locate the T offset.

An exercise test on bicycle ergometer was performed (Fig. 5): the maximal workload reached was 140 watts and the maximal heart rate was 156 bpm. In the three Frank orthogonal leads at rest, the sinus rate was 57 bpm and the QT interval was measured as 450 ms, with the prolongation occurring mainly at the expense of the ST segment. During exercise, there was an apparent shortening of the QT interval along with the faster heart rate, but the length of the ST segment remained prolonged. The VO_2 max reached 27.1 mL/kg/min corresponding to 73.6 percent of the maximal physical capacity. A 24-hour Holter recording revealed a mean heart rate of 52 bpm, ranging from 36 to 111 bpm; there were no premature beats but numerous episodes of sinus bradycardia (N = 526) and nonspecific repolarization changes (Fig. 6). These electrocardiographic features could not be related to any electrolyte imbalance: the serum sodium concentration was 146 mmol/L, serum potassium varied from 4 to 5.05 mmol/L, serum calcium was 9.75 mg/dL, serum phosphate was 3.70 mg/dL and serum magnesium was 1.80 mEq/L, all these values being within normal limits. Furthermore, the patient was not taking any psychotropic drug.

Retrospective Study

The aim of this study was to retrospectively analyze the electrocardiograms, more particularly the repolarization, of a cohort of consecutive patients with AN, and to correlate the ECG findings with anthropometric and biological characteristics.

Methods and Patients

The study population consisted of 47 patients with AN, 45 women and 2 men, with a mean age of 22 years, ranging from 13 to 45 years. These patients met the diagnostic criteria of AN according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (6). The mean body mass index was 14.7 $\pm$ 2.68 kg/m^2. Laboratory findings around the time of ECG recording were available in the majority of patients. All electrocardiograms were recorded on the same day as the laboratory work-up, except for 9 patients. In seven of these patients, there was a maximum of four day difference between the blood sample and the ECG recording. In the two remaining patients, there was a 7 day and a 14 day difference, respectively, but these patients had stable serum ionic values within the normal range. In all patients, the ECG was recorded before the correction of electrolyte abnormalities. Psychotropic drugs were taken by 13 patients, mostly antidepressant of the class of serotonin uptake inhibitors and benzodiazepines. No patient received tricyclic antidepressant. Four patients acknowledged the chronic use of laxatives. Thus, the clinical characteristics of this cohort were not different from the cohorts examined in other studies.

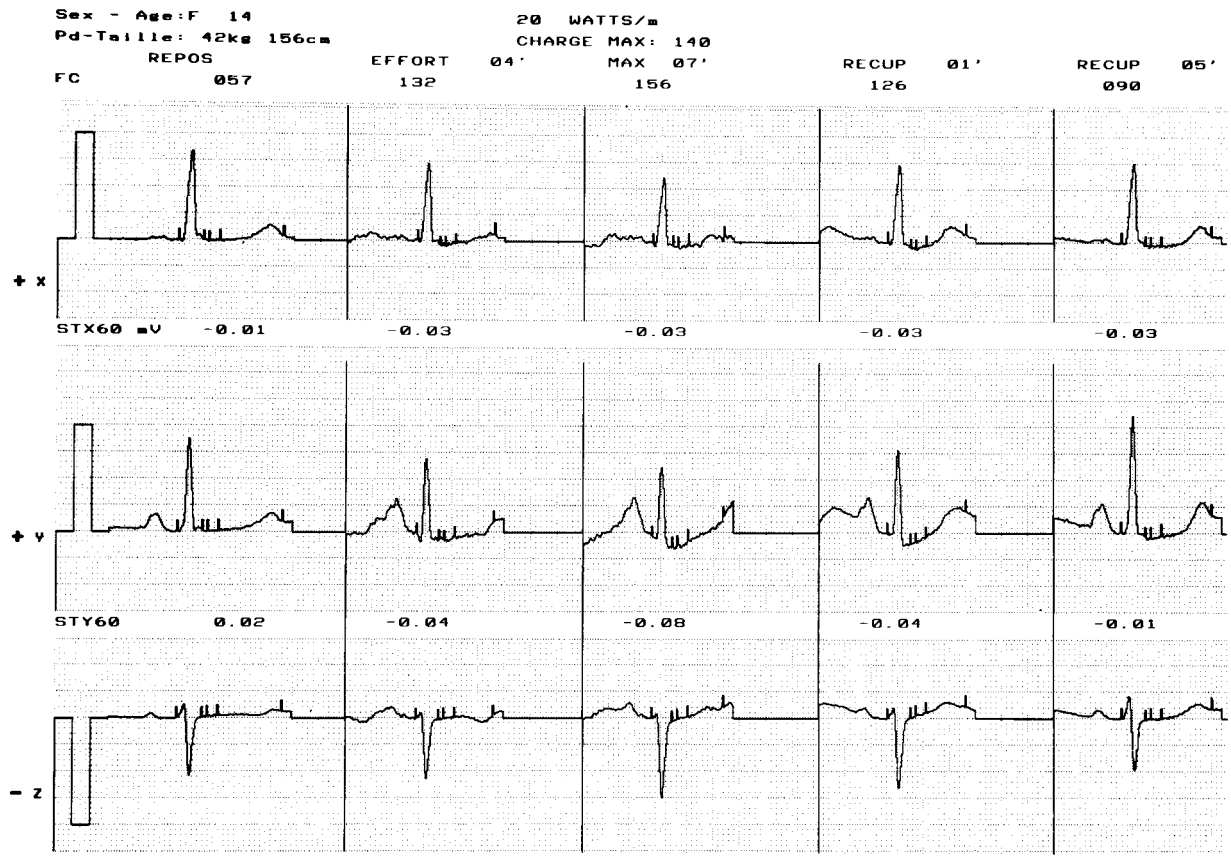

Fig. 5. Result of the maximal exercise test. Representation of the averaged P-QRS-T complex in the X, Y, Z Frank orthogonal leads at rest (first column), at mid-exercise (second column), at maximal exercise (third column), and during recovery (fourth and fifth columns). There is a shortening of the QT interval along with the faster heart rate (from 57 bpm to 156 bpm) but the ST segment remains prolonged.

The 12-lead ECGs were recorded by means of three types of computerized ECG carts: Nihon-Kohden ECAPS12, Marquette MAC12 and Cardiologic 15 from the Cardionics company. The measurements and diagnostic interpretations provided by the constructor's software were edited and validated by two of the authors (OV and CB). Special care was applied to the ventricular repolarization analysis, especially the measurement of the QT interval and T wave morphology. The end of the T wave was identified as being the crossing point of the descending limb of the T wave with the baseline by means of the tangent method. In the presence of a U wave, the end of the T wave was considered as the nadir of the curve joining the terminal segment of the T wave and the initial segment of the U wave. The QT interval was measured from the onset of the QRS complex to the T wave offset and the longest interval among the 12 leads was considered as the most likely correct. The QT interval was corrected according to the heart rate by means of the Bazett's formula ($QTc = QT/\sqrt{RR}$) (5). A prolonged QTc interval was defined as a value equal to or greater than 430 ms in adult men, 450 ms in adult women and 440 ms in the pediatric age group (1-15 years) (7).

Results

Table 1 shows the anthropometric data and ECG results, along with the blood pressure and laboratory data of the patients. Mean weight was 40 kg, mean height 161 cm and mean BMI was 14.7 ± 2.68 kg/m^2. Mean systolic and diastolic blood pressure values were 99 and 64 mmHg, respectively. Mean serum sodium concentration was 139 ± 4.4 mmol/L (range, 128-146). Serum potassium averaged 3.7 ± 0.5 mmol/L. Thirteen patients (27%) had a serum potassium level under the lower normal limit of 3.5 mmol/L and five patients (10%) had values below 3 mmol/L. Serum calcium concentration was 9.6 ± 0.6 mg/dL with only two

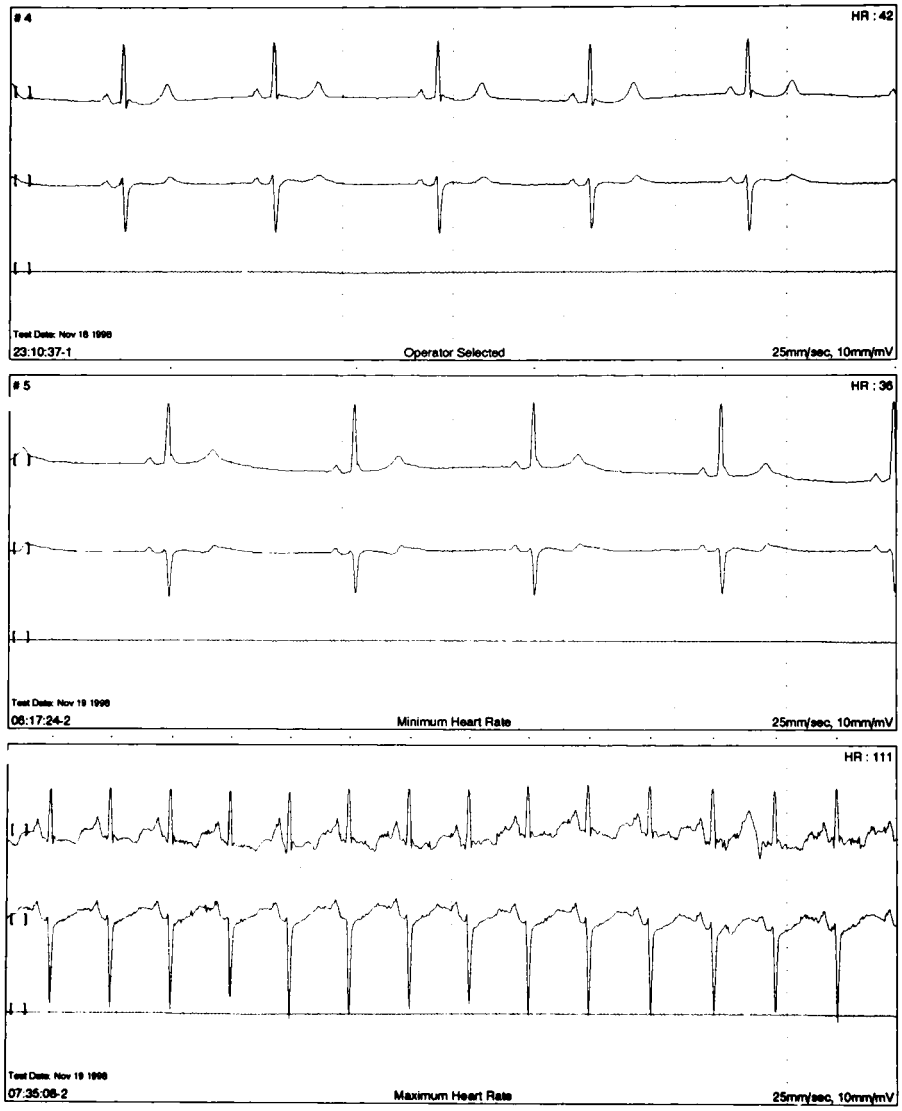

Fig. 6. Excerpts of the Holter recording during low heart rate (upper panel: 43 bpm and mid panel: 37 bpm) and fast heart rate (lower panel: 115 bpm). There is long ST segment (upper panel) and nonspecific ST depression with biplasic T wave (lower panel).

patients having values below the lower normal limit of 8.8 mg/dL. Serum phosphate level was 3.5 ± 0.6 mg/dL. Serum magnesium level was 1.7 ± 0.2 mEq/L with only 3 cases (6%) having a value below the lower normal limit of 1.45 mEq/L.

Among ECG data, sinus bradycardia defined as a heart rate lower than 60 bpm was the most frequent electrocardiographic feature, found in 38 of the 47 patients (81%). Twenty-two patients (47%) had a sinus bradycardia equal to or lower than 50 bpm, four patients (8.5%) had a marked sinus bradycardia under 40 bpm, the lowest heart rate being 33 bpm in two patients. An ectopic atrial focus was the dominant rhythm in 4 patients, a short PR interval (less than 120 ms) was present in 4 patients and there was a single case with of a first degree AV block (PR interval greater than 0.20 s). No other rhythm abnormality was observed in this

Table 1. Anthropometric, Clinical, and Electrolyte Values—QT Interval Values

	Mean	SD	Min	Max
Age (year)	22	8.2	13	45
Weight (kg)	39.8	7.1	27.5	60
Height (m)	1.61	0.25	1.47	1.87
BMI (kg/m^2)	14.7	2.7	11.9	21.9
SBP (mmhg)	99.3	17.3	70	145
DBP (mmhg)	64.5	13.6	40	100
Na^+ (mmol/L)	139.2	4.4	128	146
K^+ (mmol/L)	3.7	0.5	2.6	6.1
Ca^{++} (mmol L)	9.6	0.6	8.5	10.7
Phosph (mmol/L)	3.5	0.6	2.2	4.4
Mg (mEq/L)	1.7	0.2	1.4	2.0
QT (ms)	412.7	44.4	296	488
QTc (ms)	381.5	30.3	320	450

BMI, body mass index; Na^+, serum sodium concentration; K^+, serum potassium concentration; Ca^{++}, serum calcium concentration; Phosph, serum phosphor concentration; Mg, serum magnesium concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure.

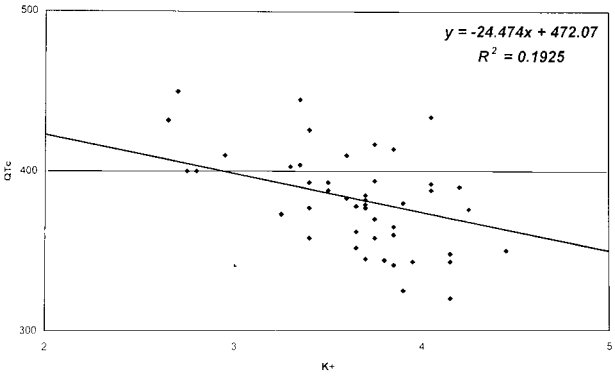

Fig. 7. Regression analysis of the QTc interval measurements (ms) on the ordinate against the serum potassium (K^+) values (mmol/L) on the abscissa. The R value in −0.44 ($P < .05$).

cohort. The next most frequent ECG feature was nonspecific repolarization changes, mostly flat T waves, seen in 9 patients.

A rightward orientation of the mean QRS axis in the frontal plane (more than +90°) was found in 8 patients but the most extreme value did not exceed +110° in 2 patients.

The mean QT interval was 413 ms and the mean QTc interval was 381.5 ms. The QTc was within normal limits in 46 of the 47 patients. In this series, a single patient, an 18-year-old woman, had a QTc value which was exactly at 450 ms, the upper normal limit for an adult woman. This patient had a marked hypokalemia with a serum potassium level at 2.7 mmol/L, and among other abnormal ECG features, an intraventricular conduction defect (QRS duration of 120 ms) and the presence of a prominent U wave.

The 2 ECG variables QT and QTc intervals were then correlated with each of the anthropometric and laboratory variables. The only significant correlation ($P < .05$) was between QTc and serum potassium level ($R = -.44$) (Fig. 7). There was no correlation ($R = .08$) between QT and QTc interval durations and BMI. However, we were unable, because of the retrospective nature of the study, to ascertain in all patients the final rate of weight loss in the weeks preceding the ECG recording. Figure 7 shows the scattergram of the QTc values plotted against the serum potassium level.

Discussion

AN is a serious illness bearing several cardiovascular risks, the most severe being sudden death which has been documented to be caused by malignant ventricular arrhythmias at least in some cases (4,8). Observations of a prolonged QT interval with subsequent ventricular polymorphic tachycardia have been reported in patients with rapid weight loss due to a lipid-protein fasting diet. Postmortem pathological analyses of the myocardium have revealed mononuclear inflammation of the interstitium affecting nerves and ganglions, and increased deposition of lipofuscin in the myocardial cells. Cardiovascular changes include diminished ventricular mass and chamber dimensions although left ventricular function may be preserved (9-11). However, some authors have reported evidence for myocardial dysfunction, both systolic and diastolic (12,13). Clinical heart failure may occur in the early stages of the refeeding period, probably because of the exacerbation of hypomagnesemia. The risk of heart failure is reduced by using a gradual realimentation and avoiding high salt intake (1). Left ventricular dysfunction as well as an increase of afterload may also be responsible for heart failure. Hypotension is a common feature in patients with AN. Exercise capacity is usually reduced, being probably more related to peripheral muscle wasting than to cardiac dysfunction. Mitral valve prolapse is also a common finding. The prolapse might be caused by an imbalance between myocardial atrophy and preserved integrity of the subvalvular apparatus (14).

Electrocardiograhic abnormalities in AN include sinus bradycardia or tachycardia, low voltage of P waves and QRS complexes, rightward QRS axis, nonspecific ST-T changes, presence of U waves, conduction disturbances, and QT interval prolongation and increased dispersion (1). The most commonly reported abnormality is sinus bradycardia which was also the predominant feature in our series, present in 81 percent of the cases with a minimal daytime value of 33 bpm in 2 patients. This sinus bradycardia probably reflects vagal hyperactivity (15). Less frequent features in our series included ectopic atrial focus (N = 4), mild right axis deviation (N = 8), and nonspecific ST-T changes, mostly flat T waves (N = 9).

Since sudden death has been reported in some patients with AN, possibly as a consequence of malignant ventricular tachyarrhythmias, particular attention has been drawn on the repolarization analysis, especially on the prolongation of the QT interval. There have been conflicting reports in the literature concerning the link between AN and lengthening of the QT interval. Isner et al reported a long QT interval in three anorectic patients who died suddenly and whose QTc values were 460,

470, and 610 ms, respectively. Two of these three patients had documented ventricular tachyarrhythmias, including torsade de pointes in one case (4). Thurston and Marks (16) reported a long QT interval in 5 of 9 anorectic patients which was unexplained by electrolyte abnormalities or drugs. Similar findings were reported by Palla and Litt (17) and Durakovic et al. (18) who found a long QT interval in about one third of their patients. Other authors failed to show a high prevalence of prolonged QT interval in patients with AN. Gottdiener et al. (10) found a normal QT interval in 11 anorectic patients, but in their study the QT interval was measured only in lead II whereas the longest QT interval is usually seen in the right precordial leads, mainly lead V2. Also, Dec et al. (9) and Powers et al. (19) reported normal QT intervals in patients with AN. In our series, the mean QT interval (413 ± 44 ms) and QTc interval (381.5 ± 30 ms) were within normal limits for the age and sex. A single patient had a QTc value of 450 ms, which was exactly the upper normal limit for adult women. This patient had a marked hypokalemia (2.7 mmol/L) which could explain her mild QTc prolongation.

Of course, these discrepancies in the assessment of the QT and QTc interval prolongation in AN among various studies may party arise from differences in the methodology used for the measurement of the QT and QTc intervals. In most studies, the QT interval measurement is based on a manual method using a paper speed of 25 mm or 50 mm per second. In cases with a slow return of the T wave toward the baseline, the determination of the true end of the T wave might paradoxically be more difficult with a paper speed of 50 mm/s. Our method was relying on computer-assisted assessment of the QT and QTc intervals, including a digital recording of the leads, presentation of the paper tracing at 25 mm/s, verification of the computer output and, if necessary, manual editing by means of a calliper and a magnifying glass. However, as in previous studies, the use of the Bazett's formula for heart rate correction of the QT interval might have undercorrected the value at slow heart rates, which is actually a common finding in patients with AN.

Finally, differences between various studies may arise form differences in the definition of "normal" limits for QT and QTc intervals. We have used a recently proposed QTc classification adjusted for age and gender in adult women, adult men and in the pediatric age group (7).

The causes for the hypothetical QT prolongation in some patients with AN remain debated. The usual causes of a long QT are the effect of drugs, metabolic and electrolytic disturbances (hypokalemia, hypocalcemia, hypomagnesemia), the congenital long QT syndrome, myocardial ischemia, subarachnoid hemorrhage, complete heart block, mitral valve prolapse and status after cardiac resuscitation. In a recent study, Cooke et al. (20) showed in 41 consecutive patients with AN, compared to 28 age- and sex-matched normal controls, that the QT interval was longer in patients with AN and that there was a tendency toward reversion to normal after refeeding. Actually, the QT interval was above the upper normal limit in 6 patients (15%) 2 of whom died suddenly. Serum calcium and magnesium concentrations were normal in all their patients, and serum potassium was below the normal range in six patients (15%) of whom two had a QT interval exceeding the upper normal limit. In another study of 30 AN patients compared to 30 controls, Durakovic et al. (18) found no correlation between serum potassium level and the longest QTc interval. Neither was there a correlation between the QT interval and the body mass index. Similarly, in our series, there was no correlation between QT and QTc values and the anthropometric data. Only a weak correlation was found between QTc value and a low serum potassium level (Fig. 7). Recently, Swenne et al. (21) reported interesting findings in a pediatric population with eating disorders: they examined the risk factors for QT prolongation in 58 young anorectic females (from 11 to 19 years of age) and found a QTc duration above 440 ms in 45% of the patients. The QTc dispersion in the patients was almost twice that of the controls. By stepwise linear regression analysis, they showed that three independent factors were influencing QTc duration and QTc interval dispersion, namely a low BMI, the final rate of weight loss and the serum sodium concentration. Other potential causes of repolarization abnormalities in AN, including QT interval prolongation and increased dispersion, have been postulated. Structural changes in the myocardium might offer an explanation: focal mononuclear infiltrates have been described in the conduction system of patients with long QT intervals associated with restrictive dieting. Autonomic imbalance has also been evoked as a potential cause of QT prolongation in AN, as a result of hypothalamic dysfunction. According to Isner (4), the autonomic nervous system might be the link between head and heart in AN. Another level of autonomic disorder is the imbalance of the sympathetic innervation of the heart with, as a consequence, an enhanced susceptibility to sympathetic activity, which in turn might lead to malignant ventricular

arrhythmias. As exercise induces activation of the sympathetic system with prolongation of the QT interval, it is therefore recommended to discourage heavy exercise in anorectic patients. Harris et al. (22) have reported a case with paradoxical prolongation of the QT interval under isoproterenol infusion administered to a 17-year-old boy with AN and profound sinus bradycardia. Autonomic imbalance was suggested as the mechanism of this paradoxical QTc interval lengthening. Consequently, these authors suggested that in patients with AN and severe sinus bradycardia, chronotropic support should be avoided, unless signs of low cardiac output attributable to the bradycardia develop.

Our two case reports shed some light on the various possible causes of repolarization abnormalities in patients with AN. In the first patient, the long QT and QTc values were clearly related to electrolyte disturbances including severe hyponatremia and hypokalemia, as well as significant hypocalcemia, hypophosphoremia and hypomagnesemia. The proof of this causal relationship was provided by the quick and complete normalization of the ECG after correction of these electrolyte abnormalities during the refeeding period.

In the second patient, although there were no significant electrolyte abnormalities, marked repolarization changes were observed including modified T wave morphology, prolongation of the QT interval at the expense of the ST segment, and difficult location of the end of the T wave leading to uncertain calculation of the QT and QTc duration and dispersion. The reasons for these repolarization changes remained unknown. The patient had no family history of long QT syndrome or sudden death. One might speculate about a link between the rate of weight loss and some metabolic disturbances, without discarding a possible influence of an underlying genetic component. Indeed, several authors have speculated whether some cases of acquired long QT syndrome might be a variant of the congenital long QT syndrome where a subclinical abnormality in a specific ionic channel would require exposure to pharmacologic agents or to metabolic disturbances to become phenotypically expressed (23,24).

In conclusion, marked repolarization changes (QT interval and/or T wave morphology) in AN patients should not be considered as a feature of the disease but should indicate the need to look for potential causes such as metabolic and electrolyte disturbances, drug effects or a possible genetic component.

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