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Changes on the electrocardiogram in anorexia nervosa: A case control study

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ABSTRACT

Purpose: Anorexia nervosa is a complex psychiatric condition with increased mortality. The electrocardiogram (ECG) may show repolarization changes which may associate with an increased risk of sudden death. Up to 80% of patients may be prescribed psychopharmacotherapies which alter the ECG, potentially compounding arrhythmic risk.
This study aimed to describe and improve understanding of ECG changes in eating disorders and assess the effect of psychopharmacotherapies.
Methods: Adolescent patients diagnosed with anorexia nervosa were reviewed. ECGs were reviewed by blinded expert reviewers, and repolarization parameters were compared to healthy controls. Patients on and off psychopharmacotherapies were compared.
Results: Thirty-eight anorexia nervosa patients off psychopharmacotherapies were age matched to 53 healthy controls. Heart rate was lower in anorexia nervosa patients (56 vs. 74 bpm, $p < 0.001$). The absolute QT interval was longer in patients compared to controls (408 vs. 383 ms, $p < 0.001$), but the QTc by Hodges' formula was similar between groups (401 vs. 408 ms, $p = 0.16$). The prevalence of T-wave flattening and inversion was also similar between groups (13% vs. 4%, $p = 0.12$) and T-peak to T-end interval (Tpe) was shorter in patients compared to controls ($p < 0.01$). ECG parameters were similar between patients on and off psychopharmacotherapies aside from off-drug patients showing lower HR (56 vs. 65, $p = 0.04$).
Conclusions: Autonomic and repolarization changes are evident on the ECG of anorexia nervosa patients, though the QTc interval was in fact similar between groups. Changes in T-wave morphology and duration may be promising metrics of repolarization effects of anorexia nervosa.

Introduction

Eating disorders affect 1–2% of the population, with an increased prevalence in adolescent females [1]. Sudden unexpected death is a known cause of death in the eating disorder population, specifically those with anorexia nervosa. Electrocardiographic changes have been described, but are not well or consistently defined; specifically, changes in the QT interval may be present and contribute to sudden unexpected death risk, but conflicting data hinders the ability to apply the findings clinically [2–4]. The relationship between QT interval and body mass index (BMI) has been investigated, although results are also heterogeneous [5,6]. Given these results, the resting QT interval does not appear to be a useful risk-stratitifcation tool in AN. However, T-wave changes are commonly implicated in sudden unexpected death risk in other conditions, but have only been described as case reports in anorexia nervosa [7–9]. Eighty percent of anorexia nervosa patients have concurrent mood disorders, often leading to treatment with psychopharmacotherapies which have well described QT prolonging effects in other populations [10]. We sought to characterize ECG changes in anorexia nervosa patients compared to healthy controls.

Methods

Patient selection

A retrospective cohort study of adolescent females treated as outpatients at the British Columbia Specialized Eating Disorders Clinic between 2010 and 2014 was performed. AN diagnosis was made by clinicians based on DSM-IV criteria. Males were excluded as there were too few to separate analyses by sex ($n = 7$), and the authors were concerned that inclusion of males may alter the results as sex-based ECG differences are well recognized [11]. Retrospective ECGs of

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age-matched healthy female controls were retrieved from previous investigations pertaining to chest pain, syncope, or palpitations with no following clinical diagnosis. Patients and controls with known comorbid medical conditions and/or family history of Long QT Syndrome were excluded. In addition, subjects with conduction disease (QRS duration >120 ms), left bundle branch block, and/or pacemaker or cardiac devices were excluded. In circumstances where multiple ECGs were performed, there was wide variability across patients regarding the timing and number of serial ECGs. As such, the ECG at the lowest BMI and therefore greatest disease severity was used. Baseline age, height, and weight were collected through review of clinical charts at the time of each ECG. Serum sodium and potassium levels were reported in patients, with lower limits of normal set at 135 mmol/L and 3.5 mmol/L, respectively based on local laboratory standards. Patients prescribed selective serotonin reuptake inhibitor (SSRI), anxiolytic, and/or atypical antipsychotic (AAP) medications were included in the psychopharmacotherapy group, wherein the ECG recorded with the lowest BMI while on medications was used for analysis.

ECG interpretation

All resting ECGs were manually read with assessment of the HR, QT interval, and T-wave by a trained reviewer (CC, CS) blinded to case/control, pharmacological status and specific demographics. The absolute QT interval was measured from the onset of the QRS segment to the intersection of the maximum downslope of the ST segment and the isoelectric line [12–14]. When measured by the trained reviewer, the QT was measured most commonly in lead V_5 or II. If the QT interval could not be measured in these two leads (i.e. T-wave flattening), then the QT interval was measured in any other lead with the most evident and longest QT. No adjustments were made for conduction abnormalities in the measurement of the QT interval. This method has been shown to result in high correlation and low interobserver variability [14–16]. A subset of 10 ECGs were read by both reviewers, wherein QT interval values within 10 ms were considered in agreement.

Hodge's formula ($QTc = QT + 1.75\ (HR-60)$) was used to calculate the corrected QT interval (QTc) as linear formulae have been shown to be superior to Bazett's formula, especially in the presence of bradycardia [17,18]. The normal QTc range was considered between 350 and 460 ms [19]. T-wave parameters were reported, including the interval from the peak of the T-wave to the end (Tpe) and T-wave morphology, including notched, inverted, flattened, peaked, or U-waves [7,20]. Tpe was measured as the difference between the absolute QT interval and the time between the onset of the QT interval to the peak of the T-wave. T waves were considered inverted if a negative deflection was present in a normally upright lead (I, II, V_3-V_6) with a negative T wave amplitude ≥0.1 mV.

Data analysis

Comparisons were made between anorexia nervosa patients not taking psychopharmacotherapy and age-matched controls, and between anorexia nervosa patients taking or not taking psychopharmacotherapy. AN patients taking psychopharmacotherapy were excluded from comparison to controls as these medications have documented effects on the ECG [21]. Categorical variables were compared with the χ^2 or Fisher's exact test. Paired *t*-tests were used to compare continuous variables between anorexia nervosa patients and age-matched controls. In a subset of participants, HR was matched (± 2 bpm) between anorexia nervosa patients and healthy controls to eliminate the need for a corection formula to compare QT intervals between groups. Multiple linear regression was used to analyze the relationships between BMI, group (control or patient), medication status, and age with QTc. Each parameter was assessed for independent influence through semi-partial correlation. All statistical tests were completed with R Software [22]. A p-value <0.05 was considered significant. The University of British Columbia Research Ethics Board approved the study.

Results

The ECGs from 38 adolescent females (age 15 ± 2 years, BMI 16.0 ± 2.2 kg/m^2) with a diagnosis of anorexia nervosa who were not taking psychopharmacotherpy were reviewed. Patients were compared to 53 healthy age-matched controls (Table 1). All patients had normal serum sodium and potassium levels. No patients had a current history of illicit drug use. Five (15%) AN patients had a history of purging. A subset of 15 AN adolescent females taking psychopharmacotherapies were also analyzed.

Comparison to healthy controls

Anorexia nervosa patients had lower heart rates compared to controls (59 ± 15 vs. 74 ± 11 bpm, $p < 0.001$), longer absolute QT intervals (405 ± 35 vs. 383 ± 25 ms, $p < 0.001$), and similar QTc intervals (401 ± 24 vs. 408 ± 19 ms, $p = 0.16$, Fig. 1). Twenty-seven anorexia nervosa patients (71%) were bradycardic (HR < 60 bpm). At lowest BMI, one anorexia nervosa patient (3%) had a QTc interval longer than the normal accepted range (>460 ms), at 463 ms with severe bradycardia (HR = 39 bpm, absolute QT = 500 ms) in the absence of hypokalemia (K^+ = 4.5 mmol/L). No patients showed a short QTc interval (<350 ms).

Abnormal T-waves were identified in 11 patients (29%), with no association with age, BMI, or medication status. The presence of any T-wave abnormality was similar in anorexia nervosa patients compared to controls (29% vs. 15%, $p = 0.11$). T-wave inversion was the most common abnormality in anorexia nervosa patients (8%, Fig. 2), followed by flattening (5%). Four controls had notched T-waves, one had flattening and one had inversion. The mean Tpe interval in anorexia nervosa patients was shorter than controls (71 ± 14 ms vs 92 ± 25 ms, $p < 0.01$). An odds ratio of 3.86 (95% CI 0.71–21.1, $p = 0.12$) was calculated to represent the risk of T-wave inversion in AN patients compared to healthy controls.

While testing age, BMI, anorexia nervosa diagnosis, and medication status, multiple linear regression did not reveal a singular significant

Table 1
Patient and control demographics and characteristics.

Parameter	Off-drug patients (n = 38)	On-drug patients (n = 15)	Controls (n = 53)	p-Value (off-drug patients vs. controls)	p-Value (off vs. on-drug patients)
Age (years)	15 ± 2	16 ± 1	15 ± 2	0.75	0.01
BMI (kg/m^2)	16.0 ± 2.2	17.7 ± 2.4	20.0 ± 2.8	<0.001	0.02
Serum K^+ (mmol/L)	4.3 ± 0.4	4.2 ± 0.3	NA	NA	0.41
HR (bpm)	56 ± 13	65 ± 15	74 ± 11	<0.001	0.04
QT interval (ms)	408 ± 36	397 ± 33	383 ± 25	<0.001	0.31
QTc interval (ms)	401 ± 24	407 ± 26	408 ± 19	0.16	0.44
Tpe (ms)	71 ± 14	68 ± 18	92 ± 25 (n = 17)	0.01	0.28
T-wave abnormality (%)	29%	33%	15%	0.11	0.78
T-wave inversion or flattening (%)	13%	13%	4%	0.12	1.0

BMI = body mass index, HR = heart rate, QTc = corrected QT interval by Hodge's formula, Tpe = T-peak to T-end interval.

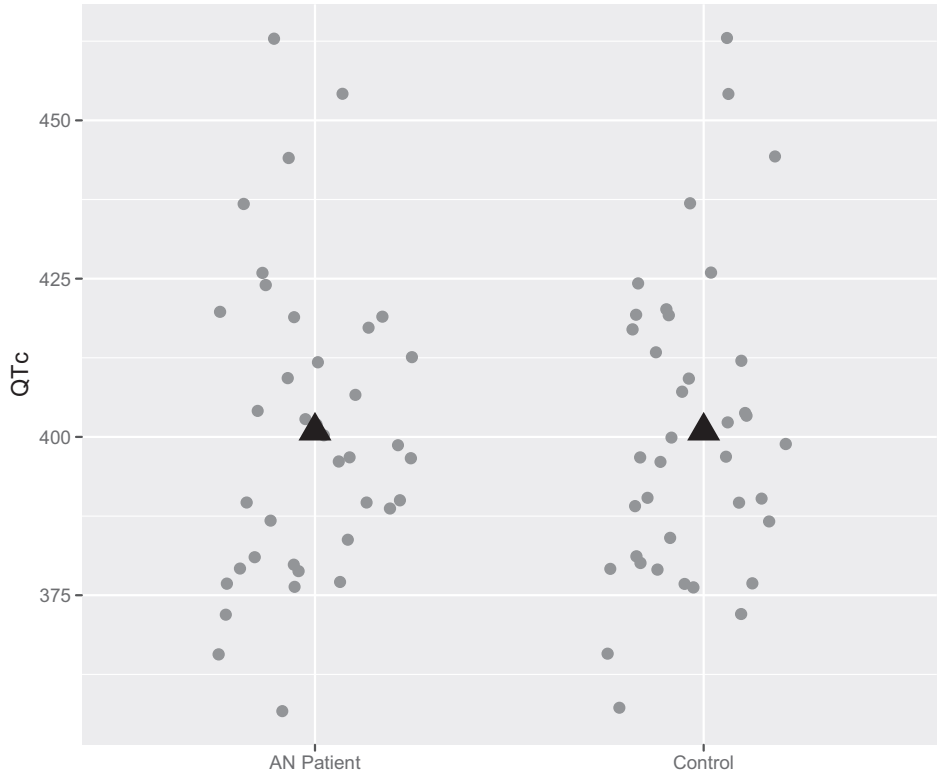

Fig. 1. Patients had similar QTc intervals compared to healthy controls (401 ± 24 ms vs. 408 ± 19 ms, $p = 0.16$). Black triangles represent sample means.

correlate to the QTc interval ($p = 0.21$–0.82). The optimal linear regression model was calculated as the following polynomial: QTc = 401–7.4 (if diagnosed with AN) + 0.7 (age) −0.2 (BMI) + 6 (if prescribed psychopharmacotherapy). When evaluating all contributors, the adjusted r^2 was −0.02 and $p = 0.67$.

QT correction formulae

To highlight the discrepancies and potential implications of QT correction formulae, the four most common QT correction formulas (Bazett, Hodges, Framingham, and Fridericia) were used to calculate QTc interval in anorexia nervosa patients, excluding those taking psychopharmacotherapies (Appendix Table A.1). All mean values were within the normal range, although the conclusions drawn were not similar. QTc by Bazett and Fridericia resulted in significantly shorter QTc in anorexia nervosa patients compared to controls ($p < 0.01$). Framingham calculated the QTc longer in anorexia nervosa patients ($p < 0.001$), while Hodges found no difference ($p = 0.22$). Two patients had QTc intervals outside the normal range by both Hodges and Bazett, one by Fridericia calculations, and eight were outside of range by Framingham.

To eliminate the use of a QT correction formula, 16 patients not taking psychopharmacotherapy and controls were matched for HR (± 2 bpm). There was no significant difference between QT values in patients or controls (380 ± 26 ms vs. 385 ± 29 ms, $p = 0.46$).

Effect of psychopharmacotherapy on the ECG

Fifteen anorexia nervosa patients (28%) received psychopharmacotherapy during treatment (Appendix Table A.2). As shown in Table 2, patients on medications had higher BMI and faster HR, although there were no significant differences in age, absolute QT interval, nor QTc interval. The presence of any T-wave abnormality was similar between groups (33% vs. 29%, $p = 0.78$).

Discussion

In this study, we demonstrated that resting corrected QT intervals in patients with anorexia nervosa are similar to healthy controls. Similarly, a recent meta-analysis showed no difference between the resting QTc interval in AN patients and healthy controls [4]. In isolated case-control studies, QTc intervals in anorexia nervosa have been described as shorter, similar, and longer, leaving ambiguity in ECG interpretation [6,25,27–30]. Similar to other forms of acquired long QT, minor secondary factors likely influence the QT interval, with additional changes across varying severity and duration of disease. Further, it is possible that QT differences at rest are not clinically relevant, but may hold implications at higher heart rates during exercise [27]. As exercise addiction is a common manifestation of AN, analyzing the QT interval throughout exercise will likely play an important role in understanding repolarization changes in AN.

Calculations of the QTc interval, and therefore the conclusions drawn from comparisons, are dependent on HR. Although Bazett's formula is most widely used both in clinic and research, AHA/ACC/HRS Recommendations do not support its use [17]. Further, a study of 100 ECG in anorexia nervosa patients deemed Hodges the most accuarate in estimating QTc [18]. The absence of a difference in the QTc interval by Hodges suggests that the resting QT interval is not likely a useful clinical marker of abnormal repolarization in the majority of the anorexia nervosa population. Morever, these results demonstrate the heterogeneity and unreliable nature of QTc correction formulae in the AN population. The inability to reach a consensus across studies on methods or results, and lack of direct correlation to adverse events suggests the resting QTc interval is not a useful measure of risk stratification in this population. A potential solution to this issue may be to compare anorexia nervosa patients and controls at matched HR, however, this does limit the generalizability of findings as bradycardic anorexia nervosa patients are less likely to be included. This limitation was observed in our study as only 16 cases were able to be included in the HR-matched subanalysis.

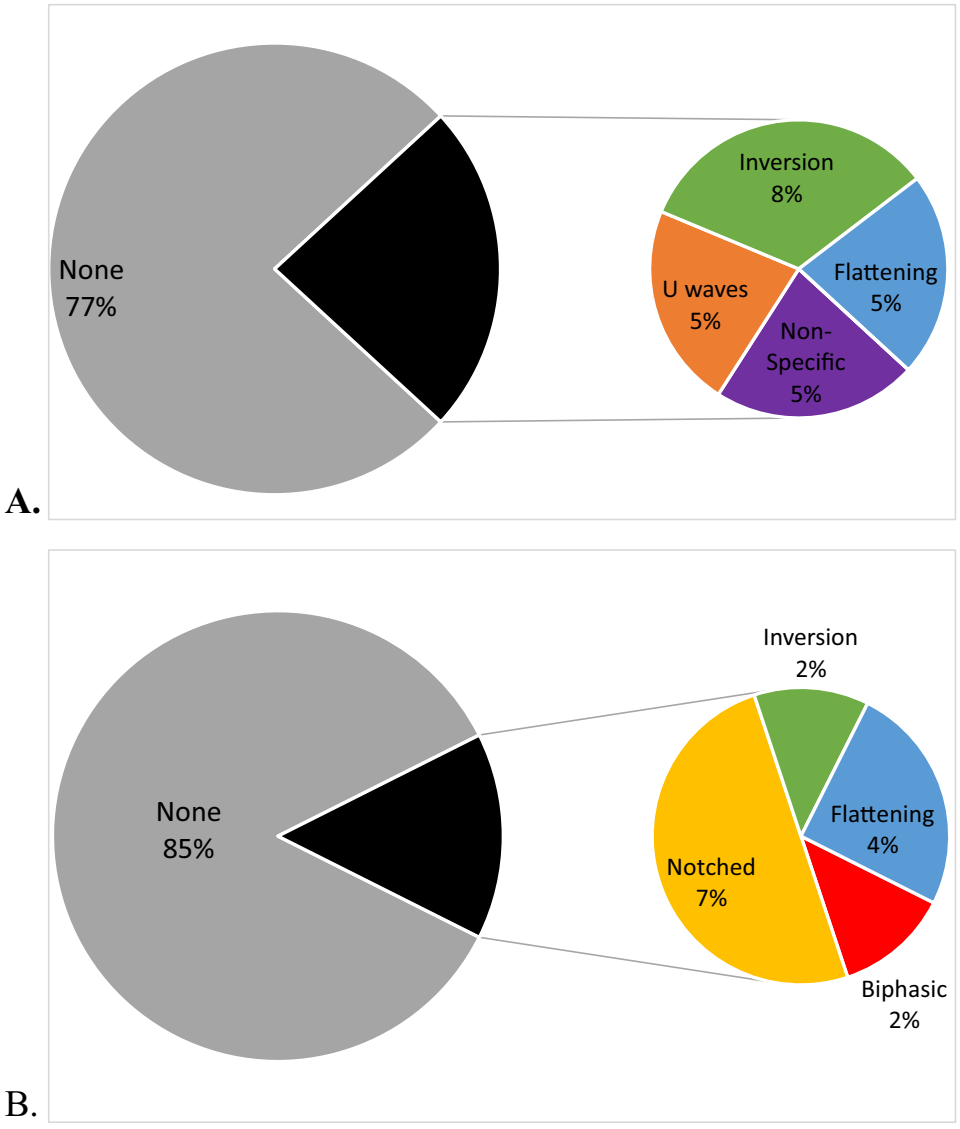

Fig. 2. The prevalence of any T-wave abnormality in AN patients (Panel A) was twice as much compared to healthy controls (Panel B; 30% vs 15%, $p = 0.07$). The combined prevalence of T-wave flattening or inversion appeared greater in AN patients (13% vs. 4%, $p = 0.10$).

Heart rate

Bradycardia is well described in AN, likely as a starvation response reflecting an increase in vagal tone [2,3,23]. Heart rate variability (HRV) has been investigated in this population; however, results have been inconclusive and at present time do not provide useful clinical insight on a population basis [24–26]. HRV may contribute to cardiac risk on an individual basis, but the heterogeneity of this factor across AN cases confounds analysis in larger groups. As such, HRV was not analyzed in this study.

Table 2
Demographics and characteristics of patients prescribed and not prescribed medications.

Parameter	Psychotropic medications (n = 15)	No psychotropic medications (n = 38)	*p*-Value
Age (years)	16 ± 1	15 ± 2	0.01
BMI (kg/m^2)	17.7 ± 2.4	16.0 ± 2.2	0.02
HR (bpm)	65 ± 15	56 ± 13	0.04
QT interval (ms)	397 ± 33	408 ± 36	0.31
QTc interval (ms)	410 ± 41	389 ± 27	0.07
T-wave abnormality (%)	33%	29%	0.78
T-wave inversion or flattening (%)	13%	13%	1.0

BMI = body mass index, HR = heart rate, QTc = corrected QT interval.

Changes in the T-wave

This is the first study to describe T-wave changes in an anorexia nervosa cohort. Abnormal T-wave morphology was more common in anorexia nervosa patients, particularly T-wave inversion and flattening, which have been associated with adverse outcomes [7,31]. All but one T-wave abnormality in healthy controls were classified as notched or inverted in lead V_2, which have been described as a normal variant in adolescents [32,33]. None of the T-wave inversion observed in anorexia nervosa patients was in lead V_2. T-wave inversion was reported in a similar prevalence to the controls of a previous study in athletic adolescents (1.5%), with lower prevalence in sedentary controls, which has been independently associated with sudden unexpected death risk [7,34]. In addition, T-wave flattening has been described as an early marker of cardiac dysfunction [31]. This morphological change has only been described in case reports of hypokalemic anorexia nervosa

patients [9,35]. The relatively high prevalence of T-wave inversion in this study (8% overall) suggests a potential contributor to the increased risk of sudden unexpected death observed in eating disorder patients, although a larger sample size would be needed to potentially elucidate a statistically significant difference from healthy controls.

The Tpe interval is thought to reflect transmural ventricular dispersion, and may increase the risk of Torsades de Pointes arrhythmia when prolonged [36]. Interestingly, the patients of the present study had longer QTa intervals compared to controls, from which we would expect longer Tpe as opposed to the observed shorter duration [37]. A potential explanation may be the morphology of the T wave, with a steeper slope of the downsloping portion of the T wave. At the cellular level, Tpe has been described as a measure of transmural repolarization; such a specific change in anorexia nervosa is plausible, although larger studies are needed to reach a more definitive conclusion [36]. In the absence of QT interval differences, Tpe interval may present as a relatively simple, accessible measure of cardiac abnormality in AN patients.

Changes in the QT interval are dynamic over disease duration, severity, and other factors: it is likely that T-wave dynamics may show similar changes, and longitudinal ECG studies in eating disorders are warranted to better assess these changes and define risk [3].

Psychopharmacotherapy

Psychopharmacotherapy did not appear to increase the QT interval among anorexia nervosa patients in our cohort, although we were limited by a small number of patients prescribed such medications. However, given the compelling and abundance of research describing QT prolongation in other populations with psychopharmacotherapy use, it is still possible certain individuals may be predisposed to QT prolongation and this measurement should be monitored [27]. Regardless of potential cardiac effects, use of these medications in the anorexia nervosa population should be evaluated with caution as current guidelines do not support psychological or weight restoration benefits [38].

Limitations

We present one of the largest single-centre comprehensive ECG reviews in anorexia nervosa patients with a matched control population. Our data is limited by the fact that only one ECG per patient was evaluated: although many patients had multiple ECGs performed, there was great variability in the timing, treatment status, and clinical data available for each ECG, which limited the ability to accurately analyze associated changes. Anorexia nervosa patients may also have significant changes in QT interval during periods of exercise or heart rate acceleration, which would not be evident during a resting ECG. Lastly, the number of patients prescribed medications was small; QT differences associated with psychopharmacotherapy might become evident in a larger sample size, or may be present with specific medications.

Conclusion

The ECGs of anorexia nervosa patients manifest several changes that include bradycardia and T-wave changes. QT changes support similar corrected intervals among anorexia nervosa patients compared to healthy controls. There remains significant variability in the QTc among anorexia nervosa and control patients that cannot be explained after adjustment. Further studies should evaluate the role of QT and T-wave changes in predicting clinical outcomes, including arrhythmic events and sudden death.

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