Characterization of Myocardial Repolarization Reserve in Adolescent Females With Anorexia Nervosa

Gareth J. Padfield, MBChB, PhD; Carolina A. Escudero, MD, MSc; Astrid M. DeSouza, MSc; Christian Steinberg, MD, PhD; Karen Gibbs, RN, CCRN; Joseph H. Puyat, MA, MSc; Pei Yoong Lam, FRACP; Shubhayan Sanatani, MD; Elizabeth Sherwin, MD; James E. Potts, PhD; George Sandor, MBChB; Andrew D. Krahn, MD

Background—Patients with anorexia nervosa exhibit abnormal myocardial repolarization and are susceptible to sudden cardiac death. Exercise testing is useful in unmasking QT prolongation in disorders associated with abnormal repolarization. We characterized QT adaptation during exercise in anorexia.

Methods and Results—Sixty-one adolescent female patients with anorexia nervosa and 45 age- and sex-matched healthy volunteers performed symptom-limited cycle ergometry during 12-lead ECG monitoring. Changes in the QT interval during exercise were measured, and QT/RR-interval slopes were determined by using mixed-effects regression modeling. Patients had significantly lower body mass index than controls; however, resting heart rates and QT/QTc intervals were similar at baseline. Patients had shorter exercise times (13.7±4.5 versus 20.6±4.5 minutes; P=0.001) and lower peak heart rates (159±20 versus 184±9 beats/min; P<0.001). The mean QTc intervals were longer at peak exercise in patients (442±29 versus 422±19 ms; P<0.001). During submaximal exertion at comparable heart rates (114±6 versus 115±11 beats/min; P=0.54), the QTc interval had prolonged significantly more in patients than controls (37±28 versus 24±25 ms; P=0.016). The RR/QT slope, best described by a curvilinear relationship, was more gradual in patients than in controls (13.4; 95% confidence interval, 12.8–13.9 versus 15.8; 95% confidence interval, 15.3–16.4 ms QT change per 10% change in RR interval; P<0.001) and steepest in patients within the highest body mass index tertile versus the lowest (13.9; 95% confidence interval, 12.9–14.9 versus 12.3; 95% confidence interval, 11.3–13.3; P=0.026).

Conclusions—Despite the absence of manifest QT prolongation, adolescent anorexic females have impaired repolarization reserve in comparison with healthy controls. Further study may identify impaired QT dynamics as a risk factor for arrhythmias in anorexia nervosa. (Circulation. 2016;133:557-565. DOI: 10.1161/CIRCULATIONAHA.115.016697.)

Key Words: anorexia nervosa ■ exercise test ■ QT interval ■ QT/RR slope ■ repolarization reserve

Anorexia nervosa (AN) is an important psychiatric disorder predominantly affecting young females, and is associated with significant morbidity and mortality.1,2 Unfortunately AN is also relatively common, with an estimated lifetime prevalence of between 0.8% and 4.2%.3 The high mortality rate in AN is multifactorial, although cardiac complications are common and are thought to contribute to one-third of deaths.4 Many of these deaths are attributable to sudden cardiac death,2,4 and a significant proportion of these may occur as a consequence of ventricular arrhythmias secondary to an acquired long-QT syndrome (LQTS).5–9 The reported prevalence of QTc prolongation in AN is highly variable, with up to 25% of patients having manifest QT prolongation,4,5 but QTc prolongation is more frequently mild and goes undetected.

Clinical Perspective on p 565

with the use of standard reference ranges.10 The severity of malnutrition is an important determinant of QTc prolongation; however, whether the risk of ventricular arrhythmia in AN can be fully assessed on the basis of the resting QTc interval is unknown. A similarly wide variation in the QTc interval exists among patients with congenital LQTS, with up to 50% of disease-causing LQTS mutation carriers having a resting QTc interval in the normal or borderline range.11,12 Exercise testing can be used in this context to demonstrate latent QT prolongation,13–15 and has now become part of the standard diagnostic and prognostic evaluation of patients with known or suspected LQTS.16 Such reduced repolarization...
reserve may also be a marker of increased risk of ventricular arrhythmias in patients with AN. Although altered QT dynamics have been described in patients with AN, the profile of QT-interval adaptation in response to graded exercise has not been defined. Furthermore, the investigation of patients with AN in whom congenital LQTS is suspected may be confounded by the presence of latent repolarization abnormalities, and the application of exercise testing in this population has not been validated. We therefore wished to describe changes in QT duration in response to graded exercise in patients with AN with reference to an age-matched healthy control population.

Methods

Study Population
The study was performed with the approval of the local research ethics committee in accordance with the Declaration of Helsinki, and the written informed consent of all volunteers and legal guardians. The study population comprised adolescent female patients referred for evaluation and treatment to British Columbia’s Children’s Hospital with a clinical diagnosis of AN based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition classification and life-threatening malnutrition. Patients were recruited consecutively at different stages of their recovery after admission to the hospital. Timing of exercise testing was determined at the discretion of the treating physician based on the patient’s physical ability and willingness to perform the test. Healthy female volunteers between 10 and 19 years of age recruited through local advertisement formed the control population. Patients underwent evaluation of serum electrolytes to exclude abnormalities that might prolong QT duration.

Exercise Protocol and ECG Analysis
Exercise testing was performed during a period of clinical stability judged by the treating physician with the use of a recumbent cycle ergometer (Lode BV, Groningen, The Netherlands) by using a 3-minute step protocol of 20 W at 60 to 75 rpm until volitional fatigue as described previously. Twelve-lead ECGs were recorded and analyzed on standard ECG paper at 25 mm/s sweep speed during rest, at 1.5 minutes into each stage of exercise, at peak exertion, and at 1 and 4 minutes postexercise. Blinded ECG analysis was performed manually. The QT interval was defined as the interval between the electrocardiograph end of P wave and onset of QRS complex and the intersection between the isoelectric baseline and a line tangential to the maximal slope of the terminal component of the T wave, averaged over 3 measurements. The lead with the longest QT interval was used for analysis. QT hysteresis was defined as the difference between the QTc interval during early exercise and recovery at a heart rate of 100 beats/min. Blinded assessment of intraobserver variability revealed no significant operator error (n=231 paired measures; r²=0.92; P<0.0001). QTc was calculated by using the Bazett formula. To avoid inaccuracies in QT measurement attributable to obscuration of the terminal portion of the T wave by the subsequent P wave (T-P fusion), and limitations of QT/correction formulas at rapid heart rates, changes in QTc at moderate accelerations in heart rate to 100 to 120 beats/min during submaximal exercise were also observed. The upper limit of normal for the resting QTc was regarded as normal at <460 ms and definitely abnormal at >480 ms as described previously.

Statistical Analysis
Statistical analyses were performed in Stata (V.13, StataCorp; College Station, TX) and graphs produced using R (R-Core Team (2013); Vienna, Austria) and GraphPad Prism (GraphPad Software, Inc; La Jolla, CA). Continuous variables are reported as mean±standard deviation or median and interquartile range where appropriate. D’Agostino and Pearson omnibus tests were used to test the normality of distribution. Independent 2-tailed Student t tests or Mann-Whitney U tests were used where appropriate for between-group comparisons, and paired tests were used for within-group comparisons of specified time points. Comparison between groups was performed using a repeated-measures 2-way analysis of variance, and posttesting was performed using a multiple comparisons Sidak test. To examine group differences in QT/RR, linear mixed-effects regression models with an unstructured covariance matrix were used. Body mass index and its interaction with log RR was included in the model to estimate QT/RR slopes. The regression equation used is displayed in the online-only Data Supplement. Because the RR values were log transformed, the coefficients for slope are interpreted as the average change in the QT interval associated with a 10% change in RR interval (95% confidence interval). The relationship between QT parameters and measures of whole-body and LV mass index were determined by using linear regression. Two-sided P values of ≤0.05 were considered significant.

Results

Baseline Characteristics
Sixty-one patients with AN and 45 healthy control subjects were enrolled. All participants were female without a personal or family history of congenital LQTS. The baseline characteristics of the study participants are displayed in Table 1. Patients were enrolled a median of 14 (interquartile range=7–24) months from the onset of symptoms of AN and 48 (interquartile range=29–75) days following hospitalization. Patients and controls were well matched, with the exception of a significantly lower body mass index (BMI) in patients (16.7±2.0 versus 19.6±2.9 kg/m²; P<0.001). Patients had gained on average 5±6 kg between hospitalization and exercise testing. Serum electrolytes including potassium (4.21±0.33 mmol/L), magnesium (0.85±0.07 mmol/L), calcium (2.28±0.18 mmol/L), and phosphate (1.34±0.15 mmol/L) were all normal in patients before exercise testing. Echocardiography was performed in 55 patients. LV ejection fraction was normal (67±5%); however, the mean LV mass index was low (21.7±4.4 [range=13.0–37.8] g/m²) in comparison with age- and sex-standardized reference ranges. Resting heart rates and QT intervals were similar between groups (Table 1). No control subjects had a QTc interval >480 ms, although 4 had a borderline QTc of 473 ms, and another had a definitely abnormal QTc of 486 ms. One patient had a borderline QTc of 473 ms, and another had a definitely abnormal QTc of 515 ms. A significant proportion (62%) of patients were abnormal at >480 ms as described previously.

Exercise Parameters
Exercise parameters are displayed in Table 1. Patients had significantly shorter exercise times than the controls, performed to significantly lower workloads, and achieved lower peak heart rates than controls (P<0.01 for all). No sustained arrhythmia was documented. Infrequent monomorphic premature ventricular contractions were observed at baseline and during recovery in 1 healthy control. In the patient group, infrequent monomorphic premature ventricular contractions were observed at baseline in 2 patients, and monomorphic premature ventricular contractions developed at peak exertion.
in 1 patient. This patient had a BMI of 15.4 kg/m² and a resting QTc of 370 ms. In both groups, QT varied directly with the RR interval at all stages of exercise, and controls therefore achieved significantly shorter QT intervals at peak exercise (Figure 1). In both groups, when QT was corrected for the RR interval (QTc), a transient increase in QTc occurred during early exercise followed by progressive shortening as the heart rate increased (Figure 2). The QTc of patients prolonged to a greater extent than control subjects during submaximal exercise, and this was despite comparable heart rates measured at a similar change from baseline (Table 1; Figures 3 and 4).

At peak exercise, patients also had significantly longer QTc intervals than controls (Table 1 and Figures 2 and 3). In comparison with baseline, the QTc of controls at peak heart rates were slightly shorter, whereas the QTc intervals of patients were paradoxically longer (Figure 3). During recovery, patient heart rates were relatively lower in comparison with the control subjects as a consequence of lower peak heart rates; however, the change in the QTc interval between 1 and 4 minutes into recovery was similar between groups with no evidence of QT hysteresis (Figure 3). In a subgroup analysis of the patient group, all measured parameters were similar irrespective of the use of potentially QT-prolonging drugs, including baseline heart rate, exercise capacity, and all QT parameters (see Table I in the online-only Data Supplement).

**Table 1. Baseline Characteristics of Adolescent Females Undergoing Exercise Testing**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=45)</th>
<th>Patients (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>15.1±1.9 [12–19]</td>
<td>15.6±1.9 [10–19]</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>19.8±2.8</td>
<td>16.7±2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise time, s</td>
<td>1240±267</td>
<td>824±271</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total work, kJ/kg</td>
<td>1.95±0.72</td>
<td>1.12±0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>75±11</td>
<td>74±15</td>
<td>0.71</td>
</tr>
<tr>
<td>Submax HR</td>
<td>114±5</td>
<td>115±6</td>
<td>0.81</td>
</tr>
<tr>
<td>∆HR at submax</td>
<td>39±11</td>
<td>40±13</td>
<td>0.46</td>
</tr>
<tr>
<td>Peak HR</td>
<td>184±9</td>
<td>159±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QT interval, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting QTc</td>
<td>426±24</td>
<td>416±29</td>
<td>0.06</td>
</tr>
<tr>
<td>QTc at submax</td>
<td>451±24</td>
<td>452±34</td>
<td>0.78</td>
</tr>
<tr>
<td>∆QTc at submax</td>
<td>24±25</td>
<td>37±28</td>
<td>0.016</td>
</tr>
<tr>
<td>Peak QTc</td>
<td>422±19</td>
<td>442±29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Between-group comparisons are made by using an unpaired t test. Submax refers to measures obtained during submaximal exertion. Data are mean±standard deviation and [range] where appropriate. BMI indicates body mass index; HR, heart rate; and ∆, change from baseline.

A comparison of the best-fit curve of several commonly used regression equations demonstrated the relationship between QT and RR interval to be curvilinear (Figure I and Table II in the online-only Data Supplement). When QT was modeled as a function of the natural log of the RR interval, and the QT/RR relationship was compared between groups using linear mixed-effects regression models, the QT/RR slope was significantly more gradual in patients than in controls, with a slower rate of QT contraction as the RR interval shortened (Table 2; Figure 5A). To further control for the potential confounding effect of heart rate, we examined QT/RR slope over a range of slower heart rates between 60 and 140 beats/min. Similar to analysis of the entire heart rate range, QT/RR slopes were significantly steeper in control subjects (Table 2). In the subgroup analysis with respect to potentially QT-prolonging drugs, the

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Uncorrected QT interval, cardiac cycle length, and exercise stage achieved by group. Control subjects were able to exercise for longer and achieved significantly higher heart rates than patients. The rate of attrition is tabulated below the abscissa. QT varied directly with the RR interval (P<0.0001 for all). Data are group means±95% confidence intervals. *Incomplete data set.
QT/RR slope was similar irrespective of these medications (Table 2; Figure II in the online-only Data Supplement).

**BMI Analyses**

When stratified according to BMI, in both the patient and control groups, subjects in the lowest BMI tertile were younger and had shorter exercise times than those with higher BMIs ($P<0.001$ for all; Table III in the online-only Data Supplement). However, heart rate and QT intervals were similar across tertiles in both groups at rest, and during submaximal and peak exercise, both in absolute terms and the change from baseline ($P>0.15$ for all; Table III and Figure III in the online-only Data Supplement). Neither BMI nor BMI percentile correlated with QT parameters at rest, submaximal, or peak exertion either in absolute terms or relative to baseline in either group (Figure IV in the online-only Data Supplement). However, patient QT/RR slopes differed progressively across BMI tertiles, with significantly steeper slopes in the upper BMI tertile in comparison with the lowest (Table 3; Figure 5B). Similarly, modeling BMI and QT/RR slope using the log transform of BMI (see Figure 2). QT corrected for heart rate by group at rest, early exercise, peak exertion, and during recovery. Myocardial repolarization adapted to exercise significantly differently in patients, with exaggerated QTc prolongation in early exercise and a failure to shorten at peak exertion. Data are group means±95% confidence intervals. *Comparison between groups performed using a repeated-measures 2-way analysis of variance. **Comparison made between groups using a multiple comparisons Sidak test.

**Figure 2.** QT corrected for heart rate by group at rest, early exercise, peak exertion, and during recovery. Myocardial repolarization adapted to exercise significantly differently in patients, with exaggerated QTc prolongation in early exercise and a failure to shorten at peak exertion. Data are group means±95% confidence intervals. *Comparison between groups performed using a repeated-measures 2-way analysis of variance. **Comparison made between groups using a multiple comparisons Sidak test.

**ΔQTc at sub-maximal heart rate**

**ΔQTc at peak heart rate**

**QT hysteresis**

*Figure 3.** Change in QTc in comparison with baseline at different stages of exercise. Submaximal heart rate is matched in both groups (114±5 vs 115±11 beats/min; $P=0.54$). QTc is significantly longer in patients both at submaximal and peak exercise. There was no QT hysteresis in either group (QTc was the same when analyzed at comparable heart rates during acceleration and deceleration). QT and RR intervals were available for all data points. Data are means±95% confidence intervals.
regression equation in online-only Data Supplement) demonstrated that a 10% increase in BMI was associated with a 5.7 increase in QT/RR slope (95% confidence interval, 9.8–103.3; \( P=0.018 \)).

**Discussion**

We have studied QT dynamics in response to graded exercise in adolescent females with anorexia nervosa in comparison with matched healthy control subjects. We demonstrate that AN is associated with impaired repolarization reserve, manifest as excessive QTc prolongation at submaximal exertion and a blunted rate-related QT shortening at peak exertion. A relatively gradual QT/RR slope during graded exercise reflects this abnormal profile of QT adaptation. Similarly, the QT/RR slope differed significantly across BMI tertiles among patients, although we did not observe a correlation between BMI or LV mass index and QT duration.

An acquired form of LQTS in the context of AN is well recognized and is thought to underlie the occurrence of lethal arrhythmias in a minority of patients.\(^5\) States of severe and rapid weight loss are more likely to be associated with overt prolongation of the QTc; however, patients with AN may have significant QTc prolongation despite having QTc intervals within the normal reference range.\(^10\) QT prolongation may occur in AN as a consequence of electrolyte abnormalities such as hypokalemia occurring as a direct consequence of malnutrition,\(^7,28\) but QT prolongation can occur in the absence of overt biochemical disturbance.\(^5,8,9\) Abnormal ion transport may also occur in malnourished cells independent of absolute serum electrolyte concentrations,\(^29\) and such abnormalities may contribute to QT prolongation in AN. Consistent with our observation of decreased LV mass in the present cohort, a variety of structural changes may occur within the myocardium of patients with AN, including myocyte autolysis and hypotrophy and an increased concentration of cellular infiltrate and fibrotic tissue.\(^29–31\) Importantly, QT prolongation also occurs in AN as a result of the dysautonomia that characterizes the condition.\(^7,32–34\) Prolongation of the QTc occurs in various forms of autonomic failure including diabetic autonomic neuropathy,\(^35\) familial dysautonomia,\(^36\) and primary autonomic failure,\(^37\) and, similarly, nonselective pharmacological autonomic blockade causes dose-dependent QTc prolongation.\(^38\) Failure to adapt the QT interval in response to changes in sympathetic innervation explains the occurrence of malignant arrhythmias in congenital LQTS. Provocation tests using epinephrine\(^39\) or exercise\(^13\) can be used to unmask QT prolongation in LQTS mutation carriers.\(^11–13,39–41\) Provocative maneuvers capable of unmasking latent QT abnormalities may therefore be useful in evaluating patients known to be susceptible to abnormalities in cardiac repolarization in general, including AN. We observed that patients with AN exhibited...
Figure 5. Uncorrected QT against RR interval and QT/RR slopes derived from linear mixed-effects regression models, with a logarithmic transformation for RR. RR=indepen-dent variable. Slopes are average QT change (milliseconds) per 10% RR interval change. A, The patients exhibit significantly more gradual slopes (13.4; 95% CI, 12.8–13.9 vs 15.8; 95% CI, 15.3–16.4; \(P<0.001\)). B, Slope progressively increases across tertiles of BMI with patients in the lowest BMI tertile exhibiting significantly more gradual slopes compared to the upper tertile (12.3; 95% CI, 11.3–13.3 vs 13.9; 95% CI, 12.9–14.9; \(P=0.026\)). The tertiles for the regression analysis were based on the patient group. BMI indicates body mass index; and CI, confidence interval.
a pattern of QT prolongation more consistent with LQT1, with progressive QT prolongation occurring during heart rate acceleration, with little evidence of QT hysteresis. The clinical significance of this is unknown.

The QT/RR slope, predominantly determined by linear regression analyses of Holter monitors, has been used as a means of characterizing QT dynamics. Abnormal QT dynamics is a feature of several disease states characterized by a susceptibility to arrhythmic death, including Brugada syndrome, ischemic cardiomyopathy, and congenital LQTS. Patients with ischemic heart disease experiencing adverse events have steeper QT/RR linear regression slopes, and patients with congenital LQTS treated with β-blockers develop flatter QT/RR linear regression slopes. However, we interpret a flatter QT/RR slope to indicate impaired dynamicity in myocardial repolarization. A hypothetical flat QT/RR slope best illustrates this: where no change in the QT interval duration would occur in response to heart rate variation. This apparent disparity may be explained by the interaction between heart rate and QT/RR slope. At faster heart rates, the slope is steeper, as reflected by the curvilinear relationship that we and other authors have described. Steeper slopes in ischemic heart disease may reflect a relative tachycardia, a powerful predictor of adverse cardiovascular events. Similarly, in LQTS, adequate β-blockade would cause a more gradual slope through the same association. For this reason, we were careful to compare groups at similar heart rates, and perform mixed-effects regression analyses, although we still observed the same phenomenon: that healthy controls have steeper QT/RR slopes.

Consistent with the primary findings of the study, we observed progressively steeper QT/RR slopes across BMI tertiles as BMI increased, despite similar exercise parameters. However, we failed to observe significant correlations between resting QT duration or changes in QT at various stages during exercise. It is therefore likely that QT/RR slope is a more sensitive measure of myocardial repolarization dynamics than simply measuring absolute QT interval or changes at peak exercise. Previous studies have found BMI to be a significant predictor of QTc duration; however, this correlation is not a universal finding, and other studies only detect a correlation with QT dispersion and LV mass index. Certainly BMI is a guide to the severity of malnutrition, although it is imperfect, and because QT duration is affected by so many factors, the association between BMI and QT may not always be readily apparent, particularly in the context of moderate or minor reductions in BMI. Although QT prolongation in AN is largely reversible with appropriate nutrition, overt autonomic dysfunction (and possibly impaired repolarization reserve) may persist for several years despite adequate refeeding and relative normalization of the BMI. Indeed, the highest BMI tertile among patients was of comparable body mass to the control group as a whole; however, despite this, the QT/RR slope was still more gradual in the patients. Therefore, BMI alone may not confidently predict arrhythmic risk, and further studies are required to elaborate on risk factors for arrhythmia in AN, possibly QT/RR slope.

Limitations
A significant proportion of the patients were receiving potentially QT-prolonging drugs that theoretically could affect QT adaptation to changes in heart rate. This is an important factor to consider in the interpretation of our results. However, we found no evidence of a QT-prolonging effect in the present study, with all measured parameters, including the resting QTc, QT/RR slope, being the same between those AN patients on potentially QT-prolonging medications and the untreated patients. In fact, the slope was numerically steeper in the medicated group. In addition, although relatively large in comparison with previous studies of myocardial repolarization disorders in AN, the sample sizes are small with respect to examining associations between abnormal QT dynamics and clinical events. Drawing conclusions regarding the clinical significance of our observations is therefore limited. Finally, serial examinations were not performed to determine the effect of refeeding on QT/RR slope.

Conclusions
Exercise testing in adolescent females with AN demonstrates impaired repolarization reserve in comparison with healthy controls, even in the absence of overt resting QT prolongation. This is manifest as excessive QTc prolongation at submaximal exertion and a blunted rate-related QT abbreviation at peak exertion. QT and RR intervals have a nonlinear relationship, and AN causes flattening of the QT/RR slope during graded exercise. Larger studies examining clinical outcome are needed to determine whether exercise testing may be used to risk stratify patients with AN.

Sources of Funding
Dr Krahn receives support from the Heart and Stroke Foundation of Canada, the Sauder Family and Heart and Stroke Foundation Chair in Cardiology, and the Paul Brunes Chair in Heart Rhythm Disorders. The study was supported by the Heart and Stroke Foundation of Canada (G-13-0002775 and G-14-0005732).

Disclosures
None.
References


23. Merri M, Moss AJ, Benhorin J, Locati EH, Alberti M, Badilini F. Relation between ventricular repolarization duration and cardiac cycle length
An important minority of patients with anorexia nervosa (AN) will unfortunately experience a sudden cardiac death. The mechanism of sudden cardiac death in AN is poorly understood, but some patients will die because of ventricular arrhythmias occurring as a consequence of an acquired long-QT syndrome. Up to 25% of patients with AN may have manifest QT prolongation; however, QT prolongation is more frequently mild and will often remain within the reference range. Although the magnitude of QT prolongation is important, whether the risk of ventricular arrhythmia in AN can be fully assessed on the basis of the resting QT interval is unknown. We have used exercise testing to demonstrate that adolescent females with AN, despite having relatively normal resting QT intervals, have impaired myocardial repolarization, manifest as a relative inability to shorten the QT interval in response to acceleration of the heart rate in comparison with healthy controls. Although we observed more gradual QT/RR slopes in patients with AN with the lowest BMI, BMI was a relatively poor predictor of resting QT or absolute changes in QT during exercise. It is therefore likely that changes occur in the myocardium of patients with AN, which persist despite a relative recovery of BMI. Whether these abnormalities are clinically relevant remains to be determined, but it may be possible that exercise testing could be used in AN to assess the risk of developing ventricular arrhythmias in the future. Further studies are required in larger cohorts of patients to examine the relationship between QT/RR slope and clinical outcomes.
Characterization of Myocardial Repolarization Reserve in Adolescent Females With Anorexia Nervosa

Gareth J. Padfield, Carolina A. Escudero, Astrid M. DeSouza, Christian Steinberg, Karen Gibbs, Joseph H. Puyat, Pei Yoong Lam, Shubhayan Sanatani, Elizabeth Sherwin, James E. Potts, George Sandor and Andrew D. Krahn

Circulation. 2016;133:557-565; originally published online January 14, 2016; doi: 10.1161/CIRCULATIONAHA.115.016697

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/6/557

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/01/14/CIRCULATIONAHA.115.016697.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
Supplemental Material
**Supplemental tables**

**Table S1**

<table>
<thead>
<tr>
<th></th>
<th>Unmedicated (N=23)</th>
<th>Medicated (N=38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>16±2</td>
<td>16±2</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>BMI (kgm(^{-2}))</strong></td>
<td>17±2</td>
<td>17±2</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Exercise time (sec)</strong></td>
<td>845±257</td>
<td>812±282</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Total Work (KJkg(^{-1}))</strong></td>
<td>1.17±0.54</td>
<td>1.09±0.60</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>LV mass index (gm(^{-2}))</strong></td>
<td>72±14</td>
<td>80±18</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR</td>
<td>73±17</td>
<td>75±14</td>
<td>0.68</td>
</tr>
<tr>
<td>Sub-max HR</td>
<td>116±16</td>
<td>114±6</td>
<td>0.41</td>
</tr>
<tr>
<td>ΔHR at sub max</td>
<td>43±13</td>
<td>39±14</td>
<td>0.25</td>
</tr>
<tr>
<td>Peak HR</td>
<td>164±20</td>
<td>156±20</td>
<td>0.12</td>
</tr>
<tr>
<td>ΔHR at peak</td>
<td>91±19</td>
<td>81±21</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>QT interval (msec)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting QT</td>
<td>374±28</td>
<td>380±27</td>
<td>0.42</td>
</tr>
<tr>
<td>QT at sub max</td>
<td>321±23</td>
<td>333±25</td>
<td>0.09</td>
</tr>
<tr>
<td>ΔQT at submax</td>
<td>-53±22</td>
<td>-48±32</td>
<td>0.48</td>
</tr>
<tr>
<td>Peak QT</td>
<td>267±32</td>
<td>278±27</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔQT at peak</td>
<td>-75±30</td>
<td>-76±34</td>
<td>0.93</td>
</tr>
<tr>
<td>Resting QTc</td>
<td>408±26</td>
<td>421±30</td>
<td>0.10</td>
</tr>
<tr>
<td>QTc at sub-max</td>
<td>445±24</td>
<td>458±39</td>
<td>0.15</td>
</tr>
<tr>
<td>ΔQTc at sub-max</td>
<td>36±30</td>
<td>37±28</td>
<td>0.94</td>
</tr>
<tr>
<td>Peak QTc</td>
<td>437±31</td>
<td>446±28</td>
<td>0.29</td>
</tr>
<tr>
<td>ΔQTc at peak</td>
<td>29±37</td>
<td>25±25</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Supplemental Table 1: Lack of effect of potentially QT prolonging drugs on exercise and QT parameters. Heart rate and exercise capacity are the same in both groups. Baseline QT intervals are similar and despite the presence of one or more drugs with the potential to prolong the QT interval, QT dynamics are unaffected.
Table S2

<table>
<thead>
<tr>
<th>Equation</th>
<th>Model Summary</th>
<th>Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>F</td>
</tr>
<tr>
<td>Linear</td>
<td>0.75</td>
<td>2411.56</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>0.82</td>
<td>3607.38</td>
</tr>
<tr>
<td>Inverse</td>
<td>0.83</td>
<td>3943.73</td>
</tr>
<tr>
<td>Power</td>
<td>0.81</td>
<td>3328.22</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>0.84</td>
<td>4250.41</td>
</tr>
</tbody>
</table>

Table S2: A greater ‘goodness of fit’ was achieved with non-linear regression models. A sigmoid relationship has the best fit though for ease of comparison of slope, logarithmic regression was used in the final analysis. Dependent Variable = QT. Independent variable = RR.
Supplemental Table 3 – Exercise parameters by BMI tertile in patients with anorexia nervosa and healthy controls. Both patients and controls in the lowest BMI tertiles were younger and had shorter exercise times with a trend to reduced total work than those with a higher BMI. QT parameters were however similar across tertiles in both groups.
Supplemental figures

Figure S1

Supplemental figure S1 – Five commonly used regression equations exhibiting the non-linear relationship between the QT and RR interval. See supplemental table S2.
Supplemental figure 2: Uncorrected QT against RR interval and QT/RR slopes derived from linear mixed effects regression models, with a logarithmic transformation for RR. RR=independent variable. Slopes between those medicated and non-medicated patients are similar (13.5 [95%CI=12.7-14.3] vs 12.0 [12.0-13.9] msec QT contraction per 10% reduction in RR interval; p=0.37).
Supplemental figure S3 – QT corrected for heart rate by group at rest, early exercise, peak exertion and during recovery in the patient group stratified according to BMI. Myocardial repolarization adaptation to exercise was similar regardless of BMI. Data are group means ± 95% confidence intervals.
Supplemental Figure S4 – Linear regression analyses of body mass index (BMI) and the corrected QT interval. Both resting and changes in QTc interval were unrelated to BMI in patients and controls.
Regression equations

Equation 1
To examine group differences in QT/RR, linear mixed effects regression models with an unstructured covariance matrix were used. The regression equation used displayed in the supplemental material was in the form:

\[ QT_{ij} = B_0 + B_1 \log(RR_j) + B_2 \text{group}_i + B_3 \text{group}_i \times \log(RR_j) + b_{0i} + b_{1i} + e_{ij}. \]

Where \( i \) = the \( i \)-th individual and \( j \) = the \( j \)-th observation; \( \text{group}_i = 0 \) if the participant belongs to the control group and \( \text{group}_i = 1 \) if the patient belongs to the patient group, \( B_0 \) = intercept; \( B_1 \) = average change in QT associated with a unit increase in the log(RR) of the control group; \( B_2 \) = average difference in QT between the control and patient groups; \( B_3 \) = average difference in the slopes of the control and patient groups; \( b_{0i} \) = random intercept; \( b_{1i} \) = random slope; \( e \) = error.

Equation 2
The relationship between QT/RR slope was stratified by tertile of BMI as described (Table 3; Figure 5B) using the following regression equation:

\[ QT_{ijk} = B_0 + B_1 \log(RR_j) + B_2 \text{BMI}_{\text{tertile}2_i} + B_3 \text{BMI}_{\text{tertile}3_i} + B_4 \text{BMI}_{\text{tertile}2_i} \times \log(RR_j) + B_5 \text{BMI}_{\text{tertile}3_i} \times \log(RR_j) + b_{0k} + b_{1k} + e_{ijk}. \]

Equation 3
The relationship between QT/RR slope and BMI, using the log of BMI was modeled using the following equation.

\[ QT_{ijk} = B_0 + B_1 \log(RR_j) + B_2 \log(BMI_i) + B_3 \log(BMI_i) \times \log(RR_j) + b_{0k} + b_{1k} + e_{ijk}. \]

Equation 4
The difference in slopes between the second and third tertile was post-estimated from Equation 2 using the formula: \( B_5 \text{BMI}_{\text{tertile}3_i} \times \log(RR_j) - B_4 \text{BMI}_{\text{tertile}2_i} \times \log(RR_j) \).

Where \( B_0 \) = intercept; \( B_1 \) = average change in QT associated with a unit increase in the log(RR) of the first BMI tertile; \( B_2 \) and \( B_3 \) = average difference in QT when the first tertile is compared to the second and third tertiles; \( B_4 \) and \( B_5 \) = average difference in the slopes of the first tertile when compared with the second and third tertile; \( b_{0k} \) = random intercept; \( b_{1k} \) = random slope; \( e \) = error.