# The QT Interval in Patients With the Turner Syndrome

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**Patients with the Turner syndrome (TS) often have longer QT intervals compared with age-matched peers although the significance of this remains unknown. We sought to determine the degree, frequency and impact of QTc prolongation in patients with TS. A chart review of all patients with an electrocardiogram (ECG) and genetically proven TS was performed. Medications at the time of the ECG were reviewed and QTc calculated. Medications were classified according to QTc risk using www.crediblemeds.com. ECG parameters were compared with an age, gender, and cardiac lesion-matched control group. Over the 10-year period of review, 112 TS patients with a mean age of 34 ± 25 years underwent 226 ECGs. At least 1 QTc prolonging medication was prescribed in 81 (74%) patients. Longer QTc interval correlated with absence of y chromosomal material (p = 0.01), older age (p <0.0001), increased number of QTc prolonging and nonprolonging medications (p <0.0001 each). During the 7.0 ± 5.1 years of follow-up, no patient had ventricular arrhythmia or unexplained sudden death. QTc was significantly shorter in matched controls using either Bazett or Hodges formula (424 ± 16 ms vs 448 ± 28 ms, p <0.0001; and 414.8 ± 16 ms vs 424.2 ± 20 ms; p = 0.0002, respectively). However, there was no difference in the frequency of QTc prolongation >460 msec (2.8% vs 2.6%, p = 0.9). In conclusion, despite frequent use of QT-prolonging medications, ventricular arrhythmias are rare in TS.**  **(Am J Cardiol 2021;140:118−121)**

Turner Syndrome (TS) is the most common genetic disorder affecting females, occurring in approximately 1 in 2,000 live female births.[1] Patients with TS have a high incidence of congenital and acquired cardiac disease[1−6] as well as a longer rate-corrected QT interval (QTc) on electrocardiogram (ECG).[7−10] The significance of this QTc prolongation remains unknown. Although an increased risk of ventricular arrhythmia and sudden death has been postulated,[7,8] there have been no longitudinal studies assessing the impact of QTc prolongation on ventricular arrhythmias and only a single case report exists of resuscitated sudden cardiac arrest from ventricular arrhythmia in a patient with TS and known cardiac disease.[11] Despite a lack of supportive data, the most recent TS guidelines recommend avoidance of medications known to prolong the QTc interval.[12] In light of the acquired co-morbidities associated with TS, this recommendation has the potential to significantly impede routine patient care. We sought to determine the prevalence of QTc prolongation in a cohort of females with TS, to compare this prevalence with an age, gender and cardiac lesion-matched control group, to assess the frequency with which QTc prolonging drugs are prescribed to TS patients, and to assess for symptomatic ventricular arrhythmias and sudden death in this group of patients.

## Methods

An IRB-approved retrospective chart review identified all patients with TS evaluated from 2000 to 2020 with ≥ 1 ECG. Demographic, karyotype, and clinical data were collected. Follow-up interval was calculated from the time of the initial ECG until last follow-up visit or death.

All ECGs were analyzed as previously described[7] and the QTc-interval was calculated using both the Bazett and Hodges formulae.[13,14] Although Bazett formula is typically used in clinical practice, Hodges formula has been found by some[15] to be less heart rate dependent and may be more appropriate in TS.[12] ECGs obtained on a gender, age, and cardiac congenital defect matched group of controls were reviewed by a single blinded observer. Percent of patients with an abnormal QTc was calculated using both the traditional definition of a QTc >440 milliseconds (msec), as well as the current guideline-based definition of a QTc interval > 460 msec.[16] Inpatient and outpatient pharmacy records were reviewed, and all medications were stratified by risk of QTc prolongation, in accordance with https://crediblemeds.org. Medications were subcategorized into medications with known, conditional, or possible risk of *torsades de pointes*, as well as medications with black box warnings. The type and number of medications that a patient received during the entire period of review, as well as at the time of an ECG, were recorded. Baseline ECGs on the patients with TS were reviewed and the following factors were explored as possible clinical correlates of QTc as measured by both Bazett and Hodges formulae: age, karyotype, presence of any form of congenital cardiac disease, presence of aortic coarctation, hypertension or presence of

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liver disease. Liver disease was defined as any elevation of liver transaminases on more than 1 occasion or structural alterations on liver imaging. Hypertension was defined as a blood pressure > 95th percentile for age for children and >140/90 mm Hg for adults. Heart rate and intervals recorded on patient ECGs were contrasted to those from the matched controls.

Because multiple patients had more than 1 ECG, a mixed model of effects accounting for repeated measures was used to assess whether correlations between clinical variables and QTc interval were present for both single and multiple entries per patient. Tests of single variable associations with QTc included T tests, Chi square analyses and Fisher's exact test, with threshold for statistical significance $p \leq 0.05$. Variables with a significant univariate association with QTc were then analyzed in a multivariate mixed model accounting for repeated measures. Model building proceeded stepwise in a multivariable general linear model with $p = 0.15$ to enter, and $p = 0.15$ to retain. Statistical computations were performed using SAS version 9.4 software (SAS corporation, Cary, NC).

## Results

There were 112 patients with an average age of 33.3 ± 25.1 years at last follow-up and an age of 21.0 ± 16.4 years at the time of initial ECG. There were 58 (52%) children <18 years in the cohort. Patients were followed for an average of 7.0 ±5.1 years subsequent to first ECG. From 2000 to 2020, 226 ECGs were performed, with 40 patients (36%) who underwent >1 ECG. Karyotype analysis was available for review in 87 (78%) patients and demonstrated the following: 45,X in 44 (50%), 45,X/46,XX in 14 (16%), isochromosome Xq in 9 (10%), ring X chromosome in 6 (7%), 45,X/46,XY in 6 (7%), and other in 8 (10%). Major congenital cardiac defects as previously defined[2] were identified in 55 patients (49%) of whom 25 (45%) required surgical or percutaneous intervention. Ischemic heart disease with or without cardiomyopathy was present in 9 (8%) patients. Hypertension was present in 55% and liver disease in 45 of the 87 (51%) who underwent testing.

An age-matched group of 112 controls without TS was assembled, consisting of an equal number of female patients with coarctation of the aorta, hypoplastic left heart syndrome, aortic valve disease, and structurally normal hearts. Controls without heart disease consisted of patients who underwent cardiac screening because of a family history of aortic aneurysmal disease who were found to be unaffected. Controls were not using any QTc prolonging medications at the time of ECG. Mean age at time of ECG for the control group was 21.1 ± 15.7 years and did not differ from that of the TS group. Baseline ECG on no medication for the TS group was compared with that of the controls. Median age was 21 (0 to 72 years) for both groups. QTc by Bazett (bQTc) and Hodges (hQTc) were evaluated as continuous and categorical variables. Statistical analysis was performed using the traditional criteria for QTc prolongation of >440 ms, as has been reported in other TS publications.[7] Repeat analysis using the current recommended criteria of QTc >460 ms was also performed. ECG parameters for patients and controls are demonstrated in Table 1.

Using a cutoff value of > 440 msec, 19 (17%) controls and 34 (38%) patients had QTc prolongation by the Bazett formula ($p = 0.0008$), and 7 (6%) controls and 13 (14%) patients had QTc prolongation by the Hodges formula ($p = 0.07$). Using current guideline definitions for QTc prolongation,[16] there remained a statistical difference between TS patients versus controls with bQTc prolongation (11% vs 2%, $p = 0.004$), but there was no difference between the groups when using Hodges formula (2.8% vs 2.6%, $p = 0.93$).

Over the course of the study, there were 2,242 outpatient prescriptions and 5,080 inpatient medication orders which were reviewed and risk stratified as noted herein. At least 1 medication associated with known or possible QTc prolongation was prescribed in 81 (74%) of the patients during the course of the study. Patients receiving QT prolonging medications were prescribed up to a median of 2 (1 to 7) such medications at any one time. Of the 992 different medications the patients received, 60 different medications were associated with the potential for QTc prolongation and fell into the following categories: 9 (15%) antidepressants, 7 (12%) antipsychotics, 9 (15%) gastrointestinal motility/antacid medications, 3 sedative/narcotics (5%), 4 diuretics (6%), 4 antihistamines (6%), 7 antibiotics/antifungals (12%), 1 anti-retroviral (2%), 5 attention deficit hyperactivity medications (8%), 2 medications for Alzheimer's and Parkinson disease (4%), 1 antineoplastic (2%), 1 immunosuppressant (2%), 1 weight reduction medication (2%), and 6 cardiac drugs (10%). The vast majority of medications in use were listed as either "not classified" or did not appear in www.crediblemeds.com.

On univariate analyses, patients with Y chromosomal material had a shorter bQTc (428.2 ± 20.7 ms) than those with a classic XO genotype (445.5 ± 25.8 ms), XX/XO mosaicism (440.9 ± 18.7 ms) or other structural alterations (442.7 ± 17.0 ms) ($p = 0.04$). There was no statistical difference in bQTc for any of the other karyotype groups ($p = 0.18$). Older age ($p < 0.0001$), increased number of QTc prolonging medications ($p = 0.0006$), and increased number of total medications (<0.0001) were also associated with greater bQT prolongation. Patients with hypertension

Table 1.
ECG parameters

| | Median Age | HR | QT | bQTc | hQTc | QRS | PR |
|---|---|---|---|---|---|---|---|
| TS | 21 (0-72) | 92 ± 27 | 366 ± 49 | 448 ± 28 | 427 ± 24 | 88 ± 18 | 126 ± 21 |
| Controls | 21 (0-72) | 78 ± 24 | 383 ± 49 | 424 ± 16 | 414 ± 16 | 86 ± 15 | 138 ± 21 |
| p value | 0.98 | <0.0001 | 0.01 | <0.0001 | 0.0002 | 0.40 | <0.0001 |

TS = Turner syndrome; HR = heart rate; QT = uncorrected QT interval (msec); bQTc = QT interval corrected with Bazett formula; hQTc = QT interval corrected with Hodges formula; QRS = QRS interval duration (msec); PR = pr interval duration (msec).

had a longer bQTc (449 ± 25 ms vs 438 ± 20 ms, p = 0.01) than normotensive patients. bQTc did not correlate with coarctation of the aorta (p = 0.3), nor presence of any congenital heart disease (p = 0.05), liver disease (p = 0.5) or heart rate (p = 0.5). When examining the relationship between clinical variables and QTc by Hodges formula, older age (p = 0.0005), use of QTc prolonging medications (p <0.0001), and number of total medications (p <0.002) remained as significant predictors of longer QTc, whereas karyotype with Y chromosomal material remained associated with a shorter QTc (p = 0.03). Although the mixed model of fixed effects did not suggest that repeated measures were a significant component of influence on predicted hQTc (p = 0.06), aortic coarctation correlated with a longer hQTc when all ECGs were analyzed (p = 0.02), but not when analysis was limited to a single ECG per patient. Hypertension remained a correlate of hQTc prolongation (p = 0.01) regardless of whether repeated measures were included.

On multivariate analysis, presence of Y chromosomal material, older age, and number of total medications, but not QTc prolonging medications, were independently associated with greater bQTc prolongation. For each year of increasing age predicted, bQT increased by 0.67 ms. Presence of Y chromosomal material increased bQTc on average 21 ms. Increasing total number of medications by 1, resulted in an increase in bQTc by 2.2 ms. Adjusted $r^2$ for this model was 0.36, indicating that 36% of the variation in bQTc could be accounted for by these 3 features. The predictive model for hQTc was less complex and demonstrated that each year of increasing age increased the predicted hQTc by 0.35 ms. Adjusted $r^2$ was 0.065, so only 6.5% of the variation in hQTc was attributable to variation in age. After accounting for older age, none of the other variables remained significantly associated with hQTc.

During the 7.0 ± 5.1 years of follow-up, 6 patients were investigated for palpitations and 6 for episodes of loss of consciousness. Etiology of palpitations was identified as atrioventricular nodal reentry tachycardia in 3 patients, atrial fibrillation in 2 patients, and atrioventricular reentrant tachycardia in 1 patient. Loss of consciousness was determined to be from syncope in 2 patients and primary seizures in 4 patients. Syncopal spells were determined to be vasovagal in nature after implantable loop recorder in 1 patient and event recorder in the other documented normal sinus rhythm at the time of symptoms. No patient had documented ventricular arrhythmias or unexplained loss of consciousness during the follow-up period.

## Discussion

The prevalence of QTc prolongation has been reported in 15% to 36% of patients with TS, depending on the definition of QTc prolongation invoked and the formula used for calculation—much higher than comparison controls.[7–9] In this study, we examined patients with TS of all ages. In the absence of QTc-prolonging medications, this cohort was found to have a similar incidence of QTc prolongation at baseline (using > 440 ms cutoff), as previously described. However, when using contemporary guidelines (QTc >460 ms), the prevalence was much lower when using either Bazett or Hodges formula: 11% and 2%, respectively. Moreover, the prevalence of QTc prolongation as calculated by Hodges formula did not differ from that of a matched control group. In contrast to others, our control group consisted of only females given that males are known to have shorter QT intervals.[12] In addition, our control group consisted of normal karyotype girls with the same spectrum of heart disease as the TS group. As a result, the QTc in our control population was longer than what others have described.[8]

The optimal method for correcting QT interval for heart rate has been the source of some debate.[15,17] Large population studies repeatedly note that the Bazett formula overestimates QTc interval at higher heart rates. We have shown that resting heart rates are significantly greater in TS patients when compared with age- and gender-matched controls, even when accounting for any underlying congenital cardiac disease. Therefore, we agree that use of Hodges formula may be preferable when measuring QTc in this specific patient population.

In contrast to previous studies, this study looked at ECGs performed longitudinally and assessed the impact of pharmacologic therapy on QTc. We demonstrated that despite the current TS guidelines advising caution regarding use of QTc prolonging drugs, their administration remains commonplace with the vast majority of patients prescribed at least 1 such medication. As expected, we found QTc intervals to be further prolonged with use of these medications. It has been speculated that patients with TS may harbor genetic mutations in one of the genes associated with long QT syndrome.[7] However, subsequent to a single publication[7] reporting such mutations, the described genetic changes were reclassified as either benign (in 8 of the 9) or as a variant of uncertain significance (1 of 9).[18] Our data is consistent with a lack of pathologic QT prolongation in this patient group, given the complete absence of ventricular arrhythmias despite the applied stressor of one or more QT prolonging medications.

TS is associated with a wide variety of age-related medical co-morbidities. Not only did we find longer QT intervals associated with drugs known or suspected to cause QT prolongation, but longer QT associated with non-QT prolonging medications. There are several possible explanations for this. First, many of the medications used were not yet risk classified and it is possible that some of the other many drugs used by these patients had the potential to cause QTc prolongation. Alternatively, many of these patients had multiple co-morbidities which increased in frequency and severity with increasing age thereby requiring more medical therapy. The longer QT on non-QTc prolonging medication may merely be a reflection of the underlying co-morbidities. Although we tried to account for the more common co-morbidities, namely liver disease, hypertension, and acquired heart disease, there is a spectrum of disease for each of these and categorical statistical analyses may not lend themselves to identifying an association.

In conclusion, girls and women with TS have longer QTc intervals than controls, but the degree of lengthening rarely meets criteria for prolongation by contemporary definition and may be primarily a reflection of higher heart rates in this patient population, due to overestimation of the

QTc by the Bazett formula. Even in those patients with greater degrees of QTc prolongation, there appears to be minimal risk of ventricular arrhythmias. Previously published recommendations for routine stress testing and ambulatory heart rate monitoring to evaluate QT prolongation in the asymptomatic patient with TS[19] are not substantiated by the literature nor the findings herein.

## Credit author statement

Noah Harahill: Investigation, writing original draft Anji Yetman: conceptualization, methodology, data curation, investigation, writing-review and editing, supervision David Danford: Formal analysis, writing-review & editing Lois Starr: resources, writing-review & editing Jennifer Sanmann: resources, writing-review & editing Jeffrey Robinson: formal analysis, supervision, writing-review & editing.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


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