Short QT Interval Prevalence and Clinical Outcomes in a Pediatric Population

Karine Guerrier, DO, MPH; David Kwiatkowski, MD; Richard J. Czosek, MD; David S. Spar, MD; Jeffrey B. Anderson, MD, MPH, MBA; Timothy K. Knilans, MD

Background—Risk associated with short QT interval has recently received recognition. European studies suggest a prevalence of 0.02% to 0.1% in the adult population, but similar studies in pediatric patients are limited. We sought to determine the prevalence of short QT interval in a pediatric population and associated clinical characteristics and outcomes.

Methods and Results—Retrospective review of an ECG database at a single pediatric institution. The database was queried for ECGs on patients ≤21 years with electronically measured QTc of 140 to 340 ms. Patients with QTc of 140 to 340 ms confirmed by a pediatric electrophysiologist were identified for chart review for associated clinical characteristics, symptoms, and outcome. Patients with and without symptoms were compared in an attempt to identify variables associated with outcome. The query included 272504 ECGs on 99 380 unique patients. Forty-five patients (35 men, 76%) had QTc ≤340 ms, for a prevalence of 0.05%. Median age was 15 years (interquartile range, 2–17), median QT 330 ms (interquartile range, 280–360), and median QTc 323 ms (IQR, 313–332). Women had significantly shorter QTc compared with men (312 versus 323 ms; P=0.03). Two deaths were noted in chart review—one from respiratory failure and the second of unknown pathogenesis in a patient with dilated cardiomyopathy.

Conclusions—Short QT interval was a rare finding in this pediatric population, with a prevalence of 0.05%. Male predominance was identified, although the median QT interval was significantly shorter in women. There seem to be no unifying clinical characteristics for this pediatric patient cohort with short QT interval. (Circ Arrhythm Electrophysiol. 2015;8:1460-1464. DOI: 10.1161/CIRCEP.115.003256.)

Key Words: cardiomyopathy, dilated ■ death ■ electrocardiography ■ pediatrics ■ short-QT syndrome

The prevalence of prolonged QT interval and arrhythmogenic potential of long-QT syndrome have been well described, but risk associated with short QT interval has only recently received recognition. Short-QT syndrome has been associated with channelopathies, increased rate of syncope, atrial fibrillation,1 and sudden cardiac death.2–4 European studies suggest a prevalence of 0.02% to 0.1% in the adult population,9,11 but similar studies in pediatric patients are unavailable. The understanding of this disease is still growing and thus far there is little knowledge of the prevalence of a shortened QT interval not associated with short-QT syndrome and its long-term outcomes. The purpose of this study was to determine (1) the prevalence of short QT interval in a pediatric population and (2) the outcomes and clinical characteristics associated with short QT interval in this cohort of pediatric patients.

Methods

This was a retrospective review of an ECG database at a single pediatric institution that provides primary to quaternary care. This study was approved by the Cincinnati Children’s Hospital Medical Center Internal Review Board (study no. 2012–3751). The ECG database was queried for consecutive ECGs completed in the outpatient or inpatient setting between July 1993 and June 2013 in patients aged ≤21 years. Previous large-scale studies12,13 have demonstrated a normal pattern of distribution of QTc interval in healthy subjects in a range of 360 to 450 ms. Based on this distribution, a QTc interval that falls outside of 2 SD from the mean could be considered abnormal. For the purpose of this study, short QT interval was defined as a QTc interval of 140 to 340 ms. The primary focus of the study was to determine the prevalence of short QT interval in this population. In addition, we evaluated the frequency of mortality, syncope, chest pain, and arrhythmia in patients with short QT interval. Symptomatic patients were defined as those with QTc 140 to 340 ms and documented syncope, chest pain, or arrhythmia in chart review.

ECG Database Query

The MUSE Cardiology Information System (MUSE; General Electric Healthcare, Buckinghamshire, United Kingdom) was queried for ECGs with a ventricular rate of 40 to 200 beats per minute and an electronically measured QTc interval between 140 and 340 ms. MUSE completed automated analysis of the 12 leads and, using superimposed medians, measured the QT interval from the Q-wave onset to the tail of the T wave (Figure). QT interval was corrected for heart rate using Bazett formula. For the purpose of this study, ECGs with electronically measured QTc <140 ms were considered artifact and excluded from analysis. Incomplete tracings, paced rhythms, and
ECGs completed during arrhythmia (supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, or atrial flutter) were also excluded.

**ECG Review**

All included ECGs were reviewed by a pediatric cardiac electrophysiologist. Ten percent of the ECGs were reviewed by a second pediatric cardiac electrophysiologist blinded to the initial interpretation. MUSE completed automated measurements of heart rate, frontal axis, PR interval, QRS interval, QT interval, and QTc interval. To verify the automated measurements <340 ms, each QT interval and QTc interval were hand-calculated by an experienced pediatric electrophysiologist. The ECGs were recorded at paper speed of 25 mm/s. The QT interval was measured in several successive complexes in leads II and V5. The longest QT interval was recorded. The QT interval was measured from the start of the Q wave to the end of the T wave, which was defined as the intercept between the isoelectric line and a tangent drawn through the maximum downward slope of the T wave. Patients with a QTc interval ≤340 ms were identified for chart review for associated clinical characteristics, symptoms, and outcome. Follow-up duration was determined by time period between ECG date and last hospital visit (inpatient or outpatient) documented in the patient’s electronic medical record. To determine the frequency of patients with congenital heart disease and arrhythmia with ECGs in our general population, 500 patients (0.9%) were electronically randomly selected from all patients ≤21 years with an ECG completed between 2009 and 2013. The electronic medical records of the 500 randomly selected patients were reviewed for documentation of congenital heart disease and arrhythmia.

**Statistical Analysis**

Demographic and clinical characteristics of the study sample were summarized using measures of central tendency, variability, and frequency. Median and interquartile range (IQR) were reported for continuous variables. Categorical variables are summarized as frequency and percentage. Differences between symptomatic and asymptomatic patients, men and women, and study patients and those in the random sample were analyzed with 2-tailed t test for continuous variables and Fisher exact test for categorical data. All statistical testing was performed at the 0.05 level of significance. Statistical analyses were performed using IBM SPSS software (International Business Machines Corporation, Armonk, NY).

**Results**

There were 309,024 ECGs completed on 121,462 unique patients aged ≤21 years during the study period. After censoring for incomplete tracings, tracings of poor quality, tracings completed during tachycardia, and paced rhythms, 272,504 ECGs on 99,380 unique patients were included in the MUSE database query. Of these, 211 ECGs had a ventricular rate between 40 and 200 beats per minute and electronically measured QTc interval of 140 to 340 ms. An additional 143 ECGs were excluded for hand-calculated QTc interval >340 ms.

**Figure.** Resting 12-lead ECG in a 14-year-old man demonstrating sinus bradycardia and sinus arrhythmia with short QT interval and early repolarization. QT, 364 ms; and QTc, 331 ms.
Patients include those who experienced syncope, chest pain, and arrhythmia. Follow-up duration, mo 10.7 (0.4–29) 18.5 (6–32) 12.6 (0–26) 0.77

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=45)</th>
<th>Symptomatic (n=15)</th>
<th>Asymptomatic (n=30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>15.4 (2–17)</td>
<td>17 (16–18)</td>
<td>14 (0.6–16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Men</td>
<td>34 (76)</td>
<td>11 (73)</td>
<td>23 (77)</td>
<td>0.82</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>9 (20)</td>
<td>2 (13)</td>
<td>7 (23)</td>
<td>0.22</td>
</tr>
<tr>
<td>Follow-up duration, mo</td>
<td>10.7 (0.4–29)</td>
<td>18.5 (6–32)</td>
<td>12.6 (0–26)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range) or as n (%). Symptomatic patients include those who experienced syncope, chest pain, and arrhythmia. P values represent the comparison between symptomatic and a symptomatic patients.

There were 68 ECGs on 45 unique patients included in study analysis. Forty-five patients (35 men, 76%) had ECGs with QTc <340 ms confirmed by a pediatric electrophysiologist, for a prevalence of 0.05%. Patient demographics are demonstrated in Table 1. The majority (78%) of the patients were white. The median age was 15.4 years (IQR, 2–17).

The random sample included 500 unique patients with an ECG with a ventricular rate between 40 and 200 beats per minute and electronically measured QTc ≥140 ms. The random sample included 265 men (53%). The majority (80%) of the patients were white. The mean age was 9.7 years±5.8.

**Clinical Outcomes**

Hospital medical chart review was completed for all 45 study patients included in analysis. Patients were followed for a median of 10.7 months (IQR, 0–29). Two deaths were noted in chart review—one from respiratory failure at the age of 6 months (female; QTc 297 ms) and the second of unknown pathogenesis in a 12-year-old patient with dilated cardiomyopathy (male; QTc 310 ms). Nine patients (20%) had congenital heart disease, including ventricular septal defect, valvular stenosis or atresia, or aortic arch abnormalities. Compared with the random sample, congenital heart disease was more frequently present in our study population although this was not statistically significant (20% versus 11%; P=0.057).

Fifteen (33%) patients were designated as symptomatic, with documented episodes of syncope, chest pain, or arrhythmia. Clinical characteristics of the symptomatic patients are demonstrated in Table 2. Of the 15 symptomatic patients, 2 (13%) patients experienced syncope, 5 (33%) had chest pain, and 1 (7%) experienced both syncope and chest pain. Nine patients had a history of arrhythmia: atrial fibrillation (1), atrioventricular nodal reentry tachycardia (1), first-degree atrioventricular block (1); also with chest pain, second-degree atrioventricular block (1), intra-atrial reentrant tachycardia (1), atrial tachycardia (1), sinus bradycardia (1), and atrioventricular reciprocating tachycardia (2). No patients were noted to have experienced ventricular fibrillation, ventricular tachycardia, or aborted sudden cardiac death in chart review. Compared with the random sample, arrhythmia was more frequently present in our study population (20% versus 1%, P=0.0009). There was only 1 study patient treated with an antiarrhythmic (digoxin). Symptomatic patients were older compared with asymptomatic patients (median age, 17 years [IQR, 16–18] versus 14 years [IQR, 0.6–16]; P=0.04). There was no significant difference in sex (P=0.82), concomitant congenital heart disease (P=0.22), or duration of follow-up (P=0.77) in symptomatic patients compared with asymptomatic patients.

**ECG Findings**

Twenty-five (56%) ECGs were completed for various cardiac reasons, including syncope (1), palpitations (4), congenital heart disease outpatient follow-up (4), and 6 to document cardiac rhythm in setting of chest pain—sinus tachycardia (2), second-degree atrioventricular block (1), premature ventricular complex (2), and sinus bradycardia (1). Other cardiac reasons for ECG included routine follow-up in patients with cardiomyopathy (3), left ventricular noncompaction (2), left ventricular systolic dysfunction (1), murmurs (2), and pulmonary hypertension (2). The remaining ECGs were completed for noncardiac reasons, including obstructive sleep apnea and preoperative evaluation.

ECG characteristics of all study patients are demonstrated in Table 3. Seventeen patients (38%) had an appropriate heart rate for age on ECG. Twenty-five patients (56%) had sinus bradycardia and 3 (6%) had sinus tachycardia. There was no significant difference in resting heart rate between symptomatic and asymptomatic patients (P=0.5). The QTc range in the study population was 277 to 339 ms. The median QT interval was 330 ms (IQR, 280–360), and median QTc was 323 ms (IQR, 313–332). Compared with men, women had shorter QTc intervals (312 versus 323 ms; P=0.03). There was no significant difference in QT (P=0.4) or QTc intervals (P=0.97) in symptomatic patients compared with asymptomatic patients. The median QTc in the congenital heart disease group was 320 ms (IQR, 311–323). There was no significant difference in QTc between patients with congenital heart disease and those without congenital heart disease (P=0.3). Early repolarization was present in 14 (31%) of the ECGs (Figure), with
no significant difference in symptomatic versus asymptomatic patients (P=0.83).

To determine the probability of short QT syndrome in this cohort of pediatric patients, the short QT syndrome diagnostic criteria offered by Gollob et al was applied to the study patients. Three patients (7%) yielded a criteria score of 4, which is suggestive of a high probability of short-QT syndrome. All 3 patients had a QTc interval <330 ms on ECG. One patient also had a clinical history of atrial fibrillation, and the remaining 2 patients had a clinical history of unexplained syncpe. Twenty-nine additional patients (64%) yielded a criteria score of 3, which is suggestive of an intermediate probability of short-QT syndrome. These patients demonstrated a QTc interval <330 ms without an associated clinical history of ventricular fibrillation, atrial fibrillation, or unexplained syncpe. The remaining 13 study patients (29%) yielded a criteria score of 2, which is considered low probability of short-QT syndrome.

### Discussion

Although the arrhythmogenic potential of long-QT syndrome has been well established, the risks associated with a short QT interval have only been recognized within the past decade. Although prevalence studies have been conducted among European and Asian adult cohorts, there is little prevalence evidence involving pediatric patients. To our knowledge, this is the largest cohort of pediatric patients with short QT interval in the literature. This study demonstrates a 0.05% prevalence rate among pediatric patients in a single institution that provides primary to quaternary care.

There seem to be no unifying clinical characteristics for pediatric patients with short QT interval. In this study, although a male predominance was identified, the median QTc interval was significantly shorter in women. This finding mirrors that of the European Short QT registry, along with others, in that a higher prevalence of short QT and associated cardiovascular events are seen in men.

The understanding of this disease is still growing and thus far there is little knowledge of long-term outcomes in pediatric patients with a short QTc interval. Thirty-three percent of our population was symptomatic, with chest pain and arrhythmia being the most frequent presentations. Twenty percent of the patients experienced arrhythmia with no sex-specific preference. Previous studies have reported on the association of short-QT syndrome and atrial fibrillation, with a proposed mechanistic underpinning of a shorter atrial effective refractory period facilitating multiple wavelets and subsequent reentry tachycardia. This is related to gain of function mutations in the inward rectifier potassium current that result in a shorter QT interval, shorter action potential duration, and reduction in the refractory period, which increase the risk of reentry tachyarrhythmia. In our study, the majority of the arrhythmia cases were atrial arrhythmias, including atrial fibrillation, atrial flutter, and intra-atrial reentry tachycardia. These findings may reflect similar manifestations of aberrations in atrial refractoriness. Villafaña et al found that 24% with short-QT syndrome experienced aborted sudden cardiac death during follow-up. In our study, no patients were documented to have experienced aborted sudden cardiac death or ventricular arrhythmia during the follow-up period. In addition, we found no difference in the frequency of early repolarization in symptomatic versus asymptomatic patients.

As genetic testing was not completed in this cohort of pediatric patients, it is unknown whether the genetic substrate for short-QT syndrome is present in the study patients. However, application of the diagnostic criteria offered by Gollob et al demonstrated that 7% of the study patients had a high probability of short-QT syndrome. A clinical history of atrial fibrillation or unexplained syncpe distinguished these patients from study patients with a QTc interval <330 ms that yielded an intermediate score. This would suggest that patients with a concerning clinical history in the setting of a shortened QT interval should have a higher consideration for genetic testing or initiation of treatment. Likewise, 64% of the study patients had an intermediate probability of short-QT syndrome and would benefit from continued medical surveillance.

Although a short QTc interval was a rare finding with a prevalence of 0.05% in this study population, the prevalence of associated congenital heart disease was considerably higher in our study cohort than in the randomly selected cohort at 20%. This propensity of short QTc interval in patients with structural congenital heart disease is a novel finding that has not been reported in the literature. Previous studies have reported on the heterogeneous dispersion in conduction delays related to myocardial remodeling in the setting of cardiac pathologies, including congestive heart failure and postmyocardial infarction states. Inherently, cardiac development results in regional differences in ion channels involved in the cardiac action potential, with notable difference between the apex and base, right ventricular outflow tract, and right ventricular free wall. It is possible that structural anomalies in congenital heart disease play a role in electrophysiological heterogeneities that may result in altered repolarization and arrhythmia. A larger cohort study would be needed to determine whether a short QT interval is associated with congenital heart disease inherently or related to postsurgical changes.

There are limitations that should be considered when interpreting our findings. This was a retrospective analysis on a selected and relatively homogenous population and is thereby vulnerable to selection bias. The reported prevalence may be underestimated because of the exclusion of patients with incomplete ECGs or ECGs completed during arrhythmia. Additional patients may have been unintentionally excluded.
because of initial electronic QT measurement. In addition, we cannot generalize the long-term outcomes for patients with short QT interval given that the follow-up period in this study was limited. Finally, it is unknown whether the study patients have a genetic substrate for short-QT syndrome as genetic testing was not completed.

Conclusions
Short QT interval was a rare finding in this retrospective review of a pediatric population, with a prevalence of 0.05%. Male predominance was identified, although the median QTc interval was significantly shorter in women. There seem to be no unifying clinical characteristics for patients with short QT interval. The findings in this pediatric patient cohort would suggest that patients with a concerning clinical history of atrial fibrillation or neonatal atrial fibrillation and bradycardia should have a higher consideration for genetic testing or initiation of treatment. Whether similar findings would be found in a nonselected pediatric population remains to be evaluated.

Disclosures
None.

References
Short QT Interval Prevalence and Clinical Outcomes in a Pediatric Population
Karine Guerrier, David Kwiatkowski, Richard J. Czosek, David S. Spar, Jeffrey B. Anderson and Timothy K. Knilans

_Circ Arrhythm Electrophysiol._ 2015;8:1460-1464; originally published online September 18, 2015;
doi: 10.1161/CIRCEP.115.003256
_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circep.ahajournals.org/content/8/6/1460

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ 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: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org//subscriptions/