Journal of Exercise Physiology**online**

Volume 15 Number 1 February 2012

Official Research Journal of the American Society of Exercise Physiologists

ISSN 1097-9751

JEPonline

Normal QT Response During Exercise Testing and Hyperventilation in Children

James Hill[1], Mary Ann O'Riordan[2], Manish Bansal[2], Justin Fiutem[2], Kenneth Zahka[1]

[1]Center for Pediatric and Congenital Heart Disease / Cleveland Clinic / Cleveland, OH, USA [2]Department of Pediatric Cardiology / Rainbow Babies & Children's Hospital / Cleveland, OH, USA

ABSTRACT

Hill JA, O'Riordan MA, Bansal M, Fiutem J, Zahka K. Normal QT Response During Exercise Testing and Hyperventilation in Children. **JEPonline** 2012;15(1):65-75. Our goal was to describe normal heart rate (HR), QT interval, and Bazett's-corrected QT (QTc) values during exercise testing in children, and to test our hypothesis that hyperventilation is associated with QTc prolongation in children. This study was a retrospective review of 200 consecutive normal exercise tests in 108 males and 92 females with low likelihood of Long QT Syndromes (LQTS) and no evidence of cardiac disease, with mean age 14.7 ± 4.0 yrs. The QT interval and RR interval were measured throughout exercise testing and hyperventilation. The QTc values were calculated using Bazett's formula. A database of HR, QT, and QTc values is presented for standing baseline and hyperventilation, and throughout exercise and recovery. Heart rate and stage of testing had independent effects on repolarization throughout exercise and recovery, while age and sex did not. We constructed reference tables of mean QT and QTc values during exercise and recovery, referenced by HR and stage. With hyperventilation, mean HR increased by 22.7 ± 12.8 beats•min^{-1}, QT shortened by 26.3 ± 21.6 ms, and mean QTc lengthened by 30.3 ± 25.4 ms$^{1/2}$ to 442 ± 26 ms$^{1/2}$ ($P<0.001$). There were no significant sex, age, or HR effects on the magnitude of QTc prolongation with hyperventilation. This study provides the largest data set for repolarization behavior during exercise testing in children without evidence of heart disease. This is also the first time that the QTc has been shown to prolong with hyperventilation. It is unknown whether this is specifically related to hyperventilation or simply explained by a limitation in Bazett's formula. It highlights exercising caution when using Bazett's formula outside the narrow reliable HR

range, especially in children and even more so during exercise. Database of normal population data is perhaps more reliable in those situations, although further validation must be done to confirm its utility.

Key Words: QT, Exercise, Pediatric, Hyperventilation

INTRODUCTION

The QT interval represents the electrical depolarization and repolarization of the ventricles, which are dependent on ion channels within the cardiomyocyte membrane. These ion channels affect the transmembrane potential and determine at each moment in the cardiac cycle the excitability and, therefore, arrhythmogenic potential of the cardiomyocytes. An important cause of sudden death due to ventricular arrhythmias in apparently healthy people are the Long QT Syndromes (LQTS), which are caused by genetic mutations either in the ion channels themselves or, in some cases, other cellular processes that directly or indirectly affect the membrane potential so as to prolong repolarization (9,10). It is very important to identify affected individuals since therapies such as ß-blockers (14) and implantable cardiac defibrillators (7,22) have been shown to decrease the risk of sudden death in certain subgroups.

There are many potential challenges to the reliable diagnosis of LQTS. Heart rate, measurement techniques, medications (16), electrolyte abnormalities, posture (20), and autonomic status (11) all affect the QT interval. To address these challenges, exercise stress testing has been used to complement the resting electrocardiogram (ECG) for the assessment of the QT interval. A confounder to using exercise to evaluate the QT interval in children is that their exercise QT response has yet to be completely defined, and that there is no consensus as to how to best account for the significant HR increase with exercise. Despite many attempts, no formula has been shown to adequately correct for HR changes during exercise. The primary objective of our study was to build a database of normal repolarization values in children throughout baseline, exercise, and recovery and to potentially demonstrate the age, sex, and workload contribution to this relationship. We also sought to address our observation that Bazett's-corrected QT (QTc) prolongation during upright hyperventilation was common in children.

METHODS

This institutional review board-approved study is a retrospective chart review of 580 consecutive patients under 23 yrs of age who underwent maximal treadmill exercise testing at Rainbow Babies and Children's Hospital in 2007 and 2008. From this population, 249 individuals were identified without structural or functional heart disease determined by normal physical examination, normal resting electrocardiogram, normal echocardiogram, and normal exercise test. None of the children had known autonomic derangements, and none was taking medications known to influence repolarization. A total of 21 studies were excluded because of the pre-test indication of "possible LQTS" based on either baseline electrocardiogram or on a family history of syncope, sudden death, or known LQTS. An additional 28 studies were excluded because of poor electrocardiographic tracings and inability to reliably measure QT interval, resulting in 200 tests included in the study.

Maximal treadmill exercise tests were performed on a GE 2000 Series Treadmill and CASE Exercise Stress System, (GE Medical Waukesha, WI) using a continuously incremental modified Bruce ramp

protocol. The full-disclosure ECG, blood pressure, (Tango+, SunTech Medical Morrisville, NC) and pulse oximetry (Masimo Radical 7, Irvine CA) were monitored during standing baseline, standing hyperventilation, exercise, and recovery.

A detailed review of electrocardiographic tracings at 50 mm/sec was done by a single investigator (JH). Interobserver agreement was determined in 20 randomly chosen exercise tests independently analyzed by two different investigators (JH, KZ). Measurements were made with electronic calipers to the nearest 3 milliseconds (ms). The QT interval and RR interval were measured with the patients standing at rest prior to beginning exercise (Base), and after 20 fast, deep breaths while standing before beginning exercise (Hyper). After a period of at least 5 min of restful sitting, they began the exercise portion of the test. The QT and RR intervals were measured at each minute of exercise for the first 5 min (E1-5), at peak exercise (Emax), as well as at each minute of recovery up to 5 min (R1-5). The initial 3 min of recovery were during active cool down walking and the subsequent 2 min in the sitting position.

The intervals were measured as per Goldenberg, Moss, and Zareba's recommended protocol (8). Specifically, we used the so-called "threshold" method where the end of the T-wave was defined by where it rejoined the isoelectric line. Whenever possible, lead II followed by V5 were used for measurements. In cases where these tracings were inadequate for measurement, all leads were examined for which most clearly showed the return of the T-wave to isoelectric baseline. We measured and averaged at least 3 and up to 5 sets of the clearest QT and RR intervals from each point in time. In cases of marked sinus arrhythmia where the R-R cycle length varied greatly, we used the R-R interval that corresponded with the HR averaged over that 10-sec period. We specifically avoided inclusion of the U-wave and included the final return of the T-wave to isoelectric baseline in the case of biphasic T-waves. When present, the U-waves were not usually found in all leads and so we were able to differentiate them from biphasic T-waves in the majority of cases. In cases of high heart rates where subsequent P-waves were very close to or starting before the end of the T-waves, the "tangent" method was used. This is where a straight line was drawn from the steepest part of the descending limb of the T-wave until it intersected with the isoelectric baseline. The corrected QT interval (QTc) was calculated using Bazett's formula ($QTc = QT/RR^{1/2}$). After Bazett's calculation, the resultant mathematical unit for QTc is $ms^{1/2}$, although it should really be considered functionally equivalent to the QT interval unit of ms since the rationale behind the formula was really to create a number that could be used interchangeably and to substitute for the QT interval.

The HR, QT, and QTc means and standard deviations were calculated for each stage. To show whether demographic (sex, age) or clinical (HR, stage) factors affected outcomes, we separated the data by sex, age groups in two-year intervals, stage of testing, and HR groups. We employed a mixed model approach in which we tested age as an ordinal variable, sex as a categorical variable, and HR as a continuous variable while accounting for the multiple observations from each subject across the different stages of the study. All two-way interaction products were included initially, and those not found to be significant were removed before a final model was constructed. The number and type of reference tables were determined by which main effects were significantly associated with independent effects on QT or QTc. The second outcome was a summary measure for each subject, calculated by subtracting the baseline QT measurement from the measurement after hyperventilation. A paired two-tailed t-test was used to determine whether the mean sined difference was significantly different from 0. Since this was only one measurement for each subject, a multiple regression model was employed and tested again for the main effects of sex, age, and HR. All analyses were done in SAS v 9.2 (The SAS Institute, Carey NC). The level of significance was set at P=0.05.

RESULTS

Table 1 summarizes the demographics of the 200 patients whose exercise tests were included in the study, as well as the indications for testing. The reasons for testing in the "other" category included hypertension, history of Kawasaki's disease with normal echocardiogram, obesity, deconditioning, or family history of cardiomyopathy. The HR, QT, and QTc mean values and standard deviations at standing baseline, standing hyperventilation, and throughout exercise and recovery are shown in Table 2 for the entire population. Figure 1 shows the mean HR and QT values throughout all conditions, and graphically illustrates the expected reciprocal relationship with decreasing QT as the HR increases. Figure 2 illustrates a similar, although much less pronounced, reciprocal relationship between HR and QTc throughout all stages *except* after hyperventilation. With hyperventilation, *both* the HR and the QTc increased.

Table 1. Patient demographics and reasons for testing.

Age in years, mean ± SD, range	14.3 ± 3.1, 6.1 to 22.7
Sex, # M/F (% of total)	108 (54%) / 92 (46%)
Primary reason for testing, # (% of total)	
Dyspnea	42 (21%)
Chest pain	38 (19%)
Syncope	32 (16%)
Palpitations	32 (16%)
Dizziness	16 (8%)
PVCs	16 (8%)
Other	24 (12%)

There was no significant age- or sex-related difference in the patients' HR throughout exercise testing. The baseline mean QTc for the entire population was 413 ± 26 $ms^{1/2}$ with females being slightly longer than males at 417 ± 22 $ms^{1/2}$ and 410 ± 26 $ms^{1/2}$, respectively ($P<0.05$). This sex-based effect disappeared throughout the remainder of testing. There was no significant correlation ($R = -0.23$) between age and baseline QTc. Upon mixed model analysis, no two-way interaction product was significant and all were removed from the model. The final model contained only the main effects of sex, age, stage, and HR. Only HR ($P<0.001$) and stage ($P<0.001$) were independently associated with QT or QTc differences. Therefore, reference tables by HR and stage were constructed without need to stratify further by sex ($P = 0.11$) or age ($P = 0.17$). Tables 3 and 4 show QT and QTc means and standard deviations grouped by HR for each stage of exercise and recovery, respectively.

With hyperventilation, the overall mean HR increased by 22.7 ± 12.8 beats•min^{-1} to 99 ± 14 beats•min^{-1}. The mean QT decreased by 26.3 ± 21.6 ms to 347 ± 29 ms, and the mean QTc increased by 30.3 ± 25.4 $ms^{1/2}$ to 442 ± 26 $ms^{1/2}$. The mean signed QTc difference after hyperventilation was significantly different from 0 ($P<0.001$). There was no significant sex, age, or HR effect (all $P>0.39$) on the magnitude of change in QTc with hyperventilation.

A total of 20 exercise tests were randomly selected from the overall group, and were independently analyzed by two different investigators (JH, KZ) to demonstrate interobserver agreement. This analysis included a total of 197 QTc measurements, with a mean difference of 2.37 $ms^{1/2}$ ± 10.8 $ms^{1/2}$ or 0.49 ± 2.6%.

Table 2. HR, QT, and QTc means (± SD) by stage.
Note: HR is in beats•min^{-1}, QT in ms, and QTc in ms$^{1/2}$.

Stage	HR	QT	QTc
Baseline	76±13	369±31	413±25
Hyperventilation	99±14	347±29	442±26
Exercise 1 min	119±15	311±30	436±28
Exercise 2 min	127±17	295±28	425±24
Exercise 3 min	135±18	282±27	420±22
Exercise 4 min	146±19	268±26	414±22
Exercise 5 min	157±18	253±24	408±22
Exercise Max	192±13	216±15	385±21
Recovery 1 min	169±15	235±20	392±23
Recovery 2 min	148±15	259±25	405±26
Recovery 3 min	137±14	273±26	411±27
Recovery 4 min	117±16	292±27	405±23
Recovery 5 min	109±14	312±28	419±24

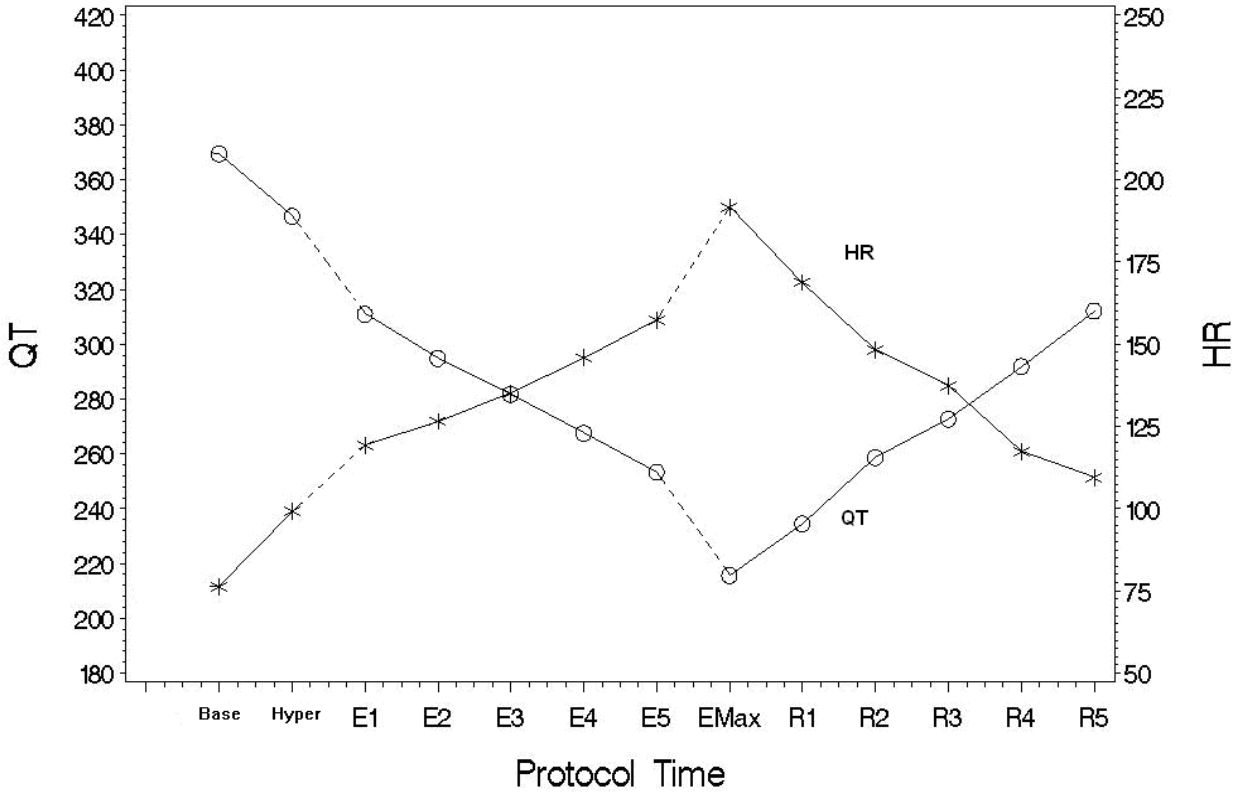

Figure 1. QT and HR means throughout exercise testing. Note the expected inverse relationship between HR and QT throughout the test. The dotted lines between points indicate variable time scale between those points for different patients, while the solid lines indicate standardized intervals.

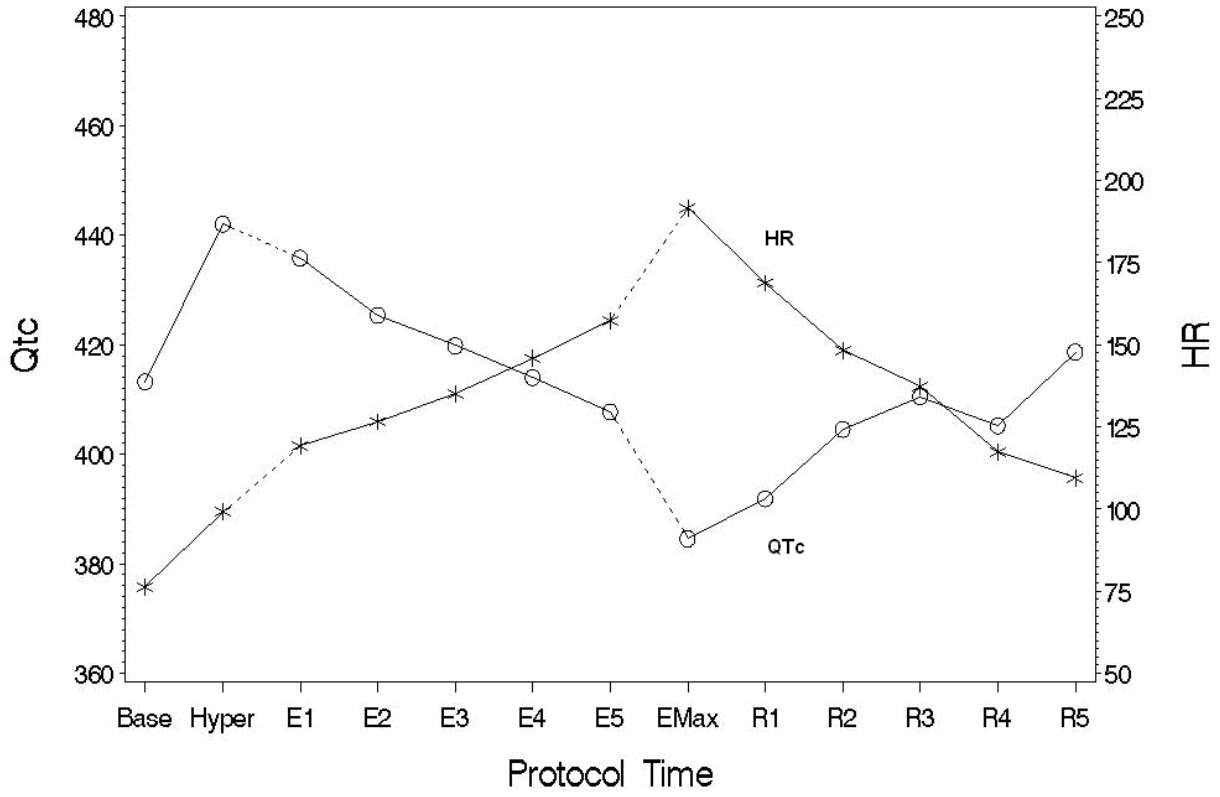

Figure 2. QTc and HR means throughout exercise testing. Note the inverse relationship between HR and QTc throughout the test, except for with hyperventilation when both HR and QTc increased. Also, note the different y-axis scale than that used in Figure 1.

Table 3. Mean QT and QTc values (± standard deviation) at each minute of exercise up to 5 min, then at maximum exercise, separated by HR groups. Note: HRs are in beats•min^{-1}, QT in ms, and QTc in ms$^{1/2}$.

	Exercise: 1 min			*Exercise: 2 min*			*Exercise: 3 min*			*Exercise: 4 min*			*Exercise: 5 min*			*Max Exercise*		
Heart Rate	*n*	*QT*	*QTc*	*n*	*QT*	*QTc*	*n*	*QT*	*QTc*	*n*	*QT*	*QTc*	*n*	*QT*	*QTc*	*n*	*QT*	*QTc*
70s	4	355±34	429±40	2	346±8	416±14												
80s	8	338±17	429±20	1	328	419	2	329±41	414±55									
90s	38	335±23	444±29	19	328±19	433±24	5	324±19	425±22	2	326±6	432±0						
100s	44	315±18	436±26	37	311±18	429±24	23	308±18	426±23	12	307±18	427±27	4	309±16	426±17			
110s	39	308±20	443±27	54	299±14	431±20	33	297±13	428±19	18	292±15	423±22	9	297±21	429±29	1	272	391
120s	20	285±23	427±33	28	284±19	424±28	55	281±14	420±20	46	281±14	422±21	18	277±11	417±16	1	266	403
130s	16	270±20	417±29	18	272±13	423±21	26	270±14	417±21	34	266±13	414±20	26	265±15	412±23	2	248±21	387±34
140s	5	266±10	426±15	11	258±18	413±27	18	259±13	413±20	25	258±11	412±16	36	255±11	410±17	2	220±5	351±13
150s	1	210	357	3	247±4	408±3	11	249±13	410±21	24	246±13	406±20	34	246±12	406±19	2	267±9	445±15
160s				3	236±5	400±8	5	232±5	396±8	11	235±15	401±26	21	236±9	402±17	12	227±12	389±21
170s							1	216	381	3	228±12	400±18	17	224±15	391±25	42	220±11	387±19
180s							1	212	379	2	219±10	391±17	3	216±7	391±8	69	213±10	383±18
190s							1	183	336	2	202±13	373±24	1	203	378	36	208±14	384±25
=200																5	204±11	388±20

Table 4. Mean QT and QTc values (± standard deviation) at each minute of recovery up to 5 min, separated by heart rate groups. Note: HRs are in beats•min^{-1}, QT in ms, and QTc in ms$^{1/2}$.

	Rec: 1 min			*Rec: 2 min*			*Rec: 3 min*			*Rec: 4 min*			*Rec: 5 min*		
Heart Rate	***n***	***QT***	***QTc***	***n***	***QT***	***QTc***	***n***	***QT***	***QTc***	***n***	***QT***	***QTc***	***n***	***QT***	***QTc***
60s													3	363±21	405±24
70s										6	343±13	409±17	9	346±15	410±16
80s				2	324±15	409±18	2	332±23	420±32	14	321±16	403±20	23	337±19	423±22
90s				1	312	416	2	323±23	426±25	20	305±19	404±26	36	322±18	424±24
100s	1	281	388	3	269±1	378±1	10	304±26	419±36	34	292±14	404±19	30	304±18	419±24
110s	2	284±20	406±24	17	286±18	415±25	35	289±21	418±29	32	288±20	413±29	26	294±21	420±28
120s	2	261±10	390±11	25	279±19	418±27	54	274±18	411±27	23	267±15	400±23	10	276±11	411±17
130s	14	256±16	398±25	45	266±18	412±27	34	265±18	410±27	8	258±12	400±21	1	289	443
140s	23	247±16	397±25	45	249±17	400±26	32	253±12	405±20	3	251±7	399±9			
150s	50	240±14	398±22	25	240±13	397±20	8	245±16	406±25						
160s	41	228±14	389±22	14	232±15	393±24	1	217	372						
170s	37	218±12	381±21	1	204	357									
180s	6	216±14	389±23	1	206	369									
190s	1	202	383												
=200															

DISCUSSION

Long QT Syndrome (LQTS) is an important cause of sudden death in otherwise healthy-appearing people. Diagnosis is important, as there are treatments that have been shown to decrease the risk of sudden death in certain patients. There are multiple reasons for both under- and over-diagnosis of LQTS, including the technical issues of how the QT interval is measured and its variability with heart rate. Multiple strategies have been devised to identify patients with LQTS including epinephrine stress testing (19), bicycle ergometry (15) and, most recently, simple bedside postural evaluation (20). None of these tests is universally accepted in current practice, and exercise testing is commonly used (21) to supplement the resting ECG. The QT interval changes with exercise are impacted by both HR changes and the neurohumoral responses to exercise. Many formulae have been devised to attempt HR correction, but none is perfect and all have been found to have specific limitations (2). This is likely because the interaction of so many different variables in each individual patient makes the QT-RR relationship too complex to develop generalizable predictions. Bazett's formula, despite known limitations at both extremes of HR, is still widely used in clinical practice (3). More recent studies have suggested that individualized HR corrections may be less biased (12,13), but these are tedious and require multiple baseline ECG measurements per subject.

The importance of taking the HR into account is magnified in the pediatric population, as there is wide variation depending on patient age and activity. Even the baseline HR for many pediatric patients is outside the range of 55 to 75 beats•min^{-1}, where Bazett's formula is most accurate. The recent publications have suggested that because of the lack of perfect correction formulae, tables of normal population QT values may be more useful (1) in children. Pediatricians are accustomed to this already, as many of the normal variables we are faced with in clinical practice are referenced from tables of general population data. However, there is limited population data in the literature for normal QT behavior with exercise in children. Several studies (3,6,15,17,18) have had control groups with exercise QT data, the largest of which included 60 patients (4), but none indexed QT values

based on HR in specific stages of testing. Most of these studies did not separately analyze patients by sex or age, and none included tabular data with specific means and standard deviations.

One major outcome of this study was the generation of a database of normal HR, QT, and QTc data at standing baseline, upright hyperventilation, and during exercise and recovery in 200 children with low likelihood of LQTS and no evidence of heart disease. There was no significant relationship found between either age or sex and QT intervals throughout exercise testing. Therefore, clinicians will be able to refer to these population values referenced only by the child's HR during a specific stage. This can be done by comparing the values to either the normal absolute QT or the normal Bazett's-corrected QTc value at a specific stage or HR. It should be noted that the traditional normal values of QTc should not be followed when using the Bazett's formula outside of the 55 to 75 beats•min^{-1} HR range. Instead, the mean QTc values in this study should be treated like additional reference values and should not be thought of as "corrected" for HR. The QTc changes noted throughout exercise and recovery are contrary to what would be expected simply from a limitation in the Bazett's formula. In the absence of physiologic factors, the Bazett's formula would be expected to show progressive lengthening of the QTc with higher HRs and return to baseline in recovery. As shown in Figure 2, the QTc in this study progressively shortens during exercise and lengthens back toward baseline in recovery. Therefore, these changes are believed to be exercise related and not mathematical phenomena.

Further studies are needed in patients with known LQTS to confirm value of the database to help differentiate between normal and abnormal repolarization. In the study by Swan et al. (17), the relationship between the QT interval and HR was different in patients with documented LQTS compared to their control population. Dillenburg et al. (6) also found that a 3-min post-exercise QTc helped identify children and adolescents with LQTS. Similarly, the exercise response of genotype-positive but phenotype-negative individuals and the response of individual LQTS mutations remain to be defined.

Certain physiologic variables are also known to play a role in repolarization, such as physical or mental stressors, autonomic state, electrolyte concentrations, and posture. This study clearly shows that hyperventilation is associated with Bazett's corrected QTc prolongation in otherwise healthy children. With the increase in HR that accompanies hyperventilation, the QTc prolongation could be a reflection of a limitation of the Bazett's formula. A recent study (5) monitoring repolarization intervals while increasing HRs with pacemakers showed that a HR increase from 80 to 100 beats•min^{-1} was associated with a mean QTc prolongation of 23 ms$^{1/2}$. We had similar results after hyperventilation, with a HR increase from 76 to 99 beats•min^{-1} and mean QTc prolongation of 30.3 ms$^{1/2}$. Despite the inability of this study to demonstrate whether the QTc prolongation has a physiologic basis due to a change in pCO_2, in autonomic tone, in serum calcium or potassium, or in some other factor related to hyperventilation, it does show an association between hyperventilation and QTc prolongation. It reinforces caution when using the Bazett's formula in clinical situations where the HR is outside a very narrow range of 55 to 75 beats•min^{-1}, which is especially important in children and in exercise. It also may explain some of the variability encountered in ECGs taken under a variety of other conditions including the stress of emergency department visits. As illustrated in Figures 1 and 2, the QTc/HR relationship after hyperventilation is significantly different from the relationship throughout exercise. If this relationship were shown to be different than in patients with known LQTS, it could potentially lead to another provocative test for the diagnosis of QT channelopathies.

A limitation of this study was not measuring the patient's end-tidal or serum pCO_2 during their hyperventilation to see if the degree of hyperventilation correlated directly with QTc. Similarly, no

serum electrolyte levels were obtained as this is not common practice in normal patients who have exercise tests for unrelated reasons. This study is also a retrospective review of previously-obtained data in individuals who had exercise testing for indications not felt to have an impact on their electrocardiogram, rather than a random sample of individuals who had then been assessed to be normal by clinical examination, resting electrocardiogram, and echocardiogram. This should be superior to recruited populations such as student athletes who might not have been as methodically evaluated. However, it would be impossible to definitively rule out LQTS in all of our patients and, given the proportion of patients who presented with syncope, there may be a slightly higher probability of inadvertently including patients with LQTS than in a truly random population sample. Also, in this study no subject race data was collected to look for potential differences in repolarization values among different races. Age and sex differences in baseline QT intervals have been noted in prior studies, and it is possible that they were not found during exercise in this study because of limited numbers once patients were subdivided into different groups.

CONCLUSIONS

When assessing repolarization parameters in children, because of limitations of the HR correction formulae, we recommend avoiding HR correction issues altogether through the use of population repolarization data indexed by HR and stage of testing. This study provides a database that describes the normal relationship between HR and the QT interval at standing baseline, throughout ramp treadmill exercise, and during recovery in children with a low likelihood of LQTS and otherwise normal hearts. As no significant correlation was identified between repolarization parameters and neither age nor sex, separate tables are not necessary. By simply taking a patient's HR and stage into account, reference QT values can be obtained. The QTc intervals are included because of their ubiquity, but again we stress that referencing QT values by HR and stage obviates the need for HR correction.

Further studies will have to be done to define exercise responses indexed by HR and stage in patients with known repolarization abnormalities, and to document the utility of this database to help differentiate normal from abnormal repolarization. Finally, this study establishes that standing hyperventilation is associated with prolongation in the Bazett's-corrected QTc interval. This result may be due to physiologic changes or simply a limitation in the Bazett's formula in which case it further highlights the importance of awareness of Bazett's limitations. However, the role of these findings in providing the basis for a possible provocative test for LQTS deserves further investigation.

ACKNOWLEDGMENT

We would like to thank Richard Sterba, MD for reviewing this manuscript, as well as Exercise ECG Technicians Andrea Lenczewski and Rhonda Greene.

Address for correspondence: Hill JA, MD, Center for Pediatric and Congenital Heart Disease, M-41, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio, USA, 44195; Phone (216) 444-2710; FAX: (216) 445-5679; Email: hillj9@ccf.org

REFERENCES

1. Abdulla R. The ways and means of correcting the QT interval. ***Pediatr Cardiol*** 1997;18:1-2.

2. Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JE, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. ***Pacing Clin Electrophysiol*** 1999;22:1397-1401.

3. Benatar A, Decraene T. Comparison of formulae for heart rate correction of QT interval in exercise ECGs from healthy children. ***Heart*** 2001;86(2):199-202.

4. Bucsenez D, von Bernuth G. The QT interval during exercise in healthy children 6-14 years old. ***J Electrocardiol*** 1989;22:17-19.

5. Chiladakis J, Kalogeropoulos A, Arvanitis P, Koutsogiannis N, Zagli F, Alexopoulos D. Heart rate-dependence of QTc intervals assessed by different correction methods in patients with normal or prolonged repolarization. ***Pacing Clin Electrophysiol*** 2010;33:553-560.

6. Dillenburg RF, Hamilton RM. Is exercise testing useful in identifying congenital long QT syndrome? ***Am J Cardiol*** 2002;89:233-236.

7. Goel AK, Berger S, Pelech A, Dhala A. Implantable cardioverter defibrillator therapy in children with long QT syndrome. ***Pediatr Cardiol*** 2004;25:370-378.

8. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". ***J Cardiovasc Electrophysiol*** 2006;17(3):333-336.

9. Hekkala AM, Viitasalo M, Vaananen H, Swan H, Toivonen L. Abnormal repolarization dynamics revealed in exercise test in long QT syndrome mutation carriers with normal resting QT interval. ***Europace*** 2010;12:1296-1301.

10. Kass RS, Moss AJ. Long QT syndrome: novel insights into the mechanisms of cardiac arrhythmias. ***J Clin Invest*** 2003 Sep;112(6):810-815.

11. Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on QT interval in normal subjects. ***J Am Coll Cardiol*** 2002;39:1820-1826.

12. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. ***Heart*** 2002;87:220-228.

13. Malik M, Hnatkova K, Batchvarov V. Differences between study-specific and subject-specific heart rate corrections of the QT interval in investigations of drug induced QTc prolongation. ***Pacing Clin Electrophysiol*** 2004;27:791-800.

14. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. ***Circulation*** 2000;101:616-623.

15. Novotny T, Semrad B, Kadlecova J, Gaillyova R. The role of ergometric testing in diagnosis of latent long QT syndrome]. ***Vnitr Lek*** 2000;46:843-847.

16. Roden DM. Drug-induced prolongation of the QT interval. ***N Engl J Med*** 2004;350:1013-1022.

17. Swan H, Toivonen L, Viitasalo M. Rate adaptation of QT intervals during and after exercise in children with congenital long QT syndrome. ***Eur Heart J*** 1998;19:508-513.

18. Viitasalo M, Rovamo L, Toivonen L, Pesonen E, Heikkila J. Dynamics of the QT interval during and after exercise in healthy children. ***Eur Heart J*** 1996;17:1723-1728.

19. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. ***Circulation*** 2006; 113:1385-1392.

20. Williams GC, Dunnington KM, Hu MY, Zimmerman TR,Jr, Wang Z, Hafner KB, Stoltz M, Hill EK, Barbey JT. The impact of posture on cardiac repolarization: more than heart rate? ***J Cardiovasc Electrophysiol*** 2006;17:352-358.

21. Wong JA, Gula LJ, Klein GJ, Yee R, Skanes AC, Krahn AD. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. ***Circ Arrhythm Electrophysiol*** 2010;3:120-125.

22. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. ***J Cardiovasc Electrophysiol*** 2003;14: 337-341.