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VENTRICULAR ECTOPY DURING TREADMILL EXERCISE STRESS TESTING IN THE EVALUATION OF LONG QT SYNDROME

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Abstract

Background—Long QT syndrome (LQTS) can present with sudden death during exertion.

Objective—To determine the diagnostic importance of exercise-induced ventricular ectopy in the evaluation of LQTS.

Methods—From 1998 to 2006, 381 patients with a referral diagnosis of LQTS had a treadmill exercise stress test. Blinded to both genotype and rendered diagnosis, the stress tests were scored for the presence of exercise-induced ventricular ectopy.

Results—The dismissal diagnosis was LQTS in only 177 (46%), catecholaminergic polymorphic ventricular tachycardia (CPVT, 16), miscellaneous cardiac disease (17), and normal (171). Exercise-induced ventricular ectopy was detected in 107 patients (28%). However, only 34 patients (9% overall) had exercise-induced ventricular ectopy greater than single premature ventricular contractions (PVCs). Among the 171 patients dismissed as normal, only 2% had ectopy greater than single PVCs. Among the genotype positive LQTS patients, no significant ectopy was recorded in 80 with LQT1, compared to either 5 (8%) with LQT2, or 3 (20%) with LQT3 ($p < 0.0001$). In contrast, exercise-induced ventricular ectopy beyond single PVCs was far more common among patients with CPVT (14/16, 88%, $p < 0.0001$) and included PVCs in bigeminy in 13 (81%), couplets in 7 (47%), and NSVT in 3 (20%). Of note, bi-directional VT was not present in any of the 16 patients diagnosed with CPVT including the 10 with genetically proven, RYR2-mediated CPVT.

Conclusion—Exercise-induced ventricular ectopy exceeding single PVCs was observed in < 10% of patients referred for LQTS evaluation including 2% of patients ultimately dismissed as normal. Exercise-induced bigeminy is strongly associated with the presence of significant cardiovascular disease but is far more likely to indicate CPVT rather than LQTS.

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Conflicts of interest: Dr. Ackerman is a consultant for PGxHealth that has released the FAMILION^{TM} genetic test for cardiac ion channel abnormalities. He is also a consultant for Medtronic and Pfizer. However, PGxHealth, Medtronic, and Pfizer did not provide financial support for this study.

Keywords

Arrhythmias; Ectopy; Electrocardiography; Exercise; Long QT syndrome; Stress Testing

INTRODUCTION

Congenital long QT syndrome (LQTS) clinically affects an estimated 1 in 2500 persons and can present as syncope, seizures, and sudden death. The fundamental defect precipitates delayed cardiac repolarization, which is associated with prolonged QT intervals on the 12-lead electrocardiogram (ECG).[1] This rhythm abnormality can degenerate into the trademark tachyarrhythmia known as torsades de pointes (TdP). The basic LQTS clinical evaluation includes a thorough personal and family history along with careful inspection of the 12-lead ECG. However, a prolonged QT interval on a 12-lead ECG, the electrocardiographic cornerstone of the diagnosis, can be difficult to recognize.[2] Furthermore, a significant percentage (20 – 40%) of patients with genetically proven LQTS have normal or borderline QTc measurements, adding even more complexity to this already challenging diagnosis.

Consequently, many additional clinical tests/tools have been utilized in the clinical evaluation of LQTS including ambulatory ECG recordings, treadmill exercise stress testing, the epinephrine QT stress test, and LQTS genetic testing. For example, mutational analysis has revealed nearly 500 LQTS-associated mutations in 3 of the LQTS-susceptibility genes that explain 75% of LQTS.[3, 4] The epinephrine QT stress test facilitates the recognition of certain LQTS subtypes, especially concealed LQT1, where paradoxical QT prolongation during low dose epinephrine predicts LQT1 with a positive predictive value of 75%.[5, 6] In other attempts to increase the diagnostic accuracy of LQTS, studies have used mental and physical stresses, including exercise stress testing, to elicit a QT interval difference in LQTS patients.[7–11]

Despite these efforts, accurately diagnosing LQTS remains a daunting task. Recently, 40% of the patients seeking a second opinion because of a previously rendered diagnosis of LQTS were dismissed without the diagnosis.[12] Here, we sought to determine the diagnostic importance of exercise-induced ventricular ectopy during treadmill exercise stress testing in the evaluation of LQTS.

METHODS

Study Cohort and Study Design

Between 1998 and 2006, 638 consecutive patients with a referral diagnosis of long QT syndrome (LQTS) were seen at the Mayo Clinic Long QT Syndrome Clinic in Rochester, Minnesota. A retrospective chart review of the 638 patients was conducted revealing that 381 individuals underwent a treadmill exercise stress test using a modified Bruce protocol during their referral evaluation for LQTS.

Independently, results from genotyping/genetic testing for the known LQTS-associated channel genes were collected.[4] Genetic test results were obtained from either the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory or the commercially available LQTS test (FAMILION®, PGxHealth, New Haven, Connecticut). Patients were assigned to one of four clinical dismissal diagnoses by a single channelopathy specialist (MJA) after their second opinion evaluation: i) LQTS (with or without genetic confirmation), ii) catecholaminergic polymorphic ventricular tachycardia (CPVT, with or without genetic confirmation), iii) miscellaneous cardiac disease, including idiopathic

ventricular fibrillation, or iv) ostensibly normal with history of vasovagally mediated syncope/presyncope (with or without subsequent negative genetic test for LQTS).

Blinded to genotype, phenotype, and the clinically rendered dismissal diagnosis, a single investigator (JMH) reviewed and scored the exercise stress tests for the presence of exercise-induced single premature ventricular contractions (PVCs), bi-, tri-, or quad-geminal PVCs, couplets, triplets, nonsustained ventricular tachycardia (NSVT), bidirectional VT, polymorphic VT/TdP, and macroscopic T wave alternans (TWA). Patients could have more than one type of exercise-induced ventricular ectopy present but the most complex type displayed (i.e. bidirectional VT/TdP > NSVT > triplets > couplets > bigeminy) was the one used for the comparisons.

Statistical Analysis

Summary statistics for categorical data were reported as number (percentage). Comparisons of the data were made using Chi-square tests. Data were analyzed using the statistical package JMP (version 6). In all cases, a p-value less than 0.05 was considered statistically significant. The authors had full access to the data and take responsibility for its integrity. Both authors have read and agree to the manuscript as written.

RESULTS

Population Characteristics

Table 1 summarizes the demographics and genetic test results of the 381/683 (56%) patients who had a treadmill exercise stress test conducted as part of their clinical evaluation. Young age (< 8 years) was the most common reason for the 302 patients who were not stress tested. Nearly 60% (226/381) were females, the average age was 24 ± 14 years, and the average resting QTc was 442 ± 37 milliseconds. Over 75% (295/381) had genetic testing. There were 156 patients (41%) with genetically confirmed LQTS and 10 patients (2.6%) with RYR2-positive CPVT (CPVT1).

Clinical Evaluation and Diagnosis

Despite a referral diagnosis of LQTS for all 381 patients, following their comprehensive clinical evaluation, only 177 (46.5%) were dismissed with a genetic/clinical diagnosis of LQTS, 16 patients (4.2%) were diagnosed with CPVT, and 17 patients (4.5%) were assigned to the category of miscellaneous cardiac diseases. Of the 17 patients in the category of miscellaneous cardiac diseases, 13 had a negative genetic test for both LQTS and CPVT. The diagnoses in this category included idiopathic ventricular fibrillation and/or anatomically abnormal hearts (bicuspid aortic valve, right ventricular outflow tract obstruction, cardiomyopathy including dilated cardiomyopathy, etc.). Of the four not yet genetically tested, two patients were diagnosed with mitral valve prolapse, one patient was diagnosed with restrictive cardiomyopathy, and the other patient was diagnosed with right ventricular outflow tract obstruction.

Finally, 171 patients (44.9%) were dismissed as ostensibly normal including 94 with a negative genetic test. The majority of those dismissed as normal who received genetic testing were seen during the era of research based genetic testing (1998–2004). Because of the paucity of clinical evidence for the remaining patients who were dismissed as normal and seen after 2004, commercial LQTS genetic testing was not recommended. Not surprisingly, the QTc was greatest in the subset dismissed as LQTS ($p < 0.0001$, data not shown).

Overall, exercise-induced ventricular ectopy was recorded in 105 patients (28%) and exercise-induced TWA was seen in only 2 patients (0.5%) (Figure 1). There was no significant statistical difference between the resting QTc and presence of all types of exercise-induced ectopy (p-value = 0.7). In addition, β-blocker use did not significantly influence the presence of ventricular ectopy during exercise (data not shown). Single, intermittent PVCs during exercise, detected in 72 of the 105 ectopy-positive patients, was the most common type of exercise-induced ventricular ectopy. Exercise-induced single PVCs only were present in 39 patients with LQTS (10%), 1 patient with CPVT (0.3%), 5 patients categorized under miscellaneous cardiovascular diseases (1%), and 27 patients dismissed as normal (7%, p = NS).

Figure 1 summarizes the type and distribution of exercise-induced ventricular ectopy **exceeding** single, intermittent PVCs that was observed in 34 patients (9% overall). For this subset, the most common type of exercise-induced ventricular ectopy was PVCs in bigeminy detected in 30/34 patients while NSVT was recorded in 10 patients. Although not ventricular ectopy, exercise-induced macroscopic TWA was evident in 2 patients; an LQT2-positive female who displayed only TWA and a male with dilated cardiomyopathy who displayed TWA and NSVT. Neither the signature arrhythmia (torsades de pointes) of LQTS nor the signature arrhythmia (bi-directional VT) of CPVT was ever detected in this entire study cohort of almost 400 subjects.

For this subset of patients (N = 35) with either exercise-induced ventricular ectopy exceeding single, intermittent PVCs or macroscopic TWA, the dismissal diagnosis was LQTS in 13, CPVT in 14, miscellaneous cardiac disease in 5 (2 with idiopathic ventricular fibrillation, 1 with dilated cardiomyopathy, 1 with mitral valve prolapse with fascicular ventricular tachycardia, and 1 with dilated cardiomyopathy plus atrial fibrillation), and normal status in 3. Thus, only 3/171 (< 2%) of the patients dismissed as normal had exercise-induced ventricular ectopy beyond isolated PVCs; all three displayed bigeminal PVCs. Resting QTc, beta blocker status, and personal history of cardiac events failed to identify this subset having exercise-induced ventricular ectopy beyond single PVCs (data not shown).

Overall, only 7 percent of the patients diagnosed with genetic and/or clinical LQTS had exercise-induced ventricular ectopy exceeding single PVCs. Among the patients with genotype positive LQTS, no exercise-induced ventricular ectopy beyond single, intermittent PVCs was recorded in the 80 patients with LQT1, compared to either 5 patients (8%) with LQT2, or 3 patients (20%) with LQT3 ($p < 0.0001$). One of two patients with LQT5 displayed exercise-induced bigeminal PVCs and no exercise-induced ventricular ectopy was recorded in the single patient with LQT7. Exercise-induced ventricular ectopy was present in 4/19 patients dismissed with only clinical diagnosis of LQTS (i.e. no genetic test results) and this ectopy included: one patient with bigeminal PVCs and NSVT, one patient with bigeminal PVCs and couplets, one with bigeminal and trigeminal PVCs, and one with bigeminal PVCs only.

In contrast, exercise-induced ventricular ectopy beyond single, intermittent PVCs was far more common among patients genetically/clinically diagnosed with CPVT (14/16, 87.5%, $p < 0.0001$) compared to those with LQTS (7%), those dismissed with a cardiac diagnosis other than LQTS/CPVT (29%), or those dismissed as normal (3%). Ten of the 14 ectopy-positive CPVT patients were females; 11 were 20 years of age or younger. Specifically, PVCs in bigeminy were recorded in 13 (81%), couplets in 7 (47%), and NSVT in 3 (19%) patients. CPVT patients often displayed more than one type of exercise-induced ventricular ectopy (75%) but notably, bidirectional VT was not present in any of the 16 patients diagnosed with CPVT including the 10 with genetically proven, RYR2-mediated CPVT.

Among the entire cohort of 381 patients, the presence of exercise-induced PVCs in bigeminy had a sensitivity (81%), specificity (96%), positive predictive value (45%), and negative predictive value (99%) for CPVT while exercise-induce NSVT was detected in 3 LQTS patients (2%), 3 CPVT patients (19%), 4 patients (24%) with a cardiac diagnosis besides LQTS/CPVT, and none of the patients dismissed as normal.

DISCUSSION

LQTS and CPVT represent two of the most common heritable arrhythmia syndromes or cardiac channelopathies affecting at least 1 in 2500 persons. Exercise is a common trigger for both LQTS- (especially LQT1) and CPVT-precipitated cardiac events including sudden death. Early detection and recognition of warning signs suggestive of their presence are necessary to prevent such sudden deaths. In fact, in a postmortem investigation of autopsy negative sudden unexplained deaths, half of the sudden death victims with a genetically identifiable channelopathy exhibited legitimate warning signs beforehand that if recognized, their sudden death might have been thwarted.[13] On the other hand, over-diagnosis of these conditions can result in unnecessary therapies and lifestyle changes. Recently, we demonstrated that 40% of the patients, seeking a second opinion because of a previously rendered diagnosis of LQTS, were dismissed as ostensibly normal with insufficient evidence to merit a diagnosis of a cardiac channelopathy.[12] Among the 381 patients evaluated for LQTS in this study, less than half were dismissed with a diagnosis of LQTS. Thus, both under-diagnosis and over-diagnosis of LQTS/CPVT continue to co-exist.

The diagnostic utility and limitations associated with the various tests used in the evaluation of these conditions must be kept in sharp focus. The 12-lead ECG remains the cornerstone in the evaluation of LQTS. However, up to 40% of patients with genetically proven LQTS have a normal QTc at rest and even when QT prolongation is expressed, the QTc is often measured inaccurately and not recognized.[2] The epinephrine QT stress test can expose patients with concealed type 1 LQTS and does so with a positive predictive value approaching 75% and a negative predictive value of 96% (for LQT1).[5, 6] The yield of LQTS genetic testing is around 75%.[14, 15]

On the other hand, the QT interval as well as the entire 12-lead ECG is almost always normal in CPVT. Instead, the treadmill exercise stress test is the most helpful diagnostic test especially when exercise-induced bidirectional ventricular tachycardia, CPVT's trademark arrhythmia, is present. However, the positive- and negative predictive value of bi-directional VT is not known. The yield of CPVT genetic testing is around 50–60% but the CPVT genetic test only recently became available as a clinical diagnostic test.

In this study, several key observations have been gleaned with respect to the diagnostic significance of exercise-induced ventricular ectopy during treadmill exercise stress testing. First, exercise-induced single, intermittent PVCs is essentially uninformative from a clinical perspective providing no distinguishing value between the patient with a significant channelopathy and an otherwise normal patient. Second, exercise-induced ventricular ectopy beyond single PVCs (i.e. bigeminy, couplets, triplets, and/or NSVT) is uncommon among patients dismissed as otherwise normal, less than 2% displayed such ventricular ectopy during exercise. Third, the presence of exercise-induced ventricular ectopy beyond single PVCs was associated with a 91% positive predictive value for a significant cardiac diagnosis. However, patients ultimately diagnosed with CPVT, rather than LQTS, were far more likely to exhibit exercise-induced ventricular ectopy beyond isolated PVCs. In fact, such ectopy during exercise was notably absent in every patient with the subtype of LQTS most prone to exercise-triggered events (LQT1). In contrast, nearly 90% of the CPVT patients were positive for ventricular ectopy during exercise. Fourth, rather than the

purported signature arrhythmia of bi-directional VT, the most common type of exercise-induced ventricular ectopy was bigeminal PVCs typically commencing at heart rates around 120 – 140 beats per minute, continuing to peak exercise and disappearing during the recovery phase. To our surprise, bi-directional VT did not occur in a single patient with CPVT.

Limitations

As with any retrospective study, there are a few limitations that must be kept in mind. First, the clinical diagnoses were rendered by a single channelopathy specialist (MJA). Since these patients were seen as part of clinical practice, it was not possible to have a second investigator independently evaluate and confirm these diagnoses. Thus, it is possible that some of the patients have been categorized incorrectly. This seems less likely as our prior study demonstrated that among the patients dismissed with definite LQTS, the yield of the genetic test was 75% whereas the yield was 0% for the patients dismissed as normal.[12]

Second, with respect to genetic testing, eighty-six patients did not have genetic testing as part of their clinical evaluation. These non-tested patients were due to patient refusal, cost, and/or clinical judgment of lack of need. Finally, our study only included those who received a treadmill exercise stress test during their evaluation. This excluded 257 patients that were evaluated during this time period. However, it is doubtful that their exclusion somehow introduced bias into this study since the vast majority was excluded simply because of inability to perform the study (too young).

CONCLUSION

Overall, exercise-induced ventricular ectopy exceeding isolated PVCs was observed in < 10% of patients referred for evaluation of LQTS. Only 2% of patients ultimately dismissed as clinically and/or genetically normal exhibited such ectopy. With a positive predictive value exceeding 90% for the presence of significant cardiac pathology, the presence of exercise-induced ventricular ectopy beyond single, isolated PVCs must prompt intense scrutiny. However, CPVT, rather than LQTS, is the far more likely diagnosis. In particular, exercise-induced bigeminal PVCs should no longer be viewed as necessarily a simple, benign arrhythmia as PVCs in bigeminy, rather than bi-directional VT, was CPVT's almost universal arrhythmia.

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Glossary of Abbreviations

CPVT	Catecholaminergic polymorphic ventricular tachycardia
ECG	Electrocardiogram
LQTS	Long QT syndrome
NSVT	Non-sustained ventricular tachycardia
PVCs	Premature ventricular contractions

TdP	Torsades de pointes
TWA	T-wave alternans

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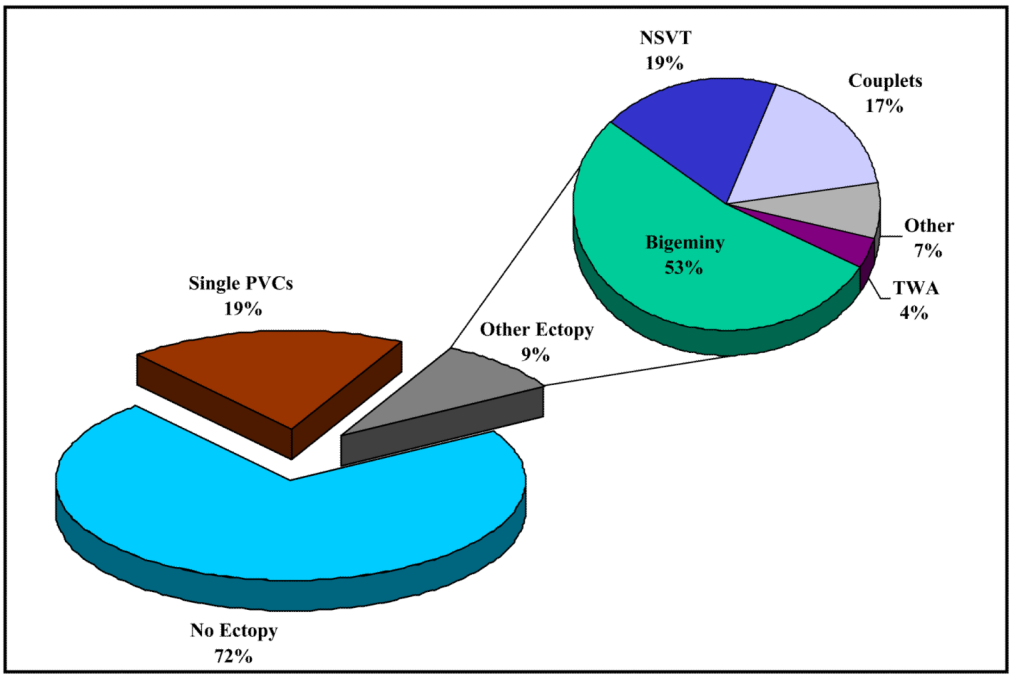

Figure 1. Spectrum and Frequency of Exercise-Induced Ventricular Ectopy

Shown is the spectrum and frequency of exercise-induced ventricular ectopy. “Other” ventricular ectopy included triplets, PVCs in trigeminy and quadgeminy. No TdP was recorded

Table 1

Demographics (n=381)

Average age at referral (years)	24±14
Sex distribution (M/F)	155/226
Average resting QTc (msec)	442±37
Genetic Positive Distribution	
LQT1	80
LQT2	58
LQT3	15
LQT5	2
LQT7	1
Catecholaminergic Polymorphic Ventricular Tachycardia	10
LQTS and RYR2 Gene Negative	129
Not Genetically Tested	86