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ORIGINAL RESEARCH

Beta-Blockers and Exercise Performance in Children with Long QT Syndrome

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ABSTRACT

BACKGROUND Young people taking beta-blockers for long QT syndrome (LQTS) have concerns about exercise performance.

OBJECTIVES This study sought to determine whether objective measures of cardiopulmonary fitness are influenced by beta-blocker dose in LQTS.

METHODS In a retrospective chart review of treadmill cardiopulmonary exercise tests (CPETs), we measured peak oxygen consumption (V_{O_2}), respiratory exchange ratio (RER), blood pressure, and percent predicted heart rate at peak exertion (%PHR), each analyzed with a linear mixed-effects model. We analyzed nadolol data (noncardioselective) as our primary analysis, then analyzed a validation cohort of atenolol data (cardioselective).

RESULTS We evaluated 220 CPETs in 93 patients with LQTS. The mean age at first CPET was 12 $\pm$ 3.9 years. In multivariable analysis, %PHR decreased by 13% for every 1 mg/kg/d increase in beta-blocker dose, demonstrating physiologic beta-blocker effects. However, we identified no correlation between nadolol dose and measures of cardiopulmonary fitness. Neither peak V_{O_2} nor peak RER was correlated with nadolol dose. Only mild blood pressure changes were observed (<9 mm Hg decrease at peak exertion per 1 mg/kg increase in nadolol dose). Increased atenolol dose was also associated with stable peak V_{O_2} and peak RER.

CONCLUSIONS In children with LQTS, we did not observe any relationship between higher nadolol doses and objective measures of effort (peak RER) or cardiopulmonary fitness (peak V_{O_2}), despite a linear dose-response between nadolol dose and %PHR. These results suggest that treatment with nadolol for LQTS does not affect most patients' peak exercise performance. These data were validated in patients from an earlier era who had been prescribed atenolol. (JACC Clin Electrophysiol. 2026;■:■-■) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise test

LQTS = long QT syndrome

RER = respiratory exchange ratio

Vo_2 = oxygen consumption

%PHR = percent predicted heart rate at peak exertion

The hallmark of long QT syndrome (LQTS) is a prolonged QT interval on electrocardiogram and an increased risk for ventricular arrhythmias, syncope, and sudden death. Beta-adrenergic receptor antagonists (beta-blockers) are first-line therapy for LQTS.[1]

Sports performance is an important issue for patients and families. This is increasingly apparent in the LQTS community as more patients participate in competitive sports.[2,3] Some young patients report decreased sports performance while taking beta-blockers. The role of beta-blocker on LQTS patients' sports performance has been questioned in these situations. To address this question, we used two widely collected, objective markers of cardiopulmonary performance. First, maximal oxygen consumption (peak Vo_2) is the highest rate at which an athlete can consume oxygen in cellular metabolism. It is a traditional metric of cardiopulmonary fitness. Second, the peak respiratory exchange ratio (RER) measures the highest ratio of carbon dioxide exhaled against the consumption of oxygen. Higher RERs are an objective proxy for a patient's drive to maximal exercise intensity. We also studied a third variable, blood pressure at rest and with exercise. While peak blood pressure does not typically affect exercise performance, it represents an additional potential side effect of beta-blocker therapy for LQTS patients.

We used the relationship between beta-blocker dose and peak heart rate as a positive control variable to demonstrate that patients were receiving sufficient doses of beta-blocker to influence their exercise physiology. There are insufficient data to establish that a specific target heart rate on beta-blockers is protective against mortality. However, in the last 25 years, opinions have coalesced around a reduction of 15% to 20% in peak heart rate. In the early 2000s, French investigators were hospitalizing patients to bring their peak heart rates below a "maximum accepted value for age" on exercise test, without stipulating a specific value.[4] By 2008, the group at Children's Hospital of Philadelphia published that "our practice is to obtain an approximately 20% reduction in maximum heart rate."[5] That recommendation was still current in 2022, when Krahn et al[6] wrote "the authors aim for heart rate blunting of 15% to 20%" and in 2025, when El Assaad et al[7] reported that "adequate beta blockade was determined as a reduction of at least 15% to 20% from the predicted maximal heart rate." Other LQTS assessments based on heart rate exist.[8]

The primary objective of our study was to analyze cardiopulmonary exercise capacity (peak Vo_2) and exercise effort (peak RER) in patients with LQTS on varying doses of nadolol.

METHODS

Patients with a diagnosis of LQTS who performed a CPET between October 2003 and April 2021 at a single center were identified by retrospective review. This time interval was chosen because it corresponded to an era with a single, consistent data collection schema in the CPET laboratory. Each LQTS diagnosis was independently verified by chart review, including expert review of electrocardiograms and testing. Drug doses and medication adherence data were obtained from retrospective review of exercise stress test reports, clinical notes, and pharmacy dispensary information (Supplemental Methods). We tabulated all CPETs in patients with LQTS including those for whom no beta-blocker was prescribed (typically during the diagnostic phase of LQTS).

Nadolol has been the primary drug of choice for LQTS in our center since the determination that noncardioselective beta-blockers were superior for treatment of LQTS and was used for primary analysis. However, a cardioselective beta-blocker (atenolol) had been prescribed for LQTS patients in our center before 2012, and so we evaluated the retrospective data for patients on atenolol as a validation cohort. Therefore, we established two cohorts, each with clinical LQTS, but with different beta-blocker prescription strategies, in order to assess whether our findings were generalizable beyond just nadolol.

Genotype was determined by clinical genetic testing, as recorded in our centralized genotype database (Progeny Genetics v11.3.4.0). All variants were reclassified for this project using guideline-based methodology.[9]

CPETs were performed with a Bruce protocol, consisting of up to 7 progressive 3-minute exercise stages on a treadmill. Continuous exhaled gas analysis determined Vo_2 and RER using standard methodology. For each CPET, the percent predicted heart rate at peak exertion (%PHR) was our primary heart rate measure:[10]

$$\%PHR = 100\left(\frac{Peak\ heart\ rate\ achieved\ [bpm]}{220 - age\ [years]}\right)$$

Dose response for %PHR was evaluated using a linear mixed-effects model. In this model, %PHR was the response variable, nadolol dose (in mg/kg/d) was a fixed effect, and unique patient identifier was a random effect. The coefficient of nadolol dose in this

TABLE 1 Demographics

Characteristic	LQTS Patients (n = 93)
Age (first CPET), y	13.6 ± 3.9
Age (all CPETs), y	15.2 ± 3.9
Weight (first CPET), kg	50.0 (34.0-61.5)
Height (first CPET), cm	155.5 (140.0-167.0)
Female	52 (54)
Number of CPETs	2 (1-3)
Genotype-positive	63 (68)
KCNQ1	42 (45)
KCNH2	18 (19)
SCN5A	1 (1)
Other	2 (2)

Values are mean ± SD, median (Q1-Q3), or n (%).
CPET = cardiopulmonary exercise test; LQTS = long QT syndrome.

model was used to quantify the dose response (the coefficient is the slope of the dose-response curve). This coefficient represents a cohort-average dose response and should not be interpreted as a within-subject effect of nadolol treatment. Similar analyses were performed to evaluate dose response for peak RER, Vo_2, and systolic and diastolic blood pressure. In part because some additional variables could not be reduced to simple covariates, sensitivity analysis was performed using the same multivariable model technique in subgroups that were defined by medication adherence, RER threshold ≥1.1 (traditionally associated with maximum exertion), and a single genotype analysis (pathogenic or likely pathogenic variants in *KCNQ1*). All models were fit using the *lme4* package in R version 4.2.3 (R Foundation for Statistical Computing).[11]

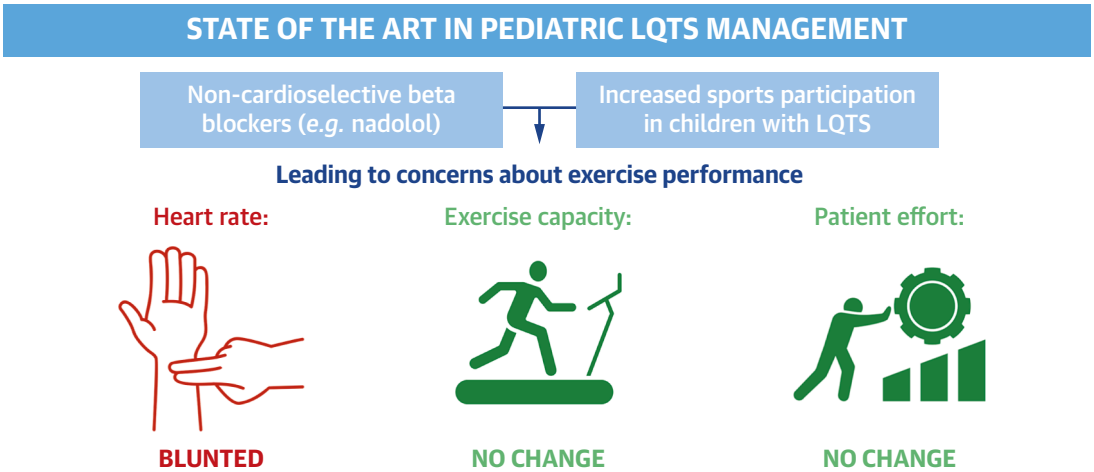
Human subjects exemption was provided by Lurie Children's Institutional Review Board.

RESULTS

STUDY POPULATION. During the study period, 93 patients with LQTS completed 220 clinical CPETs on a treadmill. Slightly more than half of patients with LQTS were female (54%), and the mean age at first CPET was 12 ± 3.9 years (range 6-24 years). The mean age across all stress tests was 15 ± 3.9 years. Further demographic data are provided in Table 1.

MEASUREMENTS OF EXERCISE CAPACITY AND EFFORT. Nadolol dose was assessed against independent metabolic markers of cardiopulmonary capacity (Vo_2) and effort (peak RER) (Central Illustration). We did

CENTRAL ILLUSTRATION Increasing Nadolol Dose in Children With LQTS Does Not Affect Average Exercise Performance



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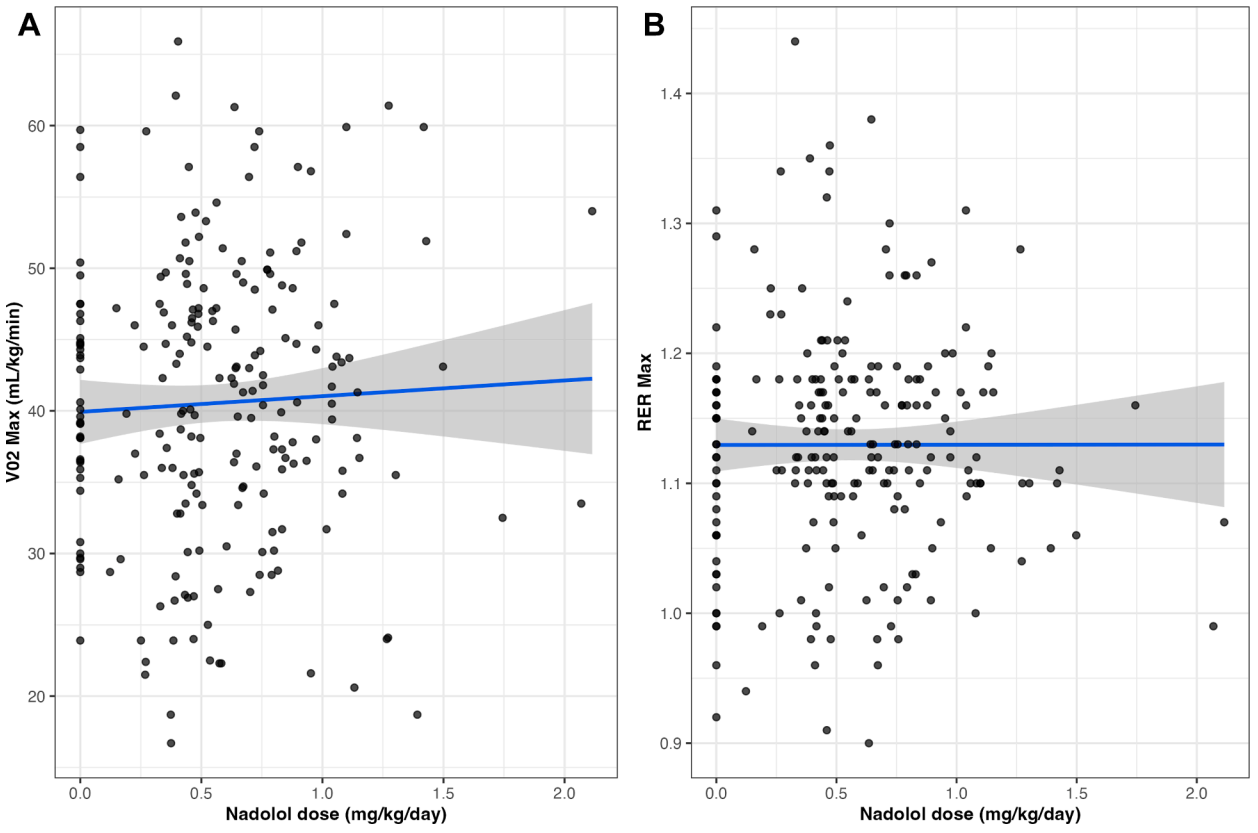
As expert recommendations and clinical practice have moved toward shared decision making with patients and families regarding arrhythmia risk during exercise, athletes with Long QT Syndrome (LQTS) have increased their sports participation. The current study demonstrates that, on average, increasing doses of non-cardioselective beta blockers were associated with blunted heart rate at peak exertion, but not associated with decreases in measurements of exercise capacity (oxygen consumption) or patient effort (respiratory exchange ratio).

FIGURE 1 Relationship Between Nadolol Dose and Measures of Exercise Performance



Nadolol dose, plotted against (A) maximum oxygen consumption (V_{O_2} Max) and (B) respiratory exchange ratio (RER), with individual exercise stress tests overlayed as black dots. The projection of a linear mixed-effects model (blue line) is displayed with a 95% CI (gray). Both 95% CIs overlap a slope of 0, demonstrating no statistical relationship between nadolol dose and either V_{O_2} Max or RER.

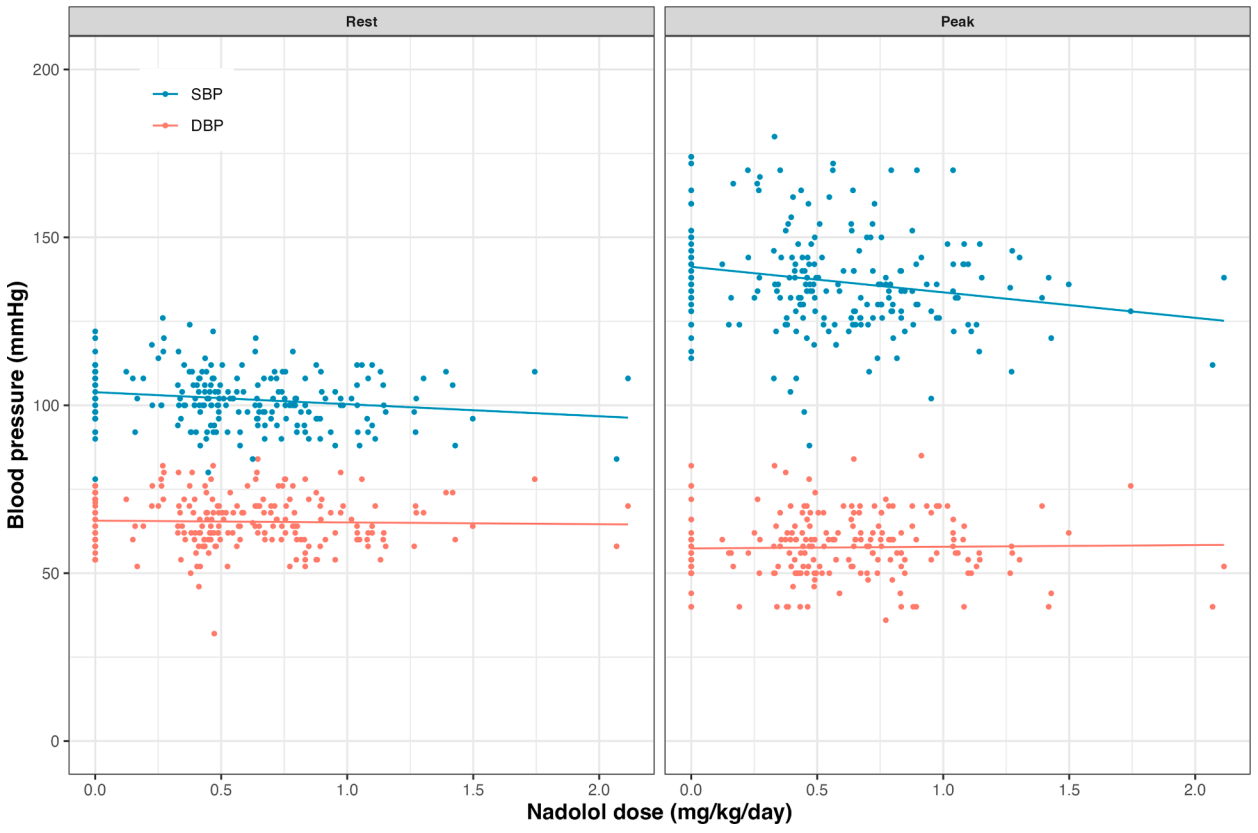
not detect any relationship between peak V_{O_2} and increasing nadolol dose (Figure 1A), nor did we detect any statistical relationship between nadolol dose and peak RER (Figure 1B).

We also evaluated the relationship between systolic and diastolic blood pressure and beta-blocker dose. There was a mild negative correlation between beta-blocker dose and blood pressure both at rest and peak exercise. At rest, the difference in blood pressure between 0 and 1 mg/kg/d of nadolol was 3.5 mm Hg (systolic) and 0.5 mm Hg (diastolic). Similarly, at peak exercise, the difference in blood pressure between 0 and 1 mg/kg/d nadolol was 8.25 mm Hg (systolic) and 0.5 mm Hg (diastolic) (Figure 2).

DOSE-RESPONSE WITH NADOLOL. To demonstrate that we were able to observe typical dose-dependent nadolol effects in this study population, we evaluated the relationship between nadolol dose and heart rate at peak exercise (ie, as a positive control). A summary of all prescribed nadolol doses is provided in Supplemental Figure 1. As expected, there was a linear response between dose of nadolol (mg/kg/d) and %PHR. The coefficient of our linear model was −13.0 (95% CI: 10.1 to 15.8; $P < 0.001$), corresponding to a reduction of 13 percentage points in the PHR associated with a 1 mg/kg/d increase in nadolol (Figure 3).

SENSITIVITY ANALYSES. To ensure that the absence of a relationship between exercise performance and nadolol dose was not due to other clinical features, we explored several sensitivity analyses, including medication adherence, RER constraints, and genotype-specific regressions. We first excluded CPET tests in which medical record or pharmacy data indicated that the patient was not reliably adherent to their treatment regimen. As expected, there was a small difference in the slope of the heart rate dose-

FIGURE 2 **Mild Decrease in Blood Pressure With Increasing Dose of Nadolol**



Univariate regression of blood pressure against beta-blocker dose at rest (left) and peak exercise (right) for patients with long QT syndrome. DBP = diastolic blood pressure; SBP = systolic blood pressure.

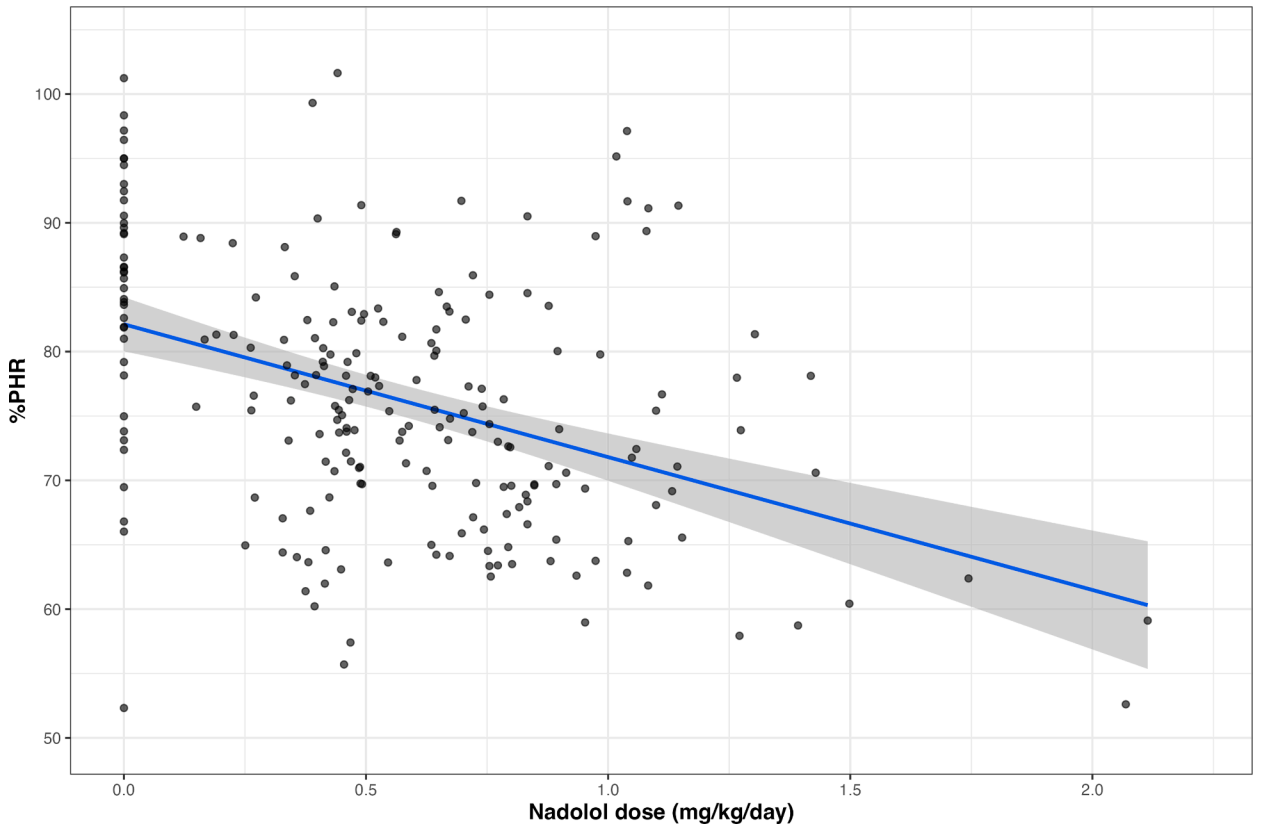
response relationship when we excluded patients with unreliable adherence (Supplemental Figures 2A and 2B). However, our conclusions of a stable peak V_{O_2} and peak RER relationship were unchanged when excluding patients with unreliable adherence.

In addition, a CPET is typically considered to have been performed at maximal effort when the RER is ≥1.1. Therefore, to ensure that our statistical conclusions about V_{O_2} and %PHR were not significantly altered by varying degrees of patient effort, we performed a sensitivity analysis that restricted our sample population to only those CPETs in which the peak RER was ≥1.1. The conclusions about exercise capacity were unchanged (we detected no dose relationship for V_{O_2}), and the heart rate dose-response relationship did not change significantly (Supplemental Figure 2C).

Polypharmacy did not significantly affect heart rate in this dataset. Patients included in the study had been prescribed 47 additional medications in various combinations (Supplemental Table). Two of these 47 medications have been reported to elevate heart rates in 10% or more of patients taking them. These medications (atomoxetine and levothyroxine) were taken by 3 patients, in 5 total CPETs. One patient was taking levothyroxine, 1 was taking atomoxetine, and 1 was taking both levothyroxine and atomoxetine. None of these 3 patients were significant outliers in beta-blocker effects during CPET compared with similar patients in the study. However, we had too few instances to draw larger conclusions for these medications outside of our study.

DOSE RESPONSE WITH ATENOLOL. We considered that that these findings might be unique to the interaction between nadolol and LQTS patients. Therefore, we also analyzed retrospective data on patients with LQTS who were prescribed atenolol to

FIGURE 3 Dose-Response Relationship Between Nadolol and Percent Predicted Heart Rate



The projection of a linear mixed-effects model is shown in blue with 95% CI in gray. %PHR = percent predicted heart rate at peak exertion.

demonstrate that these findings were not unique to nadolol. Similar to nadolol, we found no association between atenolol dose and RER or peak Vo_2 (Supplemental Figure 3). The heart rate dose-response curve was similar for atenolol, although with a different coefficient of effect because there is not a 1:1 dose equivalence between nadolol and atenolol (Supplemental Figure 4).

GENOTYPE ANALYSES. The mean QTc value at rest in LQTS patients was 474 ± 40.1 milliseconds and the mean QTc value at 4-minute recovery was 517 ± 47.4 milliseconds. Genetic analysis had been performed in 100% of the LQTS patients who were prescribed nadolol and 84% of all LQTS patients (genetic testing was not performed in the earliest years of analysis when atenolol was more common). Pathogenic or likely pathogenic variants were present in 67% of tested patients (45% *KCNQ1*, 19% *KCNH2*, 1% *SCN5A*, 2% other genotypes). The mean QTc value at rest in genotype-positive LQTS patients was longer compared with genotype-negative/unknown LQTS patients (478 milliseconds vs 468 milliseconds; $P = 0.04$).

In a final sensitivity analysis, we restricted our nadolol dose-response comparison to just patients who were genotype positive with *KCNQ1* variants (n = 42). In the absence of any beta-blocker therapy, patients with a pathogenic or likely pathogenic variant in *KCNQ1* had a slightly lower resting heart rate prior to starting exercise (78.8 beats/min vs 82.8 beats/min). During exercise, the slope of the heart rate response curve vs nadolol dose was also shallower, implying that more nadolol was required to see the same heart rate blunting in *KCNQ1*-positive patients than in all other LQTS patients (−11.8 *KCNQ1* vs −13.0 all LQTS) (Supplemental Figure 2D). However, there were no differences in our primary study conclusions about dose and exercise capacity in this subgroup. The number of patients in other genotypes was too few for additional genotype-stratified analyses.

DISCUSSION

Beta-blockers are the core treatment paradigm in LQTS. Decades into the collective experience with beta-blockers for LQTS, clinicians still grapple with how large a dose to prescribe for any given child and how to minimize the quality-of-life implications of long-term beta-blockade. This study focused on the measurable effects of beta-blockers on exercise at varying medication doses.

EXERCISE TOLERANCE. Patients and families with LQTS have begun to embrace shared decision making about sports participation. As the field acquires more data to support sports participation in LQTS,[2,3,12,13] other practical clinical considerations arise. Patients and parents frequently ask whether nadolol inhibits sports performance. Our data were reassuring, although limited by the retrospective nature of our methods. On average, treatment with nadolol for LQTS did not affect patients' peak exercise performance (RER or V_{O_2}); however, this is statistically true across many patients. Both within our dataset and in our clinical experience, individual patients may experience a decline in performance at higher beta-blocker doses. Although individual experiences are important, patients and parents can be reassured that in the reasonably large group of children who were analyzed in this study, athletic performance was statistically consistent across a range of nadolol doses.

BLOOD PRESSURE. Occasionally, parents raise the question of whether children on nadolol for LQTS will have symptoms from medication-induced hypotension. Reassuringly, there were only mild linear decreases in systolic and diastolic blood pressure at rest and at peak exertion, and on average, clinically significant changes in blood pressure did not occur at typical doses of nadolol. The mean decreases were all $<$9 mm Hg per 1 mg/kg/d of nadolol (**Figure 2**). Clinically significant hypotension, at rest or with exercise, is not likely a major side effect of nadolol at doses typical for LQTS, which matches the practical experience of most clinicians.

DOSE-RESPONSE RELATIONSHIP. Importantly, higher doses of nadolol corresponded to a lower peak heart rate during exercise in patients with LQTS. We included this analysis as a positive control in our dataset. It validates the previous V_{O_2} and RER data, demonstrating that there are measurable and clinically important changes in heart rate on the doses of nadolol prescribed in this study, even though there was no statistical effect on exercise performance.

In our linear, multivariable model, we observed a reduction in percent predicted peak heart rate of 13 percentage points for each 1 mg/kg/d increase in nadolol. The dose-response effect between beta-blockers and heart rate is the basis for clinical recommendations to increase beta-blockers in the face of inadequate peak heart rate response during CPETs. While a traditional recommendation has been to target a peak heart rate reduction of 15% to 20%,[4-7] a recent manuscript by Anys et al[8] proposed a structured paradigm to adjust dosing. The data in the present paper support the direction and overall magnitude of the published data in Anys et al. Our study extends those data beyond cycle ergometry (which is associated with a lower peak heart rate at maximal exercise) by providing a multivariable analysis in a setting in which treadmill tests are the modality of choice.

However, in contrast to the conclusions in the Anys et al paper,[8] we are not confident that this dose response curve is sufficiently robust across all participants to propose a rigid dosing schema. First, although **Figure 3** established a linear dose-response for nadolol and peak heart rate, the overlaid scatterplot demonstrates significant variability from test to test. Second, our regression data are consistent with a recent article by El Assaad et al[7] that demonstrated 40% of patients prescribed less than 0.75 mg/kg/d nadolol nonetheless had adequate chronotropic suppression. They further proposed that repeat exercise stress testing does a superior job at providing an individualized treatment plan than an algorithm. Our data support their contention that adequate heart rate suppression can happen at $<$0.75 mg/kg/d, and that substantial patient-to-patient variability exists.

Medication adherence did not appear to be a factor in our findings. While there are limitations to retrospective evaluation of medication adherence, our conclusions were unchanged when only patients with adequate adherence were analyzed. This is important because it establishes that the lack of signal between nadolol dose and exercise capacity is not likely to be due to nonadherence. Similarly, sensitivity analyses on patient effort (RER $\geq$1.1) and genotype (*KCNQ1*) also did not change our central conclusions.

Finally, we validated that the conclusions about V_{O_2}, RER, and %PHR were not exclusively linked to nadolol by repeating our analyses in patients

prescribed atenolol. Although the atenolol data were older, and most clinicians treating LQTS no longer use cardioselective agents, we saw the same effect, size, and direction as we had documented with nadolol. This suggests that results may be generalizable to other beta-blockers that share similar pharmacologic features.

STUDY LIMITATIONS. This was a retrospective study at a single center. A prospective study of exercise performance before and after starting and increasing dose is needed, especially because we provide primarily between-subject data, not exclusively within-subject data. In addition to standard limitations of retrospective analyses, patients who did experience significant declines in sports performance may have stopped beta-blockers, attended fewer clinics, or performed fewer CPETs, skewing our data distribution. Recommendations on exercise restrictions during the diagnostic phase imply that some patients may have been relatively deconditioned during early exercise stress tests (off beta-blockers). Era effects may be important. Nearly all genotype-negative/unknown patients were cared for years ago. These genotype-unknown patients have aged out of care at our pediatric center, leaving the frequency of genotype-positive patients slightly lower than contemporary genotyping studies. This is likely an artifact of extending our cohort backward to create a validation set with atenolol, not a skewed population of genotypes. However, despite these limitations, the robust nature of our central conclusions, especially in the face of multiple sensitivity analyses, implies that these data are a helpful starting point for discussions with families.

CONCLUSIONS

No relationship was found between beta-blocker dose and either peak Vo_2 or RER in children with LQTS, which is reassuring for young athletes. There was a dose-response effect between nadolol and peak heart rate, demonstrating that clinical effects were occurring at these doses, and validating the lack of change in sports performance.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Nadolol and other noncardioselective beta-blockers are first-line therapy for children with LQTS, but limited data exist about sports performance in children with LQTS while taking beta-blockers, despite the recent liberalization of sports performance guidelines. In this study, two major objective measures of sports performance (peak Vo_2 and RER) were not affected by nadolol dose. There was a linear dose response between peak heart rate during exercise and nadolol dose, validating that Vo_2 and RER relationships were not due to lack of drug response.

TRANSLATIONAL OUTLOOK: While individual patients may experience a decline in sports performance while taking beta-blockers, this study provides additional long-term data that beta-adrenergic receptor blockers are effective, safe, and usually well tolerated in children with LQTS. These data support the trend toward shared decision making surrounding sports among physicians, patients, and families.

REFERENCES

1. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963.

2. Lampert R, Day S, Ainsworth B, et al. Vigorous exercise in patients with congenital long QT syndrome: results of the prospective, observational, multinational LIVE-LQTS study. *Circulation*. 2024;150:516–530.

3. Lampert R, Olshansky B, Heidbuchel H, et al. Safety of sports for athletes with implantable cardioverter-defibrillators: results of a prospective, multinational registry. *Circulation*. 2013;127:2021–2030.

4. Villain E, Denjoy I, Lupoglazoff JM, et al. Low incidence of cardiac events with beta-blocking therapy in children with long QT syndrome. *Eur Heart J*. 2004;25:1405–1411.

5. Shah M, Carter C. Long QT syndrome: a therapeutic challenge. *Ann Pediatr Cardiol*. 2008;1:18–26.

6. Krahn AD, Laksman Z, Sy RW, et al. Congenital long QT syndrome. *JACC Clin Electrophysiol*. 2022;8:687–706.

7. El Assaad I, Heilbronner AK, Zahka K, Hammond B, Patel A, Aziz PF. Utility of cardiopulmonary exercise testing in assessing beta-blocker efficacy in LQTS: moving away from one-size-fits-all. *J Cardiovasc Electrophysiol*. 2025;36:2287–2295.

8. Anys S, Arnaud M, Minois D, et al. Dose response to nadolol in congenital long QT syndrome. *Heart Rhythm*. 2021;18:1377–1383.

9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424.

10. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67:1–48.

11. Almaadawy O, Uretsky BF, Krittanawong C, Birnbaum Y. Target heart rate formulas for exercise stress testing: what is the evidence? *J Clin Med*. 2024;13(18):5562.

12. Davydoff C, Andorin A, Minois D, et al. Does sports participation increase risk in patients with long QT syndrome? Results from a large French cohort. *Europace*. 2022;24:1675–1683.

13. Tobert KE, Bos JM, Garmany R, Ackerman MJ. Return-to-play for athletes with long QT syndrome or genetic heart diseases predisposing to sudden death. *J Am Coll Cardiol*. 2021;78:594–604.

KEY WORDS beta-adrenergic receptor antagonist, cardiopulmonary exercise test, electrophysiology, long QT syndrome, pediatric, pharmacology

APPENDIX For an expanded Methods section, supplemental table, and supplemental figures, please see the online version of this paper.