Exercise-induced QTc prolongation and implications for military service members: A case series

Austin Pagani, MGC, CGC,*† Lydia D. Hellwig, PhD, ScM, CGC,*†‡ Craig P. Dobson, MD,§ Brian N. Hughes, DO,‡ John P. Schacht, DO,§ Mark Haigney, MD‖

*From the *The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, Bethesda, Maryland, †Center for Military Precision Health (CMPH), Uniformed Services University of the Health Sciences, Bethesda, Maryland, ‡Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, §Department of Pediatric Subspecialties, Walter Reed National Military Medical Center, Bethesda, Maryland, and ‖Military Cardiovascular Outcomes Research, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.*

Introduction

Exercise is often seen as a voluntary activity with physical and mental health benefits. However, for military service members exercise is a required component of military service to ensure service members are prepared to meet the physical demands of their missions.[1] The prevalence of corrected QT interval (QTc) prolongation among highly athletic individuals has been shown to be elevated over the general population.[2–4] An international consensus statement has set the prolonged QTc cut-off as ≥470 ms for male athletes and as ≥480 ms for female athletes, but they acknowledge that 1 electrocardiogram (ECG) with a prolonged QTc warrants further evaluation, such as repeat ECG, consideration of personal and family history, and in some cases additional cardiac or genetic testing, before a diagnosis of long QT syndrome (LQTS) is made.[5] The importance of a follow-up evaluation for QTc prolongation was further demonstrated by a recent study from Dagradi and colleagues,[6] which identified a group of athletes with an acquired form of exercise-induced long QT (LQT). Individuals with exercise-induced LQT presented with QTc prolongation but showed a significant reduction in their QTc after a 3- to 6-month detraining period compared to individuals with genotypically or clinically confirmed LQTS.[6] A separate case report of a young female athlete observed this same pattern of QTc normalization following a 4-month detraining period.[7] Cases of exercise-induced LQT have also been noted to contribute to the misdiagnosis of LQTS.[8]

Herein we report 3 additional cases of exercise-induced LQT among military service members who underwent extensive cardiac evaluations with a period of exercise cessation.

KEY TEACHING POINTS

- Exercise-induced QTc prolongation, or exercise-induced long QT (LQT), is a recently described condition that can be mistaken for long QT syndrome (LQTS) if a careful evaluation, including detraining and retraining, is not performed. Following a period of detraining, individuals with exercise-induced LQT had a normalization of their QTc interval, which persisted in our cases even after resuming physical activity.
- This acquired form of QTc prolongation is a diagnosis of exclusion and should include assessments provided by a multidisciplinary cardiogenetics team.
- While missing a diagnosis of LQTS can have severe consequences, a misdiagnosis of LQTS rather than exercise-induced LQT can have a profoundly adverse impact on the patient and their family, especially in the setting of military service.

Given that military service members are required to be highly active, this population may be at an elevated risk for exercise-induced LQT. Distinguishing between this acquired form of QTc prolongation and congenital LQTS is important, as there are military-specific repercussions that could arise from an inappropriate diagnosis of LQTS.

Case reports

Case 1

An active 22-year-old male patient presented with an abnormal electrocardiogram (ECG) indicating possible QT prolongation on a screening physical examination required

KEYWORDS QTc prolongation; Long QT syndrome; Exercise; Detraining; Acquired; Cardiogenetics
(Heart Rhythm Case Reports 2023;9:759–763)

Address reprint requests and correspondence: Mrs Austin Pagani, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814. E-mail address: austin.pagani.ctr@usuhs.edu.

https://doi.org/10.1016/j.hrcr.2023.07.023

for entry into Special Forces training. The initial ECG had a QTc of 495 ms by automated measurement, which was determined to be 480 ms by an electrophysiologist (Figure 1). He reported 1 episode of syncope when he was 13 years old where he got out of bed, felt a "head rush," and then passed out. His personal history was negative for any other cardiac-related symptoms or events, and he was not taking any medications at the time of the abnormal ECG. Prior to his initial presentation in our clinic, the patient had a transthoracic echocardiogram, which showed no structural abnormalities. The patient's maternal grandmother died at age 73 due to heart failure, but there was no other reported family history of cardiovascular disease, sudden cardiac death, or unexplained death in the family.

Genetic testing including a panel of 17 genes associated with LQTS (*AKAP9, ANK2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1, TRDN*) was negative for any pathogenic or likely pathogenic variants, but did identify a variant of uncertain significance in *CACNA1C* (c.3210 G>C, p.Lys1070Asn). The *CACNA1C* gene is involved in the formation of voltage-gated calcium channels. To help interpret this variant, ECGs for all first-degree family members were recommended and familial variant testing was offered to family members with a prolonged QTc. The patient's mother and sister were the only first-degree relatives found to have a QTc at the upper limit of normal (455 ms and 450 ms, respectively), and they both tested negative for the variant of uncertain significance in *CACNA1C*.

The patient also underwent placement of an implantable loop recorder (ILR). Over the course of nearly 5 months, no arrhythmias were observed from the ILR. During this time the patient underwent a 1-month period of detraining and his QTc reduced to 440 ms. When he resumed exercise, consisting of 2–3 hours of swimming or running a day, his QTc remained between 440 and 450 ms (Figure 1). Additionally, he had a normal stress test with appropriate QT shortening and a recovery QTc that did not exceed 470 ms at 4 minutes. Since these evaluations in 2018, the patient has not had any reported cardiac issues and has gone on to serve in Special Forces.

Case 2

A previously healthy 20-year-old male patient presented with an abnormal ECG suggestive of LQTS (QTc of 518 ms by automated measurement and 486 ms by the electrophysiologist's review) following a 36-hour athletic training competition (Figure 1). The ECG was performed as routine screening for Special Forces training. At this time, he also had precordial T-wave inversions. His personal history was negative for any cardiac-related symptoms or events, and he was not taking any medications. He reported no family history of cardiovascular disease, sudden cardiac death, or unexplained death in the family.

The patient underwent an extensive cardiac workup, including cardiac magnetic resonance imaging and transthoracic echocardiography, which showed no structural abnormalities or scarring. He was noted to have mild left ventricular and atrial enlargement that was considered consistent with his elevated levels of physical activity. He had a normal stress test with typical shortening of the QT, and ambulatory monitoring was normal except for a single run of 4 beats of nonsustained ventricular tachycardia. Genetic testing including a panel of 16 genes associated with LQTS (*AKAP9, ANK2, CACNA1C, CALM1, CALM3, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B*, *SCN5A*, *SNTA1*, *TRDN*) was negative for any pathogenic variants.

Following the abnormal ECG, the patient entered a 6-week period of detraining and his QTc shortened to 440–450 ms. His QTc remained between 440 and 450 ms on subsequent ECG recordings at 12 and 15 weeks post event, although some T-wave inversions persisted. Given the lack of family history and his largely normal cardiac workup with negative genetic testing, the patient was allowed to return to physical activity, which consisted of swimming 2000 meters 3–4 times a week and running 35 miles each week. Following the return to physical activity, his QTc was 440 ms and he was released from follow-up without limitations (Figure 1). Since these evaluations in 2021, the patient has not had any reported cardiac issues and is on active duty in Special Forces.

Case 3

An active 21-year-old female patient presented with a prolonged QTc (automated measurement of 526 ms, electrophysiologist-confirmed measurement of 475 ms) during routine screening for aviation training (Figure 1). She had been participating in 3–4 hours of daily exercise as an NCAA Division 1 lacrosse player. Based on the prolonged QTc the patient was started on propranolol and recommended to significantly reduce her activity level. She had no prior cardiac-related symptoms or events, and she was not taking any medications at the time of the abnormal ECG. She reported no family history of cardiovascular disease, sudden cardiac death, or unexplained death in the family.

A repeat ECG while the patient was on propranolol produced a QTc of 410 ms. Genetic testing for LQTS (*AKAP9, ANIC2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNH2 (HERG), KCNE1, KCNE2, KCNJ2, KCNI5, KCNQ1, SCN4B, SCN5A, SNTA1, TRDN*) was negative for any pathogenic variants. To assess for exercise-induced LQT the patient discontinued propranolol, had an ILR placed, and agreed to decondition for 2–3 months before reevaluation. At her 2- and 3-month follow-ups the patient had a normal QTc of 420–440 ms. She was noted to have inferior T-wave inversions, but transthoracic echocardiography and cardiac magnetic resonance imaging did not reveal any significant structural issues. Her ILR did not detect any arrhythmias even after she returned to daily exercise. Her QTc was 420 ms on an ECG post retraining and a final stress test showed appropriate QT shortening with a recovery QTc that did not

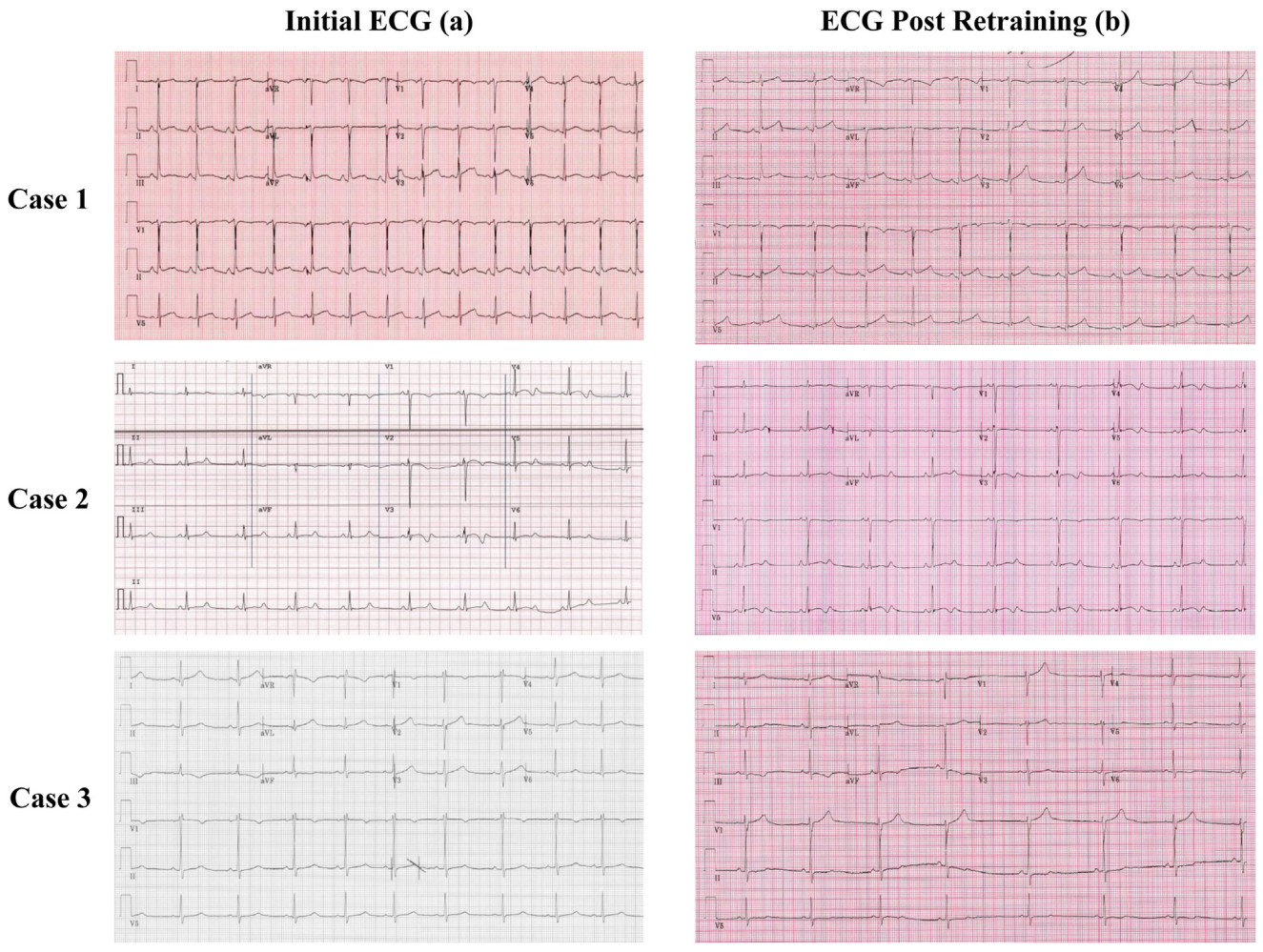

Figure 1 Electrocardiograms from the initial presentation (**a**) and post retraining period (**b**) for each case. QTc measurements by electrophysiologist review: Case 1: **a:** 480 ms; **b:** 440–450 ms. Case 2: **a:** 486 ms; **b:** 440 ms. Case 3: **a:** 475 ms; **b:** 420 ms. ECG = electrocardiogram.

exceed 440 ms (Figure 1). Since these evaluations in 2019, the patient has gone on to serve in the Navy as an aviator. A follow-up ECG in 2022 demonstrated a QTc of 410 ms.

Discussion

These 3 cases support the finding by Dagradi and colleagues[6] that exercise can induce a phenotype similar to LQTS, but in individuals with exercise-induced LQT this phenotype is reversible with detraining. The effects of detraining on ECG normalization were apparent at as early as 4–8 weeks in our cases, which is faster than previously reported.[6,7] Further research is warranted, but this suggests exercise-induced LQT evaluations may require as little as 1–2 months of detraining, which shortens the diagnostic journey of patients with suspected exercise-induced LQT. Critically, we did not observe a return of QTc prolongation among our patients after resumption of their demanding physical activity. Given that resumption of symptoms has occurred in some but not all cases of exercise-induced LQT, an individualized approach to physical activity recommendations should be considered until evidence-based management guidelines are available.[6] A proposed schedule of assessments to be undertaken by a multidisciplinary cardiogenetics team is provided in Figure 2. The cost-benefit analysis of a comprehensive evaluation in the military setting is reasonable considering the resources invested in service members; however, further investigation into the financial trade-off associated with the proposed screening measures may be beneficial, especially in the civilian setting.

Military service members, similar to elite athletes, constitute a unique population where a diagnosis of LQTS can impact not only their management, but also their career. While missing a diagnosis of LQTS could lead to fatal consequences, an inappropriate diagnosis of congenital LQTS rather than exercise-induced LQT could prevent an individual from joining the military or cause an active-duty service member to be discharged from service with or without benefits.[9,10] Further, patients and their families may receive inappropriate management, including recommendations for medication use and ECG screenings for first-degree family members, if exercise-induced LQT is not considered. A diagnosis of LQTS can also have a profound psychological impact on an individual, especially if that diagnosis

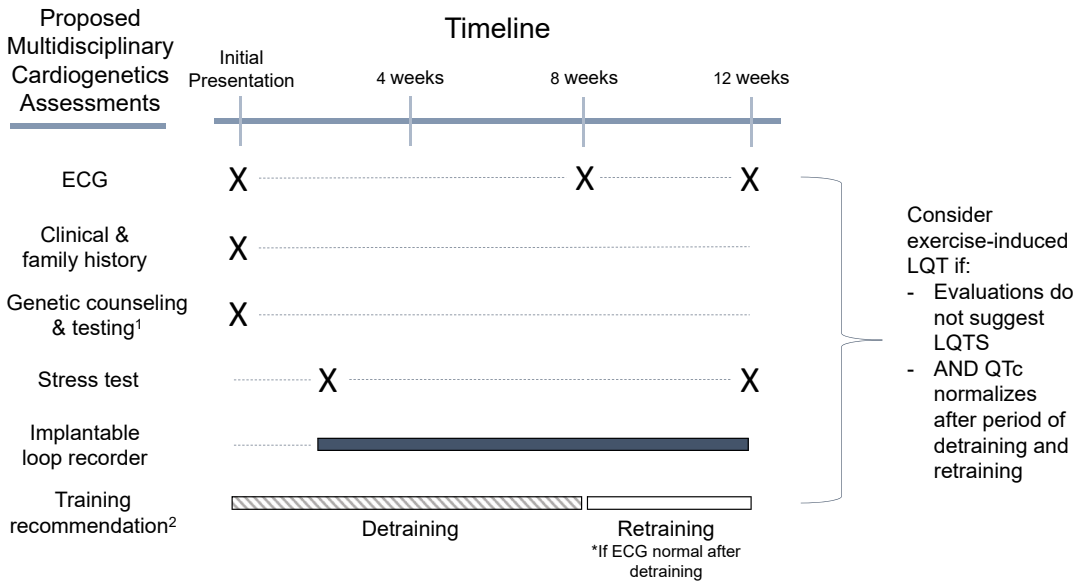

Figure 2 Schedule of proposed assessments by a multidisciplinary cardiogenetics team in the evaluation of exercise-induced long QT. [1]Genetic counseling and genetic testing should be targeted to a panel of genes associated with long QT syndrome unless there is additional personal or family history to consider. [2]During the detraining period exercise should not be performed; during the retraining period, which should only be implemented if the electrocardiogram after detraining is normal, physical activity should be resumed to the same level as before detraining. ECG = electrocardiogram; LQT = long QT; LQTS = long QT syndrome; QTc = corrected QT interval.

challenges a piece of their identity or affects their typical coping strategies, which may involve physical activity.[11]

The prevalence of exercise-induced LQT was 16.6% (33/199) in the original population of athletes from Dagradi's study who were referred with a LQTS phenotype.[6] Within a study of Swiss military conscripts, the frequency of males with QT prolongation (QTc greater than 450 ms) was found to be 0.5% (224/40,760).[12] If these statistics are applied to the current U.S. military there would be more than 1000 active service members with a prolonged QTc that could be incorrectly assumed to have LQTS. A recent review of the Mayo Clinic experience comprising 1841 patients referred for evaluation of LQTS found misdiagnosis in 16%, highlighting the need for exclusion of confounding conditions before making this diagnosis.[8] Awareness of exercise-induced LQT among military healthcare professionals is thus essential, as there are a significant amount of service members that could be affected by an inappropriate diagnosis of LQTS.

Conclusion

Exercise-induced LQT is a recently described phenomenon among highly athletic individuals. This is the first case report, to our knowledge, that identified several cases of exercise-induced LQT in military service members. The QTc prolongation observed in these cases resolved with as little as 1–2 months of detraining and symptoms were not found to return even after resumption of physical activity. Provider knowledge and appropriate assessment of exercise-induced LQT is necessary to reduce inaccurate diagnoses of LQTS and prevent unwarranted disturbances to a military service member's management, psychological health, and ability to serve. Critically, we only reached a diagnosis of exercise-induced QT prolongation after a lengthy, multidisciplinary evaluation with the full participation of the subject. QTc prolongation in athletes should be presumed to be pathologic. Although genetic testing in LQTS is an absolute requirement in this workup, a negative result is not sufficient in itself to exclude a potentially life-threatening condition. Repeated evaluation by the multidisciplinary team over a period of months is essential to reach this diagnosis of exclusion.

Acknowledgments

We would like to thank the patients described in this case series for their time and support in sharing their stories.

Funding Sources: Efforts by LDH and AP were funded by HU00012120102. Partial support was received from award # HU00011920029 from the Defense Health Agency to the Military Cardiovascular Outcomes Research program, Uniformed Services University, Bethesda, MD.

Disclosures: The authors have no financial conflicts to declare.

References

1. Department of Defense. DoD Physical Fitness and Body Fat Programs Procedures (DoD Instruction 1308.03). March 2022. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/130803p.pdf?ver=v5atpuD4j_nbloEbongDAA%3D%3D. Accessed July 13, 2022.
2. Basavarajaiah S, Wilson M, Whyte G, Shah A, Behr E, Sharma S. Prevalence and significance of an isolated long QT interval in elite athletes. Eur Heart J 2007; 28:2944–2949.

3. Sharma S, Whyte G, Elliott P, et al. Electrocardiographic changes in 1000 highly trained junior elite athletes. Br J Sports Med 1999;33:319–324.
4. Stolt A, Karila T, Viitasalo M, Mäntysaari M, Kujala UM, Karjalainen J. QT interval and QT dispersion in endurance athletes and in power athletes using large doses of anabolic steroids. Am J Cardiol 1999;84:364–366.
5. Sharma S, Drezner JA, Baggish A, et al. International recommendations for electrocardiographic interpretation in athletes. Eur Heart J 2018;39:1466–1480.
6. Dagradi F, Spazzolini C, Castelletti S, et al. Exercise training-induced repolarization abnormalities masquerading as congenital long QT syndrome. Circulation 2020;142:2405–2415.
7. Viskin S. Important developments in long QT syndrome: not only for arrhythmia specialists. Circulation 2020;142:2416–2419.
8. Bains S, Neves R, Bos JM, Giudicessi JR, MacIntyre C, Ackerman MJ. Phenotypes of overdiagnosed long QT syndrome. J Am Coll Cardiol 2023;81:477–486.
9. Department of Defense. Medical Standards for Appointment, Enlistment, or Induction in the Military Services (DoD Instruction 6130.03, Volume 1 Change 3). May 2018. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/613003_v1p.PDF?ver=9NsVi30gsHBBsRhMLcyVVQ%3D%3D. Accessed July 10, 2022.
10. Department of Defense. Medical Standards for Military Service: Retention (DoD Instruction 6130.03, Volume 2 Change 1). September 2020. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/613003_vol02.PDF?ver=vx1spUpNVLcc-0-rov00Sg%3d%3d. Accessed July 10, 2022.
11. Asif IM, Price D, Fisher LA, et al. Stages of psychological impact after diagnosis with serious or potentially lethal cardiac disease in young competitive athletes: a new model. J Electrocardiol 2015;48:298–310.
12. Kobza R, Roos M, Niggli B, et al. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. Heart Rhythm 2009;6:652–657.