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Non-sustained microvolt level T-wave alternans in congenital long QT syndrome types 1 and 2☆,☆☆

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ABSTRACT

Background: Patients with long QT syndrome (LQTS) are predisposed to polymorphic ventricular tachycardia (VT) during adrenergic stimulation. Microvolt T-wave alternans (MTWA) is linked to vulnerability to VT in structural heart disease. The prevalence of non-sustained MTWA (NS-MTWA) in LQTS is unknown.
Methods: 31 LQT1, 42 LQT2, and 80 controls underwent MTWA testing during exercise. MTWA tests were classified per standardized criteria, and re-analyzed according to the modified criteria to account for NS-MTWA.
Results: LQT1 and LQT2 patients had a significantly higher frequency of late NS-MTWA (26% and 12%) compared to controls (0%). There was no significant difference between the groups with respect to sustained and early NS-MTWA. Late NS-MTWA was significantly associated with QTc.
Conclusion: LQT1 and LQT2 patients had a higher prevalence of late NS-MTWA during exercise than matched controls. NS-MTWA likely reflects transient adrenergically mediated dispersion of repolarization, and could be a marker of arrhythmic risk in LQTS.

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Introduction

Congenital long QT syndrome (LQTS) is a group of rare inherited disorders characterized by delayed ventricular repolarization, resulting in palpitations, fainting, and sudden death due to torsades de pointes (TdP) ventricular tachycardia [1,2]. LQTS results from mutations of multiple genes encoding for cardiac ion channel proteins, which cause abnormal ion channel kinetics, with genetic subtypes 1 and 2 (LQT1 and LQT2) accounting for the majority of cases [2,3]. TdP is triggered typically during sustained exercise and recovery in LQT1 and during arousal and early exercise in LQT2 [4–6].

Microvolt T-wave alternans (MTWA), a phenomenon characterized by beat-to-beat fluctuation in T wave amplitude and morphology, is closely linked to vulnerability to ventricular arrhythmias like TdP in various experimental and clinical conditions [7]. Clinically, MTWA, as measured using the spectral method, is a strong independent predictor of spontaneous ventricular arrhythmias or death in patients with structural heart disease [8,9]. In these patients, there are well established criteria for positive, negative and indeterminate MTWA tests [10], which allow the clinician to assess risk of sudden cardiac death. In structural heart disease patients, indeterminate test results predict poor outcomes at least as well as positive tests, while only patients with negative MTWA have low risk for sudden death [11]. Two of the three major causes of an indeterminate MTWA test, high levels of ventricular ectopy and failure to achieve an adequate heart rate (HR), were previously known to predict poor outcome [12–14]. In contrast, the third factor causing an indeterminate MTWA test, the development of non-sustained MTWA (NS-MTWA), which may persist for a minute or longer, but is not sustained while HR remains elevated, has not been well-studied.

Furthermore, the use of MTWA testing in patients with LQTS has not been standardized [15]. Although visible alternans is a sign of impending TdP, abnormal MTWA has been observed in about 20% of LQTS patients and the clinical significance of this finding in the LQTS population remains unclear [16]. Even if MTWA may hold promise as

Abbreviations: DoR, dispersion of repolarization; LQTS, long QT syndrome; LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; TdP, torsades de pointes; MTWA, microvolt T-wave alternans; NS-MTWA, non-sustained microvolt T-wave alternans; HR, heart rate; GNFC, gene-negative family controls; UHC, unrelated healthy controls; VT, ventricular tachycardia.

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a predictor of individual susceptibility to arrhythmias in the LQTS population, it is not clear if the standardized criteria for MTWA positivity, which are well-studied and predictive of risk in patients with structural heart disease, might require modification in LQTS patients. Specifically, the prevalence and significance of NS-MTWA in LQTS patients is not known. Life-threatening arrhythmias tend to occur during exercise and early recovery in LQT1 patients, whereas these arrhythmias may occur during startle, early or late exercise in LQT2 subjects [6]. Thus, MTWA, like susceptibility to arrhythmia, might be present during only a portion of exercise in a given individual and fail to sustain throughout the entire period of HR elevation. We aimed to determine the prevalence of NS-MTWA in LQT1 and LQT2 patients in comparison to gene-negative relatives and unrelated healthy control subjects. We hypothesized that LQT1 patients would have a higher prevalence of NS-MTWA during sustained exercise and recovery (late NS-MTWA) and that LQT2 patients would have a higher frequency of NS-MTWA during early exercise (early NS-MTWA) relative to controls.

Methods

Patient selection

LQT1 patients (N = 31) included patients with a positive LQT1 genotype (N = 26) as well as patients whose families carried a LQT1 mutation and who had a personal resting QTc ≥470 for males (N = 3) or QTc ≥480 for females (N = 1) or obligate carrier status (N = 1). LQT2 patients included 42 patients with a positive LQT2 genotype. Gene-negative family controls (GNFC) included 45 subjects belonging to a genotyped LQT1 or LQT2 family who tested negative for the family's mutation. Unrelated healthy controls (UHC) included 35 healthy adult subjects with normal resting electrocardiograms and who denied a personal history of syncope or a family history of unexplained sudden death. GNFC and UHC subjects were combined to form the control group for this study. The institutional review board and all subjects approved the study or their parents signed informed consent.

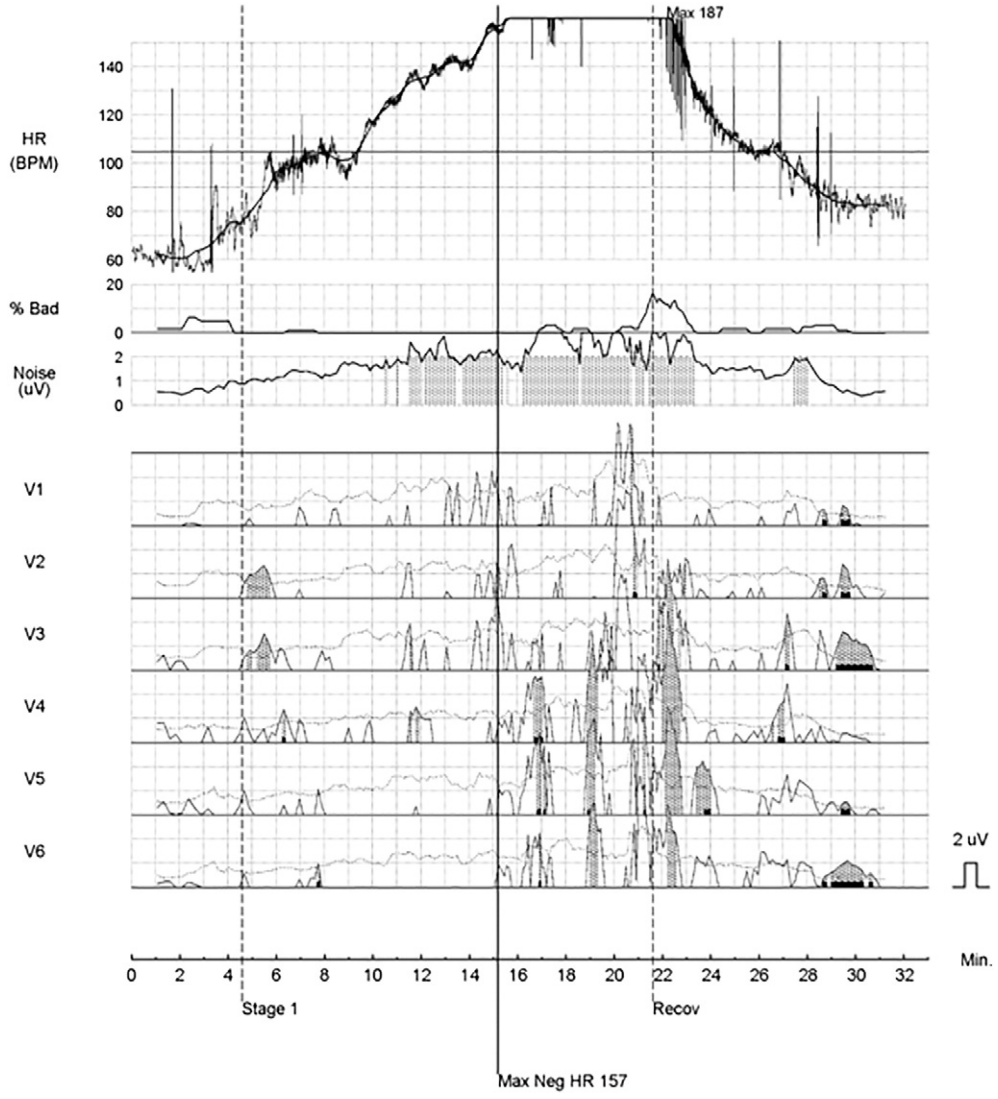

Fig. 1. Example of late NS-MTWA. The x-axis shows minutes of the study, beginning with rest and progressing through exercise and recovery. The y-axis shows multiple simultaneous recordings. The top tracing shows heart rate (HR) in beats per minute (BPM). The second line shows the percentage of bad (ectopic) beats. The third line represents noise in microvolts. MTWA in leads V1 through V6 is represented by the shaded regions below. Episodes of MTWA with magnitude over 1.9 μV and alternans to noise ratio >3 are marked by a solid bar at the bottom. In this example, there is an episode of MTWA occurring in recovery at a heart rate <105 beats/minute which is sustained for over 1 min, seen in lead V3 with confirmatory findings in lead V2. This episode does not meet criteria for sustained MTWA since it does not sustain during the entire period of heart rate elevation.

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