Assessment of Microvolt T-Wave Alternans in High-Risk Patients with the Congenital Long-QT Syndrome

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Background: Microvolt T-wave alternans (MTWA) has been used for arrhythmogenic risk stratification in cardiac disease conditions associated with increased risk of sudden cardiac death. Macroscopic T-wave alternans has been observed in patients with congenital long-QT syndrome (LQTS). The role of MTWA testing in patients with LQTS has not been established.

Objective: To determine the diagnostic value of MTWA testing in high-risk patients with LQTS.

Methods and results: We assessed MTWA in 10 consecutive LQTS index patients who survived cardiac arrest or had documented torsade de pointes tachycardia and 6 first-degree family members with congenital LQTS which had been genotyped in 13 of 16 subjects (7 index patients, 6 family members). No LQTS-causing mutation was identified in 3 index patients with overt QT prolongation. MTWA was assessed during standardized bicycle exercise testing using the spectral method and yielded negative ($n = 8$) or indeterminate ($n = 2$) results in index patients, respectively. Similarly, all first-degree family members tested MTWA negative except for one indeterminate result. Two genotype positive family members could not be tested (two children—4 and 9 years of age).

Conclusion: In patients with congenital LQTS, free from structural heart disease and with a history of life-threatening cardiac arrhythmias, assessment of MTWA does not yield diagnostic value. Hence, determination of MTWA in lower risk LQTS patients without spontaneous arrhythmic events is likely not to be useful for arrhythmia risk stratification.

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long QT syndrome; torsade de pointes; sudden cardiac death; MTWA

INTRODUCTION

Assessment of microvolt T-wave alternans (MTWA) from the surface electrocardiogram has been established as a useful tool to predict an increased risk of sudden cardiac death in different patient populations.¹ MTWA consists of alterations in T-wave amplitude in the surface ECG invisible to the naked eye and is thought to reflect beat-to-beat alternation of membrane repolarization. Both, concordant (same phase alternation among all cardiomyocytes) or discordant (alternating phases of repolarization) alternans can occur and manifest in MTWA.² Discordant alternans may subsequently

lead to generation of gradients for repolarization and susceptibility to ventricular fibrillation.

Whereas the predictive value of MTWA with respect to arrhythmogenesis has been established for a variety of different disease entities and conditions associated with structural cardiac abnormalities such as ischemic and nonischemic cardiomyopathy,^{3–5} the use of MTWA in long-QT syndrome (LQTS) has not been systematically evaluated. Clinical case reports identified macroscopic T-wave alternans (TWA) as a harbinger of life-threatening tachyarrhythmias in LQTS.^{6,7}

A family with a *KCNH2* missense mutation has previously been subjected to MTWA testing in an

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attempt to identify individuals affected by the mutation.⁸ MTWA was found to be a specific (100%) but insensitive (18%) marker for the presence of the LQTS genotype in comparison to genetically unaffected family members.⁸

The aim of the present study was to systematically evaluate the yield of MTWA testing in LQTS patients with a history of life-threatening ventricular tachyarrhythmias and in genotype-positive family members.

METHODS

Patient Selection

Consecutive patients with LQTS referred to the J. W. Goethe-University for further diagnostic work-up and treatment were screened for participation in the present study. Index patients were eligible for participation if the following criteria were met: (1) survived cardiac arrest or documented torsade de pointes ventricular tachycardia with a history of syncope; (2) a QTc interval >450 ms or genetic diagnosis of LQTS; and (3) presence of sinus rhythm. Patients with "acquired" LQTS due to QT prolonging drugs were not included in this study. All available first-degree family members were asked to participate in this study if genotyping demonstrated presence of the index LQTS mutation. One family member refused genotyping and was accordingly not enrolled in this study. All patients provided written informed consent before testing, beta-blocking agents were withheld for at least 3–5 half-lives before testing for MTWA.

Measurement of MTWA

MTWA was measured during bicycle exercise as previously described^{9,5} and was prospectively defined as positive when sustained alternans was present at rest or at an onset heart rate <110 beats/min.¹⁰ MTWA was defined as negative if the criteria for positivity were not met and at least 1 minute of artifact-free data without significant alternans was identified while the heart rate was maintained at either a level <105 beats/min or within 5 beats/min of the maximum heart rate (as long as the maximum heart rate was at least 80 beats/min and the patient exercised to maximal effort limited by fatigue or cardiorespiratory symptoms). MTWA was classified as indeterminate otherwise.

Statistical Methods

Data are presented as absolute values or mean $\pm$ SEM. Comparison of variables was performed using Mann-Whitney *U* test. A 2-sided *P* value < 0.05 was considered statistically significant.

RESULTS

Patient Population

The present report is based on observations in 10 index patients with LQTS (7 females, mean age 45 ± 5 years, Table 1) and 6 first-degree family members (3 females, mean age 35 ± 5 years, *P* = n.s.). The QTc interval (Bazett) was longer in index patients (517 ± 12 ms) compared to genetically affected first-degree family members carrying the respective mutations (448 ± 21 ms, *P* < 0.05). Two genotype positive children, 4 and 9 years of age could not be tested with MTWA technique.

Among index patients, 7 had an LQTS compatible genotype (5 mutations were found in the *KCNH2* gene, 1 in *KCNE2*, and 1 in *KCNQ1*). Three patients remained unclassified after genetic testing (Table 2) but were still included in this study as history and surface ECGs were diagnostic of LQTS. All patients had undergone full length sequencing of five major LQTS genes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*). An implantable cardioverter/defibrillator (ICD) was inserted in 8 index patients—of those 5 had a history of cardiac arrest and 3 patients had syncope with documented torsade de pointes tachycardia. The remaining 2 index patients refused ICD implantation (1 with cardiac arrest and documented torsade de pointes requiring defibrillation (Fig. 1) and 1 with recurrent syncope and documented torsade de pointes. Structural heart disease was ruled out in all index patients by echocardiography and coronary angiography.

Of genetically affected family members, none had a history suggestive of potential arrhythmia manifestations. All index patients and family members were treated with beta-blockers.

MTWA Testing

For the overall study population including index patients and family members, MTWA assessment yielded negative results in 13 studies (81%) and indeterminate in 3 (1 LQTS-1 index patient, 1 LQTS-2 index patient, and 1 LQTS-2 family member, Table 2). MTWA results were classified as

Table 1. Index Patient Characteristics

Index Patients						
Gene	Mutation	Age (Years)	Gender	History	QTc (ms)	Treatment
<i>KCNH2</i>	c.2775dupG	46	Female	SCD + CPR	510	Refused ICD, beta-blocker
	p.Pro926AlafsX14					
	c.91A>T	67	Female	Syncope + TdP	510	Refused ICD, beta-blocker
	p.Ile31Phe					
	c.2255C>G	35	Female	Syncope + TdP	520	ICD + beta-blocker
	p.Arg752Pro					
<i>KCNQ1</i>	c.3107G>A	34	Female	SCD + CPR	530	ICD + beta-blocker
	p.Gly1036Asp					
	c.1591C>T	58	Female	SCD + CPR	530	ICD + beta-blocker
	p.Arg531Trp					
<i>KCNE2</i>	c.1022C>T	44	Female	Syncope, SCD in family	530	ICD + beta-blocker
	p.Ala341Val					
Unclassified	c.269A>G	64	Male	SCD + CPR	590	ICD + beta-blocker
	p.Glu90Gly					
		37	Female	SCD + CPR	490	ICD + beta-blocker
		14	Male	SCD + CPR	450	ICD + beta-blocker
		46	Male	SCD + CPR	510	ICD + beta-blocker

c. = codon; p. = protein; ICD = implantable cardioverter defibrillator; QTc = corrected QT interval (Bazett); TdP = torsade de pointes tachycardia; SCD = sudden cardiac death; CPR = cardiopulmonary resuscitation.

indeterminate in 2 subjects who were unable to exercise sufficiently to achieve the target heart rate and in a third patient due to presence of frequent ventricular ectopic beats. The figure demonstrates an example of a negative MTWA test obtained from a patient who had previously been resuscitated from torsade de pointes cardiac arrest.

Table 2. Results of MTWA Assessment

Gene	Mutation	MTWA		
		Pos.	Neg.	Indet.
Index Patients (n = 10)				
KCNH2	c.2775dupG	0	1	0
	c.91A>T	0	1	0
	c.2255C>G	0	1	0
	c.3107G>A	0	0	1
	c.1591C>T	0	1	0
KCNQ1	c.1022C>T	0	0	1
KCNE2	c.269A>G	0	1	0
Unclassified genotype		0	3	0
Family Members (n = 6)				
KCNH2	c.2775dupG	0	1	0
	c.2255C>G	0	2	1
	c.3107G>A	0	1	0
KCNE2	c.269A>G	0	1	0

Pos. = positive; neg. = negative; indet. = indeterminate.

MTWA results in genotype positive family members (n = 6) were negative in 5 cases (1 indeterminate, Table 2).

DISCUSSION

To the best of our knowledge, this study represents the first report on a cohort of high-risk LQTS patients systematically tested by means of noninvasive MTWA assessment. The main finding is that MTWA testing does not provide further diagnostic information in high-risk congenital LQTS patients and in genetically affected first-degree family members.

Comparison to Previous Studies Using MTWA for Risk Stratification

MTWA assessment is a useful tool for risk stratification in patients with ischemic and nonischemic cardiomyopathy. In this setting, a positive MTWA result together with reduced left ventricular systolic function is a predictor of ventricular tachyarrhythmic events.^{1,3}

The value of MTWA testing in genetically determined arrhythmias is less established. Previously, MTWA was assessed in a family with congenital LQTS (26 members carrying the identical *KCNH2* mutation) in an attempt to identify patients

Figure 1. (A) depicts an episode of torsade de pointes tachycardia on a rhythm strip (paper speed: 25 mm/s) obtained during cardiopulmonary resuscitation of a long-QT syndrome index patient (harboring the *KCNH2* c.2775dupG mutation). (B) limb lead ECG recordings (I, II, III) indicated prominent QT prolongation (paper speed: 50 mm/s). Subsequently, the patient denied implantation of an ICD and remained on medical therapy with beta-blockers. The negative MTWA result obtained from this patient during the same hospital stay is illustrated in (C). Top part of the MTWA report shows heart rate increase with bicycle exercise, ventricular premature contractions (bad, %) and noise level (μV) for signal averaging. MTWA magnitude for Frank's orthogonal leads (X, Y, Z) and vector magnitude (VM) are depicted at the bottom.

affected with the mutation in comparison to unaffected family members.⁸ The authors analyzed 41 MTWA recordings obtained and documented only three abnormal test results (18%) among family members carrying the mutation ($n = 17$). The clinical phenotype varied significantly even in this genetically homogeneous population and the authors found that TWA did not add to identification of genotype-positive family members.⁸ In another study, catecholamine-induced MTWA occurred at lower heart rates in LQTS patients compared to controls but was similarly not sensitive for risk stratification of arrhythmic events.¹¹

MTWA testing has been evaluated for arrhythmia risk stratification in other genetically determined arrhythmia syndromes. Ikeda et al. used noninvasive methods including MTWA, measurements of QT dispersion, and ventricular late potentials for risk stratification in 33 patients with ECG changes compatible with a Brugada phenotype. They identified a higher percentage of ven-

tricular late potentials in Brugada patients but incidence of nonnegative MTWA results was not different from control patients. Although 58% of these Brugada patients had a history of arrhythmic events, only 16% tested MTWA positive. Consistent results were reported by Kirchhof and colleagues who studied Brugada syndrome patients with a history of arrhythmic events who were in addition inducible at electrophysiological study.¹² None of these patients had a positive MTWA result consistently implying that MTWA testing appeared to be of no use for assessing arrhythmic risk in this condition.

Potential Relation to the Mechanism of Arrhythmogenesis

Shimizu and Antzelevitch demonstrated beat-to-beat alternation of mid-myocardial (M-) cell repolarization leading to a transmural gradient of repolarization in an in vitro LQTS-3 model

(mediated through ATX-II application causing enhanced $I_{Na,late}$).¹³ TWA occurred at elevated heart rates after rapid changes in frequency. In a later study, using a modified experimental approach, mimicking LQTS-2 (d-sotalol and bradycardia) M cells caused increased dispersion of repolarization and were important in the development of torsade de pointes.¹⁴

Pathological MTWA—as opposed to the physiological phenomenon—occurs at lower heart rates in individuals at risk of arrhythmic events.¹⁵ It is this behaviour that makes it suitable for risk stratification. In the above mentioned experimental study, a heart rate above 200 beats/min was necessary to induce TWA despite the presence of a LQTS-3 substrate. In contrast to these experimental results, the incidence of clinical arrhythmias in LQTS-3 is more readily associated with bradycardia and arrhythmic episodes occurring in LQTS-2 patients are oftentimes related to auditory stimuli and associated with more rapid heart rates. Experimental studies have not yet addressed the occurrence of MTWA under LQTS conditions.

In general, MTWA is linked to alternans of repolarization occurring above a certain threshold heart rate. With further increase in heart rate a transition from concordant to discordant alternans with increased vulnerability to ventricular fibrillation may ensue.^{2,16} It appears contradictory that humans affected by a proarrhythmic condition (LQTS) and previous arrhythmia manifestation do not exhibit MTWA in vivo, even though this condition has consistently been associated with experimental in vitro TWA. The reasons for this remain unclear at present. Factors associated with fluctuations in repolarization reserve may contribute.¹⁷ Increased dispersion of ventricular repolarization may ensue mediated by low potassium levels, concomitant medication or conditions like fever.¹⁸

Limitations

The number of affected individuals is a limitation for studies in patients with rare diseases. In this trial, we studied only those who additionally had a history of significant arrhythmic events further reducing the number of eligible patients. Extrapolating from this small number of individuals tested in this study to the overall LQTS population may be difficult—however, these were “real” LQTS patients having experienced cardiac events and our observations may thus provide an important clue to

understanding how MTWA may relate to arrhythmogenic substrates in various populations.

CONCLUSION

Despite the fact that macroscopic TWA has been linked to life-threatening ventricular tachyarrhythmias in LQTS patients and despite experimental evidence for occurrence of TWA under in vitro LQTS conditions, MTWA testing in high-risk LQTS patients and in genetically affected family members yields disappointing results.

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REFERENCES

1. Hohnloser SH. T-wave alternans. In: Zipes DP, Jalife J (eds.): Cardiac Electrophysiology: From Cell to Bedside. 4th Edition. Philadelphia, PA, WB Saunders, 2004, pp. 839–847.
2. Laurita KR, Rosenbaum DS. Restitution, Repolarization and Alternans as Arrhythmogenic Substrates. In: Zipes DP, Jalife J (eds.): Cardiac Electrophysiology: From Cell to Bedside. 4th Edition. Philadelphia, PA, WB Saunders, 2004, pp. 232–241.
3. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol* 2002;89:79–82.
4. Hohnloser SH, Klingenhöben T, Bloomfield D, et al. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: Results from a prospective observational study. *J Am Coll Cardiol* 2003;41:2220–2224.
5. Klingenhöben T, Zabel M, D’Agostino RB, et al. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet* 2000;356:651–652.
6. Schwartz PJ, Malliani A. Electrical alternation of the T-wave: Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. *Am Heart J* 1975;89:45–50.
7. Malfatto G, Beria G, Sala S, et al. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. *J Am Coll Cardiol* 1994;23:296–301.
8. Kaufman ES, Priori SG, Napolitano C, et al. Electrocardiographic prediction of abnormal genotype in congenital long QT syndrome: Experience in 101 related family members. *J Cardiovasc Electrophysiol* 2001;12:455–461.
9. Rosenbaum DS, Albrecht P, Cohen RJ. Predicting sudden cardiac death from T wave alternans of the surface electrocardiogram: Promise and pitfalls. *J Cardiovasc Electrophysiol* 1996;7:1095–1111.
10. Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and classification of microvolt T wave alternans tests. *J Cardiovasc Electrophysiol* 2002;13:502–512.
11. Nemec J, Ackerman MJ, Tester DJ, et al. Catecholamine-provoked microvoltage T wave alternans in genotyped long QT syndrome. *Pacing Clin Electrophysiol* 2003;26:1660–1667.
12. Kirchhof P, Eckardt L, Rolf S, et al. T wave alternans does not assess arrhythmic risk in patients with Brugada syndrome. *Ann Noninvasive Electrocardiol* 2004;9:162–165.

13. Shimizu W, Antzelevitch C. Cellular and ionic basis for T-wave alternans under long-QT conditions. *Circulation* 1999;99:1499-1507.
14. Akar FG, Yan GX, Antzelevitch C, et al. Unique topographical distribution of M cells underlies reentrant mechanism of torsade de pointes in the long-QT syndrome. *Circulation* 2002;105:1247-1253.
15. Kamesh NG, Shorofsky SR, Sarang SE, et al. Effect of heart rate on T wave alternans. *J Cardiovasc Electrophysiol* 1998;9:703-708.
16. Pastore JM, Girouard SD, Laurita KR, et al. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation* 1999;99:1385-1394.
17. Roden DM. Long QT syndrome: Reduced repolarization reserve and the genetic link. *J Intern Med* 2006;259:59-69.
18. Burashnikov A, Shimizu W, Antzelevitch C. Fever accentuates transmural dispersion of repolarization and facilitates development of early afterdepolarizations and torsade de pointes under long QT conditions. *Circ Arrhythmia Electrophysiol* 2008;1:202-208.