HEART RATE TURBULENCE DOES NOT SEEM TO BE A GOOD PREDICTOR in LONG QT SYNDROME

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Summary

The long QT syndrome (LQTS) is associated with recurrent syncope, ventricular arrhythmias and sudden death. It was shown that heart rate turbulence (HRT) predicts mortality and sudden cardiac death following myocardial infarction. In this study our aim is to examine HRT parameters in sudden cardiac death survivors with LQTS. Four patients with LQTS (mean age 12.5±1,8) were included in the study. Their 24 hours ambulatory electrocardiograms (ECGs) were recorded with Reynolds recorder device in a drug free period. Holter recordings were analyzed with Reynolds Medical Pathfinder Software Version V8.255. HRT was determined with HRT! View Version 0.60-0.1 software program and turbulence onset (TO) and turbulence slope (TS) were determined. In Holter recordings all patients where in sinus rhythm and atrial fibrillation, ventricular and supraventricular tachycardia attacks were not observed. TO and TS values of patients were found within normal range. TO values were lower than 0 and TS values were bigger than 2.5. In conclusion, HRT has no predictive value for assessing mortality and sudden death following myocardial infarction in patients with LQTS. HRT may not be a good risk predictor for LQTS. ***(Arch Turk Soc Cardiol 2003;31:770-75)***

Key Words: *Heart rate turbulence, long QT syndrome, sudden death*

Özet

Kalp Hızı Türbülansı Uzun QT Sendromunun iyi bir Öngördürücüsü Degil mi?

Uzun QT sendromu (UQTS) elektrokardiyogramda QT uzaması, klinikte tekrarlayan senkop atakları, ventriküler aritmiler ve ani ölümle seyreden bir hastalıktır. Kalp hızı türbülansının (HRT), miyokard infarktüsü sonrasında mortaliteyi ve ani ölümü saptamada güçlü bir ön belirleyici olduğu saptanmıştır. Bizde çalışmamızda ani ölümlerin gözlendiği UQTS'lu hastalarda HRT parametrelerini araştırdık. UQTS olan 4 erkek hasta (ort yaş 12.5±1.8) çalışmaya kabul edildi. Hastaların ilaç kullanmadıkları dönemde 24 saatlik ambulatuvar elektrokardiyogram kayıtları, Reynolds marka kaydedicilerle kaydedildi. Aritmi analizi Reynolds Medical Pathfinder Software Version V8.255 ile yapıldı. HRT analizi HRT! View Version 0.60-0.1 software program yapılarak, "turbulence onset (TO)" ve "turbulence slope (TS)" değerleri belirlendi. Holter kayıtlarında, tüm hastalar sinüs ritminde idi, hiçbir hastada atriyal fibrilasyon, ventriküler ve supraventriküler taşikardi atağı gözlenmedi. Hastaların TO ve TS değerleri normal sınırlarda bulundu. Tüm hastaların TO değerleri 0 dan

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küçük, TS değerleri 2.5 dan büyüktü. Sonuç olarak HRT, UQTS'lu hastalarda ani ölümü ve mortaliteyi saptamada, miyokard infarktüsünde olduğu gibi belirleyici görünmemektedir. ***(Türk Kardiyol Dern Arş 2003;31:770-75)***

Anahtar kelimeler: *Kalp hızı türbülansı, uzun QT sendromu, ani ölüm*

The long QT syndrome (LQTS) is an important clinical disorder and it is associated with recurrent syncope, ventricular arrhythmias and sudden death. The syndrome may be familial or sporadic. There are two hereditary variants of LQTS. The autosomal recessive form is Jerwell and Lange-Nielsen syndrome associated with deafness and the autosomal dominant form is Romano-Ward syndrome not associated with deafness. Romano Ward syndrome is more common than Jerwell and Lange Nielsen syndrome[1-3].

Heart Rate Turbulence (HRT) is the physiological, bi-phasic response of the sinus node to premature ventricular contractions[4]. The underlying mechanisms of HRT have not been fully identified but they are most probably an autonomous baro-reflex. Like heart rate variability baroreflex sensitivity is the way to asses autonomic and reflex modulations of cardiac function[5]. It is proven that HRT predicts mortality and sudden cardiac death following myocardial infarction[6]. In this study our aim is to examine HRT parameters in patients with LQTS. According to our knowledge there has not been any study about HRT in LQTS.

Patients and Methods

Four patients who were diagnosed as LQTS according to Schwartz criteria were included in the study (Table 1). All the patients were in sinus rhythm and none of them had a pacemaker. Their 24 hours ambulatory electrocardiograms (ECGs) were recorded with Reynolds recorder device in a drug free period. Holter recordings were analyzed with Reynolds Medical Pathfinder Software Version V8.255 (Hertford, England). HRT was determined with HRT! View Version 0.60-0.1 software program (Munich Germany) and turbulence onset (TO) and turbulence slope (TS) were calculated. TO is defined as the difference between the mean of the first two sinus RR intervals after a ventricular premature beat (VPB) and the last two sinus RR intervals before the VPB divided by the mean of the last two sinus intervals before the VPB. Turbulence slope (TS) is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after a VPB. TO < 0 and TS > 2.5 are considered normal, TO > 0 and TS < 2.5 are considered abnormal[4].

Table 1: *Cases with positive Schwartz criteria*

Case	Age	Syncope		QT ca (msn)	LQTS Point Score
		With stress	Without stress		
1	13		+	498,2	4,5
2	14	+		455,6	3,5
3	15		+	463,3	3,5
4	7		+	611,8	5,5

RESULTS

Atrial fibrillation, ventricular tachycardia and supraventricular attacks where not observed in Holter recordings. Approximately mean VPBs was 20/24 hours. TO and TS volues were shown in Table 2.

Table 2: *TO and TS values*

Cases	TO	TS ms/rri
1	-0.058	16.10
2	-0.046	7.96
3	-0.005	5.72
4	-0.072	5.30

Case 1: Fourteen years old deaf boy has a QTc of 498 ms. Before starting beta blocker therapy he had been suffered syncope. There were no deaf person in his family and their QTc were normal. We determined 1.39 second sinus pauses and 3 VPBs/24 hours in arrhythmia analysis. His TO value is -0.058 and TS value is 16.10.

Case 2: Fourteen years old deaf boy has a QTc of 455 ms. His brother was also deaf and his QTc was 390 ms. We determined 1.46 second sinus pauses, 434 VPBs/24 hours in arrhythmia analysis. His TO value is -0.046 and TS value is 7.96.

Case 3: Fifteen years old deaf boy has a QTc of 463 ms. His uncle's two doughters were also deaf. But they did not accept cardiac examination and ECG recordings. According to Schwartz criteria this patient's score was 3,5. We determined 1.3 second sinus pauses and 30 VPBs/24 hours. His TO value is -0.005 and TS value is 5.72.

Case 4: Seven years old deaf boy has a QTc of 612 ms. There were no deaf person in his family and their QTc was normal. We determined 19 VPBs/24 hours in arrhythmia analysis. His TO value is -0.072 and TS value is 5.30.

DISCUSSION

Recurrent syncope and sudden death occur in patients with LQTS.[2] Myocardial repolarization abnormality represented as QT prolongation in ECG causes arrhythymogenic syncope and fatal ventricular arrhythmias[7,8]. The syncope attacks occur with sudden increase in sympathetic activity such as emotional stress and physical activity [9]. Although the bizarre ECG of many patients with LQTS can be helpful to recognize LQTS borderline cases require the evaluation of several variables. In these conditions Schwartz's diagnostic criteria, which was updated in 1993, are used to diagnose definitely. The score ranges from a minimum value of 0 and a maximum of 9 points and there are 3 categories:1)1.0 or less (a low probability of LQTS),2) 1-3.5 points (an intermediate probability of LQTS) and 3) 4 points or more (a high probability of LQTS)[10]. All of the patients' LQTS score in this study were ≥ 3.5.

Twenty-four hour ambulatory ECG can be helpful to verify the diagnosis and to assess the seriousness of the disease. Bradycardia, sinus pauses, ventricular arrhythmias, transient QT prolongation or episodes of T wave alternation can be determined in ambulatory ECG. Sinus pause more than 1,2 seconds that are not related sinus arrhythmia can cause torsades de pointes. Also following sinus pauses, notched T wave can be seen[10-12]. The T wave can have several morphological patterns like notched or biphasic and episodes of T wave alternans can be seen in LQTS. T wave alternans may be present at rest, but it appears mostly during physical or emotional stress and it can be seen prior to torsades de pointes[11,13,14]. We determined VPBs on all patients' Holter recordings and sinus pauses more than 1.2 second in three patients. Ventricular, supraventricular arrhythmias, T wave alternans and different T wave morphology were not detected in arrhythmia analysis.

The LQTS is a genetically complex disease. So far 6 genetic loci have been identified involving 5 mutant genes with more than 160 different mutations. The five mutant LQTS genes include KVLQT1 (LQT1), HERG (LQT2), SCN5A (LQT3), KCNE1 or minK (LQT5), and KCNE2 or MiRP1 (LQT6)[15-19]. KVLQT1, HERG, KCNE1, and KCNE2 encode potassium channel subunits[20]. SCN5A encodes the cardiac sodium channel that is found in the sodium current INa [19]. Reduced function of the repolarizing potassium channels or gains of function of the sodium channels prolong the cardiac action potential with resultant QT prolongation and a propensity to ventricular arrhythmias. The Romano-Ward syndrome (QT prolongation and normal hearing) is due to single dominant mutations of any of the identified five ionic LQTS genes. Double-dominant (recessive) mutations involving KVLQT1-KCNE1 result in the Jerwell and Lange-Nielsen syndrome, a severe form of LQTS with deafness. Double dominant

mutations of HERG-KCNE2 result in a severe LQTS phenotype in infancy, but with normal hearing [21].

HRT is the physiological, bi-phasic response of the sinus node to VPB. It was first published as a new technique in early 1999 by George Schmidt's research group. As a physiological response after a VPB brief transient acceleration and a subsequent deceleration of sinus rhythm are seen. It has been thought that transient loss of vagal activity in response to the missed baroreflex afferent input due to hemodynamically inefficient ventricular contraction is responsible for the early abrupt acceleration of heart rate and the sympathetically mediated overshoot of arterial pressure might be responsible for the deceleration of heart rate[4,6]. Baroreflex sensitivity is the relationship between the blood pressure changes and the heart rate response mediated by baroreceptor arc. It was shown that MI often significantly impairs baroreflex sensitivity[22,23] and depressed baroreflex sensitivity is associated with an increased mortality after MI[24-26]. Recent studies suggest that HRT is highly correlated with spontaneous baroreflex sensitivity[4,5,27,28] and may be used instead of baroreflex sensitivity[29].

HRT analysis can be processed from Holter recordings, intracardiac pacing in the electrophysiolgy laboratory[30-33] and implanted cardiac defibrillators[34]. The most common HRT parameters TO and TS is used to defined amount of early acceleration and rate of late deceleration of heart rate in turn in order. TO is the difference between the mean of the first two sinus RR intervals after a VPB and the last two sinus RR intervals before the VPB divided by the mean of the last two sinus RR intervals before the VPB ([(RR1 + RR2) - (RR-2 + RR-1)] / (RR-2 + RR-1) * 100). TS is the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after a VPB. TO < 0 and TS > 2.5 are considered normal[4,35].

In large trails HRT was found as a predictor of mortality[6] and cardiac arrest[36] after myocardial infarction. In subgroup analysies of Europian Myocardial Amiodarone Trial (EMIAT) TS was the strongest univariate predictor of follow-up mortality while in the Multicentre Post-Infarction Program (MPIP) it was the second most powerful univariate predictor of mortality following depressed left ventricular ejection fraction. In both of these studies combined abnormal TO and TS was the most powerful multivariate mortality predictor[6]. In another large trail univariate analysis showed that TS and combined TS and TO both produced moderately high relative risk values for cardiac arrest after myocardial infarction[36]. Moreover blunted HRT reaction within the first 24 hours of acute myocardial infarction is an independent predictor of long-term mortality[37]. HRT is diminished not only in after myocardial infarction, but also in patients with congestive heart failure[38,39], diabetes mellitus[40,41], idiopatic dilated cardiomyopathy[42-44] and Chagas disease [45]. HRT is assessed in various diseases affecting the heart but according to our knowledge there has not been any study in patients with LQTS.

In this study we found that all of the TO and TS measurements for each induviduals were not diminished (TO > 0 and TS < 2.5), both of them were in normal range. As a result HRT seems to have not got any predictive value for evaluating patients with LQTS. Although LQTS has an arrhythmogenic potential and causes fatal ventricular arrhythmias HRT parameters could not be able to predict the mortality and sudden death in this disease.

Conclusion

HRT is a noninvosive risk predictor of long term mortality and sudden death in patients with myocardial infarction even in the acute phase. Besides MI it is diminished in various diseases affecting the heart like congestive heart failure, diabetes mellitus, idiopatic dilated cardiom-yopathy and Chagas disease. Unfortunately in patient with LQTS HRT has no predictive value for assessing mortality and sudden death. HRT may not be a good risk predictor for LQTS.

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