Confounding factors about microvolt T-wave alternans testing and life-threatening ventricular arrhytmias

To the Editor,

We have read a very interesting article by Özyılmaz and Püşüroğlu (1). We want to add some comment about methodology and definitons of the study.

First of all, the connection between microvolt T-wave alternans (TWA) and beta blockers remains poorly understood. It is generally accepted that beta blockers should be stopped before applying the TWA test; however, it is only described, for the spectral method but there is not information for mma-TWA method for beta blocker using. Absence of apical aneurysm diagnosis in HCM patients of this study is interesting and may be explained by their increase in >65 TWA group. For example, prevalance of apical aneurysm in HCM patients, from 2% to 4%-8% at previous studies (2, 3). Also ventricular tachycardia and mortality were higher in that group. Absence of any apical aneursym in HCM patients evaluated with echocardiography and magnetic resonance imaging is interesting. In previous two studies, cutoff value with ambulatory rhythm holter and mma-TWA were 40 msn and 60 msn, respectively. However, authors took 65 msn as the cutoff value (which is cutoff value for patients with 110 bpm, and is used in exercise test) and nonlinear value of mma-TWA may create a tendency regarding this consequence (4, 5).

In MADIT-II study indicated that implantable cardioverter-defibrillator (ICD)-treated patients, the risk of ventricular tachycardia does not differ according to microvolt-TWA classification. Furthermore, with any risk stratification method, including LVEF, all studies are not consistent with the overall trend. Specifically, in the MASTER trial and TWA substudy of SCD-HeFT, TWA did not predict the development of appropriate ICD therapy, sudden cardiac death, and/or ventricular tachycardia/fibrillation (6, 7).

In these study statistics, TWA alternans value which is a nonlinear value is dichotomized and power of statistically p value decreased, odds ratio absurdly increased. Authors aimed to examine the relation between mma-TWA's presence and absolute SCD risk value in HCM. However, they only analyzed dichotomized SCD risk in HCM so that there is inherent correlation because of single group. Application of propensity matching may prevent the selection bias, which is possible in an observational study and may cause changes in the results. In the study, authors did not mention about the cause of abnormally high value of odds ratio. If alternative mma-TWA values were chosen or used continuously, maybe the odds ratio value would have been different. In addition, absence of use of any appropriate method can explain high odds ratio value. Since, 44 TWA patients they got 10 variables in univarite analysis. 10 variables taken by authors for 42 T-wave is at univariate analysis and this shows dense overfitting. Moreover, this type of overfitting has overestimated study's regression coefficient. Furthermore, authors should examine their data because NHYA class, left atrial enlargement, left ventricular mass are interestingly protective.

We think that continuous values of TWA assessment should be evaluated with histogram, and outcome prediction modeling should be re-evaluated. Also, adding heart rate as a confounding factor may change the results. Without determining sample size, comments for the study's power are insufficient. As a result, inappropriate modeling, cutoff choice, study definition and possible random-bias, confounding factors, and selection bias may cause results presented at this paper.

Onur Taşar, Hacer Ceren Tokgöz[1]
Department of Cardiology, Elazığ Training and Research Hospital; Elazığ-*Turkey*
[1]Department of Cardiology, İstanbul Haydarpaşa Numune Training and Research Hospital; İstanbul-*Turkey*

References

1. Özyılmaz S, Püşüroğlu H. Assessment of the relationship between the ambulatory electrocardiography-based micro T-wave alternans and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy. Anatol J Cardiol 2018; 20: 165-73. [CrossRef]
2. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation 2008; 118: 1541-9. [CrossRef]
3. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, et al. Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm: Implications for Risk Stratification and Management. J Am Coll Cardiol 2017; 69: 761-73. [CrossRef]
4. de Oliveira Antunes M, Samesima N, Pereira Filho HG, Matsumoto AY, Verrier RL, Pastore CA, et al. Exercise-induced quantitative microvolt T-wave alternans in hypertrophic cardiomyopathy. J Electrocardiol 2017; 50: 184-90. [CrossRef]
5. Doksöz Ö, Meşe T, Karaarslan U, Ceylan G, Demirpençe S, Tavlı V, et al. Assessment of Microvolt T Wave Alternans in Children with Repaired Tetralogy of Fallot during 24-Hour Holter Electrocardiography. Ann Noninvasive Electrocardiol 2016; 21: 369-75. [CrossRef]
6. Chow T, Kereiakes DJ, Onufer J, Woelfel A, Gursoy S, Peterson BJ, et al.; MASTER Trial Investigators. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. J Am Coll Cardiol 2008; 52: 1607-15. [CrossRef]
7. Gold MR, Ip JH, Costantini O, Poole JE, McNulty S, Mark DB, et al. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. Circulation 2008; 118: 2022-8.

Address for Correspondence: Dr. Onur Taşar,
Elazığ Eğitim ve Araştırma Hastanesi,
Kardiyoloji Kliniği,
İnönü Cad. No: 74 Merkez
23200 Elazığ-*Türkiye*
Phone: +90 424 238 10 00
E-mail: tasaronur@hotmail.com

DOI:10.14744/AnatolJCardiol.2018.92160

Author`s Reply

To the Editor,

Thank you very much for evaluating our article "Assessment of the relationship between the ambulatory electrocardiography-based micro T-wave alternans and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy" (1).

In the letter, the authors have mentioned that the evaluation of MTWA under β-blocker therapy might be wrong. However, as we stated in the Methodology section of the paper, and as mentioned below:

When including patients in the study in question, we paid attention to include patients who were newly diagnosed, or who did not receive any previous treatment or intervention because each process could alter the calculated 5-year risk of sudden cardiac death (the HCM risk-SCD). There was a special outpatient clinic that evaluates only patients with hypertrophic cardiomyopathy (HCM). Newly diagnosed patients with HCM from some other hospital were referred to the outpatient clinic for further investigations. Thus, we initiated drugs like β-blockers when all evaluations, including electrocardiography, holter electrocardiography, and echocardiography were completed and after the HCM risk-SCD was calculated (1). Therefore, under β-blockers or the other therapies did not affect the MTWA values. If Table 1 caused confusion, herein we expressed the overall demographics of all patients who we evaluated for MTWA during 31.7±12.7 months and included the treatment administered during this period.

Echocardiography of the patients was performed in the first evaluation and was repeated with 3 month intervals. If evaluating with echocardiography was inadequate, we used cardiac magnetic resonance imaging. Therefore, we did not think that we might have disregarded patients with apical aneurysms. Apical aneurysms are thought to be usually developed secondary to long-term contraction against the gradient in mid-ventricular obstructive hypertrophic cardiomyopathy, which is generally a rare form of cardiomyopathy. Maron et al. (2) identified left ventricular apical aneurysms (LVAA) in 28 (2.2%) of 1299 patients included in their study, and their mean age was 52±13. Rowin et al. (3) LVAAs in 93 (4.8%) of 1940 consecutive HCM patients with a mean age of 56±13 years. The number of our patients was lower than the other two studies mentioned. The mean age of our patients was 46.6±15.2 years. As observed in both studies, association of HCM and apical aneurysms is different in percentages. There is no precise information about the incidence of apical aneurysms in HCM patients.

In the literature, cutoff value for MTWA has usually been taken as 60. As the cutoff value used by us was 65, which was very close to this value and the value that we have used in our previous study (4).

MADIT II study is an old study, in which data were collected between 1996 and 2003. Patients with heart failure who had left ventricular ejection fraction (LVEF) of 40% or less were included in the study (5). Similarly, in the MASTER study that was published in 2008 patients who had a prior myocardial infarction and LVEF ≤30% were included (6). Unlike these two studies, only HCM patients with average LVEF 66.6±7.1 were included in our study. The patient group of our study is completely different from that of these studies, and it is not appropriate to compare these studies. Furthermore, science is constantly changing and renewing itself over the years. Up until now, many studies have shown that there is a relationship between sudden cardiac death or ventricular arrhythmic events, MTWA positivity (7-9).

We again evaluated whether the variables compared between the positive and negative micro T-wave alternans groups were parametric or non-parametric. Normality of the variables was assessed using visual (histograms, probability plots, values of skewness, and kurtosis) and analytical methods (Kolmogorov–Smirnov). No change was found in the statistical results compared with the previous values.

After the parametric and non-parametric evaluation, we performed Spearman and Pearson tests for the correlation. The odds ratio confidence interval for MTWA was greater than 1 for both univariate (18.091–195.030) and multivariate (13.685-464.687) analysis. Therefore, MTWA's confidence interval, which is >1, shows that MTWA positivity has an enhancing effect on risk determinants for the HCM Risk-SCD. Since the 10 parameters specified in the logistic regression analysis could affect the HCM risk-SCD value, these parameters were used to find the independent factor. We believe that our study is adequate and strong in terms of statistical analysis.

In conclusion, absence of LVAA in our patients might be associated with low average age and short follow-up duration. This is supported with high incidence of arrhythmias and thromboembolic events leading to sudden death with LVAA and lack of these complications in our patients. In addition, we believe that our sampling, study methodology, and selection of the cutoff value were consistent with the previous studies.

Sinem Özyılmaz, Hamdi Püşüroğlu
Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital; İstanbul-*Turkey*

References

1. Özyılmaz S, Püşüroğlu H. Assessment of the relationship between the ambulatory electrocardiography-based micro T-wave alternans and the predicted risk score of sudden cardiac death at 5 years in