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.

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