

Toward better risk stratification of asymptomatic Brugada Syndrome patients?

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The prognostic value of invasive electrophysiologic (EP) testing in asymptomatic Brugada Syndrome (BrS) patients remains controversial. Even though EP testing was recommended for the prognostication of asymptomatic BrS patients in the 2005 consensus statement on BrS¹, more recent guidelines have decreased the emphasis on invasive testing for risk stratification. The 2013 HRS/EHRA/APHRS consensus statement notes that there is *no consensus* on the prognostic value of EP testing, and the more recent 2017 AHA/ACC/HRS guidelines mention that invasive testing *may be considered* in risk stratification of asymptomatic patients. Specifically, the prognostic role of programmed ventricular stimulation (PVS) for evaluation of ventricular arrhythmia inducibility has shown inconsistent results.^{2, 3} However, EP testing with myocardial substrate

mapping has recently shown interesting results for the assessment of arrhythmia inducibility. In 191 patients with BrS who underwent EP testing, arrhythmogenic substrate size was an independent predictor of inducibility, and substrate ablation prevented ventricular arrhythmia re-inducibility.⁴

In this issue of the *Journal of Cardiovascular Electrophysiology*, Letsas et. al suggest a potential role for high-density electroanatomic mapping (HDEAM) in the risk stratification of BrS patients. To this end, they characterize the differences in endocardial abnormalities in the right ventricular outflow tract (RVOT) among high-risk and asymptomatic BrS patients. Given that epicardial RVOT abnormalities are believed to be the arrhythmogenic substrate in BrS^{5, 6}, and given that endocardial unipolar HDEAM helps in the localization of epicardial abnormalities^{7, 8}, the authors aimed to evaluate the clinical significance of looking at abnormal endocardial substrate.

In their retrospective analysis of prospectively collected data from 54 patients with BrS, fourteen symptomatic patients with aborted sudden cardiac death (SDC) underwent combined endocardial-epicardial HDEAM, while 40 asymptomatic patients underwent endocardial HDEAM. Comprehensive clinical evaluation and coronary angiography were performed to rule out structural heart disease and coronary artery disease, respectively. Unipolar and bipolar signals were recorded and the duration, amplitude, presence of multiple components and relation to surface QRS were analyzed. Abnormal endocardial findings were defined as low-voltage areas (LVAs) $> 1\text{ cm}^2$ with unipolar signals $< 5.3\text{ mV}$. This value was based upon its 92.4% specificity and 86.3% sensitivity for the identification of epicardial bipolar LVAs $< 1\text{ mV}$. Moreover, all patients underwent programmed ventricular stimulation (PVS) from the RV apex and/or RVOT sites. In all cases, the endocardial unipolar LVAs were found to be wider than endocardial bipolar LVAs, and the abnormalities were mostly detected on the anterior wall of the RVOT. Interestingly, endocardial unipolar LVAs were found colocalize with epicardial bipolar LVAs. Importantly, symptomatic patients displayed wider endocardial unipolar and bipolar LVAs in comparison to asymptomatic ones. Based on receiver operating characteristic (ROC) analysis, the presence of unipolar LVAs $> 14.5\text{ cm}^2$ as well as that of bipolar LVAs $> 3.68\text{ cm}^2$ significantly discriminated symptomatic from asymptomatic individuals. Furthermore, all symptomatic patients and one fourth of the asymptomatic patients were inducible during PVS. Notably, wider areas of abnormal unipolar and bipolar signals were found in inducible patients compared to non-inducible ones.

These findings demonstrate that the size of endocardial abnormalities is associated with VF inducibility. In fact, unipolar LVAs $> 13.5\text{ cm}^2$ and bipolar LVAs $> 2.97\text{ cm}^2$ significantly predicted VF inducibility. Finally, all inducible patients with positive PVS received an implantable cardioverter defibrillator (ICD).

The study is limited by the small number of high-risk patients and the differences in catheter types and methods used to characterize the abnormal substrates, given the retrospective nature of the study. These results show different endocardial findings during HDEAM in high-risk BrS patients compared to asymptomatic patients. Whether these findings can be leveraged to better risk stratify asymptomatic BrS patients need to be investigated in future larger prospective cohorts.

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