EP Update

Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Dysplasia

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In this issue of 'EP Update' we summarize the recent literature on arrhythmogenic right ventricular dysplasia (ARVD). The articles have been hand picked and reviewed by the editors of IPEJ for the benefit of readers.

Electrocardiographic differentiation of arrhythmia due to ARVD from that arising from right ventricular outflow tract

Ventricular arrhythmias due to ARVD and right ventricular outflow tract arrhythmia (RVOTA) share the same left bundle branch block pattern with inferior axis on the ECG. The former has a more malignant course while the latter has a better prognosis and is more amenable to radiofrequency catheter ablation. Hence differentiating them is of utmost clinical importance in the management of these patients. QRS notching has been mentioned to be one of the differentiating features. Ren L and associates \cite{1} studied electrocardiographic differentiation of arrhythmias in ARVD from RVOTA and concluded that in addition to QRS notching in lateral leads, QRS duration in lead I of 125 milliseconds or more and a precordial R/S transition beyond V4 are useful in differentiation. The differences are thought to be due to the patchy fibrofatty replacement of myocardial tissue in ARVD which causes slow conduction, unlike in RVOTA with structurally normal heart. Authors claim better sensitivity and specificity by increasing the cutoff value for QRS widening from 120 milliseconds to 125 milliseconds. QRS notching probably has similar significance as fragmented QRS described by other authors \cite{2} in different
conditions of structural heart disease and cardiac channelopathies.

**Usefulness of ECG for prediction of risk in ARVD**

A study by Saguner AM et al [2] evaluated 111 patients with ARVD to determine whether ECG parameters are useful in prediction of risk of major adverse cardiac arrhythmic events in ARVD. The events evaluated were death due to cardiac cause, cardiac transplantation, resuscitated sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia and arrhythmic syncope. About half of their patients had one or more of these adverse cardiac events. They found that T wave inversion in inferior leads, fragmented QRS and a precordial QRS amplitude ratio of 0.48 or less were useful predictors of arrhythmic events in ARVD. Precordial QRS amplitude ratio was calculated as the ratio of sum of QRS amplitude in leads V1-V3 to sum of QRS amplitude in leads V1-V6. This was a long term observational study with a median follow up duration of 4.6 years. Other studies have linked inferior T wave inversions in ARVD to left ventricular involvement and hence the prognostic significance. T wave inversion in more than three precordial leads was also noted to be important in prediction of cardiac events, possibly for similar reasons. One important limitation noted by the authors is a relatively high event rate in their cohort possibly indicating a referral bias towards more advanced cases. Hence the applicability of the results to a low risk cohort may not be good.

**Role of beta adrenergic stimulation in diagnosis of ARVD**

Denis A and colleagues tested the value of beta adrenergic stimulation by isoproterenol infusion in over four hundred patients referred with ventricular premature complexes or suspected arrhythmogenic right ventricular dysplasia (ARVD) [3]. Test was considered positive if either polymorphic ventricular premature complexes with at least one couplet or ventricular tachycardia of left bundle branch block pattern other than right ventricular outflow tract tachycardia was induced by isoproterenol infusion. Isoproterenol infusion given at 45 microgram per minute for three minutes had a high negative predictive value of 99.1%. But the positive predictive value was low at 43.2%. Sensitivity and specificity of the test was good at 91.4% and 88.9% respectively. It is interesting to note that 6 patients who did not have features of ARVD at initial evaluation developed features satisfying the diagnostic criteria during a mean follow up of 5.6 years. All six of them had positive isoproterenol test at the initial evaluation itself, thus giving some role in future prediction as well!

An accompanying editorial by Calkins H et al [4] cautions us that high dose isoproterenol infusion is not without risks as there is chance of arrhythmia induction and hypotension. They suggest that it should be reserved for a controlled setting as in an electrophysiology laboratory during an invasive electrophysiological study rather than just in a monitored floor.
Role of serial evaluation of at risk family members of ARVD

It is well accepted that family members of patients with ARVD need screening for the disease. But the need of longitudinal follow up of at risk family members is not well established. te Riele AS and associates [5] checked the role of serial screening of at risk family members. They evaluated all first degree relatives in case of mutation negative probands and all mutation carriers among family members of mutation positive probands. 92% of mutation carriers had a plakophilin-2 mutation. Study cohort comprised of 117 relatives from 64 families who had undergone ECG and cardiac magnetic resonance imaging. Thirty seven percent of the study cohort were diagnosed as having ARVD at first evaluation itself. Those without ARVD at initial evaluation were followed up for a mean period of 4.1 years. Thirty seven patients had complete re-evaluation including cardiac magnetic resonance imaging. Authors concluded that electrical progression is seen in one third of the at risk relatives and structural progression of the disease is rare. They also noted that electrical abnormalities precede detection of structural abnormalities, which is quite acceptable considering the fact that ARVD is predominantly an electrical disorder of the heart.

Marcus F et al [6] in an editorial comment of the study notes that though 50% of first degree relatives of an ARVD patient is likely to have the mutation, there is no strong association between mutation carriage and the phenotypic disease manifestation. Though 11 genes related ARVD are known, majority of the mutations are in 5 desmosomal genes. Genetic testing of first degree relatives is done only if a mutation is detected in the proband, which is the situation in 30-50% of the cases. As sudden death in ARVD is rare before the age of ten years, serial evaluation probably is not needed before that age, or at least cardiac magnetic resonance imaging can be deferred in those without any abnormality on the ECG. Close follow up for electrical progression which predates structural changes is needed in all relatives at risk of the disease.

Data from the North American ARVD registry

North American ARVD registry is a multidisciplinary study on various aspects of ARVD and data from 137 patients enrolled in the study has been published [7]. One hundred and eight patients in the registry have received an implantable cardioverter defibrillator (ICD). The observations suggest that antitachycardia pacing (ATP) is quite successful in terminating ventricular tachycardia in ARVD and that it should be programmed in all cases, even for fast ventricular tachycardia. It was also documented that majority of the ventricular arrhythmias are monomorphic, thus explaining the high success rate of ATP. T wave inversion in inferior leads and spontaneous ventricular arrhythmias at enrollment predicted ventricular arrhythmias on follow up. It may be noted that the same observation was also documented by Saguner AM et al [2]. Only predictor of life threatening ventricular arrhythmia was young age at enrollment.
References


