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Arrhythmogenic Right Ventricular Cardiomyopathy: ECG progression over time and correlation with long-term follow-up

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Aims: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart-muscle disease primarily affecting the right ventricle and potentially causing sudden death in young people. Our aims are to analyse the progression over time of electrocardiographic(ECG) findings and to investigate their prognostic impact.

Methods: 68 patients (69% men; age 31±19 years) with ARVC diagnosis were followed-up for a mean of 17±8 years. Follow-up included baseline ECG, 24-hour Holter ECG, signal-averaged ECG, stress test, echocardiography, cardiac magnetic resonance and electrophysiologic study (ES).

Results: During follow-up 12 (18%) patients died: 3 for sudden cardiac death (SCD), 4 for end-stage heart failure (HF), and 5 for non-cardiac causes. Aborted SCD occurred in 7 (10%) patients, syncope in 31 (46%), sustained ventricular tachycardia (VT) in 43 (63%), HF in 18 (26%), atrial fibrillation (AF) in 16 (24%) and 3 (4%) patients underwent heart transplant. Twenty-four (35%) patients had ICD implanted (15 and 5 of them received both appropriate and inappropriate interventions respectively and 7 experienced device-related complications). Of the ECG parameters registered at the enrolment, left anterior fascicular block (p=0.001), QRS duration in lead 1 (p<0.001), Epsilon wave (p<0.001), T wave inversion in V4-V5-V6 (p=0.012, p=0.001 and p=0.006) and low QRS voltages (p=0.001) progressed over time. At multivariate analysis Epsilon wave (OR 20.9, CI 95% 1.8-239.8, p=0.015) was the only predictor of the composite endpoint of SCD, HF-related death or heart transplant.

Conclusions: Besides playing a pivotal role in ARVC diagnosis, a simple ECG features as Epsilon wave is a marker of poor prognosis.

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Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a rare inherited heart-muscle disease, characterized by adipose and fibrous tissue replacement of the cardiomyocytes, that primarily affects the right ventricle (RV). Due to identification of causative mutations in genes encoding desmosomal proteins the disease is a genetic myocardial dystrophy (1).

ARVC leads to a wide spectrum of clinical manifestations, ranging from long-term favorable course to ventricular life-threatening arrhythmias, potentially causing sudden cardiac death (SCD) in young adults, and progressive right or biventricular heart failure (HF) (2). The Task Force Criteria (TFC) (3,4) base ARVC diagnosis on family history, specific electrocardiographic (ECG) features, ventricular arrhythmias, right ventricular functional and structural abnormalities, genetics and histopathological evidence of tissue replacement.

Over the past years, new therapeutic options have been progressively introduced and clinical management of patients with ARVC has shifted from the use of antiarrhythmic drugs (empirical and/or guided by the results of the electrophysiologic study (ES)) to the use of implantable cardiac defibrillators (ICD) and transcatheter ablation procedures. With this regard, to better guide clinicians in the management of ARVC patients, an international task force document (5) providing a standardized treatment flowchart has been recently published.

Although several ECG, echocardiographic and cardiac magnetic resonance features of patients with ARVC have been described, their progression over time as well as the relation with long-term clinical outcomes has seldom been reported.

Aims of the present study were to analyse the progression over time of relevant ECG findings in ARVC patients referred to a tertiary referral centre and to investigate their prognostic impact.

Methods

Out of all patients followed to our tertiary referral center between 1970 and 2014 with cardiological clinical history onset with aborted SCD, syncope, palpitations, HF, ECG abnormalities or family screening, 68 patients (69% men, age 31±19 years) fulfilled the 1994 TFC for ARVC diagnosis (also post hoc validated with 2010 TFC). Twelve (18%) cases were clustered within five families. Following ARVC diagnosis, all patients underwent physical examination and 12-lead ECG recording during routine outpatient visits for a mean follow-up of 17±8 years.

Patient's management was based on the therapeutic flowchart reported in Figure 1. Patients were defined symptomatic if had experienced ventricular arrhythmia-related clinical manifestations such as syncope, palpitations and dyspnea. Avoidance of physical efforts, beta-blockade (primarily nadolol) and ES were recommended to all patients. Based on sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) inducibility at baseline ES only beta-blocker therapy was continued or antiarrhythmic drugs (primarily sotalol or amiodarone) were started. During follow-up a second ES was proposed to evaluate antiarrhythmic drug efficacy and its results (e.g. persistent sustained VT/VF inducibility or clinical sustained VT despite maximal dose antiarrhythmic drug therapy) together with all known predictors of SCD (e.g. young age, aborted SCD or family history of SCD, ventricular tachycardia with hemodynamic compromise, unexplained syncope and RV or biventricular severe dysfunction) were taken into account for a global assessment of the most appropriate management and to decide about ICD implantation. In selected cases, to reduce persistent symptoms, alternative antiarrhythmic drug associations were used and/or radiofrequency transcatheter ablation was performed. Patients presenting with aborted SCD at baseline were directly implanted with an ICD, associated with beta-blockade therapy and, if deemed necessary, antiarrhythmic drugs.

The following adverse clinical outcomes were recorded at the routine outpatient follow-up visits and/or by medical records: all-case death (including SCD), aborted SCD, syncope, sustained VT, HF, atrial fibrillation (AF), stroke/transient ischemic attack (TIA) and heart transplant. Aborted SCD was defined as a cardiac arrest requiring cardiopulmonary resuscitation or an appropriate ICD shock on VF. For the purpose of this study clinical events were combined in a composite endpoint (CE) of SCD, HF related death or heart transplant.

Electrocardiographic parameters

Based on previously published data, the following ECG parameters were assessed: presence of sinus rhythm; heart rate; P wave: (a) morphology in lead II and in lead V1 (positive, negative or biphasic), (b) voltage (mm) in lead II and in lead V1 and (c) duration (sec) in lead II and in lead V1; P-wave electrical axis ($<0°$, $\geq 0°$ and $<90°$, $\geq 90°$); PQ interval duration (sec); QRS complex electrical axis ($<0°$, $\geq 0°$ and $<105°$, $\geq 105°$) (6); mean QRS duration in lead V1 and V6 (sec); R/S ratio in lead V1 (6); QRS duration ≥ 110 msec in V1 and V2 leads; ratio of QRS duration in leads (V1+V2+V3)/(V4+V5+V6) (7); pathologic Q waves (duration >40 msec and amplitude $>1/4$ of QRS complex) in frontal and precordial leads; R wave voltage (mm) in leads V1-V3; Epsilon wave (low amplitude potentials occurring immediately after the QRS complex in the right precordial leads); QRS dispersion >40 msec (difference in duration between the longest and the shortest QRS intervals in any lead) (8); left anterior fascicular block (rS pattern in the inferior leads and qR pattern in aVL with a front plane QRS axis of $<-30°$ and QRS duration <120 msec) (6); complete or incomplete right bundle branch block (QRS duration >120 ms and QRS duration >110 msec and <120 msec respectively, with a secondary R wave in V1-V2 and wide deep S wave in V5-V6); prolonged S wave upstroke >55 msec (from S wave nadir up to isoelectric line) (9); T wave polarity in precordial leads (positive, negative, flat); QRS voltage in each limb lead ≤ 0.5 mvolt (10).

Echocardiography

M-mode, two dimensional and Doppler echocardiography were used to evaluate cardiac chambers diameters and segmental or diffuse wall motion abnormalities. Apical four-chamber, parasternal, and subcostal echocardiographic projections were used to evaluate right ventricular outflow tract (RVOT) diameter, right ventricle (RV) dilatation, RV fractional area change (calculated by using the following formula: (end-diastolic area - end-systolic area)/end diastolic area measured in the apical 4-chamber view*) and left ventricular ejection fraction (LVEF). All the measurements were defined according to ASE recommendations of 2005 (11), in particular RV dimension has been measured from an apical four chamber view in the mid-RV and defined mildly dilated when 34-37 mm, moderately dilated when 38-41 mm and severely dilated when $\geq$ 42 mm.

Cardiac Magnetic Resonance (CMR).

CMR images were assessed for RV wall motion abnormalities (dyskinesia), RV volumes, RV and LV fibrofatty infiltration (intramyocardial high T1 signal) and LVEF. RV dilatation was defined moderate when RV telediastolic volume (TDV) was $\geq$100 ml/m² and <110 ml/m² (in male) or $\geq$90 ml/m² and <100 ml/m² (in female) while it was defined severe when RVTDV was $\geq$110 ml/m² (in male) or $\geq$100 ml/m² (in female).

Statistical analysis

Categorical variables are reported as count and percentages, while continuous variables as mean and standard deviation (SD). Changes over time of categorical and continuous ECG parameters were analyzed by McNemar lambda and paired T test respectively. Correlation between baseline ECG parameters and adverse clinical outcomes as well as between baseline ECG and echocardiographic parameters was tested in cross tabulations tables by means of the Pearson Chi-Square or Fisher's Exact Test and by one-way ANOVA respectively for categorical and continuous variables. Logistic regression was used to investigate the association between ECG parameters with the composite endpoint. All variables showing a p-value <0.1 at univariate analysis (amiodarone use, RV dyskinesia at baseline CMR considered as a marker of RV dysfunction, Epsilon wave at twelve lead

baseline ECG) were included in a multivariable model. Kaplan Meier curves were used to show composite endpoint occurrence stratified for the presence of Epsilon wave and log-rank test was used to test its association with the composite endpoint. A two sided p-value <0.05 was considered statistically significant; all analyses were performed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline features of the study population are listed in Table 1. Out of all patients 47 (69%) were men with a mean age of 31±19 years, 20 (29%) suffered hypertension, 3 (4.4%) previous stroke or TIA and 6 (8.8%) diabetes mellitus. Baseline echocardiography was performed in all study patients: the mean LVEF was almost normal (58±8%) while a moderate-severe RV dilatation was documented in 31 (46%) of them. Baseline CMR, was available in 57 patients: RV dyskinesia was observed in 16 patients (28%), RV moderate-severe dilatation in 33 (57%) and fibrofatty RV involvement in 37 patients (64%).

Referral of the 68 ARVC patients was triggered by a chief complaint of palpitations in 43 cases (63%), 15 (22%) of whom with documented sustained VT; syncope in 8 (12%); ECG abnormalities in 5 (7%); family screening in 9 (13%), 7 (10%) of whom with family history of SCD; aborted SCD and HF in 1 and 2 (1.5% and 3%) cases respectively. Overall, 54 patients (79%) presented with symptoms, 39 (72%) during effort. Family history of ARVC was present in 18 patients (26%) while 22 (32%) had family history of SCD.

Clinical management

Besides avoidance of physical efforts, all patients were started on a beta-blocker at enrolment. Baseline ES was performed in 61 patients (89%) and resulted positive for sustained VT/VF inducibility in two third 39 (64%). A follow-up ES, in order to test beta blocker and antiarrhythmic therapy efficacy, was performed in 33 patients (49%) and resulted still positive in 21 (63%). One

patient was enrolled following an aborted SCD and directly underwent ICD implantation in addition to the administration of nadolol and amiodarone. Overall 24 patients (35%) underwent an ICD implantation and 17 (25%) underwent sustained VT transcatheter ablation.

During a mean follow-up of 17±8 years 12 (18%) patients died: 3 for SCD, 4 for end-stage HF and 5 for non-cardiac causes (3 cancers, 1 car accident, 1 end-stage renal failure). Details regarding the 3 SCD events are as follows: 1) one SCD episode occurred in a 18 years old patient with positive ES despite sotalol; he had ICD implantation postponed due to patient's preferences (i.e. because of a concomitant school exam); 2) another SCD was observed in a 60 years old woman followed for 21 years that 6 months before autonomously decided to stop nadolol and amiodarone therapy; 3) the third SCD episode occurred in a 46 years old woman that following appropriate ICD shock for VF experienced a new VF episode one week later which was not recognized and left untreated by the device due to a concomitant lead fracture. Seven cardiovascular deaths occurred during follow-up, accounting for an annual cardiovascular mortality rate of 0.58% person/year (0.25% person/year for SCD and 0.33% person/year for end-stage HF). Aborted SCD occurred in 7 patients (0.58% person/year): 1 during hospitalization (before sustained VT catheter ablation) and 6 in ICD carriers. Syncope was reported in 31 patients (2.58% person/year), sustained VT in 43 patients (3.59% person/year), HF in 18 (1.50% person/year), AF in 16 (1.33% person/year), stroke/TIA in 9 (0.75% person/year) and heart transplant in 3 patients (0.25% person/year).

Overall SCD, HF-related death and heart transplant occurred in 10 patients (15%). Within the 24 (35%) ICD patients, 15 (63%) received an appropriate intervention (triggered by VF in 6 patients and by sustained VT in 9), 5 (21%) received an inappropriate intervention and 7 (29%) had device-related complications (1 pocket hematoma, 1 infection, 3 lead dislocations and 2 lead fracture). Five patients died for cardiac causes despite ICD implantation (1 for SCD secondary to lead fracture, 4 for HF) and three patients underwent heart transplantation. VT/VF induction at baseline ES did not relate with appropriate ICD interventions during follow-up (p= 0.211).

Electrocardiographic progression and correlation with prognosis

ECG parameters are detailed in Table 2. Mean time between enrolment and follow-up ECG was 10±7 (range 3-23) years. Of the ECG parameters registered at the enrolment, left anterior fascicular block (p=0.001), QRS duration in lead 1 (p<0.001), Epsilon wave (p<0.001), T wave inversion in leads V4-V5-V6 (p=0.012, p=0.001 and p=0.006 respectively) and low QRS voltages (p=0.001) showed progression over time. Table 3 presents the univariate analysis investigating the association between ECG parameters and the composite endpoint of SCD, HF-related death or heart transplant: Epsilon wave was the only ECG predictor of the adverse outcome (60% vs 24%, p= 0.016). In addition, the multivariable analysis confirmed Epsilon wave as an independent predictor of the composite endpoint (OR 20.9, CI 95% 1.8-239.8, p=0.015).

In analyzing the relationship between ECG and echocardiographic progression over time we found a significant association between RVOT dilatation and QRS duration ≥110 msec in V1 and V2 leads (p=0.037). Also, the development of moderate-severe RV dilatation showed a borderline association with the development of QRS dispersion >40 msec (p=0.060).

Kaplan-Meier plots show that Epsilon wave was significantly associated with the occurrence of CE during long term follow-up (Log Rank p value = 0.019, Figure 2).

Discussion

This single centre observational study describes long-term clinical outcome and ECG features of 68 ARVC patients referred to a tertiary referral centre for clinical management.

The prevalence of adverse events widely varies in ARVC long term follow-up studies, depending on characteristics of patients enrolled and therapeutic approaches used, with SCD and HF occurrence ranging from 2% (12) to 13% (2,13) and from 3% (2) to 10% (14) respectively.

As described in the results, in our study 3 SCD occurred in specific clinical settings as a consequence of drug therapy withdrawal, postponed ICD implantation and ICD malfunctioning (i.e VF undersensing due to lead fracture). The low percentage of SCD (4.4%) is surely influenced by

the high number of patients with an ICD (35%); what should be underlined is that patients with an ICD seem to experience a higher cardiovascular mortality, mainly driven by HF-related death, compared with those without an ICD (20% vs 4%). This may be due to the fact that ICD implantation was performed amongst patients with more advanced disease stage. Although ICD implantation is the most effective therapy for SCD prevention, inappropriate interventions and device-related complications represent important issues, especially considering the generally young age of patients with ARVC. In our cohort 24 patients received an ICD and were followed for a mean of 10 years (9.7±4.4 years). Mortality rate was high (20%), mainly secondary to HF progression, but in one patient, SCD occurred despite ICD because of lead fracture and subsequent failure in recognizing and treating a VF episode. Inappropriate interventions (21%) and device-related complications (29%) were comparable to previous published studies. In fact, previous mid-term follow-up studies (15-16) on ICD implantation in ARVC patients reported mortality rates of about 2-3%, inappropriate interventions ranging from 16% to 24% and device-related complications in about 14% of the patients. Conversely in a long term follow-up study (17) (80±43 months of follow-up) mortality rates were higher (13%) as well as incidence of device-related complications (42%). Considering all these data physicians managing ARVC patients should always keep in mind the risk of long-term complications associated with an ICD and the fact that this therapeutic approach does not modify the anatomic substrate nor slow the progression of the disease.

Until now, the role of ES in ARVC patients has been controversial (15,18,19,20). In particular, in our study the limited number of patients undergoing ICD implantation following electrophysioligc study may explain the lack of significant relationship between a positive result to ES and appropriate ICD intervention during follow-up observed in the study population. However, the use of ES to evaluate the efficacy of antiarrhythmic treatment and for risk stratification, together with appropriate indications to ICD implantation, have, in our opinion, contributed to the overall low incidence of arrhythmic deaths observed during long term follow-up.

Although several studies have analysed ECG features of patients with ARVC, their progression over time and their prognostic impact remain controversial (6,21). Several ECG abnormalities have shown to develop over time reflecting disease progression and involvement of new myocardial areas as Epsilon wave, QRS enlargement in lead 1 and T wave inversion in the precordial leads (13,22,23,24). Epsilon wave, a marker of RV delayed activation due to late electrical depolarization of isolated myocytes in the context of fibro-fatty tissue substitution, should directly be correlated with progressive RV involvement and therefore with a poor outcome. In the present study Epsilon wave was associated with the occurrence of SCD, HF-related death and heart transplant. Previous experiences, instead, somewhat failed to report this correlation: Shulin Wu et al (25) reported the presence of Epsilon wave in 80% of patients at high-risk of cardiovascular mortality (previous sustained VT and RV failure) and in 51% of low-risk patients, not reaching statistical significance (p=0.16) and Turrini et al (26) reported no difference in Epsilon wave incidence in ARVC patients with different risk (35% in patients who died suddenly, 25% in patients with sustained VT and 30% in asymptomatic patients). Syncope and HF could be considered as clinical manifestations of fast and sustained VT leading to hemodynamic compromise. In addition, in patients with ARVC, it has been previously shown that RV dysfunction is often paralleled by regional LV dysfunction, potentially contributing to clinical deterioration (27).

Several limitations should be acknowledged interpreting study results. First, the present study enrolled patients referred to a tertiary referral centre for symptoms, ECG abnormalities or family history of ARVC: considering that SCD may be the first clinical manifestation in a sub-group of high risk ARVC patients, the clinical cohort hereby considered may not be representative of the general ARVC population. Second, due to the observational design of the study, inherent biases cannot be excluded as not-simultaneous execution of baseline instrumental examinations (ECG, echocardiography and CMR). Third, considering the limited sample size and the low number of adverse clinical events the statistical power of the multivariate logistic regression model is limited. Fourth, data regarding RV ejection fraction at baseline CMR was available for a minority of

Finally, since ECG changes in ARVC are dynamic, the evaluation of two ECGs only may have not discriminated between true ECG progression and dynamic fluctuations.

Conclusion

The occurrence of adverse events such as sustained VT, HF, AF and stroke is common among patients with ARVC. ICD implantation is indeed effective in preventing SCD but the high incidence of HF-related death in this cohort of patients highlights the inability of the ICD to modify the prognosis related to the progression of the substrate of the disease. Besides playing a pivotal role in ARVC diagnosis, a simple ECG features like Epsilon wave is a marker of poor prognosis.

Figure legend.

Figure 1. Therapeutic flowchart relevant to the clinical management of the study population. *aSCD=aborted sudden cardiac death; BB=beta-blockade; AAD=antiarrhythmic drugs; ICD=implantable cardiac defibrillator; ES=electrophysiological study; SCD=sudden cardiac death.*

*Predictors of SCD: younger age, family history of SCD, ventricular tachycardia with hemodynamic compromise, unexplained syncope and RV or biventricular severe dysfunction

Figure 2. Event Free Survival from composite endpoint (CE) stratified for the presence of Epsilon wave. Patients with Epsilon wave have higher risk of CE occurrnce during long-term follow-up (Log Rank p value = 0.019).

1. Basso C, Corrado D, Marcus F, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet* 2009; **373**:1289-1300.

2. Lemola K, Brunckhorst C, Helfenstein U, Oechslin E, Jenni R, Duru F. Predictors of adverse outcome in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: long term experience of a tertiary care centre. *Heart* 2005; **91**:1167-72.

3. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994; **71**:215-8.

4. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Proposed modification of the Task Force Criteria. *European Heart Journal* 2010; **31**:806-14.

5. Corrado D, Wichter T, Link MS et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015.

6. Steriotis AK, Bauce B, Daliento L, et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2009; **103**:1302-8.

7. Peters S, Trummel M. Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: value of standard ECG revisited. *Ann Noninvasive Electrocardiol* 2003; **8**:238-245.

8. Turrini P, Corrado D, Basso C, Nava A, Bauce B, Thiene G. Dispersion of ventricular depolarization-repolarization: a noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2001; **103**:3075-80.

9. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. *Circulation* 2004; **110**:1527-34.

10. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005; 112: 2047-60

11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**(12):1440-63.

12. Leclercq JF, Coumel P. Characteristics, prognosis and treatment of the ventricular arrhythmias of right ventricular dysplasia. *Eur Heart J* 1989; **10** suppl D:61-7.

13. Blomstrom-Lundqvist C, Sabel CG, Olsson SB. A long term follow up of 15 patients with arrhythmogenic right ventricular dysplasia. *Br Heart J* 1987; **58**: 477-88.

14. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation* 2004; **110**:1879-84.

15. Roguin A, Bomma CS, Nasir K, et al. Implantable Cardioverter-Defibrillators in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *J Am Coll Cardiol* 2004; **43**:1843-1852.

16. Corrado D, Leoni L, Link MS, et al. Implantable Cardioverter-Defibrillator Therapy for prevention of Sudden Death in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. *Circulation* 2003; **108**:3084-3091.

17. Wichter T, Paul M, Wollmann C, et al. Implantable Cardioverter/Defibrillator Therapy in Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation* 2004; **109**:1503-1508.

18 Corrado D, Calkins H, Link MS et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation* 2010; **122**:1144–1152.

19 Link MS, Laidlaw D, Polonsky B et al. Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. *J Am Coll Cardiol* 2014; **64**:119–125.

20 Saguner AM, Medeiros-Domingo A, Schwyzer MA et al. Usefulness of inducible ventricular tachycardia to predict long-term adverse outcomes in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2013; **111**:250–257.

21. Peters S, Trummel M. Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: value of standard ECG revisited. *Ann Noninvasive Electrocardiol* 2003; **8**:238-245.

22. Quarta G, Ward D, Tomé Esteban M, et al. Dynamic electrocardiographic changes in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart* 2010; **96**:516-522.

23. Jaoude SA, Leclercq JF, Coumel P. Progressive ECG changes in arrhythmogenic right ventricular disease. Evidence for an evolving disease. *Eur Heart J* 1996; **17**:1717-22.

24. Piccini P, Nasir K, Bomma C, et al. Electrocardiographic Findings over time in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2005; **96**:122-126.

25. Shulin Wu, Peining Wang, Yueshuang Hou, Pingzhen Yang, Yanping Xiao, Xianzhang Zhan. Epsilon Wave in Arrhythmogenic Right Ventricular Displasia/Cardiomyopathy. *PACE* 2009; **32**: 59-63.

26. Turrini P, Corrado D, Basso C, Nava A, Thiene G. Noninvasive Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy. *Ann Noninvasive Electrocardiol* 2003; **8**:161-169.

27 Jain A, Shehata ML, Stuber M, et al. Prevalence of Left Ventricular Regional Dysfunction in Arrhythmogenic Right Ventricular Dysplasia. *Circ: Cardiovasc Imaging.* 2010; **3**(3): 290-297.