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Dynamic electrocardiographic changes in patients with arrhythmogenic right ventricular cardiomyopathy

Giovanni Quarta,1,2 Deirdre Ward,1 María T Tomé Esteban,1 Antonios Pantazis,1 Perry M Elliott,1 Massimo Volpe,2,3 Camillo Autore,2 William J McKenna1

ABSTRACT

Background and objectives Electrocardiographic (ECG) abnormalities of depolarisation and repolarisation contribute to the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC). The development of diagnostic ECG features were investigated in a genotype cohort with ARVC to provide more sensitive markers of early disease.

Methods T-wave inversion (TWI) in right precordial leads, epsilon waves, localised QRS prolongation greater than 110 ms in V1–V3 and QRS dispersion greater than 40 ms were analysed from 317 ECG from 68 genotyped patients (34 with disease-causing mutations) during follow-up of 34±28 months.

Results 16 patients (23%) had changes during follow-up, with the appearance of new ECG abnormalities in seven (10%) and dynamic changes in nine (13%). Four developed new and persistent TWI and eight had dynamic TWI in right precordial leads. Three developed new and another three had dynamic epsilon waves. No changes were observed in 10 with and 58 patients without localised QRS prolongation and in six patients with and 61 without QRS dispersion greater than 40 ms. An additional patient with QRS dispersion at baseline had normal depolarisation dispersion during follow-up. None of the nine ARVC patients with dynamic ECG changes had major structural or functional right ventricular abnormalities, suggesting an early stage of the disease.

Conclusions New or dynamic ECG changes were observed in 23%. This underscores the importance of serial ECG in the diagnosis of individuals at risk of ARVC, in whom potentially lethal arrhythmia may develop before major abnormalities are detectable with conventional imaging.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease characterised by myocyte loss with fibro-fatty replacement in the right and/or left ventricle.1 Clinical presentation is with ventricular arrhythmias, congestive heart failure and sudden cardiac death.2 The identification of mutations in five different desmosomal genes supports the hypothesis that ARVC is a disease of cell adhesion.3–8

Clinical diagnosis of ARVC is problematical and still relies on diagnostic criteria proposed over a decade ago.9 A modification of these criteria has been proposed for the diagnosis of ARVC in the setting of a known family history, in which the risk of inheriting a disease-causing gene is 50%.3 However, recent genotype–phenotype correlation studies have highlighted the fact that the former criteria lack sensitivity and the latter may lack specificity.9 10

The 12-lead electrocardiogram (ECG) is an important diagnostic tool in ARVC. ECG features of ARVC include: (1) T-wave inversion (TWI) in right precordial leads (V1–V5) above the age of 12 years in the absence of right bundle branch block, found in 46–85% in the largest series;12 13 (2) epsilon waves, present in up to 33% of ARVC patients;12 14 (3) localised QRS prolongation greater than 110 ms in right precordial leads seen in up to 64% of patients and (4) QRS dispersion greater than 40 ms in 44%.12

The aim of our study was to investigate the development/evolution of these ECG features in relation to other clinical characteristics in genotype patients who ultimately fulfilled the diagnostic criteria for ARVC. Such an evaluation was prompted by the first author's observation of spontaneous variation in ECG diagnostic features while scanning tracings of ARVC mutation carriers onto the ARVC database.

METHODS

The electrocardiographic features of arrhythmogenic right ventricular cardiomyopathy were assessed in consecutive patients diagnosed with ARVC according to the task force criteria for probands (the presence of two major, one major and two minor or four minor from different categories was considered diagnostic) and proposed modified criteria for family members.3 9 Patients were evaluated in a dedicated ARVC clinic at the Heart Hospital, University College London Hospital, London, by clinical history, 12-lead electrocardiogram (SAECG), transthoracic echocardiography, maximal upright bicycle exercise testing, 24-h ECG10 and, when necessary, by contrast echocardiography and/or magnetic resonance imaging. Sixty-eight patients who fulfilled the following criteria were included in the study: at least two good-quality 12-lead ECG recorded a minimum of 6 months apart in the absence of significant change in QRS axis in limb leads and in QRS morphology/polarity (R/S ratio) in precordial leads (to avoid comparison of ECG with different precordial lead positions); complete bundle branch block at baseline; a ventricular paced rhythm; aged 12 years or less; obstructive coronary artery disease; treatment with class 1 antiarrhythmic agents. Cardiac structural and functional abnormalities were defined by echocardiography and, when clinically indicated, by cardiac magnetic resonance, according to the criteria proposed by McKenna et al15 in 1994, and were classified as: major, when there was severe dilation (ie, ≥3 SD from normal range) and reduction in right
ventricular ejection fraction and/or localised right ventricular aneurysm and/or severe right ventricular segmental dilatation; minor, when there was mild global right ventricular dilatation (ie, ≥2 and <3 SD from normal range) and/or mild right ventricular ejection fraction reduction and/or mild right ventricular segmental dilatation and/or regional right ventricular hypokinesis. 9,15

SAECG was considered abnormal when at least two of the following parameters were present using a 40 Hz high-pass filtering; filtered QRS duration greater than 114 ms; low-amplitude signal duration below 40 μV is greater than 58 ms; the root mean square voltage in the last 40 ms of the QRS is less than 20 μV.16

ECG analysis

The ECG were recorded according to international standards17 at 25 mm/s and were enlarged two times in order to increase the accuracy of measurements; frequency filtering ranged from 0.05 to 0.5 Hz for low-frequency filtering and from 100 to 150 Hz for high-frequency filtering. ECG were analysed by GQ using digital callipers (SigmaScan Pro5 Demo; Systat, Chicago, Illinois, USA), without knowledge of the patient’s clinical data. QRS duration was measured in the precordial leads from the beginning of the Q wave, or, in absence of the latter, from the beginning of the R wave to the end of the S wave, defined as its return to the TP baseline. The mean value of three consecutive complexes was used for the analysis. Four ECG features were investigated: (1) TWI in right precordial leads (V1–V3); (2) epsilon waves, electrical potentials of small amplitude that occur at the end of the QRS complex and at the beginning of the ST segment;14 (3) localised QRS prolongation, defined when QRS duration was above 110 ms in right precordial leads (V1–V3);9 18 (4) QRS dispersion, defined when the difference between the maximum and minimum QRS values in the precordial leads was above or equal to 40 ms.13 19

Dynamic changes of ECG diagnostic features were defined by the presence and subsequent disappearance of any of the above electrocardiographic features during serial evaluation, ie, spontaneous fluctuations between diagnostic and non-diagnostic ECG abnormalities.

Statistical analysis

Continuous variables are reported as mean±SD and categorical variables are summarised as percentages. The reproducibility of the measurements of QRS intervals was assessed by two independent observers, blinded to the clinical data, in a random sample of 20 ECG. The percentage differences in QRS measurements ranged from 1% to 5% for within-observer variability and from 2% to 6% for between-observer variability. General agreement was obtained to define the presence of TWI in right precordial leads and epsilon waves in each patient (kappa value equals 1.0 according to Cohen’s k test). Continuous variables were compared by use of the Mann–Whitney U test. SPSS statistical software (SPSS Inc, version 12.0) was used for the statistical analysis.

RESULTS

Baseline patient characteristics

Baseline patient characteristics are shown in table 1. The study population of 68 patients was aged 17–74 years, mean 45.8 years. There were 33 men (48.5%). Patients were referred to the ARVC clinic for symptoms (n=14, 20.6%) following an episode of documented, symptomatic ventricular tachycardia (n=6, 8.8%), or ventricular fibrillation cardiac arrest (n=5, 4.4%), or for family evaluation (n=45, 66.2%). Thirty-one patients (45.6%) were asymptomatic at initial evaluation. Palpitation was the most common reported symptom (18 patients), followed by syncope (16 patients), shortness of breath (five patients) and chest pain (four patients). A family history of ARVC confirmed by autopsy and/or a clinical diagnosis of ARVC9 in a family member was found in 56 (82.3%) patients. Right ventricular structural and functional abnormalities were considered to be major in 18 patients (26.5%) and minor in 40 (58.8%). At baseline, 27 patients (59.7%) had TWI beyond V2, four (5.9%) had epsilon waves, 10 (14.7%) had localised QRS prolongation of the QRS complex in V1–V3, and seven (10.3%) had QRS dispersion. At least one of these features was present in 57 of 68 (84%) patients at baseline. Thirty patients had left bundle branch block (LBBB)-type ventricular tachycardia (nine sustained ventricular tachycardia, 21 non-sustained ventricular tachycardia) and 32 (47.1%) had more than 1000 premature ventricular complexes (PVC), or more than 200 PVC in the context of familial disease9 on 24-h ECG. Twenty-nine patients (42.6%) were taking antiarrhythmic therapy (amiodarone, β-blockers and/or sotalol). Mutations considered to be disease-causing were identified in 34 patients (50.0%): in desmplakin, 13 (19.1%); in plakophilin-2, 16 (23.5%); in desmoglein-2, four (5.9%) and in desmocollin-2, one (1.5%).

Follow-up

The patients were followed for 34.0±28.7 months (range 7–166 months). Forty-one (60.5%) underwent implantable cardioverter defibrillator (ICD) implantation and three had ventricular tachycardia ablation for recurrent episodes of ventricular tachycardia.

A total of 317 ECG was analysed (a mean of five ECG per patient, range 2–13). ECG changes during follow-up were observed in 16 patients (25.5%), with the appearance of new ECG abnormalities in seven (10.5%) and with dynamic ECG changes in nine (15.2%) (figure 1). In particular, four of 41 patients without TWI in V1–V3 at baseline developed TWI in right precordial leads. Eight patients (11.8%), four with and four without TWI at baseline, showed dynamic changes in repolarisation in right precordial leads (figures 1–3); one of them developed complete LBBB. Three of 64 patients without epsilon waves at baseline developed new epsilon waves during follow-up (figure 1b). Three patients showed a dynamic presence of epsilon waves (figure 4). Two of these patients also had dynamic repolarisation changes. Ten patients (14.7%) showed localised QRS prolongation in right precordial leads at baseline and 58 did not; neither subset had dynamic changes during follow-up (figure 1c).

Clinical characteristics of patients with dynamic ECG changes

Table 2 summarises the clinical characteristics of the nine patients who showed dynamic ECG changes. Gene mutations considered to be disease-causing were found in four out of nine (44%) patients (two in desmplakin and two in plakophilin-2). Every patient had either a family history of pathologically confirmed ARVC or clinical diagnosis of ARVC in a family member based on current diagnostic criteria.9 The duration of follow-up of these patients was similar to those without dynamic changes (50.4±8.2 vs 34.6±0.6 months, p=0.413). The
patients were aged 18–53 years. None had major structural abnormalities of the right ventricle. Two patients had evidence of left ventricular involvement. Patient no 7 had a left ventricular end-diastolic diameter 128% of predicted, with preserved left ventricular ejection fraction (60%) and no wall motion abnormalities. She and other members of her family carry a desmo-plakin mutation (2034insA, T586fsX594), which is associated with ARVC and predominantly left ventricular involvement. Two patients had evidence of localised QRS prolongation in V1–V3, and ‘postexcitation waves’, later on called ‘epsilon waves’.14 Subsequently, additional diagnostic electrocardiographic features were proposed including the presence of localised QRS prolongation in V1–V3,9–10 QRS and QT dispersion19 and a delayed S-wave upstroke of 55 ms or greater in V1–V3,12 although the value of the latter has been questioned as an early diagnostic marker.12 Few studies have analysed the electrocardiographic changes over time in ARVC patients. Two patients (nos 4 and 6), who experienced atypical chest pain, underwent coronary angiogram. The first showed normal coronary arteries; the latter demonstrated an abnormal origin of a small left coronary artery from the right coronary sinus, whereas a huge right coronary supplied most of the left and right ventricles; a dobutamine stress-echo showed no evidence of ischaemia. The finding of new or dynamic ECG changes was not associated with any particular disease-causing mutation (table 2).

**DISCUSSION**

Since the first description of an ARVC cohort in 1982,21 ECG abnormalities have been acknowledged as an important feature of disease expression, the most distinctive being TWI in right precordial leads (V1–V3) and ‘postexcitation waves’, later on called ‘epsilon waves’.14 Subsequently, additional diagnostic electrocardiographic features were proposed including the presence of localised QRS prolongation in V1–V3,9–10 QRS and QT dispersion19 and a delayed S-wave upstroke of 55 ms or greater in V1–V3,12 although the value of the latter has been questioned as an early diagnostic marker.12 Few studies have analysed the electrocardiographic changes over time in ARVC patients. Two patients (nos 4 and 6), who experienced atypical chest pain, underwent coronary angiogram. The first showed normal coronary arteries; the latter demonstrated an abnormal origin of a small left coronary artery from the right coronary sinus, whereas a huge right coronary supplied most of the left and right ventricles; a dobutamine stress-echo showed no evidence of ischaemia. The finding of new or dynamic ECG changes was not associated with any particular disease-causing mutation (table 2).

**Figure 1** Electrocardiographic features pattern in arrhythmogenic right ventricular cardiomyopathy patients (see text). (A) T-wave inversion in right precordial leads; (B) epsilon wave; (C) localised QRS prolongation; (D) QRS dispersion > 40 msec.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline clinical characteristics of the overall study population</th>
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<tr>
<td><strong>Baseline characteristics</strong></td>
<td>ARVC 68</td>
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<tr>
<td><strong>General</strong></td>
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</tr>
<tr>
<td>Male, n (%)</td>
<td>33 (48.5)</td>
</tr>
<tr>
<td>Current age in years, mean (±SD)</td>
<td>42.8 (14.0)</td>
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<tr>
<td>Age at diagnosis in years, mean (±SD)</td>
<td>39.3 (14.2)</td>
</tr>
<tr>
<td><strong>Symptoms, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>31 (45.6)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>18 (26.5)</td>
</tr>
<tr>
<td>Syncope</td>
<td>16 (23.6)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>5 (7.3)</td>
</tr>
<tr>
<td>Ventricular fibrillation cardiac arrest</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td><strong>Family history, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Family history of ARVC confirmed by autopsy</td>
<td>39 (57.3)</td>
</tr>
<tr>
<td>Family history of premature sudden death (&lt;35 years) due to suspected ARVC or clinical diagnosis in family member based on present criteria</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td><strong>Structural abnormalities and global or regional dysfunction, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Severe dilation and reduction in RVEF or RV aneurysm or severe segmental dilation of right ventricle with or without mild LV involvement</td>
<td>18 (26.5)</td>
</tr>
<tr>
<td>Moderate global RV dilatation and reduction in RVEF or moderate segmental dilation of right ventricle or regional RV hypokinesia with normal left ventricle</td>
<td>40 (58.8)</td>
</tr>
<tr>
<td><strong>ECGdepolarisation abnormalities, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Localised prolongation (&gt;110 ms) of the QRS complex in right precordial leads (V1–V3)</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Epsilon waves</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Late potential on signal-averaged ECG</td>
<td>39 (57.3)</td>
</tr>
<tr>
<td><strong>ECGrepolarisation abnormalities, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Inverted T waves in right precordial leads (V1–V3)</td>
<td>27 (39.7)</td>
</tr>
<tr>
<td><strong>Arrhythmias, n (%)</strong></td>
<td></td>
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<tr>
<td>Left bundle branch block type ventricular tachycardia on resting, exercise or 24 h ECG</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>21 (30.9)</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>32 (47.1)</td>
</tr>
<tr>
<td>Frequent ventricular extrasystoles (more than 1000/24 h) (Holter ECG)*</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>QRS dispersion &gt;40 ms</td>
<td></td>
</tr>
</tbody>
</table>

*Or more than 200/24 h in the context of a family history.2 ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; LV, left ventricular; RV, right ventricular; RVEF, right ventricular ejection fraction.
who fulfilled the diagnostic criteria for ARVC, 13% of whom had sustained ventricular tachycardia. Our programme involves clinical evaluation of family members of probands with clinical or pathological diagnosis of ARVC. This enables recognition of a broader clinical spectrum of ARVC, including early/asymptomatic forms, and this may account for some of the differences between our and previous studies, in which up to 90% of patients had evidence of ECG progression. Most patients showed either no changes or a progressive development of recognised ECG abnormalities of ARVC. Conversely, in a minority (13%), dynamic changes in T-wave polarity in right precordial leads, as well as in the presence of epsilon waves, were noted. QRS dispersion tended to be a more stable parameter and its disappearance (patient no 7) was mainly due to prolongation of QRS duration in V5–V6 (figure 5). This observation raises the issue of the diagnostic sensitivity of QRS dispersion in later stages of the disease, when the involvement of the left ventricle may occur or in predominantly left ventricular forms of the disease. Similarly, no changes were noted in localised QRS prolongation in V1–V3 during follow-up. In contrast, a report from 1987 in 15 patients

Figure 2  (a) The first ECG, taken from patient no 4 in December 2003, shows sinus rhythm with epsilon wave in V1 (see arrow in magnified image), T-wave inversion (TWI) in V1–V4 and left bundle branch block premature ventricular complexes (therefore it satisfies one major and one minor criterion). (b) The second ECG, taken in June 2005, shows sinus rhythm with incomplete right bundle branch block and TWI in V1 and T-wave flattening V2–V4.
showed a significant increment of QRS duration over time. However, that study was performed before the current diagnostic criteria for ARVC were issued and included highly symptomatic patients with advanced disease. 

Analysis of the clinical data of the ARVC patients with dynamic ECG changes revealed that none had major right ventricular structural or functional abnormalities, suggesting an early stage of the disease in this cohort (table 2).

In a previous study on young sudden cardiac death victims, dynamic ST elevation in right precordial leads (type 1 Brugada ECG pattern) was observed in five of six ARVC patients in whom at least two ECG were available, showing that dynamic ECG changes may also occur in structural heart disease. A transmural dispersion of repolarisation, most likely neurally mediated, from the diseased subepicardial layer and the relatively spared subendocardial muscle, has been advocated as a possible mechanism and may be partly associated with the dynamic ECG changes found in our population.

In recent years, a number of genetic and pathological studies have provided evidence that ARVC is mainly caused by dysfunction in desmosomes, specialised cell—cell adhesion structures that anchor intermediate filaments to cell membranes. It has been hypothesised that malfunction of desmosomal proteins causes cell detachment in areas where the myocardium is subjected to intense and constant mechanical stress. Disruption of the mechanical desmosomal junction eventually leads to myocyte death with an inflammatory response and fibro-fatty replacement, the pathological hallmark of ARVC. The dynamic ECG changes found in our study may reflect an active early phase of this process at a time when the mechanical defect causes electrical abnormalities in the absence of clinically detectable morphological changes. This hypothesis is supported by another clinical study, which showed no correlation between electrocardiographic abnormalities and the extent and location of right ventricular involvement detected by echocardiography in a cohort of 20 patients. Gap junction remodelling described in a young girl with Naxos disease, a recessive form of ARVC, and confirmed by another study in dominant ARVC, may play a role in the phenomenon observed in our study. The young girl with Naxos disease died aged 7 years from a non-cardiovascular cause. She had typical ECG features of ARVC and frequent ventricular arrhythmias (>14,000 PVC on 24-h ECG), mainly of right ventricular origin, but no structural heart disease detectable by echocardiography. Her entire heart was examined by expert pathologists (G Thiene, J Safitz), who could not identify macroscopic or microscopic features of ARVC. Immunohistochemical studies, however, revealed failure of appropriate localisation to the intercalated disc of plakoglobin and reduced expression of the important gap junction protein connexin-43. Spontaneous fluctuations between diagnostic and non-diagnostic ECG abnormalities have been described in inherited ion channel
**CONCLUSIONS**

This study demonstrates that some of the diagnostic features of ARVC may be dynamic. These dynamic changes were not evident in the absence of detectable clinical structural or functional alterations or the typical histological changes of fatty-fatty replacement. In contrast, when overt disease is present, ECG abnormalities may be stable or progressive, presumably because significant structural changes have occurred.

**Clinical implications**

The presence of dynamic ECG changes is important in the context of familial disease, in which it is recognised that isolated unexplained ECG abnormalities are common and may be an early marker of disease expression. This underscores the importance of serial evaluation, particularly in patients at increased risk of disease development, ie, first-degree relatives. The presence of a normal ECG and normal imaging does not imply absence of disease expression, and normal imaging does not imply absence of disease expression.

**Limitations**

The number of ECG available for each patient and the duration of the individual follow-up are limitations that may have led to an underestimation of the frequency of the dynamic ECG changes in patients with ARVC. Variable ECG filtering may have affected the detection of epsilon waves, but not the detection of dynamic TWI, which was the main dynamic electrocardiographic feature found in our ARVC cohort.

**Table 2**

<table>
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<tr>
<th>Subject</th>
<th>Gender</th>
<th>Current age (years)</th>
<th>Symptoms</th>
<th>Family history</th>
<th>RV structural/functional abnormalities</th>
<th>LV involvement</th>
<th>Localised QRS prolongation</th>
<th>Epsilon wave</th>
<th>SAECG</th>
<th>TWI in right precordial leads</th>
<th>Max no of PVC on 24 h Holter monitoring</th>
<th>NSVT</th>
<th>VT</th>
<th>Symptoms during follow-up</th>
<th>VT ablation</th>
<th>ICD implantation</th>
<th>Gene mutation identified</th>
<th>Dynamic ECG changes</th>
<th>Diagnostic criteria (major/minor)</th>
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<td>1</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
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<td>TWI</td>
<td>1/2</td>
<td>Dynamic ECG changes</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td>Palpitation, presyncope</td>
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<td>TWI</td>
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<td>-</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td>Palpitation, presyncope</td>
<td>Plakophilin 2</td>
<td>TWI</td>
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<tr>
<td>4</td>
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<td>+</td>
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<td>Plakophilin 2</td>
<td>Epsilon wave</td>
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</tbody>
</table>

Minus sign (−), absent; plus sign (+), present.

*ICD, implantable cardioverter defibrillator; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; QRSd, QRS dispersion; RV, right ventricular; SAECG, signal-averaged electrocardiogram; SDB, shortness of breath; VT, ventricular tachycardia.*

**Figure 5**

(a) The first ECG taken from patient no 7 (Table 2) shows QRS dispersion greater than 40 ms in precordial leads. (b) Subsequently, prolongation of QRS duration in V6 resulted in the disappearance of QRS dispersion.
not paralleled by progression of structural or functional right ventricular abnormalities. Recognition of these dynamic changes, albeit in a minority (13%), highlights the importance of serial evaluation for the diagnosis of ARVC. Larger cohorts with longer follow-up are needed to examine the clinical associations of arrhythmogenic right ventricular cardiomyopathy. Evidence for an evolving disease. Evidence for an evolving disease.

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Competing interests None.

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