Disease-Specific Electrocardiographic Lead Positioning for Early Detection of Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by replacement of cardiomyocytes by fibrofatty tissue, where genetic defects in desmosomal proteins, as plakophilin-2 (PKP2), contribute to disease development. Current ECG criteria for ARVC diagnosis only focus on right precordial leads, but sensitivity of current depolarization criteria is limited. This study aims to identify better depolarization criteria with better lead configurations to early detect ARVC in PKP2 pathogenic variant carriers. 64-lead body surface potential maps (BSPM) were obtained in PKP2-positive ARVC patients, PKP2 pathogenic variant carriers and control subjects without structural heart disease. Terminal QRS-integrals were determined in all leads and significantly different terminal QRS-integrals compared to controls were identified using the departure mapping technique. Departure maps showed significantly different terminal QRS-integrals in ARVC patients beyond right precordial leads. Beside conventional lead V3-V4, lead 40 showed high sensitive value (100%) in differentiation of ARVC from controls and similar depolarization abnormalities were observed in up to 40% of all PKP2 pathogenic variant carriers. New depolarization criteria were found in PKP2-positive ARVC patients that be observed beyond right precordial leads V1-V3.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by replacement of cardiomyocytes by fibrofatty tissue that leads to sudden cardiac death or heart failure. Genetic defects in desmosomal proteins, with plakophilin-2 (PKP2) being the most frequently affected gene, contribute to disease development. The current 2010 Task Force Criteria for diagnosis of ARVC is based on a complex set of major and minor criteria from different diagnostic modalities. However, mostly the diagnosis will reflect a variable degree of probability that depends on the clinical context due to heterogeneous clinical presentation.¹³ Mast et al.⁴ have determined the association between structural and electrical progression in 85 ARVC patients. The study results showed that significant structural right ventricular (RV) progression, such as RV enlargement and RV dysfunction, was associated with prior depolarization abnormalities. In other words, assuming electrical abnormalities arise prior to mechanical abnormalities, detection and screening of electrical abnormalities seems to be important for early diagnosis of ARVC. Current electrocardiographic (ECG) criteria for ARVC diagnosis include the presence of epsilon waves, prolonged terminal activation duration (TAD) and negative T-waves. All ECG criteria of ARVC focus on the presence of abnormalities in right precordial leads V1-V3, but only negative T-waves showed to be a highly sensitive criteria (79%) compared to prolonged TAD (40%) and epsilon waves (10%).¹⁵

The amount of information obtained with conventional 12-lead electrocardiography (ECG) suffices for most clinical applications. However, in some applications the use of extra ECG leads or other lead locations has proven to increase the detection rate, like Brugada Syndrome or posterior or inferior myocardial infarction.⁶⁷ This study aims to determine better depolarization criteria with a properly placed lead configuration to improve early diagnosis of ARVC in PKP2 pathogenic variant carriers.

2. Method

2.1. Study population

The study population consisted of 23 PKP2 pathogenic variant carriers and nine control subjects with symptomatic ventricular extrasystoles originating in the right ventricular outflow tract (RVOT VES). Exclusion criteria were complete right bundle branch block (QRS width > 120ms) and other structural diseases that affect ECG morphology apart from ARVC symptoms. Subjects with RVOT VES were considered to be control subjects, where subjects that showed signs of heart failure were excluded in the study.
All subjects were included in the study since 2015. The study was approved by the Medical Ethics Committee of University Medical Center Utrecht (17/907) and informed consent was obtained from each subject before enrolment.

2.2. Body surface potential mapping

67-lead body surface potential map (BSPM) was performed on each subject, including 64 torso and 3 limb leads. The anterior body surface includes 55 leads, that were placed in nine vertical strips with strip 4 located at the sternum. Electrodes were separated 4cm in the vertical strip from each other. Strip 3 and 5-9 are located at same sagittal axis as the conventional precordial ECG leads. The posterior body surface includes 9 leads, that were placed in three vertical columns. BSPM data were recorded (Biosemi, Amsterdam, The Netherlands) simultaneously with Wilson’s central terminal as reference, at a sampling frequency of 2048Hz, 24-bit/sample. Data was down-sampled to 1000Hz.

2.3. Data analysis

Per subject, ten consecutive sinus beats at resting respiration were averaged. Leads with noise were removed. QRS-onset and QRS-end were manually assigned in the square root of the mean square (RMS) from all leads. Early electrical depolarization abnormalities of ARVC disease in PKP2 pathogenic variant carriers were investigated by comparing integral maps from BSPM data with each other. Integral maps indicate a mean potential direction over intervals of the QRS complex. Focusing on delayed right ventricular activation due to fibrofatty tissue in ARVC patients, integrals over the last 60ms of the QRS complex, defined as terminal QRS integrals, were determined.

2.4. Departure mapping technique

The extent of integral deviation from the normal range of the control group was determined and defined as the departure index (DI). The departure index was calculated by

$$DI = \frac{I_N - \mu_{control}}{\sigma_{control}},$$  \hspace{1cm} (1)

where $I_N$ equals the integrals of an individual subject N, $\mu_{control}$ is the mean integral of control group and $\sigma_{control}$ is the standard deviation of the integrals in control group. Both ARVC subjects and PKP2 pathogenic variant carriers were compared with the control group. DI was calculated for each integral of each lead and integrals on the body surface leads that differ significantly (> 2 SD) from the control data were identified. Individual departure maps were grouped to determine leads that show significantly different integrals in most subjects (Figure 1).

3. Results

Seven PKP2 pathogenic variant carriers met the 2010 Task Force Criteria for ARVC, with averaged $6.6 \pm 2.4$
criteria and duration of follow-up since diagnosis 3.7 ± 3.8 years. Patients characteristics per group can be observed in Table 1.

The grouped departure maps display that lead 40, indicated with orange star, shows significantly different terminal QRS-integrals in five out of seven ARVC patients (Figure 2). Six out of sixteen PKP2 pathogenic variant carriers showed significantly different terminal QRS-integrals in lead 47. The QRS-potentials of these five ARVC subjects in lead 40 and six PKP2 pathogenic variant carriers in lead 47 were visualized in Figure 2.

The differentiation of ARVC in both terminal QRS-integrals and R-wave apex duration were determined in conventional 12-lead positions, lead 40 and 47 (Table 2).

<table>
<thead>
<tr>
<th>Grouped departure maps</th>
<th>QRS-potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARVC</strong></td>
<td><img src="image1" alt="Grouped departure maps" /></td>
</tr>
<tr>
<td>FRONT BACK</td>
<td>Lead 40</td>
</tr>
<tr>
<td><strong>PKP2</strong></td>
<td><img src="image3" alt="Grouped departure maps" /></td>
</tr>
<tr>
<td>FRONT BACK</td>
<td>Lead 47</td>
</tr>
</tbody>
</table>

Figure 2. Grouped departure maps (DI > 2) of terminal QRS-integrals (left) and QRS-potentials of orange stared lead positions (right). The grouped departure maps and QRS-potentials of ARVC vs CONTROL (upper row) and PKP2 vs CONTROL (bottom row) were visualized. Orange stars correspond to leads where most subjects showed significantly different integrals, with maximum subjects noted in left-upper corner of the grouped departure map.

The purpose of this study was to investigate terminal QRS-integrals in ARVC patients, PKP2 pathogenic variant carriers and control subjects, to identify leads that might express early depolarization abnormalities. Departure maps were determined to visualize significant differences in terminal QRS-integrals compared to the control group. The results show that depolarization abnormalities can be observed in other leads beyond conventional 12-lead ECG positions V1-V3. The grouped departure map showed that in five out of seven ARVC patients, the terminal QRS integrals exceeded twice the standard deviation from the normal range of the control group in lead 40 above conventional lead V4. In PKP2 pathogenic variant carriers, lead 47 above V5 showed most significantly different integrals. Significantly higher terminal QRS-integrals in both ARVC and PKP2 pathogenic variant carriers, can be explained by increased R-wave amplitudes (mV), delayed R-wave apex (ms), and decreased S-wave amplitude (mV) in QRS-potentials (Figure 2).

Despite the known heterogenous clinical presentation of ARVC, terminal QRS-integrals and R-wave apex duration showed to be a highly sensitive (>86%) and specific (>89%) criteria in lead V3, V4 and 40. Using these same criteria in PKP2 pathogenic variant carriers, up to 44% of all sixteen PKP2 pathogenic variant carriers met this new criteria. A properly combination of lead positions for detection of depolarization abnormalities in PKP2 pathogenic variant carriers might increase sensitivity for early subtle depolarization changes.

Presence of the found depolarization abnormalities in both ARVC patients and PKP2 pathogenic variant carriers in relation to disease progression has to be further investigated, because the results in this study could be biased due to the small sample sizes that were used. However, the high sensitive and specific criteria in lead 40 suggest that the results are likely applicable in larger
Table 2. Differentiation of ARVC subjects (n=7) and PKP2 pathogenic variant carriers (n=16) from control subjects (n=9) for both conventional 12-lead ECG positions and new lead positions found with the departure mapping technique.

<table>
<thead>
<tr>
<th>Lead</th>
<th>Cut-off value (mVms)</th>
<th>ARVC SE (%)</th>
<th>ARVC SP (%)</th>
<th>PKP2 SE (%)</th>
<th>PKP2 SP (%)</th>
<th>Cut-off value (ms)</th>
<th>ARVC SE (%)</th>
<th>ARVC SP (%)</th>
<th>PKP2 SE (%)</th>
<th>PKP2 SP (%)</th>
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<tbody>
<tr>
<td>V1</td>
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<td>100</td>
<td>6</td>
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<td>15</td>
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<td>44</td>
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<td>28</td>
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<td>86</td>
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<td>50</td>
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<td>100</td>
<td>31</td>
<td>100</td>
<td>32</td>
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</table>

Abbreviations: SE = sensitivity. SP = specificity.

sample sizes. Longer follow-up and an increase in sample size of both ARVC patients and PKP2 gene carriers is necessary. Besides, the criteria’s have to be validated in healthy subjects without RVOT VES to exclude possible bias with the current control group.

For clinical use, the feasibility of the new additional information, like delayed R-wave apex and terminal QRS-integrals, have to be clinically validated. It is hypothesized that detection of subtle depolarization abnormalities in PKP2 pathogenic variant carriers might need implementation of a computational algorithm.

5. Conclusion

This study observed that delayed ventricular activation due to disease development in PKP2-positive ARVC patients can be observed beyond right precordial leads V1-V3. Analysis of terminal QRS-integrals revealed new depolarization criteria that might increase detection of ARVC, like R-wave apex duration. Besides conventional lead V3-V4, lead 40 showed to be a high sensitive lead position in detection of new depolarization criteria.

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References


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