Noninvasive Diagnosis of Electroanatomic Abnormalities in Arrhythmogenic Right Ventricular Cardiomyopathy

Running title: Santangeli et al.; Noninvasive correlates of low voltages in ARVC

Pasquale Santangeli1,5, MD; Maurizio Pieroni1, MD; Antonio Dello Russo2, MD; Michela Casella2, MD; Gemma Pelargonio1, MD; Andrea Macchione1, MD; Antonia Camporeale1, MD; Costantino Smaldone1, MD; Stefano Bartoletti1, MD; Luigi Di Biase3,4,5, MD; Fulvio Bellocci1, MD; Andrea Natale4,5, MD, FACC.

1Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy
2Arrhythmia Dept, Institute of Cardiology, Univ of Milan, IRCCS–Centro Cardiologico Monzino
3Department of Cardiology, University of Foggia, Foggia, Italy
4Department of Biomedical Engineering, University of Texas, Austin, TX
5Texas Cardiac Arrhythmia Institute, St. David’s Medical Center, Austin, TX

Address for correspondence and reprint requests to:
Pasquale Santangeli, MD
Cardiology Department
Catholic University of the Sacred Heart,
Largo A. Gemelli 8
00168 Rome, Italy
Tel:+39-6-30154187, Fax:+39-6-3055535
E-mail: pasquale.santangeli@libero.it

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ABSTRACT

Background - The diagnostic reliability and pathophysiologic relevance of different noninvasive diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) is undefined. We tested the association between noninvasive diagnostic criteria for ARVC and the presence of low-voltage areas (LVA) detected at electroanatomic voltage mapping (EAM).

Methods and Results - Noninvasive diagnostic criteria, including ECG, signal averaged ECG (SAECG) and cardiac magnetic resonance (CMR) criteria, were compared with the presence and location of LVA detected at RV EAM in 17 patients (age 50 ± 16 years, 9 men) with biopsy-proven ARVC. Low-voltage areas were found in 15 (88%) patients. Patients with surface ECG abnormalities showed a higher degree of RV involvement compared to those without ECG abnormalities (1.8 ± 0.5 vs. 0.9 ± 0.6 number of LVA, respectively, P < 0.01). A significant association was found between SAECG abnormalities and LVA in the RV outflow tract (P = 0.03), but not between SAECG parameters and LVA in other RV regions. Among CMR findings, RV delayed enhancement was the CMR finding more significantly associated with the distribution of LVA (P < 0.01 in the free wall, P < 0.01 in the outflow tract, and P = 0.02 in the postero-inferior wall). Regional RV dysfunction also showed a good correlation with LVA, with the most significant association being found with the free wall (P = 0.01), while RV fat infiltration at CMR was not correlated with LVA.

Conclusion - In patients with ARVC, SAECG abnormalities correlate with the presence of LVA selectively in the RV outflow tract, whereas surface ECG abnormalities are associated with a more diffuse RV involvement. Myocardial delayed enhancement is the CMR finding more strongly associated with LVA, thus supporting the appropriateness of its inclusion among diagnostic criteria for ARVC.

Key words: arrhythmogenic right ventricular cardiomyopathy; noninvasive diagnosis; cardiac magnetic resonance; signal-averaged electrocardiogram; three-dimensional electroanatomic mapping.
INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by diffuse or segmental loss of right ventricular (RV) myocytes with replacement by fibro-fatty tissue and thinning of the ventricular wall. At present time, the diagnosis is based on established criteria, taking into account clinical findings and the presence of family history, morpho-functional abnormalities of the RV, and typical electrocardiographic (ECG) findings. However, diagnosis based on such criteria may be difficult because of several problems with the specificity of ECG abnormalities, and with the currently adopted methods to assess the RV structure and function. In particular, cardiac magnetic resonance (CMR), which is actually the gold standard to image the RV, is flawed by significant limitations and a high degree of inter-observer variability.

Thus far, the real diagnostic value and pathophysiological significance of each noninvasive diagnostic criterion are unclear, and no previous study compared current criteria with a diagnostic reference test. In recent years, three-dimensional electroanatomic voltage mapping (EAM) has been demonstrated a reliable tool to accurately identify and locate low-voltage areas (LVA) in the RV corresponding to areas of fibro-fatty replacement, even in patients with very early forms of the disease displaying completely normal ECG and CMR findings, thus increasing the accuracy for the diagnosis of ARVC.

The present study was designed to test the association between noninvasive diagnostic criteria and the presence of LVA detected at EAM in a consecutive series of patients with biopsy-proven ARVC.

METHODS

We studied 17 patients (age 50 ± 16 years, 9 men) admitted to our Institution (Catholic University, Rome, Italy) from January to December 2008, with an EAM-guided endomyocardial biopsy-proven diagnosis of ARVC. All patients underwent a complete noninvasive evaluation, including 12-lead ECG, 24-hour Holter monitoring, signal-averaged electrocardiogram (SAECG), two-dimensional
echocardiography and contrast-enhanced CMR. The disease was considered familial in the presence of other individuals with autopsy or biopsy-proven disease or premature (<40 years) sudden death at pedigree analysis.9

**Electrocardiogram and Signal-Averaged Electrocardiogram**

Twelve-lead ECGs were obtained in the standard lead positions and recorded at 25 mm/sec. The presence of depolarization and repolarization ECG abnormalities was assessed according to Task Force criteria.2, 11 In particular, depolarization ECG abnormalities included QRS prolongation (>110 msec) in right precordial leads (lead V1 to V3) and epsilon waves. Repolarization abnormalities consisted of inverted T waves beyond lead V1. Electrocardiograms were analyzed by two independent readers, each of whom was blinded to the results of electroanatomic mapping. The SAECG was obtained with an Arrhythmia Research Technology-101 or 1200 System, with bidirectional Butterworth filtering (40 to 250 Hz), as previously described.12 The following quantitative SAECG variables of the filtered QRS were evaluated: 1) total duration (fQRSd), 2) duration of the low-amplitude signals (<40 mV) in the terminal portion (LAS-40), and 3) root-mean-square voltage of the last 40 ms (RMS-40). Between 300 and 500 QRS complexes were averaged for each recording to reach a noise level <0.5 mV. Ventricular late potentials were considered positive when ≥2 of the following criteria were fulfilled:13, 14 a) fQRSd >114 ms, b) LAS-40 >38 ms, and c) RMS-40 <20 μV.

**Cardiac Magnetic Resonance**

Cardiac magnetic resonance was performed with a 1.5-T Signa Excite 2 scanner (General Electric Medical Systems, Milwaukee, Wisconsin) using a cardiac 8-channel phased-array coil. ECG gating and breath-hold technique were implemented to enhance image quality. Morphological evaluation of the cardiac chambers and myocardial tissue characterization were obtained by black-blood double- and triple-inversion recovery fast spin-echo sequences (repetition time 2 RR intervals, echo
time 34 ms, slice thickness 8 mm, image matrix 256 to 256, and field of view 30 to 36 cm) along axial, short-axis, and horizontal long-axis planes. Functional assessment was carried out using bright-blood steady-state free precession gradient-echo sequences. Particularly, a high-resolution FIESTA sequence (repetition time 34 ms, echo time 1.5 ms, flip angle 508, image matrix 224 to 288, field of view 30 to 36 cm) was used in axial, vertical long-axis, horizontal long-axis, and short-axis planes. Finally, inversion recovery prepared breath-hold cine gradient-echo images were obtained 20 min after intravenous administration of an MRI contrast agent (0.2 mmol/kg gadodiamide [Omniscan, Amersham Health, Princeton, New Jersey]).

Post-processing was performed on an Advantage Windows Workstation using MASS software (Medis, Leiden, the Netherlands). This software was used to view images using standardized window width and level settings. The same software was also used for measurement of RV (end-diastolic and end-systolic diameter) and RV outflow tract diameter. A RV outflow tract was defined enlarged if its short axis diameter measured more than 30 mm.15, 16 The RV systolic and diastolic diameters were measured on 4-chamber images by a line drawn from the interventricular septum to the RV free wall 1 cm below and parallel to the tricuspid valve. A RV was defined enlarged if it was equal to or larger than the left ventricular diameter measured 1 cm below the mitral valve plane. Diastolic and systolic ventricular volume measurements were obtained by summation of planimetered areas obtained from serial short-axis cine images. The first image after the R wave trigger represented the end-diastolic image. End-systolic image was defined visually as the one with the smallest ventricular cavity size. Right ventricular dilatation and dysfunction were also assessed quantitatively, according to established reference values adjusted for age, sex and body surface area.17

For qualitative reporting, the RV was divided into 5 regions: the outflow tract, the postero-inferior wall (i.e., including both the inferior and posterior segments), the free wall, the apex, and the septal wall. For each region we assessed: regional wall motion (scored from 1 normal to 4 dyskinetic), delayed enhancement (0 absent, 1 present), and intramyocardial fat infiltration (0 absent, 1 present).
Left ventricular involvement was considered present when ≥1 of the following criteria were satisfied: left ventricular global dilatation, left ventricular systolic dysfunction, left ventricular wall motion abnormalities, left ventricular intramyocardial fat, and left ventricular delayed enhancement. All CMR images were analyzed by an expert radiologist who was blinded to the clinical and electroanatomic mapping information.

**Invasive study**

The invasive study was approved by the institutional review board, and all patients gave their written informed consent. All patients were submitted to coronary and left and right ventricular angiography (right and left anterior oblique views), RV three-dimensional EAM, and EAM-guided endomyocardial biopsy.

Right ventricular three-dimensional EAM was performed with the CARTO™ system (Biosense-Webster, CA, USA), as previously described.9, 18 Briefly, mapping points were sampled with a 7F 4-mm tip Navi-Star™ catheter (Biosense-Webster, Inc.) to generate an accurate three-dimensional electroanatomic map of the RV, reflecting the shape evidenced by angiography. High-density mapping was obtained in sinus rhythm (reference channel: QRS complex) by sampling at least 200 points uniformly distributed. The voltage maps were edited setting the point density (fill threshold) at 15 mm and manually eliminating intracavitary points. To avoid low voltage recordings due to poor contact, the following tools were used: 1) the signal had to satisfy 3 stability criteria automatically detected by CARTO™ system in terms of cycle length, local activation time and beat-to-beat difference of the location of the catheter (<2%, <3 ms, and <4 mm, respectively); 2) both bipolar and unipolar signals were simultaneously acquired to confirm true catheter contact through the analysis of local electrogram (in particular the shape of the unipolar electrogram); 3) in the presence of a low voltage area, at least 3 additional points were acquired in the same site to confirm the reproducibility of the voltage measurement.7, 9, 18 A LVA was defined as an area ≥ 1 cm².
including at least 3 adjacent points with a mean bipolar voltage value of \( \leq 1.5 \) mV. A CARTO™ incorporated software was used to measure the extension of low-voltage areas, which was reported both as total RV area displaying low-voltages, and also as percent of total RV area with low-voltages.

Right ventricular endomyocardial biopsies (4-5 samples from each patient) were obtained via the femoral vein with the use of a preformed long sheath and a disposable bioptome (Cordis, Johnson and Johnson, FL, USA), and withdrawn from RV wall segments with abnormal voltage, as previously shown.\(^9\) In case of normal EAM, endomyocardial biopsies were withdrawn from conventional sites including apex and interventricular septum. The diagnosis of ARVC was made on the basis of extensive fibro-fatty myocardial atrophy with a percentage of fat >3\% and fibrous tissue >40\% associated with amounts of residual myocytes <45\% of the specimen at morphometric analysis.\(^19\)

For comparison with noninvasive diagnostic findings, the RV map of LVA was divided into five areas: the outflow tract, the postero-inferior wall (i.e., including both the inferior and posterior segments), the free wall, the apex, and the septal wall.

**Statistical Analysis**

All variables in this study did not show statistically significant deviation from normal distribution, according to Kolmogorov-Smirnov test. Unpaired Student t-test, 1-way analysis of variance, and Fisher exact test were used to compare differences across groups. Bivariate correlations analyses were assessed with Pearson test, with the measure of correlation reported as the Pearson product-moment correlation coefficient (\( r \)) and corresponding \( P \) values. The association and agreement between presence of qualitative CMR findings and distribution of LVA were evaluated by the Cohen’s Kappa test. A good level of agreement was defined as a value of Kappa \( \geq 0.61 \).\(^20\) With regard to SAECG parameters, the best cut-off values for the fQRSd, RMS-40 and LAS-40 for the diagnosis of a LVA in the RV outflow tract were identified analyzing receiver operating
characteristic (ROC) curves. Data are reported as mean ± SD, unless differently indicated. A level of P <0.05 was considered for statistical significance. Statistical analyses were done by STATA 11.1 statistical package (Stata Corporation, College Station, Texas, USA).

RESULTS

Clinical characteristics

Clinical characteristics of the patient population are presented in Tables 1 and 2. All patients had a biopsy-proven diagnosis of ARVC and fulfilled diagnostic criteria,\(^2\) with all presenting at least 2 major criteria. In particular, the presence of fibro-fatty replacement on endomyocardial biopsy\(^1^9\) was one of the two major criteria in all patients, with the other major criterion belonging to morpho-functional abnormalities in 9 patients, and to major ECG abnormalities in 8.\(^2\) The time interval from onset of symptoms to the invasive study ranged from 1 to 36 months (mean 12 ± 11 months). Four patients (24%) had a family history of ARVC and of premature sudden death due to proven or suspected ARVC, and arrhythmia-related symptoms were present in 13 (76%) patients.

Electrocardiographic findings and SAECG results

The ECG findings and SAECG results are presented in Table 2. Overall, surface ECG abnormalities were present in 8 patients (47%). Ventricular arrhythmias with left bundle branch block morphology were documented in all patients, including nonsustained ventricular tachycardia in 7 (41%), and frequent premature ventricular beats (i.e., >1,000 VPBs over 24 hours Holter monitoring) in 10 (59%) patients. The most common site of origin of ventricular arrhythmias, according to standard ECG criteria,\(^2^1\) was the outflow tract (76% of patients).

Ventricular late potentials at SAECG were present in 11 patients (65%).

Cardiac magnetic resonance results
The results of CMR imaging study are summarized in Table 2. Two patients did not undergo CMR because of claustrophobia. Cardiac magnetic resonance detected structural and/or functional RV abnormalities in 14/15 (93%) patients. Intramyocardial fat infiltration of the RV was observed in 9/15 (60%) patients. The most common location of fat infiltration was the free wall (47%) and the postero-inferior wall (40%), followed by the outflow tract (7%) and the apex (7%). Delayed-enhancement of the RV was reported in 8/15 (53%) patients, and was most commonly localized in the free wall (27%), followed by the postero-inferior wall (20%), the outflow tract (20%), and in the septal wall (7%).

The mean RV ejection fraction was 51.9 ± 4.6%. A global RV dysfunction was present in 4/15 (27%) patients, and 6/15 (40%) patients had RV dilatation. Regional RV dysfunction was present in 11/15 (73%) patients, and was most commonly noted in the postero-inferior wall (53%), followed by the free wall (33%), the outflow tract (27%), and the apex (13%).

Finally, evidence of left ventricular involvement was present in 5/15 (33%) patients and consisted of fat infiltration in 2, and of myocardial areas with delayed enhancement in 3 patients.

Invasive study results

The main results of the invasive evaluation are summarized in Table 2. The mean number of sites sampled in RV EAM was 225 ± 36. Overall, LVA were present in 15 (88%) patients, and were most commonly localized in the outflow tract (59%), and in the postero-inferior wall (53%), followed by the free wall (18%). In particular, LVA were focal in 8 patients (4 in the outflow tract, and 4 in the postero-inferior wall), while the remaining patients presented a more diffuse involvement of the RV. Overall, the mean RV area presenting low-voltages was 42.2 ± 31 cm², corresponding to an average 28.6 ± 18.4 % of the total RV area.

Correlation of results

Electrocardiogram and SAECG
Patients with surface ECG abnormalities showed a higher degree of RV involvement as compared to patients with a normal ECG (1.8 ± 0.5 vs. 0.9 ± 0.6 number of LVA, respectively, P < 0.01). The positive and negative predictive values of ECG abnormalities in identifying LVA were of 100% and 22%, respectively. With regard to ventricular arrhythmias, 90% of patients with LVA in the outflow tract had ventricular arrhythmias arising from the RV outflow tract, although such association was not statistically significant (P = 0.25).

The presence of late potentials at SAECG was significantly associated with a LVA only in the outflow tract, and not in other RV areas (Figure 1, Panel A). Moreover, a significant inverse correlation was found between all SAECG parameters and mean bipolar electrogram voltage amplitude in the outflow tract, with the most significant association being observed for the fQRSd (r = -0.75, P < 0.01) and for the RMS-40 (r = 0.76, P < 0.01), but not between SAECG parameters and mean electrogram voltages in other RV areas (Figure 1, Panel B). Of the three SAECG parameters, fQRSd showed the greater association with the presence of a LVA in the outflow tract. Indeed, a value of fQRSd ≥ 114 ms predicted the presence of a LVA in the outflow tract with high positive and negative predictive values (100% and 88%, respectively), and was also the best value found at the receiver-operating characteristics (ROC) curve with an excellent level of agreement with EAM (Kappa = 0.88).

The presence of late potentials (i.e., ≥2 positive SAECG parameters) had also high positive and negative predictive values for the diagnosis of LVA in the outflow tract (82% and 83%, respectively), with a good level of agreement with EAM (Kappa = 0.63).

Cardiac Magnetic Resonance

Right ventricular function assessed at CMR was inversely associated with the extent of RV involvement at EAM (Figure 2, Panel A).
Among CMR qualitative findings (Figure 2, Panel B), regional RV dysfunction correlated with the distribution of LVA, with the most significant association being found with the free wall (Kappa = 0.65, P = 0.01). Right ventricular areas showing delayed gadolinium enhancement were the CMR findings more strongly associated with the distribution of LVA (Kappa = 0.75, P < 0.01 in the outflow tract; Kappa = 0.72, P = 0.02 in the postero-inferior wall; and Kappa = 0.75, P < 0.01 in the free wall). Accordingly, a higher degree of RV involvement by delayed gadolinium enhancement was significantly correlated with the extension of LVA at EAM (r = 0.85, P < 0.01) (Figure 2, Panel C). Of note, RV fat infiltration at CMR did not show any association with LVA.

**DISCUSSION**

The noninvasive diagnosis of ARVC represents a major clinical challenge for cardiologists, particularly when dealing with early stages of the disease that can unpredictably cause life-threatening ventricular arrhythmias even in the absence of overt RV abnormalities. In the last years the improvement of imaging techniques (mainly CMR) and genetic analysis has modified the knowledge of the disease and the diagnostic approach. Accordingly, a modification of current diagnostic criteria, taking into account new knowledge, has been recently proposed to improve the diagnostic sensitivity,\(^{22}\) in particular of early forms.

Electrocardiographic and SAECG findings are among the most common clinical abnormalities recognized in patients suspected of ARVC. However, the pathophysiological significance of different ECG findings is still unclear and their diagnostic contribution is still considered limited.

In the present study we demonstrate for the first time that the presence of SAECG abnormalities are strongly associated with the presence of LVA in the right ventricular outflow tract, thus representing a noninvasive marker of electrical and structural abnormalities of this ventricular segment.

Previous studies on SAECG in ARVC patients mainly focused on widespread forms of the disease more often associated with the presence of late potentials.\(^{23-25}\) Nava et al. reported that in a large
population of 138 ARVC patients, the presence of late potentials mainly correlated with the extent of RV involvement, as assessed by echocardiography or angiography, with a prevalence of late potentials ranging from 30% in patients with mild forms to more than 80% in those with extensive forms of the disease. In that study, the positive predictive value of late potentials in the diagnosis of ARVC was >90%.\textsuperscript{25} Although the high positive predictive value of late potentials has been confirmed in several other studies,\textsuperscript{23, 24, 26, 27} given the variable prevalence and the low sensitivity in the diagnosis of early forms of ARVC involving only selective RV areas of the so-called “triangle of dysplasia”, SAECG is currently included among the minor diagnostic criteria for ARVC.\textsuperscript{2}

Our findings may suggest that the variable prevalence of late potentials in ARVC may be related to the presence of RV outflow tract involvement. Accordingly, the RV outflow tract could be spared in the small proportion of patients with widespread forms of ARVC but no evidence of late potentials, whereas a small percentage of patients with early forms of the disease may present a LVA selectively in the RV outflow tract, and therefore abnormal SAECG parameters in the absence of overt RV abnormalities at imaging studies. Of note, in our population, 2 of patients with late potentials presented mild or no RV abnormalities at both echocardiography and CMR, while 4 patients presented a single LVA localized in the outflow tract.

With regard to surface ECG criteria, an abnormal ECG significantly predicted higher degree of RV involvement, with a very high positive predictive value (100% in our series). On the other hand, the negative predictive value of an abnormal ECG in identifying a LVA at EAM was very low (22%), with the most important clinical implication being that a normal ECG cannot exclude the presence of RV involvement.

With regard to CMR, the sensitivity and specificity of different CMR findings for the diagnosis of ARVC is debated, since they have never been systematically compared with another diagnostic reference test. Our study demonstrates that both qualitative and quantitative CMR diagnostic criteria for ARVC are correlated with RV involvement at EAM, although different criteria showed different strengths of association with LVA. Among CMR qualitative findings, both regional RV
dysfunction and RV delayed enhancement were strongly associated with the distribution of LVA, with the most striking association being found for delayed enhancement. Our study confirms the important diagnostic role of RV regional dysfunction in ARVC, already included among major diagnostic criteria, and highlights the diagnostic relevance of myocardial delayed enhancement. Although not included among the currently adopted diagnostic criteria, myocardial delayed enhancement at CMR is being increasingly recognized as an important feature of ARVC. Tandri et al. showed that RV delayed enhancement significantly increases the specificity for ARVC diagnosis, and correlates with the histological findings of fibrosis at endomyocardial biopsies conventionally drawn from the interventricular septum. Our findings confirm and expand the pivotal diagnostic role of myocardial delayed enhancement in ARVC, demonstrating a strong correlation with the distribution of LVA. On the other hand, only 8/13 patients with LVA at EAM actually presented delayed gadolinium enhancement at CMR, which supports the concept that EAM performs better than CMR in detecting RV areas of fibro-fatty replacement. Finally, intramyocardial fatty infiltration showed the lower degree of association with LVA at EAM. The role of intramyocardial fat for ARVC diagnosis has been recently questioned by several studies. Intramyocardial fat is the most difficult to assess and the least reproducible CMR finding. The normal presence of epicardial and pericardial fat may significantly hamper the detection of intramyocardial fat. Moreover, intramyocardial fat can be found in several different pathologic conditions, and also in normal hearts, thus affecting its specificity for ARVC diagnosis.

The results of our study raise further concerns on the diagnostic role of intramyocardial fat, questioning the appropriateness of including it among ARVC diagnostic criteria.

Limitations of the study

The study population consisted of a small sample of patients with at least one major noninvasive diagnostic criterion for ARVC, therefore with clinically apparent disease (Tables 1 and 2). Whether
our findings could be extended also to a population of ARVC patients with only minor noninvasive abnormalities warrants further investigation in appropriately designed studies.

**Clinical Implications and Conclusions**

Our findings expand the current knowledge and offer a new perspective on noninvasive diagnostic criteria for ARVC. In particular, the strong correlation between SAECG abnormalities and LVA in the RV outflow tract may have important clinical implication, mostly in sporadic forms of ARVC and in younger patients with ventricular arrhythmias and mild or absent RV abnormalities.

Accordingly, our population included 5 patients with an age <40 years and 3 competitive athletes. On the basis of the observed high positive predictive value, the detection of abnormal SAECG parameters during the noninvasive workup may suggest the presence of a structural heart disease and represent the hint to perform further investigations with a focus specifically on the RV outflow tract. In addition, our results show that a normal ECG cannot exclude the presence of pathological myocardial areas in the RV. Of note, more than 40% of our overall population presented a completely normal ECG despite the presence of LVA. With regard to CMR results, our data show that the finding most strongly associated with the distribution of LVA was RV delayed enhancement.

In conclusion, an accurate revision of ARVC diagnostic criteria should reconsider the potential role of late potentials and include delayed enhancement analysis in the noninvasive evaluation of these patients.

**Conflict of Interest Disclosures:** Dr. Andrea Natale has received compensation for belonging to the speakers’ bureau for St. Jude Medical, Boston Scientific, Medtronic, and Biosense Webster and has received a research grant from St. Jude Medical. The other authors declare no conflicts of interest.
REFERENCES


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Table 1. Clinical characteristics of study patients.

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<tbody>
<tr>
<td>Age, years</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>9 (53)</td>
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<tr>
<td>Family history*, n (%)</td>
<td>4 (24)</td>
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<tr>
<td>Clinical symptoms, n (%)</td>
<td></td>
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<tr>
<td>Cardiac arrest</td>
<td>0 (0)</td>
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<tr>
<td>Syncope</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>9 (53)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Interval between onset of symptoms and enrolment (months)</td>
<td>12 ± 11</td>
</tr>
</tbody>
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Values expressed as mean ± SD, or n (%). * family history of ARVC and of premature sudden death due to proven or suspected ARVC.
Table 2. Instrumental findings of study patients.

<table>
<thead>
<tr>
<th>ECG abnormalities, n (%)</th>
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<tr>
<td>Epsilon wave</td>
<td>2 (12)</td>
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<tr>
<td>Right precordial QRS duration ≥110 ms</td>
<td>7 (41)</td>
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<tr>
<td>Inverted T waves beyond lead V1</td>
<td>4 (24)</td>
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<tr>
<th>Ventricular arrhythmias*, n (%)</th>
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<tr>
<td>Sustained VT</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Frequent VPBs</td>
<td>10 (59)</td>
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<tr>
<th>MR structural/functional abnormalities, n (%)</th>
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<tr>
<td>RV intramyocardial fat</td>
<td>9/15 (60)</td>
</tr>
<tr>
<td>RV delayed enhancement</td>
<td>8/15 (53)</td>
</tr>
<tr>
<td>RV dilatation</td>
<td>6/15 (40)</td>
</tr>
<tr>
<td>RV global dysfunction</td>
<td>4/15 (27)</td>
</tr>
<tr>
<td>RV ejection fraction, % (range)</td>
<td>51.9 ± 4.6 (45-60)</td>
</tr>
<tr>
<td>RV end-diastolic volume, mL (range)</td>
<td>163 ± 29 (110-214)</td>
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<tr>
<td>RV end-diastolic volume/BSA, mL/m² (range)</td>
<td>92 ± 19 (61-127)</td>
</tr>
<tr>
<td>RVOT enlargement</td>
<td>4/15 (27)</td>
</tr>
<tr>
<td>LV ejection fraction, % (range)</td>
<td>60.7 ± 6.1 (53-70)</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL (range)</td>
<td>153 ± 17 (120-183)</td>
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<tr>
<td>LV involvement</td>
<td>5/15 (33)</td>
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| Late potentials at SAECG                     | 11 (65) |

<table>
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<th>Programmed ventricular stimulation, n (%)</th>
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<tr>
<td>Inducibility of VT/VF</td>
<td>7 (44)</td>
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<tr>
<td>Inducible VT</td>
<td>6 (35)</td>
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<tr>
<td>Inducible VF</td>
<td>1 (6)</td>
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</table>

| Low-voltage areas, n (%)                     | 15 (88) |

Values expressed as n (%), or mean ± SD. ECG = electrocardiogram; VPBs = ventricular premature beats; VT = ventricular tachycardia; VF = ventricular fibrillation; RV = right ventricle; RVOT = right ventricular outflow tract; ARVC = arrhythmogenic right ventricular cardiomyopathy; BSA = body surface area; LV = left ventricle. * all ventricular arrhythmias had left bundle branch block morphology.
Figure Legends:

**Figure 1** - *Panel A*: association between presence of late potentials at signal-averaged electrocardiogram (SAECG) and the location of low-voltage areas (LVA) at electroanatomic mapping. *Panel B*: correlation between mean bipolar voltage values in the right ventricular outflow tract and the fQRSd (*left panel*), and the RMS-40 (*right panel*) of the SAECG.

**Figure 2** - *Panel A*: values of right ventricular (RV) ejection fraction in patients with and without low-voltage areas at electroanatomic mapping, P value from 1-way analysis of variance. *Panel B*: association between the distribution of different CMR qualitative findings and low-voltage areas at electroanatomic mapping. A Kappa value of $\geq 0.61$ indicates a good level of agreement. *Panel C*: correlation between percent of right ventricular (RV) area with low-voltages and number of RV areas with delayed gadolinium enhancement.
A

RV ejection fraction (%)

RV low-voltage areas (n)

P < 0.01

B

Agreement with LVA (Kappa)

Outflow Tract

Inferior/Posterior Wall

Free Wall

Regional Dysfunction

Delayed Enhancement

Intramyocardial Fat

C

% of RV area with low-voltages

RV areas with delayed enhancement (n)

r = 0.85

P < 0.01
Noninvasive Diagnosis of Electroanatomic Abnormalities in Arrhythmogenic Right Ventricular Cardiomyopathy
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