Noninvasive Diagnosis of Electroanatomic Abnormalities in Arrhythmogenic Right Ventricular Cardiomyopathy

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Background—The diagnostic reliability and pathophysiologic relevance of different noninvasive diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) are undefined. We tested the association between noninvasive diagnostic criteria for ARVC and the presence of low-voltage areas (LVAs) 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 LVAs detected at right ventricular (RV) EAM in 17 patients (9 men) aged 50±16 years with biopsy specimen-proven ARVC. LVAs were found in 15 (88%) patients. Patients with surface ECG abnormalities showed a higher degree of RV involvement than those without ECG abnormalities (number of LVAs, 1.8±0.5 versus 0.9±0.6, respectively; P<0.01). A significant association was found between SAECG abnormalities and LVAs in the RV outflow tract (P=0.03) but not between SAECG parameters and LVAs in other RV regions. Among CMR findings, RV delayed enhancement was more significantly associated with the distribution of LVAs (free wall, P<0.01; outflow tract, P<0.01; posteroinferior wall, P=0.02). Regional RV dysfunction also showed a good correlation with LVAs, with the most significant association being found with the free wall (P=0.01), whereas RV fat infiltration at CMR was not correlated with LVAs.

Conclusion—In patients with ARVC, SAECG abnormalities correlate with the presence of LVAs 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 LVAs, thus supporting the appropriateness of its inclusion among diagnostic criteria for ARVC. (Circ Arrhythm Electrophysiol. 2010;3:632-638.)

Key Words: arrhythmogenic right ventricular dysplasia diagnosis magnetic resonance electrocardiography mapping

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by diffuse or segmental loss of right ventricular (RV) myocytes with replacement by fibrofatty tissue and thinning of the ventricular wall.1 At present, the diagnosis is based on established criteria,2 taking into account clinical findings and the presence of family history, morphofunctional abnormalities of the RV, and typical ECG findings. However, diagnosis on the basis of such criteria may be difficult because of several problems with the specificity of ECG abnormalities3,4 and with the currently adopted methods to assess the RV structure and function.5 In particular, cardiac magnetic resonance (CMR), which is the gold standard to image the RV, is flawed by significant limitations and a high degree of interobserver variability.5,6

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Thus far, the real diagnostic value and pathophysiological significance of each noninvasive diagnostic criterion are unclear, and no previous study has compared current criteria with a diagnostic reference test. In recent years, 3D electroanatomic voltage mapping (EAM) has been demonstrated as a reliable tool to accurately identify and locate low-voltage areas (LVAs) in the RV corresponding to areas of fibrofatty replacement,7–9 even in patients with very early forms of the disease that display completely normal ECG and CMR findings.7–10 thus increasing the accuracy for the diagnosis of ARVC. The present study tested the association between
noninvasive diagnostic criteria and the presence of LVAs detected at EAM in a consecutive series of patients with biopsy specimen-proven ARVC.

**Methods**

We studied 17 patients (9 men) aged 50±16 years who were admitted to our institution (Catholic University, Rome, Italy) from January to December 2008 with an EAM-guided endomyocardial biopsy specimen-proven diagnosis of ARVC. All patients underwent a complete noninvasive evaluation, including 12-lead ECG, 24-hour Holter monitoring, signal-averaged ECG (SAECG), 2D echocardiography, and contrast-enhanced CMR. The disease was considered familial in the presence of other individuals with autopsy specimen- or biopsy specimen-proven disease or premature (<40 years) sudden death at pedigree analysis.

**ECC and SAECG**

Twelve-lead ECGs were obtained in the standard lead positions and recorded at 25 mm/s. The presence of depolarization and repolarization ECC abnormalities was assessed according to task force criteria. In particular, depolarization ECC abnormalities included QRS prolongation (>110 ms) in right precordial leads (lead V1 to V3) and epsilon waves. Repolarization abnormalities consisted of inverted T waves beyond lead V1. ECGs were analyzed by 2 independent readers, each of whom was blinded to the results of EAM.

The SAECG was obtained with an Arrhythmia Research Technology-101 or -1200 System, with bidirectional Butterworth filtering (40 to 250 Hz), as previously described. 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 or more of the following criteria were fulfilled:

1. fQRSd >114 ms,
2. LAS-40 >38 ms, and
3. RMS-40 <20 μV.

**CMR**

CMR was performed with a 1.5-T Signa Excite 2 scanner (General Electric Medical Systems; Milwaukee, Wis) 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, 256×256; 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 (fast imaging employing steady-state acquisition sequence) (repetition time, 34 ms; echo time, 1.5 ms; flip angle, 50°; image matrix, 224×288; 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 minutes after intravenous administration of an MRI contrast agent (0.2 mmol/kg gadodiamide [Omniscan; Amersham Health; Princeton, NJ]).

Postprocessing was performed on an Advantage Windows Workstation using MASS software (Medis; Leiden, The Netherlands) to view images with standardized window width and level settings. The same software also was used for measurement of RV (end-diastolic and end-systolic diameter) and RV outflow tract diameter. An RV outflow tract was defined as enlarged if its short-axis diameter measured >30 mm. 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. An RV was defined as enlarged if it was equal to or larger than the left ventricular (LV) 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. The end-systolic image was defined visually as the one with the smallest ventricular cavity size. RV dilatation and dysfuction also were assessed quantitatively according to established reference values adjusted for age, sex, and body surface area.

For qualitative reporting, the RV was divided into 5 regions: outflow tract, posteroinferior wall (ie, including both the inferior and posterior segments), free wall, apex, and septal wall. For each region we assessed and scored the following: regional wall motion (1=normal to 4=dyskinetic), delayed enhancement (0=absent and 1=present), and intramyocardial fat fibration (0=absent and 1=present). LV involvement was considered present when 1 or more of the following criteria were satisfied: LV global dilatation, LV systolic dysfunction, LV wall motion abnormalities, LV intramyocardial fat, and LV delayed enhancement. All CMR images were analyzed by an expert radiologist who was blinded to the clinical and EAM information.

**Invasive Study**

The invasive study was approved by the institutional review board, and all patients gave written informed consent. All patients were admitted to coronary and LV and RV angiography (right and left anterior oblique views), RV 3D EAM, and EAM-guided endomyocardial biopsy.

RV 3D EAM was performed with the CARTO system (Biosense-Webster; Diamond Bar, Calif) as previously described. Briefly, mapping points were sampled with a 7-F 4-mm tip Navi-Star catheter (Biosense-Webster) to generate an accurate 3D 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 the CARTO system in terms of cycle length (<2%), local activation time (<3 ms), and beat-to-beat difference of the location of the catheter (<4 mm); (2) Both bipolar and unipolar signals were simultaneously acquired to confirm true catheter contact through the analysis of the local electrogram (in particular the shape of the unipolar electrogram); and (3) At least 3 additional points in the presence of an LVA were acquired in the same site to confirm the reproducibility of the voltage measurement.

An LVA was defined as ≤1 cm², including at least 3 adjacent points with a mean bipolar voltage value of ≤1.5 mV. CARTO-incorporated software was used to measure the extension of LVA, which was reported both as total RV area displaying low voltages and as percent of total RV area with low voltages.

RV endomyocardial biopsy specimens (4 to 5 samples from each patient) were obtained through the femoral vein with the use of a preformed long sheath and a disposable bioptome (Cordis; Johnson & Johnson; Miami Lakes, Fla), and withdrawn from RV wall segments with abnormal voltage, as previously shown. In case of normal EAM, endomyocardial biopsy specimens were withdrawn from conventional sites, including the apex and interventricular septum. The diagnosis of ARVC was made on the basis of extensive fibrofatty myocardial atrophy with a percentage of fat >25% and fibrous tissue >40% associated with amounts of residual myocytes <45% of the specimen at morphometric analysis.

For comparison with noninvasive diagnostic findings, the RV map of LVAs was divided into five areas: outflow tract, posteroinferior wall (ie, including both the inferior and the posterior segments), free wall, apex, and 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 ANOVA, and Fisher exact test were used to compare differences across groups. Bivariate
correlation 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 LVAs were evaluated by the Cohen κ test. A good level of agreement was defined as κ≥0.61. With regard to SAECG parameters, the best cutoff values for the fQRSd, RMS-40, and LAS-40 for the diagnosis of an LVA in the RV outflow tract were identified by analyzing receiver operating characteristic 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 version 11.1 (StataCorp, College Station, Tex) software.

Results

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

ECG Findings and SAECG Results
The ECG findings and SAECG results are presented in Table 2. Overall, surface ECG abnormalities were present in 8 (47%) patients. 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 (ie, >1,000 over 24 hours of Holter monitoring) were documented in 10 (59%) patients. The most common site of origin of ventricular arrhythmias, according to standard ECG criteria, was the outflow tract (76% of patients). Ventricular late potentials at SAECG were present in 11 (65%) patients.

CMR Results
The results of the CMR imaging study are summarized in Table 2. Two patients did not undergo CMR because of claustrophobia; thus CMR images were available for 15 patients. CMR detected structural and functional RV abnormalities in 14 (92%) patients. Intramyocardial fat infiltration of the RV was observed in 9 (60%). The most common location of fat infiltration was the free wall (47%) and the posteroinferior wall (40%) followed by the RV outflow tract (33%), apex (27%), and septal wall (7%). Delayed enhancement of the RV was reported in 13 (86%) patients and was most commonly localized in the free wall (73%) followed by the posteroinferior wall (54%) and septal wall (27%). The mean RV ejection fraction was 51.9±4.6%. A global RV dysfunction was present in 4 (27%) patients, and 6 (40%) had RV dilatation. Regional RV dysfunction was present in 11 (73%) patients and was most commonly noted in the posteroinferior wall (55%) followed by the free wall (35%) and apex (13%). Finally, evidence of LV involvement was present in 5 (33%) patients and consisted of fat infiltration in 2 and myocardial areas with delayed enhancement in 3.
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. Overall, LVAs were present in 15 (88%) patients and were most commonly localized in the outflow tract (59%) and posteroinferior wall (53%) followed by the free wall (18%). In particular, LVAs were focal in 8 patients (4 in the outflow tract, 4 in the posteroinferior wall), whereas the remaining patients presented a more-diffuse involvement of the RV. Overall, the mean RV area presenting low voltages was 42.2 cm², corresponding to an average 28.6% of the total RV area.

Correlation of Results

**ECG and SAECG**
Patients with surface ECG abnormalities showed a higher degree of RV involvement than patients with a normal ECG (number of LVAs, 1.8±0.5 versus 0.9±0.6, respectively; \(P<0.01\)). The positive and negative predictive values of ECG abnormalities in identifying LVAs were of 100% and 22%, respectively. With regard to ventricular arrhythmias, 90% of patients with LVAs 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 an LVA only in the outflow tract and not in other RV areas (Figure 1A). 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 iQRSd (\(r=-0.75\); \(P<0.01\)) and RMS-40 (\(r=0.76\); \(P<0.01\)), but not between SAECG parameters and mean electrogram voltages in other RV areas (Figure 1B). Of the 3 SAECG parameters, iQRSd showed the greatest association with the presence of an LVA in the outflow tract. Indeed, a value of iQRSd ≥114 ms predicted the presence of an LVA in the outflow tract with high positive and negative predictive values (100% and 88%, respectively) and was the best value found on the receiver operating characteristic curve, with an excellent level of agreement with EAM (\(k=0.88\)). The presence of late potentials (ie, ≥2 positive SAECG parameters) also had 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 (\(k=0.63\)).

**CMR**
RV function assessed at CMR was inversely associated with the extent of RV involvement at EAM (Figure 2A). Among CMR qualitative findings (Figure 2B), regional RV dysfunction correlated with the distribution of LVAs, with the most significant association being found with the free wall (\(k=0.65\); \(P=0.01\)). RV areas showing delayed gadolinium enhancement were the CMR findings more strongly associated with the distribution of LVAs (outflow tract, \(k=0.75\); \(P<0.01\); posteroinferior wall, \(k=0.72\); \(P=0.02\); free wall, \(k=0.75\); \(P<0.01\)). Accordingly, a higher degree of RV involvement by delayed gadolinium enhancement was significantly correlated with the extension of LVAs at EAM (\(r=0.85\); \(P<0.01\)) (Figure 2C). 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. 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, recently has been proposed to improve diagnostic sensitivity, particularly in early forms of ARVC.
ECG and SAECG findings are among the most common clinical abnormalities recognized in patients with suspected 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 LVAs in the RV outflow tract, thus representing a noninvasive marker of electric and structural abnormalities of this ventricular segment.

Previous studies of SAECG in patients with ARVC mainly focused on widespread forms of the disease more often associated with the presence of late potentials. Nava et al reported that in a large population of 138 patients with ARVC, 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 80% in those with extensive forms of the disease. In their study, the positive predictive value of late potentials in the diagnosis of ARVC was 90%. Although the high positive predictive value of late potentials has been confirmed in several other studies, 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 currently is included among the minor diagnostic criteria for ARVC.

Our findings 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 an 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 the present study population, 2 patients with late potentials presented mild or no RV abnormalities at both echocardiography and CMR, whereas 4 presented a single LVA localized in the outflow tract.

With regard to surface ECG criteria, an abnormal ECG significantly predicted a 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 an 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 because they have never been compared systematically 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 LVAs. Among CMR qualitative findings, both regional RV dysfunction and RV delayed enhancement were strongly associated with the distribution of LVAs, with the most striking association being found for delayed enhancement. Our study confirms the important diagnostic role of RV regional dysfunction in ARVC, which is 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 increasingly is being 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 in endomyocardial biopsy specimens 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 LVAs. On the other hand, only 8 of 13 patients with LVAs at EAM actually presented delayed gadolinium enhancement at CMR, which supports the concept that EAM performs better than CMR in detecting RV areas of fibrofatty replacement.

Finally, intramyocardial fatty infiltration showed the lower degree of association with LVAs at EAM. Several studies recently have questioned the role of intramyocardial fat for ARVC diagnosis. 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 pathological conditions and in normal hearts, thus affecting its specificity for ARVC diagnosis. The results of the present study raise further concerns about the diagnostic role of intramyocardial fat, questioning the appropriateness of including it among ARVC diagnostic criteria.

**Clinical Implications**

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 LVAs in the RV outflow tract may have important clinical implications, 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 aged <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 hint at the need 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, >40% of our overall population presented a completely normal ECG despite the presence of LVAs. With regard to CMR results, our data show that the finding most strongly associated with the distribution of LVAs was RV delayed enhancement.

**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 patients with ARVC.

**Disclosures**

Dr 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.

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American arrhythogenic right ventricular dysplasia (ARVD/C) study.


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_Circ Arrhythm Electrophysiol_. 2010;3:632-638; originally published online October 11, 2010; doi: 10.1161/CIRCEP.110.958116

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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