Prognostic Value of Endocardial Voltage Mapping in Patients with

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Running title: Migliore et al.; Prognostic value of voltage mapping in ARVC/D

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Abstract:

**Background** - Endocardial voltage mapping (EVM) identifies low-voltage right ventricular (RV) areas, which may represent the electroanatomic scar substrate of life-threatening tachyarrhythmias. We prospectively assessed the prognostic value of EVM in a consecutive series of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

**Methods and Results** - We studied 69 consecutive ARVC/D patients [47 males; median age 35 years (28-45)] who underwent electrophysiological study and both bipolar and unipolar EVM. The extent of confluent bipolar (<1.5mV) and unipolar (<6.0mV) low-voltage electrograms was estimated using the CARTO-incorporated area calculation software. Fifty-three patients (77%) showed ≥1 RV electroanatomic scars with an estimated burden of bipolar vs unipolar low-voltage areas of 24.8% (7.2-31.5) and 64.8% (39.8-95.3), respectively (P=0.009). In the remaining patients with normal bipolar-EVM (n=16; 23%), the use of unipolar EVM unmasked ≥1 region of low-voltage electrogram affecting 26.2% (11.6-38.2) of RV wall. During a median follow-up of 41 (28-56) months, 19 (27.5%) patients experienced arrhythmic events, such as sudden death (n=1), appropriate ICD interventions (n=7), or sustained ventricular tachycardia (n=11). Univariate predictors of arrhythmic outcome included previous cardiac arrest or syncope (HR=3.4; 95%CI:1.4-8.8; P=0.03) and extent of bipolar low-voltage areas (HR=1.7 per 5%; 95%CI=1.5-2; P<0.001), while the only independent predictor was the bipolar low-voltage electrogram burden (HR=1.6 per 5%; 95% CI:1.2-1.9; P<0.001). Patients with normal bipolar-EVM had an uneventful clinical course.

**Conclusions** - The extent of bipolar RV endocardial low-voltage area was a powerful predictor of arrhythmic outcome in ARVC/D, independently of history and RV dilatation/dysfunction. A normal bipolar-EVM characterized a low-risk subgroup of ARVC/D patients.

**Key words:** arrhythmogenic right ventricular cardiomyopathy/dysplasia; electrophysiology; electroanatomic voltage mapping; risk stratification; ventricular arrhythmias
Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited heart muscle disease whose natural history is essentially related to ventricular electrical instability which may lead to arrhythmic sudden cardiac death (SCD), mostly in young people and athletes. Risk stratification of affected patients is mandatory for implementing therapeutic strategies aimed to prevent SCD. Current treatment strategies suggest the implantation of an implantable cardioverter defibrillator (ICD) in symptomatic ARVC/D patients with prior cardiac arrest due to ventricular fibrillation (VF), history of syncopal episodes, and sustained ventricular tachycardia (VT); in contrast, the role of prophylactic ICD therapy in asymptomatic patients or relatives presenting traditional risk factors such as family history of SCD, severe right ventricular (RV) dysfunction, and inducibility at programmed ventricular stimulation (PVS) remains controversial.

Advances in our understanding of pathobiologic processes leading to RV lesion and the related electrical instability may provide novel predictors of arrhythmic outcome. Pathologic and molecular genetic studies showed that the hallmark lesion of ARVC/D is the fibro-fatty scar, which is characterized by genetically-determined myocardial loss and fibrofatty replacement and may provide a substrate for life-threatening re-entrant ventricular tachyarrhythmias. The assessment of mechanical consequences of myocardial fibrofatty scar has been traditionally based on imaging techniques such as echocardiography and angiography. Among the techniques now available for direct imaging of ventricular myocardial lesion, endocardial voltage mapping (EVM) is an emerging tool which has the ability to accurately identify and quantify RV regions with low-amplitude electrical signals, i.e. electroanatomic scar areas, which reflect myocardial replaced tissue. Although the technique has been demonstrated to enhance the
accuracy for diagnosing ARVC/D, its value for arrhythmic risk stratification remains to be established. Hence this study was designed to prospectively evaluate the prognostic value of RV-EVM in a cohort of ARVC/D patients during a long-term follow-up.

**Methods**

**Study population**

The study population included 69 consecutive patients [47 males; median age 35 years (28–45)] with ARVC/D who were referred at the Division of Cardiology of the University of Padova, Italy for risk stratification.

All patients underwent detailed cardiac evaluation including family history, physical examination, 12-lead-electrocardiogram (ECG) recording, signal-averaged ECG; 24-hour Holter monitoring, exercise stress testing, echocardiography and cardiac catheterization including RV and left ventricular (LV) cineangiography in the right and left anterior oblique view and coronary angiography. Technical equipment, protocols, and reference values of each investigation have been reported in details elsewhere\(^{20,21,24}\).

All patients met the International Task Force (ITF) criteria (two major criteria or one major criterion plus two major criteria or 4 minor criteria) for diagnosis of definite ARVC/D. Diagnosis was established according to the original ITF criteria\(^{25}\) and confirmed using the recently revised criteria\(^{26}\).

All patients underwent intracardiac electrophysiologic study with programmed ventricular stimulation (PVS) for assessing VT/VF inducibility and high density EVM for imaging and quantification of abnormal RV-EVM.

The study was approved by the institutional review board, and all patients gave their informed consent.
Electrophysiological study

All antiarrhythmic drugs were discontinued 5 half-lives (6 weeks for amiodarone) before the electrophysiological study. Programmed ventricular stimulation protocol included 3 drive cycle lengths (600, 500, and 400 ms) and 3 ventricular extrastimuli while pacing from 2 RV sites (apex and outflow tract). Programmed ventricular stimulation was considered positive if either a VF or sustained ventricular tachycardia (VT), i.e., one that lasted ≥30 seconds or required termination because of hemodynamic compromise, was induced. Programmed ventricular stimulation was repeated after intravenous isoproterenol infusion in those patients with effort induced non sustained VT (16 of 53, 26%).

Electroanatomic voltage mapping

At the time of electrophysiologic study, all patients underwent detailed EVM by the CARTO system (Biosense-Webster) during sinus rhythm, as previously reported. A 7-F Navi-Star (Biosense-Webster) catheter, with a 4-mm distal tip electrode and a 2-mm ring electrode with an interelectrode distance of 1 mm, was introduced into the RV under fluoroscopic guidance and used as the mapping/ablation catheter. The catheter was placed at multiple sites on the endocardial surface of RV free wall [infero-basal, antero-lateral free wall, apex, and RV outflow tract (RVOT)] and septum to reconstructed the 3D-geometry of the RV chamber. Bipolar electrogram signals (filtered at 10 to 400 Hz and displayed at 100 mm/s speeds on the CARTO system) and unipolar signals (filtered at 1 to 240 Hz and displayed at 100 mm/s speeds on the CARTO system) were recorded and analyzed simultaneously with regard to amplitude, duration, relation to the surface QRS, and presence of multiple components.

Duration of an endocardial bipolar electrogram was measured as the time from the earliest electrical activity to the artefact produced by the decay of the amplified filtered signal.
Bipolar signals were recorded between the distal electrode pair, unipolar signals between the distal tip of the ablation catheter (cathode) and the Wilson central terminal.

In our study the following tools were used to avoid false low-voltage recordings: 1) adequate catheter contact was confirmed by concordant catheter tip motion with the cardiac silhouettes on fluoroscopy; 2) a recording was accepted and integrated into the map when the variability in cycle length, local activation time stability, and maximum beat-to-beat difference of the location of the catheter (automatically detected by the CARTO system) were <2%, <3 ms, and <4 mm, respectively (these parameters, combined with the stability of the impedance reading, were used to exclude low amplitude signals due to poor endocardial catheter contact); 3) in the presence of a low voltage area, at least 3 additional points were acquired in the same area to confirm the reproducibility of the voltage measurement\textsuperscript{20}. Particular attention was paid to validate the acquisition of endocardial points from the RV inferobasal region, because of the recognized risk of poor tissue contact in this area. Because of the potential high mapping error and to avoid overestimation of low-voltage RV areas due to inclusion of normal annular fibrous tissue, the immediate perivalvular areas (i.e. within 1.5 cm of the valvular locations on post-processing measurement) were excluded in the analysis of endocardial low voltages.

Values of normal RV endocardial voltages were established by RV-EVM in 6 reference patients without structural heart disease, who underwent electrophysiological study for evaluation of supraventricular tachycardia. RV septal endocardial sites (23±5) were excluded and only RV free-wall electrogram recordings (207±16 points sampled), either bipolar or unipolar, were analyzed. Normal bipolar electrograms were sharp with ≤3 rapid deflections; the mean electrogram duration was 34.8±1.2 ms and the mean amplitude 5.3±0.9 mV, with 95% of all electrogram signals <66 ms and >1.47 mV.
In addition, we analyzed the amplitude of unipolar electrograms which was 10.3±0.6 mV with 95% of all unipolar signals recorded having an amplitude >5.96 mV.

Then in the present study the reference values used to define normal RV electrogram amplitude was set at 1.5 mV for bipolar signals and 6.0 mV for unipolar signals, which were the values above which 95% of all bipolar and unipolar electrogram voltages from the endocardium of normal RVs were included.

We considered normal bipolar electrocardiograms those with sharp and ≤3 spikes, amplitude >1.5 mV and duration ≤70 ms. We defined as fragmented electrograms those characterized by multiple deflections (>3) amplitude ≤1.5 mV and duration >70 ms.

Normal amplitude electrograms (bipolar >1.5 mV and unipolar >6.0 mV) were represented in the electroanatomic CARTO map by the color purple, whereas low-amplitude signals were represented by non-purple range of colors. Color red indicated “dense scar” which was arbitrarily defined as bipolar signal amplitude <0.5 mV and unipolar signal amplitude <3.5 mV, according to previously reported criteria20-24. An EVM was considered abnormal in the presence of a single or multiple RV low voltage areas ≥1 cm² including at least 3 adjacent points with a bipolar signal amplitude <1.5 mV and an unipolar signal amplitude <6.0 mV.

Complete endocardial maps were obtained in all patients to ensure reconstruction of a 3-dimensional geometry of the RV chamber and to identify areas of abnormal electrograms in the RV free wall. The septum was excluded from the analysis (Supplemental online Figure 1). Regions showing low-amplitude signals were mapped with greater point density to delineate the extent and borders of endocardium electroanatomic scar areas.

The extent of low-voltage areas was estimated by using a CARTO-incorporated area calculation software (CARTO, Biosense Webster Inc, Diamond Bar, CA) and was expressed
both as total RV area and percentage of RV area, excluding tricuspid and pulmonary valvular annuli.

**Follow-up**

The follow-up data were obtained prospectively during regular outpatient visits at 6 to 12-months intervals. Routine ICD interrogation and ECG recordings at the time of symptoms were used to document the occurrence of spontaneous VT during follow-up. The study outcome was the index combined end point of major arrhythmic events such as sudden death (SD), cardiac arrest due to VF, sustained VT or appropriate ICD intervention. Sudden death was defined as any natural death occurring instantaneously or within one hour from symptoms onset.

Sustained VT was defined as tachycardia originating in the ventricle with rate >100 beats/minute and lasting >30 seconds or requiring an intervention for termination. Appropriate ICD intervention was defined as a device shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia and documented by stored intracardiac ECG data. Ventricular fibrillation and VT were defined as a ventricular tachyarrhythmia with a cycle length ≤ 240 ms or > 240 ms respectively. Implantable cardioverter defibrillator were routinely programmed to include a monitoring zone that identified VT with a rate >160 bpm.

**Statistical analysis**

Results are summarized as mean ± standard deviation (SD) or median with 25%-75%-iles for normally distributed and skewed variables, respectively. Normal distribution was assessed using Shapiro-Wilk test. Categorical differences between groups were evaluated by the $\chi^2$ test of the Fisher exact test as appropriate. Paired and unpaired t-tests were used to compare normally distributed continuous variables respectively obtained from the same patient and different patients; paired and unpaired Rank Sum test were used for skewed continuous variables.
Kaplan-Meier analysis was used to estimate the survival distributions of the index combined end point and to show the difference in survival between patients with normal vs abnormal bipolar-EVM and positive vs negative PVS. Start of follow-up was defined as the date of the initial EVM. Patients were censored at the time of their first event or the time of their last clinical follow-up. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up.

The independent correlation of traditional clinical predictors of arrhythmic risk in ARVC/D with the index combined end-point during follow up was determined by means of univariate and multivariable Cox regression analysis. Variables with a P value <0.15) were integrated into multivariable analysis using Cox proportional-hazard models to estimate the Hazard ratio (HR) and to identify independent predictors of major arrhythmic events. The Cox model was used to calculate the relation between amount of RV low-voltage areas and hazard ratios. Hazard ratios (HR) and confidence intervals (CI) are presented both in univariate and multivariable analysis.

The c-statistic method was used to estimate the best cut-off value of bipolar low-voltage area to discriminate between patients with and those without major arrhythmic events during follow-up. A value of P<0.05 was considered significant. Statistics were analyzed with SPSS version 17 (SPSS Inc, Chicago, Ill).

Results

Clinical characteristics

Baseline clinical characteristics and instrumental findings are summarized in Tables 1. The study population included 69 consecutive patients [47 men; median age 35 years (28-45)]. Twenty-eight patients (40%) had a family history of ARVC/D (N=12, 17%) or premature (<35 years)
sudden death (N=16, 23%). Twenty-two (32%) patients had a history of cardiac arrest or syncope. Ventricular tachycardias were documented in 53 (76%) patients and included sustained VT (N=9, 13%) or non-sustained VT (N=44, 63%). There were 15 morphologies of sustained VT, all with a left bundle branch pattern, with a superior axis in 8, inferior axis in 4, and undetermined axis in 3. Right ventricular dilatation/dysfunction were observed at echocardiography/angiography in all patients. Multiregional wall motion abnormalities (akinesia, diskinesia or bulging involving ≥2 RV regions) were found in 25 (36%) patients. Thirty-four (49%) patients were inducible at programmed ventricular stimulation to either sustained monomorphic VT (N=23) or VF (N=11). Among 8 noninducible patients, 2 experienced exercise induced arrhythmic events during follow-up.

At enrolment, 57 (82%) patients with VT or frequent premature ventricular beats were empirically treated with antiarrhythmic drug therapy which consisted of sotalol (N=22), amiodarone either alone (N=9) or in combination with beta blockers (N=14), beta blockers (N=7) and flecainide (N=5).

Electroanatomic voltage mapping

Endocardial voltage mapping was successfully acquired during sinus rhythm in all patients, with a mean number of sites sampled of 195±22.

Bipolar EVM

An abnormal bipolar RV-EVM was recorded in 53 (77%) patients. Patients with and without evidence of abnormal bipolar-EVM had similar baseline clinical characteristics, except for multiregional RV wall motion abnormalities which was significantly more prevalent in the abnormal bipolar-EVM group. In patients with an abnormal bipolar-EVM the median RV low-voltage area was 39.1 cm² (13.2-67.8) with a median percent RV area of 24.8 % (7.2-31.5)
(Figure 1). The involved RV regions were infero-basal in 49 (71%) patients, antero-lateral in 28 (40%), RVOT in 25 (36%) and apex in 15 (22%) (Supplemental online Figure 1).

Mean bipolar amplitude of local electrograms recorded from within RV electroanatomic scar areas was significantly lower than that sampled from unaffected RV areas (0.38±0.11 versus 5.2±0.6mV); P<0.001. Similarly, bipolar electrograms from low-voltage areas had a longer mean duration (78.9±18 versus 33.5±7.8ms; P<0.001) and more often extended beyond the offset of the surface QRS (64% vs 7%; P<0.001), compared with electrograms sampled from regions with preserved electrogram voltage (Figure 2). Fragmented bipolar electrograms (i.e. signals with > 3 deflections, amplitude ≤1.5mV and duration >70ms) were recorded in 47 of 53 (88%) patients with an abnormal bipolar-EVM.

In 16 patients (23%), EVM was normal, with preserved bipolar endocardial electrogram amplitude (4.8±1.3mV) and duration (35.3±0.8ms) (Figure 2).

**Unipolar EVM**

In the 53 patients (77%) with abnormal bipolar-EVM, unipolar-EVM recorded significantly more extensive RV electroanatomic scar involvement with a median RV low-voltage area of 68.5 cm² (22.9-98.7) and median percent RV area of 64.8 % (39.8-95.3) compared with low-voltages obtained by bipolar-EVM (P<0.009) (Figure 1).

In all 16 patients (23%) with normal bipolar-EVM, the use of unipolar-EVM technique unmasked ≥1 regions of low-voltage unipolar electrogram abnormality 37.3 cm² (12.1-48.9); 26.2 % (11.6-38.2) (Figure 1).

**Follow-up**

During a median follow-up of 41 (28-56) months, 19 patients (27.5%) reached the composite arrhythmic end point, with a 6.7% annual rate of major arrhythmic events. Eleven patients (16%)
had an episode of sustained VT, 7 (10%) experienced ≥1 appropriate ICD interventions, either against VF (N=4) or VT (N=3), and one (1.4%) died suddenly. Among the 4 patients who experienced VF, one underwent orthotopic heart transplantation because of intractable recurrent VF storms (Figure 3).

Table 2 shows the clinical characteristics of patients with or without major arrhythmic events during follow-up. Patients who experienced arrhythmic events significantly more often had a history of cardiac arrest or syncope (73% vs 16%; P=0.001), and abnormal bipolar-EVM (100% vs 68%; P=0.003).

Figure 4A shows Kaplan-Meier analysis of survival from the index combined end point of sustained VT, appropriate ICD intervention and SCD for the overall population, stratified by bipolar-EVM findings. Overall, the annual event rate was 11.4%/year in patients with an abnormal bipolar-EVM and 0%/year with a normal bipolar-EVM (logrank: P=0.02).

Electrophysiologic study

Overall, the annual event rate was 6.1%/year in patients who were inducible at PVS and 7.1%/year in those who were noninducible (logrank: P=0.46) (Figure 4B). Of 34 patients who were inducible at PVS, 23 (68%) did not experience major arrhythmic events during the follow-up (i.e. false positives), whereas 8 of 35 (23%) noninducible patients had malignant events (i.e. false negatives). The type of ventricular tachyarrhythmia which was inducible at the time of PVS (either VT or VF) did not predict either the presence of bipolar electroanatomic scar or the occurrence of arrhythmic events during follow-up. Patients with and without events during follow-up had a similar prevalence of RV fragmented bipolar electrograms (79% vs 64%).

Predictors of events

Univariate and multivariable analysis for predictors of adverse events during follow-up are listed
in Table 3. Univariate predictors of events were a previous history of cardiac arrest or syncope and extent of abnormal bipolar-EVM. The overall arrhythmic risk increased with percentage of abnormal bipolar-EVM (HR 1.7 per 5% abnormal EVM increase, 95% CI: 1.5-2.0; P<0.001) (Figure 5). At multivariable analysis the amount of abnormal bipolar-EVM was an independent predictor of events (HR 1.6 per 5% increase of abnormal-EVM percentage, 95% CI 1.2-1.9; P<0.001). The amount of abnormal bipolar-EVM was a predictor of events (HR 1.4 per 5% increase of abnormal bipolar-EVM percentage, 95% CI 1.1-1.9; P=0.004) even in the subgroup of 55 patients without previous sustained VT (n=9) and prior cardiac arrest (n=5). According to c-statistic, the best cut-off value for abnormal bipolar-EVM % area was 27.8% (c=0.74).

Discussion

The present study was designed to evaluate the value of the presence and extent of RV electroanatomic scar areas for predicting arrhythmic outcome in a consecutive series of ARVC/D patients. The major study findings were that: 1) abnormal bipolar-EVM was of independent prognostic significance, with the arrhythmic risk being proportional with the increased extent of RV low-voltage areas; 2) abnormal bipolar-EVM appeared to be superior in predicting major arrhythmic events over a long-term follow-up to classic clinical risk factors such as clinical history, arrhythmic background and ventricular dilatation/dysfunction; and 3) a normal bipolar RV-EVM characterized a low-risk subgroup of ARVC/D patients. These study results suggest that EVM should supplement the traditional intracardiac electrophysiologic studies for prognostic evaluation of ARVC/D patients.

Diagnostic utility of EVM

Endocardial voltage mapping has the ability to identify areas of scar tissue by recording and spatially associating low amplitude electrograms to generate a 3-D electroanatomic ventricular
The technique has been clinically validated in electrophysiological labs where it is increasingly used for substrate-based mapping and catheter ablation of scar-related VT, in either ischemic or non ischemic cardiomyopathies. In ARVC/D patients, RV bipolar low-voltage areas was demonstrated to correlate with the histopathologic finding of fibrofatty myocardial replacement at endomyocardial biopsy. Previous studies showed that EVM provides additional value for ARVC/D diagnosis. EVM has been recently reported to be significantly more sensitive than contrast-enhancement-cardiac magnetic resonance to identify RV scar lesion.

In the present study, an abnormal bipolar-EVM was demonstrated in the majority of ARVC/D patients, confirming data from previous studies. Regional distribution of bipolar low-voltage regions, with predominant involvement of the antero-lateral and infero-basal RV regions, resembled that observed in autopsy hearts of ARVC/D patients who died suddenly or underwent heart transplant, in whom the most severe atrophy and wall aneurysms were characteristically localized in the antero-infundibular wall and underneath the tricuspid valve.

**Prognostic value of abnormal EVM**

The available data based on autopsy series or observational clinical investigations suggest that predictors of SCD in ARVC/D patients include the young age at the time of diagnosis, previous cardiac arrest or syncope, VT, severe RV/left ventricular dysfunction and inducibility at PVS. Our previous retrospective analysis of clinical history of ARVC/D patients undergoing EVM, suggested that demonstration of bipolar low-voltage areas may be associated with a greater arrhythmic risk in ARVC/D patients. We previously found that during the time interval from onset of symptoms to the invasive study, 55% of patients with evidence of abnormal bipolar-EVM required an ICD because they experienced malignant ventricular
tachyarrhythmias, whereas all but one patient with preserved myocardial voltage values remained stable on antiarrhythmic therapy. The present study confirms and extends such previous observations by showing that an abnormal-EVM identifies patients at increased risk of major arrhythmic events during a prospective long-term follow-up. We found that the amount of abnormal bipolar-EVM was of independent prognostic significance, with the arrhythmic risk being proportional with the increased amount of abnormal bipolar-EVM. At univariate Cox regression analysis, an abnormal bipolar-EVM was a significant predictor for the composite arrhythmic end point, yielding an HR of 1.7 for every 5% increase in abnormal-EVM; the other variable that was found to predict adverse arrhythmic outcome included history of cardiac arrest or syncope (HR=3.4). However, the extent of abnormal-EVM appeared to be superior to classic clinical risk factors, because at multivariable analysis it remained the only independent predictor of malignant arrhythmic outcome in our patients population (HR=1.6 per 5%). It is noteworthy that according to the c-statistic method based on survival data, 27.8% abnormal bipolar low-voltage area was the best cut-off value to discriminate between patients with and without major arrhythmic adverse events during follow-up.

**Arrhythmogenic substrate**

Unlike traditional imaging techniques such as echocardiography and ventriculography which disclose RV mechanical dysfunction (either regional or global) caused by fibro-fatty myocardial replacement, EVM has the ability to accurately identify and quantify low-amplitude RV regions which represent the electrical consequences of RV scar lesions.

Ventricular tachyarrhythmias in ARVC/D are frequently the result of a scar-related macro-reentry circuit, similar to that observed in the post-myocardial infarction setting. Voltage mapping-guided catheter ablation of VT by linear radiofrequency lesions connecting or...
encircling electroanatomic scar areas has proven to successfully interrupt the arrhythmic reentry circuit in ARVC/D patients\textsuperscript{19-23}. In the majority of patients with an abnormal bipolar-EVM we recorded fragmented bipolar electrograms (i.e. > 3 deflections, amplitude ≤ 1.5 mV and duration > 70 ms) from within the electroanatomic RV low-voltage. As shown by previous studies on scar-related electrical activity in either ischemic or non ischemic heart disease, these electrographic abnormalities are the result of complex anisotropic propagation of the electrical wave-front through scar tissue which predisposes to the genesis of re-entrant ventricular tachyarrhythmias\textsuperscript{33,35}. Accordingly, we found that EVM provided prognostic value additional to traditional imaging techniques such as echocardiography and angiography, because demonstration of an electroanatomic scar area implies that the RV lesion acts as an arrhythmogenetically active myocardial substrate. This explains why the presence and amount of electroanatomic scar areas were stronger predictors of adverse arrhythmic outcome than traditional hemodynamic RV parameters such as RV dilatation/dysfunction.

**Prognostic value of normal EVM**

Failure to detect endocardial low-voltage areas in about one fourth of our patients fulfilling ITF criteria for ARVC/D remains to be explained. It is relevant that in our study unipolar-EVM unmasked the presence of large regions of confluent abnormal unipolar electrograms in patients with a normal bipolar-EVM as well as identified a greater amount of low-amplitude electrogram area in those with an abnormal bipolar-EVM. The most likely explanation for the discordant unipolar and bipolar-EVM is that fibro-fatty scar involvement of outer RV wall layers (i.e. epicardium and mid-myocardium) is detected better with unipolar mapping technique\textsuperscript{24,35}. Indeed, because the wave front of RV fibrofatty myocardial replacement in ARVC/D progresses from the epicardium to the endocardium, scar tissue in non-advanced ARVC/D may be confined to
epicardial/midmural layers, sparing (or reaching focally) the endocardial region\textsuperscript{1,11}. In our study, voltage mapping was limited to the endocardial side of the RV free wall and may have underestimated or missed non-transmural low-voltage areas. Previous studies showed that unipolar EVM recording may accurately predict the location and extent of epicardial electroanatomic scar involvement as evidenced by direct epicardial bipolar voltage mapping\textsuperscript{24,35}. Polin et al. validated the use of unipolar-EVM to identify confluent areas of signals with an amplitude <5.5mV as a strategy for approximating the degree and location of epicardial bipolar voltage abnormality in ARVC/D patients with only limited endocardial bipolar voltage changes\textsuperscript{24}. It has been suggested that unipolar-EVM provide a larger “antenna” than bipolar-EVM to detect fibro-fatty substrate involvement of epi- and mid-myocardium which is commonly present in ARVC/D patients.

It is noteworthy that in our ARVC/D study population major arrhythmic events occurred exclusively in the group of patients with RV electroanatomic scar involvement on bipolar-EVM (Figure 3). Specifically, ARVC/D patients with a preserved bipolar voltages through the RV had an uneventful arrhythmic outcome, regardless of the amount of low amplitude electrocardiogram areas evidenced by unipolar-EVM.

\textit{Voltage mapping-enhanced electrophysilogic study}

The results of this study confirm previous data showing that traditional electrophysiological study is of limited value for risk stratification of ARVC/D patients\textsuperscript{6,9}. We found that the positive predictive value of PVS for major arrhythmic events was only 32%. On the other hand, a negative PVS could not indicate better prognosis because approximately one fourth of noninducible patients experienced malignant events.

By contrast, Bhosale et. al\textsuperscript{10} reported that non-sustained VT and inducibility at PVS were
significant predictors of appropriate discharges in ARVC/D patients who received an ICD for primary prevention. The discrepancy between our study findings and those reported by Bhonsale may be related to differences in patient populations, which in the latter study also included subjects with a probable (non definite) ARVC/D diagnosis, and to different arrhythmic study end-points (i.e. composite arrhythmic end-point versus appropriate ICD intervention alone).

The addition of EVM to traditional intracardiac electrophysiologic study provides significant added value for arrhythmic risk assessment. Although recording of low-voltage, polyphasic, and abnormally wide scar-related electrograms do not necessarily require the use of electromagnetic mapping techniques, the ability of RV-EVM to generate a three-dimensional reconstruction of RV electroanatomic scar regions by spatially associating the abnormal local electrograms offers the potential not only to determine the presence but also to quantify the amount of RV myocardial tissue replaced by scar tissue, which was the most powerful predictor of adverse arrhythmic outcome in our study.

At variance with our results, Santangeli et al.36 found that fragmented electrograms were the only variable independently associated with arrhythmic events during follow-up in a series of 32 patients with ARVC/D undergoing bipolar-EVM, while the extent of electroanatomic scar was not predictive of outcome. The discrepancy between study results may be explained by a different abnormal bipolar signals definition and the different patient populations, with the Santangeli’s study including a highly selected group of ARVC/D patients, all showing an abnormal bipolar-EVM and receiving a prophylactic ICD because of inducible sustained monomorphic VT.

**Study Limitations**

Although the study cohort was relatively large for ARVC/D, a small number of patients and
outcomes were analyzed, linked predominantly to relatively low disease prevalence and low event rate. The small number of events limits both the power to detect associations and the ability to control completely for all potential confounders in the multivariable models. Nonetheless, we believe that our study results and statistical analysis indicate important trends that are of clinical relevance for arrhythmic risk stratification and management of ARVC/D patients. Further studies with larger number of patients and longer follow-up are needed to confirm the value of bipolar-EVM for predicting long-term clinical outcome of ARVC/D patients.

The different rate of ICD implantation (54% of patients with an abnormal bipolar-EVM versus 12% of those with normal bipolar-EVM) may represent a study bias with regard to arrhythmia detection. However, ICD were routinely programmed to include a monitoring zone that identified VT with a rate >160 bpm; this lessens the potential limitation of not homogeneous distribution of ICD, because slower, asymptomatic VTs remained equally undetected in both patient subgroups, regardless of ICD monitoring.

Conclusions

In conclusion, the results of the present study indicate that RV-EVM has an important prognostic value in ARVC/D patients and that the arrhythmic risk is related to regional extent of RV scar lesions. RV-EVM should supplement the traditional intracardiac electrophysiologic studies for characterization of the arrhythmic substrate and risk stratification of patients with ARVC/D.

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Conflict of Interest Disclosures: None.
References:


Table 1. Clinical characteristics of overall sample and according to results of bipolar-EVM.

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<th>Overall sample</th>
<th>Abnormal bipolar-EVM</th>
<th>Normal bipolar-EVM</th>
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<td></td>
<td>N = 69</td>
<td>N = 53 (77%)</td>
<td>N = 16 (23%)</td>
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<td>Age (yrs)</td>
<td>35 (28-45)</td>
<td>36 (28-46)</td>
<td>34 (28-44)</td>
<td>0.42</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>47 (68)</td>
<td>36 (68)</td>
<td>11 (69)</td>
<td>1.00</td>
</tr>
<tr>
<td>Family history of sudden death (&lt;35 years)</td>
<td>16 (23)</td>
<td>15 (28)</td>
<td>1 (6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Family history of ARVC/D</td>
<td>12 (17)</td>
<td>11 (20)</td>
<td>1 (6)</td>
<td>0.34</td>
</tr>
<tr>
<td>History of cardiac arrest or syncope</td>
<td>22 (32)</td>
<td>20 (37)</td>
<td>2 (12)</td>
<td>0.07</td>
</tr>
<tr>
<td>Right precordial T-wave inversion (V1-V3)</td>
<td>49 (71)</td>
<td>41 (77)</td>
<td>8 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td>Positive SAECG</td>
<td>34 (49)</td>
<td>29 (54)</td>
<td>5 (31)</td>
<td>0.13</td>
</tr>
<tr>
<td>Premature Ventricular Beats &gt; 1000/24 hours</td>
<td>59 (85)</td>
<td>45 (85)</td>
<td>15 (94)</td>
<td>0.72</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>44 (63)</td>
<td>33 (62)</td>
<td>11 (69)</td>
<td>0.81</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>9 (13)</td>
<td>8 (15)</td>
<td>1 (6)</td>
<td>0.72</td>
</tr>
<tr>
<td>RVEDV (ml/m2)</td>
<td>80 (53-97)</td>
<td>82 (65-99)</td>
<td>77 (58-90)</td>
<td>0.09</td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>40 (38-41)</td>
<td>40 (28-30)</td>
<td>40 (28-31)</td>
<td>0.82</td>
</tr>
<tr>
<td>LVEDV (ml/m2)</td>
<td>46 (55-75)</td>
<td>65 (55-77)</td>
<td>55 (55-65)</td>
<td>0.94</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50 (45-60)</td>
<td>50 (46-60)</td>
<td>49 (43-58)</td>
<td>0.26</td>
</tr>
<tr>
<td>Multiregional RV-WMA*</td>
<td>25 (36)</td>
<td>22 (41)</td>
<td>3 (19)</td>
<td>0.01</td>
</tr>
<tr>
<td>Inducibility at PVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VT</td>
<td>34 (49)</td>
<td>26 (49)</td>
<td>8 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>- VF</td>
<td>28 (41)</td>
<td>22 (42)</td>
<td>6 (38)</td>
<td>0.93</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>31 (44)</td>
<td>29 (54)</td>
<td>2 (12)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*multiregional WMA=akinesia, diskinesia or bulging in ≥2 RV regions*

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%-iles.

ARVC/D=arrhythmogenic right ventricular cardiomyopathy/dysplasia; EDV=end diastolic volume; EF=ejection fraction; FAC=fractional area change; LV=left ventricle; PVS=programmed ventricular stimulation; RV=right ventricle; SAECG=signal averaged electrocardiogram; SD=standard deviation; VT=ventricular tachycardia; WMA=wall motion abnormalities.
Table 2. Characteristics of patients with and without arrhythmic events during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Events N=19 (28%)</th>
<th>No events N=50 (72%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>34 (23-42)</td>
<td>37 (28-47)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>14 (74)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Family history of sudden death (&lt;35 years)</td>
<td>6 (32)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>History of cardiac arrest or syncope</td>
<td>14 (73)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>10 (53)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>6 (32)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>RVEVD (ml/m²)</td>
<td>80 (55-103)</td>
<td>80 (64-96)</td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>39 (40-41)</td>
<td>39 (38-40)</td>
</tr>
<tr>
<td>LVEVD (ml/m²)</td>
<td>59 (54-71)</td>
<td>65 (55-80)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50 (45-58)</td>
<td>50 (45-60)</td>
</tr>
<tr>
<td>Fragmented bipolar electrograms</td>
<td>15 (79)</td>
<td>32 (64)</td>
</tr>
<tr>
<td>Inducibility at PVS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VT</td>
<td>11 (58)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>- VF</td>
<td>9 (47)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy</td>
<td>15 (79)</td>
<td>42 (84)</td>
</tr>
<tr>
<td>Abnormal bipolar-EVM</td>
<td>19 (100)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Abnormal unipolar-EVM</td>
<td>19 (100)</td>
<td>50 (100)</td>
</tr>
</tbody>
</table>

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%-iles. Abbreviations as in Table 1.
Table 3. Predictors of arrhythmic events during follow-up.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0-1.0</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.1</td>
<td>0.4-3.3</td>
</tr>
<tr>
<td>Family history of sudden death</td>
<td>1.1</td>
<td>0.4-3.0</td>
</tr>
<tr>
<td>History of cardiac arrest or syncope</td>
<td>3.4</td>
<td>1.4-8.8</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>1.8</td>
<td>0.3-5.7</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>1.1</td>
<td>0.4-2.5</td>
</tr>
<tr>
<td>RVEVD (ml/m2)</td>
<td>1.1</td>
<td>0.9-1.3</td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>1.0</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>LVEVD (ml/m2)</td>
<td>0.9</td>
<td>0.9-1.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>1.0</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>Fragmented bipolar electrograms</td>
<td>1.2</td>
<td>0.7-3.1</td>
</tr>
<tr>
<td>Inducibility at PVS</td>
<td>1.4</td>
<td>0.5-5.0</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy</td>
<td>0.9</td>
<td>0.3-3.4</td>
</tr>
<tr>
<td>Abnormal bipolar-EVM†</td>
<td>1.7</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Abnormal unipolar-EVM†</td>
<td>1.3</td>
<td>0.6-4.3</td>
</tr>
</tbody>
</table>

† HR per 5% interval
Abbreviations as in Table 1.
Figure Legends:

**Figure 1.** Representative bipolar and unipolar RV-EVM from 2 ARVC/D patients.
- Patient #16: right anterior oblique view of RV bipolar-EVM showing preserved bipolar voltages values (A); right anterior oblique view of RV unipolar-EVM from the same patient unmasking the presence of a significant electroanatomic scar (B).
- Patient #47: compared with right anterior oblique view of bipolar RV-EVM (C), unipolar RV-EVM (D) reveals a greater burden of low-voltage electrogram area involving the RVOT, infero-basal and apex regions.

**Figure 2.** Surface ECG (top) and bipolar intracardiac electrocardiograms (bottom) sampled from within normal (A) and low-amplitude (B) RV area in the same ARVC/D patient. Normal voltage electrogram is characterized by a sharp, biphasic deflection with large amplitude and short duration (A). By comparison, electrogram recorded from low-voltage areas (i.e. electroanatomic scar) are fragmented with late activation and prolonged duration beyond the QRS complex.

**Figure 3.** Clinico-pathologic correlation between bipolar-EVM and histopathologic findings in a 18-year old ARVC/D patient who underwent heart transplantation because of refractory VF storms. (A) Antero-posterior view of bipolar-EVM featuring a large RV electroanatomic scar involving the antero-lateral, RVOT and infero-basal regions. (B) Histology of the antero-lateral right ventricular free wall from the native heart coming from transplantation. Panoramic histological section of RV anterior wall (Top) shows the massive and transmural fibro-fatty replacement of the atrophic myocardium (Heidenhain trichrome stain). Close-up of the boxed
area details residual myocytes (red) which are embedded within fibrous (blu) and fatty tissue (white) (Heidenhain trichrome stain) (bottom). End=endocardial side; Epi=epicardial side; MB=moderator band

**Figure 4.** Kaplan-Meier analysis of freedom from adverse events stratified by the presence of abnormal bipolar-EVM (A) and programmed ventricular stimulation (PVS) findings (B).

**Figure 5.** Predicted probability of reaching the combined arrhythmic end point at 1, 2, and 3 years on the basis of the extent of abnormal bipolar-EVM.
Prognostic Value of Endocardial Voltage Mapping in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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Supplemental online figure legend: Anatomic representation of regional distribution of bipolar low-voltage areas in the RV free-wall. The septum was excluded from the analysis. RVOT = right ventricular outflow tract.