Cardiac Magnetic Resonance Predicts Outcome in Patients With Premature Ventricular Complexes of Left Bundle Branch Block Morphology

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Objectives
We investigated whether the presence of right ventricular (RV) abnormalities detected by cardiovascular magnetic resonance (CMR) predict adverse outcome in patients presenting with frequent premature ventricular complexes (PVCs) of left bundle branch block (LBBB) morphology.

Background
CMR is a component of the diagnostic workup for the differential diagnosis between arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and idiopathic RV tachycardia. RV abnormalities evaluated by CMR could have prognostic importance.

Methods
Four hundred forty consecutive patients with ≥1,000 PVCs of LBBB morphology (minor diagnostic criterion of ARVC/D) and no other pre-existing criteria were prospectively enrolled. RV wall motion (WM), signal abnormalities, dilation, and reduced ejection fraction evaluated by CMR were considered imaging criteria of ARVC/D. Follow-up was performed evaluating an index composite end point of 3 cardiac events: cardiac death, resuscitated cardiac arrest, and appropriate implantable cardiac-defibrillator shock.

Results
Subjects with multiple RV abnormalities (RVA-2 group) had worse outcome than the no-RVA group (hazard ratio [HR]: 48.6; 95% confidence interval [CI]: 6.1 to 384.8; p < 0.001). Of the 61 patients in the RVA-2 group, only 6 had a definite diagnosis of ARVC/D applying the Task Force Criteria. Also, subjects with a single imaging criterion (RVA-1 group) had worse outcome than the no-RVA group (HR: 18.2; 95% CI: 2.0 to 162.6; p < 0.01). Patients with only WM abnormalities had higher prevalence of cardiac events than no-RVA (HR: 27.2; 95% CI: 3.0 to 244.0; p = 0.03).

Conclusions
In subjects with frequent PVC of LBBB morphology, CMR allows risk stratification. RV abnormalities were associated with worse outcome. (J Am Coll Cardiol 2010;56:1235–43) © 2010 by the American College of Cardiology Foundation

Premature ventricular complexes (PVCs) of left bundle branch block (LBBB) morphology and inferior axis arise from the right ventricular (RV) outflow tract or, less frequently, from the higher portion of the interventricular septum. PVCs of such morphology constitute a manifestation of idiopathic right ventricular tachycardia (IVRT) or an initial arrhythmic manifestation of arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D) (1–3). These 2 diseases initially have similar manifestations but are completely opposite in terms of the prognosis (4–6). IVRT is a disease with excellent prognosis, whereas ARVC/D is characterized by a great risk of sudden cardiac death, especially in young people involved in competitive sports (7). In Italy, where this study was conducted, ARVC/D has high incidence and is one the major causes of sudden death in the young (8). The diagnosis of ARVC/D is based on the presence of concomitant major and minor signs: functional and morphological abnormalities of the RV, electrocardiographic abnormalities, arrhythmias, and family history (9,10). Cardiac magnetic resonance (CMR) has been proposed as a valuable component of the diagnostic workup for ARVC/D (11). CMR frequently shows only minimal morphological and functional alterations that are not sufficient to diagnose ARVC/D. In the present study, we enrolled a selected group of subjects who...
only had a history of PVCs, without other clinical, electrocardiographic, and echocardiographic criteria associated with ARVC/D. The aims of the study was to evaluate the relationship between RV abnormalities detected by CMR and the clinical end points of cardiac death, resuscitated cardiac arrest, and appropriate implantable cardiac-defibrillator (ICD) shock using a long-term follow-up.

Methods

Study population. Four hundred forty consecutive subjects with frequent PVCs of LBBB morphology and inferior axis on referring clinical exam of CMR from January 2002 to March 2005 were prospectively enrolled. In order to select patients with minimal confounding factors, the following inclusion criteria were applied: 1) 1,000 or more PVCs of LBBB morphology and inferior axis on 24-h Holter electrocardiogram (ECG) monitoring; 2) normal resting echocardiogram; 3) maximal exercise test negative for ischemia; 4) normal 12-lead rest electrocardiogram; 5) no familial history of sudden death; 6) no history of coronary artery disease, cardiomyopathy, systemic hypertension, or diabetes mellitus; and 7) absence of contraindications to CMR.

Patients with frequent PVCs or ventricular bigeminism during examination were treated with an oral antiarrhythmic agent (propafenone, flecainide, or amiodarone) for 1 week before CMR examination in order to optimize ECG trigger and to obtain optimal image acquisition.

Of the initial study population, 44 subjects were excluded for claustrophobia (n = 18), body dimension above the scanner diameter (n = 5), and very frequent PVCs despite antiarrhythmic drugs during CMR (n = 21). Thus, the final population included 396 patients (mean age 33 years, 257 males).

CMR. CMR examination was performed using a 1.5-T Signa CVi scanner (GE, Milwaukee, Wisconsin) with a cardiac phased-array 8-channel coil. For the assessment of regional wall motion (WM) and left ventricular (LV) volumes and mass, cine images were used with a steady-state free precession (Fast Imaging Employing Steady-State Acquisition [FIESTA]) pulse sequence in short-axis views (from atrioventricular valve plane to the apex, 8-mm slice thickness, no gap) and in para-axial views (from diaphragm to the entire outflow tract, 5-mm slice thickness, no gap). The following acquisition parameters were applied: 30 phases, 10 to 25 views per segment depending on heart rate, NEX 1, FOV 40 cm, a matrix of 224 × 224, a 45° flip angle, TR/TE equal to 3.5/1.5, and a bandwidth of 125 kHz.

For the evaluation of fat infiltration, a fast spin echo image was acquired in the same short-axis view (8-mm slice thickness, no gap) and para-axial view (5-mm slice thickness, no gap) with the following parameters: NEX 1, FOV 40 cm, matrix of 256 × 256, a 90° flip angle, TR/TE of 1,791/41.5, and a bandwidth of 62.5 kHz. Fast spin echo images were also reacquired using a fat saturation pulse to selectively null signals from fat.

Post-processing. Using dedicated software (Mass Analysis, MEDIS, Leiden, the Netherlands), the following functional parameters were obtained from the short-axis images: RV and LV end-diastolic volume index, RV and LV end-systolic volume indexes, LV mass index, and RV and LV ejection fraction. The RV and LV volume indexes were compared with the respective reference values clustered for class age and sex (12,13). RV WM was evaluated by 2 independent expert investigators (G.D.A. and E.S.) from the short-axis and para-axial cine views and were classified as normal WM, minor WM abnormalities (hypokinetic segment), or major WM abnormalities (akinetic or bulging segment) (Fig. 1).

Similarly, fast spin echo images with and without fat saturation were evaluated by 2 independent expert investigators, and the signal from the RV wall was classified as follows: 1) normal signal if there was no evidence of hyperintense myocardium with infiltrative characteristics; or 2) signal alteration (myocardial area hyperintense in fast spin echo images and hypointense in fat saturation fast spin echo images) diffuse (more than 1 segment) if focal, but infiltrating or associated with wall thinning (Fig. 2).

Any discrepancies between the investigators were then independently adjudicated by a blinded third investigator (M.L).

Group definition. According to the Task Force diagnostic criteria for ARVC/D, CMR findings accepted as major diagnostic criteria are severe WM abnormalities (akinesia, bulging) and severe RV dilation with dysfunction (defined as mean end-diastolic volume index >4 SD above the mean reference value, and RV ejection fraction lower than 40%) (10). Minor CMR diagnostic criteria of ARVC/D are: mild WM abnormalities (hypokinesia), mild RV dilation defined as mean end-diastolic volume index >2 and <4 SD about the mean of the reference, or RV ejection fraction between 40% and 50%). Considering that all patients were positive for only a minor criterion (>1,000 PVCs in 24 h with LBBB morphology and inferior axis), the diagnosis of ARVC/D was based on the evidences of major or minor CMR criteria for ARVC/D. Therefore, on the basis of the presence or absence of these criteria, subjects were clustered in 2 groups: no-RVA group (patients without RV abnor-
malities found by CMR) and RVA group (patients with the presence of 1 or more RV abnormalities). RVA group was also subdivided into 2 groups: RVA-1 (patients with only 1 RV abnormality) and RVA-2 (patients with 2 or more RV abnormalities). Signal alteration of the RV wall that is not encompassed in the Task Force Criteria, but is considered as an imaging equivalent of fat infiltration at biopsy, was also assumed to be a major criterion but not sufficient to fulfill a definite diagnosis of ARVC/D.

**Clinical follow-up.** Follow-up was performed in all patients for a mean of 1,348 ± 120 days after the CMR examination. A clinical questionnaire was compiled by a clinical physician during periodic ambulatory visitations in our institute (93 patients, 23.5%) or telephone contact (303 patients, 76.5%). The clinical questionnaire included the definition of the major end points: cardiac death, resuscitated cardiac arrest, and appropriate ICD shock.

ICD shocks were designated appropriate if triggered by lethal arrhythmias: ventricular tachycardia above the programmed cutoff of the ICD (12 intervals at >180 beats/min), or ventricular fibrillation. A complete interrogation of the ICD was performed by the referring physician in order to confirm the appropriateness of the shock. Furthermore, the following data were obtained: New York Heart Association (NYHA) functional class, cardiac hospitalization, a diagnostic test for diagnosis of ARVC/D (electrophysiological test, myocardial biopsy, late potential monitoring), device therapy (ICD, pacemaker), and pharmacologic therapy. At the electrophysiological test, ventricular tachycardia (VT) was considered inducible if programmed electrical stimulation or isoproterenol infusion initiated sustained VT that replicated the morphology of the spontaneous PVCs. Ventricular extrastimuli were introduced at the RV apex and repeated at the RV outflow tract. A copy of the clinical report was obtained from the referring physician when events occurred.

**Statistical analysis.** Categorical variables were expressed as percentages. The continuous variables having a normal distribution were expressed as mean values, accompanied by their standard deviation. All continuous variables having a non-normal distribution were expressed as median values, accompanied by their relative 25th and 75th quartiles. Comparisons between groups were made with the chi-square test with Yates correction and t test or Mann-Whitney U test, where appropriate. Logistic regression analysis was carried out for the hazard risk evaluation of VT.
at 24-h ECG Holter monitoring as the dependent variable and age, sex, and the different groups of patients with any RV wall abnormality versus the group without any RV wall abnormality at imaging criteria as independent variables in the model. Kaplan-Meier survival curves (14) were constructed to compare the occurrence of major cardiac events among the RVA and no-RVA groups, with differences in survival curves assessed through the log-rank test. Cox proportional hazards regression analysis was carried out for the risk evaluation of major cardiac events using a fixed model with cardiac event as the dependent variable and RVA groups as independent variables. Cox univariate regression analysis was used to explore each variable in a model with cardiac event as the dependent and signal alteration, WM abnormalities, LV mass index, RV end-diastolic volume index, RV end-systolic volume index, RV ejection fraction, RV end-diastolic diameter, and RV end-systolic diameter as independent predictors.

Statistical analyses were performed using SPSS version 13 (SPSS Inc., Chicago, Illinois), and a p value <0.05 was considered significant.

Results

All of the 396 patients completed the CMR protocol without major complications. In 21 patients, the examination was repeated after pre-medication with antiarrhythmic drugs because of arrhythmic interference. A third investigator was used to adjudicate the discrepancies in image interpretation that occurred in 25 patients.

CMR results. As shown in Table 1, 126 subjects (31.8%) had RV abnormalities (RVA group). Of these, 61 subjects (15.4%) were included in RVA-2 and 65 (16.4%) in the RVA-1 group. The remaining 270 subjects (68.2%) were included in the no-RVA group. Of the 61 patients in the RVA-2 group, 6 patients had WM abnormalities (akinesia/bulging) as major criteria plus 2 minor criteria (mild-to-moderate RV dilation and frequent PVCs), allowing a definite diagnosis of ARVC/D by applying the Task Force Criteria, whereas in the remaining 55, the presence of signal alteration was assumed as an equivalent of fat infiltration. Six patients had a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD/C) using the Task Force Criteria (fat infiltration at CMR excluded).

Table 1: Diagnostic Criteria After CMR Examination in This Population

<table>
<thead>
<tr>
<th>Criteria*</th>
<th>Patients, n (%)</th>
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<tbody>
<tr>
<td>PVC</td>
<td>270 (68.2)</td>
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<tr>
<td>PVC and mild RV dilation</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>PVC and severe RV dilation</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>PVC and fat infiltration</td>
<td>22 (5.6)</td>
</tr>
<tr>
<td>PVC and fat infiltration and mild RV dilation</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>PVC and minor WM</td>
<td>16 (4)</td>
</tr>
<tr>
<td>PVC and minor WM and mild RV dilation</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>PVC and major WM</td>
<td>25 (6.3)</td>
</tr>
<tr>
<td>PVC and major WM and mild RV dilation</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>PVC and major WM and severe RV dilation</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>PVC and fat infiltration and minor WM</td>
<td>11 (3)</td>
</tr>
<tr>
<td>PVC and fat infiltration and minor WM and mild RV dilation</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>PVC and fat infiltration and major WM</td>
<td>38 (9.6)</td>
</tr>
<tr>
<td>PVC and fat infiltration and major WM and severe RV dilation</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>PVC and fat infiltration and major WM and mild RV dilation</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

*PVC indicates premature ventricular complexes (>1,000 in 24 h) of typical morphology and axis; minor WM indicates a minor wall motion abnormality (hypokinesia); and major WM indicates a major wall motion abnormality (akinesia, bulging). Signal alteration was assumed as an equivalent of fat infiltration. 15% of patients had a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD/C) using the Task Force Criteria (fat infiltration at CMR excluded).

CMR = cardiac magnetic resonance; RV = right ventricle.
alterations as only a surrogate major criterion (fat infiltration) plus at least 2 minor criteria did not allow a definite diagnosis. Of the RVA-1 group, 22 subjects (5.6%) had only signal alterations; 43 (10.8%) had only WM abnormalities. All patients had normal global and regional LV function.

All patients had normal global and regional LV function. Three patients showed signal alterations compatible with fat infiltration in LV myocardium: 1 in the interventricular septum, 2 in the inferolateral wall. All of them also showed RV WM abnormalities combined with RV signal alteration and were included in the RVA-2 group.

LV and RV functional parameters are reported in Table 2. The RVA group had significantly higher RV volumes than the no-RVA patients, whereas LV volumes were not different between those groups.

Clinical data. During the follow-up in 6 patients, an alternative diagnosis was performed: 4 in patients with normal CMR examination (1 coronary heart disease and pulmonary cancer, 1 Brugada syndrome, 1 long-QT syndrome, 1 accessory pathways); and 2 in patients with WM abnormalities of the RV wall (1 sarcoidosis and 1 pulmonary hypertension). These patients were excluded from the analysis of the follow-up data.

Nonsignificant differences between the no-RVA and RVA groups were found using the 24-h Holter ECG monitoring with regards to the number of PVCs, couplets, triplets, and episodes of ventricular bigeminsin. In 78 subjects (19.7%), episodes of VT were recorded, mostly (96%) nonsustained VT. In Table 3, the relative incidence of VT is shown for the groups of the population. The occurrence of VT was higher in patients with RV abnormalities compared with the no-RVA group.

Eleven patients were in NYHA functional class II with no significant difference between groups; the remaining were in NYHA functional class I.

An electrophysiological test was performed in 32 patients with nonsustained VT: 15 patients of the RVA-2 group (4 positive for inducible VT), in 12 patients in the RVA-1 group (3 positive for inducible VT), and in 5 patients in the no-RVA group (3 positive for inducible VT). Endomyocardial biopsy was performed in 1 patient of the RVA-2 group, confirming the presence of fat infiltration.

Following CMR examination and subsequent clinical tests, an ICD was implanted in 1 patient without any RV abnormalities because of the occurrence of 2 episodes of syncope triggered by sustained VT and a positive electrophysiological test. ICDs were implanted in 2 patients in the RVA-1 group (2 of the 3 patients with inducible VT at electrophysiologic test), and in 9 patients in the RVA-2 group (4 with inducible VT, 1 with biopsy-proven fat infiltration, 4 with RV wall abnormalities and severe RV dilation).

Clinical end points. In the follow-up, 14 major cardiac events occurred: 3 sudden cardiac deaths; 9 appropriate ICD shocks, and 2 resuscitated cardiac arrests. One more subject in the no-RVA patient group died from pulmonary cancer and was excluded from the analysis. Of the 14 major cardiac events, 1 event (appropriate ICD shock) occurred in the no-RVA group, whereas 13 occurred in the RVA group (Table 4).

The occurrence of a cardiac event was significantly higher in the RVA group than in the no-RVA group (hazard ratio

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### Table 2 Functional Parameters of LV and RV

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVA</th>
<th>No-RVA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>126</td>
<td>270</td>
<td>0.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>86 (68.3)</td>
<td>170 (63)</td>
<td>0.5</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34 ± 17</td>
<td>32 ± 16</td>
<td>0.5</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>59 ± 10</td>
<td>60 ± 7</td>
<td>0.51</td>
</tr>
<tr>
<td>RV EDVi, ml/m²</td>
<td>89 ± 25</td>
<td>78 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV ESVi, ml/m²</td>
<td>38 ± 20</td>
<td>31 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>60 ± 8</td>
<td>62 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>LV EDVi, ml/m²</td>
<td>87 ± 18</td>
<td>85 ± 17</td>
<td>0.33</td>
</tr>
<tr>
<td>LV ESVi, ml/m²</td>
<td>35 ± 12</td>
<td>33 ± 10</td>
<td>0.09</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>74 ± 18</td>
<td>71 ± 14</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* RVA indicates the group of patients with any RV wall abnormalities; no-RVA indicates the group without any RV wall abnormalities and imaging criteria.

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### Table 3 Incidence of VT at 24-h ECG Holter Monitoring

<table>
<thead>
<tr>
<th>Group*</th>
<th>n (%)</th>
<th>Occurrence of VT</th>
<th>Other Groups vs. No-RVA Group†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 95% CI p Value</td>
</tr>
<tr>
<td>Global population</td>
<td>396</td>
<td>78 (19.7)</td>
<td>— — —</td>
</tr>
<tr>
<td>No-RVA (no imaging criteria)</td>
<td>270 (68.2)</td>
<td>32 (11.5)</td>
<td>— — —</td>
</tr>
<tr>
<td>RVA</td>
<td>126 (31.8)</td>
<td>46 (37.3)</td>
<td>2.3 1.4–3.8 &lt;0.0001</td>
</tr>
<tr>
<td>RVA-1</td>
<td>65 (16.4)</td>
<td>19 (31.7)</td>
<td>1.6 0.8–2.9 0.17</td>
</tr>
<tr>
<td>Signal alteration alone</td>
<td>22 (5.6)</td>
<td>6 (29.1)</td>
<td>1.3 0.4–3.3 0.69</td>
</tr>
<tr>
<td>WM abnormalities alone</td>
<td>43 (10.8)</td>
<td>13 (41.8)</td>
<td>1.8 0.8–3.7 0.14</td>
</tr>
<tr>
<td>RVA-2</td>
<td>61 (15.4)</td>
<td>27 (44.3)</td>
<td>3.5 1.9–6.6 &lt;0.001</td>
</tr>
</tbody>
</table>

The logistic regression model is calculated using only 3 factors (age, sex, and RVA groups) to predict the occurrence of ventricular tachycardia (VT) at 24-h ECG Holter monitoring. * RVA indicates the groups of patients with any RV wall abnormalities; no-RVA indicates the group without any RV wall abnormalities and imaging criteria; RVA-1 indicates the group of patient with single RV abnormalities; RVA-2 indicates the group with combined RV abnormalities; signal alteration alone indicates patients with only RV signal alteration (equivalent of fat infiltration); WM indicates patients with only WM abnormalities. †Significance values refer to a comparison of the relevant group to the no-RVA group.

CI = confidence interval; ECG = electrocardiogram; OR = odds ratio; WM = wall motion.
Event-free survival curves for these 2 groups are shown in Figure 3. Both the RVA-2 (HR: 48.6; 95% CI: 6.1 to 384.8; p < 0.001) and the RVA-1 groups (HR: 18.2; 95% CI: 2.0 to 162.6; p = 0.01) had more cardiac events and a worse survival curve than the no-RVA group (Fig. 3).

No events occurred in patients included in the RVA-1 group presenting with only signal alteration. Compared with the no-RVA group, patients in RVA-1 with only WM abnormalities had a significantly higher incidence of cardiac events (4 events, HR: 27.2; 95% CI: 3.0 to 244.0; p = 0.03). When only sudden cardiac deaths and resuscitated cardiac arrests were considered, all 5 events occurred in the 126 subjects of the RVA group versus 270 cases of no-RVA (chi-square corrected test: 7.9; p = 0.005).

In the RVA-2 group, 3 of the 6 patients with a definite diagnosis of ARVC/D by Task Force Criteria had events, whereas 6 events were found in the remaining 56 patients without a definite diagnosis.

No cardiac events were recorded in patients younger than 20 years of age. Three cardiac events were recorded in patients between 20 and 35 years of age, 3 in patients between 35 and 47 years of age, and 8 in patients older than 47 years of age. Ten cardiac events were recorded in male patients and 4 in female.

Table 5 shows the results of the univariate analysis used in a model with cardiac event as the dependent variable and signal alteration, WM abnormalities, LV mass index, RV end-diastolic volume index, RV end-systolic volume index, RV ejection fraction, RV end-diastolic diameter, and RV end-systolic diameter as independent variables.
Discussion

The findings of the present study show that patients with frequent PVCs of LBBB morphology and inferior axis and no other pre-existing diagnostic criteria for ARVC/D can be distinguished, according to the presence of CMR morphological and/or functional RV abnormalities, in 3 groups with different outcome: those having no RV abnormalities, RVA-1 having single RV abnormalities, and RVA-2 having several RV abnormalities.

Our study population was carefully selected and was composed of patients with normal basal echocardiograms, without electrocardiogram alterations, negative exercise tests, and without family history of ARVC/D or sudden death. Moreover, we excluded patients that met the criteria for ARVC/D other than frequent PVCs arising from the RV (minor diagnostic criteria). Indeed, the results showed that patients with multiple RV abnormalities (RVA-2) had a worse event-free survival curve and higher incidence of combined end point: those having no RV abnormalities, RVA-1 having single RV abnormalities, and RVA-2 having several RV abnormalities.

In this study, we assumed the signal alteration found by CMR as an imaging equivalent of fat infiltration. This assumption could be not correct for the diagnosis of ARVC/D applying the Task Force Criteria where fat infiltration is considered a major criterion only when confirmed at biopsy. Thus, as evidenced in Table 1, using the Task Force Criteria, only 6 patients had a definite diagnosis of ARVC/D, whereas in 55, CMR raised the suspicion of this disease for the presence of multiple abnormalities but without giving a definite diagnosis. However, this evidence reinforced the results of our study: morphofunctional abnormalities found by CMR were related to prognosis even when not sufficient to make a diagnosis of ARVC/D.

These results confirm the key role of CMR in the assessment of RV function and morphology, highlighting the potential of this technique in stratifying subjects at low arrhythmic risk according to the evidence of RV morphological and functional abnormalities. These results are in agreement with a previous study showing that RV abnormalities detected by CMR constitute a source of malignant ventricular arrhythmias in the absence of a definite diagnosis of ARVC/D (15). Regarding IRVT, there are discordant results on the presence of RV abnormalities (16–18). Some studies showed CMR signal alterations in patients with IRVT (18); other studies showed only minimal WM abnormalities without signal alterations (17), whereas others did not show any kind of RV abnormalities (19,20). The reasons of these discordances may be linked to the selection criteria of subjects. In the case of our study, we adopted a strict selection criteria through which only subjects with frequent PVCs, normal echocardiography, normal ECGs, and no other criteria for ARVC/D were included, and defined IRVT subjects as those without RV abnormalities.

When we investigated the impact of the different RV abnormalities on the prognosis, no cardiac event occurred in the group of patients with fat infiltration and normal WM. This finding agrees with the results of Gaita et al. (4), showing excellent long-term prognosis in subjects with abnormal RV signals only. In contrast, patients with WM abnormalities alone had a significantly higher incidence of combined end points than the no-RVA group and a similar event-free survival curve to that observed in patients with combined abnormalities.

One other important finding was that no cardiac events were recorded in the group of patients younger than 20 years of age. In contrast, the groups containing older RVA patients showed a higher incidence of combined end points. These results could be explained by the fact that ARVC/D is an evolving disease that usually begins to manifest after 20 years of age (5). Keller et al. (21) also showed a similar result regarding a higher incidence of arrhythmic events in a small population of patients with RV abnormalities.

Study limitations. A limitation of the study was the low prevalence of cardiac events in the follow-up. This was expected, considering the low risk for cardiovascular events
of the enrolled subjects, for the middle young age, and the absence of signs or symptoms of cardiac disease.

Further studies are needed to evaluate the prognostic utility of the single RV abnormalities (WM abnormalities, wall signal alteration, RV dilation, and decreased function) as predictors of cardiac events.

Another limitation of this study is that only a minority of our population underwent an electrophysiological study during follow-up. The electrophysiological study was demonstrated to be useful for the differential diagnosis between ARVC/D and IRVT due to different arrhythmic mechanisms in these 2 diseases (15). However, patients at the moment of the enrollment had low arrhythmic risk, all of them presenting frequent PVCs only. Thus, in this population, invasive assessment was not justified. Furthermore, previous studies showed a good correlation between the site of wall abnormalities found by CMR and electroanatomic mapping (22–24). Another limitation was the lack of evaluation of fibrosis using a delayed enhancement technique that could assess the fibro-fatty variant of ARVC/D (25). However, the great difference in prognosis between the group of patients with and without RV wall abnormalities in this study could justify the avoidance of contrast media injection in this group of selected patients at low risk. Notwithstanding, a delayed enhancement technique could probably improve the accuracy of diagnosis. In fact, in the future, myocardial fibrosis could be considered as an adjunctive imaging criteria, potentially shifting patients from the intermediate group to the ARVC/D group or excluding alternative diagnoses such as coronary artery disease or a different cardiomyopathy.

Finally, this study was performed in Italy, where a higher incidence of ARVC/D, especially in the Veneto region, has been demonstrated, and young people must undergo a strict medical selection in order to participate in competitive sports (9). Studies performed in other regions may provide different results in terms of the incidence of disease and the prognosis.

Conclusions

Patients with frequent PVC of LBBB morphology and inferior axis and no other pre-existing diagnostic criteria for ARVC/D have been distinguished in 3 different groups according to the presence of RV abnormalities at CMR: at one extreme, IRVT subjects having excellent prognosis, at the other extreme, ARVD/C subjects having worse prognosis, and in the middle grey zone, subjects having few RV abnormalities and intermediate prognosis. Patients with WM abnormalities alone had significantly higher prevalence of the combined end points, whereas RV signal alteration alone was not associated with a worse prognosis than in the no-RVA patients. Finally, the incidence of cardiac events increased with age and was absent in patients younger than 20 years of age.

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REFERENCES


Key Words: arrhythmogenic right ventricular dysplasia • cardiovascular magnetic resonance • idiopathic right ventricular tachycardia • premature ventricular complexes.