Prevalence and Prognostic Value of Concealed Structural Abnormalities in Patients With Apparenty Idiopathic Ventricular Arrhythmias of Left Versus Right Ventricular Origin

A Magnetic Resonance Imaging Study

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Background—Routine diagnostic work-up occasionally does not identify any abnormality among patients with monomorphic ventricular arrhythmias (VAs) of left ventricular (LV) origin. Aim of this study was to investigate the value of cardiac MRI (cMRI) for the diagnostic work-up and prognostication of these patients.

Methods and Results—Forty-six consecutive patients (65% males; mean age, 44±15 years) with monomorphic VAs of LV origin and negative routine diagnostic work-up were included. Seventy-four consecutive patients (60% males; mean age, 40±17 years) with apparently idiopathic monomorphic VAs of right ventricular origin served as control group. Both groups underwent comprehensive cMRI study and were followed up for a median of 14 months (25th–75th percentiles, 7–37 months). The outcome event was an arrhythmic composite end point of sudden cardiac death or nonfatal episode of ventricular fibrillation or sustained ventricular tachycardia requiring external cardioversion or appropriate implantable cardioverter defibrillator therapy. The 2 groups of patients did not differ in age (P=0.14) and sex (P=0.57). No significant difference was observed between patients with VAs of LV origin and VAs of right ventricular origin about biventricular volumes and systolic function. cMRI demonstrated myocardial structural abnormalities in 19 (41%) patients with VAs of LV origin versus 4 (5%) patients with VAs of right ventricular origin (P<0.001). The outcome event occurred in 9 patients; myocardial structural abnormalities on cMRI were significantly related to the outcome event (hazard ratio, 41.6; 95% confidence interval, 5.2–225.0; P<0.001).

Conclusions—Myocardial structural changes are detected by cMRI in a non-negligible proportion of patients with apparently idiopathic monomorphic VAs of LV origin and are associated with worse outcome.

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Key Words: arrhythmias, cardiac • arrhythmogenic right ventricular dysplasia • fibrosis • heart ventricles • magnetic resonance imaging • myocarditis • prognosis

Monomorphic ventricular arrhythmias (VAs) of left ventricular (LV) origin, differently from VAs of right ventricular (RV) origin, are frequently associated with structural heart disease, such as ischemic heart disease, healed myocardial infarction, and nonischemic cardiomyopathies.1-3 However, routine diagnostic work-up (including 12-lead ECG, transthoracic echocardiography, exercise stress testing, and coronary angiography) occasionally does not identify any abnormality; in these patients, VAs of LV origin are referred as idiopathic.4 The use of cardiac MRI (cMRI) may be of potential clinical value in this setting. Besides quantifying biventricular functional parameters with high accuracy and reproducibility, cMRI allows myocardial tissue characterization, providing information about the presence of structural abnormalities (such as myocardial fatty replacement, myocardial edema, and necrosis/fibrosis), which may otherwise remain unrecognized.4

Clinical Perspective on p 462

Previous cMRI studies have investigated the prevalence of morphological, functional, and structural abnormalities in patients with idiopathic VAs originating from the RV5-14; conversely, little is known about the usefulness of cMRI for the...
identification of concealed cardiac abnormalities in patients with apparently idiopathic LV arrhythmias. Moreover, scarce data are available about the prognostic value of concealed structural abnormalities detected by cMRI in these patients.

Accordingly, the aim of this study was 2-fold: (1) to investigate the value of comprehensive cardiac magnetic resonance tissue characterization imaging, including T1-weighted imaging, T2-weighted imaging, and late gadolinium enhancement (LGE) imaging, for the detection of structural changes in patients with monomorphic VAs of LV versus RV origin and negative routine diagnostic work-up; and (2) to determine the prognostic value of concealed structural abnormalities detected by cMRI in these patients.

Methods

Patient Population
A total of 46 consecutive patients with monomorphic VAs of LV origin (ie, frequent premature ventricular beats [PVBs] >1000/24 hours, nonsustained ventricular tachycardia [NSVT], or sustained ventricular tachycardia [SVT] with right bundle branch block [RBBB] morphology) and negative routine diagnostic work-up were included in the study. Negative routine diagnostic work-up was defined on the basis of (1) absence of systemic diseases, arterial hypertension, and diabetes mellitus; (2) absence of plasma electrolyte abnormalities; (3) normal 12-lead ECG; (4) normal 2-dimensional echocardiography; and (5) absence of significant coronary artery disease, as demonstrated by maximal exercise test, multislice computed tomography or invasive coronary angiography. For comparison purpose, 74 consecutive patients with monomorphic VAs of RV origin (ie, with left bundle branch block morphology) fulfilling the same inclusion criteria were also included. Both groups of patients were referred to cMRI to assess LV and RV function, myocardial fatty replacement, myocardial edema, and necrosis/fibrosis. cMRI acquisition protocol and data analysis are described in detail in the Data Supplement.

The study was approved by an institutional review committee, and the informed consent of the subjects was obtained.

Clinical Follow-Up
Patients were followed-up (after cMRI date) by clinic visits and phone calls for a median duration of 14 months (25th–75th percentiles, 7–37 months). All necessary medical records were reviewed to determine the occurrence of hospital admission due to cardiovascular causes; mortality status, date, and cause of all death events occurred during the follow-up period were verified from the regional database. Medical records were also analyzed for the following subsequent procedures: implantation of an implantable cardioverter defibrillator (ICD) and VA ablation procedure. Analysis of all ICD interrogation records was performed to assess ICD therapies among ICD recipients; defibrillator discharges or antitachycardia overdrive pacing were considered an appropriate therapy if the device was triggered by ventricular fibrillation or ventricular tachycardia.

The outcome event was an arrhythmic composite end point, which included (1) sudden cardiac death (SCD), defined as unexpected cardiac death (within 1 hour of symptoms), and (2) nonfatal episode of ventricular fibrillation or SVT requiring external cardioversion or appropriate ICD therapy.

Statistical Analysis
Continuous variables are expressed as mean and SD or as median and 25th to 75th percentiles, when appropriate. Categorical data are presented as absolute numbers and percentages. Differences in continuous variables were assessed using the Student t test or the Mann–Whitney U test, when appropriate, for comparison between groups. χ² test or Fisher exact test, when appropriate, was computed to assess differences in categorical variables. Univariate logistic regression analysis was performed to evaluate the relationship between the presence of myocardial structural abnormalities and the following variables: age ≥40 years, male sex, family history of SCD or cardiomyopathy, presence/type of symptoms (ie, no symptoms, palpitations, or syncope), type of VAs (ie, frequent PVBs, NSVT, or SVT), and morphology of VAs (ie, left bundle branch block, RBBB and inferior QRS axis, or RBBB and superior QRS axis).

Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. Univariate Cox proportional hazards analysis was used to test the association between the outcome event and baseline covariates (age ≥40 years, male sex, family history of SCD or cardiomyopathy, presence/type of symptoms, type of VAs, morphology of VAs, and presence of myocardial structural abnormalities). Two-tailed tests were considered statistically significant at the 0.05 level.

Results

Characteristics of the Patient Population
Clinical characteristics of the study population are summarized in Table 1. No significant difference was observed between the 2 groups of patients as regard to age and sex (P=0.14 and P=0.57, respectively). Frequent PVBs were the more common VA observed among patients with VAs of RV origin (82% of patients), whereas NSVT and SVT were observed in up to 28% and 13% of patients with VAs of LV origin (P=0.013). Inferior QRS axis during VA was present in 33% of patients with VAs of LV origin; superior QRS axis was present in the remaining 67% of patients. Inferior QRS axis during VA was present in all patients with VAs of RV origin.

Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>VAs of LV Origin (n=46)</th>
<th>VAs of RV Origin (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44±15</td>
<td>40±17</td>
<td>0.14</td>
</tr>
<tr>
<td>Age ≥40 yr</td>
<td>31 (67%)</td>
<td>38 (51%)</td>
<td>0.092</td>
</tr>
<tr>
<td>Male sex</td>
<td>30 (65%)</td>
<td>44 (60%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Family history of SCD or cardiomyopathy</td>
<td>11 (24%)</td>
<td>9 (12%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic status*</td>
<td>9 (20%)</td>
<td>19 (26%)</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>31 (67%)</td>
<td>52 (69%)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (13%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Type of VA</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Frequent PVBs</td>
<td>27 (59%)</td>
<td>61 (82%)</td>
<td></td>
</tr>
<tr>
<td>NSVT</td>
<td>13 (28%)</td>
<td>10 (14%)</td>
<td></td>
</tr>
<tr>
<td>SVT</td>
<td>6 (13%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>QRS axis during VA</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior</td>
<td>15 (33%)</td>
<td>74 (100%)</td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>31 (67%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Antiarrrhythmic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>31 (67%)</td>
<td>42 (57%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Class I antiarrhythmic drugs</td>
<td>8 (17%)</td>
<td>24 (32%)</td>
<td>0.090</td>
</tr>
<tr>
<td>Class III antiarrhythmic drugs</td>
<td>10 (22%)</td>
<td>10 (14%)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD and n (%). LV indicates left ventricular; NSVT, nonsustained ventricular tachycardia; PVB, premature ventricular beat; RV, right ventricular; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; and VA, ventricular arrhythmia.

*Of note, all asymptomatic patients were athletes or military personnel diagnosed as having VAs during screening tests.
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Table 2. Cardiac MRI Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>VAs of LV Origin (n=46)</th>
<th>VAs of RV Origin (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV index (mL/m²)</td>
<td>79±19</td>
<td>74±12</td>
<td>0.16</td>
</tr>
<tr>
<td>LVESV index (mL/m²)</td>
<td>23 (19–38)</td>
<td>26 (22–32)</td>
<td>0.83</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66 (60–73)</td>
<td>65 (60–70)</td>
<td>0.88</td>
</tr>
<tr>
<td>Regional LV WMAs</td>
<td>9 (20%)</td>
<td>1 (1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>RVEDV index (mL/m²)</td>
<td>70±15</td>
<td>71±13</td>
<td>0.77</td>
</tr>
<tr>
<td>RVESV index (mL/m²)</td>
<td>19 (16–26)</td>
<td>22 (17–27)</td>
<td>0.22</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>70 (65–76)</td>
<td>70 (65–73)</td>
<td>0.56</td>
</tr>
<tr>
<td>LV intramyocardial fat signal (%)</td>
<td>8 (17%)</td>
<td>1 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV edema (%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LV LGE (%)</td>
<td>19 (41%)</td>
<td>3 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%LV LGE*</td>
<td>6 (3–12)</td>
<td>2 (0 to null)</td>
<td>0.042</td>
</tr>
<tr>
<td>RV LGE (%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Any myocardial structural abnormality (%)</td>
<td>19 (41%)</td>
<td>4 (5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or median (25th–75th percentiles) and n (%). EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LGE, late gadolinium enhancement; LV, left ventricular; %LV LGE, LGE expressed as a percentage of the LV mass; RV, right ventricular; VA, ventricular arrhythmia; and WMA, wall motion abnormality.

*Only patients with presence of LV LGE were considered for analysis.

cMRI Findings

cMRI characteristics of the study population are summarized in Table 2. No significant difference was observed between the 2 groups of patients with regard to biventricular volumes and function and LV mass index. Regional LV wall motion abnormalities were more frequently observed among patients with VAs of LV origin as compared with patients with VAs of RV origin (20% versus 1%; P=0.001); conversely, no significant difference was observed between the 2 groups with regard to regional RV wall motion abnormalities (7% versus 12%; P=0.37). Of note, no patient in both groups met neither major nor minor cMRI criteria for arrhythmogenic right cardiomyopathy/dysplasia.15

T1-weighted imaging demonstrated LV myocardial fat signal in 8 (17%) patients with VAs of LV origin while abnormal RV myocardial fat signal was observed in only 1 patient with VAs of LV origin and with VAs of RV origin, respectively. T2-weighted imaging demonstrated regional signal abnormalities of the LV suggestive of myocardial edema in only 1 patient with VAs of LV origin.

A total of 19 (41%) patients with VAs of LV origin and 3 (4%) patients with VAs of RV origin showed LV LGE (P<0.001); RV LGE was observed in only 1 patient with VAs of LV origin. Among patients with VAs of LV origin, a total of 71 LV segments showed LGE; LGE was most commonly located in the inferolateral wall (n=18), anterolateral wall (n=17), and inferior wall (n=15). LGE had a midmyocardial distribution in 20 LV segments and a subepicardial distribution in 51 LV segments. Among patients with VAs of RV origin, a total of 4 LV segments showed LGE; LGE had a midmyocardial distribution in 2 LV segments and a subepicardial distribution in 2 LV segments. Overall, myocardial structural abnormalities (ie, myocardial fatty replacement, edema, and necrosis/fibrosis) were observed in 19 (41%) patients with VAs of LV origin and in 4 (5%) patients with VAs of RV origin (P<0.001). Among the 19 patients with VAs of LV origin and myocardial structural abnormalities, 10 patients had frequent PVBs, 4 patients had NSVT, and 5 patients had SVT at presentation; QRS axis during VA had a superior orientation in 17 patients and an inferior orientation in the remaining 2 patients. Among the 4 patients with VAs of RV origin and myocardial structural abnormalities, 2 patients had frequent PVBs and 2 patients had NSVT at presentation. Figure 1 shows the distribution of myocardial structural abnormalities in the 2 groups of patients. Figure 2A and 2B and Figure IIA and IIB in the Data Supplement show examples of...
myocardial structural abnormalities demonstrated by cMRI in 4 patients with apparently idiopathic VAs of LV origin.

**Correlates of Myocardial Structural Abnormalities**

Table 3 shows the results of the univariate logistic regression analysis performed to determine the correlates of myocardial structural abnormalities. Age $\geq$ 40 years (odds ratio [OR]=4.5; 95% confidence interval [CI], 1.42–14.1; $P=0.011$), male sex (OR=8.7; 95% CI, 1.94–39.2; $P=0.005$), family history of SCD or cardiomyopathy (OR=5.0; 95% CI, 1.76–14.3; $P=0.002$), SVT (OR=7.9; 95% CI, 1.86–33.7; $P=0.005$), and VAs with RBBB morphology and superior QRS axis (OR=21.2; 95% CI, 6.2–72.8; $P<0.001$) were significantly related to the presence of myocardial structural abnormalities.

**Follow-Up Procedures and Events**

Nine patients underwent ICD implantation; indications to ICD implantation were (1) SVT at presentation (6 patients); (2) cMRI evidence of myocardial structural abnormalities associated with either history of syncope or family history of SCD or cardiomyopathy (2 patients), and (3) induction of SVT at electrophysiological study (1 patient). Nine patients underwent VA ablation procedure (7 patients for frequent PVBs and 2 patients for ventricular tachycardia); 1 patient underwent ICD implantation and, few months later, ventricular tachycardia ablation procedure. Outcome events occurred in 9 patients; no patient died during follow-up, whereas 3 patients experienced a nonfatal episode of SVT causing hemodynamic compromise and requiring cardioversion, and 6 patients received an appropriate ICD therapy.

Kaplan–Meier survival curves for the outcome event comparing patients according to QRS morphology of baseline VAs, type of baseline VAs, and presence of myocardial structural abnormalities on cMRI are shown in Figure 3. Table 4 shows the results of the univariate Cox proportional hazards analysis performed to determine the association between

**Table 3. Univariate Logistic Regression Analysis to Determine the Correlates of Myocardial Structural Abnormality**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq$ 40 yr</td>
<td>4.5 (1.42–14.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Male sex</td>
<td>8.7 (1.94–39.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Family history of SCD or cardiomyopathy</td>
<td>5.0 (1.76–14.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptoms*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>2.0 (0.54–7.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Syncope</td>
<td>5.6 (0.97–31.7)</td>
<td>0.054</td>
</tr>
<tr>
<td>Type of VA†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSVT</td>
<td>2.2 (0.74–6.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>SVT</td>
<td>7.9 (1.86–33.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Morphology of VA‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBBB and inferior QRS axis</td>
<td>2.7 (0.45–16.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>RBBB and superior QRS axis</td>
<td>21.2 (6.2–72.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NSVT, nonsustained ventricular tachycardia; OR, odds ratio; RBBB, right bundle branch block; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; and VA, ventricular arrhythmia.

*Dummy variables were created for palpitations and syncope with asymptomatic status serving as the primary comparison.

†Dummy variables were created for NSVT and SVT with frequent premature ventricular beat serving as the primary comparison.

‡Dummy variables were created for RBBB and inferior QRS axis and RBBB and superior QRS axis with left bundle branch block and inferior QRS axis serving as the primary comparison.
baseline covariates and outcome event. Family history of SCD or cardiomyopathy (hazard ratio=6.3; 95% CI, 1.68–23.5; \( P=0.006 \)), SVT (hazard ratio=19.8; 95% CI, 4.7–83.0; \( P<0.001 \)), and the presence of myocardial structural abnormalities on cMRI (hazard ratio=41.6; 95% CI, 5.2–225.0; \( P<0.001 \)) were significantly related to the outcome event.

**Discussion**

Previous studies have demonstrated that VAs of LV origin, differently from VAs of RV origin, are frequently associated with structural heart disease, with coronary artery disease and nonischemic cardiomyopathy being the most common causes.\(^{16-18}\) VAs occurring in the absence of structural heart disease or transient or reversible arrhythmogenic factors (i.e., electrolyte disorders or myocardial ischemia) are considered idiopathic or of unknown cause; absence of structural heart disease is usually suggested when routine diagnostic work-up (including 12-lead ECG, transthoracic echocardiography, and noninvasive or invasive test to rule out significant coronary artery disease) is normal.\(^2\)

There is increased interest in examining whether cMRI, which may allow identification of otherwise unrecognized myocardial abnormalities, is useful for the diagnostic work-up of patients presenting with unexplained VAs.\(^{19}\) cMRI has indeed the ability to provide comprehensive myocardial tissue characterization, through the use of T1-weighted imaging (for the identification of myocardial fatty replacement), T2-weighted imaging (for the identification of myocardial edema), and LGE imaging (for the identification of myocardial necrosis/fibrosis). The combination of these 3 tissue-imaging techniques offers a potentially useful tool for the noninvasive identification of arrhythmogenic substrate. In particular, the ability of cMRI to detect and quantify myocardial fibrosis is useful because the amount of fibrosis in cardiac disease is associated with conduction delays and increased vulnerability for arrhythmias.\(^{20,21}\)

Previous studies have investigated the clinical value of cMRI among patients with apparently idiopathic VAs of RV origin\(^{14-14}\); some authors demonstrated cMRI signal alterations in this group of patients,\(^5-8\) whereas others showed RV wall motion abnormalities without signal alterations\(^6-11\) or even any kind of RV abnormalities.\(^{12-14}\) More recently, Jeserich et al\(^{22}\) and Mavrogeni et al\(^{23}\) evaluated the value of a cMRI protocol including T2-weighted and LGE imaging in patients with unexplained VAs (frequent PVBs and ventricular tachycardia, respectively); in both studies, LV myocardial structural abnormalities (including nonischemic scarring) were observed in the majority of patients. White et al\(^{11}\) applied a cMRI protocol with comprehensive tissue characterization (including T1-weighted, T2-weighted, and LGE imaging) in 40 patients with resuscitated SCD or SVT and no abnormal findings on routine diagnostic work-up; half of these patients were diagnosed as having relevant myocardial disease. Of note, none of these recent studies addressed the site of origin of VAs. In this study, the relation between the origin of apparently idiopathic VAs (i.e., LV versus RV) determined according to the morphology of VAs on 12-lead ECG and the presence of myocardial structural abnormalities revealed by a comprehensive cMRI examination was investigated. Our data confirmed a low prevalence of myocardial structural abnormalities involving the

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**Figure 3.** Kaplan–Meier survival curves with regard to the outcome event according to QRS morphology of baseline ventricular arrhythmias (VAs; A), type of baseline VAs (i.e., frequent premature ventricular beats [PVBs], nonsustained ventricular tachycardia [NSVT], or sustained ventricular tachycardia [SVT]; B), and presence (cMRI+) or absence (cMRI−) of myocardial structural abnormalities on cMRI (C). Relative to the morphology of baseline VAs, outcome events occurred only in patients with VAs with right bundle branch block (RBBB) morphology and superior QRS axis. Relative to the type of baseline VAs, outcome events occurred in 3 patients with frequent PVBs, in 1 patient with NSVT, and in 5 patients with SVT. Relative to the cMRI findings, outcome events were observed in 8 patients with cMRI+ and in 1 patient with cMRI−. LBBB indicates left bundle branch block.
Table 4. Univariate Cox Proportional Hazards Analysis of Baseline Covariates in Relation to Outcome Event

<table>
<thead>
<tr>
<th>Symptom*</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>0.95 (0.18–4.9)</td>
<td>0.95</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.8 (0.40–20.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Type of VA†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSVT</td>
<td>1.2 (0.12–11.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>SVT</td>
<td>19.8 (4.7–83.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Morphology of VA‡

| RBBB and inferior QRS axis | … | 0.99 |
| RBBB and superior QRS axis | … | 0.19 |
| Myocardial structural abnormality | 41.6 (5.2–225.0) | <0.001 |

Outcome event is arrhythmic composite end point of sudden cardiac death or nonfatal episode of ventricular fibrillation or SVT requiring external cardioversion or appropriate implantable cardioverter defibrillator therapy. CI indicates confidence interval; HR, hazard ratio; NSVT, nonsustained ventricular tachycardia; RBBB, right bundle branch block; SCAD, sudden cardiac death; SVT, sustained ventricular tachycardia; and VA, ventricular arrhythmia.

*Dummy variables were created for palpitations and syncope with asymptomatic status serving as the primary comparison.
†Dummy variables were created for NSVT and SVT with frequent premature ventricular beat serving as the primary comparison.
‡Dummy variables were created for RBBB and inferior QRS axis and RBBB and superior QRS axis with left bundle branch block and inferior QRS axis serving as the primary comparison.

RV and the LV among patients with apparently idiopathic VAs of RV origin. Conversely, cMRI detected myocardial structural abnormalities in a non-negligible proportion (41%) of patients with unexplained arrhythmias of LV origin. Ten (22%) patients had 21 foci of LGE with subepicardial or midmyocardial distribution, possibly related to remote inflammatory tissue injury or underlying nonischemic structural heart disease. One patient had regional signal abnormalities on T2-weighted imaging and regionally matched LGE with nonischemic pattern (findings consistent with acute myocarditis). Finally, 7 patients had signal alterations indicating both myocardial fatty replacement and nonischemic scarring of the LV, mainly involving the inferior and lateral wall; in 1 patient, signal alterations on T1-weighted and LGE imaging involving the RV were also observed. Taking into account the morphology of VAs and the cMRI features, arrhythmogenic LV cardiomyopathy may be hypothesized in these patients. Dominant or isolated LV involvement has been indeed recently recognized as a rare phenotypic expression of arrhythmogenic right ventricular cardiomyopathy/dysplasia, being characterized by LV myocyte loss, fibrofatty replacement, and chronic inflammatory infiltrates, paralleling the RV changes of its right-dominant counterpart, and by an increased risk of VAs of LV origin and SCAD.

Importantly, the morphology of VAs (ie, RBBB morphology and superior QRS axis) was significantly related to the presence of concealed myocardial structural abnormalities. VAs with RBBB morphology and superior QRS axis are indeed consistent with an inferior LV wall exit, which have been rarely observed in idiopathic VAs. Interestingly, this matches with the observation that LV segments having LGE were frequently located in the inferior and inferolateral wall, suggesting the possible relationship of reentry circuits to the detected scar.

Another important finding of this study is that the presence of myocardial structural abnormalities on cMRI was a predictor of follow-up arrhythmic events among patients presenting with apparently idiopathic VAs. This finding fits with observations of previous studies that cMRI is able to identify patients at risk for arrhythmic events in several overt heart diseases, including ischemic cardiomyopathy, nonischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis.

Clinical Implications

According to the findings of this study, cMRI may be useful for the risk stratification of patients presenting with monomorphic VAs and negative routine diagnostic work-up because of its ability to better characterize the pathogenic substrate of VAs and consequently identify those subjects at higher risk of arrhythmic events during follow-up. Some clinical and ECG characteristics related to the presence of myocardial structural abnormalities (ie, age ≥40 years, male sex, family history of SCAD or cardiomyopathy, SVT, and VAs of RBBB morphology and superior QRS axis) may help to select those patients who could mainly benefit from the implementation of cMRI in the routine diagnostic work-up.

Study Limitations

This study has some limitations that should be acknowledged. First, a selection bias may have been introduced, as study population included patients presented to a tertiary referral center, which may differ from an unselected group of patients. Second, the study population was relatively small and the outcome events during follow-up were relatively few and mainly represented by ICD therapies; consequently, results should be treated as preliminary, needing to be confirmed by further studies with larger sample size and longer follow-up. Third, T1 mapping, which may allow detection of extracellular volume expansion due to interstitial fibrosis possibly representing an arrhythmogenic tissue substrate among those patients without detectable LGE, was not performed. Fourth, electroanatomical voltage mapping was performed only in few patients because of the low prevalence of refractory VAs; consequently, a rigorous relation between the origin of VAs and the site of structural abnormalities detected by cMRI cannot be confirmed. Fifth, endomyocardial biopsy has not been performed; however, it is associated to a non-negligible risk of complications, and, according to current guidelines, its diagnostic utility in patients with unexplained VAs is uncertain.

Conclusions

cMRI detects myocardial structural changes in a non-negligible proportion of patients with apparently idiopathic VAs of LV origin. In addition, myocardial structural abnormalities on cMRI are associated with worse outcome. Accordingly, cMRI should be implemented in the routine diagnostic work-up of these patients, to better characterize the pathogenic substrate of VAs.

Disclosures

None.
References


**CLINICAL PERSPECTIVE**

Excluding structural heart disease that may be associated with a risk of sudden death is an important consideration for patients with presumptive idiopathic ventricular arrhythmias (VAs). Idiopathic VAs most frequently have a left bundle branch block–like configuration and originate from the right ventricle. In this study, cardiac MRI was performed in patients with presumptive idiopathic VA including 46 patients with right bundle branch block–like configurations VA consistent with a left ventricular origin. In contrast to the infrequent abnormalities noted among patients with left bundle branch block VAs, abnormalities were seen in 41% of patients with right bundle branch block VAs. Structural abnormalities were associated with spontaneous sustained arrhythmias during follow-up. The findings support the use of cardiac MRI in the routine evaluation of patients with apparently idiopathic VAs of right bundle branch block configuration, to evaluate the possible presence of arrhythmic substrate and inform therapeutic decisions.

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SUPPLEMENTAL MATERIAL

Cardiac MRI acquisition protocol

All patients received oral antiarrhythmic therapy at least 1 week before cMRI examination in order to optimize ECG trigger and to obtain optimal image acquisition. Overall, cMRI exams were performed within 15 days from clinical presentation in all patients.

Cardiac MRI studies were performed using a 1.5 Tesla scanner (Siemens Avanto, Erlangen, Germany and Signa CVi, GE Healthcare, Milwaukee, Wisconsin) with a cardiac phased-array receiver surface coil and ECG-gating. Vertical and horizontal long-axis slices, a stack of contiguous cine short-axis slices from the atrio-ventricular ring to the apex and para-axial slices from diaphragm to the entire outflow tract were acquired using a steady-state free-precession pulse sequence (slice thickness = 8 mm, no interslice gap for long-axis and short-axis images; slice thickness = 5 mm, no interslice gap for para-axial images; TR/TE = 40-50/1.2 ms for Siemens Avanto; TR/TE = 3.5/1.5 ms for Signa CVi). For the evaluation of myocardial fatty replacement, T1-weighted imaging was performed using a double inversion recovery fast spin-echo pulse sequence using the same slice coverage as long-axis, short-axis and para-axial cine images (TE = 30 ms). Fast spin-echo images were also acquired with the same geometry using a fat saturation pulse to selectively null signals from fat. Breath-hold T2-weighted short-TI inversion-recovery fast spin-echo pulse sequence using the same slice coverage as long-axis and short-axis cine images was utilized to assess the presence of myocardial edema (TR/TE = 2 R-to-R intervals/75 ms and TI = 170 ms for Siemens Avanto; TR/TE = 2 R-to-R intervals/100 ms and TI =
150 ms for Signa CVi). LGE images were acquired using the same slice coverage as long-axis, short-axis and para-axial cine images 10 minutes after intravenous injection of 0.2 mmol/kg gadolinium-based contrast agent (Omniscan, Nycomed Amersham, Princeton, New Jersey, USA) using an inversion-recovery gradient-echo pulse sequence, individually adjusting inversion time to optimize nulling of apparently normal myocardium.

**Cardiac MRI data analysis**

All cMRI studies were analyzed offline using a dedicated software (Segment 1.9, Medviso AB, Lund, Sweden). Quantitative analyses were performed by an expert investigator blinded to clinical and ECG data. Qualitative analyses were performed by 2 independent expert investigators; any discrepancies between the investigators were independently adjudicated by a blinded third investigator.

Biventricular volumes and function and LV mass were measured using standard volumetric technique from the cine short-axis images. Volume and mass measurements were indexed to body surface area. The absence or presence of LV wall motion abnormalities (i.e. hypokinesia, akinesia or dyskinesia) was visually assessed for each LV myocardial segment, using the 17-segment cardiac model. Similarly, the absence or presence of RV wall motion abnormalities (i.e. hypokinesia, akinesia or dyskinesia of the ventricular wall showing bulging during diastole) was qualitatively assessed from the short-axis, para-axial and para-sagittal cine views. The absence or presence of major or minor cMRI criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) was also determined; the revised task force criteria were used for this purpose.
T1-weighted fast spin-echo images with and without fat saturation were visually scored for the presence of an abnormal myocardial fat signal of either the RV or LV myocardium, as previously described.\(^3\) On T2-weighted images, LV edema was considered present if signal intensity of hyperintense myocardium was >2 standard deviation (SD) above the mean signal intensity of remote myocardium.\(^5\) Images were visually assessed for the presence and distribution of LGE areas (indicative of myocardial necrosis/fibrosis) for each LV myocardial segment using the 17-segment cardiac model;\(^2\) regions of elevated signal intensity had to be confirmed in 2 spatial orientations. Patterns of LGE were visually classified as subendocardial, subepicardial, mid-myocardial, involving RV insertion areas, and transmural (Supplemental Figure 1);\(^6\) LGE was defined as transmural when occupying ≥75% of LV wall thickness. The dichotomous presence or absence of RV LGE was also determined. In addition, the quantitative extent of LV LGE was determined, as previously described.\(^7\) A region of interest (ROI) was selected in the background of the image. Mean signal intensity and SD of the ROI were measured. The LV myocardium was delimited by endocardial and epicardial contours, which were traced manually. Enhanced myocardium was defined as myocardium with a signal intensity ≥5 SDs above the mean of the ROI. The extent of LGE was expressed as a percentage of the LV mass (%LV LGE).

The dichotomous presence or absence of any myocardial structural abnormality (i.e. myocardial fatty replacement, edema, and/or necrosis/fibrosis) was finally defined for each patient.
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SUPPLEMENTAL FIGURE 1. Patterns of late gadolinium enhancement; endocardial (A), transmural (B), subepicardial (C and D) and mid-myocardial (E and F) patterns.

Adapted from Mahrholdt et al. Eur Heart J 2005;26:1461-74
SUPPLEMENTAL FIGURE 2A. A 37-year-old man without family history of sudden cardiac death or cardiomyopathy was admitted because of sustained ventricular tachycardia with right bundle branch block morphology and superior QRS axis (left panel) symptomatic for palpitations. Routine diagnostic work-up, including invasive coronary angiography, was normal. **Mid panels:** T2-weighted cardiac magnetic resonance imaging (cMRI) demonstrated increased signal of basal interventricular septum and basal anterior left ventricular (LV) wall (upper panel); regionally matched late gadolinium enhancement with non-ischemic pattern was also observed (mid and lower panel), consistent with an acute inflammatory process.

**Right panels:** right-lateral view of the endocardial bipolar voltage map of LV (upper panel) showed in red an area of pathologic low potentials (<0.5mV) consistent with the basal septal scar found at cMRI. Endocardial bipolar potentials greater than 1.5 mV are purple, lower than 0.5 mV are red and the different hues of yellow-green-blue are between 0.5 and 1.5 mV. Scar tissue is considered to have local bipolar potentials less than 0.5 mV. Sites of radio-frequency pulses application are shown as red tags in the lower panel.
SUPPLEMENTAL FIGURE 2B. A 48-year-old man was admitted because of sustained ventricular tachycardia with right bundle branch block morphology and superior QRS axis (left panel). Mid panels: T1-weighted cardiac magnetic resonance imaging (cMRI) demonstrated signal abnormalities suggestive of myocardial fatty replacement of the lateral left ventricular (LV) wall (upper panel). Regionally matched late gadolinium enhancement (LGE) with non-ischemic pattern was also observed (mid and lower panel). Further areas of LGE with non-ischemic pattern were also observed at inferior wall, interventricular septum and LV apex. Right panels: epicardial voltage map (infero-lateral view) in the upper panel showed in red an area of low voltage (<0.5mV) consistent with scarred tissue and corresponding to the infero-lateral LGE area at cMRI. Late potentials map during sinus rhythm in the lower panel showed in purple the area where was recorded delayed/fractionated electrical activity after the inscription of the QRS complex, consistent with the slow conduction pathway of the re-entrant circuit. Phrenic nerve capturing sites are indicated with black dots and sites with double potentials are indicated by blue dots. Sites of radio-frequency pulses application are shown as red tags in both panels.

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